25 June 2008 Final Report of the April 9-10, 2008 EPA Human Studies Review Board Meeting: Discussion of AEATF-II Mop and Wipe Scenarios. Pages 16-27.

p. 16 **EPA Review of AEATF-II Mop and Wipe Scenarios** (due to similarities of the mop and wipe scenarios, both exposure scenarios were reviewed together)

p. 17 Science

Charge to the Board

If the proposed research described in AEATF's proposed mop scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by mopping?

If the proposed research described in AEATF's proposed wipe scenario designs, protocol, and supporting documentation is revised as suggested in EPA's review, does the research appear likely to generate scientifically reliable data, useful for assessing the exposure of handlers who apply an antimicrobial pesticide by wiping?

Board Response to the Charge

The two proposed human studies focus on handlers during floor mopping or surface wiping with a liquid antimicrobial pesticide product to determine potential dermal and inhalation exposures. The studies are (1) AEA03, "A Study for Measurement of Potential Dermal and Inhalation Exposure During Application of a Liquid Antimicrobial Pesticide Product Using Bucket and Mop Equipment for Cleaning Indoor Surfaces," and (2) AEA02, "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." The protocols associated with these studies have many similarities. The Board's comments were therefore very similar for the two studies. All comments below can be applied to both studies, unless otherwise noted.

Study Objective

AEATF II stated that the primary purpose of the handler studies is to develop more accurate information on worker exposures to antimicrobials. AEATF II also presented information to indicate that existing human exposure data are inadequate. The Board concurred that existing data are inadequate and that the development of more accurate information is an appropriate goal.

Benefits and Risks

The Board concurred with the Agency that the generation of new data for mop and wipe activities would be of value in the assessment of risks for antimicrobial products. The Board concurred with the Agency that there are only minimal risks associated with the application of a

dilute solution of didecyl dimethyl ammonium chloride (DDAC) as described in the study protocols.

Study Design Criteria

The Board was pleased by the amount of randomization included in the design of these studies. The investigators and the Agency have indicated that they are interested in knowing the statistical distribution of the exposure level, with an acceptable bound for the relative accuracy of
p. 18 the estimated mean and 95 percentile. In both AEA03 (mop) and AES02 (wipe) studies, the same set of three sites will be used as clusters, each representing a random sample of one for three different types of buildings. In order to understand the spectrum of exposure, six volunteers will be randomly selected to fill each of six consecutive time durations. This configuration of three clusters of six handlers for each cluster is based on a simulation study under two-stage cluster sampling with an intra-class correlation coefficient of 0.3 and a geometric standard deviation (GSD) of 2.86. The sample size justification depends on these design parameters.

In an earlier mop study, conducted by the Chemical Manufacturers' Association (CMA), the estimated GSD was 3.53. It therefore appeared to the Board that the proposed AEA03 study design would not ensure three-fold relative accuracy (K=3) for the resulting estimated mean and the 95 percentile of the exposure distribution. Furthermore, in an earlier CMA wipe study the estimated GSD was 5.00, much larger than 2.86 assumed in the simulation study that was used to derive the sample size justification. Again, it appeared unlikely to the Board that the AEA02 study design would produce a three-fold relative accuracy for the resulting estimated mean and the 95 percentile of the exposure distribution.

The Board also noted that the stratified nature of selecting a cluster from each of three types of sites makes it impossible to assess the variability of exposure distribution from site to site. Likewise, because of the stratified nature of selecting one handler for each of six mopping/wiping durations, one cannot estimate the exposure distribution. The experimental design can be viewed as consisting of 18 design points with 18 data points, resulting in no degrees of freedom for estimation of variability as there are no replications at any design point. In light of these concerns, the Board recommended that the Agency reconsider the design of the study, or develop an explicit statement of the limitations on the use of data that will be collected under the proposed design.

Site selection

The studies will take place in Fresno, California, in three buildings: an office building, a retail building, and a building with large meeting spaces. The way in which the clusters have been defined suggests that they represent a fixed effect factor (i.e., building type) rather than a random effect factor. The proposed study design will not replicate this fixed effect by having more of than one building of each type. The Board acknowledged the practical considerations that led to the decision to have both studies in the same city, using the same buildings. However, it must be realized that any generalizations to moppers and wipers in other parts of the country and in other kinds of buildings would be based on expert opinion, and that such generalizations

would not be statistical generalizations. Nevertheless, the Board concurred with the Agency that some generalizations from these data would seem to be reasonable at this point in time.

Sample size

p. 19 The proposed sample size of 18 observations for each scenario did not appear to have a statistical justification, as indicated above. The Board was concerned about recommending this sample size and the 3x6 design (three sites, six workers per site) on which it is based. The concern is that all that all future scenario designs for the AEATF- II program are likely to have three clusters and six time durations, with the justification being the Board's recommending these protocols. The Board has seen this happen with insect repellency studies repeatedly. That is, a new protocol has justified its sample size by reference to a previously submitted protocol. The adequacy of the proposed sample size for future studies will be informed by the data collection and analysis of this first set of studies. In general, the Board will not consider a new protocol that has justified its sample size by reference to a previously submitted protocol.

Task duration

AEATF-II's protocol for mopping proposed that handlers mop for a maximum of 90 minutes. This value was derived from a survey conducted by the International Sanitary Supply Association (ISSA). AEATF-II calculated an average mopping duration to 83 minutes from the ISSA study data. The Board understood that this value was calculated in the following manner:

- ISSA data indicated that handlers spend, on average, 12 minutes to mop 1000 square feet.
- It was assumed that a hospital room consists of a 240 square feet (12x20) main room and a 36 square foot (6x6) bathroom for a total floor area of 276 sq ft.
- It was assumed that a worker would mop 25 such rooms for a total of 6,900 sq feet.
- Thus, 6900 square feet x 12 minutes per 1000 square feet = 82.8 minutes

A similar calculation was made for the wipe scenarios, resulting in an estimated average wiping time of 212.75 minutes.

The Board concluded that the task duration time frame was not adequate to characterize daily exposure. The Board recommended that the work time frame be expanded to exceed the 95th percentile of the ISSA survey findings.

The Board also noted that the lengths of mopping (or wiping) would be consistently tested from the longest time period to the shortest time period for each site. For this to be a valid approach, one must be willing to assume that there is no "carry-over" effect from one testing period to another. One factor that could lead to a carry-over effect would be whether residues from earlier mopping (or wiping) could affect the measurements on later study participants, especially respiratory effects. The Board recommended that these concerns be reflected in the protocols.

The Board found the explanation of potential analyses that the Agency would conduct based on these studies to be very helpful. A basic assumption for these analyses is that the distribution of exposure/unit handled is the same regardless of the number of active ingredient (Ai) units handled or the time spent mopping (or wiping). However, the mean exposure/Ai unit
p. 20 and/or variance of the exposure/unit is likely to increase with the number of units due to fatigue. This assumption could be at least partially checked by plotting exposure/Ai unit by Ai unit, though such an analysis might conflict with the second analysis identified: the assessment of the assumption of proportionality. A regression would likely be conducted for this second analysis. If the distribution of exposure/unit handled were constant or increased with the number of units handled and proportionality was demonstrated, then both the mean and the variance would be expected to increase with the number of units handled. In simple linear regression, the variance is assumed to be constant for all values of x. Thus, a weighted regression, not a simple linear regression would be needed. Because the protocol does not ensure that there will be replication of exposures for the same number of units, whether a simple or weighted regression would be more appropriate could not be fully evaluated. If, instead of time, the number of Ai units handled were the measure that defined each person's participation, the data would more likely lend themselves to a proper assessment of the assumption of proportionality.

Participation Criteria

AEATF plans to recruit subjects from among identifiable and willing professional janitors. A rationale for this decision was provided. AEATF also assumes that these professionals would have higher exposures than consumers. One Board member expressed the view that professionals have substantial experience and perhaps training in how to minimize exposure, and that consumers might have higher exposures per Ai unit handled. AEATF-II plans to recruit subjects through service providers. The Board suggested that unions also be considered in the development of the recruitment procedures.

Measurement Criteria

The Board noted that inhalation exposure from vapors would likely be low in these studies due to the relatively low volatility of the active ingredient used in the scenarios. However, the extent to which liquid aerosols generated in the mop protocol would contribute to aggregate exposure is not known. It was not clear what particle size range was expected to be generated in these studies, nor was it clear what particle size range would be captured by the sampling method. The Board suggested that a laboratory study that measured aerosol size under varying environmental conditions would be helpful in clarifying these uncertainties.

The following are key variables that will have an effect on inhalation exposure:

- Ventilation
- Temperature
- Total area treated
- Duration
- Volume of the enclosed space

The protocols state as follows: “light level, air temperature, and relative humidity of the work area for the duration of exposure monitoring will be documented with automated instrumentation logging and recording at intervals appropriate for the duration of the work period. Monitoring equipment will be calibrated or standardized according to the cooperating
p. 21 contractors’ SOPs. HVAC will be described in detail and the air turnover rate will be measured or estimated.” The Board recommended that the equipment and procedures used to characterize these environmental factors be described in greater detail, either in the protocols or in the SOPs. The Board also asked investigators to explain how the effects of such factors as ventilation, temperature and the volume of the enclosed space would be used to modify or interpret study results.

AEATF-II proposed to use dermal exposure assessment methods similar to those used by the Agricultural Handler Exposure Task Force studies; i.e., cotton garments on most of the body, handwashing, and face/neck wiping. As in its previous reports, the Board noted that these methods have the potential to underestimate exposure. The Board supported the use of a double layer of socks to capture potential exposure from spills or splashes.

Laboratory and Field Conditions

The Board considered the quality assurance and quality control procedures that accompanied these protocols to be of high quality. The Board appreciated the attention to detail provided by the investigators.

The Board raised several concerns regarding field conditions.

These studies will use DDAC, contained in the product Sani-Care Lemon Quat™ as the chemical of interest. The Board agreed that the choice of DDAC as the antimicrobial material for these studies was appropriate, given its wide use, availability, and the existence of a reliable and sensitive analytical method.

The Board encouraged the Agency and the investigators to ensure that work activities be as realistic as possible. For example, a worker should use a bucket of the disinfectant solution until it becomes dirty; the worker should then empty the bucket and pick up a fresh bucket. All of this could be done without the involvement of study staff. In general, the Board viewed the activities of the study staff described in the current protocols to be too disruptive of “usual practices”. The Board recommended that the protocols be revised to provide a more detailed description of what the workers will actually do, and that the presence of staff during the exposure period be kept to a minimum.

The Board was also concerned with what is sometimes called the “Hawthorne Effect”. That is, workers will change behavior consciously or unconsciously when they are aware that they are being observed. The current protocols indicate that there will be constant surveillance of workers, including video recording. The Board urged the Agency and the investigators to minimize these observations and to train staff to be as unobtrusive as possible.

Finally, the Board requested that the protocol provide more specificity as to where study subjects will be located while waiting to participate in the study. There was a concern that observation of some study subjects by other study subjects could alter behavior.

HSRB Consensus and Rationale

p. 22 The Board considered the AEATF-II study protocols to successfully address many design challenges. The Board appreciated particularly the clarity of the protocols, the attention to detail, and the thorough description of quality assurance and quality control procedures. The Board concurred with the Agency that existing data on handler exposures to antimicrobials are inadequate and that the development of more accurate information is an appropriate goal. The Board also concurred with the Agency that there are only minimal risks associated with the application of a dilute solution of didecyl dimethyl ammonium chloride as described in the study protocols.

While the Board concluded that the research could produce scientifically reliable data, the Board identified several contextual factors that may limit the generalizability of the findings. The Board recommended that the Agency reconsider the design of the study, or develop an explicit statement of the limitations on the use of data that will be collected under the proposed design. The Board noted that any generalizations to moppers and wipers in other parts of the country and in other kinds of buildings would be based on expert opinion, and that such generalizations would not be statistical generalizations. The Board cautioned the Agency regarding the 3x6 design in the protocols, suggesting future scenario designs for the AEATF- II program would likely have three clusters and six time durations, with the justification being the Board's recommendation of these protocols. The Board concluded that the task duration time frame was not adequate to characterize daily exposure. The Board recommended that the work time frame be expanded to exceed the 95th percentile of the International Sanitary Supply Association survey findings. The Board noted that if, instead of time, the number of Ai units handled were the measure that defined each person's participation, the data would more likely lend themselves to a proper assessment of the assumption of proportionality.

In regard to inhalation exposure assessment, the Board suggested that a laboratory study that measured aerosol size under varying environmental conditions would helpful in clarifying uncertainties regarding particle size and sampling methods. The Board raised several concerns regarding the field conditions for these studies: ensure that any carry-over effect in buildings is avoided; ensure that work activities be as realistic as possible; revise protocols to provide a more detailed description of what the workers will actually do; keep the presence of staff and intrusive observation of workers during the exposure period to a minimum; and, provide more specificity as to where study subjects will be located while waiting to participate in the study..

Finally, the Board encourages modifications of future related protocols based on the lessons learned from these initial submissions. Such adjustments are anticipated to improve the study design and subsequent results, leading to a more accurate characterization of pesticide handler exposure.

Ethics

Charge to the Board

p. 23 If the proposed research described in AEATF's proposed mop scenario design, protocol, and supporting documentation 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?

If the proposed research described in AEATF's proposed wipe scenario designs, protocol, and supporting documentation 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?

Board Response to the Charge

Brief Overview of the Studies

Each of these scenarios (mop and wipe) has been designed to develop data for a database of exposure monitoring information which will be used by the EPA for making regulatory decisions about future exposures to a variety of antimicrobial products and their active ingredients. The sponsor of both scenarios is the Antimicrobial Exposure Assessment Task Force II (AEATF-II) of the American Chemistry Council. The scenarios will be conducted on behalf of that entity by Golden Pacific Laboratories, LLC, of Fresno, California. For each of the scenarios, there will be three field sites in Fresno, California.

According to the protocols, these studies are intended to comply with the ethical standards contained in 40 CFR Part 26, subparts K and L, in addition to the requirements of FIFRA § 12(a)(2)(P), and Title 3, § 6710 of the California Code of Regulations. Both scenarios were reviewed and approved by a commercial IRB, the Independent Investigational Review Board, Inc. (IIRB, Inc.) of Plantation, Florida.

For each scenario, the protocols include detailed explanations of how the buildings in which the scenarios take place will be chosen, how the subjects will be recruited, how the informed consent of those subjects will be obtained, and what will take place during the conduct of the scenarios.

Each of the protocols requires that the subjects be at least 18 years of age, and they exclude female subjects who are pregnant or lactating.

The test substance that will be used in both scenarios is diluted Sani-Care Lemon Quat. Its two active ingredients are didecyl dimethyl ammonium chloride (DDAC) and n-Alkyl dimethyl benzyl ammonium chlorides (ADBAC).

Critique of Studies

The Board concurred with the factual observations of the ethical strengths and weaknesses of the studies, as detailed in the EPA's Science and Ethics Reviews (Carley 2008a and 2008b).

In general, the research described in these two protocols appears to comport with the applicable requirements of 40 CFR Part 26, subparts K and L. The risks to study participants,
p. 24 in general, will be minimal and would appear to be justified by the likely societal benefits, specifically the production of data that could be used by the EPA in determining acceptable exposures to antimicrobial products used in certain mopping and wiping activities.

The test compound contains two active ingredients, DDAC and ADBAC, both of which have been extensively tested in animals. The subjects will only be exposed to concentrations of the test compound at the label dilution rates. At those dilutions, animal testing has shown the compound to have low acute toxicity and a low chronic hazard profile. Both of the active ingredients have already been approved by the EPA for use in many formulations, and in many janitorial products. In addition, the test compound itself, Sani-Care Lemon Quat, has been approved by the EPA, and will only be used in the scenarios in conformity with its approved labeling. All of the subjects will be professional janitors with extensive experience in using these products, and thus unlikely to misuse them in a way that might increase their likelihood of being harmed.

Although the risks to subjects from exposure to the test compound appear very low, it should be noted that in terms of the purposes of these scenarios, it is not actually necessary that subjects be exposed to an antimicrobial product. The scenarios are intended to measure only the amount of skin, clothing and inhalation exposure when someone is engaged in certain activities relating to applying an antimicrobicide. They are not measuring the actual effects to the test subject from that exposure. Thus, it might be possible to design scenarios in which instead of an antimicrobicide, some less toxic tracer substance might be used. It would be appropriate for protocols to discuss this possibility for further minimizing risks, and to indicate why (if it is true) such an option would not allow the needed information to be collected.

Another possible risk is that of heat-related illness, given that the subjects will be required to wear two layers of clothing during the scenario activities. That risk is being minimized by the fact that those activities will take place indoors in temperature-controlled environments. In addition, subjects will be given appropriate breaks. The breaks will not only minimize the likelihood of heat-related illness, but also reduce the likelihood of cardiovascular harms.

With regard to subject selection, EPA observed that “[n]o potential subjects are from a vulnerable population” (Carley 2008a and 2008b). In this regard, it should be noted that 45 CFR § 46.111(b) states that “economically or educationally disadvantaged persons” may constitute a vulnerable population. Accordingly, given that this study is recruiting from a population of individuals who may not have substantial education, who may be relatively disadvantaged from an economic viewpoint, and many of whom may not speak or read English, it would be appropriate not to dismiss the possibility that the subjects in this study might be vulnerable to coercion and undue influence, but rather to instead recognize that there are sufficient safeguards in the design of the study to protect the subjects, even if they are vulnerable.

The study protocols included several mechanisms designed to minimize coercive recruitment and enrollment, including the fact that subjects were not recruited directly from their employers, but instead would themselves respond to flyers that have been posted.

p. 25 Compensation was not considered to be so high as to unduly influence participation, and minors and pregnant or lactating women were explicitly excluded from volunteering (pregnancy being confirmed by requiring all female volunteers under the age of 50 to undergo a urine pregnancy test). The potential stigmatization resulting from study exclusion was minimized by the use of so-called 'alternate' participants, allowing for volunteers to withdraw or be excluded from participating without unduly compromising their confidentiality.

With regard to the eligibility criteria, the Board believes that the requirement for females under the age of 50 to take a pregnancy test could be refined. It would be possible to design criteria that created a better fit between which female subjects might be able to get pregnant, and which of them are being asked to take that test. By doing this, the researchers would be showing greater respect for this group of subjects.

The protocol might provide a greater justification for why subjects older than 65 are excluded.

Most of the issues raised by the Board relate to informed consent and recruitment. With regard to the consent forms, as a general matter, given the population from which subjects are being recruited, it would be appropriate to make sure that the consent forms are at an appropriate level of readability. In at least some places, there appears to be room for further simplification.

The consent forms do not appear to describe adequately the procedures discussed in the protocol relating to (a) still photography of the subjects, (b) videotaping of the subjects, and (c) observation of the subjects by members of the study team. All of these procedures pose possible risks to the privacy and confidentiality of the subjects. The fact that each of these procedures will be part of the protocols should be adequately explained in the consent forms. That explanation should include the details relating to who will be observing and who will be taking the photographs (e.g., members of the study team, outside contractors, other subjects). In addition, both the protocol and the consent forms should explain what procedures will be in place to make sure that the photographs and videos will be stored in a way that adequately protects both the confidentiality and the privacy of the subjects, and explains what harms to subjects might result if those protections are not adequate. If subjects will be accorded the right to opt out of being photographed, that should be explained in the consent form.

In the Purpose section of the consent form, it should be explained that the underlying purpose of the study will be to collect information that will be provided to the EPA, and that the EPA would use that information to determine the appropriate standards for allowable exposures to products such as the test compound.

The consent form in one instance (the paragraph numbered 4 under Study Procedures) uses the term "same-sex person." That confusing term should be replaced with the descriptions used elsewhere in the form, such as "a researcher of your own sex."

p. 26 In the description of risks to subjects from exposure to the test compound, it is merely stated that the risks are low. If there is a known risk from getting the compound in a person's eyes, for example, that risk should be explained.

The approved version of the consent form, under the Pregnancy Risks heading, begins with "We don't know the risks to the unborn from exposure to SANI-CARE LEMON QUAT **and may be hazardous** . . ." There is a word or words missing in this sentence, and it therefore needs to be revised. More significantly, the "and may be hazardous" language differs from the language that appears in the versions of the consent forms submitted to the IRB by the researchers. The Board was not able to determine how this change in language took place. There is not documentation that the IRB asked for the change, or that the change was initiated by the researchers themselves, and that they submitted a copy of the consent form with this change to the IRB. This circumstance raises some concerns regarding whether the EPA was provided with the full documentation of what went on during the IRB approval process. The Board believes it would be appropriate for the EPA to determine how this change occurred. In addition, some members were concerned that this lack of documentation might relate to the operation of IIRB, Inc., which might reinforce prior Board concerns about the operation of that IRB.

With regard to the recruitment brochure, it would appear appropriate for that document to mention that the product which will be used in the study is Sani-Care Lemon Quat. At the beginning of that document, it fails to mention that the study will look not only at how much of the product "gets on" the workers, but also how much of it they inhale. Under the eligibility criteria, it states that subjects must be "Male or non pregnant, non or nursing female." This language needs to be corrected. And in the last sentence, the brochure incorrectly states that the EPA will use this information to reduce risks to workers. The statement should be revised to more accurately state the EPA will use the information to determine how much of the product workers will be exposed to; it is not true that it will necessarily lead to a reduction in risks to workers.

The phone texts that are used for calls to employers, and for calls to workers making inquiries, fail to mention that the study will be looking at inhalation risks in addition to risks relating to getting the compound on the worker's skin and clothing.

With regard to recruiting and obtaining the informed consent of Spanish-speaking persons, the Board agrees with the changes recommended by the EPA (Carley 2008a and 2008b). It would also be appropriate for the protocol to include a more detailed discussion of how the researchers will obtain appropriate community involvement (such as, for example, discussions with unions representing janitorial workers).

With regard to the translations into Spanish of the various documents, the Board believes that it is important to make sure that the appropriate dialect of Spanish is being used in the translations. The translation of the consent form, for example, was provided by someone from Miami, Florida, yet the study will be taking place in California. The Spanish-speaking communities in Miami and California might well use significantly different dialects of Spanish.

p. 27 It was also not clear from the documents who was producing the Spanish-language version of some of the materials, such as the recruitment brochure.

HSRB Consensus and Rationale

The Board concurred with the initial assessment of the Agency that if the proposed mop and wipe scenario design, protocol, and supporting documentation is revised as suggested in EPA's review, the research does appear to meet the applicable requirements of 40 CFR part 26, subparts K and L.