International Pharmaceutical Excipients Council of the Americas

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Chair

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OEHHA website portal: https://oehha.ca.gov/comments

Re: OEHHA Proposal to update NSRL for ethylene oxide to 0.058 micrograms per day

Dear Esther 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) and understand that the proposed updated NSRL for ethylene oxide would be 58 ng per day. 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 members would like to address the following key points/concerns:

1. Natural exposure, e.g., apples and navel oranges

a. Recommended servings for fruits and vegetables

It is well documented that eating at least 5 servings of fruit and vegetables per day promotes a healthy lifestyle. A recent study, following subjects for 30 years, demonstrated that consumption of 5 servings of fruits and vegetables per day decreased both mortality and cancer rates.[1] Most fruits (including oranges) and vegetables contain varying amounts of the plant hormone, ethylene, which is metabolized by humans and other mammals to ethylene oxide.[2,3] In rats, 30% of ethylene is metabolically converted to systemically available ethylene oxide.[2] Ripe Red Delicious apples, freshly picked from a tree, will contain approximately 100,000 ng of ethylene/g apple and after 40 days post-harvest the ethylene levels are 10,000 ng/g apple.[4] Eating an average-size red delicious apple (using the rat 30% systemic ethylene oxide availability after metabolism) would

result in a person being exposed to ~6,360,000 ng ethylene oxide. That value exceeds the proposed NSRL by 110,655,000 times and eating a 40-day post-harvest apple would only decrease the exposure 10-fold (636,000 ng). Lowering the potential ethylene metabolism to 1%, would still result in exposure to 212,000 ng ethylene oxide and exceed the proposed NSRL by >3,000,000-fold.

$$100{,}000\ ng\ Ethylene/g\ apple * 212\ g\ apple = 21{,}200{,}000\ ng\ Ethylene$$

$$21{,}020{,}000\ ng\ ethylene * 30\%\ metabolism = 6{,}360{,}000\ ng\ EtO$$

For comparison to a commodity important to California's heart, oranges (Navel or Valencia) contain ~11-20 ng ethylene per orange.[5,6] On the low end of ethylene content, exposure to ethylene oxide from eating an orange (assuming only 30% conversion ethylene to ethylene oxide) would still exceed the NSRL by ~58-fold.

As "eating an apple a day keeps the doctor away" has been an axiom since the 1860s,[7] it seems contradictory that such extremely high ethylene oxide exposure via foods results in healthier lives and lower cancer rates. While in contrast, the extremely small potential risk from technically unavoidable exposures due to non-food products purchased by the consumer, would lead to increased cancer rates.

b. Intestinal microbiome

Intestinal microbiome is a recognized source of endogenous exposure to ethylene oxide both in humans and laboratory animals.[8,9] These gastrointestinal tract microbes produce endogenous ethylene from amino acids and their intermediates[8] that is subsequently converted to ethylene oxide as described above. In fact, human gastrointestinal tract microbiome are more diverse as compared to rats and mice, and this diversity is positively correlated with human health.[10,11] In the human microbiome, there are numerous ethylene-producing bacterial species that are always detected in the analyzed human gastrointestinal tract samples, including various *Bacteroides* species, *Enterococcus faecalis* and *Escherichia coli*.[8,12,13] However, the addition of an exogenous chemical into the "pool" of endogenous and background exposures have thus far proved to be a significant challenge for the regulatory risk assessment.[14] It means that this background from endogenous ethylene production of intestinal microbiome is a significant contributor to the overall ethylene oxide daily exposure burden, even compared to the exogenous and environmental sources, that have not been appropriately, if at all, considered by EPA or OEHHA.

c. Impact on cancer cases

In terms of the risk assessment, IPEC-Americas would like to raise a question: taking into consideration our previous comments above on ethylene oxide's potential systemic exposure, would OEHHA's proposed NSRL of 58 ng/day prevent 1 additional case of cancer per 100,000 people? Combining endogenous ethylene oxide production (estimated at ~30,720 ng/day[8] to ~6,451,000 ng/day[15]), with sources of ethylene oxide from food strongly suggests that exposure <58 ng/day would not prevent 1 additional cancer. However, if the 58 ng/day limit is truly protective, then eliminating all natural sources of ethylene or ethylene oxide should reduce lymphohematopoietic cancers and breast cancers to almost zero. Obviously, this argument is "reductio ad absurdum" in terms of eliminating these cancers as you cannot eliminate the intestinal microbiome and survive, nor should anyone eliminate the consumption of fruits and vegetable, if they want to remain healthy.

OEHHA addressed the background exposures to an extent in their Initial Statement of Reasons while focusing on the relationship of smoking and ethylene oxide.[16] However, when comparing ethylene oxide blood levels between smokers and non-smokers, the difference is relatively small as smokers are exposed to only 4-fold more ethylene oxide than nonsmokers based on hemoglobin adduct levels.[17] The same author, using the NHANES 2013-2016 dataset concluded that there was no association between any cancer and levels of ethylene oxide. Thus, it appears that endogenous and food-related exposures were dismissed as potent sources of a carcinogenic exposure when developing the cancer slope factor.

Humans have evolved to handle both metabolism of ethylene (via their food supply and intestinal microbiome) to ethylene oxide and ethylene oxide produced endogenously. Exposure to ethylene oxide levels 100 to 110,000,000 times less than what is in our food or produced by our own bodies should cause OEHHA to reconsider just how much additional "safety" would be produced by the proposed NSRL.

2. OTC lawsuit and FDA ethylene oxide regulations

A recent appellate court decision[18] established that federal law pre-empts Proposition 65 warning requirements for over the counter (OTC) medications. We would expect that decision to apply to prescription drug products as well. Per the Food, Drug and Cosmetic Act[19] Sec 201 (USC 321), excipients (inactive ingredients in pharmaceuticals) are considered drugs.

– Sec 201 (USC 321)

– "(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia,….; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and ***(D) articles intended for use as a component of any article specified in clause (A), (B), or (C)****."*

The inclusion of an excipient in the definition of a drug was further confirmed as part of a presentation entitled "*FDA's Recent Quality Concerns with Excipients*" by Francis Godwin (FDA Director for Office of Manufacturing Quality, Center for Drug Evaluation and Research, Office of Compliance) during the 2023 Excipient World Conference and Expo.

Based on the US FDA defining excipients as drugs, and drugs being exempt from Proposition 65 warning requirements, excipients produced from or containing ethylene oxide should also be exempt. However, this would likely create difficulties for excipient manufacturers whose products may also be used as food additives or in industrial manufacturing. For example, some packaging (food and industrial) would require Proposition 65 labels, and some would not (excipient). Consumer product, food, and industrial manufacturers might purchase excipient grades of ethylene oxide containing materials to avoid Proposition 65 warning requirements. This would defeat the purpose behind Proposition 65 warning labels but should not violate the regulation.

3. Labeling toothpaste, sunscreen, soap, or other beneficial consumer products

A warning placed on a consumer product label does not necessarily mean the product is unsafe or that the consumer should not use it. However, the warning presents a perceptional safety concern that may result in less use of very beneficial consumer products. For example, sunscreen use can help prevent skin cancer[20] by protecting consumers from the sun's harmful ultraviolet (UV) rays. U.S. Food and Drug Administration (FDA),[21] U.S. Centers for Disease

Control and Prevention (CDC),[22] U.S. Surgeon General,[23] American Academy of Dermatology (AAD),[24] Skin Cancer Foundation[25] and other health professionals[26,27] worldwide emphasize the important health benefits sunscreens provide as part of a safe sun regimen to help prevent sunburn and reduce skin cancer risk. Labeling sunscreen with a Proposition 65 warning would make consumers less likely to use sunscreen and increase the risk of skin cancer for consumers.

Humans produce ethylene oxide from enzymatic metabolism of ethylene, which is also produced in the body, by monooxygenase P450 enzymes.[28] The proposed No Significant Risk Level (NSRL) of 58 ng/day for ethylene oxide suggests that humans would need to label themselves as containing carcinogens since all humans internally produce ethylene oxide and have detectable quantities of ethylene oxide in circulation and/or breath.[15,26]

4. **Inhalation values used for dermal and oral exposure extrapolation.**

Ethylene oxide is a gas at room temperature and was tested in the cancer bioassays in its natural state. The US EPA IRIS (2016)[29] assessment only called out the inhalation route for ethylene oxide carcinogenicity. On the other hand, NSRL value will require oral and dermal products to be now labeled with Proposition 65 warnings. This is not appropriate for several reasons. First, ethylene oxide persists the longest in the air; with a half-life of 2-5 months.[30] Second, ethylene oxide is NOT a forever chemical and the levels in products, especially in liquids, will dissipate over time due to its hydrolysis to stable ethylene glycol. In fact, the half-life of ethylene oxide in water is much shorter and on average <15 days.[28] Thus, aqueous liquids containing ethylene oxide derivatives should not be subject to Proposition 65 warnings. In other products, ethylene oxide would either react with other chemicals present or hydrolyze at a slower rate than in aqueous medium. Third, pH extremes are known to accelerate hydrolysis reaction of epoxides.[31,32] If ingested, any remaining levels of ethylene oxide would be subject to hydrolysis because of the stomach's acidic pH; hence, it is unlikely that ingestion of a small amount of ethylene oxide would result in systemic bioavailability and contribute to increased cancer incidence as epoxide hydrolysis would happen early in the gastrointestinal tract. Likewise, normal skin is also acidic, and this environment would accelerate hydrolysis of any remaining, low levels of ethylene oxide into ethylene glycol; the physiological pH of the stratum corneum is 4.1–5.8.[33] Furthermore, no evidence of dermal penetration was seen for 800 ppm ethylene oxide concentrations during a 30-minute exposures[34]; therefore, at lower ethylene oxide concentrations, such as the potential residuals found in dermal products, no dermal penetration would also be expected. Overall, exposure to low, residual levels of ethylene oxide via the dermal and oral routes should not rise to the same concern as ethylene oxide exposure via inhalation route. Hence, OEHHA's approach of deriving NSRL value from inhalation URE is not scientifically justified nor it is appropriate for ethylene oxide.

In Summary

On the basis of IPEC-America's previous scientific and regulatory arguments above, the following major points have been highlighted:

- Exposure to ethylene oxide via ethylene from foods and endogenous production, exceeds the proposed NSRL by multiple orders of magnitude indicating that the risk assessments that would need to be undertaken for Proposition 65 labelling vastly overestimate the harm caused by extremely low hypothetical exposures via non-food products.
- As human bodies evolved to address relatively large ethylene oxide exposures, the minute quantity of the proposed ethylene oxide NSRL is like a single drop of water in 20 Olympic-sized swimming pools.

- Confusing consumers by labeling products designed to prevent cancer as cancer-causing, may (although highly unlikely) decrease ethylene oxide-related cancers, but at the cost of likely increases in other cancer types such as skin cancer.
- Inhalation exposures are not appropriate to develop a NSRL that includes oral and dermal exposures because inhalation exposures from solid or liquid products that contain ethylene oxide is unlikely due to hydrolysis and other chemical reactions.

IPEC-Americas recommends that OEHHA withdraw the proposed NSRL of 58 ng/day. Additionally, IPEC-Americas requests that OEHHA reassess the current NSRL of 2,000 ng/day paying close attention to the vastly higher levels of ethylene oxide from endogenous and natural exogenous sources, and the Texas Commission on Environmental Quality ethylene oxide assessment.[35]

IPEC-Americas appreciates the opportunity to provide the comments to OEHHA. Please contact us if we can answer any questions about IPEC-Americas comments.

Respectfully yours,

Nigel Langley
Chair, IPEC-Americas

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