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VIA E-MAIL

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Re: Comments on Updated California Office of Environmental Health Hazard Assessment's (OEHHA's) Inhalation Unit Risk Factor (IUR) for Ethylene Oxide (EtO)

Dear Mr. Crist,

The California Office of Environmental Health Hazard Assessment (OEHHA) recently released a draft document updating the inhalation unit risk factor (IUR) for ethylene oxide (EtO) developed under the Air Toxics Hot Spots Program.[1] Although OEHHA did perform its own literature review to identify more recent studies published since release of the 2016 EPA IUR, OEHHA ultimately adopted the US EPA's 2016 IUR of 6.1×10^{-3} per parts per billion (ppb) or 3.3×10^{-3} per $\mu g/m^3$. One area in which OEHHA appears to differ from EPA is that OEHHA routinely uses a more conservative adjustment factor for childhood exposures than EPA when estimating lifetime residential risk.[2] However, OEHHA's age-specific factor (ASF) is not specific to EtO (i.e., it is applied to all IURs when estimating lifetime residential risks) and will, therefore, not be discussed here.

Since OEHHA has adopted EPA's IUR for use in its Air Toxics Hot Spots Program, this letter focuses on issues that have been identified with EPA's IRIS value.

EPA's IRIS value is an overly conservative value that is well below the background levels of EtO found in ambient air across the entire United States (US). Based on the IRIS evaluation, EPA concluded that long-term continuous exposure (24 hours a day, 7 days a week, for 70 years) to 0.011 ppb of EtO could increase the risk of cancer by 100-in-1,000,000, despite the fact that the

[1] OEHHA. 2023. California Office of Environmental Health Hazard Assessment. Draft Ethylene Oxide Cancer Inhalation Unit Risk Factor. Technical Support Document for Cancer Potency Factors. Appendix B. April.
[2] OEHHA (2015). California Environmental Protection Agency (Cal/EPA). Office Of Environmental Health Hazard Assessment. Air Toxics Hot Spots Program. Risk Assessment Guidelines: Guidance Manual for Preparation of Health Risk Assessments. See Section 8.2.1.

only studies that correlate EtO to increased cancer involved EtO exposures orders of magnitude higher. By comparison, monitoring across the US indicates that ambient background levels of EtO are in the range of 0.15 ppb, more than ten times EPA's acceptable risk level.[3]

Establishing an acceptable air concentration that is well below background levels creates a situation in which the entire US population is implicated as being at risk from exposure to EtO because it is ubiquitous in the air. Moreover, any apparent reduction in risk from decreasing sterilizer emissions will not be significant because the risk posed by sterilizer emissions is so much smaller than the estimated risk associated with background EtO. Not only does this make identifying health-significant contributions from sources of EtO impossible to discern, but it also renders the IRIS value highly impractical as a basis for regulation because compliance with a level below widespread background levels cannot be demonstrated.

EPA's EtO IUR should not be used to set other toxicity factors or as a basis for regulation, particularly considering the potential for medical device shortages if additional sterilizers close or their capacity is significantly reduced as a result of EPA's inflated risk factor. Use of EPA's IUR as a regulatory tool risks misleading the public about the risk of developing cancer and misallocating limited resources that could be better spent addressing more pressing air quality issues.

The flawed science underpinning EPA's EtO IUR is discussed below.

I. EPA'S IUR RELIES ON A SINGLE STUDY FROM DECADES AGO

In developing the EtO IUR, EPA failed to implement recommendations made by both the National Research Council (NRC)[4] and National Academies of Science (NAS)[5] for EPA to develop approaches for using multiple studies in dose-response assessments and move away from the old paradigm of focusing on single studies. In the case of EtO, EPA chose to rely on the one cohort study published by the National Institute of Occupational Safety & Health (NIOSH)[6] that it deemed to be the "best" study. By ignoring the NRC's and NAS's recommendation, EPA failed to give any weight to the many negative findings regarding EtO's ability to cause cancer. This is consequential because 12 of the primary 14 cohort studies of EtO production and sterilization workers failed to show a statistically significant association between EtO exposure and lymphohematopoetic

[3] Sheehan, P. J., Lewis, R. C., Kirman, C. R., Watson, H. N., Winegar, E. D., & Bus, J. S. (2021). Ethylene oxide exposure in US populations residing near sterilization and other industrial facilities: Context based on endogenous and total equivalent concentration exposures Int. J. Environ. Res. Public Health, 18(2), 607; Lewis, R.C. Sheehan, P.J. DesAutels, C.G. Watson, H.N. and Kirman, C.R. (2022). Monitored and modeled ambient air concentrations of ethylene oxide: Contextualizing health risk for potentially exposed populations in Georgia. Int. J. Environ. Res. Public Health, 19(6): 3364-3379. DOI: 10.3390/ijerph19063364; ATSDR (2022). Agency for Toxic Substances Disease Registry. Toxicological Profile for Ethylene Oxide. See Table 5-8; GA DNR (2022). Georgia Department of Natural Resources. Environmental Protection Division. Ethylene Oxide Monitoring Report. Table 16.

[4] National Research Council, National Academy of Sciences. 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

[5] NAS (2018). Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. A Consensus Study Report of the National Academies of Science Engineering Medicine. The National Academies Press, 500 Fifth Street, NW Washington, DC 20001.

[6] Steenland K, Stayner L and Deddens J (2004). Mortality analyses in a cohort of 18235 ethylene oxide exposed workers: Follow up extended from 1987 to 1998. Occup Environ Med 61(1): 2–7; Steenland K, Whelan E, Deddens J, Stayner L and Ward E (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control 14(6): 531–539. 10.1023/a:1024891529592.

cancer (LHC), while six of seven failed to show a statistically significant association between EtO exposure and breast cancer.[7]

Although the IRIS program has created processes and guidelines for synthesizing evidence and takes credit for implementing the major NAS recommendations,[8] quantitative integration of evidence from multiple studies into dose-response assessment has yet to be applied in any IRIS assessment, including the one performed for EtO in 2016.[9]

Despite the availability of quantitative exposure estimates from three independent epidemiology studies (NIOSH cohort, Union Carbide cohort [UCC] and Swedish Sterilizer cohort),[10] EPA concluded that the NIOSH study was the only study suitable for calculating an IUR. Although a smaller occupational cohort than the NIOSH cohort (1,896 vs 18,235 workers), the UCC study was high quality with a lengthy follow-up period that involved larger cumulative exposure to EtO than the NIOSH cohort (67 ppm-years vs 27 ppm-years).[11]

EPA justified not performing dose-response assessments for the UCC and Swedish cohorts for the following reasons: 1) a greater likelihood for exposure misclassification in the UCC, especially in the earlier time periods when no measurements were available (1925−1973), claiming that this was in contrast to the NIOSH exposure assessment, where exposure estimates were based on extensive sampling data and regression modeling; 2) the claim that chemical production processes like those used by UCC workers likely involved much higher and more variable exposures in the past, while the sterilization processes used by the NIOSH cohort were fairly constant in the past; and 3) a less rigorous approach was used to estimate historical

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[7] Hogstedt C, Malmqvist N, Wadman B (1979a) Leukemia in workers exposed to ethylene oxide. JAMA 241:1132–1133 Hogstedt C, Rohlen O, Berndtsson BS, Axelson O, Ehrenberg L (1979b) A cohort study of mortality and cancer incidence in ethylene oxide production workers. Br J Ind Med 36:276–280; Hogstedt C, Aringer L, Gustavsson A (1986). Epidemiologic support for ethylene oxide as a cancer-causing agent. JAMA 255:1575–1578 IARC. 1997; Bisanti L et al (1993) Cancer mortality in ethylene oxide workers. Br J Ind Med 50:317–324; Norman SA, Berlin JA, Soper KA, Middendorf BF, Stolley PD (1995) Cancer incidence in a group of workers potentially exposed to ethylene oxide. Int J Epidemiol 24:276–284International A; gency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 97. 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide) Chemical Agents and Related Occupations volume. Lyon France. IARC. 2012. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Chemical Agents and Related Occupations. 100F. Lyon France; Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM (2019 Oct) Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health 92(7):919–939. https://doi.org/10.1007/s00420-019-01438-z.

[8] EPA claims to have used multiple epidemiological studies for the dose–response assessment for EtO in Appendix C (slide 134) of the NAS (2018) document.

[9] NAS (2018). Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. A Consensus Study Report of the National Academies of Science Engineering Medicine. The National Academies Press, 00 Fifth Street, NW Washington, DC 20001.

[10] Swaen GM, Burns C, Teta JM, Bodner K, Keenan D and Bodnar CM (2009). Mortality study update of ethylene oxide workers in chemical manufacturing: A 15 year update. J Occup Environ Me51(6): 714–723. 10.1097/JOM.0b013e3181a2ca20; Mikoczy Z, Tinnerberg H, Björk J and Albin M (2011). Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: Updated cohort study findings 1972–2006. Int J Environ Res Public Health 8(6): 2009–2019. 10.3390/ijerph8062009.

[11] TCEQ (2020). Texas Commission on Environmental Quality. Ethylene Oxide Carcinogenic Dose-Response Assessment. May 15, 2020. p. 33

exposure levels in the Swedish cohort than used in the NIOSH study and the Swedish data were not well suited to the derivation of an IUR.

EPA stated that exposure misclassification was a bigger problem in the UCC than the NIOSH cohort even though measured EtO exposure data from 1957 to 1973 were available from a chemical plant in Texas that was similar to the UCC, while the only measured exposure data for the NIOSH cohort was from 1976 to 1985. Moreover, the extensive sampling that EPA refers to in defending its sole reliance on the NIOSH cohort studies was all done in the late 1970's and early 1980's.

This is not the first time that EPA has been criticized for not including the UCC in one of its dose-response assessments for EtO. While the 2007 Science Advisory Board (SAB) Panel agreed with EPA that the NIOSH cohort was the best single epidemiological data set with which to study the relationship of cancer mortality to the full range of occupational exposures, the Panel encouraged the EPA at that time to consider <u>all</u> of the available epidemiological data in developing its final IRIS assessment. Specifically, the Panel encouraged EPA to explore EtO exposures for UCC workers from its two Kanawha Valley, West Virginia facilities.[12]

In response to previous comments about not including the UCC in its dose-response analysis for EtO, EPA responded that it "… considered using the UCC data and determined that they were not of sufficient quality to add useful information to the NIOSH study's data for the derivation of unit risk estimates."[13] The truth of the matter is that if the UCC data were included in EPA's dose-response assessment for EtO, it is unlikely that the effect size could reasonably be inferred to exclude zero (i.e., to exclude being negligible) as concluded by Valdez-Flores *et. al* (2010),[14] which would make it very difficult for EPA to justify concluding that the evidence supports that EtO causes cancer, even at high historical occupational exposures, and that estimation of an IUR is warranted.

II. NEW STUDIES RELEASED SINCE THE 2016 IUR CAST DOUBT ON EVIDENCE FOR ETO-INDUCED CANCER

Despite publication of several studies since release of the 2016 IUR casting doubt on the evidence for EtO-induced cancer and the health significance of exposure to environmentally-relevant EtO levels (i.e., those in ambient air), EPA has repeatedly concluded that the new studies do not change the conclusions in the 2016 IRIS assessment and do not justify a reassessment of human health effects (derivation of a new IUR).

This reluctance to consider the entirety of the available literature is inconsistent with stated positions taken by EPA in other circumstances. For example, EPA noted in the preamble for the 2012 $PM_{2.5}$ National Ambient Air Quality Standard (NAAQS) decision[15] that setting a health

[12] SAB (2007). EPA's Science Advisory Board. Review of Office of Research and Development (ORD) draft assessment entitled, "Evaluation of the Carcinogenicity of Ethylene Oxide". December 21, 2007.

[13] EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. Appendix K, p. K-6.

[14] Valdez-Flores C, Sielken RL Jr, Teta MJ (2010) Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regul Toxicol Pharmacol 56:312–320. https ://doi.org/10.1016/j.yrtph .2009.10.001.

[15] 78 Fed. Reg. 3086 at 3098.

standard based on epidemiological studies that cannot identify a population threshold (e.g., for chemicals purported to cause cancer by a mutagenic mode of action) requires consideration of how to weigh the uncertainties in the reported associations across the distributions of concentrations in the studies and the uncertainties in quantitative estimates of risk, *in the context of the entire body of evidence*. Several studies published since the 2016 IRIS assessment that support reassessment of the IUR are discussed below.

Marsh et al. (2019)[16] did a systematic literature review and meta-analysis to evaluate the strength of evidence for EtO-induced breast cancer and LHC and found that studies showed: 1) a general lack of association between EtO and breast cancer; and 2) overall (including all studies/years) meta-relative risks (RRs) for LHC among EtO production and sterilization workers were not statistically significant, although RRs for LHC were statistically significant when the early studies were considered by themselves. Vincent et al. (2019),[17] a focused review of the epidemiological, toxicological, and mechanism of action (MOA) evidence of EtO carcinogenicity, also concluded that EtO studies judged to be of higher quality did not find statistically significant associations between EtO and breast cancer or LHC, while those in the low-quality categories found positive, statistically significant associations. Marsh et al. also concluded that the most informative epidemiology studies were those that were published later in the 2000's and 2010's. Like Marsh et al. (2019) and Vincent et al. (2019), Lynch et al. (2022)[18] concluded that there was a lack of clear and consistent evidence linking EtO and cancer.

Jain et al. (2020)[19] evaluated 2013-2016 data from the Centers for Disease Control (CDC) on a biomarker of EtO exposure (hemoglobin adduct N-2-hydroxyethyl-valine [HEV]) in the general US population and self-reported cancer diagnoses. This study concluded that there was no association between the biomarker and breast cancer in women. Kirman et al. (2020),[20] Sheehan et al. (2021),[21] and Lewis et al. (2022)[22] used HEV adduct levels from CDC for the US non-

[16] Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM (2019). Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health 92(7):919–939. https://doi.org/10.1007/s00420-019-01438-z.

[17] Vincent MJ, Kozal JS, Thompson WJ, Maier A, Dotson GS, Best EA, Mundt KA (2019). Ethylene oxide: cancer evidence integration and dose-response implications. Dose Response 17(4): 1559325819888317. https://doi.org/10.1177/1559325819888317.

[18] Lynch, H., Kozal, J. S., Russell, A. J., Thompson, W. J., Divis, H. R., Freid, R. D., ... & Mundt, K. A. (2022). Systematic review of the scientific evidence on ethylene oxide as a human carcinogen. Chemico-Biological Interactions, 110031.

[19] Jain, RB (2020) Associations between observed concentrations of ethylene oxide in whole blood and smoking, exposure to environmental tobacco smoke, and cancers including breast cancer: data for US children, adolescents, and adults. Env Sci Pollution Res, 7:20912–20919. https://doi.org/10.1007/s11356-020-08564-z https://doi.org/10.1007/s11356-020-08564-z.

[20] CR Kirman, AA Li, PJ Sheehan, JS Bus, RC Lewis & SM Hays (2020) Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management, Journal of Toxicology and Environmental Health, Part B, 24:1, 1-29, DOI: 10.1080/10937404.2020.1852988.

[21] Sheehan, P J, Lewis, R C, Kirman, C R, Watson, H N, Winegar, E D, & Bus, J S. 2021. Ethylene oxide exposure in US populations residing near sterilization and other industrial facilities: Context based on endogenous and total equivalent concentration exposures. *Int J Environ Res Public Health*, 18(2), 607.

[22] Lewis, RC, Sheehan, PJ, DesAutels, C G, Watson, HN, & Kirman, CR. 2022. Monitored and Modeled Ambient Air Concentrations of Ethylene Oxide: Contextualizing Health Risk for Potentially Exposed Populations in Georgia. *Int J Environ Res Public Health*, 19(6):3364.

smoking population to estimate the expected range of adducts from background exposure (i.e., internally produced EtO and EtO in outdoor air) and concluded that internally produced EtO is a major source of EtO exposure, while outdoor air exposure is minor. Kirman et al. noted that neither LHC nor breast cancer have been correlated to smoking, even though tobacco is the single largest source of EtO exposure, while Lewis et al. (2022) noted that monitoring results of EtO in ambient air from only one sterilizer were statistically significantly elevated compared to background. Szwiec, Friedman and Buchanan (2020)[23] reported that HEV adduct levels for non-smoking participants living in a neighborhood approximately 0.8 km (0.5 mi) from a sterilizer were significantly higher when compared to persons living farther away. However, the credibility of Szwiec, Friedman and Buchanan (2020)[24] is questionable because residential proximity can only serve as a crude proxy for exposure (does not accurately represent individual exposure to ambient conditions) and the study results are based on a total of 17 blood samples, which is too small to yield valid results.

While EtO may have appeared to increase the risk of developing LHC in early EtO studies, which were less precise, of poorer quality, and involved very high historical workplace exposures, [25] this association was not apparent in studies published later that involved lower and/or less frequent workplace exposures.[26] For example, in the meta-analysis published by Marsh et al.,[27] the precision of the meta-Relative Risks (RRs) calculated by decade of publication increased markedly in studies conducted in the 2000's and 2010's compared to those conducted in the 1980's and 1990's. In other words, Marsh et al. showed a clear reduction in effect estimates (i.e., the size of the RRs) and increased precision (i.e., reduced size of the error bars) in later studies by comparison to early studies. In fact, the association between EtO exposure and cancer has not been consistently observed, even in studies involving high cumulative workplace exposures.[28]

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[23] Szwiec, E, Friedman, L, and Buchanan, S. 2020. Levels of Ethylene Oxide Biomarker in an Exposed Residential Community. *Int J Environ Res Public Health*, 17(22): 8646.

[24] Szwiec, E, Friedman, L, and Buchanan, S. 2020. Levels of Ethylene Oxide Biomarker in an Exposed Residential Community. *Int J Environ Res Public Health*, 17(22): 8646.

[25] Hogstedt C, Rohlen O, Berndtsson BS, Axelson O, Ehrenberg L (1979b) A cohort study of mortality and cancer incidence in ethylene oxide production workers. Br J Ind Med 36:276–280; Hogstedt C, Aringer L, Gustavsson A (1986) Epidemiologic support for ethylene oxide as a cancer-causing agent. JAMA 255:1575–1578; Hogstedt LC (1988) Epidemiological studies on ethylene oxide and cancer: an updating. IARC Sci Publ 89:265–270; Hogstedt C, Malmqvist N, Wadman B (1979a) Leukemia in workers exposed to ethylene oxide. JAMA 241:1132–1133; Steenland K, Stayner L, Greife A, Halperin W, Hayes R, Hornung R, Nowlin S (1991) Mortality among workers exposed to ethylene oxide. N Engl J Med 324:1402–1407. https ://doi.org/10.1056/NEJM1 99105 16324 2004; Bisanti L et al (1993) Cancer mortality in ethylene oxide workers. Br J Ind Med 50:317–324.

[26] Mikoczy Z, Tinnerberg H, Bjork J, Albin M (2011) Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: updated cohort study findings 1972-2006. Int J Environ Res Public Health 8:2009–2019; Kiran S et al (2010) Occupational exposure to ethylene oxide and risk of lymphoma. Epidemiology 21:905–910.

[27] Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM (2019 Oct) Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health 92(7):919–939. https://doi.org/10.1007/s00420-019-01438-z.

[28] Teta MJ, Benson LO, Vitale JN (1993). Mortality study of ethylene oxide workers in chemical manufacturing: a 10 year update. Br J Ind Med 50:704–709; Teta MJ, Sielken RL Jr, Valdez-Flores C (1999) Ethylene oxide cancer risk assessment based on epidemiological data: application of revised regulatory guidelines. Risk Anal 19:1135–1155;

Not only has EPA noted that consideration of reported associations *across the distributions of concentrations in the entire body of evidence* should be considered when setting NAAQS that rely on epidemiological data,[29] it has also made judgments in setting NAAQS about the probability that the health relationships apparent in statistical associations published in studies cease to exist at some point on the continuum of lower and lower ambient pollutant concentrations. For example, EPA resisted pressure to reduce the ozone NAAQS to a lower level at least partly based on lack of evidence that reported associations observed in epidemiological studies are, in fact, causally related to related at lower levels, as well as the improbability of obtaining any health benefit if the standard were set to a lower level.

EPA should have considered the reported associations across the distribution of EtO concentrations reported in the EtO literature in estimating the IUR, particularly given the lack of clear and consistent evidence that EtO is capable of causing cancer at high exposure levels and the only evidence on the likelihood of effects at low ambient levels, albeit indirect, suggests no adverse effects.[30] EPA should have also considered the possibility that the health relationship implied by the statistical association reported in the NIOSH study ceases to exist at lower EtO concentrations present in ambient air and inside modern sterilizer facilities today.

III. EPA'S REPEATED DEFENSE OF THE NIOSH COHORT EXPOSURE ESTIMATES AS "HIGH QUALITY" IS NOT SUPPORTED

EPA repeatedly references the exposure estimates for the NIOSH cohort as being of high quality and states that the exposure assessment was based on extensive sampling and a validated regression model.[31] However, like the UCC, EtO exposure measurements in the NIOSH cohort were not collected until the mid-1970's, when workplace EtO levels were likely much lower than they had been in the distant past (i.e., the 1940's, 1950's, and 1960's). Even according to NIOSH's own exposure assessment,[32] most of the exposure data for the NIOSH cohort were collected after the late 1970's, when the health effects of EtO were already suspected and workplace concentrations are expected to have been lower than in previous decades. Therefore, historical NIOSH worker exposure estimates (all exposures prior to 1978) were based on a statistical regression model developed by NIOSH.[33]

Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM (2009) Mortality study update of ethylene oxide workers in chemical manufacturing: a 15 year update. J Occup Environ Med 51:714–723.

[29] 78 Fed. Reg. 3086 at 3098; 76 Fed. Reg. 16436 at 16483.

[30] Valdez-Flores, C., Sielken Jr, R. L., & Teta, M. J. (2010). Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regulatory Toxicology and Pharmacology, 56(3), 312-320; [30] Kirman, CR, and Hays, SM. 2017. Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. Reg Toxicol Pharmacol, 91:165-172.

[31] EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. P. 3-8, 3-15 (Table 3-1), 3-68, 4-60, 4-75, Appendix K, p. K-2, etc.

[32] Hornung, R. W., Greife, A. L., Stayner, L. T., Kyle Steenland, N., Herrick, R. F., Elliott, L. J., ... & Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. American journal of industrial medicine, 25(6), 825-836.

[33] Bogen KT, Sheehan PJ, Valdez-Flores C and Li AA (2019). Reevaluation of historical exposures to ethylene oxide among U.S. sterilization workers in the National Institute of Occupational Safety and Health (NIOSH) study cohort. Int J Environ Res Public Health 16(10). 10.3390/ijerph16101738.

While use of regression models to predict exposures for time periods lacking exposure measurements is not unusual, for the NIOSH cohort, EtO exposure measurements were available for a total of nine years (1976 – 1985), with EtO exposures predicted for the other 50 years evaluated for the cohort. In other words, exposure data were missing for most of the years included in the study. In addition, although an exposure dataset not used in developing the model was used to check the reliability of the model's predictions of exposure levels during the early years, the exposure measurements used to "validate" the model were also from the mid- to late-1970's. No measurements from the early years were available to validate the estimates made for the early years. This introduces additional uncertainty into the model because it is possible that the model is prone to larger errors at lower concentrations. Moreover, the electronic data files used in the NIOSH exposure analysis are no longer available;[34] therefore, it is hard to accept EPA's repeated unwavering defense of the NIOSH exposure assessment as "high quality."

Oddly enough, NIOSH's model predicted the lowest EtO exposures in 1938 with EtO levels increasing over time and peaking in 1978,[35] which contradicts long running experience that occupational exposures have tended to decrease as workplace standards are lowered and industrial hygiene procedures and workplace practices have improved.[36] Given the many changes in the industry that have resulted in more EtO being scrubbed/captured, more personal protective equipment (PPE) being used, not to mention the decrease in allowable worker exposure levels (with the OSHA PEL going from 50 [1983] to 1 ppm during this time), this trend defies logic and experience.

The use of increasing sterilizer volume over the years as a surrogate for exposure was the factor responsible for the increasing exposure trend over time in the NIOSH cohort.[37] Although sterilizer volumes did increase from 1938 – 1978,[38] EtO exposures in the sterilizer industry depended not only on the amount of EtO used, but also on the volumes and air turnover rates of

[34] EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. Appendix H, p. H-28.

[35] Hornung, R. W., Greife, A. L., Stayner, L. T., Kyle Steenland, N., Herrick, R. F., Elliott, L. J., ... & Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. American journal of industrial medicine, 25(6), 825-836.

[36] OSHA (2005). Occupational Safety & Health Administration. Regulatory Review of the Occupational Safety and Health Administration's Ethylene Oxide Standard; Bogen KT, Sheehan PJ, Valdez-Flores C and Li AA (2019). Reevaluation of historical exposures to ethylene oxide among U.S. sterilization workers in the National Institute of Occupational Safety and Health (NIOSH) study cohort. Int J Environ Res Public Health 16(10). 10.3390/ijerph16101738; LaMontagne, A. D., Oakes, J. M., & Lopez Turley, R. N. (2004). Long-term ethylene oxide exposure trends in US hospitals: Relationship with OSHA regulatory and enforcement actions. Amal J Public Health, 94(9), 1614-1619; Gardner MJ, Coggon D, Pannett B, Harris EC (1989) Workers exposed to ethylene oxide: a follow up study. Br J Ind Med 46:860–865.

[37] Hornung, R. W., Greife, A. L., Stayner, L. T., Kyle Steenland, N., Herrick, R. F., Elliott, L. J., ... & Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. American journal of industrial medicine, 25(6), 825-836.

[38] Pre-1960, most medical device sterilization (EO and steam) was done by hospitals or local 3rd party contract services at smaller scales for those hospitals since most devices were stainless steel reusables and would be sterilized near or at the point of use. As more single use disposable plastic devices became available, there was more volume of such devices and a need for larger scale sterilization and less use of local sterilization.

rooms in which sterilization and storage of sterilized materials took place.[39] Assuming that smaller scale EtO sterilization was less hazardous than larger commercial scale processing did not take into account the better worker PPE and monitoring protections at the commercial scale, or the increase in cycle gas washes and better vacuum phases that remove the majority of EtO before any workers access products in the chamber. It also ignored the role that device type plays in the amount of EtO that is released from the sterilized device and exposure. Hard plastic products may require a higher amount of EtO to achieve sterility (because of small crevices or joints), but they also release EtO freely in the gas wash and vacuum cycle, so they don't retain as much EtO that can then off-gas in aeration rooms. On the other hand, sterilizing interwoven products (such as gowns and drapes) may not require as much EtO, but these products retain EtO more readily (absorb more like sponges) and could have higher residuals and require more aeration time.

Bogen and colleagues[40] developed a model that better correlated with the evolution in sterilization facility industrial hygiene and operational practices than NIOSH's model. The Bogen model predicted levels during the early years that were between four and 16 times those predicted in NIOSH's model and currently being assumed by EPA. Thus, the Bogen model suggested that exposures occurring prior to 1978 (the first year that ethylene oxide sampling data were available) may have been dramatically under-predicted by the NIOSH exposure model. This is important because higher EtO concentrations in the workplace for early years implies lower EtO cancer potency than EPA is currently assuming. Bogen's model predicts that EtO releases from the storage of sterilized products was the primary contribution to total EtO concentrations in workplace air, especially during the early and middle periods (when no, or only one, vacuum and air/nitrogen wash was applied, and sterilized product storage and sterilization operations typically occurred in the same building).

In response to criticisms of the NIOSH exposure model made during review of the previous IRIS assessments (2007 and 2013) for EtO and in the *Summary of Public Comments and Responses for the Risk and Technology Review for Miscellaneous Organic Chemical Manufacturing*, EPA responded that: 1) the methodology used by Bogen to predict historical EtO concentrations were not sufficiently documented to fully evaluate the model; 2) the results of sterilizer worker interviews were not reported and the content/ relevance of the interviews was unclear; 3) supporting documentation was not provided for assumptions about the mass of residual EtO remaining in treated product for early periods; and 4) modeled industry-wide exposures for much of the earlier time periods were in excess of then current ACGIH health criteria.[41] EPA's criticism of the Bogen model for the limited scope and quantitative detail regarding assumptions used in its development is ironic given the fact that the electronic data files used in the NIOSH exposure

[39] Bogen KT, Sheehan PJ, Valdez-Flores C and Li AA (2019). Reevaluation of historical exposures to ethylene oxide among U.S. sterilization workers in the National Institute of Occupational Safety and Health (NIOSH) study cohort. Int J Environ Res Public Health 16(10). 10.3390/ijerph16101738.

[40] Bogen, K. T., Sheehan, P. J., Valdez-Flores, C., & Li, A. A. (2019). Reevaluation of historical exposures to ethylene oxide among US sterilization workers in The National Institute of Occupational Safety and Health (NIOSH) study cohort. International journal of environmental research and public health, 16(10), 1738.

[41] EPA (2020). Environmental Protection Agency. Summary of Public Comments and Responses for the Risk and Technology Review for Miscellaneous Organic Chemical Manufacturing. P. 87.

analysis are no longer available,[42] and therefore, the quantitative detail supporting the NIOSH exposure assessment cannot be evaluated either. EPA also criticized Bogen et al. for not being able to validate their pre-1978 predictions, since no actual worker measurements were available from that time. This same criticism is applicable to the NIOSH exposure model, as no pre-1978 exposure measurements are available for the NIOSH cohort either. Finally, EPA states that the accuracy of the Bogen et al. assessment is unknown, but the same can be said for the NIOSH exposure assessment. What we do know, however, is that NIOSH made assumptions about exposure that did not adequately account for changes in the industry over the decades evaluated and produced an exposure trend that is opposite of what is expected.

While models allow EPA to move forward in the face of uncertainty, when practical information suggests that the models are wrong, reconsideration of the veracity of the models is critical. Rather than simply continuing to rely on modeled exposure estimates that are no longer available for public scrutiny,[43] EPA should investigate the legitimate issues that have repeatedly been raised regarding the historical exposure estimates for the NIOSH cohort on which the 2016 IRIS value is entirely dependent.

IV. VERY HIGH EXPOSURES FROM A WORKPLACE STUDY ARE USED TO PREDICT RISK FROM ESTIMATED COMMUNITY EXPOSURES THAT ARE ORDERS OF MAGNITUDE LOWER

The EtO IUR is not "fit for purpose" because it draws on studies of very high workplace exposure levels to estimate human risks from concentrations that are a small fraction of those in the NIOSH study on which it is based. One of the reasons why the NIOSH study was chosen is because it had "very high exposures incurred in the cohort which increased the sensitivity of the study to detect an effect."[44]

Epidemiological investigations like the NIOSH study are primarily statistical evaluations that attempt to find correlations and associations between various factors and use them to predict how a disease may occur or spread under specified conditions. To evaluate EtO's cancer potency and estimate the IUR, EPA used "regression analysis", which can be thought of as fitting a line to observations of two or more phenomena. When the two correlated phenomena are exposure levels and a health effect, the line is called a "dose-response" curve. The slope of the fitted line/curve is used to generate an estimate of the "relative risk" (RR) due to exposure that increases by a particular amount. Although the terms "dose-response" and "relative risk" may imply a causal association, it is important to remember that the quantitative relationships being estimated *only reflect statistical associations*. Statistical associations between workplace exposures and cancer (or any other adverse health effect) do not necessarily mean that the exposure is causing the cancer.

[42] EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. Appendix H, p. H-28.
[43] EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. Appendix H, p. H-28.
[44] OEHHA. 2023. California Office of Environmental Health Hazard Assessment. Draft Ethylene Oxide Cancer Inhalation Unit Risk Factor. Technical Support Document for Cancer Potency Factors. p. 12.

Predictions of EtO risk made from observations in highly exposed populations (i.e., occupational cohorts) are not supported by observations in moderately exposed populations (i.e., smokers). Smokers experience about a 10-fold higher internal EtO exposure than non-smokers. Making the default assumption of low-dose linearity for the EtO dose-response relationship, smokers would be expected to experience a detectable increase in cancer (i.e., LHC and breast cancers).[45] However, the evidence for a causal relationship between smoking and breast cancer is not strong, and is instead considered to be suggestive, but not sufficient. There is only one subtype of LHC, acute myeloid leukemia (AML), with sufficient evidence of a causal relationship with smoking.[46] When the standard mortality ratios (SMRs) for AML in NIOSH workers exposed to EtO was evaluated by Valdez-Flores et al. (2010),[47] not only were they not increased, a statistically-significant negative slope was observed for the relationship with cumulative exposures. The fact that predictions of risk from observations made in highly exposed populations (i.e., NIOSH cohort) do not appear to be supported by observations in moderately exposed populations (i.e., smokers) suggests that using EPA's IUR to predict risk in populations with low exogenous exposures to EtO (i.e., the general public) is unlikely to yield accurate estimates.[48]

Little is known about health effects at low pollutant levels because they are difficult to measure. The risk of developing cancer from exposure to low levels of EtO present in ambient air is not measurable because it is very low relative to the natural background risk of developing cancer (i.e., 40% chance of developing cancer and 20% chance of dying from cancer).[49] In addition, when a person develops cancer, it is not possible to pinpoint a single cause. In fact, cancer is generally considered to be multifactorial. Many factors such as age, gender, genetics, diet, personal habits, and general health status contribute to the risk of developing cancer, making it nearly impossible to know what caused a cancer risk to become a cancer case.

In general, it is risky to extrapolate beyond the known range of a model (i.e., to predict health effects associated with concentrations much higher or much lower than those for which an association has been observed). Although the fit of a model might be "good", extrapolation relies on the assumption that the underlying behavior of the function analyzed for the observed data remains stable across all exposure levels. Extrapolation beyond the range of observed data relies on untestable assumptions about the behavior of the data beyond those for which we have observations. We do not know anything about the relationship between ambient EtO concentrations and the likelihood of developing cancer and there is no guarantee that the relationship between EtO exposure levels and the development of cancer observed in historical

[45] Kirman, CR, and Hays, SM. 2017. Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. Reg Toxicol Pharmacol, 91:165-172.
[46] US Department of Health and Human Services. (2014). The health consequences of smoking—50 years of progress: a report of the Surgeon General.
[47] Valdez-Flores, C., Sielken Jr, R. L., & Teta, M. J. (2010). Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regulatory Toxicology and Pharmacology, 56(3), 312-320.
[48] Kirman, CR, and Hays, SM. 2017. Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. Reg Toxicol Pharmacol, 91:165-172.
[49] American Cancer Society. Lifetime Risk of Developing or Dying from Cancer. https://www.cancer.org/cancer/risk-prevention/understanding-cancer-risk/lifetime-probability-of-developing-or-dying-from-cancer.html.

occupational scenarios holds for much lower community exposure levels. To the contrary, LHC is not increased in smokers, which represent a more moderately exposed population than the NIOSH cohort, and the evidence for an association with breast cancer and smoking is suggestive at best.[50] This information suggests that the relationship between EtO exposure levels and the development of cancer observed in historical occupational scenarios does not apply to much lower community exposure levels.

V. USE OF IUR AS BASIS FOR REGULATION WITHOUT CONSIDERATION OF THE IMPLICATIONS OF BACKGROUND EXPOSURE OR PRACTICAL THRESHOLDS THAT MAY OCCUR DUE TO HIGH BACKGROUND EXPOSURE

People are continuously exposed to EtO, as illustrated by detectable N7-HEG in lymphocytes isolated from people not knowingly in contact with EtO,[51] and EPA's dose-response model for EtO does not take this practical observation into account.

The mutagenicity and carcinogenicity of EtO is attributed to reaction with DNA, leading to the formation of multiple 2-hydroxyethyl adducts,[52] the most abundant of which is N7-(2-hydroxyethyl)guanine (N7-HEG). N7-HEG readily depurinates, leaving sites with miscoding potential (i.e., potential for mutation).[53] The current approach taken by EPA for estimating EtO carcinogenicity assumes that a linear relationship exists between exposure, the formation of DNA lesions, and subsequent conversion into mutations, although measurable increases in mutagenic events are only associated with relatively high doses.[54] In fact, the default position for many regulators when assessing the risk from any genotoxic carcinogens is to assume that there is no threshold in the dose-response relationship and that even very low doses pose some small incremental cancer risk. Consequently, demonstration that a chemical can form DNA adducts at

[50] US Department of Health and Human Services. (2014). The health consequences of smoking—50 years of progress: a report of the Surgeon General; Valdez-Flores, C., Sielken Jr, R. L., & Teta, M. J. (2010). Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regulatory Toxicology and Pharmacology, 56(3), 312-320.

[51] Wu KY, Scheller N, Ranasinghe A, et al. A gas chromatography/electron capture/negative chemical ionization high-resolution mass spectrometry method for analysis of endogenous and exogenous N7-(2-hydroxyethyl)guanine in rodents and its potential for human biological monitoring. Chem Res Toxicol 1999;18:722–9; Zhao C, Hemminki K. The in vivo levels of DNA alkylation products in human lymphocytes are not age dependent: an assay of 7-methyl- and 7-(2-hydroxyethyl)-guanine DNA adducts. Carcinogenesis 2002;23: 307–10; Yong LC, Schulte PA, Kao CY, et al. DNA adducts in granulocytes of hospital workers exposed to ethylene oxide. Am J Ind Med 2007;50:293–302.

[52] Walker VE, Fennell TR, Upton PB, et al. Molecular dosimetry of ethylene oxide: formation and persistence of 7-(2-hydroxyethyl)guanine in DNA following repeated exposure of rats and mice. Cancer Res 1992;52: 4328–34; Li F, Segal A, Solomon JJ. In vitro reaction of ethylene oxide with DNA and characterization of DNA adducts. Chem Biol Interact 1992;83:35–54.

[53] Walker VE, Fennell TR, Upton PB, et al. Molecular dosimetry of ethylene oxide: formation and persistence of N7-(2-hydroxyethyl)guanine in DNA following repeated exposure of rats and mice. Cancer Res 1992;52: 4328–34; Li F, Segal A, Solomon JJ. In vitro reaction of ethylene oxide with DNA and characterization of DNA adducts. Chem Biol Interact 1992;83:35–54.

[54] Henderson L, Albertini S, Aardema M. Thresholds in genotoxicity responses. Mut Res 2000;464:123–8. 23; Doak SH, Jenkins GJS, Johnson GE, Quick E, Parry EM, Parry JM. Mechanistic influences for mutation induction curves after exposure to DNA-reactive carcinogens. Cancer Res 2007;67:3904–11.

high exposures is often taken as sufficient evidence for carcinogenic potential at lower doses.[55] This is the basis for the assumption that exposure to EtO in ambient air increases the risk of cancer in communities. However, this assumption is not supported by scientific evidence.

There are two different *practical* issues with the IRIS value by comparison to the relatively high levels of EtO produced inside the body and found in background air, as described below.

The salient point being made when comparing the levels of EtO in air near sterilizers to the high levels found inside the human body is that physiological repair mechanisms, including DNA repair, are expected at endogenous levels (which are equivalent to approximately 2.9 ppb [continuous] in air for non-smokers). Internal EtO levels reflect a stressor to which humans are expected to have evolved and adapted over millions of years, and for which there is considerable variation. This likely leads to a practical threshold to DNA damage, a precursor to cancer, because biological defenses are not expected to be saturated at low EtO exposures, particularly in the range of endogenous EtO production. This practical threshold would mean that, in contrast to EPA's assumption, the slope of the dose-response curve for exogenous EtO exposure would not be expected to be linear at very low environmentally relevant concentrations. This theory is consistent with existing information on exposure levels that may cause cancer. While NIOSH sub-analyses suggested increases in male lymphoid tumors and female breast cancers when compared to internal referent groups (as opposed to cancer rates in the general public), these findings were limited to the highest cumulative exposure groups. This is consistent with exceeding biological repair mechanisms only at high exposures.

Regardless of whether EtO can be demonstrated to have a true threshold dose-response, it has been demonstrated that low doses of exogenous EtO exposure are completely swamped by the endogenous EtO levels in rat liver, spleen, and stomach,[56] implying no detectable (i.e., statistically significant) increase in risk due to EtO exposures from ambient air. Therefore, unless exogenous (external) exposures to EtO are higher than levels that are naturally found in the body, DNA damage and cancer are unlikely to occur.

The main point being made when comparing levels of EtO found in outdoor air is that the levels contributed by everyday sources of EtO (e.g., automobile and 18-wheeler exhaust, decaying vegetation, charcoal grills, etc.) are much higher than the levels contributed by EtO-utilizing sterilizers. The IRIS value is at least an order of magnitude below what everybody across the US is already exposed to from these and other everyday sources. The implication is that restricting emissions from sterilizers is unlikely to materially affect ambient concentrations or the community's risk of developing cancer potentially attributable to EtO exposure because regulation of sterilizers, no matter how punitive, will not change background levels of EtO (i.e., the amount of EtO emitted by the many other larger sources of EtO emissions). Moreover, any reductions in EtO levels in air potentially resulting from use of the IRIS value to regulate emissions

[55] Marsden, D. A., Jones, D. J., Britton, R. G., Ognibene, T., Ubick, E., Johnson, G. E., ... & Brown, K. (2009). Dose-response relationships for N7-(2-hydroxyethyl) guanine induced by low-dose [14C] ethylene oxide: evidence for a novel mechanism of endogenous adduct formation. Cancer research, 69(7), 3052-3059.

[56] Marsden, D. A., Jones, D. J., Britton, R. G., Ognibene, T., Ubick, E., Johnson, G. E., ... & Brown, K. (2009). Dose-response relationships for N7-(2-hydroxyethyl) guanine induced by low-dose [14C] ethylene oxide: evidence for a novel mechanism of endogenous adduct formation. Cancer research, 69(7), 3052-3059.

from sterilizers are unlikely to be confirmable because the current analytical detection limit for EtO in air ranges from 0.025-0.040 ppb, at least twice the level corresponding to EPA's IRIS value.

In response to comments previously made (on the 2013 EtO IRIS assessment) regarding high background exposures to EtO (from endogenous EtO and EtO levels found in ambient air), EPA has responded that the IUR is intended to predict *extra* risk (i.e., risk above background) and that background environmental and/or endogenous levels of EtO are not integral to the development of the estimates of extra risk. However, this position fails to recognize that practical risk thresholds may occur for mutagenic chemicals where high levels of naturally occurring DNA adducts also occur inside the body.[57] EPA guidelines do specify that IURs and cancer slope factors are intended to estimate extra risk (i.e., risk of developing cancer above and beyond the normal background risk (i.e., 1-in-2 or 3). This means that factors that contribute to background risk of developing cancer are intentionally left out in the development of IURs and cancer slope factors. This is a matter of EPA policy, not science.

Information on endogenous EtO levels could (and should) be used to estimate the point of departure utilized in EPA's IUR, which would result in a marked decrease in EtO's estimated cancer potency. However, taking background levels of EtO in ambient air into account need not involve changing EPA policy on deriving IURs. Instead, background EtO in the environment could be used in making risk management decisions without specifically incorporating it into the IUR. EPA could develop an approach similar to that taken by EPA in characterizing risks from soil contaminants that may also be attributed to background sources under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and by many state-based Resource Conservation and Recovery Act (RCRA) clean-up programs.[58]

According to EPA's CERCLA guidance, "In general, the presence of high background concentrations of hazardous substances, pollutants, and contaminants found at a site is a factor that should be considered in risk assessment and risk management. Contamination at a CERCLA site may originate from releases attributable to the CERCLA site in question, as well as contamination that originated from other sources, including natural and/or anthropogenic sources not attributable to the specific site releases under investigation. In some cases, the same hazardous substance, pollutant, and contaminant associated with a release is also a background constituent. These constituents should be included in the risk assessment, particularly when their concentrations exceed risk-based concentrations. In cases where background levels are high or present health risks, this information may be important to the public. Background information is important to risk managers because the CERCLA program, generally, does not clean up to concentrations below natural or anthropogenic background levels."[59] In other words, under CERCLA and many state risk-based soil cleanup programs, the risk-based cleanup goals are not themselves are not altered based on background concentrations, but regulated entities are not

[57] Swenberg JA, Fryar-Tita E, Jeong YC, et al. Biomarkers in toxicology and risk assessment: informing critical dose-response relationships. Chem Res Toxicol 2008;21:253–65. 25. Brown K, Tompkins

[58] EPA (2002). US Environmental Protection Agency. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites. EPA 540-R-01-003 OSWER 9285.7-41 September 2002.

[59] EPA (2002). US Environmental Protection Agency. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites. Appendix B: Policy Considerations for the Application of Background Data in Risk Assessment and Remedy Selection. EPA 540-R-01-003 OSWER 9285.7-41 September 2002.

required to remediate to levels that are below background. The situation with EtO is somewhat different since air regulations regulate how much of a chemical an entity is allowed to contribute to the air before the fact, rather than attempting remediation after the fact. In circumstances under which the EtO levels emitted from a particular entity do not cause a statistically significant increase in EtO above background levels, no further emission reductions should be required since they are unlikely to materially affect the community's risk. Under such an approach, the EPA IUR would not be used directly in regulating sterilizers. This approach would be much more practical given that the IUR is lower than background and current detection limits for EtO in air are ~0.025-0.040 ppb, which is two to four times the acceptable concentration in air based on EPA's IUR.

VI. ENORMOUS UNCERTAINTY IN IRIS VALUE

The enormous uncertainty in EPA's risk assessment for EtO should be taken into consideration prior to using the IRIS value in regulation or as a basis for other toxicity factors. EPA states that it strives to strike a balance in its risk assessments and that some assumptions likely overpredict and some underpredict. However, in keeping with the EPA's goal of protecting public health and the environment, default assumptions are generally made to ensure that risk to chemicals is not underestimated. In fact, EPA acknowledges that "Those values are derived using an approach that is **intended to not underestimate risk** in the face of uncertainty and variability."[60] When data are limited, more assumptions are needed, and more default factors are used. Thus, there is generally a greater tendency to overestimate risk.

Estimating health effects associated with long-term exposure to low levels of air pollution based on occupational data representing high exposure levels presents key methodological challenges,[61] including: 1) dose-response relationships estimated within a traditional regression framework cannot simply be *assumed* to represent causal relationships and can be highly sensitive to model choice for both the shape of the dose-response curve and the adjustment for confounding; 2) health effects estimation at low exposure levels might be affected by a different set of confounders than high exposure levels; 3) information on potential individual-level confounders is limited in large cohorts like the NIOSH dataset; 4) estimation of the dose-response must account for potentially larger exposure error at lower (i.e., ambient) exposure levels; and 5) identification of effect modifiers is challenged by the large number of possibilities that cannot all be tested individually.

The accuracy of a dose-response curve generated from an epidemiology study for identifying the true relationship between exposures and a particular health effect should always be scrutinized. For example, there is almost always a discrepancy between what monitoring instruments measure and what individuals throughout the workplace are actually exposed to. Depending on the amount of exposure measurement error, the true trend may not be discernible,

[60] In keeping with the EPA's goal of protecting public health and the environment, default assumptions are used to ensure that risk to chemicals is not underestimated (although defaults are not intended to overtly overestimate risk). See *An Examination of EPA Risk Assessment Principles and Practices,* EPA/100/B-04/001, available at: https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=100045MJ.TXT.

[61] Dominici F, Schwartz J, Di Q, Braun D, Choirat C, Zanobetti A (2019). Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution: Phase 1. Health Effects Institute (HEI), Report No. 200.

or it might disappear entirely, obscuring a "real" relationship.[62] Therefore, it is possible to be completely mislead by the statistical analyses that are the cornerstone of epidemiology studies. These studies often suggest that there is no threshold below which adverse effects are not seen when other evidence suggests that a "safe" level does in fact exist.

The IUR developed by Texas Commission on Environmental Quality (TCEQ)[63] illustrates the degree of uncertainty and scientific disagreement regarding EtO's cancer potency. The TCEQ performed an independent peer-reviewed analysis of the same NIOSH data that EPA used as a basis for its 2016 EtO IUR and estimated an IUR value that was 2000-fold lower than EPA's. This in turn resulted in an acceptable air concentration that was 2000 times higher than EPA's, when both are set at a cancer risk of 100-in-1,000,000.[64] Even EPA's own sensitivity analysis found that alternative models of the same NIOSH data yielded risk estimates as much as five-fold lower,[65] not to mention that EPA has developed IURs in previous evaluations of EtO's cancer potency that were considerably lower (less stringent) using the same NIOSH dataset.[66]

As previously discussed, there are EtO occupational cohort studies that do not show an elevated risk of cancer that EPA chose not to consider in developing its IUR. Most notably, the Union Carbide Corporation (UCC) cohort, which had higher exposures and longer follow-up than the NIOSH cohort (i.e., higher cumulative exposures) and showed no indication of cancer associated with EtO exposure.[67] Clearly, this indicates that EPA's 2016 IUR is not the only plausible estimate of EtO's cancer potency and the implied uncertainty calls for serious consideration prior to using the EPA's IUR as a basis for other toxicity factors or in regulation.

VII. CONCLUSION

In developing the EtO IUR, EPA failed to implement recommendations made by both the NRC[68] and NAS[69] to move away from the old paradigm of focusing on single studies in its dose-response assessments. Instead, EPA chose to rely on a single study that it deemed to be the "best", the NIOSH study. By ignoring the NRC's and NAS's recommendation, EPA failed to give any

[62] Smith, AE and Chan, NY (1997). How Statistics Can Mislead PM Policy: A Case of Smoke and Mirrors?

[63] TCEQ (2020). Texas Commission on Environmental Quality. Ethylene Oxide Carcinogenic Dose-Response Assessment. May. https://www.tceq.texas.gov/toxicology/dsd/final#e.

[64] TCEQ establishes acceptable air concentrations for chemicals as Effects Screening Levels (ESLs), based on a 10-in-1,000,000 (equivalent to 1-in-100,000) cancer risk. Therefore, the ESL for EtO was multiplied by 10 for comparison to EPA's acceptable air concentration that corresponds to a 100-in-1,000,000 cancer risk.

[65] EPA (2019). Memorandum from Paul White to Kristina A. Thayer, Director of Chemical & Pollutant Assessment Division ORD Center for Public Health and Environmental Assessment, entitled "Sensitivity of ethylene oxide risk estimates to dose-response model selection".

[66] EPA (2006). US Environmental Protection Agency. Evaluation of the Carcinogenicity of Ethylene Oxide, External Review Draft. EPA/635/R-06/003. August; EPA (2013). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. July. EPA/635/R-13/128a.

[67] Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM (2009) Mortality study update of ethylene oxide workers in chemical manufacturing: a 15 year update. J Occup Environ Med 51:714–723. https ://doi.org/10.1097/JOM.0b013 e3181a2ca20.

[68] National Research Council, National Academy of Sciences. 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.

[69] NAS (2018). Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. A Consensus Study Report of the National Academies of Science Engineering Medicine. The National Academies Press, 500 Fifth Street, NW Washington, DC 20001.

weight to the many negative studies. This is consequential because 12 of the primary 14 cohort studies of EtO production and sterilization workers failed to show a statistically-significant association between EtO exposure and LHC, while six of seven failed to show a statistically-significant association between EtO exposure and breast cancer.[70] If EPA had only included the one other highest quality cohort study (UCC), which had a lengthy follow-up and larger cumulative exposures than the NIOSH cohort,[71] it is unlikely that the effect size could have reasonably be inferred to exclude zero (i.e., to exclude being negligible), which would have made it very difficult for EPA to conclude that the evidence supports that EtO causes cancer, even at high historical occupational exposures.

The EtO IUR is not "fit for purpose" because it draws on studies of very high workplace exposure levels to estimate human risks from concentrations that are a small fraction of those in the NIOSH study on which it is based. We know very little, if anything, about the relationship between ambient EtO concentrations and the likelihood of developing cancer. There is no guarantee that the relationship between EtO exposure levels and the development of cancer observed in historical occupational scenarios holds for much lower community exposure levels. Extrapolation beyond the range of observed data relies on untestable assumptions about the behavior of the data for which observations are lacking. Predictions of EtO risk made from observations in highly exposed populations (i.e., occupational cohorts) are not supported by observations in more moderately exposed populations.[72] Therefore, use of EPA's IUR to predict risk in populations with low exogenous exposures to EtO (i.e., the general public) is unlikely to yield accurate estimates.

Despite publication of several new studies since release of the 2016 IUR that cast doubt on the evidence for EtO-induced cancer and the health significance of exposure to environmentally-relevant exposures (i.e., those in ambient air), EPA has repeatedly concluded that the new studies do not alter the conclusions of the 2016 IRIS assessment and do not justify a reassessment of the IUR. This is unfortunate because while EtO may have appeared to increase

[70] Hogstedt C, Malmqvist N, Wadman B (1979a) Leukemia in workers exposed to ethylene oxide. JAMA 241:1132–1133 Hogstedt C, Rohlen O, Berndtsson BS, Axelson O, Ehrenberg L (1979b) A cohort study of mortality and cancer incidence in ethylene oxide production workers. Br J Ind Med 36:276–280; Hogstedt C, Aringer L, Gustavsson A (1986). Epidemiologic support for ethylene oxide as a cancer-causing agent. JAMA 255:1575–1578 IARC. 1997; Bisanti L et al (1993) Cancer mortality in ethylene oxide workers. Br J Ind Med 50:317–324; Norman SA, Berlin JA, Soper KA, Middendorf BF, Stolley PD (1995) Cancer incidence in a group of workers potentially exposed to ethylene oxide. Int J Epidemiol 24:276–284International A; gency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 97. 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide) Chemical Agents and Related Occupations volume. Lyon France. IARC. 2012. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Chemical Agents and Related Occupations. 100F. Lyon France; Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM (2019 Oct) Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health 92(7):919–939. https://doi.org/10.1007/s00420-019-01438-z.

[71] TCEQ (2020). Texas Commission on Environmental Quality. Ethylene Oxide Carcinogenic Dose-Response Assessment. May 15, 2020. p. 33.

[72] Valdez-Flores, C., Sielken Jr, R. L., & Teta, M. J. (2010). Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regulatory Toxicology and Pharmacology, 56(3), 312-320.

the risk of developing LHC and/or breast cancer in early studies, which were less precise, of poorer quality, and involved very high historical workplace exposures, [73] this association is not apparent in studies published later that involved lower and/or less frequent workplace exposures.[74]

EPA has dogmatically defended the exposure estimates for the NIOSH cohort as being of high quality and states that the exposure assessment was based on extensive sampling and a validated regression model.[75] However, according to NIOSH's own exposure assessment,[76] most of the exposure data for the NIOSH cohort were collected after the late 1970's, when the health effects of EtO were already suspected and workplace concentrations are expected to have been lower than in previous decades. NIOSH's model predicted the lowest EtO exposures in 1938 with EtO levels increasing over time and peaking in 1978,[77] which contradicts long running experience that occupational exposures have tended to decrease as workplace standards are lowered and industrial hygiene procedures and workplace practices have improved.[78] The implication of higher EtO concentrations in the workplace during the early years is a lower EtO cancer potency than EPA is currently assuming. Given the many changes in the industry that have resulted in more EtO being scrubbed/captured, more PPE being used, not to mention the decrease in allowable worker exposure levels (the OSHA PEL went from 50 to 1 ppm during this time), this trend defies logic and experience. Unfortunately, the electronic data files used in the NIOSH exposure analysis are

[73] Hogstedt C, Rohlen O, Berndtsson BS, Axelson O, Ehrenberg L (1979b) A cohort study of mortality and cancer incidence in ethylene oxide production workers. Br J Ind Med 36:276–280; Hogstedt C, Aringer L, Gustavsson A (1986) Epidemiologic support for ethylene oxide as a cancer-causing agent. JAMA 255:1575–1578; Hogstedt LC (1988) Epidemiological studies on ethylene oxide and cancer: an updating. IARC Sci Publ 89:265–270; Hogstedt C, Malmqvist N, Wadman B (1979a) Leukemia in workers exposed to ethylene oxide. JAMA 241:1132–1133; Steenland K, Stayner L, Greife A, Halperin W, Hayes R, Hornung R, Nowlin S (1991) Mortality among workers exposed to ethylene oxide. N Engl J Med 324:1402–1407. https ://doi.org/10.1056/NEJM1 99105 16324 2004; Bisanti L et al (1993) Cancer mortality in ethylene oxide workers. Br J Ind Med 50:317–324.

[74] Mikoczy Z, Tinnerberg H, Bjork J, Albin M (2011) Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: updated cohort study findings 1972-2006. Int J Environ Res Public Health 8:2009–2019; Kiran S et al (2010) Occupational exposure to ethylene oxide and risk of lymphoma. Epidemiology 21:905–910.

[75] EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. P. 3-8, 3-15 (Table 3-1), 3-68, 4-60, 4-75, Appendix K, p. K-2, etc.

[76] Hornung, R. W., Greife, A. L., Stayner, L. T., Kyle Steenland, N., Herrick, R. F., Elliott, L. J., ... & Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. American journal of industrial medicine, 25(6), 825-836.

[77] Hornung, R. W., Greife, A. L., Stayner, L. T., Kyle Steenland, N., Herrick, R. F., Elliott, L. J., ... & Morawetz, J. (1994). Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. American journal of industrial medicine, 25(6), 825-836.

[78] OSHA (2005). Occupational Safety & Health Administration. Regulatory Review of the Occupational Safety and Health Administration's Ethylene Oxide Standard; Bogen KT, Sheehan PJ, Valdez-Flores C and Li AA (2019). Reevaluation of historical exposures to ethylene oxide among U.S. sterilization workers in the National Institute of Occupational Safety and Health (NIOSH) study cohort. Int J Environ Res Public Health 16(10). 10.3390/ijerph16101738; LaMontagne, A. D., Oakes, J. M., & Lopez Turley, R. N. (2004). Long-term ethylene oxide exposure trends in US hospitals: Relationship with OSHA regulatory and enforcement actions. Amal J Public Health, 94(9), 1614-1619; Gardner MJ, Coggon D, Pannett B, Harris EC (1989) Workers exposed to ethylene oxide: a follow up study. Br J Ind Med 46:860–865.

no longer available;[79] therefore, it is hard to accept EPA's unwaivering defense of the NIOSH exposure assessment as being beyond reproach. Ironically, EPA rejected another more recent exposure model for the NIOSH cohort[80] that predicted higher exposures in the early years for weakness that also apply to the NIOSH exposure model.

People are continuously exposed to EtO, as illustrated by detectable N7-HEG in lymphocytes isolated from people not knowingly in contact with EtO,[81] and EPA's dose-response model for EtO does not take this practical observation into account. EPA has often responded that the IUR is intended to predict *extra* risk (i.e., risk above background) and that background environmental and/or endogenous levels of EtO are not integral to the development of the estimates of extra risk. However, this position fails to recognize that practical risk thresholds may occur for mutagenic chemicals where high levels of naturally occurring DNA adducts also occur inside the body.[82]

Demonstration that a chemical can form DNA adducts at high exposures is often taken by regulators as sufficient evidence for carcinogenic potential at lower doses,[83] and this is the basis for assuming that exposure to EtO in ambient air increases the risk of cancer in communities. However, this assumption is not supported by scientific evidence. EPA's approach for estimating EtO carcinogenicity assumes that a linear relationship exists between exposure, the formation of DNA lesions, and subsequent conversion into mutations, even though measurable increases in mutagenic events are only associated with relatively high doses.[84] Physiological repair mechanisms, including DNA repair, are expected at endogenous levels and likely lead to a practical threshold to DNA damage, a precursor to cancer. This practical threshold would mean that, in contrast to EPA's assumption, the slope of the dose-response curve for exogenous EtO exposure would not be expected to be linear at very low environmentally relevant concentrations. Interestingly, NIOSH sub-analyses suggested increases in LHC in males and female breast cancers (when compared to internal referent groups), but these findings were limited to the highest

[79] EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. Appendix H, p. H-28.

[80] Bogen, K. T., Sheehan, P. J., Valdez-Flores, C., & Li, A. A. (2019). Reevaluation of historical exposures to ethylene oxide among US sterilization workers in The National Institute of Occupational Safety and Health (NIOSH) study cohort. International journal of environmental research and public health, 16(10), 1738.

[81] Wu KY, Scheller N, Ranasinghe A, et al. A gas chromatography/electron capture/negative chemical ionization high-resolution mass spectrometry method for analysis of endogenous and exogenous N7-(2-hydroxyethyl)guanine in rodents and its potential for human biological monitoring. Chem Res Toxicol 1999;18:722–9; Zhao C, Hemminki K. The in vivo levels of DNA alkylation products in human lymphocytes are not age dependent: an assay of 7-methyl- and 7-(2-hydroxyethyl)-guanine DNA adducts. Carcinogenesis 2002;23: 307–10; Yong LC, Schulte PA, Kao CY, et al. DNA adducts in granulocytes of hospital workers exposed to ethylene oxide. Am J Ind Med 2007;50:293–302.

[82] Swenberg JA, Fryar-Tita E, Jeong YC, et al. Biomarkers in toxicology and risk assessment: informing critical dose-response relationships. Chem Res Toxicol 2008;21:253–65. 25. Brown K, Tompkins

[83] Marsden, D. A., Jones, D. J., Britton, R. G., Ognibene, T., Ubick, E., Johnson, G. E., ... & Brown, K. (2009). Dose-response relationships for N7-(2-hydroxyethyl) guanine induced by low-dose [14C] ethylene oxide: evidence for a novel mechanism of endogenous adduct formation. Cancer research, 69(7), 3052-3059.

[84] Henderson L, Albertini S, Aardema M. Thresholds in genotoxicity responses. Mut Res 2000;464:123–8. 23; Doak SH, Jenkins GJS, Johnson GE, Quick E, Parry EM, Parry JM. Mechanistic influences for mutation induction curves after exposure to DNA-reactive carcinogens. Cancer Res 2007;67:3904–11.

cumulative exposure groups, consistent with exceeding biological repair mechanisms only at high exposures. This suggests that unless exogenous (external) exposures to EtO are higher than the equivalent levels naturally found in the body, DNA damage and cancer are unlikely to occur.

The IRIS value is at least an order of magnitude below what everyone across the US is already exposed to from everyday sources of EtO, the implication being that restricting EtO emissions from sterilizers is unlikely to materially affect ambient concentrations or the community's risk of developing cancer. Moreover, any reductions in EtO levels in air potentially resulting from use of the IRIS value to regulate emissions from sterilizers are unlikely to be confirmable because the current analytical detection limit for EtO in air ranges from 0.025-0.040 ppb, two to four times the level corresponding to EPA's IRIS value. Background EtO in ambient air could be used in making risk management decisions without specifically incorporating it into the IUR. By developing an approach similar to that taken by EPA in characterizing risks from contaminated soil, the presence of high background concentrations of EtO (relative to levels contributed by sterilizers) could be considered in making risk management decisions.[85] For example, if EtO levels emitted from a particular entity do not cause a statistically significant increase in EtO above background levels, no further emission reductions should be required since they are unlikely to materially affect the community's risk. This approach would be much more practical given that the IUR is lower than background and current detection limits for EtO.

Instead of focusing on a single study, for which assumptions about historical workplace exposures are questionable and no longer available for public scrutiny, EPA should have taken NRC's and NAS's advice and considered associations across the distribution of EtO concentrations reported in the scientific literature in estimating the IUR. This is particularly warranted given the lack of clear and consistent evidence that EtO is capable of causing cancer, even at high exposures. At a minimum, EPA should have at least considered the possibility that the health relationship implied by the statistical association reported in the NIOSH study ceases to exist at lower EtO concentrations present in ambient air and inside modern sterilizer facilities today, especially since the only evidence regarding the likelihood of developing cancer at lower EtO levels suggests that the risk of cancer is not increased at these levels.[86]

The enormous uncertainty in EPA's risk assessment for EtO should be taken into consideration prior to using the IRIS value in regulations or as a basis for other toxicity factors. Estimating health effects associated with long-term exposure to low levels of air pollution based on occupational data representing high exposure levels presents many methodological challenges. The accuracy of a dose-response curve generated from epidemiological evidence in identifying the true relationship between exposures and a particular health effect should always

[85] EPA (2002). US Environmental Protection Agency. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites. EPA 540-R-01-003 OSWER 9285.7-41 September 2002.
[86] Valdez-Flores, C., Sielken Jr, R. L., & Teta, M. J. (2010). Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regulatory Toxicology and Pharmacology, 56(3), 312-320; [86] Kirman, CR, and Hays, SM. 2017. Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. Reg Toxicol Pharmacol, 91:165-172.

be scrutinized. The IUR developed by the TCEQ,[87] which is orders of magnitude lower than EPA's, illustrates the degree of uncertainty and scientific disagreement regarding EtO's cancer potency, not to mention that EPA's own sensitivity analyses have indicated that alternative models of the NIOSH data yield lower risk estimates. Finally, there are EtO occupational cohort studies that do not show any elevation in the risk of cancer that EPA chose not to consider in developing its IUR. Clearly, EPA's 2016 IUR is not the only plausible estimate of EtO's cancer potency, and the implied uncertainty calls for serious consideration prior to using it as a basis for other toxicity factors or in regulation.

Sincerely

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[87] TCEQ (2020). Texas Commission on Environmental Quality. Ethylene Oxide Carcinogenic Dose-Response Assessment. May. https://www.tceq.texas.gov/toxicology/dsd/final#e.