



UNITED STATES ENVIRONMENTAL PROTECTION
AGENCY
WASHINGTON D.C., 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION
PREVENTION

December 20, 2016

MEMORANDUM

SUBJECT: Materials for Review by Human Studies Review Board for its
January 25-26, 2017 Meeting

TO: Jim Downing
Designated Federal Official
Human Studies Review Board
Office of Science Advisor

FROM: Michelle Arling
Human Research Ethics Review Officer (Acting)
Office of the Director
Office of Pesticide Programs

This memorandum identifies the materials that the Environmental Protection Agency's (EPA's) Office of Pesticide Programs is providing for review by the Human Studies Review Board (HSRB or Board) at the teleconference and virtual meeting scheduled for January 25-26, 2017. During the January discussion, EPA will ask the Board to respond to specific science and ethics questions focused on the research identified below.

1. Research discussed in the article titled "Methylisothiazolinone contact allergy and dose-response relationships", authored by Michael D. Lundov, Claus Zachariae, and Jeanne D. Johansen. *Contact Dermatitis* (2011) 64, 330-336;
2. Research discussed in the article 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, 115-122;
3. Research discussed 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", authored by Claus Zachariae, Anne Lerbaek, Pauline M. McNamee, John E.

Gray, Mike Wooder, and Torkil Menné. Contact Dermatitis (2006) 55, 160-166;

4. Acetylcholinesterase (also called cholinesterase) activity resulting from carbaryl exposure [based on research discussed in the article titled “Cimetidine-Carbaryl Interaction in Humans: Evidence for an Active Metabolite of Carbaryl”, authored by D. Gail May, Rebecca J. Naukam, J. Reddy Kambam, and Robert A. Branch. Journal of Pharmacology Exposure Therapy (1992) 262(3), 1057-1061]; and
5. Two unpublished study reports of an oral dosing study in humans involving malathion:
 - a. Gilles, D., Dickson, J. (2000) A randomised double blind ascending single oral dose study with malathion to determine the No Effect Level on plasma and RBC cholinesterase activity. Inveresk Research, Elphinstone Research Centre, Scotland. ICR 013177. March 20, 2000. Unpublished. (MRID 45125602); and
 - b. Aston, L.S. (2000). 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. Pacific Toxicology Laboratories, 6160 Variel Avenue, Woodland Hills, CA 91367. PTL119801. October 11, 2000. Unpublished. (MRID 45244601).

Lundov et al. Research Article

EPA has reviewed the aforementioned published article based on a repeated open application test (ROAT) involving methylisothiazolinone from both scientific and ethics perspectives. The EPA review evaluates the scientific aspects of the study to determine whether it is appropriate for quantitative use in deriving a point of departure for determination of an elicitation threshold for methylisothiazolinone (MI) for use in dermal risk assessments. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L. The objective of the study summarized in this article was to experimentally determine eliciting doses of MI dermal sensitization in a patch test and in a ROAT. The influence of phenoxyethanol on reactivity to MI in the patch test was also examined. The ROAT study was designed to represent more realistic dermal exposures that might occur to potential dermal sensitizers and potential allergic contact dermatitis reactions in people (i.e., repeated, non-occluded exposures). 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 charge questions for the HSRB’s consideration are provided below:

Charge to the Board - Science:

- Is the research described in the published article “Methylisothiazolinone contact allergy and dose-response relationships” scientifically sound, providing reliable data?

Charge to the Board - Ethics:

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

Yazar et al. Research Article

EPA has reviewed the aforementioned published article based on ROAT involving MI from both scientific and ethics perspectives. The EPA review evaluates the scientific aspects of the study to determine whether it, in combination with the other published articles, provides a scientific weight of evidence to support the derivation of a point of departure for determination of an elicitation threshold identified by the research described in the published article by Lundov et al. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L. The objective of the research summarized in this article was to examine whether allowed concentrations of MI in cosmetic rinse-off products have the potential to cause allergic contact dermatitis. To this end, human subjects were recruited for patch testing of MI at various concentrations to determine the presence of contact allergy, and for testing in the ROAT protocol to determine if the allowed concentration of MI (100 ppm) and half that concentration (50 ppm) had the potential to elicit contact dermatitis in these already sensitized individuals when the product is a rinse-off product. 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 charge questions for the HSRB's consideration are provided below:

Charge to the Board - Science:

- 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?

Charge to the Board - Ethics:

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

Zachariae et al. Research Article

EPA has reviewed the aforementioned published article based on a ROAT involving methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) from both scientific and ethics perspectives. The EPA review evaluates the scientific aspects of the study to determine whether it, in combination with the other published articles, provides a scientific weight of evidence to support the derivation of a point of departure for determination of an elicitation threshold identified by the research described in the published article by Lundov et al. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L.

The objective of the research summarized in this article was to determine the effect of time and dose per unit area on the elicitation threshold for MCI/MI. This study examined the influence of time and dose per unit area on elicitation threshold for MCI/MI using a ROAT protocol. 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 charge questions for the HSRB's consideration are provided below:

Charge to the Board - Science:

- 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?

Charge to the Board - Ethics:

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

ROAT Studies Overall Question

- When considered together, do the three studies described in Lundov et al., Yazar et al., and Zachariae et al., provide a scientific weight of evidence in support of the 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?

May et al. Research Article

EPA has reviewed the aforementioned published article based on a single-dose, human study with carbaryl and cimetidine from both scientific and ethics perspectives. The EPA review evaluates the scientific aspects of the study to evaluate whether it is sound and provides reliable data. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L. This study was conducted to measure the pharmacokinetic and pharmacodynamic response of RBC acetylcholinesterase to 1 mg/kg of carbaryl alone as well as the effect of administration of 1 mg/kg of carbaryl following pre-treatment with cimetidine. EPA is proposing to use the human data reported from this study to validate a physiologically-based pharmacokinetic (PBPK) model. If validated and accepted for use, EPA will use this PBPK model in human health risk assessments, which will allow for a more refined risk assessment. EPA anticipates that the PBPK model for carbaryl will be reviewed by the FIFRA Science Advisory Panel in summer 2017.

The charge questions for the HSRB's consideration are provided below:

Charge to the Board - Science:

- 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?

Charge to the Board - Ethics:

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

Malathion Oral Dosing Study

EPA conducted science and ethics reviews of available information concerning the research in two unpublished study reports: “A randomised 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.” The EPA science review evaluates the study to determine whether the data are sound and reliable. EPA’s science review focuses on the urinary metabolites of malathion, although the acetylcholinesterase data are also discussed, the plasma and RBC acetylcholinesterase data will not be used to set points of departure for risk assessment. Ethical aspects of the proposed research are assessed in terms of the standards defined by 40 CFR 26 subparts K and L. EPA is proposing to use the residues of urinary metabolites reported from this study to validate a PBPK model for its predictive capability of the model. If validated and accepted for use, EPA will use this PBPK model in human health risk assessments, which will allow for a more refined risk assessment. EPA anticipates that the PBPK model for malathion will be reviewed by the FIFRA Science Advisory Panel in summer 2017.

Charge to the Board - Science:

- Did the research on urinary metabolites of malathion, as described in the study reports “A randomised 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?

Charge to the Board - Ethics:

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

Documents for Review

The documents provided to the HSRB for review are listed below. EPA appreciates the HSRB members taking the time to review these materials in advance of the January HSRB meeting.

Overview Materials

1. Statistical Analysis of ROAT Studies
2. EPA White Paper: Evaluation of Carbaryl and Malathion Human Studies For Their Proposed Application in a Physiologically-Based Pharmacokinetic Model for Risk Assessment

Lundov et al. Research Article

1. Lundov et al. article
2. EPA Science Review
3. EPA Ethics Review
4. Attachment 1 to EPA's Ethics Review: Ethical Application & Correspondence from Ethical Review Board (Danish)
5. Attachment 2 to EPA's Ethics Review: Ethical Application & Correspondence from Ethical Review Board (English)
6. Attachment 3 to EPA's Ethics Review: EPA Questions to and Responses from Dr. Johansen
7. Attachment 4 to EPA's Ethics Review: Act on Research Ethics Review of Health Research Projects (Denmark)
8. Attachment 5 to EPA's Ethics Review: Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects (Denmark)

Yazar et al. Research Article

1. Yazar et al. article
2. EPA Science Review
3. EPA Ethics Review
4. Attachment 1 to EPA's Ethics Review: Ethical Application – Sweden (Swedish)
5. Attachment 2 to EPA's Ethics Review: Ethical Application – Sweden (English; translated using Google Translate)
6. Attachment 3 to EPA's Ethics Review: Ethical Application – Research Plan (English)
7. Attachment 4 to EPA's Ethics Review: Ethical Approval – Sweden (Swedish)
8. Attachment 5 to EPA's Ethics Review: Ethical Approval – Sweden (English; translated using Google Translate)
9. Attachment 6 to EPA's Ethics Review: Ethical Approval of Amendment – Sweden (Swedish)
10. Attachment 7 to EPA's Ethics Review: Ethical Approval of Amendment – Sweden (English; translated by Dr. Lidén)
11. Attachment 8 to EPA's Ethics Review: Ethical Approval – Denmark (Danish)
12. Attachment 9 to EPA's Ethics Review: Ethical Approval – Denmark (English; translated using Google Translate)
13. Attachment 10 to EPA's Ethics Review: Ethical Approval of Amendment – Denmark (Danish)
14. Attachment 11 to EPA's Ethics Review: Ethical Approval of Amendment – Denmark (English; translated using Google Translate)
15. Attachment 12 to EPA's Ethics Review: EPA Questions to and Responses from Dr. Lidén
16. Attachment 13 to EPA's Ethics Review: Act on Research Ethics Review of Health Research Projects (Denmark)
17. Attachment 14 to EPA's Ethics Review: Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects (Denmark)
18. Attachment 15 to EPA's Ethics Review: The Act concerning the Ethical Review of Research Involving Humans (2003:460) (Sweden)

Zachariae et al. Research Article

1. Zachariae et al. article
2. EPA Science Review
3. EPA Ethics Review
4. Attachment 1 to EPA's Ethics Review: Questions to and Responses from Dr. Zachariae
5. Attachment 2 to EPA's Ethics Review: Ministerial Order No 806 of 12 July 2004 on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects (Denmark)

May et al. Research Article

1. May et al. article
2. EPA Science Review
3. EPA Ethics Review
4. Attachment 1: Questions to and responses from Dr. Branch
5. Attachment 2: Email requests for IRB records

Malathion Oral Dosing Study

1. A Randomised Double Blind Ascending Single Oral Dose Study with Malathion to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity
2. 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
3. EPA Science Review
4. EPA Ethics Review