Peer Review Charge:
ATSDR's Toxicological Profile
Second Draft, Post-Public Comment

Background on Toxicological Profiles

Target audiences: Public health professionals, clinicians, and informed citizens who need a succinct interpretation of the toxicological data but may not have the resources to gather and consider all of the toxicological data themselves.

Content: The toxicological profiles provide ATSDR's evaluations concerning whether adverse health effects occur and/or at what levels of exposure. Profiles are written with an emphasis on human health effects. They also contain information about health effects in animals, potential for human exposure, and environmental fate that may help the reader to determine the significance of levels found in the environment.

Scope: In 2019, you conducted a review of the Toxicological Profile for Ethylene Oxide (EtO). After the provisional intermediate inhalation MRL was reviewed and approved by internal and interagency workgroups and after the profile went out for public comment, a data evaluation report (DER) that ATSDR was not aware of was brought to our attention. **The scope of this additional review is limited to the review of the proposed, newly updated Intermediate Inhalation Minimal Risk Level (MRL) only located in Section 1.3 and Appendix A of the Toxicological Profile for EtO.** Please note that two studies (EPA, 1994 and Snellings, 1982) will also been provided for background, but are not part of the formal review request.

In the previous draft of the Toxicological Profile for Ethylene Oxide the provisional intermediate inhalation MRL was 0.02 ppm. This MRL was based on neurological outcomes in mice that were exposed to 0, 10, 48, 104, or 236 ppm ethylene oxide for 6 hours per day, 5 days per week for 10 weeks (male) or 11 weeks (female) (Snellings, 1982a). Neuromuscular screening tests (locomotor activity, patterns of respiration, corneal response, gait, tail and toe pinch reflex, and righting reflex) were conducted in five mice after 6 weeks of exposure (females only) and near termination (males and females). The Lowest Observed Effect Level (LOAEL) identified was 50 ppm (duration adjusted to 8.9 ppm) for clinical signs of neurotoxicity (hunched posture during gait, reduced locomotor activity). A duration adjusted and human equivalent No Observed Effect Level (NOAEL) of 1.8 ppm was used as the Point of Departure (POD). A total uncertainty factor of 30 was applied (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability) an additional modifying factor of 3 was applied.

After the provisional intermediate inhalation MRL was reviewed and approved by internal and interagency workgroups and after the profile went out for public comment, a data evaluation report (DER) that ATSDR was not aware of was brought to our attention. In this study, rats were exposed to 0, 10, 33, or 100 ppm ethylene oxide 10 weeks premating (6 hours/day, 5 days/week) and during mating, gestation, and lactation (6 hours/day, 7 days/week) (EPA, 1994). The LOAEL of 30 (duration adjusted to 6.89 ppm) was based on developmental effects [post-implantation loss of F0 offspring (14% vs 7% in controls) and decreased pup body weight (6.9%) in F1 generation males]. Because the LOAEL for developmental effects (duration adjusted to 6.9 ppm) was lower than the LOAEL for neurological effects (duration adjusted to 8.9 ppm) in additional to some limitations in the neurological study, the NOAEL of 10 ppm (duration adjusted to 2.1 ppm) for developmental effects was chosen as the POD. The limitations of the neurological (Snellings, 1982a) study are: 1) The neuromuscular screening test was performed to determine the feasibility of conducting larger scale neurologic examinations in subsequent studies and was a modification of a comprehensive observational assessment of the behavioral and

physiologic state of the mouse 2) Only 5 out of the 10 or 11 mice were randomly selected for observation at 6 weeks (females only) or at termination of the study and 3) No histopathological abnormalities were noted in the spinal cord or in the brain. The duration adjusted human equivalent NOAEL of 2.1 ppm for developmental effects was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability), resulting in an intermediate inhalation MRL of 0.07 ppm. Although similar PODs were used to derive the neurological (1.8 ppm) and developmental (2.1 ppm) MRLs, the developmental MRL is higher than the neurological MRL, because no modifying factor was applied to the developmental MRL. In contrast to the previous neurological MRL where a modifying factor was applied to address the insufficient assessment of functional neurological endpoints, the endpoints in the developmental study were assessed thoroughly and no additional modifying factor was needed.

Charge to Reviewer:

As you conduct your review, if you wish to comment or suggest specific changes, please annotate directly in the text where the change or additional work is needed.

For your review, you are asked to please focus on the newly derived intermediate inhalation MRL (Section 1.3 and Appendix A of the Toxicological Profile for EtO) and answer the questions below**.**

1) Do you agree with the proposed updated intermediate inhalation MRL? Explain. If you disagree, please specify the MRL value that you would propose.
2) 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.
3) Please comment on any aspect of our MRL database assessment that you feel should be addressed.