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EPA-HSRB-16-3

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Subject: October 19-20, 2016 EPA Human Studies Review Board Meeting Report

Dear Dr. Burke,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) provide scientific and ethics reviews of two items: **A Protocol for Laboratory Evaluation of Mosquito Bite Protection from Permethrin-treated Clothing for the U.S. Army After 0, 20 and/or 50 Washings;** and a **Completed Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of Two Solid Formulations Containing an Antimicrobial.** The Board's responses to the charge questions and detailed rationale and recommendations are provided in the enclosed final meeting report.

Signed,

Liza Dawson, PhD
Chair
EPA Human Studies Review Board

INTRODUCTION

On October 19-20, 2016, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB or Board) met to address the scientific and ethical charge questions related to two items: **A Protocol for Laboratory Evaluation of Mosquito Bite Protection from Permethrin-treated Clothing for the U.S. Army After 0, 20 and/or 50 Washings;** and a **Completed Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of Two Solid Formulations Containing an Antimicrobial.**

REVIEW PROCESS

The Board conducted a public meeting on October 19-20, 2016. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notification of a Public Meetings" (EPA, 2016, pp. 68414).

Following welcoming remarks from Agency officials, the Board began its review of the first item, **A Protocol for Laboratory Evaluation of Mosquito Bite Protection from Permethrin-treated Clothing for the U.S. Army After 0, 20 and/or 50 Washings.**

The Board heard presentations from EPA for each agenda item in sequence, consisting of the Agency's review of scientific and ethical aspects of the two studies. This Final Report of the meeting describes the HSRB's discussion, recommendations, rationale and consensus in response to each charge question for each of these items.

For each agenda item, Agency staff first presented their review of the science and the Board asked the Agency presenters clarifying questions. The staff then described their review of the ethical aspects and the Board asked clarifying questions about those. The HSRB solicited public comments and next asked Agency staff to read the Charge Questions under consideration. The Board discussed the science questions first and then the ethics question. The Chair then called for a vote to confirm concurrence on a summary statement in response to each charge question.

For their evaluation and discussion, the Board considered materials presented at the meeting, oral comments, related materials and documents provided by the study sponsors, the Agency's science and ethics reviews of the studies, oral responses from a study sponsor and protocol team, and public comments made at the meeting.

CHARGE TO THE BOARD AND BOARD RESPONSE

Charge to the Board:

Is the protocol, "**Laboratory evaluation of mosquito bite protection from permethrin-treated clothing for the U.S. Army after 0, 20 and/or 50 washings**" likely to generate scientifically reliable data, useful for estimating the level of mosquito bite protection provided by different textiles treated with permethrin?

Board Response:

The Board concludes that the research reported in the completed study is sufficiently sound, from a scientific perspective, to be used to evaluate the bite protection level of permethrin-treated military clothing within the limits of the number of washes tested. The Board also had four specific recommendations for clarifications to be made in the study protocol, and additional minor points which are described in the discussion below.

- In the protocol, provide more clarity on formaldehyde, which was referenced in the Safety Data Sheet for the permethrin treated fabric; specifically, please outline the source of the formaldehyde and what level of residual formaldehyde, if any, would be expected in the treated fabrics used in this study.

- The Board recommends consistent washing of test subjects' arms before each exposure, including the control test and first exposure, to improve consistency with regard to the attractiveness of the volunteers for biting mosquitoes.

- The Board requests clarification regarding the Invexus process for treating the fabrics with permethrin. Specifically, the Board requests inclusion of data on the dermal transfer

rate following the Invexus treatment, to support the calculations of MOE for the volunteers in the study.

- The Board recommends clarifying whether the risk of anaphylaxis in the study is non-negligible, and if in fact there is such a risk, providing appropriate training and emergency measures such as Epi-Pens for use in cases of anaphylaxis; if the risk is negligible, references to such may be deleted.

HSRB Detailed Recommendations and Rationale:

The HSRB discussed the design of the bite protection study, commenting that the study design was sound and there were no major concerns about the methodology used in the study. It was noted that the fabrics tested will be used in order of least concentrated to most concentrated permethrin (untreated, then fabric washed 50 times, then 30 times, etc.) to avoid any potential carryover of permethrin from one sleeve to the next. Bite-through data (representing the ability of the mosquitoes to bite through the fabric to reach the subject's arm) from previous studies informs the sample size calculations and feasibility of the present study. Laboratory raised mosquitoes will be used for safety and consistency of results.

The Board commented that it is reasonable to conclude that the hazard presented by permethrin in this study is low, as it has been tested extensively in animals and shown to have a low toxic potency by all exposure routes. It does not appear to present an appreciable risk of dermal sensitization. It is also reasonable to conclude that the exposure of subjects to permethrin in this study will not be associated with an appreciable increase in risk of toxicity. In the extreme (and unlikely) scenario of 100% of the permethrin in the unwashed fabric being absorbed by a 70kg subject, the internalized dose would still be hundreds-fold less than the dermal NOAEL in rats. MOEs in garment workers also support a high margin of "safety buffer" in exposure levels in this study.

The Board recommended specifying the use of *non-prescription* hydrocortisone in the protocol to relieve itching of mosquito bites, to distinguish this from treatment that could be interpreted as

providing medical care in the study lab. Also, the language of the protocol mentions anaphylaxis in the context of initiating a 911 call. If the likelihood of anaphylaxis is negligible, then perhaps this reference should be deleted. If the possibility of anaphylaxis is not negligible, then emergency treatment, such as use of an EpiPen from appropriately first-aid-trained staff should be made available. The HSRB recommends that this issue be clarified in the protocol.

Comments on statistical aspects of the study

The study design using each subject as his/her own control is appropriate for removing variation arising from differences in attractiveness of subjects to the mosquitoes. The factorial structure (fabric x washings x species) is appropriate for comparisons of fabric type-number of washings combinations within and across mosquito species. In addition, this design helps minimize the number of subjects required for the study. The assumption of a binomial distribution for the proportion of bites is reasonable if mosquitoes bite independently of each other. During discussion with EPA staff, it was clarified that mosquito biting behavior should not be influenced by behavior of other mosquitoes nearby—in other words, that independence is a reasonable assumption.

Under the binomial assumption, the use of a generalized linear mixed model with a log link, and subjects as a random effect, is the appropriate model for analyzing the study data. Calculation of the required sample sizes using the assumed generalized linear mixed model is appropriate. The simulation study to obtain the sample sizes was properly designed with the assumptions clearly stated.

The statistics discussant for the Board also commented that it is unclear why the sample size for the study reported in Attachment 2 included the generalized linear model with subjects fixed and the generalized estimating equation (GEE) approach. Neither appeared to be considered or used in the final protocol. In addition, both the fixed subject model and GEE could have been analyzed using the same GLIMMIX procedure that was used for the random subjects model instead of using GENMOD.

Overall the statistical design, sample size calculations, and proposed data analysis were clearly explained and appropriate.

Testing of mosquito species to ensure that they are disease-free.

There was considerable discussion by the Board regarding the question of testing of the laboratory reared mosquitoes for pathogens. There were several questions raised. First, if there is a real risk of pathogens being transmitted by mosquitoes then a full panel of testing would be required to certify that they are disease-free; however, the proposed testing only incorporated two tests and other pathogens would not be subject to screening. On the other hand, if the laboratory-reared mosquitoes had virtually no possibility of exposure to pathogens then the screening would not only be unnecessary, but could send a false signal about risks of the study or exposure to laboratory raised mosquitoes in general. After extensive discussion the Board agreed that testing for pathogens encountered in wild mosquito populations might not make sense for laboratory reared populations. However, the Board also commented that some kind of certification of the quality and safety of the mosquito population from a laboratory supplier is needed, given that this is important for scientific reasons and for the safety of the human subjects in the study. There was some uncertainty about what kind of quality measures should be used. Chain of custody from lab to research team seemed to be an appropriate step, and perhaps US Department of Agriculture (USDA) permits for shipping, if required, could also indicate compliance with relevant security measures. The Board requested that the sponsor and EPA determine the best method for certifying that the mosquito populations used in the study will be safe and free of pathogens, and that these measures be included in the protocol document and the informed consent. The discussion of these issues was carried over from the scientific review to the ethics review of the study, given that the principal concern is with regard to risk to human subjects.

Questions about the Invexus™ process

The protocol document references the Invexus™ process for treating the fabrics with permethrin, which is a technology used to treat surfaces and materials such as textiles with various products like antimicrobials. No data were provided regarding the efficiency or durability of this process, or the amount of dermal transfer that might potentially be involved in the use of these treated fabrics. Previous studies of pesticide treated fabrics that the HSRB reviewed in past meetings had used other processes for incorporating the chemical into the fabric. Questions were raised about whether the dermal transfer was likely to be the same, or more or less than, previous

methods. EPA staff responded that the concentration of permethrin in the treated fabrics is the same as in previous applications, but that they did not have data on the rate of dermal transfer for the Invexus™ treated materials. The sponsor commented that they would provide those data as part of the application to the EPA for approval of these products. The sponsor also indicated that use of the Invexus™ process for other applications such as bed nets resulted in lower dermal transfers than previously used methodologies for fabric treatment. The estimate for dermal transfer used to calculate the MOE in this case was 15%, which in fact is a high estimate, according to EPA staff, since data from previous studies using treated uniforms showed about a 10-fold lower transfer rate.

The Board acknowledged that the *estimated* dermal transfer rate was probably higher than the *actual* rate, based on previous data, and requested that information about the transfer rate from these Invexus™-treated materials also be provided in the protocol document.

Ethics

Charge to the Board:

Is the research likely to meet the applicable requirements of 40 CFR Part 26, Subparts K and L?

Board Response

The Board concluded that the available information supports a determination that the research will be conducted in substantial compliance with 40 CFR Part 26, Subparts K and L, pending the following three changes:

- The protocol document should clearly specify that any protocol changes must receive IRB approval prior to implementation, with the exception of changes needed to eliminate apparent immediate hazards to human subjects.

- The Board recommends deleting the Spanish language recruitment materials from the study plan, as Spanish language informed consent and study implementation materials will not be provided. Therefore, recruitment of individuals who speak only

Spanish will not be feasible. Recruitment materials in English will reflect the study population of English speakers included in the study.

- As mentioned in the scientific review, appropriate documentation should be provided in the protocol and the informed consent document that the laboratory-reared mosquitoes are free of pathogens and pose no risk of disease to human subjects.

HSRB Detailed Recommendations and Rationale:

The Board discussed the ethical aspects of the study that had been thoroughly reviewed and presented by EPA staff. The Board agreed with EPA's assessment that the study was carefully designed, that risks to human subjects were minimized, and that the informed consent process was appropriate, and that the study presented an opportunity to learn valuable scientific information which could be useful in the future for protection of military personnel.

Need for clarity on IRB approval of protocol revisions

The Board recommended clarifying in the protocol document that all protocol revisions must be reviewed and approved by the overseeing IRB prior to implementation in the study. The current wording in the protocol appeared unclear, and hence rephrasing for clarity is recommended.

Question of representativeness of the study population

The issue of Spanish language recruitment materials generated considerable discussion among Board members. EPA staff commented that they supported the idea of using Spanish language materials to recruit a more diverse study population for the study, with the aim of increasing the representation of demographic and ethnic groups that are members of the military, the ultimate users of the products being tested. Members of the Board commented that using Spanish language materials without allowing for translation of all informed consent documents and providing Spanish-speaking study staff would not likely contribute to diversity since ultimately only study subjects who could understand English would be included in the study. These points also led to broader discussion about whether it essential to obtain a study population that

represented the full diversity of the US military. The Board ultimately agreed that due to the relatively small size of the study, combined with the fact that each person serves as their own control (thus eliminating worries about differences between individuals in susceptibility to mosquitoes), this provides some rationale for not requiring inclusion of non-English speakers in the study for scientific reasons. Furthermore, because the study offers no direct benefits to subjects, the Board agreed that it was equitable to include only English speakers in the study; potential participants would not be denied benefits of any type by their exclusion. Therefore, the Board recommended that for the sake of logical consistency and efficiency it is best to eliminate the Spanish language recruitment and focus solely on English-speaking participants.

Concerns about documenting safety of laboratory reared mosquitoes

Concerns about testing of mosquitoes for potential pathogens was raised during the scientific review. As mentioned above, the Board agreed that some kind of certification that mosquitoes are disease-free and are safely transported from laboratory to study site is required. The Board stated that these measures are necessary not only for safety of human subjects in the study but also for reasons of public trust. It is critical to document safety of interventions at each step so that study subjects, oversight bodies and members of the public are assured that there are no pathogen risks to human subjects through the testing procedure.

HSRB review of A Completed Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of Two Solid Formulations Containing an Antimicrobial

Science Charge to the Board

Is the research in study AEA07 likely to generate scientifically reliable data, useful for assessing the exposure of occupational workers and consumers who manually pour or scoop solid formulation antimicrobials products?

Board Response:

The Board concluded that research in study AEA07 is likely to generate scientifically reliable data, useful for assessing the exposure of occupational workers and consumers who manually pour or scoop solid formulation antimicrobial products.

HSRB Detailed Recommendations and Rationale

The Board agrees with the EPA's review of the completed report finding that the AEATF II addressed all issues identified during EPA and HSRB reviews of the study protocol and that the research team was faithful to the final protocol when carrying out the study. The protocol design and the careful execution of the study produced high quality data for exposure to powder and granular formulations during product pouring events for both commercial and consumer applications.

Given the wide range in the amount of product handled and the quality of exposure measurements (inhalation and surrogate dermal), the data was well suited for evaluating the relationship between the amount of product handled and exposure, particularly for water soluble particles of 100% active ingredient. The results for each scenario (consumer, commercial, powder, granule) and each exposure route (inhalation, long-long-dermal, short-short-dermal, etc.) satisfied or nearly satisfied all the data quality objectives resulting in good confidence in the statistics (average, median and 95th percentile) for exposure.

By extension, the results for the calculated unit exposure (UE) (i.e., exposures normalized to pounds active ingredient handled) for the most part also satisfied the data quality objectives. However, the UE results are not as generalizable as they could have been because, in this case,

the amount of active ingredient handled (AaiH) was the same as the amount of product handled (i.e., the material was prepared with ~100% active ingredient) and in the opinion of the Board, the composition of the powders and granules were not necessarily representative of other formulations. The Board was not given any information about what typical composition of solid pour formulations are, but if there are products with less than 100% a.i., then the UE calculated by the Agency would not necessarily be appropriate as is.

The Board agrees that the deviations and amendments (both recorded and identified by the Agency review) should not have impacted the quality and relevance of the data. One deviation that was identified during the Agency review was that subjects were to carry out the task as they normally would (AEA07 page 16), but the observer for ME14 gave a suggestion to not toss the powder across the pool. This suggestion likely modified the behavior of the subject. It is difficult to know what impact the modified behavior had on the outcome. There is no direct evidence that can be used to make an assessment of what the outcome would have been if the behavior had not been modified. The results for this individual, ME14, were at the high end of the distribution (second highest) even with the potential behavior modification, but could possibly have been higher if not modified. An analysis could be done to estimate what difference it would make to the statistics if the true exposure for this individual had been higher or lower.

The other unrecorded deviation as noted in the Agency review was the order of activities where the original protocol indicated randomly selecting the order of scenarios, but the final protocol and actual study always had the granule pour first followed by the powder pour. This likely had two impacts on the outcome of the study. First, for the less experienced subjects, conducting the granule pour may have provided an opportunity to "learn" the activity such that the subsequent ME would have produced exposures that were biased lower. It would be difficult to assign a numerical value to this learning effect, but given the range of product handled and the range of "experience" represented, the effect was probably small. The other possible effect of always doing the granule pour first is that there was residue or carry over between ME for the same individual (not much time elapsed between events). The protocol included measurement of the residue (pre-exposure air sampling page 69) before each event, which was helpful in assessing the potential contribution of carryover from one event to the next. The measurements showed that there was carryover and that the highest carryover was associated with events that had large

amounts of product handled. The background measured was up to several mg/m^3. The Task Force dismissed this contribution as, on average, being low relative to the average exposure during a ME (33 – 42 mg/m^3), but did not assess the percent contribution in paired analysis, i.e, from one high granule event to a second low powder event. The carryover will bias all powder samples upwards but the amount of bias is probably insignificant for most (but not all) of the powder MEs. The ultimate effect would need to be assessed statistically but likely would bias the low end of the distribution upwards (i.e., higher exposure) with no effect on the high end of the distribution.

Both the AHEATF (the task force) and the EPA review highlighted several outliers in the data. Ultimately these outliers were not removed from the data set, which is the correct approach, in the Board's opinion, given that these MEs were real observed events. Apparent statistical outliers are probably a result of the "purposeful diversity" approach used in these studies and the presence of the occasional outlier (as long as it is not related to a bad measurement) likely speak to the success of this approach in capturing the range of possible outcomes without actually conducting a fully stratified sampling design. So it is important not to exclude apparent outliers unless it can be linked to some other failure in the experimental design or measurement/analysis.

The Agency review identified limitations in the data and the Board generally agrees with the Agency's conclusions, with the exception of concerns about lack of a conceptual model as described below. The Agency mentioned the lack of representativeness caused by recruiting in one area and during one season, noting that this could lead to the subjects not being representative of the region as a whole.

Another limitation of the single location/season testing noted here is the lack of range in temperature. Intuitively the mild temperature during testing could bias the results lower, particularly for the water-soluble powders and granules (mostly for powders) because sweat moistened skin will likely have a much higher adherence factor for airborne particles than dry skin. This may be a non-issue depending on the characteristics of the cotton dosimeter because the "stickiness" of the simulated dermal surface (i.e., cotton) may already be equivalent to moist skin but that information has not been provided to the Board and was not known at the time of review. The Board noted that there may be limitations with the use of these dosimeters for the

measurement of exposure to solid residues, as there may be fall-off mechanisms that may underestimate total exposure. The adherence dynamics of fabric may not entirely represent adherence to human skin during the exposure event. In addition, during measurement activities for the determination of solid loading on skin (i.e., exposure) fall-off of solid particles may occur that result in an underestimate of exposure. These activities may include: subject walks to the changing room, removal of dosimeters, placement of dosimeters in hangers, and partitioning of dosimeters into pieces before placement in bags for analysis. The report did not describe any specific measures to reduce fall-off during these procedures.

The biggest limitation in the data is the lack of generalizability of the surrogate test substance to other solid pour granules and powder formulations. The final results do not provide a way to assess the relationship between exposure and AaiH. The results do provide an excellent data set for assessing the relationship between exposure and the amount of product handled because the surrogate test substance made up 100% of the product. To relate this data to AaiH, a number of important assumptions would need to be made about exposure pathways (direct contact, splashing, resuspension/deposition, resuspension/transport/inhalation) and the pathways may in fact be significantly influenced by the properties of the material itself, for example clumping issues, fine particle plumes, high water solubility leading to 100% adherence to wet skin, etc. It may be that "solid pour powders and granules" are always made of 100% a.i. and always are highly water soluble (sticking to wet surfaces) but that information was not available for this review.

Although the protocol and field study are scientifically reliable, what is missing from the EPA's analysis is a conceptual model showing all reasonable exposure pathways for each of the primary exposure routes (inhalation, dermal contact, indirect ingestion). A conceptual model, for example, presented as a logic model type diagram, would facilitate further planning and research about the appropriateness of the assumption of "proportionality." These diagrams, once constructed, can be used in conjunction with ongoing research to help illuminate factors that influence variance in exposure outcomes and, in this case, could help point to specific exposure pathways that may or may not follow the assumption of proportionality (and why). For example, a clump of material causing a splash will almost certainly reduce exposure by the "plume pathway" but increase exposure by the "splash pathway" but, depending on the size of the clump

will likely reduce the UE because a significant amount of product was transferred to the water without contributing to resuspension (plume). Further conceptual modeling of exposure pathways and factors influencing each of the pathways will enhance the design of research conducted on exposures, and ultimately result in better science.

Statistical comments

The study design is appropriate and the sample size is adequate. The representativeness of all Ohio users appears to be a limitation and could be factored into in a future study. The primary statistical approaches are summary statistics and linear regression models with log transformed exposure and pounds of active ingredients handled. Criteria for judging a scenario are in terms of a 3-fold relative accuracy and confidence interval width at most 1.4. The additional analyses regarding outliers and non-detect are appropriate. Alternative statistical approaches including quantile regression and log-log-logistic models are interesting. However, the linear regression model with transformed variables is simpler and is also acceptable. Overall, the study design and statistical methods used for data analysis are appropriate and acceptable.

Ethics

Charge to the Board:

Does available information support a determination that study AEA07 was conducted in substantial compliance with Subparts K and L of 40 CFR Part 26?

Board Response

The Board concludes that available information supports a determination that the study was conducted in substantial compliance with Subparts K and L of 40 CFR Part 26. The Board also recommends several measures to improve ethical standards in future studies:

- The Board recommends that EPA communicate to the overseeing IRB that an inappropriate amendment was approved in one of the protocol revisions for AEA07, specifically, a change that deleted the statement that changes to the protocol would be approved by the IRB *prior to implementation*. The Board recommends that the IRB and

the study team be informed that implementing protocol changes prior to IRB review and approval represents a violation of federal regulatory standards as well as a violation of ethical norms.

- The Board recommends updating AEATF II Standard Operating Procedures (SOPs) to provide guidance for evaluating study-related adverse events (AEs), in particular for determining whether events are likely related or unrelated to study participation. The Board also recommends developing guidance for investigators on gathering relevant medical information for evaluation of AEs through requests for access to participant medical records and other activities to acquire appropriate medical information, as needed.

- The Board recommends that future protocols require that medical professionals evaluating whether AEs are related to study participation be independent of the study team.

HSRB Detailed Recommendations and Rationale

The Board agreed with the ethics assessment provided by EPA staff, that the study was conducted in substantial compliance with regulatory standards at Subparts K and L of 40 CFR Part 26.

However, there were four ethical concerns raised by the HSRB. First, there were apparently a large number of protocol changes implemented without IRB approval. Most of the changes related to logistical matters, for example, changing the sizes of product containers used for pouring, and allowing for a longer time period for extraction of samples during laboratory analysis. While these changes did not result in increased risks to human subjects, they represent a violation of regulatory standards and norms of research oversight. In study AEA07, in many cases IRB approval was sought after changes were implemented, rather than before. The Board recommended that the study team and the reviewing IRBs be reminded that all protocol changes **must** be reviewed and approved **prior to implementation** by the study team, except when needed to eliminate apparent immediate hazards to human subjects.

Also, during one of the protocol revisions, language in the protocol that originally stated "Changes to the protocol currently require review and approval by the IRB prior to implementation" was changed, deleting the phrase "prior to implementation." This change underscored the failure to adhere to appropriate compliance measures with regard to IRB oversight. EPA staff have already communicated to the study team and the IRB that this language does not reflect ethical and regulatory standards, and the HSRB is in agreement with the Agency's approach.

The third issue discussed by the Board was the response to adverse events. During the conduct of the study, one of the study subjects experienced an AE that was determined by the study team to likely to be unrelated to the study, since the symptoms (nausea and vomiting) were unrelated to potential cyanuric acid exposure during the scripted pouring scenarios. However, there were several gaps in the procedures for responding to an AE. Because the subject in this case was taken to the emergency room for treatment, study staff needed a procedure to obtain information about the medical assessment by ER personnel. Due to HIPAA requirements, it was not obvious to study staff how to obtain relevant records. Procedures should be put in place to request that subjects authorize the study team to access medical records in case of a suspected AE, so that appropriate follow up and evaluation of the AE can be initiated if needed. In the particular case in question, the subject also should have been instructed to call the hotline provided by the chemical manufacturer for reporting potential exposures.

Fourth, the Board recommends ensuring that in all cases the medical provider or first responder who is called to assist or help evaluate an AE be independent of the study team.

US ENVIRONMENTAL PROTECTION AGENCY
HUMAN STUDIES REVIEW BOARD

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NOTICE

This report has been written as part of the activities of the EPA Human Studies Review Board, a Federal advisory committee providing advice, information and recommendations on issues related to scientific and ethical aspects of human subjects research. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the view and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does the mention of trade names or commercial products constitute a recommendation for use.

In preparing this document, the Board carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. This document addresses the information provided and presented within the structure of the charge by the Agency.