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April 12, 2013

EPA-HSRB-13-01

Glenn Paulson, PhD
EPA Science Advisor
Office of the Science Advisor
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: January 17, 2013 EPA Human Studies Review Board Meeting Report

Dear Dr. Paulson,

The United States Environmental Protection Agency (EPA or Agency) requested that the Human Studies Review Board (HSRB) provide scientific and ethics reviews of one completed study involving intentional exposure of human subjects to pesticides; specifically, a study of the Antimicrobial Exposure Assessment Task Force II (AEATF) scenario to determine dermal and inhalation exposures associated with the manual pouring of liquid antimicrobial products (AEA-05).

The enclosed report provides the Board's response to the three EPA charge questions presented at the January 17, 2013 meeting.

A completed study report from the Antimicrobial Exposure Assessment Task Force II (AEATF) in which the dermal and inhalation exposure of professional janitorial workers was monitored as they poured liquid antimicrobial pesticide products from conventional or reduced-splash containers into different sizes and types of receiving containers.

<u>Science</u>

- The Board agreed with the Agency's conclusion that the completed liquid pour study was conducted in a manner faithful to the design and objectives of the amended protocol and governing documents of AEATF.
- The Board determined that the Agency identified and adequately characterized some, not all, of the limitations that should be considered when using the data in estimating the exposure of people who pour liquid antimicrobial pesticide products. Additional limitations, statistical analyses, and technical recommendations merit attention before the data are used in exposure algorithms for estimating human exposures.

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Ethics

- The Board concurred with the Agency's assessment (Leighton, Cohen, October, 9 2012; Sherman, October, 9 2012) that the proposed research is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L.

Sincerely,

Rebecca T. Parkin, PhD, MPH
Chair
EPA 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. You may obtain further information about the EPA Human Studies Review Board from its website at http://www.epa.gov/osa/hsrb. You may also contact the HSRB Designated Federal Officer, via e-mail at ord-osa-hsrb@epa.gov

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.

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* Not present on January 17, 2013.
† Participated in the January 17, 2013 meeting via telepresence.

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INTRODUCTION

On January 17, 2013, the United States Environmental Protection Agency's (EPA or Agency) Human Studies Review Board (HSRB) met to address the scientific and ethical charge questions related to one completed study; namely, a study of the Antimicrobial Exposure Assessment Task Force II (AEATF) scenario to determine dermal and inhalation exposures associated with the manual pouring of liquid antimicrobial products (AEA-05).

REVIEW PROCESS

On January 17, 2013, the Board conducted a public face-to-face meeting in Arlington, Virginia. Advance notice of the meeting was published in the *Federal Register* as "Human Studies Review Board; Notice of Public Meeting" (76 *Federal Register* 187, 59697).

Following welcoming remarks from Agency officials, the Board heard presentations from EPA on the following topic: the Antimicrobial Exposure Assessment Task Force II (AEATF) scenario to determine dermal and inhalation exposures associated with the manual pouring of liquid antimicrobial products (AEA-05).

The Board asked the Agency presenters clarifying questions about scientific aspects of the study.

Public oral comments, including clarifications about the study conduct, were provided by:

Ms. Leah Rosenheck, President, LR Risk Consulting, Inc. (representing the Antimicrobial Exposure Assessment Task Force II)

No written public comments were submitted.

For their evaluation and discussion, the Board considered materials presented at the meeting, oral comments, and Agency background documents (e.g., the proposed study protocol; AEATF governing documents; standard operating procedures; institutional review board documentation; the HSRB's final report following its October 19, 2011, review of the protocol; AEATF's final report, tables, statistical analyses and SAS code for the study; and the Agency's science and ethics reviews of the completed study). A comprehensive list of background documents is available online at http://www.epa.gov/hsrb/.

CHARGE TO THE BOARD AND BOARD RESPONSE

<u>Assessment of Proposed AEATF Research Study AEA05: A Study for Measurement of Potential Dermal and Inhalation Exposure During Manual Pouring of a Liquid Containing an Antimicrobial.</u>

Overview of the Study

AEATF II's liquid pour study (AEA-05) was designed to measure dermal and inhalation exposures to workers and consumers when they manually pour liquid antimicrobial products from and into a variety of commonly used containers in differing scenarios (e.g., various heights, pre-measured or not). Specifically, the AEATF sought to develop unit exposures (UEs) for conventional pour (CP) and reduced splash (RS) source containers. The Agency plans to use the resulting data in exposure algorithms to estimate human exposures from pouring liquid antimicrobial products in diverse settings.

The protocol for this completed study was reviewed by the EPA and then on October 19, 2011, by the HSRB. Following recommendations of the Agency and the HSRB, the protocol was revised by the sponsors and approved by the Independent Investigational Review Board, Inc., (IIRB).

In January and February 2012, the sponsors used notices in two local newspapers and one regional bilingual publication to recruit professional janitorial workers. After screening respondents and obtaining informed consent, 22 people were enrolled in the study; 18 were study participants and four were alternates. No persons under age 18 and no pregnant or nursing women participated in this study.

From February 16 - 22, 2012, the study was conducted in two equal-sized rooms at a laboratory in Concord, Ohio. Two low-volatility active ingredients, ADBAC (N-alkyl dimethyl benzyl ammonium chloride; Maquat DS 1412-10%) and DDAC (didecyl dimethyl ammonium chloride; Maquat WP), were used in the RS and CP scenarios respectively. Participants were randomized to pour first from one type of source container (holding from 24 ounces to 5 gallons) into various receiving containers (from 2- to 50-gallon sizes). They were randomly assigned to pour different amounts of each substance (e.g., from 40 ounces to 20 gallons in the CP scenario, and from 60 ounces to 30 gallons in the RS scenario) and instructed to pour the liquids as they normally would. Each of the 18 participants poured the two substances sequentially for a total of 36 Monitoring Events (MEs). The amount poured was measured by weighing the containers before and after each ME. Participants were observed during the MEs; *i.e.*, staff recorded environmental conditions, notable activities and events and took photos and videos during each ME. Participants wore two whole-body dosimeters (WBD) (a one-piece inner WBD and a long-sleeved shirt and long pants for the outer WBD); these were sectioned into 8 specified pieces for separate analysis. Hand washes and face and neck wipes were also used to assess dermal exposures to unclothed portions of the body. All participants wore safety glasses, but no participants wore gloves during the MEs. Each participant's breathing zone inhalation exposure was measured using an OSHA Versatile Sampler (OVS) tube attached to his/her shirt collar and linked to a personal sampling pump.

Unit Exposures (i.e., expected external exposures) were normalized to pounds active ingredient handled (AaiH). Statistical analyses were conducted in SAS using three modeling

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methods: empirical simple random sampling, lognormal simple random sampling, and lognormal mixed models.

The sponsors found that pouring liquids into spray bottles resulted in the highest levels of dermal exposure, due to drips and spills; consequently, the AaiH:exposure relationship was not log-log-linear. Nearly half of the inhalation exposures were below the limit of quantification (LOQ); the RS containers typically resulted in lower values. The study design yielded data which met the 3-fold accuracy criterion, except for the spray bottles (k=3.6).

The Agency concluded that the results may be used for assessing exposures related to labeled uses of liquid pesticides that require open pouring.

Science

Charge to the Board

- Was the research reported in the Antimicrobial Exposure Assessment Task Force II (AEATF) completed liquid pour study report faithful to the design and objectives of the protocol and governing documents of AEATF?
- Has EPA adequately characterized, from a scientific perspective, the limitations on these data that should be considered when using the data in estimating the exposure of people who pour liquid antimicrobial pesticide products?

Board Response to the Charge

<u>HSRB Recommendation</u>

- In response to the first question, the Board agreed with the Agency's conclusion that the completed liquid pour study was conducted in a manner faithful to the design and objectives of the amended protocol and governing documents of AEATF.
- The Board determined that the Agency identified and adequately characterized some, not all, of the limitations that should be considered when using the data in estimating the exposure of people who pour liquid antimicrobial pesticide products. Additional limitations, statistical analyses and technical recommendations merit attention before the data are used in exposure algorithms for estimating human exposures.

<u>HSRB Detailed Recommendations and Rationale</u>

The study report is well-documented with useful observational notes. While the justification to split out the spray bottles as a separate scenario was not explained clearly, the HSRB agrees with the logic of the decision.

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During deliberation of additional limitations and technical and statistical concerns, the HSRB suggested a number of methods which could be used to strengthen the study analysis and maximize the appropriate future use of the data in exposure algorithms. Although the following comments may appear extensive, many have both positive and negative impacts on how these data might be used or interpreted.

1. Limitations

The Board agrees with most of the Agency-identified limitations that should be considered when using the data in estimating the exposure of people who pour liquid antimicrobial pesticide products; however, it has numerous science-based comments and additions. The first seven bullets refer to the limitations listed by the Agency as a series of eight "items" (Leighton and Cohen, *EPA Science Review*, 2012, 45-47).

- The first part of item #2 (Leighton and Cohen, *EPA Science Review*, 2012, 46) discusses the study design limitation imposed by using only occupational workers; *i.e.*, custodians or janitors. The Board does not fully support the Agency's conclusion that the fact that "the test subjects spilled the product on their hands when performing their pouring tasks indicated that perhaps pouring liquids is not an experienced-based skill." Notes in the Observations of Monitoring Events indicate that many of the handlers (8 out of 18 for ≈ 44%) changed their procedures as they progressed in their assigned task in ways that reduced further dripping of the product onto the outside of the product and/or receiving container (Rosenheck, *Final Report (AEA-05)*, 2012, 164-199) . This observation (along with the fact that 5 of these 8 changes were noted on the subject's second of two MEs) suggests that the participants' prior work "experience" was not as strong a factor in their handling of their assigned containers as the selection criteria might suggest.[1] However, these observations also suggest that the exposures measured on these occupational workers may not be as different from residential users as was suggested during the Board's protocol review (HSRB, *October 2011 Meeting Report*, 12-13).

- Another limitation, indirectly related to the first part of item #2 (Leighton and Cohen, *EPA Science Review*, 2012, 46), is that the repeated exposures to containers contaminated by previous spillage (as allowed by the study design) may have resulted in dermal exposures much greater than expected for a more typical task of pouring into spray bottles once-daily. The reason for this suggestion is that the protocol called for pouring from the same product container (and measuring cup, when applicable) to fill multiple (10 or 15) spray bottles, which occurred within a short time (13 to 22 minutes). While Table 6 of the Final Report indicates that virtually all of these particular custodial

[1] A statistical exploration of the correlation between the handler's work experience, expressed as either years or frequency of liquid disinfection (Rosenheck, *Final Report (AEA-05)*, 2012, 84), and the observation that an individual changed his/her work practice might (or might not) be enlightening on this point.

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workers poured a liquid disinfectant at least weekly (with about 70% listed as daily) (Rosenheck, *Final Report (AEA-05)*, 2012, 84), it seems unlikely that in their normal work they would fill so many spray bottles in such rapid succession. In the time between their more normal occupational fillings, the liquid that dripped down the side of a container during one filling session would have either been rinsed off, wiped off, or had a chance to dry before the next session started. In the opinion of the Board, based on both past experience with liquid exposure studies and physical principles, liquid ingredients on the surface of a container would transfer to a handler's skin much more readily than would a dried residue. Neither drying nor wiping was allowed within the approved protocol. While the use and storage of a rag used to wipe the drips would have been a new variable, the resulting exposures as tested were almost certainly larger than would result from normal daily uses in either an occupational or a residential setting.

The Board recommends that the registrants and Agency take note of the success of some participants in evolving their work practices, thereby reducing their dripping and splashing. Should the need arise in the future to reduce dermal exposures, both better label instructions to improve work practices and better container designs to reduce dripping could be explored to reduce exposures more consistently, not only while filling spray bottles but also for other pour scenarios.

- The second part of item #2 stated that "also part of the [study] design limitation was the fact that the study was conducted indoors" (Leighton and Cohen, *EPA Science Review*, 2012, 46). The Board noted in their review of these protocols that outdoor exposures might be larger; "Air velocity [from wind] outdoors is likely to be more variable (particularly on the high-end) than indoors" (HSRB, *October 2011 Meeting Report*, 12). Discussion at the meeting did not support the subsequent AEATF's response that "Exposure data indicate that the handling and use of chemicals indoors tend to result in higher exposures than outdoors due to the restricted potential for dilution of airborne residues" (Leighton and Cohen, *EPA Science Review*, 2012, 7). In the opinion of the Board, at least peak exposures outdoors may be larger than doing the same task indoors due to differences in both airflow patterns related to wind outdoors and psychological factors causing less of a concern for drips and spills outdoors than indoors.

- Item #2 did not mention a lack of information within the study report on ventilation velocity or handler orientation within that airflow (Leighton and Cohen, *EPA Science Review*, 2012, 46). The HSRB's review of these protocols stated "... the focus of interest in ventilation should be on the local air flow between the pouring operation (the source of exposure) and the handler." Further, the Board suggested that "...at the very least, that pattern should be measured before and/or after exposures and the orientation between the source and each handler should be documented for each ME. Alternatively, the room's

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setup and the orientation between the source and handler could be varied (e.g., rotated 90°) either within or among MEs" (HSRB, *October 2011 Meeting Report*, 11). The AEATF's response indicates in part that "More details about how the airflow will be measured will be included in the protocol" and "...the orientation of each test subject in the room with respect to the direction of air flow and the containers he is pouring will be documented" ((Leighton and Cohen, *EPA Science Review*, 2012, 9). While the room diagrams and photos in the AEATF final report provide some constraints and examples (respectively) of the orientation within the room (Rosenheck, *Final Report (AEA-05)*, 2012, 151-153), the report did not contain any details regarding either the airflow velocity or the orientation of individual handlers.[2] Thus, the Agency is unable to evaluate the potential for a consistent airflow direction or orientation to have caused the average inhalation route to be either higher or lower than would have been caused by random or variable airflows. Conversely, if the ventilation systems in the test facilities have not been modified since the exposure tests were conducted, it may still be possible (even at this late date) to conduct velocity measurements for insight into the flow within the test rooms and to take photos representative of the handler's orientation.

- Item #6 states in part that "the small sample size by itself does not create statistical limitations" and that "a notable exception is for the dermal exposure summary statistics for scenario 1a, pouring into spray bottles" (Leighton and Cohen, *EPA Science Review*, 2012, 46). The implication is that the large relative accuracy for this latter scenario is due to its small sample size. The Board suggested two alternative causes for the large relative accuracy of scenario 1a (*i.e.*, an fRA (fold relative accuracy) of 3.6 for the spray bottle).

  - The first alternative suggestion relates to the very narrow range of AaiH values engendered by not anticipating within the original protocol a desire to isolate a unit exposure value for the pouring task using a measuring cup. The range of the six AaiHs while pouring into spray bottles via measuring cups was only 1.3x (ratio of highest to lowest), *i.e.*, the amounts handled were virtually the same. In contrast, the range of AaiHs was 6.9x for the AaiH of all other conventional pours and 4.2x for all other reduced splash pours.[3] Thus, even if the sample size had been three or four times larger, the *ex post facto* study design for spray bottles had very limited power to obtain an fRA within 3-fold.

[2] The air changes per hour [ACH] that were measured do not provide air velocity information, although the Board agrees with the statement made in item #8 that "the ACH rate is not expected to have a substantial impact on the air concentrations monitored."

[3] The corresponding ranges of the "dependent variables" for regression testing (*i.e.*, the total dose in mg) were 10x, 71x, and 141x.

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- The second alternative cause for the large relative accuracy of the spray bottle scenario relates to a key concept for unit exposure values within such studies. When the concentration of the active ingredient (ai) within the test material that each ME was handling is *similar or virtually equal* (as in this study and virtually all other studies of this nature), a range of AaiHs could only have been achieved by varying the volume of test material that each ME handled, and handling a larger volume generally would require a longer handling time. Thus, an implicit (but unstated) assumption when expecting to find a correlation between AaiH and exposure to test materials of nearly equal concentration is that the exposure rate is constant throughout the handling time. At least two of the previous comments herein (*viz.*, changes in work practices and in the accumulation of drips and spills) suggest that such an assumption is invalid within this study. Thus, the high fRA could simply be the result of changes in the individual handlers' rates of exposure over the duration of the exposure time.

- The first part of item #7 describes the Agency's desire to continue using exposures normalized by AaiH as a default condition despite the results herein in which dermal exposures are not proportional with AaiH (Leighton and Cohen, *EPA Science Review*, 2012, 47). The Board concurs with the scientific validity of extrapolating unit exposure values on the basis of concentration and points out that the lack of "log-log linearity" of exposure with AaiH based on handling different volumes of the same concentration of test material (as shown by studies such as this completed study) should not be taken as evidence that weakens the applicability of unit exposures to extrapolate on the basis of different concentrations within the test material.

  The Agency asserts that, since regulation occurs at high AaiH, use of an estimator that under-predicts exposure at low AaiH and over-predicts exposure at high AaiH is conservative (Leighton and Cohen, *EPA Science Review*, 2012, 47). However, it is not clear whether this linear default assumption will only be applied at high usage. The adopted unit exposures might in the future be applied in non-occupational scenarios. The lowest threshold (breakpoint between under- and over-prediction) is on the order of 0.004 pounds ai handled for the spray bottle filling case (Leighton and Cohen, *EPA Science Review*, 40 [Figure 8]). At 0.19% solution strength, this represents a little more than 32 ounces of stock solution. Since a non-occupational spray bottle filling scenario would be very unlikely to ever involve the use of that much stock solution, all applications of the unit exposures in non-occupational settings could be expected to lead to under-prediction of exposure.[4] The Board recommends that the Agency insert language to preclude default non-conservatism in non-occupational settings.

[4] The conventional pour and reduced splash pour cases have much higher thresholds, so the problem occurs there also.

US EPA ARCHIVE DOCUMENT

- Item #7 also states that "The study could not be designed to vary the concentration of ai to further investigate this assumption because higher concentrations of ai would require the use of chemical resistant gloves" (Leighton and Cohen, *EPA Science Review*, 2012, 47). In the Board's review of the protocol (HSRB, *October 2011 Meeting Report*, 11), it agreed with that statement. However, with the results now in hand, this rationale is no longer completely valid. We now know that the hand doses while pouring are so high that the concentration could be reduced by at least 10x, perhaps up to 100x, and still yield consistently measurable exposures on the hands. Thus, in the event that more exposure data when filling spray bottles is desired at some time in the future, the concentration could easily be lowered to increase the range of AaiH values independent of handling time.

- Concerns were raised about lumping of hand and non-hand exposures for reasons over and above statistical dissimilarities between the respective data sets. EPA has traditionally assumed that a fixed fraction of material reaching the skin will be absorbed; however, the Board asserts that this is a very poor assumption. Absorption varies with both loading conditions and time of exposure. Hands are subject to higher gross loads and more frequent washing than are other body parts. Current domination of dermal exposure by the hands might be partially mitigated if absorbed doses were calculated separately.

2. Technical issues

The Board identified two technical issues for the Agency to consider. These relate to the inhalation data and may not have a substantial impact on the study's overall outcome.

- A statement in item #8 that pouring comprises a "relatively low aerosol generating application" (Leighton and Cohen, *EPA Science Review*, 2012, 47) may be true, but it overlooks a potentially useful aspect of the AEATF inhalation data. Specifically, the AEATF data contains evidence that filling containers without using a measuring cup may have generated enough aerosols to explain the differences between airborne exposures while pouring from CP containers versus pouring from RS containers; such differences were not seen while filling spray bottles. Both the differences of nearly 4x in the inhalation unit concentration values (0.015 / 0.0044 mg/m^3/lb ai) and over 4x in concentration without accounting for AaiH (3.5 / 0.82 µg/m^3) (Leighton and Cohen, *EPA Science Review*, 2012, 27) were significantly different from 1 at $p \approx 0.01$ in t-tests conducted by a Board member.[5] The difference between CP and RS containers observed

[5] This difference is consistent with the documented differences between "splash loading" and "submerged loading" of petroleum tank cars (EPA (OAQPS), *Compilation of Air Pollutant Emission Factors*, 1995, vol. 1, AP42, Section

US EPA ARCHIVE DOCUMENT

in the manual pouring scenario may be attributable to aerosols formed either from the "glugs" or/and from the fall of the liquid impacting on a surface inside the receiving container. However, because of the small doses via the inhalation route relative to the dermal route, these differences had virtually no impact in the overall results.

- The respiration rate of 1 m^3/hr = 16.7 L/min (Leighton and Cohen, *EPA Science Review*, 2012, 3 and 22) is potentially too low for Groups 2 and 3 within this scenario by as much as 60%. Just the liquid alone in the largest containers handled by Group 2 weighed over 16 lbs; and the liquid in the 5 gallon containers in Group 3 weighed 41 lbs. Pouring multiple containers weighing this much often within 3 to 17 minutes implies a metabolic work rate beyond "light." If Group 3 were classified as "moderate," their inhalation rates would be 1.6 m^3/hr for males and females combined, as shown in a recent EPA handbook (EPA, ORD. *Exposure Factors Handbook*, 2011, pp. 6-4 to 6-6 [Table 6-2]).

3. Statistical analysis

The statistical analysis of the data for this scenario raises some concerns that limit the study's utility. Five specific areas should be addressed: imputation, the arithmetic mean, q-q plots, non-constant variances, and slopes outside the range [0, 1]. An additional concern is the presentation of numerous analyses, none of which adequately represent the true design of the study. Some of the results are concerning. However, if the issues arising from the statistical analysis are fully addressed, some of the Board's concerns might be removed.

- All methods associated with imputation should be reviewed. The need for imputation results from a response falling below the detection limit. Although 0, half the detection limit and the detection limit are common approaches to imputation, maximum likelihood estimation is widely recognized as a better approach (Helsel, *Nondetects and Data Analysis*, 2005). The HSRB commends the Agency for moving in this direction. The correlation structure induced by having each worker pour from both a conventional and a reduced-splash container, as well as multiple exposure measurements taken at the time of each event, is particularly noteworthy. However, the purpose of generating five sets is to reflect the variability in the possible responses falling below the detection limit. If a single value is imputed, then the analysis reflects the variability in the data, but it fails to reflect the additional uncertainty associated with imputing a value. Consequently, the measures of variance would be biased toward zero. By averaging the five imputed values for each non-detect, as was done in the analysis of this completed study, the imputed values have less variability than the individual values, leading to a more biased variance than would have been the case had a single value been imputed. The Board recommends

Comment [w1]: Shouldn't this read "had five individual values been imputed." ?

Comment [RP2]: Jim – Do not change this. It is written exactly as Linda submitted it.

5.2.2.1.1 and Figure 5.2-2). In the tank car filling scenario, more aerosol droplets are generated when the liquid is free to fall into the receiving container versus when the end of the pipe outlet is submerged under the receiving liquid's surface.

US EPA ARCHIVE DOCUMENT

that the analysis use the five sets of values to fully capture the variability. Conduct an analysis for each data set, and average the results, with the exception of the variance. The variance is the pooled estimate of the within dataset variation plus the variation among the imputed values. The standard error is then the square root of the variance (Rubin, *Multiple Imputation for Nonresponse in Surveys*, John Wiley & Sons, 1987).[6]

- In Appendix A of EPA's Science Review, the association between the geometric mean and the arithmetic mean is discussed (Leighton and Cohen, *EPA Science Review*, 2012, Appendix A, 36). In the derivation, it is incorrectly assumed that the errors are constant. Both the pounds of active ingredient (ai) and the error differ with each observation, unlike the intercept and slope, which are constants. A Taylor series expansion could be used to derive an approximate relationship between the two. However, the derivation of which the Board members are aware does not consider the more complex setting involving a variance component, much less the two that are presented in this study (one for worker and one for the error of the model). It is not clear that the same association between the geometric mean and arithmetic mean would hold for this more complex model. This should be carefully considered and the approach justified or an appropriate reference given.

  Even if the association between the geometric mean and the arithmetic mean can be determined for this setting, the Board questions whether the arithmetic mean has value. Identifying the center of the distribution of values is the key issue. Sometimes the arithmetic mean provides the best estimate of the center, sometimes the median provides the best estimate of the center, and sometimes the geometric mean provides the best estimate of the center. The HSRB believes that, for these kinds of studies, geometric means provide the best estimates of the centers of the distributions being sampled. Furthermore, when a logarithmic transformation is used so that the assumptions associated with linear regression are more nearly met, as is the case here, a geometric mean is widely considered a better measure of the center of the distribution. The 95th percentile of the distribution, which is another metric of interest, allows an assessment of the extreme values. While it is true that the arithmetic mean is the most commonly used measure of the center of a distribution, it is not as appropriate here. The Agency should consider carefully what additional information, if any, it is providing. If only the geometric mean and the 95th percentile of the distribution are needed, then confidence intervals can be established on the log-log scale, and the endpoints back-transformed to obtain confidence intervals in the original scale.[7]

[6] It is not necessary to use a Bayesian framework to properly account for these sources of variation.

[7] Back-transforming confidence interval endpoints result in confidence intervals with the desired level of coverage. Back-transforming the mean and the variance, and then setting the confidence interval on the original scale, does not produce confidence intervals with the desired level of coverage.

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- The use of q-q (or quantile-quantile) plots is a good approach for assessing the validity of the assumption of normality of the residuals. In Figure 1, the q-q plot is for the response and not the residuals (Leighton and Cohen, *EPA Science Review*, 2012, Appendix A, 28). This causes problems because the mean is not constant, but instead differs with the group. In addition, there are two, not one, variance components, each of which is assumed to be normally distributed with a mean of 0 but different variances. Thus, the q-q plots presented are not for a single distribution but, instead, for a mixture of distributions with differing means and variances.

- The variances quite clearly differed with the group (bottle, CP and RS containers). Although this is discussed, the primary analysis does not seem to account for differences in variances, which require the weight statement in SAS's Mixed procedure. Once the within-group variances have been found to be significantly different, all analyses moving forward should account for those differences.

  The proper analysis is a mixed model analysis with subsamples and unequal variances. Based on the documents and SAS code provided, it is not evident that this is the final model being used.[8]

- The estimated slope was negative for all dermal exposure scenarios, although in no case was the slope significantly different from zero. This raised concerns because it is expected that exposure will increase as the amount of active ingredient handled increases, and a slope of zero implies that the exposure is independent of the amount handled. Yet, this is the second study for which this concern has arisen. When the Board considered closed cabs, the accidental exposure from touching contaminated surfaces led to a constant exposure (HSRB Meeting Report, January 2011, 21). In this completed liquid pour study, spills on the hands resulted in approximately constant exposure. Although it is true that one cannot conclude that either the slope is negative or zero, one can also not conclude it is greater than zero from these data. Elsewhere in the report of the completed study, reasons that the slope may truly be negative are explored (Leighton and Cohen, *Science Review*, 2012, pp.35 and 47). If, after considering these, it is determined that the slope should not be negative, perhaps consideration should be given to analyzing the exposure to the hands separately from exposure to the rest of the body. For the hands, exposure being independent of AaiH may be reasonable because the primary exposure is from accidental actions. For the rest of the body, the assumption of proportionality may be reasonable.

[8] The subsamples appear to be accounted for as repeated measures. Care needs to be taken to ensure that the two models are equivalent.

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A similar concern should be addressed when estimated slopes are greater than one. A principled approach to handling these cases should be adopted.

- Finally, numerous analyses are presented. One analysis is based on simple random sampling, but the design was not one of simple random sampling. Another analysis ignored the correlation of observations from the same worker. No analysis reflected the true design of the study, which includes clusters of MEs, variability due to workers, group associated with the type of container, and subsamples from the same worker. For some analyses, means were allowed to differ with group, but not in others. For some, variances were allowed to differ, but not in the primary analysis. It is important to consider competing models and to make readers aware that these alternatives were considered. However, in the end, it should be clear which model was used and why. For this scenario, it is important to account for the correlation among observations from the same worker, to account for differences in the means, to allow for different variances, and to justify failure to account for variation due to clusters of MEs. Enough should be presented to show when a model has been simplified or additional complexity is presented. Adding full analyses that are later found not to be appropriate makes the document more challenging to read and may lead to the use of an inappropriate model.

Ethics

Charge to the Board

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

Board Response to the Charge

<u>HSRB Recommendation</u>

- The Board concurred with the Agency's assessment (Leighton, Cohen, October, 9 2012; Sherman, October, 9 2012) that the proposed research is likely to meet the applicable requirements of 40 CFR part 26, subparts K and L.

<u>HSRB Detailed Recommendations and Rationale</u>

The Board concurred with the ethics analysis of the proposed study, as detailed in the EPA's Ethics Review (Sherman, *EPA Ethics Review*, 2012) and summarized briefly below.

1. Societal Value of Proposed Research

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- The purpose of the completed monitoring study was to determine potential dermal and inhalation exposures to occupational workers and consumers associated with the manual pouring of liquid antimicrobial products.
- Because many consumers and workers pour antimicrobial products, the research question was important; it could not be answered with confidence without new monitoring data meeting contemporary standards of quality and reliability.

2. Subject Selection

- The inclusion/exclusion criteria were complete and appropriate.
- Pregnant or nursing women were excluded from participation.
- Employees or relatives of employees of the investigators and of cleaning product manufacturers were also excluded from participation. (One subject was deemed ineligible because he was the spouse of an employee of Ricerca Biosciences LLC, the facility where the research was conducted.)
- Protections were adequate.
- Recruitment materials and interactions with potential subjects were language-appropriate.
- Subjects were recruited through newspaper advertisements, not through employers, which minimized the potential for coercion or undue influence.

3. Risks to Subjects

- The proposed test materials were EPA-registered for the use proposed, were of low toxicity to mammals, and were used in full compliance with the approved labels.
- All identified risks were characterized as of low probability.
- Risks were minimized by exclusion of candidates known to be sensitive to quaternary ammonium compounds or in poor health or with broken skin on hands, face, or neck; testing in a controlled-temperature environment; alerting subjects to signs and symptoms of heat stress; monitoring heat index with associated stopping rules; allowing subjects to rest whenever they want or need to; close observation of subjects; training of experienced technicians to minimize embarrassment; incorporation of procedures to keep results of pregnancy testing private and to permit discrete withdrawal; provision of appropriate work clothing and PPE.
- There were no reported or reserved adverse reactions.

4. Benefits

- This research offered no direct benefits to the subjects.
- The research is likely to provide reliable data about the dermal and inhalation exposure of people pouring liquid antimicrobial products from conventional and reduced-splash containers.
- These data can likely be used by EPA and other regulatory agencies to support exposure assessments for a wide variety of antimicrobial products and their uses.

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5. Risk/Benefit Balance

- Risks to subjects were thoughtfully and thoroughly minimized in the design of the research.
- The low residual risk was reasonable, in light of the likely benefits to society from new data supporting more accurate exposure assessments for antimicrobial products.

6. Independent Ethics Review

- The proposed research was reviewed and approved by the Independent Investigational Review Board, Inc., (IIRB) of Plantation Florida.
- The submitted materials included a full record of correspondence between the investigators and the IIRB.

7. Informed Consent

- Informed consent was obtained from each prospective subject and appropriately documented in the language preferred by the subject.
- The proposed monetary compensation was not so high as to unduly influence participation.

8. Respect for Subjects

- Subject-identifying information was recorded only once; all subsequent data records and reports refer to individual subjects only by a randomly selected code.
- Provision was made for discrete handling of the pregnancy testing required of female subjects on the day of testing.
- Candidates and subjects were free to decline to participate or to withdraw at any time for any reason, without penalty.

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