DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHANE

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

February 2024

Peer reviewers for the Post-Public Comment Draft 4 of the Toxicological Profile for 1,2-Dichloroethane were:

David C. Dorman, DVM, Ph.D., DABVT, DABT
Professor of Toxicology
North Carolina State University
College of Veterinary Medicine
Department of Molecular Biomedical Sciences
Raleigh, North Carolina

Ivan Rusyn, M.D., Ph.D.
University Professor
KC Donnelly Professor of Veterinary Physiology and Pharmacology
Chair, Interdisciplinary Faculty of Toxicology
Director, Superfund Research Center
Texas A&M University
College Station, TX

James V. Bruckner, Ph.D.
Professor Emeritus of Pharmacology & Toxicology
Department of Pharmaceutical & Biomedical Sciences
College of Pharmacy
University of Georgia
Athens, Georgia

Comments provided by Peer Reviewer #1

ATSDR Charge Questions and Responses and Reviewer Comments

MRLs

QUESTION: Do you agree with the proposed acute-duration inhalation MRL value and how it was derived? 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: The document presents the rationale and derivations in a logical and clear manner and I agree fully with the proposed acute-duration inhalation MRL that was the outcome of these calculations.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the proposed acute-duration inhalation MRL value and how it was derived? 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: The total UF was selected and implemented appropriately, and I agree with applying an UF of 30.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the proposed intermediate duration inhalation 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 3: The Agency did not use a LOAEL to derive intermediate duration inhalation MRL, but instead they used lowest model-averaged BBMCL1SD value of 14.763 ppm for central distance/total distance (%) was selected as the POD based on the data from Zhong et al. (2022). The health endpoint chosen is well supported, and the Agency used the latest BMD modeling approach to derive a POD.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the proposed intermediate-duration oral MRL value and how it was derived? 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 4: The total UF was selected and implemented appropriately, and I agree with applying an UF of 30.

RESPONSE: *No response needed.*

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses and Reviewer Comments

MRLs

QUESTION: Do you agree with the proposed acute-duration inhalation MRL value and how it was derived? 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 choice of study, outcome, LOAEL, and derived MRL.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the proposed acute-duration inhalation MRL value and how it was derived? 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: The uncertainty factors account for human variability and interspecies differences. These factors are appropriate, and I agree with their application to deriving this MRL.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the proposed intermediate duration inhalation 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 3: I agree with the choice of study, outcome, LOAEL, and derived MRL.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the proposed intermediate-duration oral MRL value and how it was derived? 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 4: The uncertainty factors account for human variability and interspecies differences. These factors are appropriate, and I agree with their application to deriving this MRL.

RESPONSE: *No response needed.*

Annotated Comments on the Toxicological Profile

COMMENT 5: The Reviewer requested the following editorial change. Page 2, Line 17: delete extraneous ‘in’ (…exposure in were observed in animal studies…)

RESPONSE: *The editorial change was made as noted in the comment.*

COMMENT 6: Page 2, Line 18: The differences in response… even though this is a broad summary it would help the reader to have key differences in responses mentioned (e.g., differences in outcomes).

RESPONSE: *The Reviewer's request for additional information pertains to a statement in Section 1.2. The following revision was made in Section 1.2 to provide additional clarity.*

> For oral exposure studies in animals, there are differences between gavage exposure and drinking water/feed exposure. Generally, effects are observed at lower doses in gavage studies compared to drinking water or feed studies. For example, in intermediate-duration studies, the lowest gavage dose producing death was 240 mg/kg/day (NTP 1991), compared to 4,926 mg/kg/day in a drinking water study (NTP 1991).

COMMENT 7: The Reviewer requested the following editorial change in Section 1.2. Page 6, Line 10, 20, 31 (elsewhere): remove hyphen (1,2-dichloroethane).

RESPONSE: *No change was made in response to this comment. The hyphen between 1,2 and dichloroethane (1,2-dichloroethane) is correct.*

COMMENT 8: Page 7, Line 8 (remove male) and Line 9 (…included significant pathological…) – what is meant by significant? Increased severity or incidence?

RESPONSE: *In Section 1.2, "male" was removed from the following sentence:*

> A study in male mice reported reproductive toxicity after intermediate-duration inhalation exposure to 1,2-dichloroethane…..

*Regarding the Reviewer's request for additional clarity on the phrase "*significan*t* pathological changes,*" the sentence was revised to delete the word "significant" from the following sentence:*

> A study in mice reported reproductive toxicity after intermediate-duration inhalation exposure to 1,2-dichloroethane; effects included significant pathological changes in the testes; vacuolar degeneration of germ cells in the testes; decreased sperm concentration, motility, and progressive motility; and increased abnormalities of the sperm head, body, and tail (Zhang et al. 2017).

COMMENT 9: Page 7, Line 26: "…due to confounding by co-exposures to various other chemicals…" some caution is warranted here since this is true for most/all human epidemiology studies. The issue is whether co-exposures and other risk factors have been adequately considered in the analysis.

RESPONSE: *In Section 1.2, the sentence noted above was revised as follows:*

> Epidemiological studies that have investigated associations between occupational or oral exposure to 1,2-dichloroethane and increased incidences of cancer are inadequate for assessing carcinogenicity in humans because studies did not adequately assess confounding by co-exposures to various other chemicals (Austin and Schnatter 1983a, 1983b; Benson and Teta 1993; Goldberg et al. 1995; Hansen 2000; Hogstedt et al. 1979; Isacson et al. 1985; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983).

COMMENT 10: Page 7, Line 32: "…The former studies were limited by use of a single exposure concentration (that was lower than the concentration resulting in tumors in the study by Nagano et al. [2006]) and by an abbreviated exposure duration." What is meant by an abbreviated exposure duration (e.g., less than two years) – it may be more informative to the reader to provide the exposure conditions.

RESPONSE: *In Section 1.2, the sentence in the comment above was revised as follows for clarity.*

> The former studies were limited by use of a single exposure concentration (that was lower than the concentration resulting in tumors in the study by Nagano et al. [2006]) and by early mortality, respectively.

COMMENT 11: Page 8, Line 20: "The inhalation database was considered adequate for derivation of an acute-duration inhalation MRL for 1,2-dichloroethane, and inadequate for derivation of intermediate- and chronic-duration inhalation MRLs, as the most sensitive endpoints for these durations are for serious effects" – I found this confusing since Table 1.1 (page 11) provides an intermediate inhalation MRL.

RESPONSE: *ATSDR thanks the Reviewer for identifying this error. In response, the sentence in Section 1.3 was revised.*

> The inhalation database was considered adequate for derivation of an acute- and intermediate-duration inhalation MRL for 1,2-dichloroethane, and inadequate for derivation of a chronic-duration inhalation MRL, as the effects occurring at the lowest exposure concentrations are serious effects.

COMMENT 12: Page 8, Line 27: "Data were insufficient to derive an acute-duration oral MRL due to uncertainty about the validity of results at the lowest effect level based on differences in effect between gavage doses and drinking water doses." Is this by policy? It is unclear why this is the case – the results are likely valid (i.e., the study quality is sufficient for ATSDR to trust the reported findings) and provide useful hazard information. The issue of dose rate is important – and if there is a lack of confidence in gavage studies then the inclusion/exclusion criteria used in the literature search should have reflected this concern.

RESPONSE: *The statement above in the Reviewer's comment is in Section 1.3. The information in Section 1.3 pertaining to MRLs is intended to be a very brief overview. A detailed rationale for not deriving an acute-duration oral MRL is provided in Appendix A. For clarity, the following revision was made in Section 1.3.*

> Data were insufficient to derive an acute-duration oral MRL due to uncertainty about the validity of results at the lowest effect level based on differences in effect between gavage doses and drinking water doses. Briefly, there is a notable difference in toxicokinetics between gavage and drinking water administration. With gavage administration, bolus dosing leads to saturation of the detoxification/excretion mechanism and exacerbates toxicity (see Section 3.1). This is described in more detail in Appendix A.

COMMENT 13: Page 13, Line 18: … cancer was assessed in animals exposed by inhalation and oral routes… dermal carcinogenesis studies were also available.

RESPONSE: *The sentence referred to in the comment above was revised as shown below in Section 2.19.*

There were studies of comprehensive noncancer endpoints in animals exposed by inhalation and oral routes, and cancer was assessed in animals exposed by inhalation, oral, and dermal routes.

COMMENT 14: Page 13, Line 20: It should be noted that cytochrome P450 metabolism of 1,2-dichloroethane appears to be saturable at gavage doses… provide species.

RESPONSE: *The sentence noted above is in Section 2.1. It was revised as shown below to indicate the species.*

It should be noted that cytochrome P450 metabolism of 1,2-dichloroethane appears to be saturable in rats at gavage doses ~25 mg/kg and inhalation concentrations of ~150 ppm, both of which correspond to blood levels of 5–10 µg/mL.

COMMENT 15: Page 13, Line 21: "A longer-term oral study of drinking water exposure failed to corroborate the results of the gavage study." Did the longer term study include outcomes evaluated in the shorter study? If not, I'd avoid using the term corroborate since less sensitive outcomes were examined.

RESPONSE: *The Reviewer's comment refers to a statement in Section 2.1 of the profile. The sentence was revised as shown below for increased clarity.*

However, a longer-term oral study of drinking water exposure did not observe adverse immunological effects.

COMMENT 16: Table 2-1 – it's not clear what % body weight decrease is deemed a SLOAEL – e.g., Zhong et al reported a 27% decrease whereas Payan et al reported a 24% decrease during pregnancy (which may have added toxicologic significance) – that was considered a LOAEL. In the Zhong study its unclear why cerebral cortical vacuolization was not considered a SLOAEL since this finding is consistent with cerebral edema; an effect considered a SLOAEL.

RESPONSE: *Per ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov), decreased terminal body weight of 10–20% relative to control is considered a LOAEL. Decreased terminal body weights >20% relative to control or weight loss (relative to body weight at the start if exposure) are considered SLOAELs. In Table 2-1, the entry for body weight for the Zhong et al. (2020), states "*LOAEL:18% decrease in body *weight in males; SLOAEL: 27% decrease in body weight in females," is consistent with guidance. The body weight entry for the Payan et al. (1995) gestational exposure study in Table 2-1 was corrected to indicate that the effect on body weight (24% decreased body weight gain during GDs 6–21) is a SLOAEL to be consistent with guidance.*

ATSDR agrees with the Reviewer's comment that cerebral vacuolation reported by Zhong et al. (2020) should be considered a SLOAEL. This is consistent with ATSDR's Draft Guidance for the Preparation of Toxicological Profiles (cdc.gov). In Table 2-1, LOAEL for the Zhong et al. (2020) study was revised to a SLOAEL.

COMMENT 17: Table 2-2. Daniel et al: Gross pathologic changes in lungs of rats that died – not all gross findings would be considered a SLOAEL – more details are needed here.

RESPONSE: *ATSDR reevaluated the Daniel et al. (1994) study regarding gross pathological changes. The gross pathological change to lung of rats that died was diffuse reddening. ATSDR agrees with the*

*Reviewer that this gross pathological change is not a SLOAEL. In Table 2-2, the SLOAEL was revised to a LOAEL and the description of the effect was revised to "*Reddening of the lungs of rats that died.*"*

COMMENT 18: Page 55, Line 10: … found mean body weight loss of 3.32 g… it would be more clear to report this as a % change in body weight.

RESPONSE: *The Reviewer's comment pertains to the body weight loss reported by Zhang et al. (2017). In Section 2.3, the sentence indicated above was revised to include the percentage body weight loss.*

> Zhang et al. (2017) found a mean body weight loss of 3.32 g in male mice (approximately 15% body weight loss relative to the beginning of exposure) in the 173-ppm exposure group under similar exposure conditions.

COMMENT 19: The Reviewer requested the following editorial change. Page 57, Line 20: change to … increased lipid peroxidation (malondialdehyde) and elevated levels of key antioxidant…

RESPONSE: *The revision as noted in the comment above was made in Section 2.4.*

> Additionally, increased lipid peroxidation (malondialdehyde) and elevated levels of key antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) in lung tissue were seen at days 1 and 5 after exposure (Salovsky et al. 2002).

COMMENT 20: The Reviewer asked that additional information be added to the profile: Page 58, Line 34: … Fat droplets were found in the myocardium of two… give number of monkeys used in this study.

RESPONSE: *The following revision was made in Section 2.5.*

> Fat droplets were found in the myocardium of two of two monkeys exposed to 200 ppm for 7 hours/day, 5 days/week for 25 weeks; no control animals were used (Heppel et al. 1946).

COMMENT 21: Page 59, Line 30: Chen et al. (2015) noted increased white blood cell counts in the cerebrospinal fluid of factory workers occupationally exposed to unknown concentrations of 1,2-dichloroethane for at least 10 months. This is more appropriately considered a neurologic effect rather than a hematologic finding.

RESPONSE: *The Reviewer considers an increase in white blood cells in the cerebrospinal fluid to be a neurological effect, rather than a hematological finding. ATSDR disagrees with the Reviewer. An increase in white blood cells reflects a change in the number of white blood cells produced in bone marrow or other tissues involved in hematopoiesis, rather than a neurological effect. Therefore, no change was made in response to this comment.*

COMMENT 22: The Reviewer requested the following editorial change. Page 60, Line 8: change to: …Yodaiken and Babcock (1973) both observed hepatic damage…

RESPONSE: *The revision suggested by the Reviewer was made in Section 2.6.*

> Hepatic disorders may result in abnormalities in coagulation tests; Martin et al. (1969) and Yodaiken and Babcock (1973) both observed hepatic damage, including atrophy, damaged hepatocytes, and necrosis.

COMMENT 23: The Reviewer requested the following editorial change. Page 62, Line 23: delete 'in': …1,2-dichloroethane leads to in liver damage…

RESPONSE: *The editorial change in the comment above was made in Section 2.8.*

In animals, acute-duration inhalation exposure to 1,2-dichloroethane leads to liver damage. Serum levels of enzyme indicators of hepatic damage (e.g., AST, ALT, sorbitol dehydrogenase [SDH]) were elevated in rats exposed to 850 ppm for 4 hours (Brondeau et al. 1983).

COMMENT 24: The Reviewer requested the following editorial change. Page 63, Line 26: change to: …have not found serious liver effects ~~like those reported in humans~~

RESPONSE: *The portion of the sentence in the comment above was deleted in Section 2.8.*

Studies in orally exposed animals have not found serious liver effects.

COMMENT 25: Page 64, Line 32: Depletion of glutathione may also contribute to hepatic toxicity (see: Jean PA, Reed DJ. Utilization of glutathione during 1,2-dihaloethane metabolism in rat hepatocytes. Chem Res Toxicol. 1992 May-Jun;5(3):386-91. doi: 10.1021/tx00027a011.)

RESPONSE: *In the comment above, the Reviewer is requesting that information on the effect of glutathione depletion as a potential contributor to hepatic toxicity of 1,2-dichloroethane be added to the profile. The following sentence was added to Section 2.8:*

In addition, since glutathione conjugation is a primary metabolic pathway for 1,2-dichloroethane, depletion of glutathione may also contribute to hepatic toxicity (Jean et al. 1992).

COMMENT 26: Page 95, Line 4: the following sentence is unclear: This may relate to higher solubility vehicles with regard to the absorption of xenobiotics.

RESPONSE: *The Reviewer's comment pertains to a sentence in Section 3.1.1. This sentence has been removed from the profile.*

COMMENT 27: Page 114, Line 8; Page 159, Line 32: "However, these measurements would have to be made at a known time since exposure, since 1,2-dichloroethane is rapidly eliminated from the body (see Section 3.1.4)." It's not clear to me if the goal is to confirm exposure. Measurement of 1,2-dichloroethane in body fluids, exhaled breath would indicate exposure occurred even if the exposure window and time to sampling was unknown. The rapid elimination would limit the time when sampling may result in a positive result.

RESPONSE: *To provide additional clarity regarding use of biomarkers, the following revisions was made in Section 3.3.1.*

Levels of 1,2-dichloroethane in breath, blood, and urine may be used to indicate exposure to this chemical. However, 1,2-dichloroethane is rapidly eliminated from the body (see Section 3.1.4); thus, if measurements are not made close to the time of exposure, 1,2-dichloroethane may not be detected. Therefore, the rapid elimination would limit the time when sampling may result in detection of 1,2-dichloroethane.

COMMENT 26: Regarding the following sentence in the profile (Page 132, Line 30: …*expected to volatilize from water surfaces, with the rate of volatilization depending on water flow and depth*), the Reviewed noted that *"it will also be temperature dependent."*

RESPONSE: *The suggested revision was made in Section 5.4.1:*

> Based on a Henry's law constant of 0.14 kPa-m^3/mol at 25°C (Haynes et al. 2015), 1,2-dichloroethane is expected to volatilize from water surfaces, with the rate of volatilization depending on water flow, depth, and temperature.

COMMENT 27: Page 143, Line 3: "1,2-Dichloroethane has been used as a lead scavenger in leaded aviation gasoline, and its approximate concentration in gasoline is 0.07 g/L (Henderson et al. 2009)." Indicate this is a historic concentration rather than a current use.

RESPONSE: *The Reviewer's suggestion to indicate historical use of 1,2-dichloroethane as a lead scavenger was added to the profile in Section 5.5.4, as follows:*

> Historically, 1,2-dichloroethane was used as a lead scavenger in leaded aviation gasoline, and its approximate concentration in gasoline was 0.07 g/L (Henderson et al. 2009).

COMMENT 28: Page 151, Line 18: "Additional studies are needed to characterize the effects of oral exposure to 1,2-dichloroethane via environmentally relevant modes of administration (e.g., drinking water or diet) to provide an appropriate basis for deriving an acute-duration oral MRL." The use of further development and use of PBPK models to extrapolate from gavage to drinking water rodents studies might also be of value to exploit the existing gavage data.

RESPONSE: *The Reviewer is referring to a statement in Section 6.2 of the profile. In response to this comment, the following sentence was added to the profile:*

> Such data may lead to the development and use of PBPK models to extrapolate from gavage data to more environmentally relevant exposures.

COMMENT 29: Page 152, Line 23: identify species (…saturable at approximately 25 mg/kg/day (gavage) and 150 ppm (inhalation)…_).

RESPONSE: *The Reviewer's comment requests identification of the species to a statement in Section 6.3. The sentence was revised as follows:*

> Toxicokinetic studies (see Section 3.1) have shown that the enzymes involved in the biotransformation of 1,2-dichloroethane are saturable at approximately 25 mg/kg/day (gavage) and 150 ppm (inhalation) in rats (D'Souza et al. 1988; Reitz et al. 1982; Spreafico et al. 1980).

COMMENT 30: Page 153, Line 22: "The relevance of the endpoint (lethality due to massive streptococcal challenge) in mice to immune function is known, but its suitability as a basis for MRL derivation is uncertain." It's unclear why this relevant outcome is not considered suitable for derivation of an MRL. In essence this is an in vivo bioassay for immunologic function.

RESPONSE: *The Reviewer is referring to statement regarding the Sherwood et al. (1987) study. This study used the streptococcal challenge test to evaluate potential immune effects of single exposures to 0, 2, 5, and 11 ppm 1,2 dichloroethane. A decreased immune response to challenge was observed at 11 ppm, with a NOAEL for immune effects of 5 ppm. However, substantial lethality was observed in both the 5- and 11-ppm exposure groups compared to controls. Therefore, the NOAEL for immunological effects cannot be used to derive an acute-duration inhalation MRL due to lethality. The following was added to the profile to provide additional clarity in Section 6.2.*

> The streptococcal challenge test was used to evaluate potential immune effects of single exposures to 0, 2, 5, and 11 ppm 1,2 dichloroethane. A decreased immune response to challenge was observed at 11 ppm, with a NOAEL for immune effects of 5 ppm. However, substantial lethality was observed in both the 5- and 11-ppm exposure groups compared to controls. Therefore, the NOAEL for immunological effects cannot be used to derive an acute-duration inhalation MRL due to increased lethality.

COMMENT 31: Page 154, Line 15: Induction of enzymes could also play a role across other outcomes as well.

RESPONSE: *The Reviewer's comment pertains to the following statement in Section 6.2:* "Another possible explanation for the different outcomes of acute- and intermediate-duration oral exposure is that 1,2-dichloroethane may induce its own metabolism during the longer exposure period, thus reducing the dose to the immune cells."

This following sentence was added to the profile in Section 6.2:

> In addition to immune effects, induction of enzymes involved in 1,2-dichloroethane metabolism could also play a role across other outcomes.

COMMENT 32: The Reviewer requested the following editorial change. Page 162, Line 1: Bold text the following: Children's Susceptibility.

RESPONSE: *In Section 6.2 of the profile, "Children's Susceptibility" is bolded.*

COMMENT 33: Page 164, Line 15: Indicate that no ongoing studies were identified.

RESPONSE: *In Section 6.2, the following sentence was added.*

> No relevant ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database.

COMMENT 34: General comment regarding research needs identified in the monograph: The draft document indicates the need for dermal studies. It's unclear why these are considered a data need sine: "Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure."

RESPONSE: *The goal of ATSDR toxicological profiles is to provide an overview of all potential adverse health effects associated with inhalation, oral, and dermal exposure. Even though ATSDR does not currently derive MRLs for dermal exposure, information is needed to more fully define topical effects at site application and systemic effects resulting from dermal exposure to 1,2-dichloroethane. Therefore,*

ATSDR considered there to be a need for additional dermal exposure studies to more completely evaluate possible effects. Dermal exposure is a relevant component of exposure in humans.

Comments provided by Peer Reviewer #3

ATSDR Charge Questions and Responses and Reviewer Comments

MRLs

QUESTION: Do you agree with the proposed acute-duration inhalation MRL value and how it was derived? 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 selection of degeneration/necrosis of the olfactory epithelium as the critical health endpoint, and with the point of departure for the MRL.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the proposed acute-duration inhalation MRL value and how it was derived? 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 do not agree with all of the adjustments that resulted in reduction of the reported LOAEL of 107.5 ppm to the proposed MRL of 0.1ppm. I understand and do agree with the adjustment from intermittent to continuous exposure. I have a problem, however, with some steps in derivation of the Human Equivalent Concentration. The equation used to account for species differences in extrathoracic surface area and air ventilation/flow rate is reasonable. Use of this equation would result in an approximate 5-fold reduction in the humane LOAEL. Nevertheless, the authors fail to take into account species differences in regional blood flow, air:blood partition coefficient and metabolism of DCE. Cardiac output and tissue blood flow rates in rats are substantially greater than in humans. One would anticipate that the same would be true in the extrathoracic region, resulting in more rapid and extensive absorption of DCE from the inhaled air into cells in that area. Gargas et al. (1989) reported DCE blood:air partition coefficients (PCs) of 19.5 and 30.4 or humans and rats, respectively. The rats' higher PC should enhance DCE flux (i.e., absorption from the air into olfactory cells and on into the bloodstream). DCE is metabolically activated to cytotoxic, genotoxic products such as choroacetaldehyde and episulfonium ions. Rats typically metabolize volatile organic compounds, such as DCE, more efficiently/extensively than do humans. This is true for the oxidative pathway catalyzed by cytochrome P4502E1 and the reductive pathway involving glutathione conjugation. One would anticipate more extensive metabolic activation of DCE to reactive metabolites in rats, although I do not know whether this has been demonstrated in the olfactory epithelium. The regional gas dose ratio (RGDR) calculation does not take species differences in metabolic activation, regional blood flow or blood:tissue PC into account. <u>These factors</u> would favor enhanced susceptibility in the rat.

RESPONSE: *ATSDR thanks the Reviewer for this insightful comment. Please note that the U.S. Environmental Protection Agency (EPA) currently uses the same method as ATSDR to derive human equivalent concentrations (HECs). ATSDR will take the Reviewer's comments into consideration when the Agency re-evaluates its methodology for calculating HECs.*

QUESTION: Do you agree with the proposed intermediate duration inhalation 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 3: I agree with the selection of neurobehavioral and histopathological in mice for derivation of the proposed intermediate-duration MRL. Derivation of the point of departure (LOAEL) is also reasonable, as is the adjustment for intermittent exposure.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the proposed intermediate-duration oral MRL value and how it was derived? 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 4: I do not think that a 10-fold interspecies uncertainty factor is justified for the reasons I have discussed above (for question 1).

RESPONSE: *The Reviewer disagrees with the 10-fold interspecies uncertainty factor for the intermediate-duration oral MRL, stating that the value is not justified for the same reasons given in Comment 2. However, in Comment 2, the Reviewer disagrees with the 10-fold interspecies uncertainty factor for the acute-duration inhalation MRL based on the approach that ATSDR used to derive the HEC. Derivation of a HEC only applies to inhalation exposure, not to oral exposure. For oral exposure, a full interspecies uncertainty factor of 10 is applied if physiologically based pharmacokinetic models have not been used to adjust for interspecies differences. Therefore, no change was made in response to this comment.*