UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: March 27, 2023

SUBJECT: Response to Public Comments for the Ethylene Oxide (EtO) Draft Risk Assessment (DRA)

PC Codes: 042301	DP Barcode: 460746, 461470
Decision Number: 569904, 572393	Docket No.: EPA–HQ–OPP–2013–0244
Regulatory Action: Registration Review	Case No.: 2275
Risk Assessment Type: Response to Comments	CAS No.: 75-21-8

FROM: Timothy Dole, CIH, Senior Scientist Timothy C. Dole
Tim McMahon, Ph.D., Senior Science Advisor MP for TM
Risk Assessment Branches 1 and 2
Antimicrobials Division (7510P)

Digitally signed by MELISSA PANGER
Date: 2023.03.27 14:39:22 -04'00'

Digitally signed by MELISSA PANGER
Date: 2023.03.27 14:39:49 -04'00'

THRU: Melissa Panger, Ph.D., Branch Chief
Andrew Byro, Ph.D., Risk Assessment Process Leader ANDREW BYRO Digitally signed by ANDREW BYRO Date: 2023.03.27 14:31:20 -04'00'
Jeannette Martinez, Ph.D., Senior Scientist JEANNETTE MARTINEZ Digitally signed by JEANNETTE MARTINEZ Date: 2023.03.27 14:28:21 -04'00'
Risk Assessment Branch 1
Antimicrobials Division (7510P)

TO: Jessica Bailey, Chemical Review Manager
Matthew Manupella, Team Leader
Reevaluation Branch
Antimicrobials Division (7510P)

A Draft Risk Assessment (DRA) was completed for ethylene oxide (EtO) (PC Code 042301) in November of 2020 (US EPA, 2020). The EPA received several public comments on the DRA, which can be found in docket number EPA-HQ-OPP-2013-0244. This document provides the EPA's responses to the scientific comments on the 2020 DRA. Regulatory comments will be addressed in the Proposed Interim Decision (PID).

During the 60-day public comment period for the DRA, which opened on November 20, 2020, and closed on January 19, 2021, comments were submitted by the Texas Commission on

Environmental Quality (TCEQ), Earthjustice, et al., the Louisiana Chemical Association (LCA), and the University of California (UCC). Additional comments were submitted by the American Chemistry Council (ACC) and the Ethylene Oxide Task Force (EOTF) on March 19, 2021, after the comment period had closed. However, the comments have been considered and were determined to be similar to comments received from the TCEQ and the LCA and are addressed in the EPA's responses to those commenters. Substantive science comments related to the 2020 DRA, and the EPA's responses to those comments are summarized below. The EPA thanks all commenters for their comments.

Comments Submitted by the Texas Commission on Environmental Quality (TCEQ)

Comments were submitted as a 5-page document by the Texas Commission on Environmental Quality (TCEQ). This document is stored in the EtO docket (EPA-HQ-OPP-2013-0244) as Document ID EPA-HQ-OPP-2013-0244-0032.

TCEQ Comment: The TCEQ suggested that the Office of Pesticide Programs (OPP) should formally conduct an independent, critical scientific review of available carcinogenic ethylene oxide dose-response assessments and select the most scientifically supported approach and unit risk factor for the cancer assessment.

EPA Response: In the 2020 DRA, OPP presented multiple perspectives on cancer evaluations for EtO, including the 2016 IRIS assessment (US EPA, 2016), the TCEQ derived value (TCEQ, 2020), and the EOTF derived value (MRID 51258401), but did not choose a single value for risk extrapolation. Since the publication of the 2020 DRA, and in contexts other than the registration review of EtO, EPA has continued to consider the best approach for characterizing the cancer risk associated with inhalation exposure to EtO. While there are some uncertainties associated with all of the approaches in characterizing the cancer risk (as discussed in the 2020 DRA), the EPA has determined that the 2016 IRIS assessment should be used to characterize the cancer risk associated with inhalation exposure to EtO.

The 2016 IRIS assessment went through "unusually extensive processes for the consideration of public comment and external peer review" and is considered by EPA's Office of Research and Development (ORD) to be the "best available scientific information regarding cancer risks from EtO[1]." In developing the 2016 IRIS assessment, ORD "utilized extensive advice" from the Science Advisory Board (SAB) and incorporated recommendations from the SAB into the 2016 IRIS assessment to address uncertainties identified by the SAB[2]. Further, since the publication of the 2020 DRA, the EPA has repeatedly expressed favorable views of the 2016 IRIS assessment, including comparison to the other EtO cancer inhalation risk characterization approaches cited in the 2020 DRA[3,4].

[1]Memo from W. Cascio (ORD) to J. Goffman (OAR), ORD Review of Comments on the IRIS Ethylene Oxide Assessment Contained in the ACC Request for Correction Submitted Regarding EPA's National Air Toxics Assessment, Aug. 25, 2021, Page 1.
[2] Id, page 4.
[3] US EPA, 2022. Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review – Final Action. FR Doc. 2022-27522, Filed: 12/20/2022.
[4] US EPA, 2021. EPA Should Conduct New Residual Risk and Technology Reviews for Chloroprene- and Ethylene Oxide-Emitting Source Categories to Protect Human Health, Report No. 21-P-0129, U.S. EPA Office of Inspector General, May 6, 2021.

TCEQ Comment: TCEQ argues that epidemiological data are insufficient to demonstrate that EtO is a known human carcinogen.
EPA Response: As discussed in the 2016 IRIS assessment (US EPA, 2016), ethylene oxide is characterized as 'carcinogenic to humans' using the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (USEPA, 2005). These guidelines state that the descriptor "carcinogenic to humans" is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer. The descriptor 'carcinogenic to humans' is also appropriate when there is a lesser weight of epidemiologic evidence that is strengthened by specific lines of evidence set forth in the guidelines (US EPA, 2005), which are discussed in the 2016 IRIS assessment and satisfied for EtO.

TCEQ Comment: The TCEQ argues that the weight of epidemiological evidence does not sufficiently support breast cancer as an endpoint that should be included in EtO risk estimates.

EPA Response: As discussed above, the EPA has determined that the 2016 IRIS assessment (US EPA, 2016) should be used to characterize the cancer risk associated with inhalation exposure to EtO. The 2016 IRIS assessment includes breast cancer as an endpoint that should be included in EtO risk estimates.

Comments Submitted by Earthjustice, et al.

Comments were submitted in Document ID EPA-HQ-OPP-2013-0244-0038 by a group of Non-Governmental Organizations (NGOs) in a 28-page document that has Earthjustice as the point of contact. These NGOs included the following: Breast Cancer Prevention Partners; California Communities Against Toxics; Citizens 4 Clean Air, Not for Profit (NFP); Clean Air Council; Clean Power Lake County; Earthjustice; Environmental Justice Health Alliance for Chemical Policy Reform; Natural Resources Defense Council; Say No to EtO Georgia; Sierra Club; Stop Sterigenics; Students Against Ethylene Oxide; and Union of Concerned Scientists.

Earthjustice Comment: Earthjustice states that ethylene oxide is a known, potent carcinogen.

EPA Response: OPP agrees with this comment and as stated on page 19 of the 2020 DRA:

> "The carcinogenicity of EtO by the inhalation route has been examined in published studies conducted in experimental animals and in data from epidemiological studies in humans. The results of these studies have been characterized by The National Toxicology Program (NTP, 1987; NTP, 2016) and USEPA/ORD/IRIS (USEPA, 2016) in classification of EtO as a carcinogen."

Earthjustice Comment: Earthjustice argues that OPP must apply the 2016 IRIS cancer value for ethylene oxide because it is the most well-supported, peer-reviewed scientific assessment of cancer risks.

EPA Response: Since the publication of the 2020 DRA, and in contexts other than the registration review of EtO, EPA has continued to consider the best approach for characterizing the cancer risk associated with inhalation exposure to EtO. While there are some uncertainties associated with all of the approaches in characterizing the cancer risk (as discussed in the 2020

DRA), EPA has determined that the 2016 IRIS assessment (US EPA, 2016), which includes inhalation unit risk estimates (*i.e.* cancer values) should be used to characterize the cancer risk associated with inhalation exposure to EtO, and OPP is applying the 2016 IRIS value in the DRA Addendum (US EPA, 2023).

Earthjustice Comment: Earthjustice argues that EPA understates ethylene oxide's risks to workers by assuming the use and effectiveness of PPE. EPA significantly understates the risks to workers exposed to ethylene oxide at sterilization facilities, in violation of FIFRA. For many workplaces, EPA reduces worker exposures to ethylene oxide by a factor of 1,000 based on the assumption that workers will be provided, trained on, and protected by supplied air respirators.

EPA Response: The assessment of sterilization worker exposures is based on exposure data for contract sterilization plant workers that were included in a registrant submission of 1,273 full shift air sampling results from 25 facilities (MRID 50231101). These data indicate that respirators were not worn during any part of the work shift for 662 samples. Respirators were worn for the entire work shift for 6 samples and for part of the work shift for 605 samples. The duration of respirator use ranged from 5 minutes to 480 minutes with an average of 153 minutes. The 8-hour TWA for the 662 samples where workers did not wear respirators ranged from 0.013 ppm (one half the LOD of 0.026 ppm) to 2.4 ppm with a mean of 0.27 ppm. The 8-hr TWAs for the 611 workers who wore respirators were calculated by dividing the exposure by the APF of 1,000 for the portion of the day when respirators are worn and adding that exposure to the exposure during portion of the day when respirators are not worn. The 8-hour TWAs for these 611 workers range from 0.013 ppm to 2.2 ppm with an arithmetic mean of 0.18 ppm.

The 8-hour TWAs for the workers who wore respirators were calculated by assuming that they wore full face pressure demand supplied air respirators because these respirators have been worn in sterilization facilities for the last several years in response to the discontinuation of the production of full face gas masks that were worn previously. Full face, pressure demand, supplied air respirators have an assigned protection factor (APF) of 1,000 (OSHA, 2009) because they have a regulator that controls the airflow to maintain a positive pressure inside the facepiece.

Earthjustice Comment: Earthjustice states that under the Toxic Substances Control Act (TSCA), EPA has previously "agree[d] that a hierarchy of controls should be applied and that PPE should be the last option to control exposures." Earthjustice indicates that this hierarchy is consistent with the best available science, and it has been adopted or endorsed by OSHA, the National Institute for Occupational Safety and Health (NIOSH), the American Public Health Association, the American Conference of Governmental Industrial Hygienists, and others and that there is no basis for EPA to adopt a different approach under FIFRA. Earthjustice indicates that the Draft Risk Assessment is fundamentally inconsistent with that hierarchy and that by assuming that worker exposures will be reduced 1,000-fold because of the use of PPE, EPA would never consider whether those reductions could be more effectively and reliably attained through other controls that are higher on the hierarchy. Instead of beginning with the control of "last resort," EPA should measure occupational exposures and risks without the use of PPE and consider respirators when selecting mitigation measures only after all preferred controls have already been exhausted.

EPA Response: The EtO concentrations were measured in the breathing zones of the workers outside of any respiratory protection that was worn. These concentrations ranged from 0.002 to 35 ppm with an average of 1.2 ppm. When accounting for the use of respirators, the exposures range from 0.002 to 4.6 ppm with an average of 0.23 ppm. EPA acknowledges that other controls will be needed to mitigate the cancer risk. EPA intends to propose additional controls in the Proposed Interim Decision (PID) for EtO.

Earthjustice Comment: Earthjustice argues that EPA understates ethylene oxide's neurological risks. In their submission, Earthjustice argues that the EtO DRA cites "peripheral neuropathy, impaired hand-eye coordination and memory loss… in case studies of chronically exposed workers at estimated average exposure levels as low as 3 ppm." However, Earthjustice also states that the EtO DRA does not use the epidemiological data in assessing the risk of neurotoxicity of EtO, but instead relies upon a repeated dose inhalation toxicity study in the mouse. Further, Earthjustice claims that the mouse study is misinterpreted, as there were neurological effects observed ("statistically significant reductions in locomotor activity, affecting 80 percent of the exposed mice, at that dose."). Therefore, in their view, the 50 ppm dose cannot be considered a NOAEL, and risks of neurotoxic effects from exposure to EtO are therefore understated.

EPA Response: The EPA does not agree with the comment. The EPA notes that the Agency for Toxic Substances and Disease Registry (ATSDR) Ethylene Oxide Toxicological Review (https://www.atsdr.cdc.gov/toxprofiles/tp137.pdf) further clarifies the statement regarding the human case reports cited in this comment, stating that "…effects were seen at estimated average exposure levels as low as 3 ppm; however, short-term exposures may have been as high as 700 ppm for some of these workers." Therefore, it is clear that there is uncertainty in the actual level of exposure that resulted in neurological signs of toxicity in these reports. Further, in the Minimal Risk Level (MRL) selection worksheet for ethylene oxide, the ATSDR assessment considered that the available case studies in humans reporting neurological effects did not provide adequate exposure-response data from which to derive a point of departure.

For the assessment of non-cancer inhalation risk, the ATSDR assessment relied upon the Snellings (1984) study in the mouse, as did the EPA. The ATSDR assessment MRL worksheet cited a NOAEL value of 10 ppm and a LOAEL value of 50 ppm from the Snellings (1984). This differs from the EtO 2020 DRA use of 50 ppm as the NOAEL value from the same study. The basis of the LOAEL value is neurological signs of toxicity in both assessments; the ATSDR selected the 10 ppm value as the NOAEL.

The EPA does not plan to re-visit this issue, as the mitigations of EtO risks are driven by the carcinogenicity assessment and would be protective of non-cancer effects, including neurological effects mentioned above.

Earthjustice Comment: Earthjustice argues that EPA fails to apply the required children's safety factor when calculating ethylene oxide's risks.

EPA Response: EPA does not agree with this comment. The toxicology database for EtO and its degradate Ethylene Chlorohydrin (ECH) is considered complete for evaluating and

characterizing toxicity, assessing children's susceptibility as required in the Federal Food, Drug, and Cosmetic Act (FFDCA) and selecting endpoints for pertinent exposure pathways. The database contains an acceptable developmental toxicity study in the rat for EtO, and an acceptable two-generation reproductive toxicity study in the rat for EtO and its degradate ECH. In the analysis of the developmental and reproductive toxicity data for EtO, OPP determined that for EtO, there is no evidence of increased (quantitative) susceptibility following *in utero* exposures in rats or after post-natal exposure in the two-generation reproduction study in rats. There is evidence for increased qualitative susceptibility based on delayed ossification in the fetuses in rat developmental study and post implantation loss observed in two-generation reproduction study in rats. There is low concern for the delayed ossification, since the delays were seen in the presence of significant decreases in maternal body weights at the dose that caused the delayed ossification. Also, the post implantation loss is attributed to both maternal and developmental toxic effects.

EPA also determined that for ECH, there is no evidence of quantitative susceptibility after post-natal exposure in the two-generation reproduction study in rats. There is evidence of qualitative susceptibility based on increased incidence of runts in offspring in the two-generation reproduction study in rats. However, there is low concern for the increased incidence of runts since the increased incidence was observed in the presence of significant alterations in various organ weights and atrophy of the uterus, vagina and cervix in adult females at the same dose.

Based on these considerations of toxicity and estimates of exposure that are not likely to be underestimates, EPA reduced the FQPA safety factor to 1X for EtO and ECH.

Earthjustice Comment: Earthjustice states that, "EPA claims that "[a]n aggregate assessment for [ethylene oxide] was not conducted since there are no food, drinking water or residential exposures to [ethylene oxide]." According to Earthjustice, this statement is "factually inaccurate, and it reflects an impermissibly narrow interpretation of EPA's aggregate risk assessment obligations."

Earthjustice also states that, "[t]here is [also] evidence that some foods such as flour and spices retain measurable ethylene oxide and byproducts several months after fumigation." This statement is taken from page 113, section 5.5.4, of the ATSDR Toxicological Profile for ethylene oxide that is available for public comment (ATSDR, 2020). Three references are cited in support of this statement: NIOSH 1981; Parod 2014; and EPA 2017b. These references are available in the ATSDR reference list from the Toxicological Profile.

EPA Response: The EPA concurs with the statement "[t]here is [also] evidence that some foods such as flour and spices retain measurable ethylene oxide and byproducts several months after fumigation." This statement is found in the final ATSDR Toxicological Review for ethylene oxide, (section 5.5.4, page 117). The NIOSH 1981; Parod 2014; and EPA 2017b references are cited to support the statement. The references, however, appear to have been included in error as they do not support the statement. There is no mention of ethylene oxide residues in flour or spices in NIOSH 1981; Parod 2014 or EPA 2017b. In addition, flour is not a legal use site of EtO in the United States. The following commodities have established tolerances for EtO and ECH - dried herbs and spices (except basil), licorice roots, dried peppermint & spearmint tops, sesame seeds, dried vegetables, and walnuts. If any commodity other than those listed is found to

have residues of EtO or ECH in the United States, it would be considered adulterated and would be subject to seizure and removal from the channels of trade.

Further, as noted in the 2020 EtO DRA **(**page 38), "EtO is not considered a residue of concern for dietary exposure because data from EtO spice sterilization studies indicate that EtO residues disappear rapidly after sterilization and are unlikely to be found in spices available for consumption." In addition, as also stated in the 2020 EtO DRA, "[a] drinking water exposure assessment was not conducted because… uses of EtO for indoor food and nonfood uses will result in insignificant exposure to drinking water resources."

As there is no dietary or drinking water exposure to EtO from the EPA registered uses, EPA did not perform an aggregate risk assessment for EtO.

Comments Submitted by the Louisiana Chemical Association (LCA)

Comments were submitted by the Louisiana Chemical Association (LCA) in Document ID EPA-HQ-OPP-2013-0244-0035. This document has 10 pages.

LCA Comment: LCA commends the EPA Office of Pesticide Programs (OPP) for, a) acknowledging the lack of stakeholder consensus concerning the appropriate methodology for the cancer dose-response assessment of EtO, and, b) presenting multiple perspectives on the cancer evaluation *i.e*., EPA (2016), Texas Commission of Environmental Quality (TCEQ, 2020), and Exponent (2020; Ethylene Oxide Task Force [EOTF] submission).

EPA Response: EPA appreciates the comment, however, since the publication of the 2020 DRA, and in contexts other than the registration review of EtO, EPA has continued to consider the best approach for characterizing the cancer risk associated with inhalation exposure to EtO. While there are some uncertainties associated with all of the approaches in characterizing the cancer risk (as discussed in the 2020 DRA), the EPA has determined that the 2016 IRIS assessment (US EPA, 2016) should be used to characterize the cancer risk associated with inhalation exposure to EtO. See the responses above.

LCA Comment: LCA strongly supports the methodology used by TCEQ in its May 15, 2020, final Ethylene Oxide Cancer Dose-Response Assessment Document (TCEQ, 2020) to derive the inhalation unit risk factor (URF), namely the use of the Cox proportional hazards model to perform the EtO cancer dose-response assessment based on lymphoid cancer only. Several substantial issues with EPA's assessment were identified by the TCEQ (2020) (*e.g*., model fit criteria calculations, visual misrepresentation of model fit, statistically significant model over-predictions). TCEQ's toxicologist summarized the rationale underlying the choice of model for the cancer dose-response assessment as follows in an article published by the Houston Chronicle:

> *"To derive the ethylene oxide cancer dose-response assessments, both EPA and TCEQ used data from a United States-based group of workers who were exposed to very high concentrations of ethylene oxide for many years and who experienced an increased rate of lymphoid cancers. From this data, both TCEQ and EPA had to estimate what the risk would be to a person who was exposed to typical environmental concentrations of ethylene oxide,*

which can be millions of times lower than the occupational levels the workers had been exposed to.

The first step in this extrapolation is to determine how the chemical could cause cancer: In this case, ethylene oxide can cause cancer by causing damage to DNA. Based on that mechanism, the standard and conventional risk assessment method is to use a mathematical dose-response model that essentially draws a best-fitting straight line from the high dose data (from the worker exposure study) down to low doses (so it is applicable to ambient exposures). This is the standard method that TCEQ used, and using that method, agency toxicologists were able to accurately predict the number of cancers that were observed in the worker study. In contrast, instead of using the standard straight-line risk model, EPA chose to assume that low doses of ethylene oxide are more potent than high doses for causing cancer (this is called a supra-linear model, and is the unconventional model that TCEQ referred to). EPA's model was shown by TCEQ to significantly over-predict the number of cancers that were observed in the worker study, which is how we mathematically demonstrate that EPA's method over-predicts cancer risk.

In addition, the human body naturally produces low levels of ethylene oxide, with background levels being higher in smokers. Using EPA's risk assessment, the background levels of ethylene oxide in the population would be predicted to cause more lymphoid cancer than is actually observed in the general population (and ignoring any other potential cause of lymphoid cancer). In this way, we also know that EPA's model over-estimates the cancer potency of ethylene oxide."

EPA Response: As discussed above in response to the TCEQ comments, EPA has determined that the risk value from the 2016 IRIS assessment should be used to characterize the cancer risk associated with inhalation exposure to EtO.

LCA Comment: LCA notes inconsistencies in table numbers within the DRA. For example, page 41 refers to ambient air concentration data in Table 16, but the table itself is labeled Table 15. Similarly, page 43 refers to available exposure data in Table 17, but the table itself is labeled Table 16.

EPA Response: The commenter is correct that there are several tables starting with Table 13 that are incorrectly numbered and referenced in the 2020 DRA. Not all of the table titles were formatted as table captions and included in the table numbering system.

Comments Submitted by University of California (UC)

Comments were submitted by the University of California (UC) in Document ID EPA-HQ-OPP-2013-0244-0039. This document has 30 pages.

UC Comment: UC states that the Texas Commission on Environmental Quality (TCEQ) and EtO Task Force (EOTF) assessments inappropriately discount the breast cancer risk and therefore drastically underestimate the potential risks of Ethylene Oxide to women.

EPA Response: As discussed above in response to the TCEQ comments, EPA has determined that the risk value from the 2016 IRIS assessment should be used to characterize the cancer risk associated with inhalation exposure to EtO.

UC Comment: UC states that the TCEQ assessment uses a model for lymphoid cancer that does not reflect the data, uses a number of non-standard and non-health-protective procedures in the calculation of the risk estimate for lymphoid cancer from that model, and uses an erroneous "reality check" to support the use of that model. The EOTF assessment improperly chooses the same model and obtains the same risk estimate as TCEQ.

EPA Response: As discussed above in response to the TCEQ comments, EPA has determined that the risk value from the 2016 IRIS assessment should be used to characterize the cancer risk associated with inhalation exposure to EtO.

References

ATSDR (Agency for Toxic Substances and Disease Registry). 2020. Toxicological Profile for Ethylene Oxide – Draft for Public Comment. September, 2020. https://www.regulations.gov/document/ATSDR-2016-0004-0003

ATSDR. 2022. Toxicological Profile for Ethylene Oxide. August, 2022 https://www.atsdr.cdc.gov/toxprofiles/tp137.pdf

International Program on Chemical Safety (IPCS), 1985. Environmental Health Criteria 55: Ethylene Oxide. World Health Organization (WHO), Geneva, http://www.inchem.org/documents/ehc/ehc/ehc55.htm

IPCS. 2003. Concise International Chemical Assessment Document 54 – Ethylene Oxide, WHO, p 1-57. http://www.inchem.org/documents/cicads/cicads/cicad54.htm

Master Record Identification (MRID) 44359401. Mandella, R. (1997) A 13-Week Inhalation Neurotoxicity Study of Ethylene Oxide (498-95A) in the Rat Via Whole-Body Exposures with Recovery: Final Report: Lab Project Number: MA-RR-97-2388: 95-6099: TOX-73B/95083. Unpublished study prepared by Huntingdon Life Sciences. 1089 pages.

MRID 44256402. Mandella, R. (1997) An Acute Inhalation Neurotoxicity Study of Ethylene Oxide (498-95A) in the Rat via Whole-Body Exposures: Final Report: Lab Project Number: 95-6097: TOX-73B/95081: 956097. Unpublished study prepared by Huntingdon Life Sciences. 648 pages.

MRID 50231101. Johnston, J. (2017) Ethylene Oxide Exposures for Ethylene Oxide Sterilization Plant Workers. Project Number: 1296/001/05. Unpublished study prepared by Acta Group, L.L.C. 59 pages.

MRID 51258401. Cancer Risk Estimates for Ethylene Oxide Based on Epidemiological and Biological Weight-of-Evidence. Submitted by the Ethylene Oxide Task Force, prepared by Exponent, Inc. and Summit Toxicology. Report No. 1296.001-11. Dated March 11, 2020.

NIOSH (National Institute for Occupational Safety and Health). 1981. Ethylene oxide (EtO): Evidence of carcinogenicity. NIOSH Current Intelligence Bulletin 35. Cincinnati, OH: PB85119121.

NTP (National Toxicology Program). (1987). Toxicology and carcinogenesis studies of ethylene oxide (CAS no 75-21-8) in B6C3F1 mice (inhalation studies). National Toxicology Program Technical Report Series 326: 1-114.

OSHA (Occupational Safety and Health Administration). 2009. Assigned Protection Factors for the Revised Respiratory Protection Standard, 3352-02, OSHA, U.S. Department of Labor, 2009.

Parod RJ. 2014. Ethylene oxide. In: Encyclopedia of Toxicology. 3rd ed. London, England: Elsevier Inc., 535-538. http://doi.org/10.1016/B978-0-12-386454-3.00021-X.

Snellings, W. M., C.S. Weil, and R.R. Maronpot. 1984. A subchronic inhalation study on the toxicologic potential of ethylene oxide in B6C3F1 mice. Toxicology and Applied Pharmacology, 76: 510– 518.

TCEQ. 2020. Ethylene Oxide, Carcinogenic Dose-Response Assessment. CAS Registry Number: 75-21-8. Development Support Document, Revised Draft,. Joseph T. Haney, Allison Jenkins, Jessica L. Myers. Toxicology, Risk Assessment, and Research Division. Texas Commission on Environmental Quality (TCEQ). January 31, 2020.

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

US EPA. 2016. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, (CASRN 75-21-8) in Support of Summary Information on the Integrated Risk Information System (IRIS). 635/R-16/350Fa. National Center for Environmental Assessment (NCEA), Office of Research and Development (ORD), US EPA, Washington, DC. December 2016.

US EPA. 2017. Summary Fact Sheet on Ethylene oxide: 75-21-8. Included in the EPA Health Effects Notebook for Hazardous Air Pollutants. https://www.epa.gov/sites/default/files/2016-09/documents/ethylene-oxide.pdf. March 20, 2017. Updated December 20, 2018.

US EPA. 2020. Ethylene Oxide (EtO). Draft Human Health and Ecological Risk Assessment in Support of Registration Review. D458706. Office of Pesticide Programs (OPP), Office of Chemical Safety and Pollution Prevention (OCSPP), US EPA. November 2, 2020.

US EPA. 2021. EPA Should Conduct New Residual Risk and Technology Reviews for Chloroprene- and Ethylene Oxide-Emitting Source Categories to Protect Human Health, Report No. 21-P-0129, U.S. EPA Office of Inspector General, May 6, 2021.

US EPA. 2021a. ORD review of comments on the IRIS Ethylene Oxide assessment contained in the ACC Request for Correction submitted regarding EPA's National Air Toxics Assessment. Wayne E. Cascio, MD, Acting Principal Deputy Assistant Administrator for Science Office of Research and Development, August 25, 2021.

US EPA, 2022. Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review – Final Action. FR Doc. 2022-27522, Filed: 12/20/2022.

US EPA. 2023. Ethylene Oxide (EtO). Addendum to "Draft Human Health and Ecological Risk Assessment in Support of Registration Review" - Inhalation Exposure Risk Assessment in Support of Registration Review. D467242. OPP, OSCPP, US EPA. March 24, 2023.