International Pharmaceutical Excipients Council of the Americas

Joseph Zeleznik
Chair

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Esther Barajas-Ochoa
Office of Environmental Health Hazard Assessment
P. O. Box 4010
Sacramento, California 95812-4010
OEHHA website portal: https://oehha.ca.gov/comments

Re: OEHHA Proposal for separate NSRL limits for ethylene oxide via inhalation (0.058 micrograms per day) and oral (1.5 micrograms per day) route

Dear Ms. Barajas-Ochoa,

Members of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) have reviewed OEHHA's proposal to update a Proposition 65 No Significant Risk Level (NSRL) for ethylene oxide by amending Title 27, California Code of Regulations, Section 25705(b). IPEC-Americas members appreciate OEHHA soliciting comments on this proposal and would like to thank you for the opportunity to share our thoughts, as found below in the IPEC-Americas comments. In addition, members of IPEC-Americas have reviewed comments prepared by the American Chemistry Council (ACC) and with this letter would like to endorse their comments.

IPEC-Americas Background

IPEC-Americas represents more than 50 excipient manufacturers, distributors, and pharmaceutical/biopharma companies. IPEC-Americas is dedicated to working closely with regulatory authorities, industry organizations and scientific bodies (globally) to advance public health on matters relating to the quality, safety, manufacture, distribution, use and functionality of excipients. IPEC-Americas is the sole association representing excipients. A complete list of IPEC-Americas member companies can be found at: https://ipecamericas.org/what-ipec-americas/member-companies. This response represents the current thinking of the IPEC-Americas membership.

IPEC-Americas Comments

IPEC-Americas understands that the proposed updated NSRL for ethylene oxide would be 58 ng per day for inhalation and establishment of a separate NSRL of 1500 ng/day for the oral route. IPEC-Americas agrees that oral and inhalation routes of exposure could be separated. However, as previously communicated in IPEC-Americas June 14, 2023, comments to OEHHA (attached), IPEC-Americas does not agree with OEHHA proposal to decrease the oral NSRL to 1500 ng/day from 2000 ng/day. To support IPEC-Americas position, we have highlighted the following key points/concerns:

1. **Rationale for the Proposed Modifications**

   a. *Limitation of the Proposed NSRL Value to the Inhalation Route*

   The inhalation NSRL value is based on the USEPA's IRIS (2016) assessment and the epidemiological human inhalation dataset for ethylene oxide (EO). Oral exposure to EO, or its metabolic precursor, ethylene, falls under different physiological and kinetic considerations from inhalation exposure.

2. Development of Proposed NSRL for the oral route

a. Selection of Study and Cancer Findings

IPEC-Americas agrees with the selection of the oral study (Dunkelberg 1982[1]) for use in the development of the oral NSRL but disagrees with the human relevance of the cancer findings. The rat forestomach (where EO induced tumors occurred) has no human equivalent. In Dunkelberg, rats were administered ethylene oxide (olive oil vehicle) on an empty stomach. At low doses, ethylene oxide is hydrolyzed to ethylene glycol in acidic stomach pH environment where the food or ingested substance persists for some residence time before emptying into the small bowel. Orally, ethylene oxide is hydrolyzed to an unreactive ethylene glycol (which is metabolized by the liver and excreted), humans would not typically be exposed orally to ethylene oxide alone on an empty stomach. This would limit absorption and bioavailability and therefore limit carcinogenic potential. Dunkelberg does not identify any finding of forestomach irritation which would be expected from a reactive chemical at elevated oral doses. In any case, utilizing forestomach tumor data for cancer risk assessment should consider relevant human doses,[2] i.e., food. The lack of tumors at other sites in the rat suggests a route-specific and rat-specific etiology. Furthermore, human endogenous and food exposures to ethylene oxide vastly exceed the revised proposed oral NSRL (1500 ng/day) and at the high end of human exposures, are similar to the human equivalent[3] of the highest dose (4,838,710 ng/kg BW, human equivalent dose) in Dunkelberg.

b. Calculation of the Oral No Significant Risk Level

It appears that endogenous and food-related exposures were dismissed as potent sources of exposure to ethylene and ethylene oxide when developing the oral cancer slope factor and subsequent NSRL. Endogenous ethylene oxide production (estimated at 30,720 ng/day[4] to 6,451,000 ng/day[5]), with sources of ethylene oxide from food (e.g., ~6,360,000 ng ethylene oxide from a medium Red Delicious apple) strongly suggests that oral NSRL of 1500 ng/day vastly overestimates the harmful impact of the chemical.

Final Comments

Ethylene oxide is a naturally occurring substance that is present in everything from fresh fruits to the human body. The levels being considered in these proposed NSRLs are insignificant compared to endogenous levels and therefore would lead to an infinitesimal increase in cancers, if any. The unintended consequences of this proposed rulemaking could result in drug shortages, increased cost to consumers and decreased availability of consumer products, including those designed to limit cancer (sunscreens) and thereby negatively impact human health.

IPEC-Americas raises the same point to OEHHA as from the correspondence in June 2023: taking into consideration ethylene oxide's potential systemic exposure via endogenous production consumption, we question whether or not OEHHA's revised proposed oral NSRL of 1500 ng/day would actually prevent 1 additional case of cancer per 100,000 people. Following the “reductio ad absurdum” argument, eliminating food and endogenous (microbiome) sources of ethylene oxide would most likely eliminate most, if not all, cases of ethylene oxide-induced cancers. Additionally, the relevance of rat forestomach tumors to the human risk assessment is minimal without supporting oral epidemiological evidence and the lack occurrence of other tumors in orally exposed rats.

In Summary

IPEC-Americas strongly recommends that OEHHA withdraw the revised proposed oral NSRL of 1500 ng/day. Additionally, IPEC-Americas strongly urges OEHHA to reassess the current NSRL of 2,000 ng/day paying closer attention to the vastly higher levels of ethylene oxide from endogenous and natural exogenous sources to determine if, in fact, the existing NSRL is overly restrictive and should instead be increased.

Joseph Zeleznik

Chair, IPEC-Americas

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1 Dunkelberg H. Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. Br J Cancer. 1982 Dec;46(6):924-33. doi: 10.1038/bjc.1982.303

2 Deborah M. Proctor, Nicole M. Gatto, Sandra J. Hong, Krishna P. Allamneni, Mode-of-Action Framework for Evaluating the Relevance of Rodent Forestomach Tumors in Cancer Risk Assessment, *Toxicological Sciences*, Volume 98, Issue 2, August 2007, Pages 313–326, https://doi.org/10.1093/toxsci/kfm075

3 US FDA Center for Drug Evaluation and Research (CDER) (2005) Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. https://www.fda.gov/media/72309/download

4 Kirman CR, Li AA, Sheehan PJ, Bus JS, Lewis RC, Hays SM (2021) Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management. J Toxicol Environ Health B Crit Rev 24(1):1–29. https://doi.org/10.1080/10937404.2020.1852988

5 Kirman, C, Hays, S. 2017. Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen. Regulatory Toxicology and Pharmacology. 91:165-172. https://doi.org/10.1016/j.yrtph.2017.10.032

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