May 15, 2006

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
April 4-6, 2006 Public Meeting
Docket Number: EPA-HQ-ORD-2006-0187

Committee Members: (See Roster – Attachment A)

Dates and Times:	Tuesday, April 4, 2006; 8:30AM – 6:00 PM Wednesday, April 5, 2006; 8:30AM – 6:00PM Thursday, April 6, 2006 8:30 AM – 1:00PM (See Federal Register Notice Attachment B)	
Location:	Holiday Inn – Rosslyn at Keybridge, Arlington, Virginia	
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.
	Vice Chair:	William S. Brimijoin, Ph.D.
	Board Members:	David C. Bellinger Ph.D. Gary L. Chadwick, PharmD, MPH, CIP Janice Chambers, Ph.D. D.A.B.T. Richard Fenske, Ph.D. MPH Susan S. Fish, PharmD, MPH Suzanne C. Fitzpatrick, Ph.D. D.A.B.T. Kannan Krishman, Ph.D. KyungMann Kim Ph.D., FCCP 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.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as 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 introduced the board members. George Gray, Ph.D. (EPA Science Advisor)

welcomed board members and Susan Hazen (Acting Assistant Administrator, Office of Prevention, Pesticides and Toxic Substances, EPA) provided opening remarks. Paul Lewis, Ph.D. (Designated Federal Officer, HSRB, Office of the Science Advisor, EPA) explained the meeting administrative process and Celia Fisher, Ph.D. explained the responsibilities of the board as outlined in the HSRB charter She explained that board members were assigned as primary and secondary discussants to answer questions posed by EPA on both the scientific and ethical evaluation of specific pesticides under review. Dr. Fisher explained that the Board would evaluate the science of each study first, because part of the ethics evaluation depends upon the risk-benefit calculus and if a human dosing study does not have scientific validity than it has to "benefit." Dr. Fisher then provided the scientific criteria that she would ask the Board to apply to each study: (1) Did the research design and implementation meet scientific standards? (2) Do the data generated by the protocol have implications for the Agency's Weight of the Evidence (WOE) determination, and when applicable, aspects of the risk assessment. The Chair concluded with the criteria that she would ask the Board to apply to each study: (1) Did the study fail to fully meet specific ethical standards prevalent at the time the research was conducted? (2) Was the study "fundamentally unethical" (There was clear and convincing evidence that the research was intended to seriously harm participants or failed to obtain informed consent cf. Final Rule 26.104)? (3) Was the conduct of the study "significantly deficient" relative to the ethical standards prevailing at the time: Is there is clear and convincing evidence that: (a) The deficiencies identified could have resulted in serious harm (based on knowledge available at the time the study was conducted); *or* (b) The information provided to participants could seriously impair informed consent?

Session 1: Introduction

In the Session 1 Overview, Mr. William Jordan (Office of Pesticide Programs [OPP], EPA) explained that the Food Quality Protection Act (FQPA, 1996) required a review of tolerance limits for all pesticides currently in the market place. The FQPA strengthened and expanded review of human studies data. The HSRB provides scientific and ethical review of human studies based on recommendations by the National Academy of Science (NAS) report "Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues". EPA strives to use the best science with the highest ethical qualities. In his presentation, "Summary of EPA's Requirements for Protections for Subjects of Human Research", Mr. Jordan provided a history of EPA rulemaking with respect to Human Studies and described protections for the subjects of human studies conducted by 1st, 2nd and 3rd parties. Mr. Jordan explained that EPA is required to document its scientific and ethical assessments of completed, intentional human dosing research, and to obtain HSRB review for certain types studies on which EPA intends to rely under the pesticide laws. Ethical deficiencies must be established by clear and convincing evidence which is to say more than a "preponderance of the evidence," but less than "beyond a reasonable doubt".

Following Mr. Jordan's presentations, Mr. Michael Metzger (OPP, EPA) presented EPA's approach to assessing human health risks of pesticides using data from

human studies. Mr. Metzger provided a summary of toxicological terminology and explained that EPA's preferred endpoint for cumulative risk assessment is the benchmark dose (BMD) because the BMD uses all the data points from one or more toxicity studies to statistically derive a dose-response curve. Mr. Metzger also explained OPP's application of safety factors and uncertainty factors. Safety and uncertainty factors are generally 10-fold factors, used to derive the RfD and RfC from experimental data. They include: 1) intraspecies – variability among humans; 2) interspecies – extrapolating animal data to humans; 3) extrapolating from less-than-lifetime to lifetime exposures; 4) LOAEL to NOAEL; 5) incomplete data base and; 6) FQPA for protection of children.

OPP's assessment of ethical conduct during human studies was provided by Mr. John Carley (OPPP, EPA). Mr. Carley explained that in December 2001, EPA asked the NAS for advice on consideration of human studies and announced that it would not rely on third-party human toxicity studies until it issued regulations. This moratorium was challenged by CropLife America, and others, and was overturned by the courts. The Agency reverted to its previous practice of considering third-party human studies on a case-by-case basis, applying the Common Rule. The Agency's Human Studies Working Group (HSWG) was asked to develop ethics review guidance to ensure consistent interpretation and implementation of the CropLife decision. The HSWG focused on Emanuel et al., supplemented with an article by Miller "Clinical Research with Healthy Volunteers: An Ethical Framework". EPA did not rely on completed research if there is clear and convincing evidence that the research was fundamentally unethical, or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. EPA did not find clear and convincing evidence to suggest that any of the research presented to the HSRB for this week's meeting were fundamentally unethical.

Next, Ray Kent, Ph.D. (OPP, EPA) provided an assessment of the type and scope of toxicity studies used by OPP and explained which human studies need HSRB's review. Systemic toxicity, dermal irritation or sensitization and eye irritation studies need HSRB review. Epidemiological (including poisoning or incident data) and *In vitro* studies do not require HSRB review. No guidelines exist for human absorption, distribution, metabolism and excretion (ADME) studies, but future ADME studies may be subject to HSRB review. All human toxicity studies are considered for their relevance to the overall risk assessment. Relevant studies are reviewed for scientific quality and ethics. The role of a study in a risk assessment is determined in a weight of evidence analysis encompassing the whole toxicity database.

The next presentation was a summary of the human studies for consideration by the HSRB, as presented by Louis Scarano, Ph.D. (OPP, EPA). Dr. Scarano said that the Agency will provide a detailed description of 11 human studies that are being considered for use in tolerance setting for 8 pesticides. The studies are proposed for use in single chemical and cumulative assessments.

Session 2: Carbamate Pesticides

Overview

Session 2 was started by Anna Lowit, Ph.D. (OPP, EPA) who explained that organophosphate pesticides are included in a common mechanism group based on inhibition of AChE by phosphorylation. Effects are seen in the brain, peripheral nervous system and are measured using surrogate indicators such as AChE inhibition in RBC and plasma. The HSRB was asked to assess scientific conduct and study design as well as ethical conduct.

Dr. Lowit also explained OPP's policy on the use of cholinesterase inhibition data for the risk assessment of organophosphorous (OP) and carbamate pesticides. OP and carbamate pesticides constitute common mechanism groups. Both classes of chemicals inhibit AChE but OPs phosphorylate the active site while carbamates carbamylate the active site. Because AChE inhibition is a key event in the mode of action leading to neurotoxicity for both common mechanism groups, avoiding AChE inhibition protects subject from downstream toxic effects. Inhibition of blood AChEs is not an adverse effect, but may indicate the potential for adverse effects on the nervous system. Thus, blood AChE inhibition data are used as surrogate measures of potential toxic effects of the peripheral and central nervous systems. RBC AChE results are preferred over plasma results but both should be assessed in context to both statistical and biological significance. There is no fixed percentage of change used to separate adverse from non-adverse effects.

Science and Ethics of the Aldicarb Human Studies

Details of the aldicarb human study were provided by Linda Taylor, Ph.D. (OPP, EPA) and Elissa Reaves, Ph.D. (OPP, EPA). The aldicarb human study was conducted in 1992. Based on the study design, the Agency proposed to apply the following safety factors:

- LOAEL to NOAEL factor: an additional 10x uncertainty factor (UF) was needed to account for extrapolating from a LOAEL to NOAEL
- FQPA Factor: a Special Hazard Based FQPA safety factor was not needed because the BMD analysis showed that the young are approximately 2X more sensitive than adults. However, this 2X sensitivity was accounted for in the point of departure of 0.005 mg/kg/day.
- A total uncertainty factor of 300 (10X for intraspecies variations, 3X for interspecies differences, and 10X LOAEL to NOAEL) was recommended.

A summary of the EPA's ethical review for aldicarb was provided by John Carley (OPP, EPA). The aldicarb human study was conducted in the United Kingdom in 1992 and cites and asserts compliance with Declaration of Helsinki (1989) and the principles of good clinical practice. Mr. Carley used the ethical framework to evaluate the aldicarb human study and provided a comparison to relevant principles from the Declaration of Helsinki. Mr. Carley concluded that because of the supplemental submissions, more is known about this study than most. Although some gaps remain, these gaps were not clear and convincing evidence that the research was fundamentally unethical. Some

deficiencies were apparent relative to the cited 1989 Declaration of Helsinki.

Science and Ethics of Methomyl and Oxamyl Human Studies

Elissa Reaves, Ph.D. (OPP, EPA) explained that methomyl and oxamyl were members of the N-methyl carbamate (NMC) common mechanism group sharing inhibition of AChE as the common mechanism of toxicity. Rat brain ChE data provides the relative potency factor (RPF) and point of departure (POD) for the cumulative assessment. The methomyl human study was conducted in 1998, the oxamyl human study in 1999.

The Agency's weight of evidence (WOE) documents for methomyl and oxamyl described the study design and results of the human studies and also discussed the Agency's conclusions regarding the usefulness of the study in the cumulative risk assessment for the NMCs. For methomyl, the Agency concluded that the human toxicity study supports a 10x inter-species uncertainty factor for methomyl in the cumulative risk assessment of NMCs. For oxamyl, the Agency concluded that the human toxicity study was sufficiently robust for reducing the 10x interspecies (i.e., animal to human) uncertainty factor in the cumulative risk assessment.

During the ethical summary for methomyl, Mr. Carley (OPP, EPA) explained that the human study was a randomized, double-blind, ascending oral dose study used to establish a NOAEL. The unpublished study was conducted by Inveresk Clinical Research in 1998. It was among the first post-FQPA human studies of ChE inhibition and it was designed as a 6-level escalating-dose protocol, with no further escalation after greater than or to 40% ChE inhibition. One subject who received a lead dose in session two experienced greater than 40% ChE inhibition. Investigators proceeded with session 3, omitting the lead dose and later amended study protocol to add an intermediate (lower) dose. The methomyl human study cites and asserts compliance with Declaration of Helsinki (1996) and the principles of good clinical practice. Mr. Carley used the ethical framework to evaluate the methomyl human study and provided a comparison to relevant principles from the Declaration of Helsinki. Mr. Carley concluded that there were some gaps in the record, but the gaps were not clear and convincing evidence that the research was fundamentally unethical. Some deficiencies were apparent relative to the cited 1996 Declaration of Helsinki

For oxamyl, Mr. Carley stated that the human study was a randomized, double-blind, ascending oral dose study. The unpublished study was conducted by Inveresk Clinical Research in 1999. The study followed the methomyl human study and was designed as a 5-level escalating-dose protocol, with no further escalation after greater than or equal to 40% ChEI or greater than or equal to 25% at two successive time-points. After original five dose levels were well tolerated, a sixth higher dose was added. Mr. Carley concluded that there were some gaps in the record, but the gaps were not clear and convincing evidence that the research was fundamentally unethical.

Public Comments

Mr. Angus Cameron, Regulatory Affairs Manager at Inveresk Research from 1985 to Feb 2002**.**

Mr. Cameron stated that Inveresk is one of world's largest, full service contract research organization, conducting pre-clinical testing in animals for pharmaceuticals, agrochemicals, and industrial chemicals. Inveresk conducts Phase I testing of new and established molecules conducted on healthy volunteers at a 62 bed clinical unit in Edinburgh, Scotland. Inveresk's Independent Research Ethics Committee was established in 1979 to advise Inveresk Research on the ethical acceptability of clinical research, providing written standard operating procedures which are reviewed annually. Inveresk Research procedures are designed to ensure complete safety of all subjects in all studies and to ensure that the highest ethical standards are met.

Neil Carmichael, Ph.D. Bayer CropScience

Dr. Carmichael explained that the objectives of the aldicarb human study were to characterize the dose response and time course of ChE inhibition following administration of aldicarb using a double blind design and to demonstrate the relative sensitivity of male and female humans compared to animals. The aldicarb human study addressed questions raised by regulatory authorities about aldicarb toxicity and risks to humans and was accepted for use in the Agency's risk assessment in 1993. Bayer CropScience believed the human study represented the most relevant and appropriate data for setting the RfD and the interspecies safety factor for aldicarb. The HSRB was charged with reviewing the ethical and scientific considerations pertaining to study conduct, including the scientific justification and risk/benefit questions. It is inappropriate for EPA to ask the HSRB to render weight-of-evidence (WOE) judgments with only a limited sampling and summarization of the available information and data.

Jennifer Sass, Ph.D. Natural Resources Defense Council

Dr. Sass stated that aldicarb has been banned in seven countries, restricted in six countries and is listed by the World Health Organization (WHO) as 1a, extremely hazardous. One of the critical issues in evaluating the scientific validity of the aldicarb human study design was statistical power. A study with inadequate power to find an effect is by definition unethical. There are roughly 19 million children in the United States less than or equal to 5 years of age. If a toxicant harmed 1 child in 1,000, that would place 19,000 children at risk nationwide. A study with adequate power to detect an increase in deficit from 1% to 2% would require 3,017 subjects in each group to yield a power of 0.8, at p= 0.05. Studies with sample sizes <50 have about a 3% chance of finding an effect if it were present. Dr. Sass summarized NRDC's position on human studies: 1) studies should only be considered where they have demonstrated validity of study design, statistical power, and sample size; 2) industry sponsorship may bias study design, data analysis, or interpretation (this also applies to in-house IRBs); 3) study subjects are usually limited to healthy adults, often males, and are not representative of

the general population; and 4) risks accrue to subjects, while argued benefits accrue to society (pesticide residue in food have no known health benefits).

Aldicarb

Charge To The Board

Aldicarb is a *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. Aldicarb can, at sufficiently high doses, lead to a variety of clinical signs. The Agency is conducting an acute, aggregate (single chemical, multi-route) risk assessment of aldicarb. In addition, aldicarb 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 "Weight of the Evidence" (WOE) document and Data Evaluation Records (DERs) for aldicarb describe the study design and results of the aldicarb acute oral, human toxicity study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human study in the acute, aggregate, single chemical risk assessment and in the cumulative risk assessment for the NMCs. Regarding the aldicarb human study, the Agency has concluded that the study is sufficiently robust for reducing the inter-species (i.e., animal to human) uncertainty factor in the aggregate and the cumulative risk assessments.

Please comment on the scientific evidence that supports whether the aldicarb human study is sufficiently robust for reducing the inter-species (i.e. animal to human) uncertainty factor in:

a. single chemical, aggregate risk assessment and
b. cumulative risk assessment.

Board Response to the Charge

Drs. Chambers and Dr. Bellinger highlighted the study strengths and weaknesses. During Board discussion it was concluded that a NOAEL based on RBC and plasma AChE inhibition and clinical signs for males could be determined. The RBC AChE inhibition was dose and time dependent in both males and females. For the single chemical aggregate risk assessment, referring to the Agency's Data Evaluation Report, the Agency concluded that the NOAEL/LOAEL for males was based upon sweating. While sweating is a possible clinical sign resulting from ChE inhibition, this finding was not consistently dose related in the subjects. The WOE concluded that whole blood ChE inhibition would be the critical endpoint. Blood ChE was probably a more important endpoint. The ChE data, while probably incomplete, is consistent within the study. The measures were dose and time dependent in both sexes and were expected.

For the cumulative risk assessment, aldicarb is an N-methyl carbamate. Thus, the endpoint had to be ChE inhibition. The dose response data from the human study support calculation of BMD_{10} and $BMDL_{10}$ because there were a number of doses included. Due to the rapid reactivation of carbamylated ChE, it is unclear whether accurate ChE inhibition values were obtained in the human study because the earliest time point measured was one-hour after dosing and the assay technique was incorrect. The WOE document stated that the human and rat ChE inhibition were comparable. However, there was some question as to whether they were recorded at the same time along with the recovery patterns. It should be possible to extrapolate this; however the study has a low number of subjects. Thus, while this information could be extrapolated, the low number of subjects makes this difficult.

Dr. Fisher summarized the Board's scientific considerations for aldicarb. The Board raised concerns about study design. The study had weaknesses but was still useful. The Agency should use the data with caveats for study weaknesses. The data derived was sufficient and consistent with clinical signs. While data are lacking such as peak inhibition, the same information is limited with animal studies. Thus, while this was not a critical flaw, the weaknesses should be considered. Missing peak data was not critical for the inter-species factor. It should be recognized that blood analysis was not conducted correctly, but results are consistent with clinical signs. Both Dr. Chambers and Dr. Bellinger agreed that this study did have some usefulness. In summary the human study appears to be scientifically valid for use in both the aggregate and cumulative risk assessment

Charge to the Board

Ethical considerations

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

In light of the ethics committee's instruction that the lay summary be "greatly expanded," and the fact that the materials used to obtain informed consent listed a limited range of symptoms of carbamate toxicity (excluding some reported as adverse effects in the study), included multiple references to the test material as a drug, and failed to identify dose levels to be administered to male subjects, whether, the materials used to obtain informed consent should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted

Whether the absence from the protocol of discussion of the potential risks to subjects or benefits to society of conducting the proposed research (as required by the 1989 Declaration of Helsinki, Principle # 4, with which the research asserted compliance) should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of this study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.

- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

Board Response to the Charge

Dr. Nelson lead the Board's discussion concluding that the study failed to fully meet the specific ethical standards prevalent at the time the research was conducted. These deficiencies were primarily in the area of informed consent. The Board also recognized that having the stopping rule based on 70% AChE inhibition raised the possibility of exposing subjects to inappropriate risk. However, the Board acknowledged that data existed to suggest that the doses used in the study would likely not achieve this level. The Board agreed with EPA's assessment that there was not clear and convincing evidence that the conduct of the research was fundamentally unethical. The research as designed and conducted was not intended to seriously harm participants nor failed to obtain informed consent.

The Board expressed concern that the informed consent process may also have been deficient but lacked direct evidence. Nevertheless, the Board did not believe that these deficiencies could have resulted in serious harm based on the knowledge available to the investigators at the time, nor seriously impaired the informed consent of the research subjects. Thus, the Board concluded that there was no ethical objection to the use of the data from this study, given the absence of clear and convincing evidence that the research was fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time.

Dr. Menikoff was also concerned about informed consent. Compared to consent forms used for other studies this form gave very little information. Other consent forms comment that people have died from exposure to this compound. This might be a significant deficiency from ethical standard. Dr. Philpott expressed concern about the reuse of female subjects. Recycled subjects knew that they would receive aldicarb in the second dosing. This also compromised the double-blind test protocol.

Dr. Fisher summarized the HSRB ethical considerations for aldicarb. The Board agreed with Mr. Carley's list of ethical deficiencies. However, the Board did not believe that these issues were serious enough to rise to the level significantly unethical. As for informed consent, if doses in the study were not near the lethal limit, stating that mortality could occur was not needed. Board concerns that their review might consider the study as significantly deficient would include the lack of information on informed

consent and the choice of 70% stopping rule. However, there were mitigating circumstances so the Board did not conclude that the study was significantly deficient.

Methomyl

Charge to the Board

Scientific considerations

The Agency's WOE document and DER for methomyl describe the study design and results of the methomyl acute oral, human study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human study in the cumulative risk assessment for the NMCs. For methomyl, the Agency has concluded that the human toxicity study supports a 10X inter-species uncertainty factor for methomyl in the cumulative risk assessment of the NMCs.

Please comment on the scientific evidence that supports this conclusion.

Board Response to the Charge

Dr. Lehman-Mckeeman listed strengths and weaknesses of the study When the study was designed, dose escalation was planned to range from 0.1-0.5 mg, with 40% ChE inhibition as the stopping point. The highest dose tested was 0.3 mg/kg. When a subject dosed at 0.3 mg/kg exceeded the stopping point of 40% ChE inhibition 8 hours after dosing, higher exposures were dropped. The study was altered when this finding was discovered. A subject in the lowest dose group exceeded 40% inhibition after eight hours. This was considered to be a spurious finding. The placebo group tested at 20% ChE inhibition at eight hours. Overall strengths of the study included clear dose-response findings which indicated that this was a scientifically valid study that can be used to inform selection of an uncertainty factor. Dr. Krishnan added that the results at eight hours were probably spurious findings since placebo assays run at the same time gave comparable numbers. Dr. Krishnan had no major concerns, regarding scientific validity of findings. With appropriate rat studies, this study can be informative for risk assessment.

Dr. Fisher summarized the Board's scientific considerations for methomyl. The study did provide clear dose-response and time-dependence results. While the study captured peak of inhibition, it had a small sample size and no female subjects. The baseline ChE inhibition was based on 2 pre-dose measures. More pre-dose information would have improved the estimate of baseline ChE inhibition. The decision to limit the protocol to 0.3 mg/kg appears appropriate. Thus, the Board concluded that the study was scientifically valid.

Charge to the Board

Ethical considerations

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

- Whether the investigators' decision to administer a dose to additional subjects in session 3, when one subject receiving that dose in session 2 displayed RBC ChEI greater than 40%, a response that triggered the protocol's anti-escalation provision, should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted;

- Whether the timing of the investigators' report to the ethics committee of the adverse effects observed in one subject during session 2 should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted;

- Whether the failure of the investigators to request approval from the ethics committee for certain amendments to the approved protocol, as required by the protocol, when the changes were administrative and had no effect on the safety of the subjects should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

- Whether the absence from the protocol of discussion of the potential risks to subjects or benefits to society of conducting the proposed research (as required by the Declaration of Helsinki, Principle # 5) should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of this study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.

- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted

Board Response to the Charge

Dr. Menikoff led the Board's response and had three principle concerns with the study: 1) when were the results for the subject with greater than 40% ChE inhibition available? It is unclear whether this result was available before moving on to the 3rd session; 2) was there a need to report this finding to IRB? The issue of this being a spurious finding is critical because if it was not they couldn't proceed; and 3) the addition

of the lower dose group of 0.2 mg/kg/dose was a significant change to the study protocol that could have resulted in serious harm and should have been brought to the IRB chair. The IRB should have had input into each of these three issues. However, while Dr. Menikoff did see these as deficiencies, there was not clear and convincing evidence of fundamentally unethical research that could have resulted in serious harm.

Dr. Fisher summarized the HSRB ethical considerations for methomyl. The Board agreed with the first three points made by Mr. Carley. The study was deficient because it did not have a report of risks and benefits to subjects. Also, it was deficient in not seeking a response from the IRB regarding the addition of a new dosing level. The Board did not believe that these deficiencies were significant because they did not appear to seriously compromise participants' rights or welfare.

Oxamyl

Charge to the Board

Similar to aldicarb and methomyl, oxamyl is a member of the N-methyl carbamate (NMC) common mechanism group based on its ability to inhibit acetylcholinesterase via carbamylation and is thus included in the NMC cumulative risk assessment. The Agency has previously completed the acute, aggregate (single chemical, multi-route) risk assessment of oxamyl. The Agency is now considering the use of the oxamyl acute oral, human toxicity study to inform the inter-species uncertainty factor in the cumulative risk assessment of the NMCs.

Scientific considerations

The Agency's WOE document and DER for oxamyl describe the study design and results of the oxamyl acute oral, human toxicity study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human study in the cumulative risk assessment for the NMCs. For oxamyl, the Agency has concluded that the human toxicity study is sufficiently robust for reducing the 10X inter-species (i.e., animal to human) uncertainty factor in the cumulative risk assessment.

Please comment on the scientific evidence that supports this conclusion.

Board Response to the Charge

Dr. Fitzpatrick enumerated the oxamyl human study strengths and weaknesses which followed almost the same protocol as methomyl. Dr Fitzpatrick listed five critical factors of human study design including: 1) dose selection based on animal data; 2) purity of the compound tested; 3) the mode of compound administration – oral, would have been most relevant to exposure via food; 4) comparable methods between species including participants of both genders would have been more beneficial; and 5) the study should include a statistical method to justify sample size. The study dosing and measurements were the same as for animal studies and the measurements were close and

consistent. The study reported an NOAEL and LOAEL and the study design was robust enough to justify estimation of a safety factor. The Board could not comment on the BMD_{10} estimate because animal data were not provided. Dr. Kim added that false positive rates and study power operate together. In a drug trial, false positives are good for drug companies; for pesticides, the sponsor would like to show no differences. Toxicity studies rarely include statistics on Type 1 error because they do not want to show difference. There was an incentive on the part of a sponsor to make multiple adjustments because this lowers the power. Of all the studies the Board had reviewed so far, this study was the most robust. Despite the lack of justification for sample size, this study does well to support determination of uncertainty factors and the lack of difference in genders.

Dr Fisher summarized the Board's scientific considerations for oxamyl. The study was useful and robust with multiple dosages and multiple exposure times. Dose randomization and dosing levels were chosen appropriately to approximate the NOAEL and LOAEL. In terms of sample size, the Board requested the Agency to comment on Type I and Type II error bias and how this influences EPA's use of the data to draw statistical conclusions.

Charge to the Board

Ethical considerations

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

- Whether inclusion in the protocol submitted to the ethics committee of a factually inaccurate statement regarding unavailability of data on accidental or incidental exposure to oxamyl should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted;

- Whether the absence from the protocol of any discussion of the potential risks to subjects or benefits to society of conducting the proposed research (as required by the Declaration of Helsinki, Principle # 5) should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of [this/each] study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.
- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

Board Response to the Charge

Dr. Philpott initiated the Board's response raising three issues: 1) applicable ethical and regulatory standards; 2) informed consent; and 3) study design to minimize the risk to participants. Dr. Philpott concluded that the study was consistent with Declaration of Helsinki, Common Rule and 21 CFR but had concerns about whether a clear discussion of risk was provided to subjects. Existing information on incidences of accidental exposure was not provided to the subjects. There was no evidence that the study was designed in a fashion to cause serious or unintended injury. Dr. Menikoff acknowledged informed consent issues but concluded that based on the knowledge available to the Board, this would not rise to the level of unethical

Dr. Fisher summarized the Board's ethical considerations for oxamyl. This study did not justify human exposure and informed consent documents may have been deceptive. However, the Board agreed with Mr. Carley and did not believe that the study was significantly deficient.

Session 3: Organophosphate Pesticides

Session 3 began with an overview of organophosphate pesticide toxicity provided by Anna Lowit, Ph.D. (OPP, EPA). Dr. Lowit explained that organophosphate pesticides are members of a common mechanism group. Organophosphate pesticides inhibit AChE by phosphorylation affecting brain and peripheral nervous system (e.g., nerves in diaphragm, muscles). Blood (RBC, plasma) AChE inhibition is used as a surrogate indicator of ChE inhibition.

Science and Ethics of Azinphos Methyl (AZM) Human Studies

John Doherty, Ph.D. (OPP, EPA) provided a weight of evidence (WOE) comparison of human and animal studies for azinphos methyl (AZM) for single chemical and organophosphate cumulative risk assessment. Dr. Doherty provided details for the AZM Repeat Dose Human Study conducted at Inveresk Laboratory (Scotland) in 1999. The study included 28 daily doses of 0.25 mg/kg (mkd) AZM in 8 adult males dosed orally by capsule, with a placebo group of 4 adult males dosed orally with lactose capsules. The objectives of the study were to determine the NOAEL for plasma ChE and RBC AChE and assess for possible reactions to treatment. The Agency's WOE document and DER for AZM describe the study design and results of the AZM repeat dose, oral, human toxicity study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human study in the worker risk assessment and in the cumulative risk assessment for the OPs. For AZM, EPA concluded that the repeat dose human study was technically scientifically acceptable. The NOAEL of 0.25 mg/kg/dose from human study was selected as the endpoint for short (1-30 days) and intermediate (1- 6 months) term occupational exposure risk assessments. Data from animal studies support selection of the human study. Animal NOAELs and LOAELs were ~0.5 to 1 mg/kg/day, and the 10x interspecies uncertainty factor could be dropped. Following this presentation, the Board expressed concerns regarding the assumption that

steady state had been achieved and how the NOAEL was determined.

A summary of EPA's ethical review of the AZM 28-day oral study was provided by Mr. John Carley. For AZM, Mr. Carley stated that the study was conducted at Inveresk Clinical Research in 1999. The subjects were residents in the clinic throughout testing. In addition they were provided medical supervision throughout testing and post-dosing until they returned to baseline ChE levels. The study cites and asserts compliance with Declaration of Helsinki (1996) and the guidelines for good clinical practice. Mr. Carley concluded that there were deficiencies relative to the cited 1996 Declaration of Helsinki but concluded that these deficiencies were not clear and convincing evidence that the research was fundamentally unethical.

Science and Ethics of Dichlorvos (DDVP) Human Studies

Ray Kent, Ph.D. (OPP, EPA) reviewed two DDVP human studies being considered for use in the single chemical assessment; a single administration, single dose study and a repeat administration, single dose study. The first study involved a single oral dose study of six adult males dosed with of 70 mg DDVP and measuring AChE 24 hours after dosing. Since data in rats indicated that peak inhibition of RBC AChE occurred 1-3 hours after oral dosing with DDVP, the failure to measure RBC AChE in humans until 24 hr post-dosing was judged to be a critical deficiency. The acute human study was not being relied upon to either establish an acute RfD or to decrease the interspecies uncertainty factor. The repeated dosing study included nine adult male subjects - 6 dosed subjects and 3 placebo subjects. The dosed subjects received 7 mg DDVP each day for 21 days. RBC AChE was measured 7 times before dosing and 9 times on dosing days 1 through 18 and 3 times post dosing. Even though RBC AChE was not measured until 24 hours post dosing, there was a clear pattern of response over 21 days. The data indicated that 0.1 mg/kg is a LOAEL in humans. The DDVP repeat dose human study was selected to assess short (less than 30 days) and intermediate (less than 6 months) exposure durations by oral and dermal routes.

Since the acute human study was not being relied upon to either establish an acute RfD or to decrease the interspecies uncertainty factor, Mr. Carley's ethics discussion for DDVP were limited to the 21-day oral study. This study was conducted at Medeval (United Kingdom) in 1997 using adult males. The subjects were non-resident, unsupervised, and self-reported all effects. The subjects' ChE levels continued to decline after the end of dosing and subjects were not followed back to baseline ChE levels. The study cites and asserts compliance with the Declaration of Helsinki (1989). In summary, Mr. Carley concluded that there were some gaps in the record, but the gaps were clear and convincing evidence that the research was fundamentally unethical. Some deficiencies were apparent relative to the cited 1989 Declaration of Helsinki.

Public Comments

Monty Eberhardt, Ph.D., CIH and Dan Van Goethem, M.S., DABT

Bayer CropScience and representing Makteshim Agan of North America

Dr. Eberhardt and Mr. Van Goethem stated that they respect the role of the HSRB in providing guidance and oversight to those sponsoring intentional dosing studies for submission to EPA but said that they feel it is unfair to ask the HSRB to render WOE judgments about these studies in a much broader regulatory context with only a small sampling of the available information and data. Dr. Eberhardt and Mr. Van Goethem said that the safety database for AZM was current and complete and includes both animal studies and studies in human volunteers. The animal studies demonstrated that AZM wais not carcinogenic, mutagenic, teratogenic or a reproductive toxicant and that inhibition of cholinesterase is the most sensitive indicator of exposure. The human studies confirmed that humans are no more, and perhaps less, sensitive than animals to AZM's cholinesterase inhibiting effects. The knowledge gained from these studies was being used in safety assessments. The commenters agreed with EPA's interpretation that there is not clear and convincing evidence that the conduct of this study was fundamentally unethical. However, they disagreed with EPA's interpretation that the study's value was limited to establishing a human ChE NOAEL. In addition, no evidence for use to establish RfDs, REIs, or safe levels for workers existed. They also disagreed that the informed consent materials were insufficient and were open to ideas on ways to improve future informed consent materials. Dr. Fisher explained that the charge of HSRB was not to evaluate WOE or make judgments about all the data but to evaluate the studies presented to them for scientific validity and ethical considerations.

Robert J. Levine, MD, Professor of Medicine and Co-Director, Yale University's Interdisciplinary Bioethics Center representing Amavac Chemical Corporation

Dr. Levine spoke to the ethics of research involving children as subjects. He stated that there was an ethical requirement to use all historical data. Forbidding research involving children and pregnant women virtually guarantees the future occurrence of Thalidomide-like disasters. The use of historical data puts no new subjects at risk. If EPA must disqualify data from children and pregnant women, it should not disqualify data from non-pregnant adults involved in the same studies. Dr. Levine stated that the disqualification of any historical data creates ethical problems and that in some cases the data from disqualified research could be of vital importance to the regulatory decision. It would be unethical to repeat the research under otherwise ethically acceptable conditions. A weight-of-evidence approach is an acceptable method of developing a probative data set from multiple studies when each of the studies is – for one reason or another – unsuitable for the intended purpose. Public exposure of errant sponsors and investigators is usually sufficient to deal with ethical transgressions for academics. The NIH might bar service on committees or their eligibility for grants. The FDA may also impose criminal sanctions, fines and/or imprisonment.

Mr. Ian Chart, Amvac Chemical Corporation

Mr. Chart stated that all DDVP human studies were commissioned or completed before 1996 so they were not performed in response to FQPA. The DDVP human

database has been developed by many organizations (WHO, CDC and FDA) over many years, addresses the 10X default interspecies factor, and is so robust that it can also address the intraspecies factor. Amvac disagreed with EPA's position that a WOE argument is only as robust as the individual studies. DDVP is unique as it has/had pharmaceutical, veterinary, and public health pesticidal uses. There are hundreds of human studies on DDVP and it is unlikely that such a vast database will ever be developed for a pesticide again. The DDVP human database is unique and should be treated in totality. Mr. Chart stated that weight of evidence analysis of adult-only biomarker data should not be disqualified merely because some of the data in the full database are available on children and/or pregnant women. It is inappropriate to dismiss individual studies without considering the database as a whole. The human studies considered together are scientifically relevant and ethically valid. The DDVP human database provides more than sufficient scientifically sound information to warrant reduction of the interspecies uncertainty factor.

Laura Plunkett, Ph.D. DABT, Integrative Biostrategies representing for Amvac Chemical Corporation

Dr. Plunkett presented the findings of a study completed in March 2006 (Plunkett et al.). The study was undertaken to examine the magnitude of interspecies differences in adult responses to DDVP exposure. The DDVP human database is uniquely large and robust, with studies examining a variety of endpoints and issues. The large human database (more than 300 studies) was reviewed, along with a robust animal database, to identify information useful for dose-response analyses. Some studies dismissed by the Agency in its weight of evidence and used in this analysis. A total of 10 human studies and 9 animal studies were used to construct a new DDVP interspecies database. Dr. Plunkett stated that all of the studies chosen had sufficient documentation to ensure that the research was conducted in a way to produce scientifically reliable data on RBC cholinesterase response to DDVP exposure.

Thomas Starr, Ph.D. TBS Associates representing Amvac Chemical Corporation

Dr. Starr stated that the human DDVP data do provide sufficient scientifically sound information to warrant reduction of the 10X interspecies factor. This conclusion was based on AMVAC's analysis for non-pregnant adults making use of a comprehensive data base, not just one study or one dosing study. This analysis included 138 dose-duration data points for animals and 77 dose-duration data points for humans. The conclusion from the analysis was that non-pregnant adult humans were not 10X more sensitive than non-pregnant adult animals to RBC cholinesterase inhibiting effects of DDVP. Humans appear to be no more sensitive than animals, thus a 1x interspecies factor is scientifically warranted. To exclude these data and their implications from full and fair consideration was not scientifically defensible.

Jennifer Sass, Ph.D. Natural Resource Defense Council

Dr. Sass began with general comments regarding statistical power which is one of the critical issues in evaluating the scientific validity of a study. A study with inadequate power to find an effect is by definition unethical. Studies with sample sizes less than 50 had about a 3% chance of finding an effect if it were present. For DDVP, EPA determined that the human repeated dose study was well supported by several animal studies and should serve as the basis for short- and intermediate-term risks. NRDC believed that there was no value-added from the human studies that were not already available from well-conducted animal studies, epidemiological and biomonitoring data. The human study data are often limited to healthy adults and do not capture differences across the population, chronic effects, and effects from early-life stage exposures. With respect to AZM, Dr. Sass cited ethical concerns regarding a test done on eight volunteers who were hospitalized for a month, were dosed with a known poison, took repeated blood and urine tests, and gave up many freedoms, all for just £1500. This suggests participants were economically distressed. Dr. Sass also expressed ethical concerns regarding the informed consent documents used for this study and the adverse effects experienced by test subjects. By their own retrospective power calculation, the AZM study had no statistical power to detect fluctuations in the ranges reported in the study (i.e. within 15% of baseline). NRDC concluded studies should only be considered where they will *a priori* have demonstrated validity of study design, statistical power, and sample size.

Ms. Shelly Davis, Farmer Worker Justice Fund

Ms. Davis commented on the scientific flaws of the AZM study including the use of an average of all subjects to establish the baseline used to determine whether AChE occurred. This is incorrect because there is great variability with respect to this measure in humans. Each individual baseline should have considered the control. The California Department of Health and Environmental Assessment also pointed out the researchers did not record symptoms of the test subjects. It is not uncommon for people to have clinical signs. Ms. Davis stated that these are fundamental flaws in the study design and that this study was fundamentally unethical and scientifically flawed.

Azinphos methyl

Charge to the Board

Azinphos methyl (AZM) is an organophosphate pesticide (OP). Consistent with other OPs, AZM elicits neurotoxicity through the inhibition of the enzyme, acetylcholinesterase, via phosphorylation of the active site. At sufficiently high doses, exposure to AZM can lead to a variety of clinical signs. The Agency is developing an assessment to estimate risk to workers from exposure to AZM. In addition, AZM is a member of the OP common mechanism group and is thus included in the cumulative risk assessment for the OPs.

Scientific considerations

The Agency's WOE document and DER for AZM describe the study design and results of the AZM repeat dose, oral, human toxicity study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human study in the worker risk assessment and in the cumulative risk assessment for the OPs. For AZM, the Agency has concluded that the human toxicity study is appropriate for developing a point of departure for extrapolation of risk to workers exposed to AZM via the dermal and inhalation routes. For the cumulative risk assessment, the Agency has determined that because no cholinesterase inhibition was seen in the human toxicity study, it is not possible to evaluate whether steady state had been reached in humans at 28 days of exposure. Thus, the Agency has concluded that the AZM repeat dose, oral, toxicity study is not sufficiently robust for informing the inter-species factor in the cumulative risk assessment of the OPs.

Please comment on the scientific evidence that supports the conclusions for the

a. the use of the human toxicity study to develop a point of departure for extrapolation of risk to workers in the worker risk assessment and

b. the determination that the human toxicity study cannot be used to inform the inter-species factor in the cumulative risk assessment.

Board Response to the Charge

Dr. Bellinger highlighted the strengths of the study including double-blind protocol, subjects resided in a clinic, a standardized diet, no alcohol or cigarettes and plasma and RBC values analyzed. Study weaknesses included low number of subjects, the use of a modified Elman's method, some aspects of the statistical analysis and failure to acknowledge intra-individual differences by lumping pre-dose AChE levels. Dr. Bellinger expressed limited confidence in the study due to the statistical analysis and the fact that it was a single dose NOAEL study. Dr. Fenske added that registrants should be discouraged from submitting single dose NOAEL studies. There were some adverse effects noted during the study and a grading system for these types of observations. Nonetheless, it is important to note that these effects were attributed to a viral infection, ward conditions, and diet based on judgments of a clinical team rather than measured observation. Even a few of these were considered adverse effects, this may have altered the conclusions. Dr. Lebowitz noted that if recorded symptoms were due to irritation due to the compound or to some other cholinergic effect, the standard deviation of AChE inhibition was 20%. Dr. Lebowitz expressed serious doubts about the usefulness of the study even with animal data.

After further discussion by the Board, Dr. Fisher summarized the Board's findings to include Dr. Bellinger's recommendation that an additional UF be included to account for study weaknesses. In addition, based on the way study was evaluated, the Board did not believe the study was applicable to address worker risk.

Charge to the Board

Ethical considerations

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

Whether the informed consent materials – which refer to "the company" and "supervising doctor", without further identification, and contain no discussion of who would benefit from the research – should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and,

Whether the absence from the protocol of any discussion of the potential risks to subjects or benefits to society of conducting the proposed research (as required by the 1996 Declaration of Helsinki, Principle # 5, with which the research asserted compliance) should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of [this/each] study:

OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.

Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

Board Response to the Charge

Dr. Nelson stated that if the science lacked validity than the ethical question needs to be revisited. If we proceed with the assumption that the science issues could have informed any of the standards, than the points raised by Mr. Carley do not reach the level of significantly deficient. Dr. Philpott was troubled by the question of undue inducement of this financially disadvantaged group. Dr. Chadwick expressed concerns regarding amendments to the study protocol submitted to IRB chair. Amendment 1 was a change in study objectives but was seen as having no ethical consequence and did not need prior approval.

DDVP

Charge to the Board

Like AZM, DDVP is an organophosphate pesticide (OP) which elicits neurotoxicity through the inhibition of acetylcholinesterase, via phosphorylation of the active site. The Agency is conducting an aggregate (single chemical, multi-route,

multi-duration) risk assessment of DDVP. In addition, DDVP is a member of the OP common mechanism group and is thus included in the cumulative (multi-chemical, multi-route) risk assessment for the OPs.

Scientific considerations

a. The Agency's WOE document and DER for DDVP describe the study design and results of the DDVP repeat dose, oral human study. The WOE document also discusses the Agency's conclusions regarding the usefulness of this study in the aggregate risk assessment and in the cumulative risk assessment for the OPs. For the single chemical risk assessment, the Agency has concluded that the human study is sufficiently robust for developing a point of departure for estimating dermal, incidental oral, and inhalation risk from exposure to DDVP in the single chemical risk assessment. For the cumulative risk assessment, the Agency has determined that results of the DDVP multi-dose human toxicity study do not support reducing the default 10X inter-species factor in the cumulative risk assessment of the OPs.

Please comment on the scientific evidence that supports the conclusions for the

i. the Agency's conclusions for use of the human study for developing a point of departure for estimating risk in the single chemical, aggregate risk assessment and

ii. the Agency's determination that the human study cannot be used to reduce the interspecies factor in the cumulative risk assessment.

b. The Agency has concluded that other human studies made available to the Board do not provide sufficient scientifically sound information to warrant any reduction in the 10X inter-species uncertainty factor used to derive reference dose values for DDVP based on animal toxicity endpoints.

Please comment on the scientific evidence that supports these conclusions.

Board Response to the Charge

Dr. Lehman-Mckeeman stated that for OPs, the disposition of the compound, kinetics, pharmacodynamics, and reactivation of the enzyme were all important. The way the enzyme recovers is based on RBC turnover so OPs are different from carbamates. For the repeated dose study, the strengths were placebo control, 7 pre-dose measurements of AChE, 21-day dosing administered in a corn oil capsule, with RBC AChE as the primary measurement. Repeat dosing paradigm was good for OPs. Each subject was compared to a pre-dose baseline and low but significant inhibition of AChE was measured. Study weaknesses were are single dosage levels that gave no perspective on dose-response relationship, low number of subjects (i.e. 6 subjects, 3 controls), and single sex (all male subjects) were used. The study was performed for 21 days but final sampling data was conducted on day 18. On day 18, AChE inhibition was approaching 16%. There was an effect on day 18, but is unclear whether a steady state was reached.

Follow-up testing showed 2 subjects had 22 and 24% inhibition following secession of dosing.

Dr. Fisher summarized the Board findings on the scientific considerations for DDVP. Numerous technical limitations to the study design and execution were noted, including the omission of plasma cholinesterase measurements. This greatly limited the study value. Investigators have an obligation to provide appropriate oversight of subjects until indications of the effects of the administered dose were no longer present. This was not done. The Board considered continued intentional dosing without collection of blood samples for cholinesterase analysis not scientifically defensible. However, the observation of a statistically significant change in RBC cholinesterase did provide evidence to support the conclusion that the dosage evaluated in the repeat human dosing study can be used as a LOAEL for the single chemical aggregate risk assessment. The consensus of the HSRB was that the scientific limitations of the study design did not justify its use in the cumulative risk assessment and recommended that the default interspecies uncertainty factor should be applied for the cumulative risk assessment.

Ethical considerations

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

Whether references to the test material as a drug and other statements that could indicate the study constituted medical research, that appear in the materials used to obtain informed consent should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted;

Whether the administration of the test material for three additional days without monitoring subjects' cholinesterase levels following the detection of cholinesterase inhibition > 20 % in some subjects should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

Whether the lack of medical surveillance of subjects, following the termination of dosing, to establish the subjects' cholinesterase levels returned to normal should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of the Gledhill repeated dose study:

OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical; and

Whether there is clear and convincing evidence that the conduct of the Gledhill repeat dose study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

Board Response to the Charge

Dr. Menikoff stated that the risks in this study were not different with what the Board has seen in other studies and that useful information did result from this study. There were deficiencies in the informed consent documents with respect to risk of cancer. Continuing to dose without follow-up testing was consistent with ethical standards at the time. The lack of medical monitoring post-dosing is consistent with ethical standards at the time. Therefore, the study was not fundamentally unethical. It was not likely that subjects would have been seriously harmed so there was no clear and convincing evidence that the study was fundamentally unethical. Dr. Nelson agreed but questioned the scientific findings on the worth of the study. Since the study never reached steady state, they may have been really close, but this is a serious deficiency. Dr. Philpott stated that a lab should never justify use of word "drug" for a pesticide or by saying that a "generic informed consent form" was used.

Dr. Fisher summarized the Board's findings concluding that the study could have been improved. However, virtually every study in existence could be improved to minimize risk. The standard of clear and convincing evidence is quite high and places burden of proof on the HSRB, not on the study sponsor. There was a conclusion on the part of EPA that the data, although limitations were evident, were robust enough to be used in the risk assessment. There was a need to know if the study yielded information worthy of the risk incurred by subjects. The Board's report should reflect tepid endorsement of this study but the consensus was the study did not reach the threshold of significantly deficient.

Session 4: Other Pesticides

The Chair modified the meeting agenda to have the EPA presentation, public comments and Board discussion for each pesticide proceed in that order.

Science and Ethics of Ethephon Human Studies

Abdallah Khasawinah, Ph.D. (OPP, EPA) provided an overview of two human studies with ethephon. Ethephon human studies showed clinical signs at much lower doses. Animal studies demonstrated inhibition of blood ChE activity without concurrent clinical toxicity and no increased pre-and/or post-natal toxicity in experimental animals. Effects in the human study were not transient and reflect the toxicokinetics of ethephon. Repeated exposures did not lead to cumulative toxicity. Ethephon is rapidly absorbed, metabolized and eliminated. The Agency's WOE document and DERs for ethephon describe the study design and results of the ethephon repeat dose, oral, human toxicity studies. The Agency had concluded that the 28-day human study is sufficiently robust to establish a point of departure for extrapolating acute and chronic dietary risk

Mr. John Carley (OPP, EPA**)** stated that the 28-day study was conducted at Litton Bionetics (USA) in 1971. The subjects were closely observed only for the first eight hours and doses were self-administered on weekends. Effects were self-reported. No

standard of conduct was cited so the Declaration of Helsinki (1964) was assumed to have prevailed. FIFRA §12(a) (2) (p) also applied because the research was conducted in the United States. There were many gaps in the record, but the gaps were not clear and convincing evidence. The informed consent materials were not available, but the report stated subjects were thoroughly informed and signed consent forms. There is no evidence that the research was fundamentally unethical. There were some deficiencies relative to the cited 1964 Declaration of Helsinki.

Public Comments

Neil Carmichael Ph.D., Bayer CropScience

Dr. Carmichael stated that Bayer Crop Sciences (BCS)'s position on human volunteer studies with ethephon was that these two studies date from another era (i.e. 1970s). BCS agreed that there is no evidence that they are unethical but there was no institutional memory of these studies and archives are not traceable. The data were not consistent between the two studies and BCS can not defend the scientific robustness of the studies. BCS defers to EPA in the use of these studies.

Charge to the Board

Ethephon is an organophosphorus compound that, upon absorption into plants, forms ethylene gas which is an important component of the plant hormone complex. The Agency is conducting an aggregate (single chemical, multi-route) risk assessment of ethephon.

Scientific consideration

The Agency's WOE document and DERs for ethephon describe the study design and results of the ethephon repeat dose, oral, human toxicity studies. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human studies in the aggregate, single chemical risk assessment. The Agency has concluded that the 28-day human study is sufficiently robust to establish a point of departure for extrapolating acute and chronic dietary risk.

Please comment on the scientific evidence that supports this conclusion.

Board Response to the Charge

Dr. Leibowitz believed that the second study can be informative about the first study even though it was a single dose study. With respect to the first study, the 28 day study, his principle concern was that irritant symptoms, cholinergic symptoms, and any symptoms other than those associated with ChE inhibition were important. Two of the controls were also symptomatic which complicate the issue. Some test and control subjects had irregular erythrocytes which could be due to infections. The second study indicated no symptoms were reported but Dr. Lebowitz was skeptical about statements

like these (were measures negative or just not reported?). Since the 1977 study included only one dose level, the NOAEL was based on this dose. No higher dose was given. In the second study, no symptoms were reported. The differences in plasma and RBC AChE inhibition were probably a problem of study design or assay techniques. Thus, Dr. Lebowitz agreed that both studies supported the LOAEL selected by EPA. Dr. Krishnan agreed with Dr. Leibowitz and concluded that the selection of NOAEL/LOAEL seems reasonable but he was surprised by the large margin between animals and humans with no mechanistic explanations. Dr. Krishnan was concerned about ethylene because the cancer assessment for ethylene showed a maximum of 3000 ppm with no evidence of carcinogenicity. In terms of the high dose study, Dr. Krishnan agreed that it may be useful for validating the LOAEL. For most studies of this type, each subject serves as their own control. Thus, the baseline was the average of measures from three other subjects. However this doesn't change the outcome and probably was an appropriate endpoint. The high dose study seemed to be a reasonable source for determining LOAEL.

Dr. Fisher summarized the Board conclusions stating the Board's report will show consistent reasoning across the pesticides studied. While the two studies seem to converge in support of LOAEL, the Board raised some concern about the control group being symptomatic. The study provided no model to explain differences in animal and human data. These studies do have usefulness to EPA in determining a LOAEL.

Ethical considerations

Charge to the Board

In its ethics review of this research, EPA documented that the study reports contained very little information concerning the ethical conduct of the research and that the available information raised no ethical concerns. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of each study:

OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical; and

Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

Board Response to the Charge

Dr. Philpott described the study as a 28-day study conducted in 1971, before the Common Rule and FIFRA 12(a)(2)(p). Thus, there were few regulatory statutes by which to judge standards. The low dose study (1977) occurred after FIFRA12 (a) (2) (p), so FIFRA does apply. Here again there is very little information with which to make ethical decisions. In the high dose study, the only statement the Board had was that all

subjects were thoroughly briefed about the nature and risks of the compound. The low dose study may have been better but records cannot be found. The Board was asked to determine whether there was clear and convincing evidence of unethical conduct. Dr. Philpott had serious concerns about the nature of voluntary and informed consent. Subjects were probably lab employees. The volunteers experienced unpleasant clinical effects including extreme gastrointestinal effects (e.g. explosive diarrhea and abdominal pain) for four weeks, yet none chose to withdraw. This was suspicious. The low dose study may have taken clinical measurements but they weren't reported.

Dr. Fisher summed up the Board's findings by stating that despite clear deficiencies in study design, 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. Since the studies show greater sensitivity of humans, even if the studies were fundamentally unethical, the Board may reject the methodology, but still recommend their use by the Agency because its use would increase public protection.

Science and Ethics of Hydrogen Cyanide/Amygdalin Human Studies

William Dykstra, Ph.D. (OPP, EPA) provided an overview of the scientific consideration of human studies conducted with hydrogen cyanide. The Agency's WOE document described a lack of data appropriate for developing an acute dietary risk assessment for hydrogen cyanide. The WOE and DER present the results from a clinical trial with amygdalin and the usefulness of this clinical trial in the acute dietary risk assessment for hydrogen cyanide. The Agency had concluded that the clinical trial is appropriate for establishing a point of departure in the acute dietary risk assessment for hydrogen cyanide.

The EPA ethics review for the amygdalin clinical trial was given by Mr. John Carley (OPP, EPA). Mr. Carley stated that two articles report on clinical trial of Laetrile for advanced human cancers conducted at four centers in the U.S. from 1980-1981. The clinical trial was conducted under FDA application, so it was subject to 21 CFR parts 50 and 56. Ethical conditions were reported much more completely than is typical of published articles from that period. No noteworthy deficiencies relative to HHS regulations were found. There was no evidence that the research was fundamentally unethical or significant deficient relative to prevailing ethical standards at the time. When sodium cyanide was used as a fumigant, hydrogen cyanide was generated by acidification. Because residues of HCN may remain on fumigated citrus, the Agency is conducting an acute dietary risk assessment of hydrogen cyanide.

Public Comments

None

Charge to the Board

When sodium cyanide is used as a fumigant, hydrogen cyanide is generated by acidification. Because residues of HCN may remain on fumigated citrus, the Agency is conducting an acute dietary risk assessment of hydrogen cyanide.

Scientific considerations

The Agency's WOE document describes a lack of data appropriate for developing an acute dietary risk assessment for hydrogen cyanide. The WOE and DER present the results from a clinical trial with amygdalin and the usefulness of this clinical trial in the acute dietary risk assessment for hydrogen cyanide. The Agency has concluded that the clinical trial is appropriate for establishing a point of departure in the acute dietary risk assessment for hydrogen cyanide.

Please comment on the scientific evidence that supports this conclusion.

Board Response to the Charge

Dr. Bellinger provided study strengths including the large number of subjects, serial assessment of blood cyanide levels and good clinical definition of outcome considered as tumor progression. Study weaknesses included the study was not double blind, it did not include a placebo group and that the study was designed to assess the efficacy of amygdalin as a cancer treatment. Thus, such information on toxic effects was less clinical, more antidotal. Subjects were terminal cancer patients and may represent a sensitive subgroup. Conclusions regarding toxicity were based on several patients who developed symptoms related to cyanide toxicity that subsided when the dose was discontinued. Oral dosing did not begin until patients had 21 day IV treatment. It was unlikely that this introduced any bias because by the oral route amygdalin excreted in urine remain unchanged. Whole blood cyanide levels were mostly undetectable. This study was probably the best we will ever see for assessing the acute endpoint of cyanide toxicity.

Dr. Fisher summarized the Board comments concluding that data from the amygdalin trial could be used in the acute dietary risk assessment for hydrogen cyanide. Despite its limitations, this study provided the best data we are likely to ever have to establish a POD for this purpose. Given the severity of the effect, the steepness of the dose-response, and the apparent inter-individual differences in response to a given dose, it would be imprudent to undertake an intentional dosing study of healthy humans in order to establish a LOAEL and NOAEL for hydrogen cyanide.

Charge to the Board

Ethical considerations

In its ethics review of this research, EPA did not identify any deficiencies with respect to the ethical conduct of this research. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of this study:

OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical; and
whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

Board Response to the Charge

Dr. Menikoff believed that publication of the study demonstrates support for the Agency's conclusion of compliance with existing standards. This is a treatment study with therapeutic benefits and research was done early in the development of ethical standards. Dr. Menikoff was comfortable that this research was not fundamentally unethical. He also believed that a rule for when to pursue supporting documentation was needed.

Dr. Fisher summarized Board discussions concluding that the study was not fundamentally unethical or significantly deficient because of clinical equipoise. Dr. Menikoff's recommendation regarding supporting documentation was noted. The Board suggested that there should be guidance to investigators on the type of ethics documentation required. The Agency could provide an outline of this policy, possibly in the fall.

Science and Ethics of Amitraz Human Studies

John Liccione, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA) presented the science and ethics of amitraz human studies, respectively. Dr. Liccione said that three human studies of amitraz will be presented including a single oral dose study, an acute dermal dose study, and an oral metabolism study. Numerous animal studies were also available. The single oral dose study was double blind with frequent monitoring of pulse, respiration rate, blood pressure, temperature, ECGs, psychomotor performance. The single oral dose study reported no treatment-related effects and a NOAEL = 0.125 mg/kg. The acute dermal study was a double blind, sequential dosing study. Doses were given as aqueous 1:1 slurry every 2.5 hours over 10 hours according to random schedule. Monitoring of clinical signs included ECG, psychomotor measurements, hematology, clinical chemistry, and urinalysis. The dermal study also reported no effects and supported a NOAEL of 24 mg/kg. This was a double blind study with adequate monitoring for potential neurotoxicity but had a limited number of male subjects. A metabolism study of two healthy human subjects receiving a single dose (0.25 mg/kg) of 14C-amitraz (>95% purity) by capsule was also discussed. This study had no control group and no statistical analysis. The metabolism study reported consistent effects in both subjects which are also consistent with animal observations. These studies show

clear signs of neurotoxicity which was consistent with animal observations. Humans appear to be the most sensitive species. The Agency proposed to use these human studies for amitraz tolerance setting.

Mr. Carley stated that the research was conducted at FBC Ltd., Chesterford Park Research Station in the United Kingdom in 1984 as part of a multi-species study of comparative metabolism. No standard of ethical conduct was cited so the Declaration of Helsinki (1983) was assumed to have prevailed. There were many gaps in the record, but the gaps were not clear and convincing evidence that the research was fundamentally unethical. Some deficiencies were noted relative to the Declaration of Helsinki (1983).

Public Comments

None

Charge to the Board

Exposure to amitraz can result in neurotoxicity as evidenced by clinical signs such as ataxia, ptosis, emesis, labored respiration, muscular weakness, tremors, hypothermia and bradycardia. The Agency is conducting an aggregate (single chemical, multi-route) risk assessment of amitraz.

Scientific considerations

The Agency's WOE document and DERs for amitraz describe the study design and results of the amitraz acute oral and dermal toxicity human studies and the human metabolism study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human studies in the single chemical risk assessment for acute and chronic oral exposures in addition to dermal and inhalation exposures of various durations. For oral exposure, the Agency has concluded that the combined results from the single oral dose study and human metabolism study establishes a dose response relationship in human subjects and that the single oral dose study is appropriate for developing a point of departure for acute and chronic dietary risk, short-term oral exposure, and inhalation exposures of various durations. The Agency has further concluded that the human dermal study is appropriate for developing a point of departure for dermal exposures of various durations.

Please comment on the scientific evidence that supports these conclusions.

Board Response to the Charge

Dr. Fenske was concerned why the 1984 metabolism study was conducted at such a high dose level. The 1992 study reduced the dose based on earlier findings but lacked a critical discussion of psychomotor endpoints. There were many ways to measure reaction time and this wasn't described in the study. Some subjects had increased reaction time at doses above placebo that were found to be statistically

insignificant. The dermal study was also based on reaction time data but the apparatus used to measure reaction time wasn't described. For the dermal study, the material was applied to small areas of the skin. High doses applied to small areas do not always result in high internal dose. Once the skin is covered, the rest of the material isn't available for absorption. The Agency needs to re-examine oral study endpoints to determine if it support the NOAEL. Dr. Fenske would not support using the dermal study for support of the NOAEL. Dr. Bellinger agreed with Dr. Fenske on the utility of data. With seven subjects, there was no chance that psychomotor effects could be seen, especially given the high degree of variability with respect to psychomotor effects. Dr. Bellinger was also uncomfortable with the dermal study because no LOAEL was demonstrated.

Charge to the Board

Ethical considerations

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

With respect to the Campbell (1984) research, whether the lack of medical surveillance of subjects, following the termination of dosing, to establish that subjects' signs of adverse effects had returned to normal should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

With respect to the Cass (1992) and the Langford (1998) studies, whether references to the test material as a drug and other statements that could indicate the study constituted medical research, that appear in the materials used to obtain informed should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of each study:

OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.

Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

Board Response to the Charge

Dr. Nelson discussed the studies in temporal order starting with the metabolic study. Clearly the subjects had a response to the compound. There was speculation that the subjects were the two principal investigators so there was doubt that they had good medical supervision. For the oral dosing study, the risks were not listed in the informed consent form. There probably wasn't any extreme risk. What was not considered for the dermal study is the choice of dose and dose escalation design. Was the study designed in

a way so they could anticipate risk? Dr. Nelson concluded that the study does not meet the standard of fundamentally unethical and there is no clear and convincing evidence of unethical design.

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 my 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.
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

Attachment B
Federal Register Notice Announcing Meeting

Federal Register: March 9, 2006 (Volume 71, Number 46)]
[Notices]
[Page 12194-12196]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr09mr06-52]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2006-0187; FRL-8042-6]

Human Studies Review Board; Notice of Public Meeting and Proposed Candidates for Membership to the Board

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. In addition, OSA is soliciting public comment on its proposed list of candidates for membership to the HSRB.

DATES: The public meeting will be held April 4-6, 2006 from 8:30 a.m. to approximately 5 p.m., eastern time.

Location: Holiday Inn Rosslyn at Key Bridge, 1900 North Fort Myer Drive, Arlington, VA 22209. The telephone number for the Holiday Inn Rosslyn at Key Bridge is 703-807-2000.

Requests to Present Oral Comments and Special Accommodations: To submit requests for special accommodation arrangements or requests to present oral comments, notify the DFO listed under FOR FURTHER INFORMATION CONTACT. To ensure proper receipt by EPA, your request must identify docket ID number EPA-HQ-ORD-2006-0187 in the subject line on the first page of your response. Additional information concerning the submission of requests to present oral comments and submission of written comments is provided in Unit I.E.

FOR FURTHER INFORMATION CONTACT: Any member of the public who wishes further information should contact Paul I. Lewis, Designated Federal Official (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.

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2006-018, 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-2006-0187. 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-2006-0187. 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, 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.

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://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 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, charge/questions to the HSRB, HSRB composition and the meeting agenda will be available by mid March 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/.

C. What Should I Consider as I Prepare My 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 unit. To ensure proper receipt by EPA, it is imperative that you identify docket ID number EPA-HQ-ORD-2006-0187 in the subject line on the first page of your request.

1. Oral comments. Oral comments presented at the meetings should not be repetitive of previously submitted oral or written comments. Although requests to present oral comments are accepted until the date of the meeting (unless otherwise stated), to the extent that time permits, interested persons 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, March 29, 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 approximately 5 minutes unless prior arrangements have been made. In addition, each speaker should bring 30 copies of his or her comments and presentation slides for distribution to the HSRB at the meeting.

2. Written comments. Although written comments will be accepted until the date of the meeting (unless otherwise stated), the Agency strongly encourages that written comments be submitted, using the instructions in Unit 1.C. no later than noon, eastern time, March 29, 2006 to provide the HSRB the time necessary to consider and review the written comments. It is requested that persons submitting comments directly to the docket also notify the DFO listed under FOR FURTHER INFORMATION CONTACT. There is no limit on the extent of written comments for consideration by the HSRB.

3. Seating at the meeting. 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.

F. Background

At the inaugural meeting of the HSRB, EPA will provide a broad overview of the Agency's approach to the assessment of the potential risk to human health from the use of pesticides and how EPA uses data from human studies in such risk assessments. The Agency will then present to the HSRB its scientific and ethics reviews of approximately two dozen completed human studies concerning the following pesticide active ingredients: aldicarb, amitraz, azinphos-methyl, dichlorovos (DDVP), ethephon, methomyl, oxamyl, and sodium cyanide. The studies being reviewed 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 ethical or scientific reasons. The Agency will ask the HSRB to advise the Agency on a range of scientific issues and on how the studies should be assessed against the provisions in sections 26.1701-26.1704 of EPA's final human studies rule.

II. Proposed Candidates for Membership to the Board

On January 3, 2006, the EPA, OSA announced a request for nominations of qualified individuals to serve on the HSRB (Federal Register 71 116). Per the Federal Register notice, the OSA requested nominees who are nationallyrecognized experts in one or more of the following disciplines:

(a) Biostatistics. Expertise in statistical design and analysis of human subjects research studies.

(b) Human toxicology. Expertise in pharmacokinetic and toxicokinetic studies, clinical trials, and toxicology of cholinesterase inhibitors and other classes of environmental substances.

(c) Bioethics. Expertise in the ethics of research on human subjects; research ethics.
(d) Human health risk assessment.

EPA carefully considered the qualifications of nominees who agreed to be further considered and has identified candidates from whom EPA expects to select members to serve on the HSRB. EPA now invites comments from members of the public for relevant information or other documentation that the OSA should consider in the selection of HSRB members. The names of the candidates, together with a short biographical description of their qualifications, appear on the Agency's Web site at http://www.epa.gov/osa/hsrb/. Please e-mail your comments no later than noon, eastern time, March 14, 2006, listed under FOR FURTHER INFORMATION CONTACT. Any information furnished by the public in response to this Web site posting will be combined with information already provided by the candidates, and gathered independently by the OSA. Prior to final selection of HSRB members, the combined information will be reviewed and evaluated for any possible financial conflict of interest or a possible appearance of a lack of impartiality. The information will also be used to ensure appropriate balance and breadth of expertise needed to address the charge to the Board. The EPA Science Advisor will make the final decision concerning who will serve on the HSRB.

Dated: March 2, 2006.
George Gray,
EPA Science Advisor.

Attachment C
April 2006 Meeting of the HSRB
Meeting Agenda

HOLIDAY INN – ROSSLYN AT KEY BRIDGE
ARLINGTON, VA

HSRB WEB SITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566 1752
Docket Number: EPA-HQ-ORD-2006-0187

Tuesday, April 4, 2006

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

8:45 a.m. **Welcome**
George Gray, Ph.D. (EPA Science Advisor)

9:00 a.m. **Opening Remarks**
Ms. Susan Hazen (Acting Assistant Administrator, Office of Prevention,
Pesticides and Toxic Substances, EPA)

9:15 a.m. **Meeting Administrative Procedures**
Paul Lewis, Ph.D. (Designated Federal Officer, HSRB, EPA)

9:20 a.m. **Meeting Process**
Celia Fisher, Ph.D. (HSRB Chair)

Session 1: **Introduction**

9:30 a.m. **Session 1 Overview**
Mr. William Jordan (Office of Pesticide Programs [OPP], EPA)

9:35 a.m. **Summary of EPA's Protections for Subjects of Human Research**
Mr. William Jordan (OPP, EPA)

10:05 a.m. **Break**

10:20 a.m. **EPA, OPP Approach to Assessing Human Health Risks of Pesticides Using**
Data From Human Studies
Mr. Michael Metzger (OPP, EPA)

10:45 a.m. **EPA, OPP Assessment of Ethical Conduct of Human Studies**
Mr. John Carley (OPP, EPA)

11:15 a.m. **EPA, OPP Assessment of Individual Human Studies**
Ray Kent, Ph.D. (OPP, EPA)

11:40 a.m. **A Summary of Human Studies for Consideration by the Human Studies**
Review Board
Louis Scarano, Ph.D. (OPP, EPA)

11:50 a.m. **Lunch**

Session 2: Carbamate Pesticides

1:00 p.m. **Session 2 Overview**
Anna Lowit, Ph.D. (OPP, EPA)

1:05 p.m. **EPA, OPP Policy on "The Use of Data on Cholinesterase Inhibition for Risk Assessment of Organophosphorous and Carbamate Pesticides"**
Anna Lowit, Ph.D. (OPP, EPA)

1:20 p.m. **Science and Ethics of Aldicarb Human Studies**
Linda Taylor, Ph.D. (OPP, EPA), Elissa Reaves, Ph.D. (OPP, EPA) and
Mr. John Carley (OPP, EPA)

1:50 p.m. **Science and Ethics of Methomyl Human Studies**
Elissa Reaves, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)

2:20 p.m. **Science and Ethics of Oxamyl Human Studies**
Elissa Reaves, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)

3:00 p.m. **Break**

3:15 p.m. **Public Comments on Session 2**

4:15 p.m. **Board Discussion and Writing Session**

A. Aldicarb

Aldicarb is a *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. Aldicarb can, at sufficiently high doses, lead to a variety of clinical signs. The Agency is conducting an acute, aggregate (single chemical, multi-route) risk assessment of aldicarb. In addition, aldicarb 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 "Weight of the Evidence" (WOE) document and Data Evaluation Records (DERs) for aldicarb describe the study design and results of the aldicarb acute oral, human toxicity study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human study in the acute, aggregate, single chemical risk assessment and in the

cumulative risk assessment for the NMCs. Regarding the aldicarb human study, the Agency has concluded that the study is sufficiently robust for reducing the inter-species (i.e., animal to human) uncertainty factor in the aggregate and the cumulative risk assessments.

Please comment on the scientific evidence that supports the conclusions for the

a. Single chemical, aggregate risk assessment and
b. Cumulative risk assessment

2. *Ethical considerations:*

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

- In light of the ethics committee's instruction that the lay summary be "greatly expanded,"
  and the fact that the materials used to obtain informed consent listed a limited range of symptoms of carbamate toxicity (excluding some reported as adverse effects in the study), included multiple references to the test material as a drug, and failed to identify dose levels to be administered to male subjects, whether, the materials used to obtain informed consent should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted.

- Whether the absence from the protocol of discussion of the potential risks to subjects or benefits to society of conducting the proposed research (as required by the 1989 Declaration of Helsinki, Principle # 4, with which the research asserted compliance) should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of this study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.

- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

B. Methomyl

Methomyl is a member of the *N*-methyl carbamate (NMC) common mechanism group based on its ability to inhibit acetylcholinesterase via carbamylation. The Agency has previously completed the acute, aggregate (single chemical, multi-route) risk assessment

of methomyl. At the present time, the Agency is considering the use of the methomyl acute oral, human toxicity study to inform the inter-species uncertainty factor used in the cumulative risk assessment of the NMCs.

1. *Scientific considerations:*

   The Agency's WOE document and DER for methomyl describe the study design and results of the methomyl acute oral, human study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human study in the cumulative risk assessment for the NMCs. For methomyl, the Agency has concluded that the human toxicity study supports a 10X inter-species uncertainty factor for methomyl in the cumulative risk assessment of the NMCs.

   Please comment on the scientific evidence that supports this conclusion.

2. *Ethical considerations:*

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

   - Whether the investigators' decision to administer a dose to additional subjects in session 3, when one subject receiving that dose in session 2 displayed RBC ChEI greater than 40%, a response that triggered the protocol's anti-escalation provision, should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted;

   - Whether the timing of the investigators' report to the ethics committee of the adverse effects observed in one subject during session 2 should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted;

   - Whether the failure of the investigators to request approval from the ethics committee for certain amendments to the approved protocol, as required by the protocol, when the changes were administrative and had no effect on the safety of the subjects should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

   - Whether the absence from the protocol of discussion of the potential risks to subjects or benefits to society of conducting the proposed research (as required by the Declaration of Helsinki, Principle # 5) should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of this study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.

- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

C. Oxamyl

Similar to aldicarb and methomyl, oxamyl is a member of the *N*-methyl carbamate (NMC) common mechanism group based on its ability to inhibit acetylcholinesterase via carbamylation and is thus included in the NMC cumulative risk assessment. The Agency has previously completed the acute, aggregate (single chemical, multi-route) risk assessment of oxamyl. The Agency is now considering the use of the oxamyl acute oral, human toxicity study to inform the inter-species uncertainty factor in the cumulative risk assessment of the NMCs.

1. Scientific considerations:

The Agency's WOE document and DER for oxamyl describe the study design and results of the oxamyl acute oral, human toxicity study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human study in the cumulative risk assessment for the NMCs. For oxamyl, the Agency has concluded that the human toxicity study is sufficiently robust for reducing the 10X inter-species (ie, animal to human) uncertainty factor in the cumulative risk assessment.

Please comment on the scientific evidence that supports this conclusion.

2. Ethical considerations:

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

- Whether inclusion in the protocol submitted to the ethics committee of a factually inaccurate statement regarding unavailability of data on accidental or incidental exposure to oxamyl should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted;

- Whether the absence from the protocol of any discussion of the potential risks to subjects or benefits to society of conducting the

proposed research (as required by the Declaration of Helsinki, Principle # 5) should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of [this/each] study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.

- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

5:00 p.m. Adjourn

Wednesday, April 5, 2006

8:30 a.m. Convene Meeting
Celia Fisher, Ph.D. (HSRB Chair)
8:40 a.m. Follow-up From Previous Day's Discussion
Mr. William Jordan (OPP, EPA)
8:50 a.m. Board Discussion and Writing Session (continued)
10:15 a.m. Break

Session 3: Organophosphate Pesticides

10:30 a.m. Session 3 Overview
Anna Lowit, Ph.D. (OPP, EPA)
10:35 a.m. Science and Ethics of Azinphos Methyl Human Studies
John Doherty, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
11:00 a.m. Science and Ethics of DDVP Human Studies
Ray Kent, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)
11:45 a.m. Lunch
12:45 p.m. Public Comments on Session 3
2:00 p.m. Board Discussion and Writing Session

D. Azinphos methyl

Azinphos methyl (AZM) is an organophosphate pesticide (OP). Consistent with other OPs, AZM elicits neurotoxicity through the inhibition of the enzyme, acetylcholinesterase, via phosphorylation of the active site. At sufficiently high doses, exposure to AZM can lead to a variety of clinical signs. The Agency is developing an

assessment to estimate risk to workers from exposure to AZM. In addition, AZM is a member of the OP common mechanism group and is thus included in the cumulative risk assessment for the OPs.

1. *Scientific considerations:*

The Agency's WOE document and DER for AZM describe the study design and results of the AZM repeat dose, oral, human toxicity study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human study in the worker risk assessment and in the cumulative risk assessment for the OPs. For AZM, the Agency has concluded that the human toxicity study is appropriate for developing a point of departure for extrapolation of risk to workers exposed to AZM via the dermal and inhalation routes.

For the cumulative risk assessment, the Agency has determined that because no cholinesterase inhibition was seen in the human toxicity study, it is not possible to evaluate whether steady state had been reached in humans at 28 days of exposure. Thus, the

Agency has concluded that the AZM repeat dose, oral, toxicity study is not sufficiently robust for informing the inter-species factor in the cumulative risk assessment of the OPs.

Please comment on the scientific evidence that supports the conclusions for the

a. Worker risk assessment and
b. Cumulative risk assessment

2. *Ethical considerations:*

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

- Whether the informed consent materials – which refer to "the company" and "supervising doctor," without further identification, and contain no discussion of who would benefit from the research – should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and,

- Whether the absence from the protocol of any discussion of the potential risks to subjects or benefits to society of conducting the proposed research (as required by the 1996 Declaration of Helsinki, Principle # 5, with which the research asserted compliance) should be considered

significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of [this/each] study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.

- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

E. DDVP

Like AZM, DDVP is an organophosphate pesticide (OP) which elicits neurotoxicity through the inhibition of acetylcholinesterase, via phosphorylation of the active site. The Agency is conducting an aggregate (single chemical, multi-route, multi-duration) risk assessment of DDVP. In addition, DDVP is a member of the OP common mechanism group and is thus included in the cumulative (multi-chemical, multi-route) risk assessment for the OPs.

1. Scientific considerations:

a. The Agency's WOE document and DER for DDVP describe the study design and results of the DDVP repeat dose, oral human study. The WOE document also discusses the Agency's conclusions regarding the usefulness of this study in the aggregate risk assessment and in the cumulative risk assessment for the OPs. For the single chemical risk assessment, the Agency has concluded that the human study is sufficiently robust for developing a point of departure for estimating dermal, incidental oral, and inhalation risk from exposure to DDVP in the single chemical risk assessment. For the cumulative risk assessment, the Agency has determined that results of the DDVP multi-dose human toxicity study do not support reducing the default 10X inter-species factor in the cumulative risk assessment of the OPs.

Please comment on the scientific evidence that supports the conclusions for the

i. Single chemical, aggregate risk assessment and
ii. Cumulative risk assessment

b. The Agency has concluded that other human studies made available to the Board do not provide sufficient scientifically sound information to warrant any reduction in the 10X inter-species uncertainty factor used to derive reference dose values for DDVP based on animal toxicity endpoints.

Please comment on the scientific evidence that supports these conclusions.

2. Ethical considerations:

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

- Whether references to the test material as a drug and other statements that could indicate the study constituted medical research, that appear in the materials used to obtain informed consent should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted;

- Whether the administration of the test material for three additional days without monitoring subjects' cholinesterase levels following the detection of cholinesterase inhibition > 20 % in some subjects should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

- Whether the lack of medical surveillance of subjects, following the termination of dosing, to establish the subjects' cholinesterase levels returned to normal should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of the Gledhill repeated dose study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical; and

- Whether there is clear and convincing evidence that the conduct of the Gledhill repeat dose study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

3:15 p.m. Break

Session 4: Other Pesticides

3:30 p.m. **Session Overview**
Ray Kent, Ph.D. (OPP, EPA)

3:35 p.m. **Science and Ethics of Ethephon**
Abdallah Khasawinah, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)

4:00 p.m. **Science and Ethics of Sodium Cyanide Human Studies**
William Dykstra, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)

4:30 p.m. **Science and Ethics of Amitraz Human Studies**
John Liccione, Ph.D. (OPP, EPA) and Mr. John Carley (OPP, EPA)

5:00 p.m. **Adjournment**

Thursday, April 6, 2006

8:30 a.m. **Convene Meeting**
Celia Fisher, Ph.D. (HSRB Chair)

8:45 a.m. **Follow-up From Previous Day's Discussion**
Mr. William Jordan (OPP, EPA)

9:30 a.m. **Public Comments on Session 4**

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

10:45 a.m. **Board Discussion and Writing Session**

F. Ethephon

Ethephon is an organophosphorus compound that, upon absorption into plants, forms ethylene gas which is an important component of the plant hormone complex. The Agency is conducting an aggregate (single chemical, multi-route) risk assessment of ethephon.

1. *Scientific considerations:*

   The Agency's WOE document and DERs for ethephon describe the study design and results of the ethephon repeat dose, oral, human toxicity studies. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human studies in the aggregate, single chemical risk assessment. The Agency has concluded that the 28-day human study is sufficiently robust to establish a point of departure for extrapolating acute and chronic dietary risk.

   Please comment on the scientific evidence that supports this conclusion.

2. *Ethical considerations:*

In its ethics review of this research, EPA documented that the study reports contained very little information concerning the ethical conduct of the research and that the available information raised no ethical concerns. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of each study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical; and

- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

G. Hydrogen Cyanide / Amygdalin

When sodium cyanide is used as a fumigant, hydrogen cyanide is generated by acidification. Because residues of HCN may remain on fumigated citrus, the Agency is conducting an acute dietary risk assessment of hydrogen cyanide.

1. Scientific considerations:

The Agency's WOE document describes a lack of data appropriate for developing an acute dietary risk assessment for hydrogen cyanide. The WOE and DER present the results from a clinical trial with amygdalin and the usefulness of this clinical trial in the acute dietary

risk assessment for hydrogen cyanide. The Agency has concluded that the clinical trial is appropriate for establishing a point of departure in the acute dietary risk assessment for hydrogen cyanide.

Please comment on the scientific evidence that supports this conclusion.

2. Ethical considerations

In its ethics review of this research, EPA did not identify any deficiencies with respect to the ethical conduct of this research. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of this study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical; and

- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

H. Amitraz

Exposure to amitraz can result in neurotoxicity as evidenced by clinical signs such as ataxia, ptosis, emesis, labored respiration, muscular weakness, tremors, hypothermia and bradycardia. The Agency is conducting an aggregate (single chemical, multi-route) risk assessment of amitraz.

1. Scientific considerations:

The Agency's WOE document and DERs for amitraz describe the study design and results of the amitraz acute oral and dermal toxicity human studies and the human metabolism study. The WOE document also discusses the Agency's conclusions regarding the usefulness of the human studies in the single chemical risk assessment for acute and chronic oral exposures in addition to dermal and inhalation exposures of various durations. For oral exposure, the Agency has concluded that the combined results from the single oral dose study and human metabolism study establishes a dose response relationship in human subjects and that the single oral dose study is appropriate for developing a point of departure for acute and chronic dietary risk, short-term oral exposure, and inhalation exposures of various durations. The Agency has further concluded that the human dermal study is appropriate for developing a point of departure for dermal exposures of various durations.

Please comment on the scientific evidence that supports these conclusions.

2. Ethical considerations

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

- With respect to the Campbell (1984) research, whether the lack of medical surveillance of subjects, following the termination of dosing, to establish that subjects' signs of adverse effects had returned to normal should be considered significantly deficient relative to the ethical standards prevailing when the study was conducted; and

- With respect to the Cass (1992) and the Langford (1998) studies, whether references to the test material as a drug and other statements that could indicate the study constituted medical research, that appear in the materials used to obtain informed should be considered

significantly deficient relative to the ethical standards prevailing when the study was conducted; and

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b. The Agency asks that the Board provide comment on the following, taking into account all that is known about the ethical conduct of each study:

- OPP's conclusion that there is not clear and convincing evidence that the conduct of the research was fundamentally unethical.

- Whether there is clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing when the study was conducted.

12:00 p.m. Lunch
1:00 p.m. Board Discussion and Writing Session (continued)
4:30 p.m. Adjournment

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