Excerpt from the HSRB Final Report of the June 2009 Meeting (report dated 10-26-09)

p. 32 **Assessment of Proposed AHETF Scenario and Protocol AHE-120: Water-Soluble Packing Mixing and Loading.**

Overview of the Study

This proposal presents an agricultural handler exposure scenario involving mixing/loading of pesticides enclosed in water-soluble packets (WSP). The protocol calls for study participants to mix and load one of two WSP-enclosed surrogate pesticides (acephate and carbaryl) into a variety of tanks containing water in a variety of agricultural spraying operations. A total of 25 participants (described in the protocol as "Monitoring Units" [MUs]) will be observed; 5 volunteers each from five different growing regions will be enrolled using a purposive sampling method.

Dermal exposure will be measured by a whole body dosimeter (WBD) worn beneath the subject's outer clothing. Hand wash and face/neck wipe samples will also be collected prior to, during, and after completion of pesticide loading and mixing procedures. Airborne concentrations of the surrogate will be monitored in the participant's breathing zone using an OSHA Versatile Sampler (OVS) tube sample collector connected to a personal sampling pump. Additional measures will also record environmental conditions at the time of monitoring, and observers will make field notes, photographs and videos of participant activity throughout the monitoring event.

p. 33 The results of sample analysis under the mixing/loading of water-soluble packets scenario, will be posted to the AHED® database, where they will be available to the EPA and other regulatory agencies for statistical analysis. The proposed documentation will report a confidence-interval-based approach to determine the relative accuracy for the arithmetic mean and 95th percentile of unit exposures. The Agency proposes to use these data to estimate daily dermal and inhalation exposures of agricultural handlers who are mixing/loading pesticides in water-soluble packets under a variety of mixing and loading scenarios.

Science

Charge to the Board

If the proposed mix/load WSP field study protocol AHE120 is revised as suggested in EPA's review and if the research is performed as described: Is the research likely to generate scientifically reliable data, useful for assessing the exposure of handlers who mix and load soluble or wettable powder pesticides in water-soluble packaging?

Board Response to the Charge

HSRB Recommendation

Given the lack of existent reliable and sound data in this area, the Board concurred with the Agency's assessment (Evans and Sherman 2009) that this protocol will generate data that are scientifically valid and that *may* be useful for assessing the exposure of handlers who mix and load soluble or wettable powder pesticides in water-soluble packaging. The Board cautioned that these data are likely to be useful for creating distributions of worker exposure only if worker exposure is found to be proportional to the amount of active ingredient handled (AaiH).

The Board also recommended a number of protocol modifications, as listed below. Additional Board review of the protocol is not required prior to study implementation.

HSRB Detailed Recommendations and Rationale

The Board concluded that the proposed monitoring and quality assurance and control methods appear adequate, particularly in the supplemental SOPs provided by the AHETF in response to the Agency's initial science and ethics review (Collier 2009b; Evans and Sherman 2009). The protocol and supplemental SOPs adequately address a number of key scientific issues, including: the scientific objective, the quantification of the test materials, the data collection and compilation methods and summary of test results, the justification for selection of the test substances, and the QA/QC requirements. The Board also commended the AHETF and the Agency for taking the time to plan, test, and revise different scenarios and approaches, and for pilot testing some aspects of these and related protocols. The protocol presented to the Board was well thought out and written as a result.

p. 34 The Board did raise a number of concerns, however, about the perceived inadequacies in the study design, including issues of sample size and the use of inappropriate statistical analyses. The Board raised many of these issues previously when it reviewed earlier AHETF protocols. Both the AHETF and the Agency will need to acknowledge the limitations of the study design that occur in the AHETF handling scenarios and either change their goals accordingly, or add appropriate statistical methods or data management approaches to extrapolate from the data obtained from these limited scenarios to the wider regulatory purposes that these data will be used for. Some Board members expressed the concern, for example, once these data are inside the AHED® database, some users may overlook the limitations of the original study design and use the data to generate the typical statistical distributions in error.

Illustrating this point, the Board raised concerns about the types of statistical analyses proposed for the water-soluble packing scenario presented here. The proposed study will rely on a purposive sampling strategy, for example, but the researchers propose to treat the monitoring data as if "it were collected as a two-stage random sample from an infinite population" (Collier 2009a). The Board questioned the validity of this approach, noting that the data will be collected from a non-random non-population based sample. There is no statistical theory that can be applied to non-random samples of this type. Thus, the statistical analyses proposed, including mixed model approaches, are not valid.

The Board also raised concerns about the key objective of the study – namely, to determine the relationship between measured worker exposure and AaiH. In particular, the Board

disagreed with the Agency's assessment that "past studies have shown that AaiH is strongly associated with exposure and is a meta-factor associated with differences in equipment and spraying practices" (Evans and Sherman 2009). To expect a linear relationship between AaiH and worker exposure seems logical; one should expect that a consistently small fraction of the amount of pesticide that a worker handles would be deposited onto their skin. Data previously presented by the AHETF to the Agency's FIFRA Scientific Advisory Panel (SAP), however, did not demonstrate a linear relationship between worker exposures of the amount of active ingredient handled. There are a number of factors that may explain why there is not a clear linear relationship between measured worker exposure and AaiH, including ecological, engineering, and statistical factors. As submitted, the AHETF protocol will not be able to distinguish between these different factors nor allow researchers to determine the true relationship between exposure and AaiH. For example, there are a number of uncontrolled ecological variables that may influence worker exposure, including: environmental conditions, the types of equipment used, the types of crops treated, grower preferences, etc. Indeed, some workers will likely experience mixing and loading conditions that are atypical for normal use of the active ingredient being monitored. Myriad sources of natural variation are likely to have a marked impact on worker exposure. Given the relatively small sample size of each monitoring cluster in this exposure scenario, these sources of natural variation will likely introduce considerable estimation bias into the final data.

Finally, current consensus is that estimates of the geometric mean, the arithmetic mean, and the 95th percentile need to be accurate within three-fold of the actual population value. The current protocol includes no methods to validate the actual population data and determine whether the resulting estimates fall within this necessary range.

p. 35 ***Ethics***

Charge to the Board

If the proposed mix/load WSP field study protocol AHE120 is revised as suggested in EPA's review and if the research is performed as described: Is the research likely to meet the applicable requirements of 40 CFR part 26, subparts K and L?

Board response to the Charge

HSRB recommendation

The Board concluded that the protocol submitted for review, if modified in accordance with EPA (Evans and Sherman 2009) and HSRB recommendations, is likely to meet the applicable requirements of 40 CFR 26, subparts K and L.

HSRB Detailed Recommendations and Rationale

The submitted documents assert that the study will be conducted in accordance with the ethical and regulatory standards of 40 CFR 26, Subparts K and L, as well as the requirements the US EPA's GLP Standards described at 40 CFR 160 (Collier 2009a). The requirements of FIFRA

§12(a)(2)(P) and, where applicable, the California State EPA Department of Pesticide Regulation study monitoring (California Code of Regulations Title 3, Section 6710) also apply. The protocol was reviewed and approved by an independent human subjects review committee, IIRB, Inc. of Plantation, FL prior to submission.

1. The Board concurred with the conclusions and factual observations of the ethical strengths and weaknesses of the study, as detailed in the EPA's Ethics Review (Evans and Sherman 2009). The proposed study is likely to meet the applicable ethical requirements for research involving human participants, in accordance with the following criteria:

    a. *Acceptable risk-benefit ratio*. The risks as noted in the study protocol are five-fold: 1) heat-related illness; 2) accidental exposure to the surrogate chemicals; 3) injury associated with scripted field activities; 4) allergic reaction to surfactants using for hand washing; and 5) psychological stress and/or breach of confidentiality for pregnancy test results. These risks are minimized appropriately and are justified by the potential societal benefits, particularly data on occupational exposure of agricultural workers to pesticides during mixing and loading activities.

    - The greatest risk to participants is that of heat-related illness, given that the participants will be required to wear two layers of clothing during the scenario activities. This risk is lessened but not eliminated by the application of appropriate stopping rules (including cessation of all monitoring activities when the ambient heat-index exceeds 105°F) and frequent monitoring of participants. Participants will be given frequent breaks, access to ample amounts of water or sports drinks, and educated about the dangers and symptoms of heat-related illness. Appropriate medical management procedures are also in place.

p. 36

    - The surrogate materials consist of two common pesticides, acephate and carbaryl, both of which have been extensively tested. The participants will only be exposed to concentrations of the surrogate compound at accepted exposure thresholds.

    - Participants will be selected from volunteers with experience handling these or similar compounds in WSP mixing and loading scenarios. Thus, all of the participants will have extensive experience in using these or similar products, and thus unlikely to misuse them in a way that might increase their likelihood of being accidentally exposed.

    - Participants will be reminded about safe handling practices and procedures, wear appropriate PPE, and will be monitored for any accidental or unintended product exposure.

    - Allergic reactions to the surfactants used in hand washing are usually mild and easily treated with over-the-counter steroidal creams. The study will exclude participants who have a history of severe skin reactions to such detergents.

- Minor and pregnant or lactating women are excluded from participation, with pregnancy either confirmed by over-the-counter pregnancy testing on the day of study or by opt-out. The potential stigma resulting from study exclusion due to pregnancy is also appropriately minimized.

b. *Voluntary and informed consent of all participants*

- There is the possibility that the participants in this study might represent particularly vulnerable populations, susceptible to coercion and undue influence. The study protocol, however, includes several mechanisms designed to minimize coercive recruitment and enrollment.

- Monetary compensation is not so high as to unduly influence participants.

- Spanish translations of the informed consent documents, informational packets, and recruitment flyers were provided. Researchers will be working with local Spanish-speaking community members to ensure that the appropriate regional dialect of Spanish is used.

c. *Equitable selection of study participants*

- The study is designed to recruit an appropriately diverse population of participants who represent skilled agricultural workers in the 5 study locations.

p. 37

- Community representatives and advocates are appropriately involved in the recruitment and enrollment of study participants.

2. The Board recommended that the study protocol be modified to address the few concerns noted in the EPA's Ethics Review (Evans and Sherman 2009). In addition, the Board also addressed three concerns of the Agency and the sponsors (Collier 2009c) with respect to representativeness, language, and release of individual exposure data.

- The Board recommended that the AHETF implement the proposed protocol changes designed to address issues of representativeness.

- As noted above, the Board concluded that the proposed protocol changes designed to address concerns of language in the informed consent and related documents are likely to yield translations that are written in the appropriate regional dialect of Spanish.

- The Board commended the Task Force for wanting to release individual exposure data to participants promptly but recommended that these data only be released once the study is complete, except in those instances where data collected from individuals suggest an unusually high level of exposure and thus a clear need to mitigate exposure risks.