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January 17, 2024

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

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Subject: ASTA Comments on Proposed Oral NSRL for Ethylene Oxide
Exponent Project No. 2400281.000

Dear Ms. Barajas-Ochoa:

These comments are submitted on behalf of the American Spice Trade Association (ASTA) on the development of an oral No Significant Risk Level (NSRL) for ethylene oxide1. ASTA represents the U.S. spice industry in the global marketplace. These comments make two broad points: (1) ASTA supports the development of an oral NSRL for ethylene oxide, distinct from the previously developed inhalation NSRL, and (2) ASTA believes that, while OEHHA used the best available information to calculate an oral NSRL, OEHHA's documentation on the derivation of the NSRL could be scientifically strengthened by acknowledging that the NSRL was derived based on rat forestomach tumors, whose relevance to humans is doubtful.

To be clear, ASTA does not believe that there is sufficient evidence for a finding that there is carcinogenic risk from ethylene oxide via oral exposure from spices. Indeed, key federal agencies, including the U.S. Food and Drug Administration (FDA) and U.S. Environmental Protection Agency (EPA) have concluded that exposure to ethylene oxide residues from oral spice consumption does not pose a public health risk. ASTA refers you to ASTA's comments dated June 14, 2023, submitted on OEHHA's original proposal to lower the current NSRL for ethylene oxide, which we continue to believe are due consideration by OEHHA. (A copy is enclosed with these comments.) That said, ASTA prefers that OEHHA establish a safe harbor

[1] California Environmental Protection Agency, Office of Office of Environmental Health Hazard Assessment (OEHHA). 2023. Safe Drinking Water and Toxic Enforcement Act of 1986. Notice of modification to proposed regulation and addition of one document to rulemaking file. Title 27, California Code of Regulations Article 7. No Significant Risk Levels. Ethylene Oxide. December 19, 2023.

NSRL for oral exposures to ethylene oxide, as proposed, rather than a lower safe harbor NSRL for all routes of exposure.

ASTA Supports the Development of an Oral NSRL for Ethylene Oxide

In April of 2023, OEHHA proposed an NSRL for ethylene oxide based on the EPA cancer risk potency from its Integrated Risk Information System (IRIS)[2]. The EPA cancer risk estimate was developed from an analysis of data collected by the National Institute of Occupational Safety & Health (NIOSH) of workers exposed to ethylene oxide in the sterilization industry[3,4]. The workers that were the subjects in the NIOSH study were predominantly exposed to ethylene oxide via inhalation. The NSRL of 0.058 micrograms per day was intended to apply all routes of exposure. The current proposal derives an alternative oral NSRL of 1.5 micrograms per day that will apply to oral exposures.

Oral and inhalation exposures of ethylene oxide are fundamentally different. For example, the available rodent carcinogenicity studies for ethylene oxide find tumors at different sites for oral exposure (forestomach) compared to inhalation exposure (lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure). Therefore, route-specific NSRL values are necessary.

Strengthening the Oral NSRL Proposal

The OEHHA oral NSRL is based on the Dunkelberg (1982)[5] 150-week rat oral gavage chronic study. The study included twice weekly exposures of ethylene oxide at 0, 7.5, and 30 mg/kg. The study duration was nearly 3 years, which is well beyond the current guideline of 2 years for a rat carcinogenicity study (U.S. EPA, 2015)[6] and the dosing method was via gavage, whereas modern carcinogenicity studies typically employ dietary dosing. The study found forestomach tumors with incidences of 0/50, 8/50, 29/50, for the 0, 7.5, and 30 mg/kg dose groups. The tumor incidence in both treated groups was statistically significant. There was no elevation of systemic tumors.

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[2] US Environmental Protection Agency. 2016. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CAS Registry Number75-21-8) in Support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC, EPA/635/R-16/350Fa.

[3] Steenland K, Whelan E, Deddens J, Stayner L, Ward E (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control 14(6):531-9.

[4] Steenland K, Stayner L, Deddens J (2004). Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. Occup Environ Med 61(1):2-7.

[5] Dunkelberg H (1982). Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. *British Journal of Cancer*. 46: 924-933.

[6] U.S. Environmental Protection Agency (U.S. EPA). 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001. Risk Assessment Forum, U.S. Environmental Protection Agency. Washington, DC.

Humans do not have forestomachs, and authoritative bodies that evaluate chemical carcinogenesis have generally regarded rat forestomach tumors as of dubious human relevance. For example, the International Agency for Research on Cancer (IARC)[7] states that:

> "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) 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).

As acknowledged by Dunkelberg, the gavage dosing may explain the tumor findings. And, as IARC notes, a gavage exposure could result in prolonged exposure in epithelial tissues. Indeed, the reported forestomach tumors were associated with substantial hyperplasia, which suggests severe tumor-promoting irritation.

While ethylene oxide is considered weakly genotoxic (Gollapudi et al., 2021)[8], there were no systemic tumors in Dunkelberg. Thus, the forestomach tumors occurred at doses that did not cause tumors at other sites. This is further evidence that the forestomach tumors were likely caused by the unusual gavage dosing in Dunkelberg and that these tumors are not relevant to human oral exposure.

Other authoritative bodies agree with IARC on the relevance of forestomach tumors. The European Chemicals Agency (ECHA) in its guidance on the Classification, Labeling, and Packaging[9] state that "tumours observed only in these tissues [including the forestomach in

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[7] International Agency for Research on Cancer (IARC). 2003. Predictive Value of Rodent Forestomach and Gastric Neuroendocrine Tumours in Evaluating Carcinogenic Risks to Humans. Technical Publication Number 39. World Health Organization. International Agency for Research on Cancer. Lyon, France.

[8] Gollapudi BB, Su S, Li AA, Johnson GE, Reiss R, Albertini RJ. 2020. Genotoxicity as a toxicologically relevant endpoint to inform risk assessment: A case study with ethylene oxide. Environ Mol Mutagen 61(9): 852–871.

[9] https://echa.europa.eu/guidance-documents/guidance-on-clp

rodents], with no other observed tumours are unlikely to lead to classification" (ECHA, 2017).[10] Given that no other tumors were observed, this statement suggests that ECHA would not classify ethylene oxide as a carcinogen via oral exposure based on Dunkelberg.

There is also a published 2-year rodent dietary that OEHHA did not cite. In this study of highly fumigated feeds by Bär and Griepentrog (1969)[11], there was no elevation of systemic tumors. Ethylene oxide concentrations in the rat diet were in the order of 53-1,400 ppm maintained by weekly fumigation of the feed. The histopathology in the study included the liver, kidney, heart, spleen, brain, but it is not clear if the stomach was included, so it is unknown if there were forestomach tumors. Nonetheless, the study supports the finding in Dunkelberg of a lack of systemic tumors, further supporting that the forestomach tumors in Dunkelberg are not relevant to humans. A translated copy of Bär and Griepentrog (1969) is provided with the comments from the American Chemistry Council. It is acknowledged that the documentation is limited for this study done more than 50 years ago, but it adds to the weight-of-evidence for a lack of systemic tumors.

ASTA acknowledges that there are limited data available for deriving an oral NSRL for ethylene oxide and that the Dunkelberg study is the only study from which an oral NSRL can be calculated. However, OEHHA's document would be scientifically stronger if it acknowledged the limitations of using the forestomach tumors in Dunkelberg to calculate an NSRL. Some suggested language follows:

> "While Dunkelberg provides the only oral study for which an NSRL can be calculated, it is acknowledged that the forestomach tumors found in Dunkelberg are potentially irrelevant to humans. Humans do not have forestomachs and various international agencies caution against using forestomach tumors for human risk assessment, particularly from a gavage exposure study and with a lack of evidence for systemic tumors."

Thank you for considering these comments.

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[10] European Chemicals Agency (ECHA). 2017. Guidance on the application of the CLP criteria. Guidance to Regulation (EC) no. 1272/2008 on classification, labelling and packaging (CLP) of substances and mixture. Version 5.0.

[11] Bär F, Griepentrog F. 1969. Long-term diet study in rats with feed fumigated with ethylene oxide (Ger.). Bundesgesundheitsblatt (Federal Health Bulletin) 11: 106-107.

Sincerely,

Richard Reiss, ScD
Group Vice President & Principal Scientist

Enclosures

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