UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

Subject: Transmittal of Charge Questions for the April 2006 Meeting of the Human Studies Review Board.

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The first public meeting of EPA's new Human Studies Review Board (HSRB or Board) is scheduled for April 4-6, 2006. This meeting will address scientific and ethical issues surrounding toxicity studies involving intentional exposure of human subjects to eight pesticide active ingredients: aldicarb, amitraz, azinphos-methyl (AZM), dichlorvos (DDVP), ethephon, methomyl, oxamyl, and sodium cyanide. This memorandum provides the Board with a series of questions that the Agency is seeking comment on in connection with OPP's ethical and scientific review of these studies.

CHARGE AND ISSUES FOR HSRB

The Agency is asking the HSRB to review a number of completed intentional dosing, human toxicity studies and to provide advice to EPA on the degree to which it is ethically and scientifically appropriate to rely on the results of these studies in actions under the pesticide laws.

EPA's decisions about whether it is ethical to rely on a particular intentional exposure human study will comply with the provisions of the recently promulgated regulation in 40 CFR Part 26, "Protections for Subjects in Human Research." 71 Fed. Reg. 6138 (February 6, 2006). This rulemaking takes effect on April 7, 2006, and will thus apply to all decisions under discussion during the HSRB's meeting. The Agency, however, recognizes that application of the standards in the new regulation will involve the exercise of judgment. Therefore, the Agency has posed specific questions about how to apply the new rule when assessing the ethical conduct of each study under review.

EPA's evaluation of the scientific strengths and weaknesses of these studies is not limited by statutory or regulatory standards, and therefore EPA has considerable discretion about whether (and if so, how) to rely on a particular study. The Agency recognizes that the quality of the different studies presented for the Board's review varies considerably – with the studies showing differences in, for example, the numbers of subjects, gender representation, numbers of treatment groups, the rigor of observation of potential adverse events, and the degree of control for confounders. The Agency also thinks that the scientific value of a particular human study will depend, in part, on the quality of the rest of the toxicity data base available for the test compound. Therefore, EPA believes that the decisions about how to use the results of human studies must be made on a case-by-case basis, taking all of these different factors into account. The Agency's Weight of the Evidence (WOE) documents for each chemical provide the Agency's conclusions about how to use (or not) the human studies in human health risk assessment . The Agency has focused its questions for the Board on the scientific evidence that supports these conclusions.

The Agency's primary goal for the first HSRB meeting is to get comment and advice regarding the various human toxicity studies available for the eight chemicals under review. However, the Agency recognizes that because we are at a very early stage of interpreting and applying the new rule, the Board's advice will help to inform future assessments of other studies.

Part 1. *N*-Methyl Carbamate Pesticides

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. 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

2. 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.

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. 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

2. 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.

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. 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

2. *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.

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. *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.

2. 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.

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. *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.

2. *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.

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. *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.

2. *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.

G. 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. 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.

2. *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.

H. 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. 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.

2. *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.