Disposition of Peer Review Comments for Toxicological Profile for Ethylene Oxide

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

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

Mary Beth Genter, Ph.D., DABT
Professor
Department of Environmental Health
University of Cincinnati
2600 Clifton Avenue
Cincinnati, OH 45221

Thomas E. McKone, Ph.D.
Energy Analysis and Environmental Impacts Division
Lawrence Berkeley National Laboratory
1 Cyclotron Road, 90R2002
Berkeley CA 94720

Ivan Rusyn, M.D., Ph.D.
Professor
Department of Veterinary Integrative Biosciences
College of Vet Medicine & Biomedical Sciences
Texas A&M University
College Station, TX 77843-4458

Comments Provided by Peer Reviewer #1

ATSDR Charge Questions and Responses

QUESTION: Do you agree with the proposed updated intermediate inhalation MRL? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 1: The discovery of the EPA (1994) report is a welcome addition and will strengthen the overall support for the intermediate-duration inhalation MRL for ethylene oxide. In fact, the proposed MRL of 0.07 ppm is consistent with that derived using neurological effects. My comments on the 2019 draft stated my disagreement with the need for an additional factor of 3 that was, in my expert opinion, poorly rationalized. Specifically, I have stated that "The NOEL is based on a functional test in absence of histological observations. As stated below, there is ample data on neurotoxicity of EO, albeit little dose-response data. I would not characterize this as a deficient database and because the study used had an actual NOEL, I would not include this additional factor of 3. Therefore sub-chronic MRL should be 0.06 ppm." Thus, derivation of multiple candidate MRLs and their close proximity is consistent with the practice recommended by the National Academies Report "Review of the Environmental Protection Agency's Draft IRIS Assessment of Tetrachloroethylene" (2010). Therefore, I agree with the proposed updated intermediate inhalation MRL of 0.07 ppm.

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 2: I believe that the total UF of 30 is justifiable and am pleased that no additional factors have been applied (see response to #1 above).

RESPONSE: *No response needed.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT 3: No further comments.

RESPONSE: *No response needed.*

Comments Provided by Peer Reviewer #2

ATSDR Charge Questions and Responses

QUESTION: Do you agree with the proposed updated intermediate inhalation MRL? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 1: I do agree with the proposed updated intermediate inhalation MRL due to the fact that the 1994 EPA study is more robust, with longer exposure duration (premating, mating, during pregnancy, through lactation), with depressed body weight of the offspring and preimplantation losses as the endpoints. In Snellings et al., 1984a, wherein mice were treated for 10 or 11 weeks' duration, behavioral assessments were done on only 5 mice per group, which would be considered an inadequate study design by today's standards.

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 2: I agree that endpoints in the developmental study were assessed thoroughly and no additional modifying factors, beyond those applied to account for differences in species, and interindividual sensitivity among humans, are needed.

RESPONSE: *No response needed.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT 3: No further comments.

RESPONSE: *No response needed.*

Comments Provided by Peer Reviewer #3

ATSDR Charge Questions and Responses

QUESTION: Do you agree with the proposed updated intermediate inhalation MRL? Explain. If you disagree, please specify the MRL value that you would propose.

COMMENT 1: Yes I agree with the updated intermediate inhalation MRL. The selection of the 1994 EPA study is appropriate because it is a well-documented study of birth outcomes in rats exposed for 10 weeks in three dose groups and a control group. The number of animals used (28/sex/group) provides the opportunity to obtain a relatively robust estimate of LOAEL and NOAEL for the rat exposures. The quality of the study and the significance of a reproductive outcome eliminate the need for the additional modifying factor of 3 that was applied to the neurological effects obtained from the very limited neurotoxicity study carried out by Snellings et al (1984a). I agree with the calculation used to convert the intermittent rat exposure to an equivalent continuous exposure. I also agree with the approach used to develop the human-equivalent exposure based the regional gas dose ratio (RGDR) and setting the RGDR to 1 because of the higher blood-air partition coefficient in rats that would lead to a lower human equivalent exposure, and possibly not be as health protective. I also agree with the approach used to obtain the total uncertainty factor and give my explanation for that in response to Question 2) below.

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 2: I agree with each component of the total uncertainty factor. It is standard practice to use a factor of 3 to account for the use of animal data for humans and there is nothing in the 1994 EPA study that suggests that some other value should be used for Ethylene Oxide. Also it is standard practice to use an uncertainty factor of 10 to account for human variability and there is nothing unique to either Ethylene Oxide or the 1994 EPA study that would compel one to select an alternate value for human variability. Although an additional modifying factor of 3 was used for establishing the provisional intermediate inhalation MRL of 0.02 ppm in the 2019 Toxicological Profile for Ethylene, it is not needed for the revised provisional MRL based on the 1994 EPA study. Unlike the EPA study of birth outcomes in rats, the 2019 MRL was based on neurological outcomes in which there were limitations due to number of animals used and due to subjectivity in some observations. However, there may be a need to address any public confusion with regard to the MRL going from 0.02 to 0.07 ppm. It should be made clear that this results from reducing uncertainty as a result of having a better and more relevant study. For example it is important to recognize that, without the added modifying factor of 3 in the 2019 MRL (used to account for added uncertainty), the provisional MRL, based on factors of 3 for animal-to-human uncertainty and 10 for human variability, would have been 0.06 ppm, which is close to the revised MRL of 0.07 ppm. The added modifying factor was needed to account for uncertainty that arises from limitations of the neurological-outcomes study of Snellings et al. (1984a). But the application of the factor of 3 is a one-sided treatment of uncertainty, aiming for the lower confidence bound. In a two-sided analysis of confidence bounds the modifying factor around the MRL of 0.06 would range from 0.02 to 0.18 ppm. So in effect we are seeing a reduction of the confidence interval allowing less uncertainty around the provisional MRL.

RESPONSE: *The Reviewer suggested that ATSDR provide an explanation to address potential public confusion regarding changing the provisional intermediate-duration inhalation MRL of 0.02 ppm to the MRL of 0.07 ppm. Note that the 2019 version of a profile was a draft for public comment (not the final version of the profile) and the MRLs were provisional values. The final profile will replace the draft for public comment version of the profile on ATSDR's website. To avoid confusion, ATSDR does not provide explanations regarding changes from provisional to final MRLs.*

ATSDR agrees that the new intermediate-duration inhalation MRL of 0.07 ppm has less uncertainty than the provisional MRL of 0.02 ppm.

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT 3: I have no additional comments.

RESPONSE: *No response needed.*