Final Minutes of the
United States Environmental Protection Agency (EPA)
Human Studies Review Board (HSRB)
January 25–26, 2017, Public Meeting
HSRB Website: www.epa.gov/osa/human-studies-review-board

Committee Members:	(See EPA HSRB Members List—Attachment A)	
Date and Time:	Wednesday, January 25, 2017, 1:00–5:00 p.m. EST Thursday, January 26, 2017, 1:00–5:00 p.m. EST (See *Federal Register* Notice—Attachment B)	
Location:	Via Teleconference and Webinar	
Purpose:	The EPA HSRB provides advice, information and recommendations on issues related to the scientific and ethical aspects of human subjects research.	
Attendees:	Chair:	Liza Dawson, Ph.D.
	Vice Chair:	Edward Gbur, Jr., Ph.D.
	Board Members:	Jennifer Cavallari, Sc.D., CIH Gary L. Chadwick, Pharm.D, M.P.H., CIP Alesia Ferguson, Ph.D. George C. J. Fernandez, Ph.D. Kyle L. Galbraith, Ph.D. Jewell H. Halanych, M.D., M.Sc. Walter T. Klimecki, D.V.M., Ph.D. Randy Maddalena, Ph.D. Jun Zhu, Ph.D.
Meeting Summary:	Meeting discussions generally followed the issues and general timing as presented in the Meeting Agenda unless noted otherwise.	

Wednesday, January 25, 2017

Convene Public Meeting

Mr. Jim Downing (Designated Federal Officer [DFO], HSRB [or Board], Office of the Science Advisor [OSA], EPA [or the Agency]) convened the meeting at 1:00 p.m. and welcomed Board members, EPA colleagues and members of the public. He expressed appreciation to the Board members for their service and thanked EPA's Office of Pesticide Programs (OPP) for preparing for this meeting. As DFO, Mr. Downing, under the Federal Advisory Committee Act (FACA), serves as liaison between the HSRB and EPA and is responsible for ensuring that all FACA requirements are met regarding the operations of the HSRB. Also in his role as DFO, he must work with appropriate Agency officials to ensure that all applicable ethics regulations are satisfied. HSRB members were briefed on federal conflict-of-interest laws and have completed a standard government financial disclosure report, which has been reviewed to ensure that all ethics requirements are met.

Mr. Downing informed the Board that several interesting topics will be discussed during the meeting. He noted that agenda times are approximate, and the group will strive to allow adequate time for Agency presentations, public comments and the Board's thorough

deliberations. Copies of all meeting materials are available on the HSRB website at www2.epa.gov/osa/human-studies-review-board. Following the presentations, time was scheduled for the Board to direct questions of clarification to EPA staff and the sponsors of the studies discussed. This time was used for points of clarification, rather than Board discussion. A period was also scheduled for public comments.

In accordance with FACA requirements, meeting minutes, including a description of the matters discussed and conclusions reached by the Board, are prepared and must be certified by the meeting Chair within 90 days. The approved minutes will be available on the HSRB website at www.epa.gov/osa/human-studies-review-board. The HSRB also will prepare a final report in response to questions posed by the Agency, which will include the Board's review and analysis of materials presented. The final report will be available on the HSRB website at www.epa.gov/osa/human-studies-review-board. Mr. Downing then turned the meeting over to the HSRB Chair, Dr. Liza Dawson.

Virtual Meeting Operations

Dr. Dawson reviewed the operating procedures for the virtual meeting. She instructed Board members to use the Adobe Connect meetings feature that allows them to raise their hands in the webinar to be recognized by the Chair when offering comments. When voting, the Board members used the polling function in the webinar to agree or disagree with the proposal.

Introduction of Board Members

Dr. Dawson welcomed the Board members and asked them to introduce themselves, providing their names, affiliations and areas of expertise. She noted a change in the agenda: the follow-on discussion on mosquito repellency testing has been moved to the end of today's discussions.

Opening Remarks

Dr. Thomas Sinks, Director, OSA, welcomed Board members and thanked them for supporting EPA and providing irreplaceable third-party review for human subjects research. He expressed appreciation to Mr. Downing for his continued dedication in preparing for these meetings, including conducting meetings remotely from the office as situations become necessary. Dr. Sinks also thanked OPP for conducting scientific reviews and providing the background for the many human research topics. Recognizing that the change in Administration, as it does every federal cycle, brings changes to the various federal agencies, EPA remains committed to properly reviewing human subjects research and will continue to do so with the guidance and advice of the HSRB.

Brief Update on the Research Discussed at the Last HSRB Meeting

Ms. Michelle Arling, OPP, the new Human Research Ethics Review Officer, updated members on OPP's activities. In January 2017, final revisions to the Federal Policy for the Protection of Human Subjects, the Common Rule, were published in the *Federal Register*. These efforts were led by an Interagency Working Group composed of representatives from the Department of Health and Human Services (HHS) and 15 other federal departments and agencies. The major changes to the Common Rule in the final ruling include establishing new guidelines for the informed consent process; allowing the use of broad consent from a subject for storage, maintenance, and secondary research use of identifiable private information and identifiable biospecimens; establishing new exempt categories of research based on their risk profile; establishing a requirement for U.S.-based institutions engaged in cooperative research to use a

single Institutional Review Board (IRB) for research taking place within the United States; and removing the requirement to conduct continuing review of ongoing research for studies that undergo expedited review. The final rule can be accessed from the Office of the Federal Register website: www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects. These changes will affect EPA's Code of Federal Regulations (CFR) Title 40, Part 26, Subpart A, but not Subparts K and L, which are not linked to the Common Rule. OPP is reviewing the final revisions to the Common Rule and will consider whether changes to the parts of EPA's rule on the protection of human subjects related to review of research by third parties are warranted.

The Board was reminded of the review of the research discussed in the article titled "Assessing Intermittent Pesticide Exposure From Flea Control Collars Containing the Organophosphorus Insecticide Tetrachlorvinphos (TCVP)" at the January 2016 HSRB meeting, and the standards applicable to the Agency's reliance on research as provided in 40 CFR, Part 26, Subpart Q, §26.1703, §26.1704(b), and §26.1706. Since the HSRB's review, OPP posted notice of EPA's proposal to rely on data from human research on TCVP exposure from flea collars in the April 11, 2016, *Federal Register*. In December 2016, OPP posted to its website and to the *Federal Register* docket for TCVP an explanation regarding its decision to rely on these data; this satisfies the last requirement for EPA's reliance on otherwise unacceptable data. EPA's final risk assessment included (1) risks and concerns for individuals, including children, in residential settings exposed to dust and powder products in pet collars; and (2) exposure of workers applying TCVP. The Agency has contacted the pesticide manufacturers to initiate discussions with them to reduce exposure and resolve potential risks identified in the human health risk assessment. The Agency will issue a proposed decision in 2017 for public comment.

Ms. Arling updated the Board on the activities regarding the Agricultural Handler Exposure Task Force (AHETF) exposure study to determine the potential dermal and inhalation exposure for workers who mix and load water-soluble packets (WSP), which are applied as liquid sprays. During the initial stages of this study, which the HSRB discussed in July, the AHETF identified work practices that the task force, EPA and state regulators all agreed were contrary to the proper use of WSPs as an engineering control intended to reduce exposures these practices likely substantially increased exposures because of improper use. As a result, the AHETF, in consultation with EPA, California's Department of Pesticide Regulation (CDPR) and the Canadian Pest Management Regulatory Agency (PMRA), drafted a set of best practices for handling and adding WSPs to spray tanks. These draft instructions are aimed at ensuring that WSPs are allowed to dissolve properly in water and preventing WSPs from being ruptured by streams of water or other means. EPA consulted with state pesticide regulators through the State Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Issues Research and Evaluation Group (SFIREG) and the American Association of Pesticide Safety Educators (AAPSE) about the proposed language, and formed an OPP workgroup to determine how to address the states' input. The OPP workgroup incorporated the states' comments into the revised label language, which was then shared with the states and the AHETF. OPP determined that approximately 200 products are sold in water soluble packaging and OPP will engage the pesticide registrants for those 200 products to revise their product labels to include the updated best management practice language to alleviate this problem. EPA plans to send letters detailing these revisions to all registrants of these products.

Regarding other actions since the October meeting, OPP is awaiting the HSRB's final report before engaging in follow-up with study sponsors on the Antimicrobial Exposure Assessment Task Force's (AEATF's) II Solid Pour Study and the protocol submitted by i2L Research/Triton.

Topic 1: Follow-on Discussion on Mosquito Repellency Testing

Dr. Dawson reminded members of OPP's proposal to the HSRB on testing insect repellency in field studies and the questions on whether new guidance to address conducting these studies considering the current Zika virus situation would be needed. EPA proposed that field testing for skin-applied repellents represents both the most realistic use conditions and provides the highest level of confidence that the efficacy claim on the product label is accurate. Questions of whether the risks of Zika transmission should be mitigated and the methods involved were brought to the attention of the Board. EPA offered the adoption of certain limitations if such field studies are to continue, such as additional exclusion criteria for subjects and rules on selection of testing sites in areas with no evidence of active transmission.

Dr. Dawson noted the Board's approval to defer formal recommendations on repellency field testing to the January 2017 meeting. In developing the draft working outline of the deliberations to compose formal recommendations, she engaged the opinions of vector biologists and entomologists who have expertise in the study of transmissions of vector-borne pathogens: Dr. Kacey Ernst, University of Arizona; Dr. Laura Kramer, New York State Department of Health; and Dr. Harry Savage, Centers for Disease Control and Prevention (CDC). Recognizing the depth and complexity involved in providing a response to EPA on the impact of Zika outbreaks on mosquito repellency testing, Dr. Dawson suggested extending invitations to these and similar experts to join in the Board's discussions of these issues at the next HSRB meeting. It will be necessary for the Board to address and define the broad issue of "evidence" or "no evidence" of active Zika transmissions in regards to field testing, risks and acceptability of those sources of evidence to EPA's continuing to conduct field testing, and mitigations warranted (e.g., there may be some tradeoff in site selection, as sites that are most relevant might be more risky, and those that are less risky might be least relevant for studying repellency). Engaging experts to survey the landscape will be one place to begin to address these issues. Experts will be able to speak broadly on the types and sources of Zika virus data available (e.g., mosquito population surveillance data and human cases of disease), as well as on other epidemiological factors. The Board then will be able to make informed scientific and ethical recommendations to EPA about the identifiable risks, the acceptability of those risks and mitigations required for field testing.

Mr. Downing pointed out that Consultant to the HSRB, Dr. Kendra Lawrence, has expertise in entomology and also could join the discussions on the Zika virus and field testing issues at the March 2017 Board meeting. Dr. Dawson will work with Mr. Downing to organize a discussion on vector biology at the next meeting; relevant materials for the discussion will be circulated to the Board in advance of the meeting.

EPA Overview of Physiologically Based Pharmacokinetic (PBPK) Modeling

Dr. Sarah Gallagher, OPP, explained that the Agency intends to utilize data from two human dosing studies for the evaluation of chemical-specific physiologically based pharmacokinetic (PBPK) models for human health risk assessment. Currently, PBPK models are being developed for several pesticides. These models allow risk assessors to convert an external applied dose from an animal toxicity study into an internal dose at the target organ. These models incorporate biological and chemical properties that determine pharmacokinetic processes (i.e., absorption, distribution, metabolism, excretion), and thus, allow the internal dose to be predicted from an external applied dose. These models can allow risk assessors to characterize human health risk based on the assumption that a similar tissue response will arise from an equivalent tissue dose allowing for the prediction of a human dose that will produce a given effect, irrespective of the species and exposure conditions for the experimental data, and thereby, reducing uncertainty associated with extrapolations based on external dose. The Agency reviewed the human studies for two acetylcholinesterase (AChE) inhibitors, carbaryl and malathion to

ensure that they were conducted ethically and using sound scientific methods, and concluded that these studies are appropriate to evaluate the PBPK models. EPA requested comments from the HSRB on these evaluations. After receiving input from the HSRB, EPA will conduct evaluations of the PBPK models, and then present the models to the FIFRA Scientific Advisory Panel (SAP) for external peer review later in 2017.

Although both studied pesticides are AChE inhibitors, carbaryl is an N-methyl carbamate (NMC) pesticide and malathion is an organophosphate pesticide (OP). For both classes, the initiating event is inhibition of the enzyme acetylcholinesterase. This inhibition results in the accumulation of the neurotransmitter acetylcholine and ultimately results in nervous system toxicity. The NMCs and OPs are differentiated by their mode of action (MOA) at the active site of AChE; NMCs inhibit the enzyme by carbamylation of the serine hydroxyl group, a reversible process; and OPs inhibit the enzyme via phosphorylation of the serine hydroxyl group, which is irreversible.

The carbaryl and malathion human studies have both similarities and differences. The carbaryl study is a literature study, provides a summary of statistics, and includes pharmacokinetic (PK) data (e.g., plasma carbaryl concentrations) and pharmacodynamic (PD) data (e.g., red blood cell [RBC] AChE inhibition). The malathion study is a registrant-sponsored study that was conducted under good laboratory practice (GLP) guidelines. It contains more extensive information including the raw data, analytical method validation information, and similar PK (e.g., plasma malathion/malaoxon concentrations and urinary metabolites) and PD (e.g., RBC AChE inhibition) data to the carbaryl study.

In OPP's AChE policy, which describes the use of AChE data in human health risk assessments, OPP considers a combination of statistical and biological considerations and uses a 10 percent inhibition in AChE to set a point of departure for risk assessment. The 2004 report of the National Academies of Science (NAS) titled "Intentional Human Dosing for EPA Regulatory Purposes: Scientific and Ethical Issues," provides guidance on studies where no biological effect is observed at the doses used or no observed effect level (NOEL)-only studies. These are studies where a biological response is not observed at any of the tested doses. The NAS's concern was that the absence of effects does not provide evidence that the study would have been able to detect an effect if it were present. Therefore, the NAS concluded that these studies are not useful for risk assessment and advised against using them. EPA proposed to use the results of the carbaryl and malathion human studies in a different manner, and therefore, remains consistent with the NAS recommendation. All of the data on pesticidal and metabolite concentrations will be utilized, comparing the human data to the model predictions. The situation differs somewhat for the AChE data. For carbaryl, the mean acetylcholinesterase inhibition measured was greater than 25 percent, and therefore, the response is considered to be treatment-related according to OPP's AChE policy. In contrast, no treatment-related AChE inhibition was observed for malathion, making it a NOEL study. EPA, therefore is proposing to use the AChE inhibition data from the carbaryl human study to evaluate the PBPK model, since the study was able to identify a treatment-related effect. In contrast, the AChE inhibition data from the malathion study will not be used.

Dr. Cecilia Tan, OPP, provided an overview of PBPK modeling and began by summarizing EPA's typical risk assessment, which uses default uncertainty factors. Generally, a dose response relationship of the chemical being assessed is performed in animals and is used for establishing a point of departure, such as the no observed adverse effect level (NOAEL) or benchmark dose level (BMDL) This point of departure in animals is then divided by an interspecies uncertainty factor (UF_A), which has a default of 10-fold, to establish a point of departure in humans. The point of departure in humans then is divided by an intraspecies

uncertainty factor (UF_H) to derive the reference dose (RfD) that is protective of variability within the human population.

Dr. Tan detailed efforts that have led to revising the default values for inter- and intra-species extrapolation to empirically derived values. In the 2009 National Research Council (NRC) report "Science and Decisions: Advancing Risk Assessment," EPA was advised to continue to expand the use of the best and most current science to support or revise default assumptions. The 2013 Institute of Medicine (IOM) report "Environmental Decisions in the Face of Uncertainty" supports the use of scientifically derived extrapolation factors, rather than default factors, if (1) adequate scientific evidence on the differences in the metabolism or MOA of a chemical in animals versus humans had been determined; and (2) those factors reflect the differences between animals and humans more accurately than default factors. In 2014, EPA published a report titled "Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors (DDEF) for Interspecies and Intraspecies Extrapolation," which provides guidance to risk assessors. The goal is to maximize the use of available data and improve the scientific support for a risk assessment.

Dr. Tan also described the 2004 NAS report "Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues", which evaluated the potential for using PBPK modeling to determine DDEFs for risk assessment. This report emphasized that successful development of such models would depend on the availability of PK data in humans. In September 2006, EPA released a final report describing the evaluation and applications of PBPK models in health risk assessment, which concluded in the Agency's acceptance of this method as a scientifically sound approach to estimating internal dose of a chemical to a target and for evaluating and describing the uncertainty in risk assessments. PBPK models intended for use in risk assessment, such as interspecies extrapolation of the dose-response relationship, should be evaluated to ensure that they provide simulations of PK profiles consistent with the experimental data.

Dr. Tan summarized EPA's proposed use of the carbaryl and malathion data for PBPK modeling and noted that both studies are considered reliable for the intended use related to PBPK model evaluation. The human PBPK model was developed using the rat model, which was calibrated using rat PK data, and human *in vitro* metabolism measurements. EPA plans to use the carbaryl plasma concentration and AChE inhibition data obtained in the human studies to increase confidence in results from the human model. The PD and PK data summarized in the published paper will be compared to PBPK model predictions. Preliminary simulations of the model revealed that model predictions were consistent with the study data, so it is unlikely that the human data will be used beyond that point.

The 2004 NAS report previously referenced states that useful PK data can be developed in humans using very low doses of chemicals—doses that cannot cause adverse effects (AE) or detectable biological changes in research participants. The malathion study contained PD data, the AChE inhibition data, which did not show inhibition of enzyme; EPA will not use these data. But, EPA plans to use the measured PK data, which include urinary metabolites, malathion monocarboxylic acid (MCA) and dimethyl phosphate (DMP) concentrations, and plasma malathion and malaoxon even though they are below limits of quantitation (LOQ). EPA plans to compare the urinary MCA and DMP data and the LOQ for malathion and malaoxon with model predictions. Unlike the carbaryl study, there is no preliminary simulation for the malathion study. If the trend of the model predictions is not consistent with the study data, then the urinary metabolite data may be used to adjust model parameters to improve agreement between the model and observed data.

Dr. Dawson invited Board members to ask questions on the PBPK overview. In response to a query by an HSRB member on the 10 percent inhibition in AChE in risk assessment, EPA clarified that the 10 percent inhibition is used as the benchmark response level for establishing regulatory endpoints regardless of whether a point of departure was set on AChE inhibition in the RBCs, plasma, or brain.

An HSRB member asked whether a different study would be needed for validating the model if the model predictions for malathion PK did not agree with the study data and which parameter would be used for adjusting the model. EPA responded that the urinary excretion rate would likely be the first parameter that modelers would adjust. There are no plans to review other studies to validate the current model. Given that two types of PK data are available from the malathion study, one could be used to adjust the model and the other would be used for validation.

Dr. Dawson asked for clarification of the use of PK data for modeling when there are no detectable biological changes. EPA pointed out that PK data could be an indication of the presence of chemical in the plasma or tissues, without necessarily representing a biological response to that chemical. Time-course data, even when they are below LOQ, are useful PK data.

An HSRB member asked about the statistical analysis to ensure that the proposed model aligns with the study data. EPA pointed out that the PBPK model output (e.g., preliminary simulations), goodness-of-fit, and validation will be reviewed by the FIFRA SAP and are outside of the scope of today's HSRB review. Dr. Dawson explained that a separate group will provide advice/comments on the PBPK model and the uses of the model. EPA clarified that the Board will provide comments on the scientific and ethical aspects of the studies discussed in today's meeting that will be used to develop a PBPK model. After discussions with the SAP on the models and nonhuman research, OPP will update the HSRB on the status of the PBPK model development. In general, it is important for the Board to understand OPP's process, but the objective is to focus on the charge questions.

Some HSRB members wondered about the rationale for choosing the preliminary simulation model design for the carbaryl data and whether it was dependent on the chemical being evaluated or modeled. The curve does not appear to be the best fit for the PD data. EPA pointed out that the PBPK model is a predictive model and not a curve-fitting model. Selections for simulations are based on human physiology (e.g., tissue volume) and compartmentalization of the chemical. HSRB members observed that the simulation model for the carbaryl PD data closely resembles a deterministic mathematical model. A probabilistic model might be a better choice. EPA confirmed that the simulation was a deterministic model and noted that some PBPK models use a probabilistic model.

Topic 2: Published article: "Cimetidine-Carbaryl Interaction in Humans: Evidence for an Active Metabolite of Carbaryl," by D. G. May, R. J. Naukam, J. R. Kambam, and R. A. Branch. *Journal of Pharmacology Exposure Therapy* (1992) 262(3): 1057–61.

Dr. Dawson introduced Topic 2 and asked Dr. Gallagher to present EPA's science review.

EPA Science Assessment

Dr. Gallagher provided an overview of the research published in the article titled "Cimetidine-Carbaryl Interaction in Humans: Evidence for an Active Metabolite of Carbaryl."[1] Carbaryl is one of the most widely used broad spectrum insecticides. Toxicity studies in laboratory animals (e.g., rat model) using carbaryl reveal that the nervous system is the primary target organ and that this neurotoxicity is mediated by the inhibition of AChE. Data from studies in rats for carbaryl demonstrate a mode of action for NMCs that involves rapid onset and rapid and complete recovery. This mode of action is seen across the large database available for carbamates, which includes both rat and human studies. These data are consistent with the results of the carbaryl human study, increasing the confidence in the results from the human study EPA presented.

The objective of the study reported in May *et al.* (1992) was to evaluate the effect of cimetidine, a histamine H_2 receptor antagonist that is known to reduce the activity of cytochrome P450 (CYP450) isozymes, on carbaryl PK and PD in humans. EPA proposed to use the AChE inhibition data and carbaryl plasma concentration data for the evaluation of the human PBPK model. The human data will be compared to the time-course simulations from the model to evaluate predictive capability. Currently, the data are not expected to be used to further adjust parameters.

The study design consisted of administering a single oral dose of 1.0 milligram per kilogram (mg/kg) carbaryl to four normal nonsmoking, drug-free male subjects. The dose was based on previous research by Knaak *et al.* (1968) that demonstrated that human subjects are able to tolerate carbaryl at doses up to at least 1.0 mg/kg without symptoms. Each subject was dosed on two separate occasions: (1) carbaryl alone, and (2) carbaryl following a 3-day pretreatment with cimetidine. Blood was collected at various time points. The plasma carbaryl concentrations were measured using high performance liquid chromatography (HPLC) and the RBC AChE activity was measured using the Ellman method. The control values were the level of RBC AChE activity in the subjects prior to carbaryl administration. AChE inhibition was calculated as the percentage of inhibition as compared to the control. Results showed that following a single 1 mg/kg dose of carbaryl, the half-life of AChE inhibition was 2.6 hours and the mean peak plasma concentration was 0.26 microgram per milliliter (µg/mL). There was a strong correlation between internal dose and percent AChE inhibition. Together, the data from the human study demonstrated the expected NMC MOA response, which includes rapid onset and rapid recovery of AChE activity. These data are consistent with the results from animal studies.

EPA concluded that no scientific issues were identified during the review of this study and plans to use the carbaryl plasma concentrations and AChE inhibition data to evaluate the predictive capability of the PBPK model. Although the raw data are not available, the Agency is confident that the study is scientifically valid for use in evaluation of the PBPK model based on the use of standard methods, well-accepted analytical methods and the agreement of the study

[1] May, D.G., Naukam, R.J., Branch, R.A. *Cimetidine-Carbaryl Interaction in Humans: Evidence for an Active Metabolite of Carbaryl*. Journal of Pharmacology Exposure Therapy (1992) 262(3): 1057–61.

findings with data obtained from animal studies. Preliminary PBPK model simulations have shown reasonable agreement between model predictions and observed data.

Board Questions of Clarification—Science

Dr. Dawson invited Board members to ask questions for clarification. Noting no questions of clarification, Dr. Dawson asked Ms. Arling to present EPA's ethics review.

EPA Ethics Assessment

Ms. Arling provided EPA's ethics assessment. The presentation and subsequent ethics reviews provided details on the study subjects, inclusion criteria, consent process, respect for subjects, risks and risk minimization, independent ethics review, completeness of documentation, substantive acceptance standards, and findings and conclusion. She informed the Board that Mr. Downing had circulated the final ethics review of the carbaryl oral dosing study with human subjects just prior to the start of this HSRB meeting and that it replaces the interim ethics review distributed earlier. Per the published article, four male subjects, 23 years to 43 years of age were enrolled in the study and recruited from a pool of participants who had previously participated in short-term drug disposition studies conducted at the Center for Clinical Pharmacology, Vanderbilt University. As noted in the ethics review document, Dr. Branch's responses to Ms. Arling's requests for information about the study imply that he may have been one of the subjects in the study. When discussing recruitment, he mentioned that "some subjects were researchers, like myself." When responding to a question about compensation, he noted that he believed "each of the other subjects received $250" for their participation in the study.

Dr. Branch is now a professor emeritus at the University of Pittsburgh. After Ms. Arling received a response to the initial questions about the ethical conduct of the study by email on November 13, 2016 she sent several follow up emails requesting clarification (November 27, December 9, December 15, January 10, January 17). Ms. Arling tried to contact Dr. Branch by telephone several times as well, but his telephone number was not functioning. Ms. Arling also contacted his university requesting assistance in reaching him – they confirmed that his telephone number was not working and offered to try to get a message to him through a family member requesting that he contact her. None of these attempts resulted in more information about whether Dr. Branch was a subject in the study.

Apparently healthy males were recruited for enrollment into the study. No females or children were enrolled in the study.

According to Dr. Branch, people were excluded from participation if they were female, were not healthy (e.g., history of chronic disease; recent acute medical problem; abnormal hematology, renal or liver function tests after physical examination), were smokers, drank alcohol daily, used either therapeutic or non-therapeutic drugs for the week before or during the study.

No information was provided in the article about the consent process. In response to a question from EPA, Dr. Branch noted that subjects were informed orally and in writing about the identity, nature, and function of the test substances to which they would be exposed. Dr. Branch also noted that: "a full oral explanation for the motivation and design for the study was provided prior to obtaining written informed consent."

According to Dr. Branch's recollection, subjects were compensated around $250 – $100 for each study day, plus $50 for taking a drug suspected of inducing a drug interaction. Participation in the study was voluntary and subjects were free to withdraw from the study at any

time. Subjects information was kept confidential – names or identifying information were not included in the published article or in any materials provided to EPA.

The primary risks to subjects were symptoms related to AChE inhibition and overstimulation of the nervous system, causing headaches, nausea, abdominal distress and blurred vision. Symptoms were minimized through dose selection, inclusion/exclusion criteria, and a stopping rule. The dose of carbaryl used in the study (1.0 mg/kg) was selected based on previous research, some of which involved human subjects showing that doses at this level "are well tolerated without symptoms." The risks of participating in the study were minimized through the selection of apparently healthy adults, exclusion of people who smoked, drank, or took drugs or whose blood test results were abnormal. According to Dr. Branch, the study had a stopping rule whereby a subject would not proceed to receive the second dose of carbaryl if the subject experienced "unpleasant symptoms" after administration of the first dose. No subject's participation in the study was stopped.

Both the published article and Dr. Branch noted that the research was approved by an independent ethics review body. Dr. Branch said the research received approval prior to implementation.

Dr. Branch indicated to EPA that he no longer had any records associated with the study and recommended that EPA contact the Vanderbilt IRB.

EPA contacted the IRB but could not obtain any materials associated with this study. OPP contacted both the Vanderbilt Institutional Committee for the Protection of Human Subjects and Vanderbilt Clinical Trials Center by email and by telephone to request records relating to the ethical conduct of the study discussed in the article. Ms. Arling did not receive a written response from either entity. In a telephone conversation on December 9, 2016, a representative of the Vanderbilt Institutional Committee for the Protection of Human Subjects indicated they could provide their records associated with the review of research only to the primary investigator. In a telephone conversation on December 15, 2016, a representative of the Vanderbilt Clinical Trials Center indicated that the General Clinical Research Center no longer exists and suggested contacting the Institutional Committee for the Protection of Human Subjects to request the records associated with Dr. Branch's research.

As noted in the interim ethics review memo, the organization submitting this article to EPA for consideration (Tessenderlo Kerley, Inc., or TKI) was responsible for providing to EPA at the time of submission information about the ethical conduct of the study or documentation of its efforts to obtain such information.

On January 10, 2017, EPA received documentation of TKI's efforts to obtain information about the ethical conduct of the study. According to a representative of TKI, "Dr. Branch confirmed to Dr. Pastoor (a representative of TKI) that there was a review of the study design by the Vanderbilt Office for Human Research Protections, or OHRP, (formerly called the Vanderbilt Institutional Review Board, or IRB), and suggested that we contact Vanderbilt directly to obtain the records of the review."

Dr. Pastoor placed several telephone calls and sent a series of emails to those listed as contacts on the Vanderbilt OHRP webpage. TKI contacted the medical director of Vanderbilt's Human Research Protection Program (HRPP), who confirmed that the IRB records for this 25-year old study are no longer available. The director of the Vanderbilt's HRPP explained to TKI that the university's IRBs had been registered with the federal government since 1966, indicating that this study would have undergone the proper IRB review. TKI satisfied the

requirement of 26.1303 by providing email documentation of its efforts to obtain the ethics-related information.

Ms. Arling discussed the standards applicable to EPA's reliance on the research. EPA 40 CFR §26.1703 prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children. The 40 CFR §26.1704 regulation prohibits reliance on data if there is clear and convincing evidence that conduct of the research was fundamentally unethical or was deficient relative to the ethical standards that placed participants at increased risk of harm or impaired their informed consent. In addition, FIFRA §12(a)(2)(P) makes it unlawful to use pesticide in human tests without fully informed and fully voluntary consent.

All subjects were at least 18 years of age and pregnant or nursing women were excluded. According to both Dr. Branch and the published article, the study design was approved prior to implementation by a Vanderbilt IRB. Although the information provided to and approved by the IRB was not available to EPA for review, lack of information does not by itself provide clear and convincing evidence that the research was fundamentally unethical.

The prevailing standard at the time was a policy on the protection of human subjects, a precursor to the Common Rule. This required review of proposed research and establishes criteria for approval of such research: risks to subjects must be minimized and reasonable in relation to anticipated benefits (to subjects and/or to resulting knowledge), equitable subject selection, documented informed consent from participants, protection of subjects' privacy and confidential data, and additional safeguards to protect vulnerable subjects. There is no evidence that the research was deficient relative to these standards in a way that placed participants at increased risk of harm or impaired their informed consent.

As described earlier, subjects were fully informed and their consent was fully voluntary, without coercion or undue influence. EPA found no evidence that participating as a subject in one's own research is fundamentally unethical.

Available information indicates that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to prevailing ethical standards in a way that would have impaired subjects' informed consent or placed them at increased risk of harm. EPA concluded that no barriers exist under law or regulation to the Agency's reliance on this research from an ethical perspective.

Board Questions of Clarification—Ethics

Dr. Dawson invited Board members to ask questions for clarification. An HSRB member noted that the Center for Clinical Pharmacology that was referenced as the place where participants worked was located at the University of Pittsburgh and not Vanderbilt University. EPA will verify the location of the Center for Clinical Pharmacology and make the necessary changes to Agency documents.

An HSRB member pointed out that the study design excluded women/females and wondered whether that was the normal practice regarding ethics before adoption of the Common Rule. EPA is not aware of any guidance to support the exclusion of women at the time this study was conducted, but will review the applicable standards. Dr. Dawson commented that women had been excluded from clinical studies for quite some time based on the issues of reproductive toxicity, and that may have been the rationale used in this study. The practice of excluding women from clinical studies was challenged in the 1990s, and the bioethics and clinical research communities worked diligently to make changes. Dr. Dawson added that although the Common Rule was not in effect at this time, a previous version of the Common Rule applied; this version

did not include specific prohibitions against including women, but researchers often defaulted to exclusion of women due to safety concerns. Another HSRB member explained that the Common Rule was not adopted until 1991, and this study may have been conducted before then. The study was more than likely reviewed under the HHS and Public Health Service (PHS) regulations of 1981, which later became the Common Rule. This study's IRB would have been measured under the same standards. The U.S. Food and Drug Administration (FDA) had jurisdiction over product development research before the adoption of the Common Rule, and FDA viewed the risks to unborn children as justification to not enroll women of reproductive potential in many clinical trials.

Dr. Dawson, noting no further questions of clarification, asked Mr. Downing to call for public comments.

Public Comments

Mr. Downing announced that no public comments were received for this topic. He called for any comments from the meeting attendees, and no public comments were offered.

Board Discussion—Science

Before beginning the Board's discussion, Dr. Dawson read the following science charge into the record:

> Is the research described in the published article "Cimetidine-Carbaryl Interaction in Humans: Evidence for an Active Metabolite of Carbaryl" scientifically sound, providing reliable data?

Dr. Dawson asked discussants Drs. Walter Klimecki and Jennifer Cavallari to provide their comments. Dr. Klimecki commented that EPA articulated well the study's design and results. The study authors' ability to evaluate the PK and PD of carbaryl in the inhibition of AChE demonstrates an appropriate design. He agrees with EPA that the basic science of the study is therefore sound. The data derived in the study in regards to analytical approaches to generating PK and PD data were reasonable.

Regarding the charge question of whether the research is providing reliable data, Dr. Klimecki affirmed that from an experimental and analytical standpoint, the study provided reliable data. However, because the study addressed xenobiotic metabolism, which is highly individually variable, and did not include a broad scope of subgroups, the study had limited reliability when applied to a larger population.

Dr. Klimecki had no objections to the use of this study for the purpose envisioned at EPA. He noted minor editorial changes needed in EPA's report that would not affect the science, and he will forward those changes following close of the meeting. Dr. Cavallari agreed with Dr. Klimecki's comments that the study is scientifically sound and does provide reliable data.

Dr. Jun Zhu provided a statistical review of the study. The small sample size poses a problem for statisticians, but if the data are not being used to infer to a larger group, then it is less of a concern. The study did not provide detailed descriptions on statistical analysis, data, or software used. EPA's model simulations showed good correlation to the study data and increases confidence in the data.

Dr. Dawson solicited comments on the science assessment from the Board members. She noted a cross-cutting theme of the study design that the small sample size affects the

generalizability of the data to a larger population, but this is not a concern for the intended use of the data.

An HSRB member commented that the body weight of the study participants could play a role in the metabolism of carbaryl because the dose was calculated as 1 mg/kg of body weight. Making observations relative to body weight could affect outcome data and modeling of the design.

Hearing no further comments, Dr. Dawson asked Dr. Klimecki to present the statement in response to the charge question for voting by the Board. The response was read into the record by Dr. Klimecki:

> The Board concludes that the research described in the published article "Cimetidine-Carbaryl Interaction in Humans: Evidence for an Active Metabolite of Carbaryl" was a scientifically sound study that provided experimentally reliable data of a small set of human subjects that may or may not be generalizable to the human population.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Klimecki's response statement.

All the Board members present approved the response statement.

Board Discussion—Ethics

Dr. Jewel Halanych reviewed the ethical aspects of the study and read the following charge into the record:

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

Dr. Halanych stated that EPA's ethics assessment was thoroughly presented. She noted the exclusion of women and the age of the study, which was conducted prior to current guidelines on the ethical considerations of including women in clinical research.

Dr. Dawson solicited comments on the ethics assessment from the Board members. Hearing no comments, Dr. Halanych read the following response to the charge question into the record:

> The Board concluded that while the research was conducted before the implementation of 40 CFR, the available information supports a determination that the research was conducted in substantial compliance with Subparts K and L of 40 CFR Part 26.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Halanych's ethics review statement.

The HSRB unanimously approved the response statement.

Topic 3: Unpublished Study: "A Randomized Double-Blind Ascending Single Oral Dose Study with Malathion to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity" and "A Randomized Double-Blind Study With Malathion to Determine the Residues of Malathion Dicarboxylic Acid (DCA), Malathion Monocarboxylic Acid (MCA), Dimethyl Phosphate (DMP), Dimethyl Thiophosphate (DMTP), and Dimethyl Dithiophosphate (DMDTP) in Human Urine."

Dr. Dawson introduced Topic 3 and asked Dr. Yung Yang, OPP, to present EPA's science review.

EPA Science Assessment

Dr. Yang detailed the research in the unpublished study, "A Randomized Double-Blind Ascending Single Oral Dose Study with Malathion to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity" and "A Randomized Double-Blind Study with Malathion to Determine the Residues of Malathion Dicarboxylic Acid (DCA), Malathion Monocarboxylic Acid (MCA), Dimethyl Phosphate (DMP), Dimethyl Thiophosphate (DMTP), and Dimethyl Dithiophosphate (DMDTP) in Human Urine." The study objectives were to measure (1) plasma and RBC AChE activity in human subjects exposed to a single dose of malathion and (2) residues of urinary metabolites from human subjects exposed to malathion. EPA proposes to use the urinary and plasma concentration data to validate a PBPK model. The study was designed as a randomized, double-blind, ascending single oral dose study with malathion. Healthy adults, 27 males and 7 females, were randomized into seven treatment blocks and received a single oral dosing of malathion ascending from 0.5 mg/kg to 15 mg/kg. Control subjects, 11 males and 3 females, received a placebo. Sessions 1 through 6 were all male subjects and session 7 was made up of female participants. Subjects' vital signs, monitored after each dosing session, did not show any treatment-related effects. Based on these observations, session 7 females were dosed at the 15 mg/kg concentration. Following exposure, plasma and RBC AChE activities, plasma malathion and malaoxon concentrations, and urine metabolites were measured.

Study results showed no treatment-related effects on RBC and plasma AChE activities, even at the highest dose tested. The plasma levels of malathion and malaoxon measured as the highest tested dose and were both below the LOQ. Rapid excretion of malathion residues were observed 12 hours after treatment and clearance occurred within 24 hours. The primary urinary metabolites excreted over the 48-hour period were MCA, DMTP, DCA, DMP and DMDTP, in that order. Statistical analysis was not performed on the urinary and plasma concentration data. EPA plans to use the raw data, and statistical analysis will not be needed.

EPA concluded that the study was conducted in compliance with the Principles of Good Clinical Practice and GLP guidelines. The study was deemed scientifically sound and EPA plans to use urinary and plasma concentration data to validate a PBPK model for malathion. Dr. Yang reiterated that EPA does not plan to use the AChE inhibition data from the malathion human study.

Board Questions of Clarification—Science

Dr. Dawson invited Board members to ask questions for clarification. An HSRB member asked whether the study design (e.g., female versus male dosing regimens) would be considered in future use of the raw data, given that statistical analysis is yet to be completed, and noted that the purpose for collecting these data was not clear. EPA replied that the PBPK models will be evaluated by comparing model simulations with raw data.

Dr. Dawson noted the challenge of commenting on raw study data that have not been statistically analyzed or used to draw specific conclusions. The HSRB added that the data have been collected from sources of varying quality; the HSRB should be concerned primarily with determining whether these data provide a solid foundation on which to build a model that can begin by addressing limited questions and develop over time. EPA expressed appreciation for the comments from the HSRB and acknowledged the unique application of this scientific and ethical review. OPP's integration of PBPK modeling into its risk assessments is becoming more prevalent, and the upcoming FIFRA SAP will review all aspects of several new PBPK models that could greatly expand their use in pesticide regulation. EPA emphasized that HSRB's charge is to determine whether the data are scientifically sound and that model validation will be conducted by the FIFRA SAP.

Dr. Dawson noted that the HSRB should provide a comment if the number of variables for which data had not been collected was a concern; she added that this issue is only one part of a longer process and questioned whether additional sources of data would be used to develop the models. EPA pointed out that carbaryl and malathion have been studied extensively for decades and these data, combined with recent reports on human metabolism of these chemicals, build confidence in the development of reliable PBPK models. A PBPK model requires many parameters and substantial knowledge of human physiology and understanding of pharmacokinetic behaviors of these chemicals, but many of these elements already are in risk assessments developed by EPA and will be reviewed by the FIFRA SAP. EPA added that the Agency has confidence in the ability of the existing risk assessments to account for exposure differences among individuals, although supplemental information is out of the scope of the discussion and therefore was not provided to the HSRB. Dr. Dawson thanked EPA for confirming the extensive knowledge underlying these models.

Dr. Dawson, noting no further questions of clarification, asked Ms. Arling to present EPA's ethics review.

EPA Ethics Assessment

Ms. Arling provided EPA's ethics assessment. This research was conducted from 1998 to 1999, and study reports containing protocol and amendments and correspondences with the IRB were submitted to EPA in 2000, prior to EPA's Rule for Protection of Human Subjects, which became effective in 2006. The documentation on the ethical conduct of the study is contained in the study reports and was provided to the HSRB prior to today's meeting. She noted that the science review reported on data from two different studies, but references discussed in the ethics review are from the primary study report titled "A Randomized Double-Blind Ascending Single Oral Dose Study with Malathion to Determine the No Effect Level in Plasma and RBC Cholinesterase Activity."

Forty-eight subjects, 38 males and 10 females, who were recruited from the surrounding areas by use of a generic advertisement for volunteer participation, were enrolled in the study. Before the start of the study, subjects were randomly assigned to the malathion and placebo groups.

Regarding inclusion/exclusion criteria, subjects ages 18 to 50 years old with normal pre-screening exams were enrolled. Pregnancy status was confirmed by urinary test at the screening exam and at the pre-dosing exam the day before the dose was administered. Exclusion criteria focused on any conditions/behaviors that could affect AChE, to minimize the chances of a participant experiencing an inhibition of AChE from anything other than participation in the study. Each volunteer's personal physician was consulted and asked to confirm that the volunteer was healthy and able to participate in the study; also requested that MDs notify study sponsors if

any symptoms related to ChE exposure manifested after study ended. A total of 51 subjects were recruited and 48 subjects were enrolled. Two subjects recruited did not enroll in the study because they could not swallow capsules, and one subject was not enrolled because he/she had abnormal blood test results at the screening. These subjects were replaced prior to the administration of the malathion dose with alternates who met the inclusion and exclusion criteria.

The informed consent process included providing oral and written information to potential subjects that explained the study procedures, risks and discomforts. At the screening visit, each subject was informed of the nature and risks of the study and given a copy of the volunteer consent form and information to review. On admission to the clinic on the evening prior to dosing, written informed consent was obtained from each volunteer. Each subject's general practitioner was asked if they had any objections to their patient's participation before the start of the study. Each subject provided written informed consent before start of the study.

The information sheet provided to subjects during the consent process included a section on the risks involved in the study. Risks included symptoms related to AChE inhibition, such as headache, nausea, abdominal distress and blurred vision. Study and risks were explained orally during an in-person meeting and in writing through the consent materials. The doses were selected based on previous research which showed that they were unlikely to have measurable effects on cholinesterase and that not likely to cause any clinical signs. To minimize discomfort, participants were offered the option of giving blood samples through a cannula (a single puncture) or repeated blood draws. The protocol was amended to require confirmation of no significant inhibition of cholinesterase activity at each dose level before proceeding to the next higher dose level. Subjects were monitored by medical staff throughout the study.

Forty-four AE were reported in 20 of the 48 subjects; four AE were reported before the start of the study and 40 occurred after dosing. The investigator evaluated each event at the time it was reported, while the study was blinded. Some events were considered possibly related to study participation. However, a second evaluation considered the dose received, clinical results such as cholinesterase inhibition, and other factors, resulted in a determination that no adverse effects were likely related to the subjects' participation in the study. According to the report, "among treated subjects, there was no evidence that there was an increased incidence of adverse events with increasing dose level." There was one serious adverse event that required the subject to be hospitalized. However, the event was not related to the test compound.

Regarding respect for subjects, the consent form and information provided to volunteers noted that subjects were free to withdraw at any time during the study without penalty. The information did describe the risks of withdrawing after the dose was administered. No subjects withdrew from the study. Subjects were compensated for their participation. At the completion of the study, each subject received £450 (about $640 at the time the study was conducted). There is no information on compensation provided to the three subjects who were recruited and participated in the screening but who were not enrolled in the study. Subjects were informed that their information would be kept confidential. Subjects are identified by a number, not by name. The subjects' identities are not revealed in the study report.

The reviewing body was independent of Inveresk Research. The study report includes the constitution of the ethics committee (p. 290), which specifies that it is "an ad hoc committee of independent advisors comprising a panel of consultant physicians and surgeons, general practitioners, lay person (including ministers of religion), and nurses. Their function is to advise Inveresk Research on the ethical acceptability of clinical research." The normal composition of the committee was four medical practitioners, a lay member, and a nurse. A document dated October 29, 1998 and signed by the Secretary of the Independent Inveresk Research Ethics Committee noted that it "is completely independent of "Inveresk Research" and no member of the

Committee is employed by the company." The documentation from the meetings at which the protocol and some amendments were discussed include which members were present and their roles. The final protocol was approved on October 28, 1999.

The protocol stated that each amendment would be documented, signed, and dated by the study director, and sent to the sponsor and ethics committee for approval. (p. 169) The study director documented each amendment and notified the study sponsor, but did not send all amendments to the ethics committee for approval. Amendments 1 and 2 were reviewed and approved by the ethics committee prior to implementation. Amendments 3, 4 and 5 were not submitted to the ethics committee, deviating from the protocol. These amendments were not related to interactions with the subjects; rather, they were about the handling of the samples after collection. These amendments did not negatively affect participants' rights, health or safety, because they were made after the clinical portion of the study concluded. The dosing study concluded in March 1999. Amendment 3 was made in May 1999 (p. 239). Amendment 4 was made in September 1999. Amendment 5 was made in December 1999. However, the amendments should have been submitted to and approved by the ethics committee prior to implementation. Deviations from the protocol related to sample collection were reported on page 43 of the primary study report. These deviations did not negatively affect the rights, health, or safety of the subjects.

Ms. Arling discussed the standards against which EPA reviewed the research to determine whether it was acceptable from an ethical standpoint to rely on the data. EPA cannot rely on research that involves intentional exposure of pregnant or nursing women, or of children. EPA also cannot rely on research if there is clear and convincing evidence that the research was fundamentally unethical, or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent. The standards in place at the time this research was conducted was the Declaration of Helsinki. The key ethical principles in the Declaration of Helsinki are respect for persons (informed, voluntary consent, freedom to withdraw, and protection for vulnerable populations), beneficence (do not harm, and maximize possible benefits and minimize possible harms) and justice (equitable subject selection, adequate but not unduly high compensation).

The research did not involve intentional exposure of pregnant or nursing women, or of children. Women were tested for pregnancy at two points prior to dosing (screening and pre-dose exam). Women were excluded if breastfeeding. No person under 18 years old was enrolled in the study. There is nothing in the documentation EPA reviewed to indicate that the research was fundamentally unethical. Furthermore, the research seemed consistent with the ethical standards at the time. The study was reviewed prior to implementation by an independent ethics body, subjects were informed of the risks of participating, subjects gave written informed consent prior to enrolling, subjects were free to withdraw from the study at any time without negative effects (though the potential risks to the subjects of early withdrawal were explained) the dose selection was designed to escalate only after the previous dose showed no significant clinical effects and were chosen based on previous animal and human studies, subject selection did not seem unequitable and was conducted according to the screening criteria approved by the IRB, and finally, subjects were compensated for their participation. Some amendments were not reviewed and approved by the IRB, and there were several deviations to the proposal. However, in EPA's opinion, there is no clear and convincing evidence that the research was deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

The consent form and informational materials did tell subjects that the test substance was malathion, a pesticide.

Available information indicates that the malathion oral dosing study under EPA consideration was conducted in substantial compliance with the prevailing ethical standards of the time. EPA's finding is that there were no significant deficiencies in the ethical conduct of the research. There are no barriers under law or regulation to EPA's reliance on this research from an ethical perspective.

Board Questions of Clarification—Ethics

Dr. Dawson invited Board members to ask questions for clarification. There being none, Dr. Dawson asked Mr. Downing to call for public comments.

Public Comments

Mr. Downing announced that no public comments were submitted into the record. He called for any comments from the meeting attendees, and no public comments were offered.

Board Discussion—Science

Dr. Dawson asked discussants Drs. Klimecki and Cavallari to provide their comments. Dr. Klimecki read the following science charge into the record:

> Did the research on plasma levels of malathion and malaoxon, and urinary metabolites of malathion, as described in the study reports "A Randomized Double-Blind Ascending Single Oral Dose Study With Malathion to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity" and "Determination of Residues of Malathion Dicarboxylic Acid (DCA), Malathion Monocarboxylic acid (MCA), Dimethyl Phosphate (DMP), Dimethyl Thiophosphate (DMTP), and Dimethyl Dithiophosphate (DMDTP) in Human Urine," generate scientifically sound, reliable data?

Dr. Klimecki commented that the study was conducted under scientifically sound standards, which included appropriate analytical methods, assay validations and quality control. The study generated scientifically sound and reliable data that should be useful for EPA model development.

Dr. Zhu provided a statistical review of the study. She pointed out that the statistical analysis was not the main focus in making comments related to modeling, and other guidance may be necessary to provide useful comments.

Dr. Dawson asked for comments from the Board members. She noted that the HSRB does not intend to provide comments on the use of these data for purposes other than modeling; although there are other concerns about the data, these concerns may not be relevant to the charge of the HSRB at this time. The HSRB commented that a flawed study design could have consequences for the ethics of the study; for example, the randomization of treatment groups seemed highly improbable given the presence of all female participants in one group. EPA explained that participants assigned to treatment groups 1 through 6 were randomized according to dosing, but the study protocol stated that female participants would be tested only at the highest tolerable dose in males. The rationale for this protocol may have been related to minimizing exposure and risks to women, which was the standard practice at the time of the study, but the study design cannot be commented on due to its age. Dr. Dawson agreed that the study design is not ideal by modern standards; the question to ask, however, is whether the design was sufficient to produce usable data. Standard practice is to include in HSRB's final report to EPA a list of concerns and caveats and a statement that these would not implicate the data as

unusable. The HSRB emphasized that if the Agency planned to use these data to develop a universal model, the concerns would be applicable; however, if the intent is to construct an initial model that would be built upon and revised, these data provide a sufficient foundation. Dr. Dawson commented that the data seem sufficient for the purposes described; concerns about use of the data for any purpose other than those proposed are not within the charge of the HSRB.

Hearing no further comments, Dr. Dawson asked Dr. Klimecki to present the statement in response to the charge question for voting by the Board.

> The Board concludes that the research on plasma levels of malathion and malaoxon, and urinary metabolites of malathion, as described in the study reports "A Randomized Double-Blind Ascending Single Oral Dose Study With Malathion to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity" and "Determination of Residues of Malathion Dicarboxylic acid (DCA), Malathion Monocarboxylic acid (MCA), Dimethyl Phosphate (DMP), Dimethyl Thiophosphate (DMTP), and Dimethyl Dithiophosphate (DMDTP) in Human Urine," generated scientifically sound and reliable data, for the purposes that have been proposed by EPA.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Klimecki's response statement.

All the Board members present approved the response statement.

Board Discussion—Ethics

Dr. Halanych reviewed the ethical aspects of the study and read the following charge into the record:

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

Dr. Halanych agreed with EPA's ethics review and conclusions. She noted one aspect related to safety that was not highlighted. Study participants resided in the clinic 2 days following the exposure and were closely monitored for AE.

Dr. Dawson solicited comments on the ethics assessment from the Board members. Hearing no comments, Dr. Halanych read the response to the charge question into the record.

> The Board concluded that while the research was conducted before the implementation of 40 CFR, the information provided supports a determination that the research was conducted in substantial compliance with 40 CFR part 26, Subparts K and L.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Halanych's ethics review statement.

The HSRB unanimously approved the response statement.

Closing Remarks

Mr. Downing expressed appreciation to the Board members for their participation. He stated that the Board is scheduled to reconvene at 1:00 p.m. on January 26, 2017, to discuss three published studies. Mr. Downing adjourned the meeting for the day at 5:11 p.m.

Thursday, January 26, 2017

Convene Public Meeting

Mr. Downing reconvened the meeting at 1:00 p.m., introduced himself, and welcomed back the Board members, EPA colleagues and members of the public. The Agency expressed appreciation to the HSRB members for their time and diligent work in preparing for the meeting, and thanked OPP staff for their efforts in preparing the scientific and ethical reviews on the topics for the meeting.

Mr. Downing informed the Board that three interesting topics will be discussed during today's meeting. He noted that according to FACA, time is allowed for public comments following each topic discussed. Mr. Downing informed the Board that written comments from the American Chemistry Council (ACC) have been received and copies were distributed to the Board prior to the meeting. As noted on the agenda, ACC will present its public comments to the Board at the allotted times.

Mr. Downing again thanked the Board members for their participation in this meeting and then turned the meeting over to the HSRB Chair, Dr. Liza Dawson.

Introduction of Board Members

Dr. Dawson requested that the Board members introduce themselves again. The members did so, providing their names, affiliations and areas of expertise.

Follow-Up Discussion From the Previous Day

Noting no follow-up discussion, Dr. Dawson proceeded to the next item on the agenda: EPA overview of Repeat Open Application Test (ROAT) studies.

EPA Overview of ROAT Studies

Dr. Timothy McMahon, OPP made a presentation to the HSRB titled: Dermal Sensitization Assessment for Methylisothiazolinone (MI)—Use of Human Studies. Specifically, the presentation was for the purpose of presenting human studies of dermal sensitization or allergic contact dermatitis to MI, methylchloroisothiazolinone (MCI) or an MCI/MI mixture. EPA is requesting HSRB's feedback on EPA's scientific and ethical assessments of three studies involving human subjects that examined elicitation thresholds from dermal exposure to MI or MCI/MI. The HSRB's recommendations will help the Agency conduct a quantitative assessment of dermal sensitization hazard to support the registration review of MI as an antimicrobial pesticide.

Dr. McMahon began by describing the mechanistic phases of allergic contact dermatitis (ACD)—induction (activation of immune mechanisms resulting in sensitization) and elicitation or challenge (responses induced in sensitized individuals after subsequent allergen exposure).

Sensitization differs from dermal irritation in that sensitization includes a delayed response from exposure and "immunological memory." This immunological memory can last a lifetime in sensitized individuals; in dermal irritation, the effect is reversible. For assessment of dermal sensitization, EPA uses mainly qualitative methodologies to assess whether a pesticide chemical is positive or negative for ACD when evaluating product safety in humans. Methods do exist, however, for quantitative assessment of ACD, including induction threshold measurement via human patch testing, mouse local lymph node assay (LLNA) and derivation of 'sensitization' reference doses using results of the LLNA and appropriate uncertainty factors. Elicitation thresholds also can be measured quantitatively through a minimum elicitation threshold (MET) approach. By inference, protection against elicitation is protective against induction because induction thresholds usually are higher than elicitation thresholds for sensitizers.

Assessing ACD quantitatively would allow determination of the sensitization potential and risk of pesticides for preservation of commonly used products (e.g., plastics, wood) for which labeling is not possible. In 2004, EPA became interested in developing quantitative methods for dermal sensitization hazard assessments for chemicals. This approach was presented by the Agency to the FIFRA SAP, using hexavalent chromium (a known dermal sensitizer also used in wood for preservation) as a case study to illustrate quantitative approaches. The Agency also presented available quantitative methods for determination of induction and elicitation thresholds, including the LLNA and MET approaches. The FIFRA SAP supported the Agency's effort at developing quantitative methods for dermal sensitization potential. In addition, the FIFRA SAP recommended that the MET and LLNA would be appropriate methods for sensitization data collection and that a level for protection against elicitation also would be protective against induction.

Dr. McMahon described MI as a chemical in the isothiazolinone class; it is a dermal sensitizer in animal tests and is used for both pesticidal and nonpesticidal purposes. An increase of MI contact dermatitis in the human population has been observed in the past few years. As a result, several regulatory entities have established their recommended numerical induction thresholds for MI use based on results from human and animal studies. Dr. McMahon noted that if the HSRB finds that the human studies are not scientifically or ethically adequate, the Agency will rely on results from an animal study in which dermal irritation potential of MCI/MI was determined in rats. EPA currently views dermal sensitization as more appropriate point of departure than dermal irritation; preliminary calculations indicate that the sensitization point of departure is four times more protective of public health than using the dermal irritation point of departure.

Dr. McMahon provided an overview of three human ROAT studies. EPA is proposing to use a Weight of Evidence (WOE) approach to determine the point of departure for MI in three human studies—Lundov et al. 2011 (*Contact Dermatitis* 64: 330–6), Yazar et al. 2015 (*British Journal of Dermatology* 173: 115–22), and Zachariae et al. 2006 (*Contact Dermatitis* 55: 160–6). These studies used patch testing for confirming MI or MCI/MI sensitivity and ROAT for determining elicitation thresholds to MI or MCI/MI in human subjects. These studies had strengths that include, but are not limited to, the presence of a blinded study design and the use of subjects with confirmed sensitivity to MI or MCI/MI. However, the studies had limitations: raw data from the studies are not available, there were a small number of test subjects, and EPA could not reproduce some of the statistical analyses included in the published articles. EPA considered another ROAT study [Isaksson et al. 2014 (*Contact Dermatitis* 70: 238–60)] but did not use it because there was a lack of sufficient information regarding the test subjects, blindedness, ethical conduct, etc.

Due to the lack of raw data, EPA conducted independent statistical data analysis of the studies. Therefore, the Agency proposes to use a NOAEL/lowest observable effect (LOAEL)

approach with the data from the ROAT study portions. The patch tests and ROAT protocols were used throughout these studies. Patch tests determine the skin's sensitivity to a chemical, whereas the ROAT protocol determines the elicitation threshold and clinical relevance of allergen exposure upon patch testing. EPA concludes that the Agency considers that the human data provide a more relevant risk assessment of dermal exposure to MI than animal studies.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification. An HSRB member asked how the application of material compared with the ROAT approach in the animal studies that were presented to the Board for review. EPA clarified that the animal studies featured repeated applied doses; they were not looking for sensitization.

An HSRB member asked how the elicitation outpoint was defined; in other words, what is the dose regime/scheme (e.g., per day application) of the chemical that typically results in a reaction in humans when assessing elicitation points? EPA noted that the doses in the studies are not accumulated, but mirror what the Agency deems as the "real-world" amount of chemical exposure. Incidents are graded according to the amounts that are applied.

An HSRB member asked about the rationale behind the Agency's proposal to use the three research articles that looked at MI and MCI/MI (Lundov et al., Yazar et al., and Zachariae et al.), and not the Isaksson et al. study. EPA explained that these articles were the only studies they could find, and selection was based upon the Agency's evaluation of open literature studies according to the EPA's guidance (i.e., adequate scientific information for quantitative data use, ethical criteria).

An HSRB member wondered if the dose required for elicitation for allergic response is related to the dose used for induction of an allergic response. EPA clarified that the subjects were known to be sensitive to the chemical. Dose-response relationships exist in general, but they were not known for these studies.

Hearing no additional questions of clarification, Dr. Dawson asked Dr. McMahon to present EPA's science review.

Topic 4: Published article: "Methylisothiazolinone Contact Allergy and Dose-Response Relationships," by M. D. Lundov, C. Zachariae, and J. D. Johansen. *Contact Dermatitis* (2011) 64: 330–36.

EPA Science Assessment

Dr. McMahon provided a science assessment of the "Methylisothiazolinone (MI) Contact Allergy and Dose-Response Relationships" study (Lundov et al.). The study's purpose was twofold: (1) to determine the elicitation doses for MI using two tests, a patch test and a ROAT protocol, and (2) to test the applicability of a previously established model equation for conversion between patch test and ROAT data to MI. The Agency focused on the ROAT portion of the study because of the lack of raw data and relevance to exposure scenarios.

Dr. McMahon described the design of the ROAT study. There were 11 test subjects (2 women and 9 men) and 14 control subjects (6 women and 8 men); of test subjects who completed the ROAT, 9 had a previous MI allergy, and 2 were recruited from individuals with a MCI/MI allergy. He described the dosage scheme for the study, which was designed to include the maximum amount allowed in cosmetics (100 ppm), the lowest concentration recommended

for cosmetics in Europe (50 ppm), and the concentration of MI sufficient for use as a preservative when used in combination with phenoxyethanol (5 ppm).

The study ROAT protocol involved application of solution on the forearm twice daily for 21 days. The solution was provided in four bottles and applied by a micropipette to ensure volume accuracy. Bottles containing ethanol or water were used as controls. The corresponding MI doses were 0, 0.0105, 0.105 and 0.210 microgram MI per square centimeter ($\mu g/cm^2$) per application. A grading of allergic/irritant skin responses was recorded by trained staff on days 2, 3, 4, 7, 14 and 21, with a minimum score of 5 for a positive reaction using the scale published by Johansen et al. (1997). The exposure was ended if the reaction responses scored 5 or higher. Similarly, if no reactions occurred or the sum of scoring was less than 5, all exposures were completed after 21 days. The application scheme was developed by Lundov et al. The scoring scale used was modeled after a study from Dr. Jeanne Johansen et al. (*Contact Dermatitis* 39: 95, 1997), which included four scored variables: involved area of application, erythema (involvement and strength), papules and vesicles. The potential societal benefits from increased understanding of concentrations of MI that cause adverse effects outweigh the small risks associated with the study.

Dr. McMahon summarized the study results: 9 of the 11 test subjects completed the 21-day ROAT protocol. Seven test subjects (64 percent) reacted to the highest (0.210 $\mu g/cm^2$) and middle (0.105 $\mu g/cm^2$) MI doses, whereas two test subjects (18 percent) reacted to the lowest dose (0.0105 $\mu g/cm^2$). He presented the strengths of the study: The test subjects comprised both males and females with prior MI sensitivity, the study design was blinded, a lowest observable effect (LOAEL) was identifiable, and the skin loading design aligns with potential skin loading expected for registered pesticide uses. Several factors were deemed as weaknesses: The study had a low number of participants, and males and females were not represented equally. Also, the lack of raw data limited the use of statistical analysis. Therefore, the NOAEL and LOAEL approach was recommended to obtain the point of departure (POD) because of the apparent statistical challenges with the data.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification. In response to an HSRB member's question, EPA confirmed that there will be no analysis of the patch test results.

Hearing no further questions of clarification, Dr. Dawson asked Ms. Arling to present EPA's ethics review.

EPA Ethics Assessment

Ms. Arling provided the ethics assessment of the "MI Contact Allergy and Dose-Response Relationships" study. The information included in Ms. Arling's presentation and ethics review memo are taken from the published article, email communication between EPA and Dr. Johansen, a secondary author on the article, and the information provided Dr. Johansen related to the review and approval of the research by an independent ethics body. All of this information was provided to the HSRB along with the ethics review memo.

The test subjects were recruited from the Gentofte Hospital from a pool of 52 patients who had previously had a positive reaction to MI. In addition, 50 patients who had an allergy to MCI/MI were invited, because about 40 percent of patients with this allergy had a concomitant allergy to MI, and five agreed to participate. Patients were initially contacted by mail. About a week after the mailing, Dr. Lundov contacted potential test subjects by telephone.

Healthy control subjects were recruited through an advertisement posted on the internet. The advertisement explained the purpose of the study, outlined the study procedure and timing, and invited interested persons to contact Dr. Lundov by email or telephone. The advertisement was approved by the independent ethics body that reviewed and approved the study proposal.

In telephone calls with potential test and control subjects, Dr. Lundov explained the purpose, the duration, and the process of the study. After providing the information and the opportunity for potential subjects to ask questions, Dr. Lundov invited interested subjects to the clinic for more information and to enroll in the study, provided all inclusion and exclusion criteria were satisfied. All subjects signed a written consent form prior to enrollment in the study.

The study design called for 20 test subjects and 20 control subjects. More than 100 potential test subjects were contacted initially to invite them to participate in the study. The study proposal was amended a month after the initial approval to add a second mailing of letters to potential test subjects who did not respond to the first mailing. In the end, a total of 11 test subjects (two women, nine men) and 14 control subjects (six women, eight men) were enrolled in the study. Of the test subjects who completed the ROAT, nine were those with a previously identified MI allergy, and two were those recruited from MCI/MI allergic patients.

Study enrollment was dependent upon several inclusion and exclusion criteria. Females were asked if they were pregnant or breastfeeding prior to enrollment in the study; no pregnancy testing was conducted. The test subjects must have experienced a positive reaction to MI, have no active eczema in the test areas and no treatment with hormone creams at or near the test area within 2 weeks of the study commencement. Control subjects could have no allergy to MI or MCI/MI, have no eczema or other skin diseases, and have no treatment with corticosteroids within three weeks prior to the study.

Ms. Arling reviewed the process of consent. All subjects provided written consent prior to enrollment. According to the information provided by Dr. Johansen, after receiving information by telephone from Dr. Lundov, the principal investigator, potential subjects were invited to the clinic for a meeting and to enroll in the study. At the in person meeting at the clinic, Dr. Lundov provided information about the study again, including reviewing the consent form and "Participant Information to Study Patients." Potential subjects were invited to bring another person, such as a family member or friend, with them to the initial meeting. Dr. Lundov verified that the inclusion/exclusion criteria were met and answered any questions prior to obtaining written informed consent and enrolling subjects in the study.

Immediately following the consent process, the subjects were enrolled and the study began. The patch test was initiated and subjects were given instructions and prepared for the ROAT.

At the subjects' first visit to the clinic, after providing written consent to participate in the study, the study commenced. The patch was applied to the subject's back, and four areas of three centimeters by three centimeters each were marked on the forearms for the repeated open application study. Subjects received instructions in how to apply the solution according to the study design, applying solutions from four different bottles, twice daily. In order to help ensure that subjects used the proper amount of the product for each application, the solution was provided in four numbered bottles and the solutions were applied by a fixed-volume micropipette. Five sets of solutions were weighed before and after the ROAT, and as a result the authors concluded that the subjects had followed the application scheme and were exposed to the proposed amount of MI.

The readings of the patch test and ROAT were conducted at a hospital-based clinic by trained medical personnel. In addition to scheduled readings, subjects were instructed to visit the clinic at any point if they developed a reaction at a test site.

Risks to subjects included developing reactions at the test sites (forearms and back) and for control subjects, becoming sensitized to MI. Ms. Arling reiterated that the selection criteria excluded people with active eczema at the test sites, or widespread active eczema on any area of the body.

The doses used in the ROAT corresponded to the maximum amount of MI permitted in cosmetics (100 ppm), the lowest concentration of MI recommended by manufacturers (50 ppm), and the concentration of MI sufficient for use as a preservative when combined with phenoxyethanol (5 ppm). The maximum dose selected for the patch test was 60 µg/cm^2 or 2000 ppm. Although higher than the concentration acceptable for use as a preservative in cosmetics, this concentration corresponds with the concentration for patch testing MI recommended by the American Contact Dermatitis Society in its 2013 Core Allergen Series (www.contactderm.org/files/public/2013_CoreAllergenList(corrected).pdf).

Ms. Arling noted again that test substances were applied by fixed volume micropipette, to help ensure application of the proper amount of the test substance during the ROAT.

Subjects were compensated 500 kroner, or about $71, per visit. They were expected to visit the hospital-based clinic up to six times during the study – at the consent meeting/study initiation, on day 2, day 3 or 4, day 7, day 14, and day 21. Each visit was expected to last about 30 minutes. Subjects also were instructed to visit the clinic between reading days if a reaction occurred between visits. The information provided during the consent process orally and in writing informed subjects that they were free to withdraw at any time. The study proposal also called for a subject's participation to be stopped in a specific area of the ROAT if they had a reaction in that area scoring 5 or above on the reading scale, as described by Dr. McMahon.

Nine test subjects completed all 21 days of the ROAT. One test subject lost the solution and application equipment and did not receive a new set for 4 days. Another test subject only applied the solutions for the ROAT for 19 days due to travel.

Subjects information was kept confidential – names or identifying information were not included in the published article or in any materials provided to EPA.

The study proposal (protocol) and informational and consent materials were reviewed and approved by an independent ethics body, the Capital Region of Denmark, prior to implementation of the study. The study was conducted in accordance with the Declaration of Helsinki.

The study proposal was approved on May 17, 2010. An amendment was approved on June 3, 2010, allowing for a second mailing to potential test subjects.

The study did not include the number of subjects proposed (20 test subjects and 20 control subjects). Otherwise, the study appeared to be conducted in compliance with the proposal approved by the independent ethics body.

Ms. Arling reviewed the standards against which EPA reviewed the research to determine whether it was acceptable from an ethical standpoint to rely on the data. EPA cannot rely on research that involves intentional exposure of pregnant or nursing women, or of children. EPA also cannot rely on research if there is clear and convincing evidence that the research was

fundamentally unethical, or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent.

The protocol stated that the study would be conducted according to the principles in the Declaration of Helsinki II (p. 331). In addition to the Declaration of Helsinki, the study was subject to the requirements of the Danish "Act on Research Ethics Review of Health Research Projects" (Attachment 4 to EPA's ethics review memo) and "Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects" (Attachment 5 to EPA's ethics review memo). The key ethical principles in the Declaration of Helsinki are respect for persons, beneficence and justice.

The Danish Act establishes requirements for review of research protocols prior to implementation by an independent ethics committee, for providing information to and obtaining informed consent from study participants, and for adequate respect for study participants (e.g., confidentiality of data, adequate compensation, insurance coverage for study-related adverse effects).

The Ministerial Order prohibits biomedical research unless informed consent has been obtained, and establishes the elements of informed consent, including that participation is voluntary and subjects are free to withdraw at any time without negative effects. Potential subjects must receive information on the study orally and in a written document, both presented in a manner the potential subject can understand, prior to giving written consent to participate in the study.

Ms. Arling presented EPA's findings for this study. All subjects were at least 18 years old, and pregnant or nursing women were excluded. Ms. Arling did not identify any significant deficiencies in the ethical conduct of the research. The protocol/study proposal was reviewed and approved by an independent ethics body in Denmark. The study appears to have been conducted in compliance with the ethical standards in place at the time the study was conducted. Subjects received information about the study orally and in writing in advance of providing written informed consent, subjects were compensated for their participation, and confidentiality of subjects' identities was maintained. The amendment to the study did not compromise the safety, consent, or rights of subjects.

Ms. Arling presented EPA's conclusion that there were no barriers under law or regulation to EPA's reliance on this research from an ethical perspective.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification. Hearing no questions of clarification, Dr. Dawson asked Mr. Downing to call for public comments.

Public Comments

In response to Mr. Downing's call for public comments, Dr. Monika Schoester, Isothiazolinone Task (IT) Force of the ACC, presented an introduction to dermal sensitization, current approaches to risk assessment, and considerations on published studies. She reviewed the process of dermal sensitization and described the distinction between the two sensitization phases: induction (first exposure to sensitizing allergen; priming of immune system) and elicitation (subsequent exposure to sensitizing allergen resulting in physical symptoms). She remarked that the use of dermal sensitizers in studies or in commercial products requires global regulatory frameworks to identify potential hazards. These adverse effects typically are measured

using the mouse LLNA model. The risk assessment of sensitizers can be measured qualitatively and quantitatively. Early identification allows implementation of the appropriate risk management measures.

Dr. Schoester stated that induction is the universally accepted endpoint for risk assessment. Preventing induction is the goal because this process prevents subsequent elicitation. Thresholds for elicitation are variable, individually specific and, therefore, unreliable in assessing risk. Currently, no global regulatory frameworks or animal models use elicitation data as a standard in risk assessment.

EPA proposes using elicitation as an endpoint for risk assessment in the global regulatory community. Specifically, studies in open literature indicate a different approach from the normal methodology of risk assessment. EPA's suggested approach requires sensitizing humans with novel chemicals to establish elicitation endpoints. This approach has not been peer reviewed or externally validated. Consistent ethical standards must be applied to ensure the highest standards of protection for human subjects. The IT Task Force has identified and will present the ethical and technical deficiencies in the studies presented by EPA.

Dr. Schoester remarked that insufficient details were provided on procedures, practices and standards of the regional ethics review boards. The test or control subjects were exposed to up to 2,000 ppm MI or 1,000 ppm MI, respectively, which is greater than the sensitization induction threshold or EPA-approved use rate. The use of increased concentrations of MI may have stimulated an immune response, which would negatively affect the interpretation of the results. Subjects may have been sensitized during the study, and such a high induction dose could lower the elicitation threshold in previously sensitized individuals; the experimental conditions, therefore, may influence the outcome. Also, the statistical analysis and dose response in the study were not reproducible. The ACC IT Task Force concluded that the Lundov et al. findings are unsuitable for the purpose of quantitative risk assessment of products containing MI.

Noting no further public comments, Dr. Dawson proceeded to the next item on the agenda: Board Discussion on Science. Dr. Dawson asked Drs. Alesia Ferguson and Randy Maddalena to provide their comments and Dr. George Fernandez to provide his statistical review.

Board Discussion—Science

Dr. Ferguson read the science charge into the record:

> Is the research described in the published article "Methylisothiazolinone Contact Allergy and Dose-Response Relationships" scientifically sound, providing reliable data?

Dr. Ferguson noted that the study's scientific validity, reliability and reproducibility were the focus of her review. Assuming that elicitation is a concern in the general population, the use of MI may cause allergic contact dermatitis; therefore, determining the level of protection against induction in certain individuals is important. She noted that adherence plays an important role in reliability and validity. In the Lundov et al. study, the use of a micropipette increased reliability of adherence. However, from an exposure standpoint, incorporating a table outlining the lowest elicitation dose (ED) and exposure conditions for the Lundov et al., Yazar et al., and Zachariae et al. studies would have been helpful.

Regarding the Lundov et al. article, Dr. Ferguson noted that enhanced clarity of the patch test design is important because of the influence of induction levels on stimulating elicitation. Dr. Ferguson agreed with EPA's plan to use elicitation thresholds and concluded that the article

provides scientifically sound and reliable data related to the exposure conditions. One weakness is that demographically, the study lacked gender balance and an adequate number of subjects.

Dr. Maddalena added that upon review of the Lundov et al., Yazar et al., and Zachariae et al. studies, he agrees with the assessment that a large segment of the population already has experienced MI sensitivity (induction). Therefore, assessing elicitation thresholds is important. Regarding the Lundov et al. article, he noted an apparent inadequate representativeness of the population because of the use of known patients in the study who presumably developed stronger reactions to MI.

Dr. George Fernandez provided a statistical review of the Lundov et al. article. He commented that the authors used a standard logistic regression analysis to estimate the dose-response relationship in the patch test. The ED_{50} (median effective dose) and 95 percent confidence level also were calculated from the dose response curve. EPA performed an analysis using the data reported in the article for verification of the dose response curve results. Dr. Fernandez noted that he reviewed the supplemental data EPA provided and concluded that the ED_{50} values and the 95 percent confidence level reported in the article were not reproducible. He expressed concern with performing a separate logistical regression—the same subjects were used with or without the phenoxyethanol treatment, which violates the statistical independence of doing the separate logistical regression analysis. He noted that generalized linear mixed models were more suitable for this type of analysis. The author's use of the Spearman's rank correlation statistical analysis was not appropriate. Dr. Fernandez ended his review by saying that he agreed with the Agency's conclusion that from a statistical point of view, the results reported in the article are not statistically reproducible.

Dr. Dawson asked for comments from the Board members. She expressed concern that certain subjects might have been exposed to other products outside of the study protocol that influenced the reaction to the drug in the controls. The HSRB indicated that this was not a major concern and that confidence should be applied when evaluating whether subjects followed the study instructions. EPA clarified that the subjects were instructed by the authors not to use any products (e.g., soaps) containing MI, MCI/MI or phenoxyethanol; this would have limited most exposures in the areas of the patch tests.

Dr. Dawson was provided confirmation that the NOAEL/LOAEL approach was used due to the inability to reproduce the statistical analysis and dose response. Dr. Fernandez agreed with this use of the data due to the inability to statistically validate the results.

Hearing no further comments, Dr. Dawson asked Dr. Ferguson to present the statement in response to the charge question for voting by the Board. The response was read into the record by Dr. Ferguson:

> The Board concludes that the research described in the published article "Methylisothiazolinone Contact Allergy and Dose-Response Relationships" is scientifically sound, and provides reliable data for the exposure conditions expressed in the article and for deriving LOAEL.

An HSRB member pointed out that a NOAEL effect was not determined in this study. The proposed LOAEL is a point estimate derived from two people and was no different from the response in the controls. There are problems with the dose-response curve and insufficient data to repeat statistical analysis.

In response to an HSRB member's question, EPA clarified that among the subjects recruited for the Lundov et al. study and exposed to MI, the control group had no sensitization and the test group had previously tested positive for allergy to MI or MCI/MI.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Ferguson's response statement.

The HSRB unanimously approved the statement.

Board Discussion—Ethics

Dr. Gary Chadwick reviewed the ethical aspects of the study and read the charge into the record:

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

Dr. Chadwick reviewed the results of the Lundov et al. study by mentioning that there were no reported severe adverse reactions to the applied compound. Upon review of Subpart Q, Dr. Chadwick recommended that the available information supports the determination that the study is in compliance with that Subpart. The study may be used in actions under the FIFRA and the Food, Drug and Cosmetic Act, which will provide necessary regulatory determinations for this research.

Dr. Dawson asked for comments from the Board members. Regarding the ACC's assertion that the study posed an unacceptable human risk due to the concentration of chemical, the HSRB indicated that this may create a long-lasting pathological condition in chemical sensitivity. However, this possibility was deemed improbable, and the HRSB commented that regulatory standards used were sufficient.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Chadwick's statement, which he read into the record:

> The Board concludes that the available information supports a determination that the research was conducted in substantial compliance with Subparts K and L of 40 CFR Part 26.

The HSRB unanimously approved the response statement.

Topic 5: Published article: "Methylisothiazolinone in Rinse-Off Products Causes Allergic Contact Dermatitis: A Repeated Open-Application Study," by K. Yazar, M. D. Lundov, A. Faurschou, M. Matura, A. Boman, J. D. Johansen, and C. Lidén. *British Journal of Dermatology* (2015) 173: 115–22.

Dr. Dawson invited Dr. McMahon to present EPA's science assessment.

EPA Science Assessment

Dr. McMahon provided an overview of the research published in the article titled "Methylisothiazolinone in Rinse-Off Products Causes Allergic Contact Dermatitis: A Repeated Open-Application Study" as WOE in support of the 2011 study by Lundov et al. The purpose of the study was to examine whether the allowed concentrations of MI, or 100 ppm, in cosmetic

rinse-off products and half of the allowed concentration, or 50 ppm, would cause allergic contact dermatitis. EPA is proposing to use the results of this study, in combination with results from other ROAT studies, to set a human dermal sensitization endpoint/point of departure in its risk assessment for methylisothiazolinone.

The study enrolled 22 test subjects and 21 control subjects. Nineteen test subjects, sensitive to MI and 19 control subjects with no allergy to MI completed the study. The ROAT was carried out as follows: (1) 10 MI-allergic subjects and 19 control subjects applied liquid soap containing 100 ppm MI to one arm and control soap without MI (hereafter, control soap) to the other arm; (2) nine additional MI-allergic subjects applied 50 ppm MI and control soap in the same manner. The soaps were randomized to the test areas, and subjects and assessors were blinded to the treatment. Applications consisted of one press of the soap dispenser followed by distribution over a 50-cm^2 area on the ventral forearm for 21 days, with rinse-off occurring 20 to 25 seconds after exposure. Skin loading was 0.24 $\mu g/cm^2$ per day for 50 ppm concentration and 0.48 $\mu g/cm^2$ per day for 100 ppm concentration. Soap containers were weighed before and after use, and controls use the same soap formulation as the MI. A positive reaction was defined as "area on involvement" more than 25 percent of the area of application, including erythema and signs of infiltrations.

Results showed that seven of nine test subjects were positive in the ROAT at 0.24 $\mu g/cm^2$ per day, and 10 of 10 test subjects were positive in the ROAT at 0.48 $\mu g/cm^2$ per day. These results were statistically significant compared to the control group, in which no positive reaction was observed. The control group did not show a positive reaction at 100 ppm MI and therefore was not tested at 50 ppm MI. The LOAEL for this study is 0.24 $\mu g/cm^2$; no NOAEL was established in this study.

The study strengths include the use of a separate control group, reproducible statistical analysis, blind study design, and an identifiable LOAEL. Conversely, study weaknesses included not identifying the gender of the subjects and the lack of availability of the raw data. As a WOE to the relationship between skin loading and response frequency, EPA combined data from the Lundov et al. 2011 study with this study. EPA concluded that the study supports derivation of a point of departure for elicitation of dermal sensitization from dermal exposure to MI.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification. An HSRB member asked about the reproducibility of data given that the study investigators appear to have made additional assumptions to reach some of the conclusions; for example, the controls were assumed to be negative at 50 ppm MI. A consultant to EPA (Dr. Jonathan Cohen) confirmed that the study investigators did not test control subjects at the 50 ppm MI, and it was logical to assume that if the response was negative at 100 ppm MI, then the lower concentration also would be negative. Another HSRB member noted that the loading data differ in regards to the number of applications of product in the Lundov et al. and the Yazar et al. studies and asked how that would affect the WOE. EPA replied that the studies were different in design, leave-on versus a rinse-off, which affects the loading value, but the relative response would remain positive.

Hearing no additional questions of clarification, Dr. Dawson asked Ms. Arling to present EPA's ethics review.

EPA Ethics Assessment

Ms. Arling provided the ethics assessment and noted the documents EPA reviewed concerning the ethical conduct of the study.

Test subjects received information by mail, followed by a telephone call from the study director asking if they had received the information, had questions, and were interested in participating in the study. If a potential subject was interested in participating, then they were invited to visit the appropriate clinic (either Stockholm or Copenhagen) to receive information orally, to provide consent, and to enroll in the study.

Control subjects were recruited in Sweden and Denmark through ads posted on websites specific to each country where the study was conducted. The ads were posted in Swedish and Danish, respectively. Interested parties were contacted by email and invited to visit the appropriate clinic to receive information orally, to provide consent and to enroll in the study.

In total, 22 test subjects and 21 control subjects were enrolled, but only 19 test subjects and 19 control subjects completed the ROAT. Two potential test subjects were recruited but not included because they did not have a positive reaction to MI during the confirmatory patch test. Another subject who was recruited and enrolled discontinued participation during the ROAT after 5 days; this subject did not experience any reaction during the period of participation.

Two control subjects were enrolled but did not complete the ROAT; one had problems following instructions and one chose to discontinue participation after 1 day of the ROAT.

The main enrollment criteria for subjects were being at least 18 years old, not being pregnant or breastfeeding, not having any active skin conditions on the forearms or back (where the patch test and ROAT would occur), and having no systemic immunosuppressive therapy and no excessive exposure to UV light for the three weeks prior to the study.

Study enrollment started with a patch test; only subjects who had the appropriate reaction to the confirmatory patch test proceeded to the ROAT. During this phase, two enrolled test subjects did not proceed to the ROAT portion of the study because they did not have patch test reactivity to MI.

Females were asked if they were pregnant or breastfeeding prior to enrollment in the study; no pregnancy testing was conducted.

Ms. Arling reiterated that all subjects were provided written consent prior to enrollment. After receiving information by telephone (test subjects) or email (control subjects), interested persons were invited to the clinic for a meeting and to enroll in the study. At the in person meeting at the clinic, a medical professional associated with the study provided information about the study again, including reviewing the consent form and informational materials. Potential subjects were invited to bring another person, such as a family member or friend, with them to the initial meeting. The person providing the information verified that the inclusion/exclusion criteria were met and answered any questions prior to obtaining written informed consent and enrolling subjects in the study.

Immediately following the consent, the subjects were enrolled and the study began. The patch test was initiated, and subjects were told to return on day 4 for a reading of the patch test and to move forward with the ROAT if the patch test results were acceptable.

The risks to subjects were provided on the consent form and included developing a skin irritation at the site of the patch test or ROAT, and allergic reactions in subjects not sensitized to MI. Risks were minimized by use of approved concentrations of MI, limiting the ROAT time, and stopping the ROAT when a positive reaction was observed. The informational materials and consent form explained and acknowledged the risks of participating in the study. Steps were

taken to minimize risks to subjects, including dose selection, limiting the period of the ROAT, and stopping the ROAT when a positive reaction was identified. Subjects were instructed to visit the clinic between readings if a reaction developed. Further, the dispenser for the soaps used in the trial were designed to dispense the intended amount of soap. Subjects were instructed very specifically on the procedure for the ROAT. According to the study director, when the results showed that 10 out of 10 test subjects reacted to the liquid soap containing 100 ppm of MI, further test subjects used liquid soap containing 50 ppm of MI.

Regarding respect for persons, subjects were told orally and in writing that they were free to withdraw at any time. One control subject withdrew from participation in the ROAT after five days of participation. The subject did not have any reaction during the ROAT. In Sweden, subjects received 500 SEK (~$55) for participation in the patch test, and 2500 SEK (~$275) for participation in the ROAT. This included up to five visits for instructions and assessment of reactions, as well as application of the test products five times a day for up to 21 days. In Denmark, subjects received 500 DEK (~$71) per visit, up to a maximum of eight visits. This covered visits for instructions, patch testing, and readings during the ROAT. The subjects' information was not revealed in the article or in any of the materials provided to EPA. Topical steroid cream was offered to all subjects, and provided to some subjects who had strong positive reactions, i.e., several vesicles within a test area. According to Dr. Liden (the study director in Sweden), no subject had any severe or widespread reaction requiring other medical treatment.

In Denmark, the study was reviewed and approved by the regional ethics review board in the Capital Region, Denmark. In Sweden, the study was reviewed and approved by the regional ethics review board in Stockholm. Upon the finding that 10 of 10 test subjects had positive reactions to MI at the concentration of 100 ppm, the study was amended for additional subjects enrolled in the ROAT to use a soap with MI at a concentration of 50 ppm rather than 100 ppm. This amendment did not negatively affect participants' rights or health and safety.

Ms. Arling described the substantive acceptance standards applicable to EPA's reliance on the research that include 40 CFR §26.1703, 40 CFR §26.1704, and FIFRA §12(a)(2)(P). The study was conducted in accordance with the Declaration of Helsinki, the Danish Act, Ministerial Order, and the Swedish Act. The prevailing standards in place at the time the study was conducted included the Declaration of Helsinki, and in Denmark, the Danish "Act on Research Ethics Review of Health Research Projects" and "Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects". In Sweden, the ethical standards in place at the time the study was conducted included "The [Swedish] Act concerning the Ethical Review of Research Involving Humans (2003:460)". EPA provided copies of these standards with the ethics review memo.

The key ethical principles in the Declaration of Helsinki are respect for persons, beneficence and justice. The Danish Act establishes requirements for review of research protocols prior to implementation by an independent ethics committee, for providing information to and obtaining informed consent from study participants, and for adequate respect for study participants (such as confidentiality of data, adequate compensation, insurance coverage for study-related adverse effects). The Ministerial Order prohibits biomedical research unless informed consent has been obtained, and establishes the elements of informed consent, including that participation is voluntary and subjects are free to withdraw at any time without negative effects. Potential subjects must receive information on the study orally and in a written document, both presented in a manner the potential subject can understand, prior to giving written consent to participate in the study. The Swedish Act seeks to protect individuals' rights by establishing requirements for research involving human subjects to be reviewed and approved by an ethics committee, outlining the information to be provided to potential subjects, mandating that study

sponsors obtain informed consent from subjects prior to enrolling them in the study, and protecting subjects' personal/confidential information.

All subjects were at least 18 years of age; pregnant or nursing women were excluded. Although there was no pregnancy testing of female subjects, they were asked prior to enrollment whether they were pregnant or nursing, and there is no evidence that any pregnant women were included. Ms. Arling noted that she did not identify any significant deficiencies in the ethical conduct of the research. The protocol/study proposal was reviewed and approved by independent ethics bodies in Denmark and Sweden. The study appears to have been conducted in compliance with the ethical standards in place in each country at the time the study was conducted. The protocol was reviewed and approved by independent ethics bodies, subjects received information about the study orally and in writing in advance of providing written informed consent, subjects were compensated for their participation, and confidentiality of subjects' identities was maintained. Ms. Arling reiterated that subjects were fully informed and their consent was fully voluntary, without coercion or undue influence.

The amendment to the study reducing the concentration of MI in the test substance did not compromise the safety, health or rights of subjects.

In conclusion, available information indicates that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to prevailing ethical standards in a way that would have impaired subjects' informed consent or placed them at increased risk of harm. Ms. Arling found no barrier in law or regulation to EPA's reliance on this research from an ethical perspective.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification. Hearing none, Dr. Dawson asked Mr. Downing to call for public comments.

Public Comments

In response to Mr. Downing's call for public comments, Dr. Germaine Truisi presented ACC's ethical and technical review of the published research titled "Methylisothiazolinone in Rinse-Off Products Causes Allergic Contact Dermatitis: A Repeated Open-Application Study" authored by K. Yazar, M. D. Lundov, A. Faurschou, M. Matura, A. Boman, J. D. Johansen, and C. Lidén, *British Journal of Dermatology* (2015) 173: 115–22. ACC identified critical points in the ethical conduct of the study. Details on procedures, practices and standards of the regional ethics review boards were not included in the article, and attempts to secure that information were not successful. Comparison of regional ethics review boards to equivalent HSRB standards was not possible.

The positive patch test, which was the study's inclusion requirement for enrolling subjects, was performed with 2000 ppm MI. This concentration far exceeds the known threshold (1000 ppm) for irritation and induction of sensitization and could potentially stimulate the immune system and affect study results. The period between patch testing and enrollment in a ROAT was not indicated. In reviewing the technical aspects of the study, ACC noted that the ROAT solutions were administered by the subjects. There was no information on prior exposure to MI, and information from the study was not generalizable to the human population. The ROAT design differed from the standard protocol. This exaggerated application rate combined with the daily cleansing routine could lead to disruption of the skin barrier. In consideration of the deficiencies described, the ACC IT Task Force considers the Yazar et. al. 2015 study unsuitable for obtaining a point of departure for quantitative risk assessment of products containing MI.

Board Discussion—Science

Dr. Dawson asked Drs. Ferguson and Maddalena to provide their comments. Dr. Ferguson read the science charge into the record:

> Is the research described in the published article "Methylisothiazolinone in Rinse-Off Products Causes Allergic Contact Dermatitis: A Repeated Open-Application Study" scientifically sound, providing reliable data?

Dr. Ferguson stated that EPA should provide a rationale for requiring a risk assessment for elicitation. She asked for additional guidance because it is unclear whether this assessment is to establish a point of elicitation to provide a recommended MI concentration. Dr. Ferguson raised several concerns with the study. Regarding contact dermatitis, immune-related diseases are increasing in the general population. It is not well understood whether eczema contributes to induction, or if it is related to elicitation.

She highlighted some additional points of consideration, including the area of compound application (i.e., location on the forearm), structural areas of the skin, and components of the soap in the control groups. In the study, calculating the pump rate and determining the weight of the application bottles helped ensure adherence. What requires further discussion is the issue of dosing, because the compound application was a rinse-off method; the applied dose reported is not reflective of the actual dose. Therefore, the precise dose that leads to an elicitation response is unknown. She concluded her review by saying that the study provides scientifically sound and reliable data for the exposure condition (rinse-off), therefore the LOAEL can be derived.

Dr. Maddalena also pointed out that the number of applications across studies is an issue that should be addressed in the risk assessments or analysis of data. No evidence suggests that the same effects would occur with increasing dose and area of the exposure. He concluded that, overall, the study was conducted well, and the controls and doses were adequate.

Dr. Edward Gbur provided the statistical review. The study test subjects were recruited based on their positive responses to a high dose of MI in prior studies; however, the process used for randomizing these participants into the 100 ppm MI and 50 ppm MI groups was not clear. In regards to comparing responses between the MI treated and control groups, the study authors listed a *p*-value for 50 ppm MI when the control group had not been tested at that dose. He detailed statistical analyses that were a concern and should be addressed. Statistical analysis comparing the patch test to the ROAT was determined using the McNemar test, which is the test applied for paired nominal data. The study authors concluded that ROAT activity was higher, thus a one-sided conclusion; they also used Kendall's Tau, a non-parametric measure of correlation, for association of a positive patch and a positive ROAT. Dr. Gbur concluded that the statistical analyses used were appropriate and were based on reliable data, but caution should be used in acceptance of the study conclusions on statistics.

Dr. Dawson asked for comments from the Board members. An HSRB member clarified that when considering increasing area of skin versus increasing doses, the dose per area is the important measurement. The true dose is not known due to variations in each subject's application, although steps were taken to standardize the application across users (application was based on one press of the soap dispenser followed by distribution over the area with a single use applicator, followed by rinsing the area after 20-25 seconds). The actual dose that is causing the observed effect and the time between applications in this study are not necessary for EPA's risk assessment because this study is being used as part of the weight of evidence in support of the

point of departure selected from the Lundov study. EPA is not using this study to derive a point of departure or in the risk assessment.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Ferguson's scientific review statement:

> The Board concludes that research described in the published article "Methylisothiazolinone in Rinse-Off Products Causes Allergic Contact Dermatitis: A Repeated Open-Application Study" is scientifically sound and provides reliable data for the exposure conditions used and for deriving the LOAEL.

The HSRB unanimously approved the response statement.

Board Discussion—Ethics

Dr. Chadwick reviewed the ethical aspects of the research and read the following charge into the record:

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

Dr. Chadwick agreed with EPA's ethical review. The design of the study was such that risks would be minimal and the study was conducted in compliance with applicable standards.

Dr. Dawson asked for comments from the Board members. An HSRB member asked whether the charge question on ethics should cite 40 CFR, Part 26, Subpart Q as the applicable standard for submitting third-party research. EPA replied that 40 CFR, Part 26, Subparts K and L, in general apply to this review. Subpart Q focuses on EPA's evaluation of the research, not the conduct of research. Dr. Dawson pointed out that some of the studies discussed at this meeting were conducted prior to Subparts K and L and suggested that Subpart Q might be applicable.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Chadwick's statement, which she read into the record:

> The Board concludes that the available information supports a determination that the research was conducted in substantial compliance with Subpart Q of 40 CFR Part 26.

The HSRB unanimously approved the statement.

Topic 6: Published article: "An Evaluation of Dose/Unit Area and Time as Key Factors Influencing the Elicitation Capacity of Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) in MCI/MI-Allergic Patients," by C. Zachariae, A. Lerbaek, P. M. McNamee, J. E. Gray, M. Wooder, and T. Menné. *Contact Dermatitis* (2006) 55: 160–6.

Dr. Dawson invited Dr. McMahon to present EPA's science assessment.

EPA Science Assessment

Dr. McMahon summarized the research published in the article titled "An Evaluation of Dose/Unit Area and Time as Key Factors Influencing the Elicitation Capacity of

Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) in MCI/MI-Allergic Patients" as part of the WOE in support of the 2011 study by Lundov et. al. The aim of the study was to evaluate the importance of two factors—time and concentration (dose/unit area)—in the elicitation capacity of MCI/MI in MCI/MI-allergic patients by means of a ROAT experimental design. A total of 29 test subjects with sensitivity to 100 ppm MCI/MI and 10 control subjects were recruited into the study. Confirmatory patch testing was conducted prior to subjects' enrolling in the study and prior to initiation of the ROAT. Of the 29 test subjects recruited, 25 tested positive for MCI/MI and 4 were negative for MCI/MI; thus, a total of 25 test subjects were enrolled in the study.

The ROAT was carried out in two phases. In ROAT 1, test and control subjects were exposed on 9 cm^2 of forearm to 0.025 µg/cm^2 (2 ppm) MCI/MI for four weeks. Following was a 4-week washout period, a second ROAT, ROAT 2, was performed in the same test and control subjects, exposing them to 0.094 µg/cm^2 (7.5 ppm) MCI/MI for four weeks. Seven of 25 test subjects showed a positive response to MCI/MI in ROAT 1 at 0.025 µg/cm^2/day, and 14 of 25 test subjects showed a positive response in ROAT 2 at 0.094 µg/cm^2/day. The study authors confirmed that separate sites on the skin were used in the first and second ROAT. The average time to reaction in ROAT 1 was 16.5 days and 12.1 days in ROAT 2.

The strengths of this study were the double-blinded, placebo-controlled and dose-response design. Also, statistical results of Fisher's exact test to compare test subjects to controls could be reproduced, and a LOAEL could be defined. Conversely, weaknesses of the study were nonreproducibility of logistic regression analysis to compare the proportions of reactions in ROAT 1 and ROAT 2 and the lack of access to the raw data. The addition of data from this study, Zachariae et. al. 2006, to data from the Lundov et al. 2011 study and the Yazar et al. 2015 study provides WOE in support of derivation of a point of departure for elicitation of dermal sensitization from dermal exposure to MI.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification. An HSRB member asked about the basis for selecting a 4-week washout period between the first and second ROAT and whether that was a standard period sufficient to ensure minimal to no carryover. EPA was not aware of a standard washout period and will contact the study authors for additional information. Commenting on the duration of the washout period, the HSRB member pointed out that the second ROAT used a higher concentration and the washout period may not be as relevant as it would if the dose had been lower or the same as ROAT 1.

Hearing no additional questions of clarification, Dr. Dawson asked Ms. Arling to present EPA's ethics review.

EPA Ethics Assessment

Ms. Arling provided the ethics assessment and noted that the published article and responses from the primary investigator to questions from EPA were used in reviewing the ethical conduct of the study. Materials on the consent process and the independent ethics review could not be obtained.

The test subjects were recruited from the Gentofte Hospital from a pool of patients who previously had a positive reaction to a patch test of MCI/MI at a concentration of 100 ppm. Potential test subjects received information about the study by mail, and Dr. Zachariae, the primary investigator, contacted them by telephone to invite them to participate. Healthy control subjects were recruited through an advertisement posted in the area local to the study location.

The advertisement invited interested persons to contact Dr. Zachariae by telephone. Dr. Zachariae contacted control subjects by telephone and provided written materials about the study by mail.

The inclusion criteria were being at least 18 years of age, not being pregnant or breastfeeding, and not having widespread eczema at any site. Females were asked if they were pregnant or breastfeeding prior to enrollment in the study; no pregnancy testing was conducted. A total of 29 test subjects and 10 control subjects were recruited into the study. The patch testing was conducted prior to enrollment in the study and initiation of the ROAT. For four test subjects, the patch test results were negative or doubtful, and as a result they were not enrolled into the study. Twenty-five test subjects were enrolled in the ROAT study.

Regarding the consent process, Dr. Zachariae contacted interested persons by telephone and provided information about the study in writing. He provided information about the study orally to all potential subjects. The information provided included the procedure for the study and the purpose, i.e., to evaluate the concentration of MCI/MI for the reaction of eczema in a ROAT. Participants were informed of the substances to which they would be exposed during the research. Dr. Zachariae noted that all subjects provided written informed consent prior to enrolling in the study, but he could not provide the consent form and informational materials to EPA because the study was conducted in 2006 and he no longer has access to the materials.

As with the previously presented ROAT studies, the risks of participation included developing skin irritation/eczema at the test site. Dr. Zachariae noted that he explained the study and risks of participation to subjects prior to obtaining their informed consent. There was a wash out period between the two ROAT sessions to allow subjects to recover from any reactions that occurred as a result of participation in the first ROAT prior to participating in the second ROAT. No subjects withdrew. According to Dr. Zachariae's recollection, no subjects required medical treatment as a result of their participation in the study.

Regarding respect for persons, subjects' privacy was maintained; their identities were not revealed in the published article and private information was maintained under lock and key by Dr. Zachariae. Subjects were not compensated for their participation in the study. Dr. Zachariae noted to EPA that subjects participated to further science and research in this area.

According to the article, the research was approved prior to implementation by the local ethics committee. Dr. Zachariae could not recall the name of the committee or provide any materials associated with the independent ethics review (e.g., protocol, amendments, correspondence) because the study was conducted more than 10 years ago and he no longer has the records.

Ms. Arling noted the substantive acceptance standards applicable to EPA's reliance on the research, including 40 CFR §26.1703, 40 CFR §26.1704, and FIFRA §12(a)(2)(P). There is no information in the article about the standards under which the study was conducted. The prevailing standards at the time the study was conducted include the Declaration of Helsinki. In addition to the Declaration of Helsinki, the 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects by the Council for International Organizations of Medical Sciences (CIOMS) is also informative regarding the prevailing ethical standards. In Denmark, the standards in place at the time the study was conducted included "Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects" (Attachment 2). The key ethical principles in the Declaration of Helsinki and 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects are respect for persons, beneficence and justice. The Ministerial Order prohibits biomedical research unless informed consent has been obtained, and establishes the elements of informed consent, including

that participation is voluntary and subjects are free to withdraw at any time without negative effects. Potential subjects must receive information on the study orally and in a written document, both presented in a manner the potential subject can understand, prior to giving written consent to participate in the study.

Ms. Arling presented her findings. All subjects were at least 18; pregnant or nursing women were excluded. Although there was no pregnancy testing of female subjects, they were asked prior to enrollment whether they were pregnant or nursing and there is no evidence that any pregnant women were included. Documentation associated with the independent ethics review or protocol/design of the study was not available to EPA. However, there is nothing in the information available that provides compelling evidence that the research was fundamentally unethical. The subjects were volunteers, they provided written informed consent, and the researcher attempted to protect their safety by instructing them to return between ROAT result readings if a positive reaction developed. Furthermore, there is no evidence that the research was deficient relative to the prevailing standards at the time in way that placed participants at increased risk of harm or impaired their informed consent. According to Dr. Zachariae, subjects provided informed consent, they were informed of the study procedures and possible risks, the study was approved by an independent ethics body prior to implementation, and children and pregnant and breastfeeding women were excluded from participation.

Ms. Arling concluded that available information indicates that there is no clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to prevailing ethical standards in a way that would have impaired subjects' informed consent or placed them at increased risk of harm.

Board Questions of Clarification

Dr. Dawson invited Board members to ask questions for clarification. The HSRB expressed concerns that the primary investigator was unable to recall the name of the independent ethics review committee. This had been an issue with older studies and discussed in prior HSRB meetings. In general, vigorous efforts should be made to acquire the information about the ethics review for studies proposed for use by the agency. The HSRB and EPA agreed that efforts will continue to be made to identify the ethics review committee in such cases, however, an absence of evidence is not evidence of negligence, as sometimes the records are no longer in existence.

Hearing no additional questions of clarification, Dr. Dawson asked Mr. Downing to call for public comments.

Public Comments

In response to Mr. Downing's call for public comments, Dr. Germaine Truisi presented ACC's ethical and technical review of the published research titled "An Evaluation of Dose/Unit Area and Time as Key Factors Influencing the Elicitation Capacity of Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) in MCI/MI-Allergic Patients," authored by Claus Zachariae, Anne Lerbaek, Pauline M. McNamee, John E. Gray, Mike Wooder, and Torkil Menné, *Contact Dermatitis* (2006) 55: 160–6. ACC noted that the deficiencies in this study were similar to those of the Yazar et. al. 2015 study. Regarding ethics, a lack of details on procedures, practices and standards of the regional ethics review boards was evident, and comparison of regional ethics review boards to equivalent HSRB standards was not possible. The inclusion criteria for confirmatory patch test is performed with 100 ppm MCI/MI. This concentration is above the threshold (20 ppm) for induction and sensitization. The period between patch testing and enrollment in a ROAT was 7 days, and individuals exposed to the ROAT were

likely to have active dermatitis. The same subjects were exposed to both concentrations of MCI/MI. In reviewing the technical aspects of the study, ACC noted that the ROAT solutions were administered by the subjects. The information from the study was not generalizable to the human population. The MCI/MI was dissolved in 10 percent ethanol, a skin irritant. The study design used a limited number of doses and was not sufficient to assess dose response. In consideration of the deficiencies described, the ACC IT, considers the Zachariae et. al. 2006 study unsuitable for obtaining a point of departure for quantitative risk assessment of products containing MCI/MI.

In response to Dr. Dawson's call for other public comments, Stuart Hindle, The Dow Chemical Company, inquired about the fact that some studies test only MCI, while one study tested an MCI/MI mixture and about the relationship of MCI to MI in regard to benchmarking for risk assessment. EPA explained that compounds have been extensively tested and characterized over many years and that they have similar induction/elicitation properties. These data will be used as WOE with other MI studies to support making informed decisions on risk assessment.

Board Discussion—Science

Dr. Dawson asked Drs. Ferguson and Maddalena to provide their comments. Dr. Ferguson read the science charge into the record:

> Is the research described in the published article "An Evaluation of Dose/Unit Area and Time as Key Factors Influencing the Elicitation Capacity of Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) in MCI/MI-Allergic Patients" scientifically sound, providing reliable data?

Dr. Ferguson reiterated her question to EPA: Is it necessary to establish a distinction between MI and MCI for the risk assessment determination? She reminded the Board that the Lundov et al. article states that MCI is a more potent sensitizer than MI and that the compounds have been used together in the past. A risk assessment must therefore be performed on the combined formulation. She also expressed concern that the study did not present enough information about the surfactant's vehicle effect, that is, helping the chemical move through the skin into the bloodstream; the accumulated exposure; and what area of the skin is affected.

Dr. Ferguson noted that the "ROAT 2" (higher dose) should not be addressed by EPA at this time and asked for clarification on whether the Lundov et al. study used subjects with active eczema. She was unclear on whether this study met the 13th criteria out of 16, which may address whether the results of the study are scientifically sound. Dr. Ferguson questioned how MI might react with MCI.

Dr. Ferguson stated that given the type of exposure, the data are sound and reliable for use in determining the LOAEL for the MCI/MI mixture.

Dr. Maddalena commented that the study was designed well and contains scientifically sound data, but the data technically do not support a point of departure for MI, since an MCI/MI mixture was used.

Dr. Gbur provided the statistics review. The study utilized standard statistical methods for data analysis. The Fisher's exact test was used appropriately for comparisons between test and control subjects. Logistic regression analysis compared the proportions of positive reactions in ROAT 1 and ROAT 2. The authors stated that subject effect in the model was assumed to be nonrandom, but provided no details on how they arrived at that conclusion. Dr. Gbur was not sure

whether the use of the generalized linear mixed model was an analysis the study authors considered. He agreed that the data were scientifically sound.

Dr. Dawson asked for comments from the Board members. An HSRB member expressed concerns on the use of MCI/MI data as a point of departure for MI. EPA clarified that data from this study would not be used to derive a point of departure for MI. EPA has evaluated these chemicals as a group in recent years; data suggest there are differences in the potency but there is a parallel increase in sensitivity for each chemical. Although the mixture could introduce speculation, it does fit into the concentration response.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Ferguson's scientific review statement:

> The Board concludes that research described in the published article "An Evaluation of Dose/Unit Area and Time as Key Factors Influencing the Elicitation Capacity of Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) in MCI/MI-Allergic Patients" is scientifically sound and provides reliable data for its exposure conditions and for deriving the MCI/MI LOAEL.

The HSRB unanimously approved the statement.

Board Discussion—Ethics

Dr. Kyle Galbraith reviewed the ethical aspects of the research and read the following charge into the record:

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

Dr. Galbraith stated that the study provided relevant information to support compliance with EPA standards. The researchers indicated that study participants were at least 18 years old and did not include pregnant women. A local ethics committee reviewed and approved the study, and the study was conducted using GLP guidelines. Standards prevailing at the time of the study agree with EPA standards and risks were appropriately minimized. Based on the information provided, the study was conducted in compliance with 40 CFR, Part 26, Subparts K and L.

Dr. Dawson asked for comments from the Board members. The HSRB recognizes that the standard 40 CFR, Part 26, Subparts K and L may not be the charge for these older studies. EPA confirmed that Subpart Q was relevant and emphasized the main objective is that the research was conducted according to EPA standards. Dr. Dawson would clarify with the EPA which regulatory citation is appropriate.

Hearing no further comments, Dr. Dawson called for a vote on Dr. Galbraith's statement, which he read into the record:

> The Board concludes that the available information supports a determination that the research was conducted in substantial compliance with Subpart Q of 40 CFR Part 26.

The HSRB unanimously approved the statement.

ROAT Studies Overall Question

Dr. Dawson invited Dr. Ferguson to provide comments on the ROAT studies overall question, noting the charge:

> When considered together, do the three studies described in Lundov et al., Yazar et al., and Zachariae et al. provide a scientific WOE in support of establishing a point of departure for determination of an elicitation threshold for methylisothiazolinone (as identified in Lundov et al.) for use in dermal risk assessments?

Regarding the WOE approach, Dr. Ferguson noted that her opinion has not changed since her earlier written comment, but she would offer some minor edits. She indicated the presence of variability across all three studies with respect to the methods of chemical application and study objective. It is recognized that elicitation to MI products might occur at lower product concentrations than currently are allowed. Determining the precise elicitation point of a specific product is difficult to accomplish from these studies. Typical usage or application rates for the general public or high-risk individual are not discussed, making it difficult to associate a dosage rate with an elicitation point. Care must be taken to compare appropriate doses across studies, regardless of the product application.

Dr. Ferguson expressed concern regarding the wording for EPA's WOE overall conclusion and expressed the relevance of the word "loading." She suggested changing the term "applied dose" to "daily dose" specifically (for the Lundov et al. study, the 0.021 µg/cm^2 per day; for the MCI/MI study, 0.025 µg/cm^2 daily; for the Yazar et al. study, 1.2 µg/cm^2 per day). The elicitation dose may vary because of the rinse-off application method. An important undiscussed point is the number of days to an observable reaction. Dr. Ferguson noted that the statistical significance across the studies was not strong and how it relates to parts per million in different products is variable.

Regarding dose safety, Dr. Ferguson indicated that such information is already available. EPA's risk assessment, therefore, should not consider application per day, accumulation of the applied dose, time of response, etc. Information about commercially available products and how they are used (expected volume per application) is important for safety. She expressed concern that the current calculations of safe loading doses may be not accurate. Studying the concentration of MI or MCI/MI in products, skin retention, induction or product absorption in people is important. The absorption of pesticides into the bloodstream also is a safety concern. She suggested that when EPA is performing risk assessment/risk mitigation, the Agency should address lowering the preservative concentrations in products. She noted that she did not think that the studies established a point of departure for elicitation threshold in MI-allergic patients. However, the studies present reliable data regarding exposure conditions and justified a need for risk assessment and more controlled studies.

In response to Dr. Dawson's question, Dr. Ferguson wondered if the goal of EPA was to find the LOAEL from the studies or to establish a point of departure in induced subjects. Dr. Ferguson reiterated that when EPA performs a risk assessment for elicitation, the applied dose per day and cumulative dose rate are more important factors to address than the loading rate. Dr. Ferguson agreed with Dr. Dawson's suggestion that the data alone cannot establish a definitive point of departure and stated that this is related to variability.

In response to the charge question, Dr. Ferguson stated that the three studies provide a scientific weight of evidence in support of establishing a point of departure for determination an elicitation threshold of MI for use in dermal risk assessment.

Dr. Dawson asked for comments from the Board members. Hearing no comments, Dr. Dawson called for a vote on Dr. Ferguson's statement, which she read into the record:

> The Board concludes that when considered together, these three studies described in Lundov et al., Yazar et al., and Zachariae et al. provide scientific WOE in support of establishing a point of departure for determination of an elicitation threshold for methylisothiazolinone (as identified in Lundov et al.) for use in dermal risk assessments.

The HSRB unanimously approved the statement.

Adjournment

Dr. Dawson thanked the Board members for their efforts and turned the meeting over to Mr. Downing.

Mr. Downing announced that the next HSRB meeting is scheduled for March 17, 2017, from 2:00 p.m. to 4:00 p.m. for the HSRB to finalize its report from the January 25–26, 2017, meeting and discuss other topics.

Mr. Downing thanked the HSRB members for their participation and adjourned the meeting at 5:43 p.m.

Respectfully submitted:

Jim Downing
Designated Federal Officer
Human Studies Review Board
United States Environmental Protection Agency

Certified to be true by:

Liza Dawson, Ph.D.
Chair
Human Studies Review Board
United States Environmental Protection Agency

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

Attachment A

EPA HUMAN STUDIES REVIEW BOARD MEMBERS

Chair

Liza Dawson, Ph.D.
Research Ethics Team Leader
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Vice Chair

Edward Gbur, Jr., Ph.D.
Professor
Agricultural Statistics Laboratory
University of Arkansas
Fayetteville, AR

Members

Jennifer Cavallari, Sc.D., CIH
Assistant Professor
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George C. J. Fernandez, Ph.D.
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Randy Maddalena, Ph.D.
Physical Research Scientist
Indoor Environment Group
Lawrence Berkeley National Laboratory
Berkeley, CA

Jun Zhu, Ph.D.
Professor of Statistics and of Entomology
Department of Statistics
University of Wisconsin–Madison
Madison, WI

Consultant to the Board

Kendra L. Lawrence, Ph.D., BCE, PMP
Health Sciences Product Manager
U.S. Army Medical Materiel Development Activity
Fort Detrick, MD

Attachment B

***FEDERAL REGISTER* NOTICE ANNOUNCING MEETING**

ENVIRONMENTAL PROTECTION AGENCY

[FRL-9957-50-ORD]

Human Studies Review Board; Notification of a Public Meeting

AGENCY: U.S. Environmental Protection Agency.

ACTION: Notice.

SUMMARY: The Environmental Protection Agency (EPA) Office of the Science Advisor announces two separate public meetings of the Human Studies Review Board to advise the Agency on the ethical and scientific reviews of EPA research with human subjects.

DATES: A public virtual meeting will be held on January 25–26, 2017, from 1:00 p.m. to approximately 5:00 p.m. Eastern Time each day. A separate, subsequent teleconference meeting is planned for Friday, March 17, 2017, from 2:00 p.m. to approximately 3:30 p.m. for the HSRB to finalize its Final Report of the January 25–26, 2017 meeting.

ADDRESSES: Both of these meetings will be conducted entirely by telephone and on the Internet using Adobe Connect. For detailed access information visit the HSRB Web site: http://www2.epa.gov/osa/human-studies-review-board.

FOR FURTHER INFORMATION, CONTACT: Any member of the public who wishes to receive further information should contact Jim Downing on telephone number (202) 564–2468; fax number: (202) 564–2070; email address: downing.jim@epa.gov; or mailing address Environmental Protection Agency, Office of the Science Advisor, Mail code 8105R, 1200 Pennsylvania Avenue NW., Washington, DC 20460. General information concerning the EPA HSRB can be found on the EPA Web site at: http://www.epa.gov/hsrb.

SUPPLEMENTARY INFORMATION:

Meeting access: These meetings are open to the public. Meeting materials are available at the HSRB Website: http://www2.epa.gov/osa/human-studies-review-board for questions on document availability, or if you do not have access to the Internet, consult with Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.**

Special accommodations. For information on access or services for individuals with disabilities, or to request accommodation of a disability, please contact Jim Downing listed under **FOR FURTHER INFORMATION CONTACT** at least 10 days prior to the meeting to give EPA as much time as possible to process your request.

How May I Participate in This Meeting?

The HSRB encourages the public's input. You may participate in these meetings by following the instructions in this section.

1. Oral comments. Requests to present oral comments during either conference call will be accepted up to Noon Eastern Time on Wednesday, January 18, 2017, for the January 24-25, 2017 meeting and up to Noon Eastern Time on Friday, March 10, 2017 for the March 17, 2017 conference call. To the extent that time permits, interested persons who have not pre-registered

may be permitted by the HSRB Chair to present oral comments during either call at the designated time on the agenda. Oral comments before the HSRB are generally limited to five minutes per individual or organization. If additional time is available, further public comments may be possible.

2. Written comments. Submit your written comments prior to the meetings. For the Board to have the best opportunity to review and consider your comments as it deliberates, you should submit your comments by Noon Eastern Time on Time on Wednesday, January 18, 2017, for the January 24–25, 2017 conference call and up to Noon Eastern Time on Friday, March 10, 2017 for the March 17, 2017 conference call. If you submit comments after these dates, those comments will be provided to the HSRB members, but you should recognize that the HSRB members may not have adequate time to consider your comments prior to their discussion. You should submit your comments to Jim Downing listed under **FOR FURTHER INFORMATION CONTACT.** There is no limit on the length of written comments for consideration by the HSRB.

Background

The HSRB is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act 5 U.S.C. App.2 § 9. The HSRB provides advice, information, and recommendations on issues related to scientific and ethical aspects of human subjects research that are submitted to the Office of Pesticide Programs to be used for regulatory purposes. The major objectives of the HSRB are to provide advice and recommendations on: (1) research proposals and protocols; (2) reports of completed research with human subjects; and (3) how to strengthen EPA's programs for protection of human subjects of research.

Topics for discussion. On Wednesday, January 25, 2017, EPA's Human Studies Review Board will consider three published articles:

1. Methylisothiazolinone Contact Allergy and Dose-Response Relationships, authored by Michael D. Lundov, Claus Zachariae, and Jeanne D. Johansen. *Contact Dermatitis* (2011) 64: 330–6.

2. Methylisothiazolinone in Rinse-Off Products Causes Allergic Contact Dermatitis: A repeated Open-Application Study, authored by K Yazar, M.D. Lundov, A. Faurschou, M. Matura, A. Boman, J.D. Johansen, and C. Lidén. *British Journal of Dermatology* (2015) 173: 115–22.

3. An Evaluation of Dose/Unit Area and Time as Key Factors Influencing the Elicitation Capacity of Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) in MCI/MI-Allergic Patients, authored by Claus Zachariae, Anne Lerbaek, Pauline M. McNamee, John E. Gray, Mike Wooder, and Torkil Menné. *Contact Dermatitis* (2006) 55: 160–6.

Then on Thursday, January 26, 2017, the HSRB will consider:

1. Published article: Cholinesterase Activity Resulting From Carbaryl Exposure.

2. Unpublished article: A Randomized Double Blind Study With Malathion to Determine the Residues of Malathion Dicarboxylic Acid (DCA), Malathion Monocarboxylic Acid (MCA), Dimethyl Phosphate (DMP), Dimethyl Thiophosphate (DMTP), and Dimethyl Dithiophosphate (DMDTP) in Human Urine.

Meeting materials for these topics will be available in advance of the meeting at http://www2.epa.gov/osa/human-studies-review-board.

On Friday, March 17, 2017, the Human Studies Review Board will review and finalize their draft Final Report from the January 25–26, 2017 meeting. The draft report will be available prior to the conference call at http://www2.epa.gov/osa/human-studies-review-board.

Meeting minutes and final reports. Minutes of these meetings, summarizing the matters discussed and recommendations made by the HSRB, will be released within 90 calendar days of the meeting. These minutes will be available at http://www2.epa.gov/osa/human-studies-review-board. In addition, information regarding the HSRB's Final Report, will be found at http://www2.epa.gov/osa/human-studies-review-board or from Jim Downing listed under **FOR FURTHER INFORMATION CONTACT**.

Dated: December 13, 2016.
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