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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 29, 2007

MEMORANDUM

Subject: Transmission of materials for review by the Human Studies Review Board for its June 2007 Meeting

To: Paul Lewis, Ph.D.
Designated Federal Official
Human Studies Review Board
Office of Science Advisor (8105R)

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This memorandum describes the materials being provided for review by the Agency's Human Studies Review Board (HSRB or Board) at the meeting scheduled for June 26 - 28, 2007. This meeting will address scientific and ethical issues surrounding:

- A research proposal from Carroll-Loye Biological Research to evaluate the efficacy of two conditionally registered products containing picaridin in repelling mosquitoes in the field.

- A research proposal from Insect Control & Research, Inc. to evaluate the efficacy of two unregistered products containing picaridin in repelling mosquitoes in the field.

- A completed study measuring the effects on human subjects of acute inhalation exposure to acrolein.

- Three completed studies of the efficacy and side effects of 4-aminopyridine used as a therapeutic agent.

- Extensive background materials concerning research to quantify the level of exposure received by people who mix, load, and apply pesticides. These materials were prepared by the Agricultural Handlers Exposure Task Force and by the Antimicrobial Exposure Assessment Task Force.

Each of these topics is described more fully below.

A. Proposed Carroll-Loye Picaridin Insect Repellent Efficacy Study

EPA requires data from efficacy studies using appropriate insect species to support claims of greater efficacy than have previously been approved.

EPA's regulation, 40 CFR §26.1125, requires the sponsor or investigator to submit to EPA, before conducting a study involving intentional exposure of human subjects, materials describing the proposed human research in order to allow EPA to conduct scientific and ethics reviews. In addition, EPA's regulation, 40 CFR §26.1601, requires EPA to seek HSRB review of the research proposal.

In previous meetings the HSRB has reviewed and commented favorably on several proposed insect repellent efficacy protocols to be conducted by Carroll-Loye Biological Research, submitted by Dr. Scott Carroll. Dr. Carroll has submitted a proposal for new research to evaluate the efficacy of two conditionally registered repellent products containing the active ingredient picaridin. The research protocol, identified as LNX-001, describes a field study of the efficacy of the test formulations against mosquitoes. The proposal bears many similarities to the protocols EMD-004, SCI-001, and WPC-001 that the HSRB has previously reviewed.

EPA has reviewed Dr. Carroll's protocol and has concluded that, with some required refinements, it appears likely to generate scientifically sound, useful information and to meet the applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L. The sponsor wishes to submit the data to EPA later this year to satisfy the requirement to provide efficacy data imposed when it received a conditional registration for picaridin. In the interest of providing a thorough and timely response to the proposal, and since EPA finds the protocol generally meets applicable scientific and ethical standards, EPA is presenting this protocol for review at the Board's June 2007 meeting.

Review materials. EPA is providing the following materials to the HSRB in the folder identified as "Carroll-Loye Repellent Protocol LNX-001":

a. C-L Protocol LNX-001

b. EPA Science & Ethics Rvw C-L Protocol LNX-001

Charge Questions.

1. Protocol LNX-001 from Carroll-Loye Biological Research:

a. If the proposed research described in Protocol LNX-001 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes?

b. If the proposed research described in Protocol LNX-001 from Carroll-Loye Biological Research is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

B. Proposed ICR Picaridin Insect Repellent Efficacy Study

EPA requires data from efficacy studies with human subjects to support claims of efficacy of a new pesticide product intended to repel insects that transmit human diseases.

EPA's regulation, 40 CFR §26.1125, requires the sponsor or investigator to submit to EPA, before conducting a study involving intentional exposure of human subjects, materials describing the proposed human research in order to allow EPA to conduct scientific and ethics reviews. In addition, EPA's regulation, 40 CFR §26.1601, requires EPA to seek HSRB review of the research proposal.

Dr. Niketas Spero has submitted a proposal for new research to evaluate the efficacy of two new formulations of a skin-applied repellent product containing picaridin, to be conducted by Insect Control & Research, Inc. (ICR). The research protocol, identified by Protocol ID G0590307001A044, describes a field study of the efficacy of the test formulations against mosquitoes.

EPA has reviewed ICR's protocol and has concluded that, with a number of required revisions, it appears likely to generate scientifically sound, useful information and to meet the applicable provisions of the EPA regulations in 40 CFR part 26, subparts K and L. The sponsor wishes to submit the data to EPA later this year in support of an application to register one or more new picaridin products. In the interest of providing a thorough and timely response to the proposal, and since EPA finds the protocol can meet applicable scientific and ethical standards, EPA is presenting this protocol for review at the Board's June 2007 meeting.

Review materials. EPA is providing the following materials to the HSRB in the folder identified as "Insect Control & Research Inc. Repellent Efficacy Protocol 1A 044":

a. Redacted Protocol 1A 044

b. EPA Science & Ethics Rvw ICR Protocol 1A 044

The sponsor of the proposed ICR research with picaridin has asserted a claim of confidentiality covering the identity of the sponsor, the percentage of the active ingredient in the test formulations, and the identities and amount of the inert ingredients in the test formulations. The sponsor has provided this information to EPA in separate documents that EPA is not providing to the Board. The Agency will, however, summarize our conclusions based on our review of this information at the Board's June meeting.

Charge Questions.

2. Insect Control & Research's Proposed Picaridin Protocol:

a. If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the efficacy of the test substances for repelling mosquitoes?

b. If the proposed research described in ICR's proposed picaridin protocol is revised as suggested in EPA's review, does the research appear to meet the applicable requirements of 40 CFR part 26, subparts K and L?

C. Completed Inhalation Study with Acrolein

In its reregistration program EPA reexamines the safety of previously registered pesticides. The Agency is currently reviewing pesticides containing the active ingredient acrolein. Acrolein is registered for use as a biocide in agricultural and industrial water supply systems. It is also formed as a byproduct in various industrial processes and is a component of cigarette smoke.

In a review of the published scientific literature, EPA identified a study published in German in 1977 in which human subjects were exposed to acrolein for various durations and at varying concentrations in an inhalation chamber. Researchers collected data on subjective irritation sensations and on eye-blink and respiratory rates. The Agency intends to use the results of this study in its hazard assessment to derive a "point of departure" (POD) for assessing acute toxicity resulting from acute exposure to this chemical.

The Agency's regulation, 40 CFR §26.1602, requires EPA to seek HSRB review of an EPA decision to rely on the results of any study if the research was "initiated before April 7, 2006, and the research was conducted for the purpose of identifying or measuring a toxic effect." EPA has reviewed the study, applying the standards in 40 CFR §§26.1703 and 26.1704. Those provisions state:

§26.1703 Prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children.

Except as provided in §26.1706, in actions within the scope of §26.1701 EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.

§26.1704 Prohibition on reliance on unethical research with non-pregnant, non-nursing adults conducted before April 7, 2006

Except as provided in §26.1706, in actions within the scope of §26.1701, EPA shall not rely on data from any research initiated before April 7, 2006, if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. This prohibition is in addition to the prohibition in §26.1703.

The Agency's reviews concluded that the data are scientifically sound and that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or significantly deficient relative to the ethical standards prevailing at the time the research was conducted. Nor is there evidence to show that the subjects included nursing or pregnant women or children.

Review materials. EPA is providing the following materials to the HSRB in the folder identified as "Acrolein Acute Inhalation Toxicity Study":

a. Weber-Tschopp in German

Weber-Tschopp, A., *et al.* (1977) "Experimentelle Reizwirkungen von Akrolein auf den Menschen." Intl. Arch. Occup. Environ. Hlth. (40): 117-130.

b. Weber-Tschopp in English MRID 47060601

Weber-Tschopp, A., *et al.* (1977) "Experimentally induced irritating effects of acrolein on man." Intl. Arch. Occup. Environ. Hlth. (40): 117-130.
a. This is a complete English translation of Item (a) above.

c. EPA WOE Document—Acrolein

Memorandum from Abdallah Khasawinah, Ph.D. to Jack Housenger, Associate Director Health Effects Division, "Human Studies Review Board: Weight of Evidence Discussion for Acrolein." May 25, 2007.

Additional background documents cited in EPA WOE Document:

c.1 IRIS 2003 Acrolein

U.S. EPA (2003) Toxicological Review of Acrolein (CAS No. 107-02-8) In Support of Summary Information on the Integrated Risk Information System (IRIS). Document No. EPA/635/R-03/003. 106 p.

c.2 ASTDR 2005 Acrolein

U.S. Department of Health and Human Services (2005) Draft Toxicological Profile for Acrolein. Prepared by Public Health Service, Agency for Toxic Substances and Disease Registry. 254 p.

d. EPA Ethics Rvw MRID 47060601 Weber-Tschopp

Charge Questions

3. Weber-Tschopp et al. inhalation study on acrolein

a. The Agency has concluded that this study contains information sufficient for assessing human risk resulting from potential acute inhalation exposure. Please comment on whether the study is sufficiently sound, from a scientific perspective, to be used to estimate a safe level of acute inhalation exposure to acrolein.

b. Please comment on the following:

(1) Is there clear and convincing evidence that the conduct of the study was fundamentally unethical?

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

D. Completed Studies on the Therapeutic and non-Therapeutic Effects of Administration of 4-aminopyridine

In its reregistration program EPA reexamines the safety of previously registered pesticides. The Agency is currently reviewing pesticides containing the active ingredient 4-aminopyridine (4-AP). 4-AP is registered by EPA as a bird repellent under the name Avitrol. It has also been investigated as a drug to treat various neurological diseases, and was recently approved for the treatment of chronic functional motor and sensory deficits resulting from Guillain-Barré syndrome.

In a review of the published scientific literature EPA identified three studies in which human subjects were exposed to 4-AP to evaluate whether it alleviated neurological symptom in patients with either spinal cord injury or multiple sclerosis. These clinical trials also report on the non-therapeutic effects of 4-AP. The Agency intends to use the results of these studies to derive a point of departure for assessing the risks to humans resulting from all potential durations of exposure–acute, short term, intermediate or subchronic, and chronic exposure.

The Agency's regulation, 40 CFR §26.1602, requires EPA to seek HSRB review of an EPA decision to rely on the results of any study if the research was "initiated before April 7, 2006, and the research was conducted for the purpose of identifying or measuring a toxic effect." EPA has concluded that the three studies with 4-AP are subject to HSRB review under 40 CFR §26.1602. The Agency reviewed the studies, applying the standards in 40 CFR §§26.1703 and 26.1704. Those provisions state:

> **§26.1703 Prohibition of reliance on research involving intentional exposure of human subjects who are pregnant women (and therefore their fetuses), nursing women, or children**.
>
> Except as provided in §26.1706, in actions within the scope of §26.1701 EPA shall not rely on data from any research involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> **§26.1704 Prohibition on reliance on unethical research with non-pregnant, non-nursing adults conducted before April 7, 2006**
>
> Except as provided in §26.1706, in actions within the scope of §26.1701, EPA shall not rely on data from any research initiated before April 7, 2006, if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. This prohibition is in addition to the prohibition in §26.1703.

The Agency's reviews concluded that the data are scientifically sound and that there is no clear and convincing evidence that the conduct of any of the research was fundamentally unethical or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted. None of the studies included as subjects nursing or pregnant women or children.

Review materials. EPA is providing the following materials to the HSRB in the folder identified as "4-Aminopyridine Human Effects"

a. 47093601 Grijalva et al 2003

Grijalva, I., *et al.* (2003) Efficacy and Safety of 4-Aminopyridine in Patients With Long-Term Spinal Cord Injury: A Randomized, Double-Blind, Placebo-Controlled Trial. Pharmacotherapy 23(7):823-834. MRID 47093601.

b. 47093602 Segal et al 1999

Segal, J., *et al*. (1999) Safety and Efficacy of 4-Aminopyridine in Humans with Spinal Cord Injury: A Long-Term, Controlled Trial. Pharmacotherapy 19(6):713-723, 1999. MRID 47093602.

c. 47093603 Van Diemen et al 1993

Van Diemen, H., *et al.* (1993) 4-Aminopyridine in Patients with Multiple Sclerosis: Dosage and Serum Level Related to Efficacy and Safety. *Clinical Neuropharmacology* vol. 16 No. 3, pp. 195-204. MRID 47093603.

d. EPA WOE Document—4-Aminopyridine

Memorandum from Abdallah Khasawinah, Ph.D. to Jack Housenger, Associate Director Health Effects Division, "Human Studies Review Board: Weight of Evidence Discussion for 4-Aminopyridine." May 27, 2007.

Additional background documents cited in EPA WOE Document:

d.1 U. S. EPA (1989)

U. S. EPA (1989) Health and Environmental Effects Document for 4-Aminopyridine. Prepared by EPA Office of Research and Development. Available from National Technical Information Service under document no. PB-91-216333. 72 p.

d.2 Spyker et al 1980

Spyker, D., *et al.* (1980) Poisoning with 4-Aminopyridine: Report of Three Cases. *Clinical Toxicology* 16(4), pp. 487-497.

d.3 NCI 2006

National Cancer Institute (2006) Aminopyridines. Unpublished report prepared by Technical Resources International, Inc. under Contract N02-CB-07007. (06/03; rev. 11/05; 3/06.) 47 p.

e. EPA Ethics Rvws MRIDs 47093601-02-03

Charge Questions

4. Studies on Effects of 4-Aminopyridine

a. The Agency's weight-of-evidence (WOE) document for 4-aminopyridine describes the study design and results of three clinical trials (**Grijalva et al. 2003, Segal et al. 1999, and Van Diemen et al. 1993)**. The WOE document also discusses the Agency's conclusion that these studies provide sufficient information to establish a point of departure for the assessment of the risk to humans resulting from all potential durations of exposure to 4-AP. Please comment on whether the studies are sufficiently sound, from a scientific perspective, to be used to derive a point of departure for estimating risk to humans from exposure to 4-AP.

b. Please comment on the following:

Is there clear and convincing evidence that the conduct of any of the clinical studies was fundamentally unethical?

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

E. Background Materials Relating to the Design of Research on the Levels of Exposure Received by Pesticide Handlers

Under FIFRA, EPA requires that all pesticide products must be "registered" before they may be sold or distributed in commerce. The applicant for registration has the burden of demonstrating that its pesticide will not cause "unreasonable adverse effects on the environment." Among other potential risks, EPA requires applicants to provide information that allows EPA to assess the potential for adverse effects on people who mix, load, or apply a pesticide (referred to as pesticide "handlers.") Accurately characterizing handlers' potential exposure is essential to EPA's risk assessment and regulatory decision-making.

EPA currently relies on a collection of exposure studies mostly contained in the Pesticide Handlers Exposure Database (PHED) to develop estimates of handlers' potential exposure. When dealing with pesticide that have low volatility, EPA assumes that, if field data are corrected for chemical-specific losses under field conditions, the amount of exposure a handler receives is independent of the chemical composition of the pesticide he is using, and that his exposure depends on the amount of active ingredient handled, as well as the particular activity, the particular type of pesticide formulation and the particular type of equipment used. The Agency uses the PHED data to develop estimates of "unit exposures" – expressed as an amount of exposure per amount of active ingredient handled – for specific scenarios. (A scenario is defined by the activity, formulation, and equipment, e.g. applying a liquid formulation by using airblast

equipment in an open cab.) Using this information, EPA estimates handlers' potential exposures for each use of a pesticide and compares those levels with toxicity data. If the comparisons show potential exposure is acceptably low, EPA concludes there is no risk to handlers. If, however, the comparisons show that in some scenarios a handler may receive unacceptably high exposure, EPA takes actions to mitigate the risk. The range of possible actions to reduce handlers' exposure includes requiring the use of personal protective equipment, reduced application rates, changes in formulation, use of specific types of application equipment or engineering controls, or prohibition of the use pattern.

The data currently used to estimate handlers' potential exposure has a number of limitations. The Agency believes that data from new handler exposure studies would provide a much sounder basis for estimating potential exposure. In particular, new data should provide a basis for characterizing the distribution of unit exposures across the population of handlers performing activities in each scenario. Two industry groups have arisen to undertake the research necessary to develop new databases – the Agricultural Handlers Exposure Task Force (AHETF) and the Antimicrobials Exposure Assessment Task Force II (AEATF). The AHETF is focusing on studies that relate to the use of pesticides in agriculture, and the AEATF will characterize exposures received by people while handling antimicrobial pesticides, e.g., disinfectants, materials preservatives, etc.

Both Task Forces would like to initiate research soon – the AEATF during the winter of 2007–2008, and the AHETF during the pesticide use season in 2008. At least some Task Force studies would involve intentional exposure of a human subject. EPA's regulation, 40 CFR §26.1125, requires the sponsor or investigator to submit to EPA, before conducting research involving intentional exposure of a human subject, materials describing the proposed human study in order to allow EPA to conduct scientific and ethics reviews. In addition, EPA's regulation, 40 CFR §26.1601, requires EPA to seek HSRB review of the research proposal.

The HSRB has considered the prospect of new handler research at two previous meetings. In June 2006 the Board reviewed five proposed protocols developed by the AHETF. The Board raised questions and made numerous comments on both scientific and ethical aspects of the proposals.

Over the past year EPA and the Task Forces have worked hard to address the issues identified by the HSRB. In response to scientific concerns raised by the HSRB, EPA analyzed the existing handler exposure database and relevant scientific literature, and presented its analysis to the FIFRA Scientific Advisory Panel (SAP) in January 2007. The Agency asked the SAP to comment on, among other topics, the "limitations [of existing data] and on EPA's conclusion that additional data could improve significantly EPA's ability to estimate worker exposure." The SAP report was released April 2, 2007, and is available at: http://www.epa.gov/scipoly/sap/meetings/2007/january/january2007finalmeetingminutes.pdf . At its April meeting the HSRB received a copy of the SAP report and a presentation by two members of the Panel that prepared the report.

In addition, for the April 2007 HSRB meeting EPA prepared a draft document identifying the major elements of the recruitment and enrollment processes that should be considered by investigators as they prepare protocols for handler exposure research. The document discussed broad principles which should be considered in the course of research design. In the future, through a participatory process involving investigators, workers, and other stakeholders EPA intends to add to the document specific best practices, and to identify publicly available resources that contain additional discussion, information, and guidance relevant to the implementation of general ethical principles in occupational exposure research. The draft document is available at: http://www.epa.gov/osa/hsrb/files/meeting-materials/apr-18-20-2007-public-meeting/DraftFrameworkForDevelopingBest-Practices0315007.pdf

Both the AHETF and AEATF have prepared extensive materials explaining and justifying their proposed research, and have revised these materials in response to EPA comments. These materials, which are being provided to the HSRB for discussion at its June 2007 meeting, generally explain the scope of the proposed research programs and describe the general framework for conducting the research. In addition, each Task Force has provided Standard Operating Procedures which will guide the conduct of the studies. These materials provide essential background information to support the Board's evaluations of Task Force protocols and related materials at subsequent meetings. Since EPA regards the proposed studies as "research involving intentional exposure of human subjects," EPA regulations require the Agency and the Board to review these proposals before the investigators initiate the studies.

Review materials. EPA is providing the following materials to the HSRB in the folder identified as "Background Materials on Pesticide Handler Research":

a. AHETF Volume 1 – Transmittal Document for HSRB Materials.

This volume consists of a cover letter, a list of documents, and a list of companies that are members of the AHETF.

b. AHETF Volume 2 – Submission of Materials for June 2007 HSRB Meeting.

This volume contains multiple chapters. Together, the Table of Contents and Chapter 1 provide a helpful guide to understanding the contents of this volume. Chapter 1, in particular, attempts to provide a "roadmap" to the larger AHETF submission by indicating where in the Task Force's submissions materials relating to each item specified in 40 CFR 26.1125 appears (or will appear). Chapter 2 is the AHETF's "Governing Document," which describes the scope of the overall research program and the general principles that will determine the study design for each protocol. Subsequent chapters contain the AHETF's Standard Operating Procedures, a justification for the design of the sampling strategy, and a justification for the number of clusters and monitoring units for each scenario and other information.

c. AEATF Governing Document.

This document is officially named the "Antimicrobial Exposure Assessment Task Force II (AEATF) Governing Document for a Multi-Year Antimicrobial Chemical Exposure Monitoring Program – Interim Draft Document, May 21, 2007." Like Chapter 2 of the AHETF submission, the AEATF's "Governing Document" describes the scope of the overall research program and the general principles that will determine the study design for each protocol. Appendices to the AEATF's Governing Document contain, among other things, a justification for the design of the sampling strategy and a justification for the number of clusters and monitoring units for each scenario.

d. AEATF example protocol.

This example protocol is entitled "A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using Trigger Spray and Wipe or Ready to Use Wipes for Cleaning Indoor Surfaces" (Draft Version, 5/21/07). Even though the draft has not received IRB approval and EPA has not prepared a written review, the AEATF provided this draft protocol in order to illustrate how the general principles for study design would translate into the development of the protocol for an individual study. This draft also illustrates the additional material the AEATF would expect to provide as part of a protocol.

c. AEATF SOPs.

This document, called "Standard Operating Procedures (SOPs) for a Multi-Year Antimicrobial Chemical Exposure Monitoring Program - Interim Draft Document, May 21, 2007," contains a subset of AEATF SOPs, including all those cited in the example protocol.

Discussion Topics and Charge Questions. Although EPA and the Task Forces do not expect to present specific IRB-approved protocols to the HSRB until the October 2007 meeting, EPA believes that it would be helpful to EPA and the Task Forces for the Board to provide guidance on selected issues potentially affecting all of the protocols before they are submitted for review. After consultation with the Chair of the Board, EPA has identified several broad topics that merit in-depth discussion. For each topic, EPA plans to make a short presentation describing: how the Task Forces addressed the topic (noting differences between AHETF and AEATF where relevant), what the SAP said (if anything) about the topic, and what position EPA takes with respect to the issues arising under the topic. The Agency has formulated charge questions that suggest the kinds of advice from the HSRB which would be most useful to us as we review specific protocols from the Task Forces in anticipation of submitting them for HSRB review at upcoming meetings.

1. Overview of the Task Force materials – EPA will provide an explanation of key terms and concepts used in the Task Forces' submissions, i.e., "research program," "scenario," "cluster," "monitoring unit," and "study." The Agency will then discuss how it expects to use the information contained in various types of Task Force documents: the Governing Documents for the research program, the SOPs, the scenario-level design plans, the protocols for specific studies, study-specific reports, and the scenario monographs reporting completed work.

No Charge Question.

2. Discussion of risks & benefits of handler research – EPA will describe and comment on the presentations in the Task Forces' Governing Documents concerning the risks and benefits of the proposed research and what EPA expects to see in connection with individual study proposals.

Charge Questions:

EPA thinks that the Governing Documents prepared by each of the Task Forces contain useful general summaries of the kinds of risks that subjects may encounter when participating in particular studies performed as part of the overall research programs. EPA also believes that the Governing Documents contain a good discussion of the anticipated benefits of the overall research programs.

While EPA expects that the benefits of the data collected for a particular scenario will likely justify the risks associated with the studies undertaken to generate the data, EPA does not believe that the Governing Documents, by themselves, provide sufficient information to conclude that individual studies are justified. This can only be decided on the basis of study-specific risks to subjects and study- or scenario-specific benefits in the form of knowledge expected to result from the research. Thus, for each proposed study EPA will expect the Task Forces to provide a detailed discussion of:

- the risks to subjects from participation in that study,
- the specific measures taken to minimize those risks, and
- the expected benefits of the data for each scenario in which the resulting data will be used.

Will the Task Forces' Governing Documents considered in conjunction with the additional study- and scenario-specific information specified above provide an adequate basis for assessing whether the risks of conducting a particular study are justified by the expected benefits of the proposed research? If not, what additional information should be provided for an IRB, EPA, and the HSRB?

3. Addressing potential sources of underestimation bias –The Agency will discuss and comment on the need for the proposed research to collect data to support an assessment of the potential for underestimation of exposure due to inefficient residue removal by hand rinses and face/neck wipes, or due to dermal absorption of the surrogate material during the exposure period.

Charge Questions:

While both the AHETF and AEATF intend to include the residues measured by hand rinse and face/neck wipe procedures as part of the overall exposure calculation for each subject, they do not propose to correct hand or face/neck exposure estimates to account for the possibility of incomplete recovery of residues from the skin. Nor do they propose any correction mechanism to account for possible residue breakthrough underneath WBD. Because of the similarity in exposure estimates relying on biomonitoring and passive dosimetry methods (as reported in the Task Forces' and EPA presentations to the January 2007 SAP), the Task Forces argue that significant underestimation is unlikely and that corrections are unnecessary.

The SAP agreed that passive dosimetry "can generate data that can be used to develop relatively predictive estimates of worker exposure for a wide variety of scenarios and activities" – though they also stated that a biomonitoring supplemental, or "add-on", can provide a useful check on the method.

EPA believes it is important to consider how the contributions from the hands or from the face and neck influence overall exposure before deciding whether to require residue removal efficiency studies. Based on calculations of the sensitivity to potential underestimation due to incomplete residue removal associated with differing contributions to overall exposure from the hands, face, and neck, EPA has concluded generally that:

- If measured exposures from hands, face and neck contribute < 20% of the total, no additional research would be required to characterize the efficiency of residue removal procedures, and no corrections or adjustments would be made to estimates of exposure.

- If measured exposure from hands, face and neck represents from 20% to 60% of the total, the Task Forces should conduct research to characterize the efficiency of the residue removal procedures or, in the absence of such data, the Agency would assume a conservative level of efficiency for a residue removal procedure and adjust the estimates of exposures accordingly.

- If measured exposure from hands, face and neck represents > 60% of the total, the Task Force should conduct research to characterize the efficiency of the residue removal procedure(s).

EPA acknowledges that use of absorbent cotton gloves as an alternative to hand rinses is another approach that could avoid underestimation of the residues on hands. The Agency believes, however, that this method could overestimate potential hand exposure.

Though a biomonitoring "add-on" option could potentially address both residue removal inefficiencies and dosimeter breakthrough, biomonitoring requires substantial knowledge of the relationship between dermal exposure and urinary metabolite levels over time. To quantify this relationship would require additional human research and would represent a significant incremental cost. In addition, biomonitoring would require subjects to participate for several days longer, to ensure any prior exposures to the test material had time to clear their systems, and to collect urine samples long enough after the test exposure to capture the urinary metabolites.

Nonetheless, it would be useful in the discussion of specific scenarios and protocols to consider whether the surrogate pesticides used are readily absorbed through the skin and whether, in the particular scenario under study, subjects will be handling high amounts of active ingredient and whether their exposures will be primarily to their hands, face, and neck or to other parts of the body. In scenarios involving a readily absorbed surrogate compound and relatively high levels of hand/face/neck exposure, collecting urine to support an overall correction factor (or "add-on") may be justified.

In conclusion, given the costs, logistical difficulties, and the additional uncertainties with biomonitoring described above, and the fact that substantial underestimation by WBD is not likely, the options described above for the hand and face/neck collection/removal methodologies are considered the most appropriate for correction of potential underestimation by passive dosimetry techniques.

Has EPA appropriately characterized the limitations on the scientific usefulness of a handler database that does not include data characterizing the efficiency of residue removal procedures? If not, what limitations have been overlooked?

Has EPA identified the relevant scientific and practical considerations affecting the choice to include biomonitoring, and has EPA appropriately characterized the limitations on the scientific usefulness of the resulting data if no biomonitoring is conducted? If not, what other considerations should bear on a decision to conduct biomonitoring in addition to WBD?

4. QA/QC controls – The Agency will describe and comment on the various Standard Operating Procedures that the Task Forces have established to ensure high quality data.

Charge Question:

In collaboration with officials in the Canadian Pesticide Regulatory Management Authority and the California Department of Pesticide Regulation, EPA has worked with the Task Forces as they developed a set of Standard Operating Procedures to ensure the data resulting from their proposed research is of high quality. The Task Force SOPs reflect current, state-of-the-art methods for quality assurance and quality control in the collection, storage, and analysis of analytical samples. Therefore EPA believes that the resulting data will be of very high quality.

Do the Task Forces' Standard Operating Procedures appear adequate to ensure that the data resulting from the proposed research will be of high quality? If not, what other Quality Assurance or Quality Control procedures need to be addressed?

5. Design of scenario-level sampling strategies – The Agency will describe and comment on the Task Forces' approach to deciding how to arrange clusters and select conditions for specific monitoring units (MUs)—i.e., their "purposive diversity sampling strategy—and their justification for collecting "covariate" information. The Agency will also address the comments from the SAP on this topic, specifically the SAP's recommendation to consider the alternative of a stratified random sampling strategy.

Charge Questions:

The AHETF has indicated that it plans to identify clusters and specify conditions for monitoring units using a "purposive diversity sampling strategy." The SAP report included a suggestion that the AHETF consider identifying for each scenario any major factors other than the amount of active ingredient handled (AaiH) that may influence handler exposure, and then selecting clusters and MUs in a manner that is statistically representative of the distribution of the target population with respect to those factors. The AHETF asserts that it would be impractical to implement the SAP's advice fully, because adequate data to develop stratified sampling frames is generally unavailable, and they could not afford the added logistical costs associated with identifying appropriate subjects in that manner. The AEATF has indicated that it also plans to use a "purposive diversity sampling strategy" to select clusters and MUs.

Although EPA would like additional scenario-specific information to characterize the adequacy of available data and likely costs to implement the SAP advice, EPA generally expects that for most scenarios significant improvement on the proposed purposive diversity sampling strategies will not be feasible. EPA recognizes that the approaches planned by the AHETF and AEATF will produce a distribution of handler exposures for each scenario that does not necessarily represent the true distribution of exposures in the target population for that scenario. But EPA believes that the range of exposures covered by the data collected using the

AHETF and AEATF approaches will span a large portion of the true distribution of handler exposures, that the data collected will represent a major improvement over data available to the Agency today, and that the resulting data will be adequate for regulatory decision-making.

With regard to the AHETF and AEATF plans to conduct their proposed handler research using purposive diversity sampling strategies:

> Has EPA identified the relevant scientific and practical considerations affecting the choice of a strategy for sample selection? If not, what other considerations should bear on the choice?
>
> Does the HSRB agree with EPA that the Task Forces should provide scenario-specific information about the availability of data to identify significant variables (other than AaiH) potentially influencing exposure and about the feasibility of developing a sampling strategy to address those variables quantitatively? If not, what additional information is needed?
>
> Has EPA appropriately characterized the limitations on the scientific usefulness of the resulting data attributable to the choice of the sampling strategy? If not, what has EPA overlooked?

6. Statistical justification for number of clusters and monitoring units – The Agency will describe and comment on the Task Forces' approach to determining the number of clusters and the number of monitoring units in each cluster to achieve a pre-established benchmark level of precision in estimating the distribution of exposures. The Agency will also address the comments from the SAP on this topic.

Charge Question:

> The AHETF and AEATF have indicated that, for each scenario, they generally plan to collect data from enough clusters and monitoring units (MUs) so that the estimates of the geometric mean, arithmetic mean, and 95th percentile of the resulting distribution will fall within ±3-fold of the true value for the target population. The Task Forces have provided a statistical analysis for concluding that five clusters of five MUs each and three clusters of six MUs each will achieve that benchmark for precision for AHETF and AEATF scenarios, respectively. These analyses incorporate certain data-based assumptions about the statistical characteristics of the expected data. The SAP concluded that the AHETF used a scientifically acceptable approach for demonstrating that the proposed number of clusters and MUs for a scenario would achieve the target level of precision.
>
> EPA believes that the target benchmark of K = 3 is generally reasonable for most scenarios. Based on the SAP's advice and our view that the Task Force analyses

used reasonable assumptions about coefficients of variation and intra-class correlation, EPA also thinks that the analyses provided by the AHETF and AEATF adequately justify their proposals regarding number of clusters and number of MUs. For each study proposed by the Task Forces, and for all scenarios to which the data would relate, EPA will expect to receive a scenario-specific discussion of the target value for K, as well as a discussion of the data available to support an estimate of the coefficient of variation and the (study location) intra-class correlation. Finally, EPA will expect the Task Forces to identify the number of existing MUs currently available for a scenario from the Pesticide Handlers Exposure Database or other sources and to discuss how the data points resulting from each proposed study will fit into the scenario database.

What additional information, if any, would the HSRB need to assess the adequacy of the justification for the number of clusters and number of MUs in specific AHETF and AEATF study proposals?

7. Within-Worker variability – The Agency will describe and comment on the Task Forces' position on collecting data on multiple days of exposure of a subject performing the same scenario activity. The Agency will also address the comments from the SAP on this topic.

Charge Question:

The AHETF and AEATF have decided not to collect exposure data on a single subject who performs the same activity on different days. The SAP advised that such "repeated measures" could provide data to assess within-worker variability important for more accurate estimates of the distribution of the means of handlers' multi-day exposures. A majority of the SAP, however, also advised that collecting data on different subjects would be a more valuable use of research resources than collecting repeated measures. The SAP noted, however, that the proposed handler research does offer an opportunity to collect "repeated measures" data.

EPA agrees with the Task Forces and with the SAP. We prefer that the Task Forces direct their finite research resources to the collection of exposure data on different MUs, rather than to collection of repeated measures from a single subject performing the same activity on different days. EPA recognizes that the data resulting from the research proposed by the Task Forces therefore will not support quantitative estimates of the extent of within-worker variability. The Agency further understands that it will have to make assumptions about within-worker variability when performing multi-day exposure assessments.

Has EPA appropriately characterized the limitations on the scientific usefulness of a database that does not include repeated measures? If not, what limitations has EPA overlooked?

8. Subject recruitment and enrollment issues –The Agency will identify several issues that arise in connection with the processes of recruiting and informing potential subjects who might participate in the handler exposure studies that the Task Forces propose to conduct, and will comment on how the Task Forces are approaching these issues.

Charge questions:

EPA is impressed by the progress made by the Task Forces in incorporating comprehensive and appropriate protections for human subjects into their planned research programs. The Governing Documents are by their nature generalizations, but they provide a solid basis for developing scenario- and study-specific processes for community involvement and for recruiting, informing, and seeking consent from potential subjects. One area still needing refinement is handling of language differences; when subjects' language of preference is Spanish, to the maximum degree possible the recruiting and consent processes and the field research itself should be conducted in Spanish, with minimal reliance on interpreters. The key to accomplishing this is to include on the field research teams qualified investigators and observers/monitors who are bilingual in English and Spanish.

Does the Board agree that the Governing Documents and associated SOPs of the AHETF and AEATF research programs include comprehensive and appropriate protections for human subjects of the research? If not, what has been overlooked?

In singling out the handling of language differences as an area requiring further refinement, has EPA overlooked other areas in need of revision? If so, what?