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Submitted via OEHHA Website: https://oehha.ca.gov/comments

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Re: ACC Comments on Draft No Significant Risk Levels (NSRLs) for Ethylene Oxide

The Ethylene Oxide Panel of the American Chemistry Council appreciates the opportunity to provide comments on the OEHHA's modification to the proposed Proposition 65 No Significant Risk Levels (NSRLs) for ethylene oxide (EtO) announced on December 19, 2023. The modification is the addition of a newly derived proposed NSRL of 1.5 micrograms per day (µg/day) specifically for oral exposures, and the re-designation of the previously proposed NSRL of 0.058 µg/day to be used specifically for inhalation exposures.

We support OEHHA's derivation of a proposed oral NSRL since scientific evidence shows that the potential health risk of EtO exposures is notably different depending on the exposure routes. However, OEHHA should acknowledge that deriving the proposed oral NSRL based on rodent forestomach tumors findings from the Dunkelberg (1982) 150-week oral gavage study is highly conservative for the following key reasons explained in greater detail in Appendix 1.

- The use of rodent tumor findings in the forestomach (which humans do not develop) from Dunkelberg's female rats-only study very conservatively assumes these tumors are relevant to humans. No other treatment-related tumors were reported (IARC, 2012; Dunkelberg, 1982).

- A 2-year dietary study by Bär & Griepentrog (1969)[1] of male and female rats exposed to EtO fumigated feeds found no cancers in any systemic organs consistent with Dunkelberg (1982). Although a limited study in scope, the exposures are more relevant to potential EtO consumer exposures compared to daily gavage.

[1] The original German report and English translation are attached.

- From a risk management perspective, there are little or no dietary (food and water) EtO exposures expected (U.S. EPA, 2023).

In conclusion, we support OEHHA's derivation of an oral NSRL for EtO and urge OEHHA to clarify the uncertainties resulting in the highly conservative use of the rodent forestomach tumors endpoint.

Sincerely,

William Gulledge

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Appendix 1: Detailed Comments for the Proposed Modification

1. OEHHA's derivation of an oral NSRL based on Dunkelberg (1982)'s forestomach tumor findings in female rats only implicitly assumed, very conservatively, that those tumor findings are relevant to human health risk assessment. There is uncertainty on whether tumor findings in the rodent forestomach (which humans lack) are relevant to human health risk assessment.

    a. The International Agency for Research on Cancer (IARC) has evaluated the human relevance of experimental rodent forestomach tumor findings (IARC, 2003). While IARC (2003) concluded rodent forestomach squamous epithelial carcinomas are relevant to human risk assessment for genotoxic substances, such as EtO is assumed to be, the conclusion was made with caveats that are directly relevant to the Dunkelberg (1982) findings. IARC (2003), specifically emphasized that the method of exposure and organ-specificity of the tumors are critical considerations:

        > "In evaluating the relevance of the induction of forestomach tumours in rodents for human cancer the exposure conditions in the experiments have to be considered. The exposure conditions during oral administration are unusual (***particularly if gavage dosing is employed*** [emphasis added]) in that physical effects may result in high local concentrations of test substances in the forestomach and prolonged exposure of the epithelial tissue. Such factors may contribute to responses that may be unique for the forestomach. Nevertheless, carcinogens that are DNA-reactive and cause forestomach tumours in rodents — even if they only caused tumours at this site — should be evaluated as if they presented a carcinogenic hazard to humans. DNA-reactive agents with a high organ-specificity may be rare, however, because a carcinogen acting through a genotoxic mechanism would be expected to induce tumours at a number of sites" (IARC, 2003; p 13).

    The EtO treatment method used by Dunkelberg (1982) was gavage bolus treatment that IARC (2003) had highlighted as a factor causing tumor findings that may be "unique for the forestomach." In addition, increased tumors were only found in the forestomach, which IARC (2003) also noted is unusual for genotoxic substances. Thus, the reported forestomach tumors may be secondary to the method of gavage bolus EtO treatment. The tumors were associated with substantial hyperplasia which is indicative of severe tumor-promoting irritation at the local site. Importantly, Dunkelberg (1982) explained that the method of treatment may explain the tumor findings, and cited an earlier study of EtO fumigated rat feed dietary study that did not find increased tumor incidence.

    > "It is likely that the regimen of treatment employed in our experiment (viz., the twice weekly administration instead of once weekly and the greater number of animals) may have been important factors in enabling us to achieve a positive

result. Furthermore, the use of a larger volume of solvent may have improved the absorption of the test substance into the epithelium of the stomach. The importance of the method of treatment in carcinogenicity studies of ethylene oxide by the oral route is demonstrated by the negative results obtained when rodent food fumigated by a high concentration of ethylene oxide was administered to rats for the whole of their life-time. The slow release of the compound from solid food under the latter conditions may have prevented a sufficient amount from penetrating the epithelium (Bär & Griepentrog, 1969)" (Dunkelberg, 1982; p 931).

Similarly, the European Chemicals Agency (ECHA) in its guidance on the Classification, Labeling, and Packaging state that "tumours observed only in these tissues [including the forestomach in rodents], with no other observed tumours are unlikely to lead to classification" (ECHA, 2017).

In summary, OEHHA should discuss the conservative use of the Dunkelberg (1982) findings based on the questionable human relevance of rodent forestomach tumors.

b. Consistent with Dunkelberg (1982), a 2-year rodent dietary study of highly fumigated feeds by Bär and Griepentrog (1969) found no increased systemic tumors. Although a limited study in scope, the exposures are more relevant to potential EtO consumer exposures compared to daily gavage. This study histologically examined liver, kidney, heart, spleen, and brain.. In this study by researchers at the German Federal Health Authority,[2] EtO concentrations in the rat diet were in the order of 53 – 1,400 ppm maintained by weekly fumigation of the feed. These feed concentrations were measured immediately after fumigation as well as 6 days after fumigation. Evaluations included appearance behavior, growth development, mortality, organ weights, and pathological-histological examination. Mortality of EtO-exposed rats was found to be marginally lower than the control group. The authors concluded a toxicological effect could not be observed in comparison to the controls (original German article and an English translation of this study are attached).

c. While Gollapudi et al. (2021) found that EtO is a weak genotoxicant, the absence of systemic tumor findings by Dunkelberg (1982) and Bär & and Griepentrog (1969) suggests that the doses were insufficient to cause systemic carcinogenicity at the doses tested. Therefore, basing the NSRL on the forestomach tumors in the co-presence of severe irritation, and which occurred at doses that did not cause systemic tumors, is conservative.

[2] The authors were researchers at the German Federal Health Authority's Max von Pettenkofer-Institut des Bundesgesundheitsamtes (https://de.wikipedia.org/wiki/Bundesgesundheitsamt). The paper was published in the German *Federal Health Bulletin* (https://www.rki.de/EN/Content/Institute/Committees/EB-BGB/EB-BGB_node_en.html).

2. From a risk management perspective, EtO exposure from the oral pathway via food and water are expected to be minimal or none as recently concluded by the U.S. EPA's Office of Chemical Safety and Pollution Prevention (U.S. EPA, 2023):

> "In the 2020 DRA, EPA did not identify any dietary risks of concern for EtO or ECH. A quantitative dietary assessment was not conducted for EtO since sterilization studies show that EtO residues disappear rapidly after sterilization and are unlikely to be found in spices available for consumption. EtO residues are expected to be present on commodities immediately after the fumigation process (e.g., 24 hours) and may be present as the commodity enters the channels of trade; therefore, a tolerance for EtO is needed and was established with 2005 residue data for the single chamber fumigation process required on product labels. However, the EtO residues are expected to completely dissipate by the time the commodity is available for consumption (e.g., 2 months) and thus a quantitative dietary assessment for EtO was not conducted. ***Because exposures to residues of EtO in food and drinking water are expected to be minimal to none, no dietary risks are expected*** [emphasis added]" (U.S. EPA, 2023).

3. The Dunkelberg (1982) study involved EtO treatment for 150 weeks (nearly 3-years) and is expected to result in higher tumor incidence than a conventional 2-year study. Higher tumor incidence results in a lower, more conservative NSRL. U.S. EPA's Guidelines for Carcinogen Risk Assessment (2005) states that "Current standardized carcinogenicity studies in rodents test at least 50 animals per sex per dose group in each of three treatment groups and in a concurrent control group, usually for 18 to 24 months, depending on the rodent species tested (OECD, 1981; U.S. EPA, 1998c)." The Dunkelberg study is considerably longer at nearly 3 years and there were no control stomach tumors. Thus, use of the 3-year daily gavage study is highly conservative for deriving the oral NSRL for potential dietary exposures.

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