DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR CHLOROMETHANE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

June 2023

Peer reviewers for the intermediate-duration inhalation MRL in the post-public comment draft of the Toxicological Profile for Chloromethane were:

Lili Tang, Ph.D.
Associate Professor
Biological Sciences Department
University of Georgia
Athens, Georgia

James S. Bus, Ph.D.
Senior Managing Scientist
Center for Toxicology and Mechanistic Biology
Midland, Michigan

Vilhjálmur Rafnsson MD, Ph.D.
Professor in Preventive Medicine
University of Iceland
Reykjavik, Iceland

Comments provided by Reviewer #1

ATSDR Charge Questions and Responses and Reviewer Comments

QUESTION. Do you agree with the proposed MRL value and how it was derived? Explain. If you disagree, please specify the MRL value that you would propose. Do you agree with the health endpoint and the point of departure (LOAEL) for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 1: I concur with the selection of the neurotoxicity endpoint based on observation of a statistically significant decrement in wire performance function at 149 ppm reported in female rats beginning on test day 40 (Mckenna at al., 1981b). However, in order to strengthen the rationale for the endpoint selection, clarification should be provided indicating that the decrement in performance was continued to be observed through to the end of the study.

RESPONSE: *The MRL worksheet was revised to clearly indicate that the decrement in performance was observed through the end of the experiment.*

> Sensorimotor testing showed a significant decrease in the ability of female rats to perform the wire maneuver (inability of the animals to raise their hindquarters to the top of the wire while grasping with forelimbs) at 399 ppm beginning at day 16 and 149 ppm beginning at day 40, and persistent throughout the remainder of the study.

COMMENT 2: The McKenna et al. (1981b) data described in the March 15, 2023 ATSDR Memorandum (Sam Keith) states (p.6) that the MRL derivation was also based on evidence of reduced hindlimb clasping at 149 ppm. However, the data and ATSDR analysis only marginally support this LOAEL for this endpoint in that the effect was seen in female rats only at 399 ppm, and in male rats at ≥149 ppm only on days 16-39 (p. A-12; l.4-8). The discontinuity in the time response (an absence of evidence of progression or simple continuation at later time points, and in contrast an absence of later time point responses) suggests hindlimb clasping may not have been treatment related in male rats at ≥149 ppm. The ATSDR text (p.A13, l.25-27) also focuses only on the "statistical changes" in hindlimb clasping in female rats at 399 ppm, while offering no comment on the potentially limited toxicological significance of hindlimb clasping responses in male rats at ≥ 149 ppm.

RESPONSE: *The profile addresses the MRL derivation correctly, based solely upon wire maneuver decrement and not hindlimb clasp since the latter occurred at a higher dose. The ATSDR Memorandum was adjusted to be consistent with the MRL worksheet (Appendix A). Additionally, the MRL worksheet was revised to indicated that impaired hindlimb clasping occurred intermittently in male rats at ≥149 ppm.*

> In males, hindlimb clasping was only transiently at ≥149 ppm, observed only on days 16–39.

QUESTION. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 3: I concur with the choice of uncertainty factors that is consistent with ATSDR guidance and practice.

RESPONSE: *No response needed.*

Comments provided by Reviewer #2

ATSDR Charge Questions and Responses and Reviewer Comments

QUESTION. Do you agree with the proposed MRL value and how it was derived? Explain. If you disagree, please specify the MRL value that you would propose. Do you agree with the health endpoint and the point of departure (LOAEL) for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 1: I agree with the proposed MRL value and understand why it came so late in being. ATSDR had received new information concerning one critical study. The intermediate-duration inhalation MRL for chloromethane is called "provisional" and I did not find explanation for the use of this word in the text. Consider whether it is appropriate to explain why the MRL is stated as provisional. In the critical study (McKenna et al 1981b) histopathological exposure-related lesions were not observed, however, neurological effects were found.

RESPONSE: *The "provisional" has been removed since the MRL has undergone peer review. It is standard ATSDR practice to label an MRL as "provisional" while it is undergoing internal, interagency, and peer review. Once the value is finalized, "provisional" is removed.*

QUESTION. Do you agree with the health endpoint and the point of departure (LOAEL) for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 2: I do agree with the health endpoint and the point of departure.

RESPONSE: *No response needed.*

QUESTION. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 3: I have no comment on the components of the total uncertainty factor, the total uncertainty factor seems to me as of usual magnitude.

RESPONSE: *No response needed.*

Comments provided by Reviewer #3

ATSDR Charge Questions and Responses and Reviewer Comments

QUESTION. Do you agree with the proposed MRL value and how it was derived? Explain. If you disagree, please specify the MRL value that you would propose. Do you agree with the health endpoint and the point of departure (LOAEL) for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 1: I agree with proposed 0.3 ppm (0.6 mg/m3) as MRL for intermediate chloromrthane exposure. This new MRL was derived from the intermediate inhalation exposure study in the most sensitive animal species, Sprague-Dawley rats, with the most sensitive and susceptible non-cancer endpoint, neurologic effects. MRL was estimated based on NOAEL of the animal study (51 ppm) and NOAEL human equivalent concentration (9 ppm) and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability). The proposed MRL was also based on comprehensive systematic literature review. Therefore, I agree to new intermediate MRL.

RESPONSE: *No response needed.*

QUESTION. Do you agree with the health endpoint and the point of departure (LOAEL) for the MRL? If you disagree with either one, please specify what they should be.

COMMENT 2: Yes, I agree with the health endpoint, neurologic effect, and the point of departure (LOAEL) for the newly proposed MRL.

RESPONSE: *No response needed.*

QUESTION. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT 3: Yes, I agree with each component of the total uncertainty factor of 30, because neurologic effects induced by chloromethane exposure found in many studies with different animal species were similar, therefore, use of 3 for extrapolation from animals to humans is appropriate. 10 for human variability is a most common practice in risk assessment.

RESPONSE: *No response needed.*