March 31, 2023

Mr. William Gulledge
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Via Electronic Mail: Bill_Gulledge@americanchemistry.com

Re: Ethylene Glycol (EG)- Proposed Health Risk Limit Rules

Dear Mr. Gulledge:

Thank you for submitting comments dated March 8th, 2023, from the Ethylene Glycols Panel (EGs Panel) of the American Chemistry Council (ACC) on the proposed amendment to the Health Risk Limits (HRL) Rule for ethylene glycol. Below is a summary of *your comments (italics)* and MDH's responses.

1. The ACC EGs Panel commented that the Neeper-Bradley (1995) study was not appropriate for use in MDH's calculated drinking water guidance because ethylene glycol was administered to animals via gavage (a procedure where a chemical is administered all at once through a tube, directly to the stomach), creating internal doses that ACC states would not be likely to occur in humans. Additional information outlining processes in rats affecting the internal dose associated with developmental effects, experiments using rats and rabbit embryos, and information on species differential placenta formation were summarized to support the conclusion that humans are not the most sensitive species to the developmental effects of ethylene glycol.

MDH does not agree with the ACC EGs Panel that the gavage route of exposure used in the Neeper-Bradley (1995)[1] developmental mouse study is inappropriate to use in deriving drinking water guidance. As previously stated in MDH's response dated January 20th, 2023, to ACC's prior comments, MDH takes into consideration all available data from toxicology studies using oral routes of administration, including gavage studies, when deriving drinking water guidance. As required by our methodology laid out in the 2008 Statement of Need and Reasonableness (SONAR) [2], MDH takes a health-protective approach that "humans are at least as sensitive as

the most sensitive mammalian species for which there are toxicological data. Substantial evidence that the response seen in laboratory animals is due to a mechanism that does not exist in humans can overcome this assumption." After reviewing the information submitted by the ACC EGs Panel, MDH determined that the limited data on the human kinetics of ethylene glycol's toxic metabolite glycolic acid and placental transfer of glycolic acid in comparison to rodents were insufficient to rule out the possibility that pregnant women exposed to ethylene glycol would not incur developmental effects to their unborn children.

Additionally, the data provided by the EGs Panel only addressed differences between species that could affect the amount of glycolic acid that reached a developing organism. Notably, no evidence was provided that a developing child would be less sensitive to its adverse developmental effects than other species. Therefore, in accordance with MDH's methodology laid out above and MDH's mission to protect the health of all Minnesotans, including sensitive populations and the most vulnerable, MDH selected the developmental endpoint from the Neeper-Bradley (1995)[1] study to derive a guidance value as mice were identified as the most sensitive species for this effect.

2. ACC's EGs Panel commented that 21 publications have come out since the National Toxicology Program (NTP) published their report on ethylene glycol related developmental toxicity in 2004 and they are relevant and must be considered in the human health risk assessment.

MDH appreciates the detailed list of publications provided by the EGs Panel. MDH notes that six of the articles included in the list provided by EGs Panel were, in fact, included in our review and cited on our summary sheet. Additionally, studies that were summarized or cited in other publications were not necessarily cited on our summary sheet for ethylene glycol. NTP's 2004 report[3] is one example of a publication that was cited on our summary sheet and summarized other studies that were not cited individually by MDH.

MDH reviewed the remaining 15 publications the EGs Panel recommended for incorporation into the risk assessment and determined that these publications would not have altered our guidance values and were therefore not cited.

3. ACC's EG Panel commented that the term 'skeletal malformations' is an incorrect characterization of the adverse effect seen in Neeper-Bradley (1995) and 'skeletal variation' is more appropriate to characterize the extra 14th rib observed in some fetuses.

This is an issue of terminology that does not ultimately influence MDH's selection of this endpoint for use in guidance derivation. MDH notes that both an increase in the incidence of an extra 14th rib and an increase in total malformations (including skeletal malformations) were reported in Neeper-Bradley (1995)[1]. Experts in developmental toxicology state that an extra 14th rib may be classified as either a malformation or variation[4,5]. MDH considers this effect adverse, which is a more health-protective approach and is in line with our methodology[2] and developmental toxicity risk assessment guidance from the US Environmental Protection Agency[6].

4. ACC's EGs Panel disagreed with our statement that there is not enough evidence in humans to support the use of the PBPK model published and refined in their provided citations.

MDH acknowledges that the EGs Panel feels there is sufficient evidence supporting the use of the published physiologically based pharmacokinetic (PBPK) model given the thorough documentation of its development cited in their comments, but respectfully disagrees. Basing guidance development decisions on the output from a PBPK model with unresolved uncertainty around human glycolic acid metabolism, especially for glycolic acid kinetics throughout pregnancy, may result in a guidance value that does not protect the most sensitive lifestage against developmental effects. Therefore, in accordance with our methodology[2], MDH will continue to propose basing the short-term guidance value on the Neeper-Bradley (1995)[1] study and use the default body weight scaling methodology to calculate the human equivalent dose.

5. ACC's EGs Panel disagreed with MDH's statement that there is not enough evidence to deviate from MDH's health-protective position that "humans are at least as sensitive as the most sensitive mammalian species for which there are toxicological data. Substantial evidence that the response seen in laboratory animals is due to a mechanism that does not exist in humans can overcome this assumption" (SONAR, 2008/9)" and state that studies they've cited show clear evidence of species differences in placental transporters that demonstrate humans are not more sensitive than rodents.

MDH acknowledges that ACC's EGs Panel considers the presented information on differences in placental transporters between rodents versus humans and rabbits sufficient to demonstrate that humans are not more sensitive than rodents. However, MDH respectfully disagrees and notes there is still uncertainty as to whether the differences observed during those specific gestational days are representative of the kinetics for the comparative species during other potentially sensitive windows in gestation. As MDH stated in its prior response to comments dated January 20, 2023, the function of the placenta is complex and dynamic during the course of pregnancy. Transporters that allow for the passage of nutrients and some chemicals across the placenta may be more or less active and/or present at different times in pregnancy.

Without more information, MDH will retain the health-protective position that humans may be just as susceptible to developmental effects as mice following exposure to ethylene glycol and its toxic metabolite, glycolic acid.

6. ACC's EGs Panel disagreed with MDH's statement that the authors of Moore et al. 2016 did not report functional consequences of their findings. Additionally, ACC argues that the findings from Ellis-Hutchings et al. 2014 and Moore et al. 2016, along with kinetic data, and findings from rodent and rabbit developmental studies provide clear evidence that the rodent animal model is not appropriate for use in human health risk assessment of developmental toxicity.

MDH acknowledges that ACC disagrees with our interpretation of the conclusions stated by Moore et al.[7] MDH is confident in our response because Moore et al. clearly state the need for additional studies to fully compare rodents and humans: "Given the complexity of monocarboxylic acid transport across the trophoblast, further data from specifically designed, integrated studies are required to elucidate the functional significance…" MDH agrees with this statement.

Accordingly, as stated in previous responses above and in the previous response to comments dated January 20th, 2023, MDH does not agree that the presented information sufficiently demonstrates that the findings from the critical study in mice are irrelevant to human health risk assessment. As directed by our methods[2], MDH selected a POD based on developmental effects from the most sensitive species, the mouse in this case, to derive the short-term guidance value.

7. ACC's EGs Panel commented that the 21 studies they noted were not part of the NTP 2004 report and the risk assessment should be re-done to include the additional studies.

Please see response to item #2 for more information on how MDH has reviewed the 21 studies ACC has recommended for incorporation.

8. ACC's EGs Panel concludes that renal toxicity should be the critical effect used in the ethylene glycol oral risk assessment, citing the NTP's 2004 report's conclusions as support. ACC also notes that Environment Canada and Health Canada did not use developmental effects in their review.

MDH follows the risk assessment methodology laid out in our 2008 SONAR[2]. Our analysis, conducted within that methodological framework, resulted in a final guidance value based on a developmental health endpoint. Our analysis also acknowledges experimental and clinical observations of renal toxicity and lists the kidney system as a co-critical effect.

While MDH cannot speak to the methodologies and analytical practices of other agencies or organizations, we do note that both California Environmental Protection Agency[8] and the Agency for Toxic Substances Disease Registry[9] (an arm of Centers for Disease Control) also selected Neeper-Bradley (1995)[1] as the basis of their health-based values.

The proposed MDH HRL resulting from our analysis is necessary to fulfill MDH's mission statement "to protect, maintain, and improve the health of all Minnesotans." Therefore, in accordance with our obligation and authority under Minnesota Statutes 114.0751[10] and 103H.201[11], MDH maintains its proposed HRL for ethylene glycol in order to "adequately protect the health of infants, children, and adults."

Sincerely,

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