December 10, 2007

Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
November 13, 2007 Public Teleconference Meeting
Docket Number: EPA-HQ-ORD-2007-0403

Committee Members: (See EPA HSRB Members list – Attachment A)

Dates and Times:	Tuesday, November 13, 2007, 1:00 PM – 3:00 PM (See *Federal Register* Notice – Attachment B)	
Location:	via teleconference	
Purpose:	The EPA HSRB provides advice, information, and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Celia B. Fisher, Ph.D.
	Board Members:	Alicia Carriquiry, Ph.D. Janice Chambers, Ph.D., D.A.B.T. Richard Fenske, Ph.D., MPH Suzanne C. Fitzpatrick, Ph.D., D.A.B.T. Dallas E. Johnson, Ph.D. Kannan Krishnan, Ph.D. Michael D. Lebowitz, Ph.D., FCCP Jerry A. Menikoff, M.D. Rebecca Parkin, Ph.D., MPH Sean Philpott, Ph.D., M.Bioethics Richard R. Sharp, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the meeting Agenda (Attachment C), unless noted otherwise in these minutes.	

Introductory Remarks, Meeting Administrative Procedures, and Meeting Process

Dr. Celia Fisher (HSRB Chair) opened the teleconference meeting with an introduction and identification of the HSRB members participating in the call. Dr. Fisher explained that the purpose of the meeting was to review and approve the June 27-29, 2007 draft HSRB meeting report (Attachment D).

Dr. Paul Lewis (Designated Federal Officer [DFO], HSRB, Office of the Science Advisor [OSA], EPA) thanked Dr. Fisher and the Board for their participation in the teleconference and

for their review of the draft June 27-29, 2007 HSRB meeting report. Dr. Lewis explained that the HSRB is subject to Federal Advisory Committee Act (FACA) requirements. As the DFO, Dr. Lewis serves as liaison between the HSRB and EPA, or the Agency. He works with the appropriate officials to ensure compliance with all appropriate ethics regulations. Each member of the Board has filed a standard government financial disclosure form that has been reviewed by EPA to ensure that all ethics disclosures have been met.

Dr. Lewis stated that the documents discussed by the HSRB, including the draft June 27-29, 2007 HSRB meeting report, are available at the public docket; the address for the docket was included in the *Federal Register* notice announcing this teleconference meeting. As per FACA requirements, the meeting minutes will include descriptions of matters discussed and the conclusions reached by the Board. As the DFO, Dr. Lewis will prepare the minutes and have them certified by the HSRB Chair within 90 calendar days of the meeting. In addition, the minutes will be available at the public docket and posted on the HSRB Web site.

Public Comments

Dr. Fisher invited oral public comment on the draft June 27-29, 2007 HSRB meeting report. No oral public comments were presented.

Board Discussion and Decision on Report

Dr. Fisher introduced the written comments submitted by the EPA Office of Pesticide Programs (OPP) and stated that the Board discussion during the teleconference would focus on questions and points of clarification raised by OPP. Dr. Fisher suggested that the Board adopt all OPP recommendations that were factual, grammatical, or editorial corrections.

The Board's letter to Dr. George Gray (Science Advisor, EPA) summarizes the Board consensus and rationale regarding charge questions raised at the June 27-29, 2007 meeting. OPP's comments on the letter are related to comments made within the body of the draft meeting report; therefore, Drs. Fisher and Lewis will revise the letter as needed based on Board discussions during the teleconference.

Proposed Carroll-Loye Picaridin Insect Repellent Efficacy Study LNX-001

Dr. Fisher asked if Board members had any suggested changes to the HSRB Consensus and Rationale related to scientific considerations (p. 17, lines 39-43). No Board members requested changes.

OPP's written comments suggested that the minimum and maximum numbers of subjects participating in this study were incorrect within the meeting report text. "The number of participants enrolled in this study thus will total a minimum of 25 volunteers and a maximum of 37 volunteers, a number that appears to be adequately justified (Carroll 2007a; Carroll 2007b)" (p. 19, lines 11-13). OPP's written comments stated that the minimum number of subjects should be 22 and the maximum should be 54. Dr. Fisher requested feedback from the Board on whether to delete the sentence or incorporate OPP's suggested changes. Dr. Sean Philpott

disagreed with OPP's comment because the minimum of 22 participants does not take into account the 3 alternate participants. Dr. Philpott indicated that he had discussed the number of study participants in great detail with Dr. Scott Carroll (Carroll-Loye Biological Research, Inc.) during preparation of this section of the draft meeting report and concluded that a maximum of 37 participants will participate in both field studies. Dr. Fisher stated that the sentence in the meeting report concerning minimum and maximum numbers of participants would not be revised.

Within the ethics discussion for this study (p. 19, lines 23-38), OPP's written comments requested clarification on whether the Board intended to state that the protocol meets the standards of 40 Code of Federal Regulations (CFR) 26.1125 rather than state that it meets all requirements of 40 CFR part 26, subparts K and L, being that the paragraph focused specifically on 40 CFR 26.1125. Dr. Philpott, who authored this section of the meeting report, explained that he had replicated the language used in the charge question, but agreed that the meeting report could be changed to cite the specific documentation requirement.

Dr. Fisher inquired if Board members had changes or comments for the HSRB Consensus and Rationale related to ethical considerations (p. 21, lines 4-10). No changes were suggested.

Proposed ICR Picaridin Insect Repellent Efficacy Study

Dr. Fisher asked if Board members had changes or comments for the HSRB Consensus and Rationale related to scientific considerations (p. 24, lines 24-29). No changes were suggested.

For the Board's discussion of the background of the picaridin study, OPP's written comments suggested several changes to the text in order to clarify the difference between a confirmed bite (a bite confirmed by another bite in the same or the next subsequent exposure period) and the premise in the Insect Control and Research, Inc. (ICR) protocol that ICR staff will determine whether to count an event as a bite (p. 25, lines 31-37). Dr. Fisher stated that she planned to incorporate OPP's comments. Dr. Philpott agreed that OPP's changes were correct and would more accurately reflect EPA guidelines. In the following paragraph, OPP's written comments clarified that a rate of 1 to 10 landings per minute, not a "minimum" rate of 1 to 10, is necessary for conducting the field trial (p. 25, line 45). Dr. Fisher proposed revising the sentence as follows: "A minimum rate of 1 and a maximum rate of 10 landings per minute are necessary for the field trial to be conducted." The Board members agreed with this change.

OPP's written comments questioned the use of quotation marks around the phrase "substantially compliant" (p. 26, line 36). Drs. Philpott and Fisher agreed to remove the quotation marks, but noted that the Board had discussed at a previous meeting the meaning of "substantially compliant" and that the definition remains unclear. In the same sentence, OPP's written comments requested clarification of the phrase "the regulatory requirements of review and documentation" (p. 26, line 37). The Board agreed to revise the phrase as follows: "…the regulatory requirements of review and documentation in 40 CFR 26.1125…"

On page 27, lines 26-28, OPP's written comments clarified that EPA guidelines do not mention landings as an endpoint, although EPA has accepted studies that use landings as an

endpoint. Dr. Philpott explained that this passage was intended to reflect ICR's and toXcel's justification for use of time to first confirmed bite (FCB) by referring to EPA guidelines in their written response to OPP. Dr. Fisher noted that OPP may be concerned that this statement suggests that EPA guidelines do call for landings with intent to bite. She proposed adding a sentence to this passage to clarify that use of landings with intent to bite as an endpoint is not part of EPA's guidelines. Dr. Philpott agreed with this proposed revision.

Dr. Fisher asked if Board members had changes or comments for the HSRB Consensus and Rationale related to ethical considerations (p. 29, lines 37-41). No changes were suggested.

Completed Inhalation Study with Acrolein

OPP's written comments requested clarification of the Board's consensus that "…the study was sufficiently sound, from a scientific perspective, to be used to estimate a safe level of acute inhalation exposure to acrolein for the population tested" (p. 33, lines 44-45). OPP inquired as to whether the Board meant that the results cannot be generalized beyond the population tested. Dr. Fisher suggested revising the sentence to reflect that the Board did not believe the results could be generalized to younger or older population groups than those used in the study. Board members agreed with this revision.

Regarding the Weber-Tschopp et al. study, the Board states that "…post hoc benefit is not relevant…" (p. 37, line 2) and OPP's written comments requested clarification. The Board discussed that at least one Board member found the risk-to-benefit balance to be inappropriate. Dr. Fisher proposed revising the text as follows to clarify the Board's position: "…post hoc benefit is not relevant to the prospective risk-benefit balance…" Dr. Jerry Menikoff agreed with the suggested change.

Dr. Fisher asked if Board members had changes or comments for the HSRB Consensus and Rationale related to ethical considerations (p. 37, lines 7-13). No changes were suggested.

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

Dr. Fisher inquired if Board members had changes or comments for the HSRB Consensus and Rationale related to scientific (p. 40, lines 10-20) and ethical considerations (p. 42, lines 22-28). No changes were suggested.

Design of Research on the Levels of Exposure Received by Pesticide Handlers

<u>Risks and Benefits of Handler Research</u>

OPP's written comments expressed a general concern that the draft meeting report focused on the Agricultural Handlers Exposure Task Force (AHETF) to the exclusion of the Antimicrobial Exposure Assessment Task Force (AEATF). Based on OPP's comments, Dr. Richard Fenske, who authored this section of the meeting report, made revisions throughout this section and submitted his revisions to Dr. Fisher prior to the teleconference. On page 43,

lines 20-24, Dr. Fenske suggested revising the text to include risks relevant to the AEATF protocols, as described in the June 2007 HSRB meeting minutes. Dr. Fisher inquired about the Board's critique (p. 43, lines 30-31) and how discussion of AEATF should be incorporated. Dr. Fenske suggested the addition of a sentence noting that most of the Board's comments are applicable to the AEATF document in addition to AHETF document. Reference to "the document" should be changed to plural ("the documents").

On page 44, lines 6-7, Dr. Fenske proposed adding a sentence to indicate that participants would receive the benefits of use of test substances at no cost; however, Mr. John Carley (OPP, EPA) clarified that the benefit of free product would not apply to AEATF protocols because most of these protocols would be performed in leased vacant buildings. Participants recruited from janitorial service companies would apply the products. Dr. Fenske agreed to modify the text to reflect this.

Dr. Fenske explained that the subsequent paragraph (p. 44, lines 15-26), concerning use of farm equipment, is applicable only to the AHETF and not the AEATF. On page 44, lines 28-37, Dr. Fenske suggested the addition of text at the end of the paragraph to indicate that the same recommendations could be applied to the AEATF, but risks for AEATF protocols would be lower.

Dr. Fisher requested comments on the HSRB Consensus and Rationale (p. 45, line 24 through p. 46, line 2). Dr. Fenske suggested the addition of AEATF to the first line of the consensus statement, indicating that both groups have provided the HSRB with appropriate and useful governing documents. Dr. Fenske also proposed the addition of AEATF to the final sentence of the paragraph, concerning the ability of data collected by both task forces to improve the quality of risk assessments and provide valuable societal benefits. Dr. Fenske agreed to incorporate the discussed revisions into this section of the report and to submit the revised text to Drs. Fisher and Lewis after conclusion of the teleconference.

Addressing Potential Sources of Underestimation Bias

OPP's written comments stated that although face/neck wipe sampling is not mentioned in the draft Agency 875 guidelines, EPA would not reject studies including face/neck wipes (p. 46, lines 44-46). Dr. Michael Lebowitz suggested adding a statement clarifying that wipe sampling is not included in EPA guidelines, but EPA will accept such information. Dr. Fisher clarified that the sentence will be changed as follows: "This method was not among those recommended by the Agency in its 1987 Subdivision U Agency guidelines for pesticide handler exposure studies, but this does not mean that EPA would not accept its use." Dr. Fenske agreed with this revision.

OPP's written comments also questioned the following statement: "Nor was wipe sampling included as an appropriate method in the 1997 guidance document produced by the Organization for Economic Cooperation and Development (OECD 1997)" (p. 47, lines 1-3). OPP commented that page 29 of the OECD document states: "Exposure to the head, neck and face should be determined by measuring deposition on a cotton hat or cap, on a hood as part of the whole body dosimeter, or on a head patch as for the patch method. Exposure to the face and

neck could also be determined through the use of wipe samples." Dr. Fenske stated that he agreed with OPP's comment and suggested deleting the entire sentence.

On page 48, lines 1-2, OPP's written comments requested clarification of the sentence describing potential underestimation of exposure using removal techniques that remove only chemicals that have not been adsorbed onto or absorbed into the skin. OPP's comments explained that hand rinse and face wipe methods are designed to remove adsorbed materials. Dr. Fenske suggested revising this sentence as follows: "Removal techniques typically underestimate exposure, since they can only remove chemicals that have not been adsorbed irreversibly onto or absorbed into the skin." The Board agreed with this revision.

OPP's written comments suggested deleting the paragraph on page 48, lines 28-34. Dr. Fenske agreed to delete the first two sentences from this paragraph. He believed it would be appropriate to retain the remainder of the paragraph, and to add a sentence indicating Board support of Agency plans to evaluate the relative importance of hand, neck and face exposure from each study as planned by the task forces. He recommended adding language contained in OPP's comment regarding evaluation of data from each study, and recommended spelling out "Task Forces" and "whole body dosimetry," rather than using acronyms. Dr. Fenske will incorporate the revisions discussed during the teleconference into this section and will submit the revised text to Drs. Fisher and Lewis.

Dr. Fenske also suggested modifying the sentence "In both cases, a validation study for recovery efficiency of wash or wipe samples can be tested *in vitro*…" (p. 49, lines 21-22) to "…could be tested *in vitro*…"

OPP's written comments pointed out that the HSRB Consensus and Rationale (p. 49, line 27) was not included in the draft meeting report; therefore, Dr. Fisher developed a draft of the conclusions for Board approval. Dr. Fisher read her draft text and Dr. Fenske reviewed the draft Consensus and Rationale and agreed to incorporate revisions discussed during the teleconference and to submit the revised text to Drs. Fisher and Lewis.

Dr. Fisher requested comments on the HSRB Consensus and Rationale regarding the appropriateness of not including concurrent biomonitoring in the protocols (p. 50, lines 26-30). No changes were suggested.

<u>QA and QC Controls</u>

OPP's written comments noted that the HSRB Consensus and Rationale related to quality assurance (QA) and quality control (QC) controls (p. 51, line 21) was not included in the draft meeting report; therefore, Dr. Fisher developed a draft of the conclusions for Board approval. "Overall, the SOPs [Standard Operating Procedures] outlining the overall administration, report generation and quality assurance (QA) oversight seems reasonably complete. The HSRB reviewers noted two major areas that should be expanded and/or revised for additional clarity, namely the SOPs that focused on data quality and sample integrity and compliance." Dr. Lewis requested that "The HSRB reviewers…" be changed to "The Board…" No other changes were suggested.

Design of Scenario-Level Sampling Strategies

OPP's written comments requested clarification on whether the Board's description of the number of handler-days included both the AHETF and AEATF programs (p. 51, lines 39-40). "It was estimated that this would include approximately 1.1 million handlers and approximately 2 million handler-days." Dr. Fenske suggested revising the text to "It was estimated by the AHETF that this would include…"

OPP's written comments also questioned the Board's statement that "…complex probability sampling is more typical for these types of projects" (p. 51, lines 42-43) and requested more specificity in regard to the types of projects the Board was referring. Dr. Fenske agreed that this sentence is confusing and suggested that the sentence be deleted. Dr. Fisher asked Mr. Carley if he found this revision to be acceptable and he indicated agreement with the change. On page 51, line 45, the Board decided to revise "Complications associated with complex probability sampling…" to "Considerations associated with sampling…"

Dr. Alicia Carriquiry questioned the sentence referring to selection bias as a particular issue for protocols that will only use volunteers (p. 52, lines 1-2); she asked Mr. Carley to provide an example of a study that does not use volunteers. Mr. Carley suggested that studies based on Census data do not use volunteers and clarified that EPA had not asked for revision or clarification of this particular sentence. Dr. Carriquiry noted that selection bias is an issue for all protocols, not "a particular issue for these protocols…" Dr. Lebowitz stated that the use of the term "volunteers" may be problematic because there is concern about inappropriate pressure to participate placed on potential participants since they are workers; he felt that selection bias is an issue and that the sentence is accurate. For the AHETF, participants represent a convenient sample, not a randomly selected sample. Dr. Carriquiry remarked that she believed the purpose of this sentence was for EPA to justify use of purposive diversity sampling (PDS) by stating that if random sampling is used, people can refuse to participate. The Board agreed to delete this sentence.

OPP's written comments stated: "The primary purpose of the Task Forces' proposed research is collection of improved measurements of the range of individual handler exposure-days for the various scenarios. Generation of data to assess the relationship of the active ingredient to exposure is a secondary goal." The Board agreed with OPP's comment and agreed to change the phrase "the primary driver of the study design" (p. 53, line 16) to "an important driver of the study design."

OPP's written comments indicated that the discussion regarding study factors and variables (p. 53, lines 17-29) is specific to the AHETF program and that it would be helpful for the Board to include comments concerning the AEATF program. Dr. Lebowitz clarified that the entire paragraph refers to the AHETF program and that the AEATF was not discussed in this regard during the June 2007 HSRB meeting. Dr. Fenske suggested adding, "For example, in the AHETF study…" The Board agreed to this revision.

On page 53, lines 27-29, "The Board concluded that any attempt at diversity sampling should include an appropriate number of non-certified applicators." OPP's written comments indicated that this recommendation seemed to reflect an incomplete understanding of the regulatory requirements regarding applicator certification. Many applicators who apply restricted use pesticides are not themselves certified, but make applications under the supervision of a certified applicator. Dr. Fenske referred to Board discussion during the June 2007 HSRB meeting concerning the wide variety of qualifications of certified applicators and variations in the quality of supervision of those working with them. This prompted the Board to include a statement within the draft meeting report concerning inclusion of an appropriate number of non-certified handlers because these workers are likely to have the highest exposure levels. Mr. Carley agreed that Dr. Fenske's response clarified the Board's intent but noted that most handlers participating in the AHETF protocols will be non-certified. He agreed that the Board's statement concerning inclusion of non-certified handlers could remain, but that it should be clarified that this recommendation refers to AHETF protocols. Dr. Fenske suggested that for the HSRB Consensus and Rationale (p. 53, lines 35-44), a sentence could be added indicating that Board discussions at the June 2007 meeting focused on AHETF and that not all recommendations would apply to the AEATF.

On page 53, lines 31-33, "The Board recommended that the Agency develop a process whereby the critical variables associated with exposure are ranked, accompanied by an appropriate rationale and justification for the ranking." OPP's written comments requested clarification on whether the HSRB was suggesting that EPA define the process by which the task forces should identify and rank all critical variables and fully document their rationale and justification for the ranking. Dr. Fisher clarified that the Board believed a process would be needed, but did not want to define a specific process. Dr. Lebowitz added that if EPA wishes to use the data in the most optimal fashion, EPA should develop a process for identification, ranking, documentation, and justification of critical variables and should provide the Board with the rationale and documentation. This should be done before the exposure experiments are conducted. Dr. Fenske recommended that OPP be allowed some degree of flexibility in defining these activities. Mr. Carley commented that EPA believes strongly that the task forces should rationalize and document all critical factors included in designing sampling strategies. EPA plans to require this information in order for the data to be usable, but EPA is not interested in defining the actual process. Dr. Fisher suggested that the word "process" could be removed. Mr. Carley suggested recommending that EPA ensures that the critical variables associated with exposure are ranked and that justification for the ranking is described. Dr. Fisher agreed and added that this should occur prior to data collection and these activities should be performed by both task forces. The Board agreed to revise the sentence as follows: "For both AHETF and AEATF, the Board recommended that prior to data collection the Agency ensure critical variables associated with exposure are ranked…" Mr. Carley noted that the same sentence appears within the HSRB Consensus and Rationale (p. 53, lines 42-44). There were no further comments for the HSRB Consensus and Rationale (p. 53, line 35-44) other than revising the last sentence.

OPP's written comments pointed out that the HSRB Consensus and Rationale (p. 55, line 6) for the charge question regarding the need for scenario-specific information, the availability of data to identify significant variables potentially influencing exposure, and the

feasibility of developing a sampling strategy to address the variables quantitatively was not included in the draft meeting report. Dr. Fisher prepared a draft of this text and distributed it to the Board for review: "The Board recommended that the following information was necessary for it to provide its scientific advice:

- Scenario-specific information detailing variables that might influence exposure and its effect;
- A feasible sampling strategy including specifics of population to be tested (including its size), a list of relevant variables and how they would be collected and analyzed;
- Information on relationships between scenario-specific exposure assessment and the representative exposure in such scenarios in the target population;
- Essential environmental variables including site description, temperature, humidity, and wind levels as well as subjects' external clothing, work history and type of pesticide application;
- Relevant data on inter-subject variability; and
- A data analysis plan."

Dr. Fisher asked the Board members for comments on the proposed conclusion. No changes were suggested.

On page 56, lines 6-7, the meeting report states, "The sample size that we are concerned with in these studies is 25 and not 5 as is argued in the Governing Documents." OPP, in its written comments states, "OPP thinks the effective sample size of a 5 X 5 sampling design would be somewhere between 5 and 25. As described in Snijders and Bosker (p. 23), based on an ICC [intraclass correlation coefficient] of 0.3 (for sampling locations) the effective sample size is approximately 11 for this design." Dr. Carriquiry noted that the effective sample size of 11 appears to be correct; however, she felt OPP's written comment concerning the usefulness of random sampling for such a small sample size was incorrect. She believes random sampling is preferable to PDS for small samples. Dr. Carriquiry agreed to re-phrase this paragraph to address issues regarding the appropriateness of random sampling and to confirm that the sample size and 5 X 5 sampling design was appropriate. Dr. Carriquiry will submit the revised text to Drs. Fisher and Lewis.

OPP's written comments requested clarification of the phrase "conceptually large" (p. 56, lines 17-18). Dr. Carriquiry explained that "conceptually large" usually refers to infinity, which is described as 30 by statisticians; this refers to the number of purposive samplers, not the sample itself. She explained that the point of referring to a "conceptually large" number of purposive samplers was to imply that purposive sampling can be unbiased; this is true only if there are many purposive samplers and the data are averaged over their sample. Dr. Fisher agreed to clarify this sentence to read that "This is true if we have a large number of purposive samplers and average over them (central limits theorem)."

OPP's written comments requested clarification of the Board's conclusion that EPA's arguments regarding the cost of random sampling were not convincing and that use of random sampling would cost more than PDS. Dr. Carriquiry explained that, relative to the cost of collecting and analyzing the data, the difference in costs between using PDS versus random

sampling was not large. PDS is less costly, but the difference is not large relative to the cost of the entire study. Dr. Lewis agreed to add a line to this paragraph clarifying the Board's position on cost. Dr. Carriquiry noted that the Board was speculating about costs in the absence of relevant information and suggested that the task forces present cost estimates for both sampling strategies relative to other costs. Dr. Fisher interjected that she was unsure whether such a discussion would fall under the purview of the Board, but perhaps such issues could be discussed during the Board work group meeting at which sampling issues for the task forces will be discussed.

OPP's written comments questioned whether the Board's suggestions regarding random sampling (p. 56, lines 40-41) also applied to AEATF research. Dr. Carriquiry stated that the recommendations would be slightly different and offered to re-write recommendations for the AEATF. Dr. Lewis cautioned that it could be problematic to add new recommendations to the meeting report without Board discussion and approval. Dr. Carriquiry clarified that the recommendations would not be new, but would merely be re-phrased to apply to the AEATF (i.e., removing references to farming equipment). Dr. Fisher noted that purposive selection of locations (p. 56, line 42) would apply to AEATF, although counties or groups of counties would refer only to AHETF. She proposed deletion of "(e.g., counties or group of counties)" from the first bullet. The suggestion regarding farming operations (p. 56, lines 43-44) would apply only to AHETF. Board suggestions regarding stratification of producers by crop and size (p. 56, line 45), and random selection of producers (p. 57, lines 1-2) could be re-worked to apply to AEATF by changing "producers" to "operations" and by describing appropriate AEATF variables for stratification and selection. The Board agreed to change the fourth bullet as follows: "Randomly select operations and within operations, randomly select operators." Mr. Carley suggested use of the term "handler" rather than "operator." The Board agreed to this revision. In response to OPP's comment, the Board agreed to remove the last suggestion concerning focusing on fewer scenarios (p. 57, lines 3-4).

Regarding the Board's suggestion to randomly select producers within sub-stratum and randomly select handlers within producers, OPP's comments inquired how to cope with a low rate of response and limited pool of applicants. Dr. Carriquiry explained that the main sampling unit is the operation and that, within the operation, there may be one or two handlers; the main concern is whether the operation agrees to participate. Mr. Carley stated that previous task force experience suggests that random selection of operations will yield a response rate significantly lower than 10 percent. He asked the Board for guidance for coping with this expected low response rate. Dr. Carriquiry noted that the low response rate would affect both PDS and random sampling strategies; however, if PDS is used, operators known to be willing to participate will be chosen which raises significant selection bias issues. She added that a 10-percent response rate seems unusually low. Dr. Fisher clarified that both PDS and random sampling designs do not solve the issue of the low response rate, but random sampling may be able to provide a degree of variability that PDS cannot. Dr. Carriquiry explained that choosing operations using PDS may result in selection of sites that have characteristics different than other sites that may have been chosen using a random sampling design; this would decrease the representativeness of the results.

Mr. Carley recommended that the text within the meeting report stating that random sampling is no more costly than PDS (p. 56, lines 29-40) should be revised, in light of the Board's discussion during the teleconference concerning lack of information on costs; the sentence could be changed to indicate that random sampling may be no more costly than PDS. He re-iterated that EPA needs advice from the Board for coping with the expected low response rate. Dr. Lebowitz explained that random sampling avoids biases and assumptions and allows the data to be used more effectively for risk assessment activities. Dr. Fisher suggested that the report state that "random sampling is no more impractical and may be no more costly within the context of the costs of the whole study than PDS. Irrespective of response rate, random sampling provides more information regarding the representativeness of participating sites or operations." Dr. Carriquiry offered to add a sentence indicating that the Board wishes to consult with experts who have experience with low response rates. Dr. Fisher remarked that this subject should be addressed during the Board's work group discussions.

For the HSRB Consensus and Rationale (p. 57, lines 8-18), OPP's written comments inquired as to why exposure experiments for regulatory purposes should be based on random sampling. Dr. Lebowitz explained that risk assessments based on biased samples have been shown to be inaccurate and also have raised legal issues; EPA has been sued because of risk assessments derived from biased samples. The more representative the population from which risk assessment decisions are made, the more likely the risk assessment will be legally acceptable. Dr. Fisher agreed to add a statement indicating that risk assessments based on random samples tend to have less bias, are more informative, and defensible for regulatory purposes. Mr. Carley stated that although he understood this conclusion, the report does not indicate that the Board deliberated on this matter during the June 2007 HSRB meeting; he suggested adding information concerning this conclusion to the report. Dr. Lebowitz suggested adding a reference to a National Academy of Sciences report that described this issue. He agreed to send the reference to Dr. Lewis, who offered to place the reference in the meeting report. In addition, the Board agreed to change "will be used for regulatory purposes" to "will be used by EPA" and agreed to remove the word "particularly" from the sentence (p. 57, line 14).

Statistical Justification for Number of Clusters and Monitoring Units

On page 57, lines 39-40, the meeting report states: "In both programs, the purposive sampling is used to select clusters and MUs [monitoring units] within clusters, and as such the sampling of the clusters and the MUs within clusters is not random." In its written comments, OPP stated that the task forces propose purposive selection of the sites, but once a location is selected, the task forces will randomly draw subject from among the workers who volunteer; therefore, selection of MUs within a cluster is proposed to be random. Dr. Carriquiry explained that random selection of sites is important and subsequent selections are less important. For example, a state could be purposively selected, then operations randomly selected within the strata. Selection of monitoring units within a cluster also should be random. The Board agreed to revise the sentence as follows: "In both programs, the purposive sampling is used to select clusters; however, the sampling of MUs within clusters will be random." The Board determined that the remainder of the paragraph was correct.

On page 58, lines 26-28, the meeting report states: "As long as a cluster size of 5 is not exceeded, the same total number of MUs (N=25) will also achieve this same level of relative accuracy even if the number of MUs per cluster varies." OPP's written comments indicated that this statement did not appear to agree with the results of the task force simulations regarding variation in cluster sizes. Dr. Carriquiry explained that the number of MUs per cluster should be approximately equal, and suggested adding "slightly" to the end of the sentence. The Board agreed with this revision.

On page 59, lines 16-17, the draft meeting report states: "…the choice of only three clusters by the AEATF seems risky and it should be increased if at all possible." In its written comments, OPP indicated that the Board's conclusion in the draft report seems inconsistent with the Board's recommendations made during the June 2007 meeting. Dr. Carriquiry explained that the Board agrees that increasing the number of clusters is costly; however, if the task forces can afford it, increasing the number of clusters would be an effective way to increase sampling. She suggested removing the word "strong" from line 22 to emphasize that from an analysis point of view, increasing the number of clusters is desirable, but the Board is aware of cost limitations. She also suggested including OPP's comment regarding increased costs when adding more clusters. The following sentence will be added to the end of the paragraph (p. 59, line 24): "Costs increase if you have to rent more buildings instead of studying more subjects per building."

Regarding the HSRB Consensus and Rationale (p. 59, line 32-34), OPP's written comments stated that the Agency believes that the potential sampling bias is unknown and not measurable. The Board agreed with OPP's comment concerning the inability to measure bias and agreed to delete the following sentence from the meeting report: "Unless the surrogate sampling method of purposive sampling is changed to the more statistically appropriate clustered random sampling, the sponsors should consider monitoring the potential bias resulting from such surrogate sampling."

Within-Worker Variability

OPP's written comments stated that the Agency believes the "impact of ignoring the within-person variance" (p. 60, line 10) is modest and acceptable since the Agency is interested in the distribution of single-day exposures, not the distribution of usual exposures.

Dr. Carriquiry stated that if OPP is interested in only single-day exposure, a large number of workers would need to be monitored instead of repeated measurements of the same worker. She questioned OPP's need for single-day measurements rather than collecting data over many days to determine usual exposure. Dr. Janice Chambers questioned the ability to obtain repeated measurements of a worker if the exposure scenario would not be repeated, as may occur in some agricultural settings. Dr. Carriquiry stated that it would be desirable to average exposure over conditions (wind, temperature, etc.) because the exposure will change. Measuring exposure only on a single day determines exposure only for that set of conditions and is irrelevant from a policy point of view. Dr. Chambers noted that such repeat measurements require including similar scenarios, but random sampling will eliminate some of these scenarios. Dr. Fisher suggested recommending that repeat measures be collected for some workers to determine within-worker

variability for a subset of the handlers. If it is not possible to collect repeated measurements on the same person under the same conditions, time could be used as a repeated variable to determine if exposure remains consistent. Dr. Carriquiry argued for changing the sampling design rather than collecting information from the same conditions for different handlers. The variance of distribution will be higher than what it should be. She added that it is easier to increase the sample size than to increase the number of observations per worker. She recommended deleting lines 19-21 and 23-24 on page 60 of the draft meeting report. Dr. Fisher suggested adding to the sentence beginning on line 14, "If the objective of the study is to obtain an estimate of the mean exposure of workers in a given scenario *or to obtain an estimate of the one-day distribution of exposure*…" In line 36, the word "however" will be removed.

Based on OPP's comments, the Board agreed to delete the following sentence (p. 61, line 14): "The gain in information is likely to more than compensate for the increased cost." The Board also agreed to replace the word "replicate" (p. 61, lines 4 and 6) with "within-person repeated observations."

OPP's written comments pointed out that the HSRB Consensus and Rationale (p. 61, line 40) was not included in the draft meeting report. Dr. Fisher asked the Board members for suggestions on the conclusion for this issue. Dr. Carriquiry suggested that the Board recommend that the task forces collect data for as many handlers as cost will allow. Dr. Fisher suggested adding a statement indicating that the lack of choosing a within-person design is limiting if EPA wishes to obtain data on usual exposure; however, if EPA wishes to collect data on one-day exposure, their approach is not limiting, but the Board recommends that as many handlers as possible are observed.

Subject Recruitment and Enrollment Issues

OPP's written comments requested explanation of the basis for assuming vulnerability of many of the prospective subjects (p. 62, line 35). Dr. Menikoff clarified that, in this case, vulnerability referred to economic (i.e., working for an employer who wishes to participate in the study), educational, and language issues. Dr. Fisher proposed revising the beginning of the sentence as follows: "Give the language, economic and educational characteristics of the prospective subjects…" OPP's written comments also explained that many employers, such as farmers or an aerial application service, do not have as many as 50 employees who could participate in the study (p. 62, line 38). The Board agreed to lower the example of "25 out of 50" to "5 out of 10."

Dr. Fisher asked the Board members for comments on the HSRB Consensus and Rationale for this section (p. 62, lines 43-46). No changes to the text were suggested.

Summary and Next Steps

Dr. Fisher asked each Board member for their approval of the revised June 27-29, 2007 draft meeting report, including acceptance of the points of factual clarification and grammatical changes raised by OPP which were not discussed during the teleconference. All Board members in attendance at the teleconference meeting approved the report.

Dr. Lewis thanked Board members for their preparation for and participation in the conference call and for their work on the report. Dr. Lewis stated that he and Dr. Fisher will revise the report based on comments made during the teleconference. The revised report will be released at regulations.gov and posted on the HSRB Web site. The next face-to-face HSRB meeting is scheduled for January 15-18, 2008.

The meeting was adjourned by the Chair.

Respectfully submitted:

Paul I. Lewis, Ph.D.
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:

Celia B. Fisher, Ph.D.
Chair
Human Studies Review Board
United States Environmental Protection Agency

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by Board members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the Board members. The reader is cautioned to not rely on the minutes to represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final report prepared and transmitted to the EPA Science Advisor following the public meeting.

Attachments

Attachment A	HSRB Members
Attachment B	Federal Register Notice Announcing Meeting
Attachment C	Meeting Agenda
Attachment D	June 27-29, 2007 EPA Human Studies Review Board Meeting Proposed Final Draft Report

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

Celia B. Fisher, Ph.D.
Marie Ward Doty Professor of Psychology
Director, Center for Ethics 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

Alicia Carriquiry, Ph.D.
Professor
Department of Statistics
Iowa State University
Ames, IA

Gary L. Chadwick, PharmD, MPH, CIP*
Associate Provost
Director, Office for Human Subjects Protection
University of Rochester
Rochester, NY

Janice Chambers, Ph.D., D.A.B.T.
William L. Giles Distinguished Professor
Director, Center for Environmental Health Sciences
College of Veterinary Medicine
Mississippi State University
Mississippi State, MS

Richard Fenske, Ph.D., MPH
Professor
Department of Environmental and Occupational Health Sciences
University of Washington
Seattle, WA

Susan S. Fish, PharmD, MPH*
Professor, Biostatistics & Epidemiology
Boston University School of Public Health
Co-Director, MA in Clinical Investigation
Boston University School of Medicine
Boston, MA

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

Dallas E. Johnson, Ph.D.
Professor Emeritus
Department of Statistics
Kansas State University
Manhattan, KS

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

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

Michael D. Lebowitz, Ph.D.
Professor Emeritus of Medicine
University of Arizona
Tucson, AZ

Lois D. Lehman-Mckeeman, Ph.D.*
Distinguished Research Fellow, Discovery Toxicology
Bristol-Myers Squibb Company
Princeton, NJ

Jerry A. Menikoff, M.D.
National Institute of Health
Office of Human Subjects Research
Bethesda, MD

Rebecca Parkin, Ph.D., MPH
Associate Dean for Research and Public Health Practice
School of Public Health and Health Services
The George Washington University
Washington, DC

Sean Philpott, Ph.D., M.Bioethics
Policy and Ethics Director
Global Campaign for Microbicides
Program for Appropriate Technology in Health
Washington, DC

Ernest D. Prentice, Ph.D.*
Associate Vice Chancellor for Academic Affairs
Professor of Genetics, Cell Biology and Anatomy
Professor of Preventive and Societal Medicine
Omaha, NE

Richard R. Sharp, Ph.D.
Director of Bioethics Research
Department of Bioethics
Cleveland Clinic
Cleveland, OH

* Not in attendance at teleconference

Attachment B

Federal Register Notice Announcing Meeting

Human Studies Review Board (HSRB); Notification of Public Teleconference

[Federal Register: October 24, 2007 (Volume 72, Number 205)]
[Notices]
[Page 60361-60362]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]

ENVIRONMENTAL PROTECTION AGENCY
[EPA-HQ-ORD-2007-0403; FRL-8486-1]

Human Studies Review Board (HSRB); Notification of a Public Teleconference To Review Its Draft Report From the June 27-29, 2007 HSRB Meeting

AGENCY: Environmental Protection Agency (EPA).
ACTION: Notice.

SUMMARY: The EPA Human Studies Review Board (HSRB) announces a public teleconference meeting to discuss its draft report from the June 27-29, 2007 HSRB meeting.

DATES: The teleconference will be held on November 13, 2007 from 1 to approximately 3 p.m. Eastern Time.

Location: The meeting will take place via telephone only.

Meeting Access: For information on access or services for individuals with disabilities, please contact the Designated Federal Officer (DFO) at least 10 business days prior to the meeting using the information under **FOR FURTHER INFORMATION CONTACT**, so that appropriate arrangements can be made.

Procedures for Providing Public Input: Interested members of the public may submit relevant written or oral comments for the HSRB to consider during the advisory process. Additional information concerning submission of relevant written or oral comments is provided in Unit I.D. of this notice.

FOR FURTHER INFORMATION CONTACT: Members of the public who wish to obtain the call-in number and access code to participate in the telephone conference, request a current draft copy of the Board's report or who wish further information may contact Crystal Rodgers-Jenkins, EPA, Office of the Science Advisor, (8105), Environmental Protection Agency, 1200 Pennsylvania Avenue, NW., Washington, DC 20460; or via telephone/voice mail at (202) 564-5275. General information concerning the HSRB can be found on the EPA HSRB Web site at http://www.epa.gov/osa/hsrb/.

ADDRESSES: Submit your written comments, identified by Docket ID No. EPA-HQ-ORD-2007-0403, by one of the following methods:

Internet: http://www.regulations.gov: Follow the on-line instructions for submitting comments.

E-mail: ord.docket@epa.gov.

Mail: Environmental Protection Agency, EPA Docket Center (EPA/DC), ORD Docket, Environmental Protection Agency, Mailcode: 28221T, 1200 Pennsylvania Ave., NW, Washington, DC 20460.

Hand Delivery: The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Avenue, NW., Washington, DC. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding Federal holidays. Special arrangements should be made for deliveries of boxed information. Please contact (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for special instructions.

Instructions: Direct your comments to Docket ID No. EPA-HQ-ORD-2007-0403. EPA's policy is that all comments received will be included in the public docket without change and may be made available online at http://www.regulations.gov, including any personal information provided, unless the comment includes information claimed to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Do not submit information that you consider to be CBI or otherwise protected through http://www.regulations.gov or e-mail. The http://www.regulations.gov Web site is an "anonymous access" system, which means EPA will not know your identity or contact information unless you provide it in the body of your comment. If you send an e-mail comment directly to EPA, without going through http://www.regulations.gov, your e-mail address will be automatically captured and included as part of the comment that is placed in the public docket and made available on the Internet. If you submit an electronic comment, EPA recommends that you include your name and other contact information in the body of your comment and with any disk or CD-ROM you submit. If EPA cannot read your comment due to technical difficulties and cannot contact you for clarification, EPA may not be able to consider your comment. Electronic files should avoid the use of 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, especially studies on substances regulated by EPA, or to persons who are or may be required to conduct testing of chemical substances under the Federal Food, Drug, and Cosmetic Act (FFDCA) or the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). Since other entities may also be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Access Electronic Copies of This Document and Other Related Information?

In addition to using regulations.gov, you may access this **Federal Register** document electronically through the EPA Internet under the **Federal Register** listings at http://www.epa.gov/fedrgstr/.

Docket: All documents in the docket are listed in the http://www.regulations.gov index. Although listed in the index, some information is not publicly available, e.g., CBI or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, will be publicly available only in hard copy. Publicly available docket materials are available either electronically in http://www.regulations.gov or in hard copy at the ORD Docket, EPA/DC, Public Reading Room. The EPA/DC Public Reading Room is located in the EPA Headquarters Library, Room Number 3334 in the EPA West Building, located at 1301 Constitution Ave., NW., Washington, DC. The hours of operation are 8:30 a.m. to 4:30 p.m. Eastern Time, Monday through Friday, excluding Federal holidays. Please contact (202) 566-1744 or e-mail the ORD Docket at ord.docket@epa.gov for instructions. Updates to Public Reading Room access are available on the Web site (http://www.epa.gov/epahome/dockets.htm).

The June 27-29, 2007 draft HSRB meeting draft report is now available. You may obtain electronic copies of this document, and certain other related documents that might be available electronically at www.regulations.gov and the EPA HSRB Web site at http://www.epa.gov/osa/hsrb/. For questions on document availability or if you do not have access to the Internet, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

C. What Should I Consider as I Prepare 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.

D. How May I Participate in This Meeting?

You may participate in this meeting by following the instructions in this section. To ensure proper receipt by EPA, it is imperative that you identify docket ID number EPA-HQ-ORD-2007-0403 in the subject line on the first page of your request.

1. *Oral comments.* Requests to present oral comments will be accepted up to November 6, 2007. To the extent that time permits, interested persons who have not pre-registered may be permitted by the Chair of the HSRB to present oral comments at the meeting. Each individual or group wishing to make brief oral comments to the HSRB is strongly advised to submit their request (preferably via e-mail) to the person listed under **FOR FURTHER INFORMATION CONTACT** no later than noon, Eastern time, November 6, 2007, in order to be included on the meeting agenda and to provide sufficient time for the HSRB Chair and HSRB DFO to review the meeting agenda to provide an appropriate public comment period. The request should identify the name of the individual making the presentation and the organization (if any) the individual will represent. Oral comments before the HSRB are limited to 5 minutes per individual or organization. Please note that this includes all individuals appearing either as part of, or on behalf of an organization. While it is our intent to hear a full range of oral comments on the science and ethics issues under discussion, it is not our intent to permit organizations to expand these time limitations by having numerous individuals sign up separately to speak on their behalf. If additional time is available, there may be flexibility in time for public comments.

2. *Written comments.* Although you may submit written comments at any time, for the HSRB to have the best opportunity to review and consider your comments as it deliberates on its report, you should submit your comments at least 5 business days prior to the beginning of this teleconference. If you submit comments after this date, those comments will be provided to the Board members, but you should recognize that the Board members may not have adequate time to consider those comments prior to making a decision. Thus, if you plan to submit written comments, the Agency strongly encourages you to submit such comments no later than noon, Eastern Time, November 6, 2007. You should submit your comments using the instructions in Unit 1.C. of this notice. In addition, the Agency also requests that person(s) submitting comments directly to the docket also provide a copy of their comments to the person listed under **FOR FURTHER INFORMATION CONTACT**. There is no limit on the length of written comments for consideration by the HSRB.

E. Background

The EPA Human Studies Review Board will be reviewing its draft report from the June 27-29, 2007 HSRB meeting. Background on the June 27-29, 2007 HSRB meeting can be found at 72 FR 31323 (June 6, 2007) and at the EPA HSRB Web site http://www.epa.gov/osa/hsrb/. The Board may also discuss planning for future HSRB meetings.

Dated: October 18, 2007.
Elizabeth Lee Hofmann,
Deputy Director, Office of the Science Advisor.
[FR Doc. E7-20953 Filed 10-23-07; 8:45 am]
BILLING CODE 6560-50-P

Attachment C

11/7/07

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD (HSRB)
PUBLIC TELECONFERENCE MEETING
NOVEMBER 13, 2007
1:00 pm -3:00 pm (Eastern Time)

HSRB MEETING FOR REVIEW AND APPROVAL OF
DRAFT JUNE 27-29, 2007 HSRB MEETING REPORT *
HSRB WEB SITE http://www.epa.gov/osa/hsrb/
Docket Telephone: (202) 566-1752
Docket Number: EPA-HQ-ORD-2007-0403
Meeting location via telephone only
Members of the public may obtain the call in number at (202) 564-5275

1:00 PM **Introduction and Identification of Board Members** – Celia Fisher, Ph.D. (HSRB Chair)
1:10 PM **Meeting Administrative Procedures** – Paul Lewis, Ph.D. (Designated Federal Officer, HSRB, OSA, EPA)
1:15 PM **Meeting Process –** Celia Fisher, Ph.D. (HSRB Chair)
1:20 PM **Public Comments**
1:30 PM **Board Discussions and Decision on Report –** Celia Fisher, Ph.D. (HSRB Chair)

A. Proposed Carroll-Loye Picaridin Insect Repellent Efficacy Study LNX-001

1. 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?

2. 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

1. 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?

2. 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

1. 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.

2. Please comment on the following:
    a) Is there clear and convincing evidence that the conduct of the study was fundamentally unethical?
    b) Is there clear and convincing evidence that the conduct of the study was significantly deficient relative to the ethical standards prevailing at the time the research was conducted?

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

1. 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.

2. Please comment on the following:
    a) Is there clear and convincing evidence that the conduct of any of the three clinical studies (Segal et al., 1999; Grijalva et al., 2003; Van Diemen et al., 1993) was fundamentally unethical?
    b) 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. Design of Research on the Levels of Exposure Received by Pesticide Handlers

<u>Risks and Benefits of Handler Research</u>

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?

Addressing Potential Sources of Underestimation Bias

1. 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?

2. 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?

QA and QC Controls

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?

Design of scenario-level sampling strategies

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

1. 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?

2. 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?

3. 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?

Statistical justification for number of clusters and monitoring units

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?

Within-Worker variability

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?

Subject recruitment and enrollment issues

1. 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?

2. 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?

2:45 PM **Summary and Next Steps –** Celia Fisher, Ph.D. (HSRB Chair) and Paul Lewis, Ph.D. (Designated Federal Officer, HSRB, EPA)

3:00 PM **Adjournment**

*Please be advised that agenda times are approximate. For further information, please contact the Designated Federal Officer for this meeting, Crystal Rodgers-Jenkins via telephone: (202) 564-5275 or e-mail: rodgers-jenkins.crystal@epa.gov.