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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: November 3, 2020

SUBJECT: **Ethylene Oxide (EtO).** Draft Human Health and Ecological Risk Assessment in Support of Registration Review.

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Decision No.: 564848	**Registration No.:** NA
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Risk Assess Type: Single Chemical Aggregate	**Case No.:** 2275-1
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1.0 Executive Summary

This memorandum serves as AD's and HED's human health and ecological draft risk assessment (DRA) for the currently registered conventional and antimicrobial pesticidal uses of ethylene oxide (EtO) in support of Registration Review.

The EtO pesticide registration review case includes EtO and its reaction products ethylene bromohydrin (EBH), ethylene chlorohydrin (ECH), and ethylene glycol (EG). Formation of EBH and ECH result from fumigation of foods with EtO due to interaction with natural bromides and chlorides present in the food. Formation of EG results from high sterilization concentrations of EtO, where EtO reacts with moisture to form EG. This assessment primarily focuses on EtO (for the inhalation route) and ECH (for the dietary route) since (1) residue level comparisons from sterilization studies and toxicity comparisons from literature reports indicate that dietary assessments of ECH are protective for residues of EG, (2) residue levels of EBH are insignificant compared to the residue levels of ECH, and thus it is sufficient to regulate only residues of ECH for dietary exposure, and (3) measurements of EtO from a spice sterilization study indicate that it dissipates rapidly after sterilization and is unlikely to be found in spices available for consumption.

OPP has collaborated with the Office of Research and Development's (ORD) Integrated Risk Information System (IRIS) and Office of Air and Radiation (OAR) during their assessment process of EtO to further inform the cancer evaluation characterization and the work that is currently ongoing to characterize and mitigate exposures in the sterilizer industry. Additionally, as part of the pesticide registration review process, OPP routinely meets with stakeholders, including the EtO industry. At a meeting in 2019, given the lack of consensus among stakeholders around the approach for addressing the cancer dose-response assessment for evaluating EtO, OPP suggested to industry that an analysis on the biological understanding regarding EtO cancer outcomes may be useful in evaluating the biological plausibility of the various inhalation unit risk values.

OPP is presenting multiple perspectives on cancer evaluations for EtO within this document but has not chosen a single value for risk extrapolation, nor has OPP provided a critical review of the available approaches. OPP recognizes that, despite several years of study by EPA and various stakeholders, there are differences in the approach for addressing the cancer dose-response assessment for EtO. Although there is general scientific consensus that EtO is a known human carcinogen based on lymphoid cancer, there is not agreement on the use of breast cancer data associated with EtO exposure in the determination of the inhalation unit risk value. There is also not agreement on the dose-response modeling approaches used to characterize carcinogenic potency. As the approaches and perspectives summarized in this risk assessment are different and have an impact on EtO carcinogenicity risk characterization, it is prudent for OPP to consider these different perspectives and the range of possible cancer risk calculations. As described in this document, OPP has briefly summarized the cancer dose response evaluations provided by ORD/IRIS, Texas Commission on Environmental Quality (TCEQ), OPP's Registration Eligibility Decision (RED) document, and the EtO Task Force (EOTF) submission developed by Exponent, Inc.

Based on the range of cancer inhalation unit risks (IUR) provided in this qualitative assessment, EPA believes that further mitigation of EtO exposure is required. The EOTF, who represent EtO registrants, submitted a mitigation proposal to OPP in February 2020. Mitigation options range from

emissions abatement technologies, parameter monitoring, respiratory protective equipment, and the elimination of minor uses such as artifacts, archival materials, and library objects. Detailed mitigation will be proposed in the Proposed Interim Decision following the publication of this DRA.

Hazard Assessment

EtO: EtO is a colorless, highly reactive gas. The primary route of exposure is by inhalation. Once absorbed, EtO is distributed throughout the body and metabolized to ethylene glycol and to glutathione conjugates. EtO is an electrophilic agent and alkylates nucleophilic groups in macromolecules such as hemoglobin and deoxyribonucleic acid (DNA). EtO is genotoxic in almost all available studies, and the weight of evidence supports a mutagenic mode of action for carcinogenicity of EtO. Evidence of carcinogenicity is observed in chronic inhalation carcinogenicity studies in rats and mice, where tumors of the lymphohematopoietic system, brain, lung, connective tissue, uterus, and mammary gland are observed. In humans employed in EtO-manufacturing facilities and in sterilizing facilities, there is evidence of an increased association with cancer of the lymphohematopoietic system and of breast cancer mortality in females. While there is agreement on the association of EtO exposure with cancer of the lymphohematopoietic system, the assessments presented herein differ in concluding that there is insufficient evidence for breast cancer and the TCEQ and EOTF do not include breast cancer in their quantitative risk assessments. Neurotoxicity is also observed in repeat dose toxicity studies with EtO in experimental animals and from exposure in humans. In animal studies, drooping eyelids, low arousal and no response to touch, ataxia, decreased hind-limb grip strength, landing foot splay and decreased motor activity have been identified in neurotoxicity studies using rodents. Demyelination of sciatic nerve has been reported in monkeys treated with EtO for two years. Peripheral neuropathy, impaired hand-eye coordination and memory loss have been reported in workers exposed to EtO for longer periods.

Occupational exposure limits for EtO have been established by the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH). The purpose of these limits is to reduce cancer risks for workers exposed to EtO. In the 1980s, OSHA established a Permissible Exposure Limit (PEL) of 1 ppm as an 8-hour time weighted average (TWA) and 5 ppm as a 15-minute Short Term Exposure Limit (STEL). These values are enforceable. NIOSH has established recommended exposure limits (REL) of 0.1 ppm as an 8-hour TWA and 5 ppm as a STEL and ACGIH has established a Threshold Limit Value (TLV) of 1.0 ppm as an 8-hour TWA. Both the NIOSH RELs and the ACGIH TLV are recommended values that are not enforceable.

ECH: Ethylene chlorohydrin (ECH) is a reaction product of EtO. It is formed in EtO-fumigated commodities whenever a chloride ion is present. ECH is not an animal metabolite. Results of the guideline two-generation reproductive toxicity dietary study in rats indicated decreased body weights and organ weight changes in parental males and females. Females also exhibited atrophy of the uterus, vagina and cervix. Offspring effects included decreased body weights and organ weight changes; these offspring effects occurred at the same doses associated with maternal toxicity. Reproductive changes consisted of a decrease in the total number of follicular counts, decreased ovary/uterus/cervix/oviduct weights, and delayed sexual maturation. The limited, published acute toxicity studies indicate that ECH is toxic both by oral, inhalation and dermal routes. Limited

evidence suggests that ECH could produce marked eye and dermal irritation in rabbits. Dermal sensitization effects were not identified for ECH.

Several studies indicate that ECH is a weak base pair substitution mutagen in bacteria and the mutagenicity in bacteria is enhanced in the presence of rat liver S9 extract (NTP 1985). ECH tested negative in the mutagenicity tests using mammalian cell cultures (*in vitro*) or rodents (*in vivo*). However, in one test, ECH induced DNA repair in human fibroblasts *in vitro*. ECH tested negative for dominant-lethal mutations or heritable translocations in mouse. Based on a weight-of-evidence (WOE) approach, the Hazard and Science Policy Council (HASPOC) recommended that chronic/carcinogenicity studies in rats and mice be waived based on the decision that it is appropriate to bridge available data from an National Toxicology Program (NTP) study (NTP TR 477, 1998) on propylene chlorohydrin (PCH), which is a chemical structurally similar to ECH (TXR 0057357). The NTP study on PCH indicated no evidence of carcinogenicity in rats or mice.

EG: Like ECH, ethylene glycol (EG) is a reaction product of EtO. The results of published literature studies indicate toxicity at doses at or near the limit doses. The results of a well-conducted 2-year toxicity study in rats and mice demonstrated kidney toxicity at the limit dose in rats. Renal effects were noted primarily in male rats and included histological lesions, increased water consumption, alterations in urinary parameters, and increased creatinine and blood urea nitrogen levels. Both males and females exhibited calcium oxalate crystals in the urine and increased kidney weights at this limit dose. There was also mortality at the limit dose in males only. No toxicity was observed in mice at any dose. Several published literature studies indicate that EG may cause developmental toxicity (skeletal and external malformations) in rodents. However, these effects were noted at doses near or at the limit dose. Since the developmental effects are seen only at high doses, there is a very low degree of concern for these effects at lower levels of exposure.

Published studies on mutagenicity tests in bacteria and mammalian cells were consistently negative. The chromosomal aberrations tests in Chinese hamster ovary cells and DNA damage in rat hepatocytes were also negative. The *in vivo* genotoxicity tests are also negative for dominant lethal mutations in rats and chromosomal aberrations of bone marrow cells in mice exposed to ethylene glycol. No evidence of carcinogenicity was reported in the published chronic carcinogenicity studies on EG in rodents. EG is not likely to be carcinogenic to humans.

Residue Chemistry

Tolerances for EtO and ECH are established under 40 CFR 180.151 for herbs and spices (except basil), dried vegetables, walnuts, licorice roots, leaves of peppermint and spearmint, and sesame seed. Two spice sterilization studies form the basis for current tolerances and the current dietary assessment: 1) MRID 43218001, EtO Persistence Study in Spices and Black Walnut, 1994; and 2) MRID 46625301, EtO Express Residue Study, 2005. The 1994 study provided residue data reflecting traditional sterilization methods for spices, herbs, walnuts, and dried vegetables at the following time intervals: 0 day, 2 weeks, and 2 months after fumigation. Residue data were reported for EtO and its metabolites ECH, EBH, and EG. Relatively high residues were found in this study. An improved sterilization process, EtO Express, was used for the second study conducted in 2005 involving 29 herbs and spices. Residue data for EtO and ECH were reported at the following time intervals: 0 day, 24 hours, and 72 hours. Current tolerances are based on the EtO Express residue data collected 24 hours after fumigation, while dietary assessments are based on ECH residues collected at the 72-hour interval. These time intervals are considered health protective as

information from the spice industry indicates that treated spices will not enter commerce within 24 hours of treatment nor will treated spices be available for purchase within 72 hours of treatment. All domestic spice sterilization work now uses the EtO Express method; thus, it is appropriate to base tolerances and dietary estimates on the results of the EtO Express sterilization study.

Dietary Exposure

A food only chronic dietary risk assessment was conducted for ECH using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID, ver. 3.16) which incorporates food consumption data from the United States Department of Agriculture (USDA) National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA; 2003-2008). A dietary assessment was not conducted for EtO since sterilization studies show that no EtO residues will be present in spices at the time of consumption. Acute and cancer analyses were not conducted as toxicological effects attributable to a single dose were not identified and the chronic assessment adequately accounts for all chronic toxicity, including potential carcinogenicity. The conservative chronic analysis assumed 100% crop treated, and tolerance-level residues. All processing factors were set to 1 since drying procedures are performed prior to sterilization. No residues are included in the dietary exposure assessment for drinking water, as uses of EtO for indoor food and nonfood uses will result in negligible exposures from drinking water. The resulting chronic exposure estimates do not exceed the Agency's level of concern (LOC; 100% of the chronic population adjusted dose (cPAD)); children 3-5 years old were the most highly exposed population subgroup at 6.6% the cPAD, while that for the US Population was 2.7% cPAD.

Residential Exposure

There are no uses of EtO resulting in direct residential applications; therefore, residential handler and post-application exposures are not expected (see non-occupational “bystander” exposures).

Aggregate Risk Assessment

An aggregate assessment for EtO was not conducted since there are no food, drinking water or residential exposures to EtO. For the metabolites of EtO (ECH and EG), there are no water or residential exposures; the only exposure route is through food. Thus, an aggregate assessment was not conducted for ECH or EG.

Non-Occupational Bystander Exposure

Although there are no direct residential applications of EtO, those who live or work near sites where EtO fumigation occur (i.e., defined herein as “bystanders”) may potentially be exposed via inhalation to EtO emissions that travel off-site. EtO is a listed hazardous air pollutant (HAP) under Clean Air Act (CAA) section 112(b). In 1992, commercial sterilization facilities were included in EPA’s initial listing of major and area sources of HAP emissions. 57 Fed. Reg. 31,576, 31,592 (July 16, 1992). Thereafter, EPA promulgated EtO emission standards for commercial sterilizers and fumigation operations. 59 Fed. Reg. 62,585 (Dec. 6, 1994); 40 C.F.R. Part 63, subpart O. Pursuant to CAA section 112, EPA is required to review and, if necessary, revise these standards eight years after promulgation for residual risk and every eight years based on advancements in technology. Based on its initial review of the standard, EPA did not identify any significant developments in practices, processes, or control technologies and determined that the risk attributable to emissions of EtO from sources within this source category following the establishment of these emissions standards was acceptable. 71 Fed. Reg. 17,712 (April 7, 2006). (Note, this residual risk review was based on EPA’s 1985 health assessment document for EtO.) The second technology review was due

in 2014. Within EPA, the responsibility for developing the CAA emission standards and other requirements applicable to the commercial sterilizer and fumigation operations source category rests with the Office of Air and Radiation's (OAR) Office of Air Quality Planning and Standards (OAQPS). Therefore, OPP is collaborating with OAQPS in their efforts to assess and mitigate EtO emissions from EtO sterilization facilities. To meet its statutory duty to review and, if necessary, revise the emissions standard, OAR is currently in the process of reviewing information collected under CAA section 114 from EtO commercial sterilization facilities on facility characteristics, control devices, work practices and costs for emission reductions collected. OPP will continue to work with OAQPS during their assessment and review of this information. In addition, OPP plans to work collaboratively with OAQPS during the risk mitigation phase of the Registration Review process. Specifically, mitigation for the protection of workers and the surrounding communities will likely focus on emissions reductions proposed by OAR in their upcoming rulemaking on commercial EtO sterilizers.

Occupational Exposure

There is potential for occupational handler inhalation exposure from the registered uses of EtO. OPP has obtained personal breathing zone (PBZ) air monitoring data from registrant submitted studies or downloaded exposure data from the OSHA website for contract sterilization plants, health care facilities and spice treatment facilities. These PBZ air monitoring data represent observational monitoring during routine workdays and are expressed as 8-hour time weighted average (TWAs) when compared to the OSHA PEL-TWA of 1.0 ppm or as 15-minute TWAs when compared to the OSHA PEL-STEL of 5 ppm.

Exposure data for contract sterilization plant workers were included in a registrant submission of 1,273 results from 25 facilities. The results are reported as 8-hour TWAs and range from 0.002 to 4.6 ppm with an arithmetic mean of 0.23 ppm. The 8-hour TWAs for workers who wore respirators were calculating by assuming that they wore full face supplied air respirators. These respirators have an assigned protection factor of 1,000 (OSHA, 2009) which means that they reduce exposures by a factor 1,000x when they were wearing the respirators.

Exposure data for health care facilities were included in a registrant submission of 647 sample results that were collected in hospitals in 2012. The results ranged from 0.0007 ppm (the limit of detection) to 10.1 ppm with an arithmetic mean of 0.12 ppm. The exposure data represent actual exposures and have not been modified to account for respiratory protection.

Occupational exposure data from OSHA for the years 2008 through 2019 were downloaded and time weighted averages (TWAs) were calculated for each facility. For the 8 facilities involved in medical equipment production or contract sterilization, the TWA EtO air concentrations ranged from 0.0013 to 1.5 ppm. Two of these facilities had TWA air concentrations of 1.4 ppm and 1.5 ppm that exceed the OSHA PEL of 1.0 ppm. For the 7 facilities involved in health care or veterinary care, the TWA EtO air concentrations ranged from 0.0061 to 0.022 ppm with most of the samples reported as non-detect. The OSHA data are the actual exposures and have not been modified to account for respiratory protection.

In support of the use of EtO for the sterilization of spices, the American Spice Trade Association (ASTA) submitted exposure monitoring of two workers at each of two facilities. Each worker was monitored for 10 days. EtO average air concentrations, assuming respirator protection, ranged from

0.015 to 0.858 ppm, with an overall average of 0.076 ppm. Five samples for EtO in a spice facility are also reported in the OSHA database, with only one sample showing detectable EtO residues (0.16 ppm for a 240-minute sample) and the remaining samples reported as non-detects.

Ecological Risk

For both the spice and commercial sterilization uses, due to the toxicity of EtO to non-target organisms and the potential for exposure, terrestrial animals in the vicinity or downwind of a treatment vent may be at risk from exposure. For aquatic organisms, risks are not expected due to limited exposure potential. Due to the potential risks to terrestrial organisms, the Agency is not able to make a 'no effects' determination for Federally listed species or their designated critical habitats.

2.0 Established and Recommended Tolerances

Table 1 is a summary of tolerance revisions recommended for EtO. The current tolerance expression should be revised to read as follows:

(a) General (1). Tolerances are established for residues of the antimicrobial agent and insecticide EtO, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only EtO in or on the commodity.

(b) General (2). Tolerances are established for residues of the EtO reaction product ethylene chlorohydrin, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only ethylene chlorohydrin (2-chloroethanol), in or on the commodity.

Table 1. Summary of Tolerance Revisions for Ethylene Oxide (40 CFR §180.151)[1].

Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
40 CFR §180.151(a)(1) ethylene oxide			
Herb and spice group 19, dried leaves, except basil	--	7	Commodity definition revision.
Herb and spice, group 19, dried, except basil	7	remove	Commodity definition revision.
Peppermint, dried leaves	--	7	Commodity definition revision.
Peppermint, tops, dried	7	remove	
Spearmint, dried leaves	--	7	Commodity definition revision.
Spearmint, tops, dried	7	remove	
Walnut	50	7	Lower residues with EtO Express
40 CFR §180.151(a)(2) ethylene chlorohydrin			
Herb and spice group 19, dried leaves, except basil	--	940	Commodity definition revision.
Herb and spice, group 19, dried, except basil	940	remove	Commodity definition revision.
Peppermint, dried leaves	--	940	Commodity definition revision.
Peppermint, tops, dried	940	remove	
Spearmint, dried leaves	--	940	Commodity definition revision.
Spearmint, tops, dried	940	remove	
Walnut	-	100	Spice sterilization study LOQ.

[1] For complete list of established/recommended tolerances see the IRLS in Appendix C.

2.1 International Harmonization

Codex has not set Maximum Residue Limits (MRLs) for EtO or ECH. Canada has set MRLs for herbs and spices (and sesame, seed) for both EtO and ECH. As these levels match the U.S. tolerances, there are no international harmonization issues at this time.

3.0 Data Requirements and Label Recommendations

Currently, all labels indicate the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) is an 8-hr time weighted average (TWA) of 1 ppm[1] and the Excursion Limit (EL) for 15 minutes is 5 ppm. All labels require personal protective equipment (PPE) consisting of a long-sleeved shirt, long pants, shoes plus socks, chemical-resistant gloves and a respirator. If the worker could have eye or skin contact with EtO or EtO solutions, they must wear chemical-resistant attire (e.g., apron or footwear) and face-sealing goggles, a full-face shield, or a full-face respirator. There are no EtO solutions registered, only gas, and therefore, language relating to EtO solutions are not necessary.

4.0 Ethylene Oxide Formulations and Use Patterns

As of August 31, 2020, there were 18 registered Section 3 products and 1 Section 24(c) containing EtO as an active ingredient (a.i.). EtO is formulated and marketed as a pressurized gas. The end-use formulations are all gas mixtures of EtO and other gases (e.g., carbon dioxide) in varying concentrations. Table 2 presents a summary of the registered antimicrobial and conventional uses of EtO.

Antimicrobial Uses: The registered antimicrobial uses of EtO include the fumigation/sterilization of medical or laboratory equipment, pharmaceuticals, and aseptic packaging (21CFR §201); and to sterilize artifacts, archival material, library objects, and musical instruments. The antimicrobial products are packaged as bulk cylinders for use in tractor trailer sized chambers in contract sterilization facilities or as cartridges for use in oven sized chambers in health care facilities.

The application rates are not generally listed on the labels. The FDA website indicates that two voluntary consensus standards (ANSI AAMI ISO 11135:2014 and ANSI AAMI ISO 10993-7:2008(R)2012) describe how to develop, validate, and control EtO sterilization processes for medical devices and the acceptable levels of residual EtO and ethylene chlorohydrin left on a device after it has undergone EtO sterilization. These standards help ensure levels of EtO on medical devices are within safe limits since long-term and occupational exposure to EtO has been linked to cancer. The link to the FDA website is as follows: https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/ethylene-oxide-sterilization-medical-devices.

Conventional Uses: EtO is a commodity fumigant/sterilant registered for use to reduce microbials on whole and ground spices or other seasoning materials (40 CFR §180). Additionally, a special local need registration (North Carolina) is currently in place for the treatment of beehives/beekeeping equipment. The use of EtO for the treatment of spices currently represents less

[1] Per the Ethylene Oxide Standard 29 CFR 1910.1047.

than 10 percent of the total EtO pesticide use. The American Spice Trade Association (ASTA) estimates that less than 50% of spices in the U.S. are treated with EtO each year (ASTA, 2017[2]). There are eight products currently registered for treatment of spices. These are all formulated as pressurized gas contained in cylinders. Sterilization/fumigation with EtO must be performed only in vacuum or gas tight chambers designed for use with EtO. It is used in vacuum chambers at full strength (100%) for herbs and spices. The maximum application rate is 500 mg/L (or 31.22 lb a.i./1000 ft^3) in a sealed chamber.

Table 2. Summary of EtO Registered Uses

EPA Reg. No.	% a.i.	Registration Type	Use Site
36736-2	100	EP	Medical/lab items; pharmaceuticals; packaging; spices; seasonings; artifacts, archival material, library objects
36736-3	80	EP	Medical/lab items; pharmaceuticals; packaging; spices; seasonings; artifacts, archival material, library objects
36736-4	10	EP	Medical/lab items; pharmaceuticals; packaging; spices; seasonings; artifacts, archival material, library objects
36736-5	20	EP	Medical/lab items; pharmaceuticals; packaging; spices; seasonings; artifacts, archival material, library objects
36736-6	12	EP	Medical/lab items; pharmaceuticals; packaging; spices; seasonings; artifacts, archival material, library objects
36736-7	8.5	EP	Medical/lab items; pharmaceuticals; packaging; spices; seasonings; artifacts, archival material, library objects
36736-8	100	Technical	Medical/lab items; pharmaceuticals; packaging; spices; seasonings; artifacts, archival material, library objects
58779-5	100	EP	Medical/lab items; pharmaceuticals
69340-1	89.4	EP	Surgical instruments; hospital instruments; hospital critical equipment; heat labile materials; oral and inhalation equipment; diagnostic instruments/equipment; hospital critical rubber/plastic items; hospital materials; first aid equipment; veterinary hospital premises; veterinary hospital instruments; veterinary hospital critical equipment; human face gear; contact lens
69340-2	97	EP	Surgical instruments; heat labile materials; oral and inhalation equipment; diagnostic instruments/equipment; hospital critical rubber/plastic items; hospital materials; first aid equipment; human face gear; contact lens
69340-4	96	EP	Surgical instruments; surgical prosthetic parts; hospital instruments; oral and inhalation equipment; diagnostic instruments/equipment; hospital critical rubber/plastic items; hospital materials; surgical dressings; hypodermic needles/syringes; veterinary hospital instruments
69340-5	90	EP	Surgical instruments; hospital instruments; oral and inhalation equipment; diagnostic instruments/equipment; hospital critical rubber/plastic items; hypodermic needles/syringes; veterinary hospital instruments
69340-6	96	EP	Surgical instruments; hospital instruments; oral and inhalation equipment; diagnostic instruments/equipment; hospital critical rubber/plastic items; hypodermic needles/syringes; veterinary hospital instruments
69340-7	97	EP	Surgical instruments; hospital instruments; sterilizers; veterinary hospital instruments
69340-9	97	EP	Surgical instruments; hospital instruments; sterilizers; veterinary hospital instruments
7182-1	100	EP	Medical/lab items; pharmaceuticals; packaging; seasonings; artifacts, archival material, library objects

[2] Clean, Safe Spices: Guidance from the American Spice Trade Association. 2017 Update. https://www.astaspice.org/food-safety/clean-safe-spices-guidance-document/

EPA Reg. No.	% a.i.	Registration Type	Use Site
73711-5	100	EP	Surgical instruments; hospital instruments; oral and inhalation equipment; diagnostic instruments/equipment; hospital critical rubber/plastic items; hypodermic needles/syringes; veterinary hospital instruments
89514-1	100	EP	Medical/lab items; pharmaceuticals; packaging; spices; seasonings; artifacts, archival material, library objects
SLN NC140003	8.5	EP	Beekeeping equipment (parent label: 36736-7)

Note: All End Use Products (EPs) and technical products are formulated as pressurized gas.

5.0 Anticipated Exposure Pathways

Humans may be exposed to the degradates of EtO in food, since EtO may be applied directly to spices. Exposures through drinking water are not expected since residues are not expected in water due to the use pattern. Dermal exposures are not expected given the high vapor pressure of EtO and based on the delivery systems (which include pressurized cylinders). There are no uses of EtO resulting in direct applications by consumers which are also defined as "residents"; however, there is the potential for non-occupational bystander inhalation exposures. Occupational short-, intermediate-, and long-term inhalation exposures are possible from the registered uses of EtO. Occupational handlers may be exposed while removing treated materials (e.g., medical equipment, spices, etc.) from treatment chambers and immediately after application during aeration (e.g., forklift drivers). Occupational post-application inhalation exposures may also occur from activities associated with aeration of treated materials in places such as contract sterilizer facilities.

6.0 Hazard Assessment

OPP assessed EtO in 2008 in the Registration Eligibility Decision (RED) document. The 2008 RED, as well as the current document, considers inhalation exposure to EtO and dietary exposure to ECH as degradates on spices. The toxicity databases for EtO and its degradates are considered complete. OPP has collaborated with ORD/IRIS and OAR during their assessment process of EtO to better understand how the cancer evaluation is characterized. Additionally, as part of the pesticide registration review process, OPP routinely meets with stakeholders, including the EtO industry. At a meeting in 2019, given the lack of consensus around the approach for addressing the cancer dose-response assessment for evaluating EtO, OPP suggested to industry that an analysis on the biological understanding regarding EtO cancer outcomes may be useful in evaluating the biological plausibility of the various inhalation unit risk values, which they submitted and is discussed below.

OPP is presenting multiple perspectives on cancer evaluations for EtO within this document but has not chosen a single value for risk extrapolation, nor has OPP provided a critical review of the available approaches. OPP recognizes that, despite several years of study by EPA and various stakeholders, there are differences in the approach for addressing the cancer dose-response assessment for EtO. Although there is general scientific consensus that EtO is a known human carcinogen based on lymphoid cancer, there is not agreement on the use of breast cancer data associated with EtO exposure in the determination of the inhalation unit risk value. There is also not agreement on the dose-response modeling approaches used to characterize carcinogenic potency. As the approaches and perspectives summarized in this risk assessment are different and have an impact on EtO carcinogenicity risk characterization, it is prudent for OPP to consider these different

perspectives and the range of possible cancer risk calculations. As described in this document, OPP has briefly summarized the cancer dose response evaluations provided by ORD/IRIS, Texas Commission on Environmental Quality (TCEQ), OPP's Registration Eligibility Decision (RED) document, and the EtO Task Force (EOTF) submission developed by Exponent, Inc.

After the publication of the RED, the EPA/ORD's National Center for Environmental Assessment's Integrated Risk Information System (NCEA/IRIS) program published a reevaluation of the inhalation carcinogenicity of EtO in December 2016, which resulted in a revised inhalation unit risk estimate (IUR). During the IRIS evaluation process, public comments were received that debated the carcinogenic potential of EtO. IRIS released a memorandum in 2019 on modeling comparisons and assessment of uncertainty (USEPA 2019). An evaluation of EtO was released by the TCEQ in 2020. TCEQ based its dose-response analysis on some of the same data sets used in the IRIS evaluation (i.e., Steenland, 2004), but derived different results from its dose-response analysis. In addition to the peer-reviewed dose-response evaluations by EPA/ORD and TCEQ, an evaluation of the EtO inhalation carcinogenic potential was conducted by Exponent, Inc. and submitted to EPA/OPP in 2020 by the EOTF (MRID 51258401).

Sections 6.1 through 6.3 below provide a summary of (1) the toxicity profile for ECH, EG and EtO along with the oral endpoints for ECH used to assess the dietary exposures resulting from EtO fumigation of spices; (2) the non-cancer inhalation endpoints selected for EtO during the 2008 RED; (3) the different approaches and perspectives to the cancer assessment for EtO from the 2008 RED, ORD/IRIS 2016 evaluation and their 2019 memorandum discussing sensitivity of EtO risk estimates to dose-response model selection, TCEQ (2020), and EOTF (2020); and (4) the occupational exposure limits established for EtO.

6.1 Oral Toxicity of Ethylene Oxide (EtO) Degradates/Reaction Products

6.1.1 Available Toxicology Studies for Ethylene Chlorohydrin (ECH)

Ethylene chlorohydrin (ECH) is a reaction product of EtO. It is formed in EtO-fumigated commodities whenever a chloride ion is present. ECH is not a metabolite formed in animals.

With the exception of reproductive toxicity, there are no guideline studies (acute, subchronic, developmental, immunotoxicity, or chronic toxicity studies) available in the database for ECH. Since ECH is a degradate/reaction product, not an active ingredient (ai), there are no specific data requirements for ECH. However, a number of toxicological studies were required for ECH as part of the 2006 Tolerance Reassessment Decision (TRED) data call in: a developmental toxicity study in rabbits, chronic/carcinogenicity studies in rats and mice, and a chronic toxicity study in dogs. The agency no longer requires a chronic toxicity study in dogs for ECH. Based on a weight-of-evidence (WOE) approach, the Hazard and Science Policy Council (HASPOC) recommended that chronic/carcinogenicity studies in rats and mice be waived based on the decision that it is appropriate to bridge available data from an NTP study (NTP TR 477, 1998) on propylene chlorohydrin (PCH), which is a chemical structurally similar to ECH (TXR 0057357). The requirement for a developmental rabbit toxicity study was recently evaluated by HASPOC per current toxicology practices taking into consideration the use of open literature studies and appropriateness of intravenous (iv) data. Based on a WOE approach, considering all the available

hazard and exposure data for ECH, the HASPOC recommended that rabbit and rodent developmental toxicity studies be waived at this time (TXR # 0058035, J. Leonard, 05/14/2020). Available toxicity studies on ECH, including those bridged with PCH, are summarized in the toxicity profile table in Appendix A.

6.1.2 Oral Toxicity of Ethylene Chlorohydrin (ECH)

The limited, published acute toxicity studies indicate that ECH is toxic both by oral (Category II) and dermal (Category I and II, respectively) routes, and is toxic by the inhalation route of exposure in some species (Category II in rats and mice and Category IV in guinea pigs). Limited evidence suggests that ECH could produce marked eye and dermal irritation in rabbits. Dermal sensitization effects were not identified for ECH.

Results of the guideline two-generation reproductive toxicity study in rats (conducted by the dietary route of exposure) revealed the following parental, offspring and reproductive effects: the parental LOAEL in males is 160.6 mg/kg/day based on decreased body weights, increased liver weight, and decreased spleen, kidney, and adrenal gland weights (NOAEL = 82.4 mg/kg/day [males]); the parental LOAEL in females is 209.6 mg/kg/day based on decreased body weights, clinical signs and decreased ovary, uterus/cervix/oviduct, adrenal gland, pituitary, spleen and kidney weights, increased liver weight, and atrophy of the uterus, vagina and cervix (NOAEL = 95.8 mg/kg/day [females]); the offspring LOAEL is 160.6 mg/kg bw/day (males)/209.6 mg/g/day (females) based on decreased bodyweight, decreased spleen and thymus weights, and increased incidence of runts (NOAEL = 82.4/95.8 mg/kg/day M/F); the reproductive LOAEL is 209.6 mg/kg bw/day based on a decrease in the total number of follicular counts, decreased ovary/uterus/cervix/oviduct weights, and delayed sexual maturation (NOAEL = 95.8 mg/kg/day).

There is no guideline combined chronic toxicity/carcinogenicity study on ECH available in rodents via the oral route of exposure. Results of NTP 2-year dermal studies with ECH revealed no evidence of toxicity or carcinogenicity in rats and mice following dermal exposures (NTP 1985). For PCH, a structurally similar chemical to ECH and differing only by an additional methyl group, there was no evidence of chronic toxicity or carcinogenicity in rats or mice exposed in the drinking water for 2 years (NTP 1998) at the highest dose tested for mice: 150 mg/kg/day (males), 210 mg/kg/day (females) for the first several months and 100 mg/kg/day for both sexes for remainder of the study; and for rats: 65 mg/kg/day (males/females) during the first several months and 34 mg/kg/day for both sexes for the remainder of the study.

Several studies indicate that ECH is a weak base pair substitution mutagen in bacteria and the mutagenicity in bacteria is enhanced in the presence of rat liver S9 extract (NTP 1985). ECH tested negative in the mutagenicity tests using mammalian cell cultures (*in vitro*) or rodents (*in vivo*). However, in one test, ECH induced DNA repair in human fibroblasts *in vitro* (NTP 1985). ECH tested negative for dominant-lethal mutations or heritable translocations in mouse (NTP 1985). Based on a weight-of-evidence (WOE) approach, the Hazard and Science Policy Council (HASPOC) recommended that oral chronic/carcinogenicity studies in rats and mice be waived based on the decision that it is appropriate to bridge available data from an NTP study (NTP TR 477, 1998) on propylene chlorohydrin (PCH), which is a chemical structurally similar to ECH (TXR 0057357). The NTP study on PCH indicated no evidence of carcinogenicity in rats or mice.

Limited evidence suggests that ethylene chlorohydrin is rapidly absorbed in rats and majority of the administered radioactivity (77-80%) was eliminated in urine within 24 hours of ingestion (Grunow and Altmann, 1982, as cited in NTP, 1985). About 90% of the radioactivity in the urine was in the form of thiodiacetic acid and thionyldiacetic acid. Less than 5% of the administered radioactivity in total is excreted in feces and in expired air. Peak levels of radioactivity were found in blood 1 hour after administration and the radioactivity was reduced to 50% after approximately 4 hours (Grunow and Altmann, 1982, as cited in NTP, 1985).

6.1.3 Toxicity Endpoint and Point of Departure Selections for ECH

Table 3 summarizes the toxicological doses and endpoints selected for dietary risk assessments for ECH.

Acute dietary (all populations): No toxicological endpoint attributable to a single oral dose was identified in the available toxicology studies with ECH that would be applicable to females (13-50 years old) or to the general population (including infants and children). An acute endpoint was previously selected for this subpopulation based on a NOAEL (82.4 mg/kg/day) from a published developmental study in mice (Courtney et al. 1982). This published study was re-evaluated during Registration Review and found to be unacceptable due to a number of deficiencies (e.g., excessive mortality at high dose, insufficient number of pregnant mice, no information on stability and concentration analyses, limited fetal examinations, lack of individual animal data) (TXR # 0058035, J. Leonard, 05/14/2020).

Chronic dietary (all populations): The two-generation reproduction study in rats (MRID 48794601) was selected to evaluate chronic dietary exposures with a POD of 82.4 mg/kg/day (parental/offspring NOAEL in males). The parental LOAEL is 160.6 mg/kg bw/day (males) based on decreased body weights, increased liver weight and decreased spleen, kidney weights, and adrenal gland weights. The offspring LOAEL is 160.6 mg/kg bw/day (males) based on decreased bodyweight (F1 and F2 generation), decreased spleen and thymus weights, and increased incidence of runts (F1 and F2 generation). The chronic population-adjusted dose (cPAD) of 0.824 mg/kg/day is based on the NOAEL of 82.4 mg/kg/day divided by 100-fold (10X for interspecies extrapolation, 10X for intraspecies extrapolation, and 1X for FQPA SF).

Based on the lack of postnatal qualitative or quantitative susceptibility in the two-generation reproduction study in the rat, the HASPOC recommended that a developmental rabbit or rodent toxicity study be waived. The chronic POD from a dietary two-generation reproductive toxicity study is conservative and protective of potential developmental effects. Therefore, the FQPA factor is reduced to 1X.

A chronic dietary endpoint was previously selected from a NOAEL (45 mg/kg/day) identified in a published developmental study in rats (Oser et al. 1975). This published study was re-evaluated during Registration Review and found to be unacceptable due to a number of deficiencies (e.g., purity of test material not reported, lack of individual animal data, data on effects not summarized, number of animals per group not specified) (TXR # 0057357, S. Gallagher, 06/16/2016).

Table 3. Toxicological Doses and Endpoints for Dietary Exposures for Ethylene Chlorohydrin

Exposure Scenario	Point of Departure (POD)	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary – (General Population, including Infants and Children)	An endpoint was not identified as acute effects of concern for this exposure scenario were not observed in the database			
Chronic Dietary (All populations)	Parental/offspring NOAEL = 82.4 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.824 mg/kg/day cPAD = 0.824 mg/kg/day	**Two-generation Reproductive Toxicity Study (Rats) -** MRID 48794601 The parental LOAEL is 160.6 mg/kg/day (males) based on decreased body weights, increased liver weight and decreased spleen, kidney weights, and adrenal gland weights. The offspring LOAEL is 160.6 mg/kg/day (males) based on decreased bodyweight (F1 and F2 generation), decreased spleen and thymus weights, and increased incidence of runts (F1 and F2 generation
Cancer	No evidence of carcinogenic potential. A cancer assessment is not required.			

6.2 Ethylene Glycol (EG)

6.2.1 Available Toxicology Studies for EG

Ethylene glycol (EG) is a reaction product of EtO. There are no guideline studies available in the database for EG. Since EG is a degradate/reaction product and not an active ingredient (ai), there are no specific data requirements for EG. However, there are a number of published literature studies which have provided sufficient information to characterize the toxicity of EG. These include oral subchronic toxicity studies, developmental and reproductive toxicity studies, chronic toxicity and carcinogenicity studies, and mutagenicity studies. The results of these studies indicate toxicity via the oral route only at doses that are at, or near, the limit doses, and no carcinogenic potential. Available toxicity studies on EG are summarized in the toxicity profile table in Appendix A.

6.2.2 Toxicological Profile for EG

The results of the published toxicity studies in rats and mice demonstrated kidney toxicity at the limit dose in rats. Renal effects were noted primarily in male rats and included histological lesions (tubular cell hyperplasia, tubular dilation, peritubular nephritis, hydronephrosis), increased water consumption, alterations in urinary parameters (reduced specific gravity and pH, increased urine volume), and increased creatinine and blood urea nitrogen levels, at 1,000 mg/kg/day. Both males and females exhibited calcium oxalate crystals in the urine and increased kidney weights at the limit dose. There was also mortality at the limit dose in males only. No effects were observed in male or female rats administered dose levels of 40 and 200 mg/kg/day. No toxicity was observed in mice at any dose. There is confidence in this study since it included a large number of animals (30/sex) for examination, and thorough measurements of many parameters at several intervals of the study in both rats and mice.

Several published literature studies indicate that EG may cause developmental toxicity (skeletal and external malformations) in rodents. However, these effects were noted at doses near or at the limit dose. Since the developmental effects are seen at high doses, there is a very low degree of concern.

Published studies on mutagenicity tests in bacteria and mammalian cells were consistently negative. The chromosomal aberrations tests in Chinese hamster ovary cells and DNA damage in rat hepatocytes were also negative. The *in vivo* genotoxicity tests are also negative for dominant lethal mutations in rats and chromosomal aberrations of bone marrow cells in mice exposed to EG.

No evidence of carcinogenicity was reported in the published chronic carcinogenicity studies on EG in rodents. Ethylene glycol is not likely to be carcinogenic to humans.

The toxicity of EG (renal effects) is different than ECH (body weight and organ weight changes, histology in the females), and noted at doses at or near the limit dose. For ECH, toxicity was noted at much lower doses than those in the EG toxicity studies. Thus, it would not be appropriate to add EG residues to the ECH dietary assessment due to the toxicity profile of EG (toxicity at or near the limit dose).

6.3 Ethylene Oxide (EtO)

6.3.1 Available Inhalation Toxicology Studies for EtO

Toxicology studies for EtO cited in this risk assessment were conducted by the inhalation route, and consist of subchronic, developmental, reproductive, chronic toxicity, and carcinogenicity studies. These studies are listed in the 2007 risk assessment for EtO by the Health Effects Division, OPP (D338729).

6.3.2 Toxicity Endpoint and Point of Departure Selections for Non-Cancer Effects

The inhalation exposure duration for populations potentially exposed to EtO, including occupational/workers and those living in the vicinity of contract sterilizers (i.e., bystanders) include short-, intermediate-, and long-term exposure durations. The non-cancer inhalation endpoints for

these exposure durations are available in the revised risk assessment for the RED (D338729) and have not been revised. Although OPP is no longer using the body weight gains, the point of departure is also based on the reproductive toxicity effects observed at the same LOAEC/NOAEC concentrations. The inhalation endpoints are also shown below in Table 4. For purposes of this assessment, the more relevant long-term exposure duration (i.e., all populations are exposed for the long-term duration, it is the more conservative POD, and exposure data are not available at this time to delineate individual's exposure on a ST/IT versus LT duration) for non-cancer inhalation exposure to EtO has been assessed using data from a two-generation reproduction study in rats (MRID 42788101). In this study, rats were exposed (whole body) by inhalation to EtO at concentrations for 6 hours /day (5 days/week) during pre-mating and 7 days/week during mating, on gestational days (GDs) 0-20, and on lactational days (LDs 5-28). The systemic LOAEC was determined as 33 ppm based on decreased mean body weight gains in F0 males and females and F1 males during premating period. The NOAEC was established as 10 ppm (presented below in Table 4).

Additionally, reproductive toxicity was observed at 33 and 100 ppm. It was manifested as a decreased number of live pups per litter in both generations ($p \leq 0.01$) due to significantly increased post-implantation loss at 33 ppm (two-fold increase) and 100 ppm (six-fold increase) in F1 offspring and at 100 ppm in F2 offspring (four-fold increase). In addition, at 33 and 100 ppm, mean pup body weight gains were decreased significantly ($p \leq 0.05$ or $p \leq 0.01$) in both F1 and F2 generations during the latter part of lactation, i.e., LD 21.

Based on increased post-implantation loss (two-fold) and decreased live pups per litter in F0 generation, the reproductive NOAEC and LOAEC were determined as 10 and 33 ppm, respectively. Based on decreased mean pup body weight gain in both generations, the offspring NOAEC and LOAEC were determined as 10 and 33 ppm, respectively.

Table 4. Non-Cancer Inhalation Toxicological Doses and Endpoints for EtO

Exposure Scenario	Dose Used in Risk Assessment	Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Inhalation Short-Term (1 - 30 days) and Intermediate-Term (1- 6 months)	Occupational Exposure NOAEC= 50 ppm (HEC = 37.5 ppm or 68 mg/m^3 after being adjusted for occupational exposure duration) Bystander Exposure NOAEC = 50 ppm (HEC = 8.9 ppm or 16 mg/m^3 after being adjusted for continuous exposure duration)	Occupational and Bystander LOC = 30 UF_A = 3x UF_H = 10x	Subchronic Inhalation Toxicity Study in Mice (Snellings et al., 1984a) LOAEC = 100 ppm based on neurological effects (altered gait, decreased motor activity, and abnormal righting reflex) and absolute and relative spleen weight decreases in females

Exposure Scenario	Dose Used in Risk Assessment	Level of Concern (LOC) for Risk Assessment	Study and Toxicological Effects
Inhalation Long-Term (> 6 months)	Occupational Exposure NOAEC= 10 ppm (HEC = 7.5 ppm or 13.5 mg/m^3 after being adjusted for occupational exposure duration) Bystander Exposure NOAEC = 10 ppm (HEC = 1.79 ppm or 3.2 mg/m^3 after being adjusted for continuous exposure duration)	Occupational and Bystander LOC =30 UF_A = 3x UF_H = 10x	Two Generation Reproduction Study, Inhalation Exposure, Rats (MRID 42788101) Systemic LOAEC = 33 ppm based on decreased mean body weight gains in F0 males and females and F1 males during premating period. Reproductive LOAEC = 33 ppm based on increased post implantation loss (two-fold) and decreased live pups per litter in F0 generation were observed. Offspring LOAEC = 33 ppm based on decreased mean pup body weight gain in both F0 and F1 generations.

UF_A = interspecies extrapolation factor; UF_H = intraspecies variation factor; NOAEC = no observed adverse effect concentration; LOAEC = lowest observed adverse effect concentration

Study NOAEC are adjusted to human equivalent concentrations (HECs) for occupational scenario (i.e., animal NOAEC of 10 ppm (6h/day, 5d/7d in week) is adjusted to human NOAEC of 7.5 ppm (8 h/day, 5d/7d in week), assuming the regional gas dose ratio (RGDR) is similar between animals and humans (10 ppm x 6h/8h =7.5 ppm); For continuous exposures such as bystanders (e.g. RfC), rat NOAEC of 10 ppm would be converted to HEC of 1.79 ppm [10 ppm x (6h/24h) x (5days in week/7days in week) =1.79 ppm] assuming similar RGDR between animals and humans (USEPA,1994); similar HEC calculations conducted for NOAEC of 50 ppm for ST/IT durations.

The air concentration in terms of ppm was converted to mg/m^3 using the following equation: air conc. mg/m^3 = (44.06 (EtO MW) / 24.45) x air conc. ppm. This yields a conversion factor of 1.8 mg/m^3 per ppm.

6.3.3 Cancer Inhalation Evaluation of EtO

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.

In the 14th Annual Report on Carcinogens (https://ntp.niehs.nih.gov/go/roc14), EtO is stated as "known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological studies and studies on mechanisms of carcinogenesis." Further, "An increased risk of cancer has been demonstrated in epidemiological studies of workers using ethylene oxide as a sterilant for medical devices and spices and in chemical synthesis and production. Evidence for a common mechanism of carcinogenesis in humans and experimental animals comes from studies that have found similar genetic damage in cells of animals and workers exposed to ethylene oxide. The DNA-damaging activity of ethylene oxide explains its effectiveness as a sterilant, and this same property accounts for its carcinogenic risk to humans."

In the 2016 evaluation of EtO inhalation carcinogenicity by USEPA/ORD/IRIS (USEPA 2016, page 1-1) it was stated that, "*Although the evidence of carcinogenicity from human studies was deemed*

short of conclusive on its own, EtO is characterized as "carcinogenic to humans" by the inhalation route of exposure based on the total weight of evidence, in accordance with the U.S. Environmental Protection Agency's (EPA's) 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a). The lines of evidence supporting this characterization include: (1) strong, but less than conclusive on its own, epidemiological evidence of lymphohematopoietic cancers and breast cancer in EtO-exposed workers, (2) extensive evidence of carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure, (3) clear evidence that EtO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EtO carcinogenicity, and (4) strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage in humans exposed to EtO."

In this draft risk assessment, EPA/OPP is presenting the differing approaches and perspectives on characterization of EtO as a carcinogen. In addition to the 2016 NTP and IRIS characterizations as summarized above, the 2008 EPA RED, the 2016 USEPA/ORD/IRIS evaluation 2019 memorandum discussing IRIS (that includes the sensitivity of EtO risk estimates to dose-response model selection), the 2020 TCEQ decision support document, and the 2020 EOTF analysis (MRID 51258401) are also presented. Conclusions regarding both lymphohematopoietic and breast cancer incidence and mortality associated with inhalation exposures to EtO are summarized from each document. It is noted where there is general agreement on association of EtO inhalation exposure with increased cancer incidence (such as lymphohematopoietic cancers), and where there are differing perspectives (such as the significance of EtO inhalation exposure associated with increased breast cancer incidence and mortality).

6.3.3.1 Summary of Laboratory Animal Carcinogenicity Data

In the 2008 EtO RED, it was recommended that a range of unit risk estimates for continuous exposures (24-hrs/day, 7 days/week) ranging from 2.22 E-02 $(mg/m^3)^{-1}$ to 2.67 E-03 $(mg/m^3)^{-1}$ be considered for carcinogenicity risk assessment purposes, based on lung adenomas/carcinomas in male B6C3F1 mice at the high end and brain tumors in male F344 rats at the low end. These unit risk values were taken from the 2006 IRIS evaluation of EtO carcinogenicity and reviewed by the agency's Science Advisory Board (USEPA, 2007). Unit risks for tumors were calculated from studies conducted by the National Toxicology Program (NTP, 1987), Lynch et al. (1984), and Snellings (1984). Unit risks were again published in the 2016 IRIS assessment of carcinogenicity, including a study by Garman (1985) which reported increased incidence of brain tumors in rats. Tables 5, 6, and 7 provide the IUR estimates for mice and rats from the 2016 IRIS assessment (USEPA 2016).

Table 5. Tumor incidence data in B6C3F1 mice (NTP 1987)[a] and exposure-response modeling[b]

Gender/tumor type	EtO Concentration (Continuous Exposure[c])			EC10 (LEC_{10})[d], (mg/m^3)	Unit risk ($0.1/LEC_{10}$) (per mg/m^3)
	0 ppm	50 ppm (16.3 mg/m^3)	100 ppm (32.7 mg/m^3)		
Males					
Lung adenomas plus carcinomas	11/49	19/49	26/49[e]	6.94 (4.51)	2.22×10^{-2}

Females					
Lung adenomas plus carcinomas	2/44	5/44	22/49[f]	14.8 (9.12)	1.1×10^{-2}
Malignant lymphoma	9/44	6/44	22/49[g]	21.1 (13.9)	7.18×10^{-3}
Uterine carcinoma	0/44	1/44	5/49[h]	32.8 (23.1)	4.33×10^{-3}
Mammary carcinoma[i]	1/44	8/44[g]	6/49	9.69 (5.35)	1.87×10^{-2}

[a]Incidence data were adjusted by the EPA by eliminating the animals that died prior to the occurrence of the first tumor or prior to 52 wk, whichever was earlier. 1 ppm = 1.83 mg/m^3.
[b]Statistical analyses and exposure-response modeling were conducted by the EPA (USEPA, 2016).
[c]Adjusted by the EPA to continuous exposure (24 hr/day, 7 day/wk) from experimental exposure conditions of 6 hr/d, 5 d/wk;
[d]Calculated by the EPA using Tox_Risk program.
[e]$p < 0.01$ (pairwise Fisher's exact test).
[f]$p < 0.001$ (pairwise Fisher's exact test).
[g]$p < 0.05$ (pairwise Fisher's exact test).
[h]$p = 0.058$ by pairwise Fisher's exact test compared to concurrent controls; however, uterine carcinomas are rare tumors in female B6C3F$_1$ mice, and $p < 0.0001$ by pairwise Fisher's exact test compared to the NTP historical control incidence of 1/1,077 for inhalation (air) female B6C3F$_1$ mice fed the NIH-07 diet.
[i]Highest dose was deleted in order to fit a model to the dose-response data.
EC_{10} = effective concentration (modeled) corresponding to a 10% extra risk of tumor incidence; LEC_{10} = lower 95% (one-sided) confidence limit on the EC_{10}.

Table 6. Tumor incidence data in Lynch et al. (1984) study of male F344 rats and exposure-response modeling results

Tumor type	EtO Concentration (continuous exposure)[a]			EC_{10} (LEC_{10})[b] (mg/m^3)	Unit risk (0.1/LEC_{10}) (per mg/m^3)
	0 ppm	50 ppm (19.1 mg/m^3)	100 ppm (38.1 mg/m^3)		
Splenic mononuclear cell leukemia[c]	24/77	38/79[d]	30/76	7.11 (3.94)	2.54×10^{-2}
Testicular peritoneal mesothelioma	3/78	9/79	21/79[e]	16.7 (11.8)	8.5×10^{-3}
Brain mixed-cell glioma	0/76	2/77	5/79[e]	65.7 (37.4)	2.68×10^{-3}

[a]Adjusted by the EPA to continuous exposure from experimental exposure conditions of 7 hr/d, 5 d/wk; 1 ppm = 1.83 mg/m^3.
[b]Calculated by the EPA using Tox_Risk program.
[c]Highest dose deleted while fitting the dose-response data.
[d]$p < 0.05$ (pairwise Fisher's exact test).
[e]$p < 0.01$ (pairwise Fisher's exact test).
EC_{10} = effective concentration (modeled) corresponding to a 10% extra risk of tumor incidence; LEC_{10} = lower 95% (one-sided) confidence limit on the EC_{10}.

Table 7. Tumor incidence data in Snellings et al. (1984) and Garman et al. (1985) reports on F344 rats[a] and exposure-response modeling results[b]

Gender/tumor type	EtO Concentration (continuous exposure)[c]				EC_{10} (LEC_{10})[e] (mg/m^3)	Unit risk ($0.1/LEC_{10}$) per mg/m^3
	0 ppm[d]	10 ppm (3.27 mg/m^3)	33 ppm (10.8 mg/m^3)	100 ppm (32.7 mg/m^3)		
Males						
Splenic mononuclear cell leukemia	13/97 (13%)[f]	9/51 (18%)	12/39[g] (32%)	9/30[g] (30%)	12.3 (6.43)	1.56×10^{-2}
Testicular peritoneal mesothelioma	2/97 (2.1%)	2/51 (3.9%)	4/39 (10%)	4/30[g] (13%)	22.3 (11.6)	8.66×10^{-3}
Primary brain tumors	1/181 (0.55%)	1/92 (1.1%)	5/85[g] (5.9%)	7/87[h] (8.1%)	36.1 (22.3)	4.5×10^{-3}
Females						
Splenic mononuclear cell leukemia	11/116 (9.5%)	11/54[g] (21%)	14/48[h] (30%)	15/26[i] (58%)	4.46 (3.1)	3.23×10^{-2}
Primary brain tumors	1/188 (0.53%)	1/94 (1.1%)	3/92 (3.3%)	4/80[g] (5%)	63.8 (32.6)	3.07×10^{-3}

[a]Denominators refer to the number of animals for which histopathological diagnosis was performed. For brain tumors, Garman et al. (1985) included animals in the 18-month and the 24-month sacrifice and found dead or euthanized moribund of those alive at the time of the first brain tumor, whereas for the other sites, Snellings et al. (1984) included animals only at the 24-month sacrifice.

[b]Statistical analyses and exposure-response modeling were conducted by the EPA.

[c]Adjusted by the EPA to continuous exposure from experimental exposure conditions of 6 hr/d, 5 d/wk; 1 ppm = 1.83 mg/m^3.

[d]Results for both control groups combined.

[e]Calculated by the EPA using Tox_Risk program.

[f]Numbers in parentheses indicate percentage incidence values.

[g]$p < 0.05$ (pairwise Fisher's exact test). [h]$p < 0.01$ (pairwise Fisher's exact test). [i]$p < 0.001$ (pairwise Fisher's exact test).
EC_{10} = effective concentration (modeled) corresponding to a 10% extra risk of tumor incidence; LEC_{10} = lower 95% (one-sided) confidence limit on the EC_{10}.

6.3.3.2 Cancer Inhalation Evaluations Using Epidemiology Studies

Since publication of the RED, the carcinogenicity of EtO has been reviewed by the EPA's IRIS program based on human epidemiology data and published in 2016 (USEPA 2016). In 2019, IRIS released a memorandum that discussed the dose-response models that were considered in the 2016 IRIS assessment. The memorandum compared the various models that were considered for lymphoid and breast cancer in addition to the two-piece linear spline model that was selected to derive an inhalation unit risk in the 2016 assessment. Both the TCEQ and EOTF submission by Exponent also evaluated the same epidemiology studies but did not determine sufficient evidence for breast cancer. A letter peer review of the draft TCEQ development support document (DSD) was completed in April 2020. The EOTF submission by Exponent was not peer reviewed. With the exception of the 2008 RED, where characterization of EtO carcinogenicity was based on animal data, the other evaluations were based on the same NIOSH occupational cohort data. Therefore, a brief summary of the cohort data is presented below.

6.3.3.2.1 Brief Summary of the Steenland et al. (2004) study

A summary of the Steenland et al. (2004) study is presented below, taken from the 2016 IRIS assessment and edited for brevity. NIOSH conducted an industry-wide study of 18,254 workers (45% male and 55% female) in 14 plants where EtO was used (Steenland et al., 2004; Stayner et al., 1993; Steenland et al., 1991). Most of the workers were exposed while sterilizing medical supplies and treating spices, and in the manufacture and testing of medical sterilizers. Individual exposure estimates were derived for workers from 13 of the 14 plants. The procedures for selecting the facilities and defining the cohort are described in Steenland et al. (1991), and the exposure model and verification procedures are described in Greife et al. (1988) and Hornung et al. (1994). Briefly, a regression model was developed to allow estimation of exposure levels for time periods, facilities, and operations for which industrial hygiene data were unavailable. The data for the model consisted of 2,700 individual time-weighted exposure values for workers' personal breathing zones, acquired from 18 facilities between 1976 and 1985. The data were divided into two sets, one for developing the regression model and the second for testing it. Seven out of 23 independent variables tested for inclusion in the regression model were found to be significant predictors of EtO exposure and were included in the final model. (See Appendix A, Section A.2.8, of the IRIS assessment for more details on the NIOSH exposure assessment and its evaluation) Results of the original follow-up study through 1987 are presented in Steenland et al. (1991) and Stayner et al. (1993). The cohort averaged 26.8 years of follow-up in the extended follow-up study through 1998, and 16% of the cohort had died (Steenland et al., 2004).

The overall standard mortality ratio (SMR) for cancer was 0.98, based on 860 deaths (Steenland et al., 2004). The SMR for (lympho) hematopoietic cancer was 1.00, based on 79 cases. Exposure-response analyses, however, revealed exposure-related increases in hematopoietic cancer mortality risk, although when analyzed by sex, the effect was primarily in males. In categorical life-table analysis, men with >13,500 ppm-days of cumulative exposure had an SMR of 1.46 (Obs = 13). In internal Cox regression analyses (i.e., analyses in which the referent population is within the cohort) with exposure as a continuous variable, statistically significant trends in males for all hematopoietic cancer ($p = 0.02$) and for "lymphoid" cancers (NHL, lymphocytic leukemia, and myeloma; $p = 0.02$) were observed using log cumulative exposure.

In internal categorical analyses, statistically significant odds ratios (ORs) were observed in the highest cumulative exposure quartile (with a 15-year lag) in males for all hematopoietic cancer (OR = 3.42; 95% CI = 1.09−10.73) and "lymphoid" cancer (OR = 3.76; 95% CI = 1.03−13.64). The exposure metrics of duration of exposure, average concentration, and maximum (8-hour TWA) concentration did not predict the hematopoietic cancer results as well as did the cumulative exposure metric.

Although the overall SMR for female breast cancer was 0.99, based on 102 deaths, the NIOSH mortality follow-up study reported a significant excess of breast cancer mortality in the highest cumulative exposure quartile using a 20-year lag period compared to the U.S. population (SMR = 2.07; 95% CI = 1.10−3.54; Obs = 13). Internal exposure-response analyses also noted a significant positive trend for breast cancer mortality using the log of cumulative exposure and a 20-year lag time ($p = 0.01$). In internal categorical analyses, a statistically significant OR for breast cancer

mortality was observed in the highest cumulative exposure quartile with a 20-year lag (OR = 3.13; 95% CI = 1.42−6.92).

6.3.3.2.2 IRIS 2016 Assessment

In the 2016 IRIS characterization, inhalation unit risk (IUR) estimates associated with 1% extra risk for excess lymphoid cancer mortality using a life-table analysis and the lower spline segment from a two-piece linear spline model were developed for evaluating the potential cancer risks posed by inhalation exposure to EtO. The IRIS evaluation was developed over a 10-year period with two rounds of peer review by the agency's Science Advisory Board (SAB), once in 2007 and again in 2014. The reader is referred to both of the SAB reviews and the 2016 IRIS EtO evaluation for an in-depth assessment of the SAB comments and response by IRIS. The 2007 SAB review is located at: https://yosemite.epa.gov/sab/sabproduct.nsf/fedrgstr_activites/Eto%20Inhalation%20Carcinogenicity?OpenDocument and the 2014 SAB review is located at: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=282012.

According to the IRIS evaluation (2016, page 2-2), "*An external review draft of this carcinogenicity assessment (U.S. EPA, 2006a) was peer reviewed by a panel of the EPA's Science Advisory Board (SAB) in 2007 (SAB, 2007). See Appendix H for a summary and the EPA's disposition of SAB and public comments on the 2006 external review draft. In response to comments from that SAB review, the EPA conducted extensive new exposure-response modeling of certain epidemiologic data. In addition, the EPA updated the assessment to reflect new literature through May 2013 (see Appendix J). In July 2013, the EPA released a revised draft for public comment (U.S. EPA, 2013a, b), and that draft assessment was discussed at the EPA's December 2013 IRIS Bimonthly Public Meeting. Appendix K contains the EPA's responses to the public comments that were received on the July 2013 draft. A further revised external review draft (U.S. EPA, 2014a, b) was reviewed by another panel of the SAB in 2014−2015 (SAB, 2015), primarily to receive comments on the expanded exposure-response modeling of the epidemiologic data. See Appendix I for the EPA's disposition of SAB comments on the 2014 draft. Finally, the EPA has further updated the assessment to reflect new literature through July 2016; this new literature did not substantively impact the conclusions of the assessment (see Appendix J).*"

The unit risk estimates for cancer mortality and incidence were based on the human data from the Steenland et al. (2004) study. IUR estimates for EtO were calculated under the assumption that relative risk is independent of age, as well as under the assumption of increased early-life susceptibility. The latter assumption is the basis for the ultimate estimates proposed in the IRIS assessment. IUR estimates based on results of animal carcinogenicity testing were also calculated. The calculated IUR estimates are shown in Table 8.

Breast cancer incidence risk estimates were calculated directly from the data from a breast cancer incidence study of the same occupational cohort (Steenland et al., 2003). Using the same life-table approach, the lower spline segment from a two-piece linear spline model, and linear low-dose extrapolation, a unit risk estimate of 8.1×10^{-4} per $\mu g/m^3$ (1.5×10^{-3} per ppb) was obtained for breast cancer incidence. A unit risk estimate for breast cancer mortality was also calculated from the cohort mortality data; however, the incidence estimate is preferred over the mortality estimate.

Combining the incidence risk estimates for the two cancer types resulted in a total cancer unit risk estimate of 3.3×10^{-3} per $\mu g/m^3$ (6.1×10^{-3} per ppb).

Because the weight of evidence supports a mutagenic mode of action for EtO carcinogenicity, and as there are no chemical-specific data from which to assess early-life susceptibility, increased early-life susceptibility was assumed, according to the EPA's Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (U.S. EPA, 2005b). With application of the age-dependent adjustment factor (ADAF), which would be applied when assessing risks to general populations, the total cancer unit risk estimate is 5×10^{-3} per $\mu g/m^3$.

In addition, as noted in the IRIS characterization, IUR risk estimates were developed for environmental exposure levels up to about 40 $\mu g/m^3$ [22 ppb]. The IUR risk estimates are not applicable to higher level exposures, such as those that may occur occupationally, which appear to have a different exposure-response relationship as noted in Table 8 below.

Table 8. IRIS Evaluation of Continuous EtO Concentrations for Inhalation Unit Risks.

Source	Cancer Type	Inhalation Unit Risk (IUR)		Comment
		$(\mu g/m^3)^{-1}$	$(ppm)^{-1}$	
EPA/IRIS (2016)[a]	Lymphoid (human F/M)	2.6E-3	4.76	Source: Table 1-1 USEPA (2016b)
	Breast (human F)	7E-4	1.28	
	Total (human F)	3E-3	5.49	[a]These unit risk estimates are not intended for use with continuous lifetime exposure levels above 40 $\mu g/m^3$ (22 ppb or 0.022 ppm).

To convert unit risk estimates to $(ppm)^{-1}$, multiply the $(\mu g/m^3)^{-1}$ estimates by 1,830 $(\mu g/m^3)$/ppm;
To convert air concentrations from ppb to $\mu g/m^3$ divide ppb by 1.83 ug/m^3 /ppb (i.e. 1 ppb = 1.83 ug/m^3)
[a]These (upper-bound) unit risk estimates are intended for use in age dependent adjustment factor (ADAF) calculations and less-than-lifetime adult exposure scenarios (U.S. EPA, 2005b). Note that these are not the same as the unit risk estimates derived directly from the human data in Section 4.1 of the IRIS report (USEPA 2016) under the assumption that relative rate (i.e., rate ratio), or more generally, relative risk (RRs) are independent of age. See Section 4.4 of the IRIS report (USEPA 2016) for the derivation of the adult-based unit risk estimates.

According to IRIS (2016, page 4-99), "*The unit risk estimates derived in the preceding sections were developed for environmental exposure levels, where maximum modeled levels are on the order of 1−2 μg/m³ … i.e., roughly 0.5−1 ppb, and are not applicable to higher exposures, including some occupational exposure levels. …The occupational exposure scenarios of interest to the EPA include …exposure levels in the nonlinear range of some of the models (i.e., above the maximum exposure level at which the low-dose-linear unit risk estimates apply). Therefore, extra risk estimates were calculated for a number of occupational exposure scenarios of possible concern. Extra risk estimates are estimates of the extra cancer risk above background and are the same type of estimate that one gets from multiplying a unit risk estimate by an exposure level*."

The extra cancer risk estimates presented by IRIS for total cancer (lymphoid and breast cancers) are shown in Table 9. The EtO air concentrations used to illustrate the cancer risks range from 0.1 ppm to a maximum of 1.0 ppm, which is the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL).

Table 9. IRIS Extra Risk Est. for Total Cancer Incidence for Occupational Exposure Levels

8-hour TWA (ppm)	Maximum likelihood [risk] estimate[a,b]	Upper-bound [risk] estimate[a,b]
0.1	0.037	0.081
0.2	0.058	0.13
0.3	0.072	0.15
0.4	0.085	0.18
0.5	0.094	0.19
0.6	0.10	0.20
0.7	0.10	0.21
0.8	0.11	0.21
0.9	0.11	0.21
1.0	0.11	0.22

[a]Assuming a 35-yr exposure between ages 20 and 55 years.
[b]From combining results for lymphoid cancer incidence in both sexes and breast cancer incidence in females.

*Source: Table 4-30 of EPA/635/R-16/350Fa, December 2016 (USEPA 2016).

6.3.3.2.3 IRIS 2019 Memorandum: IRIS EtO Assessment - Modeling Comparisons & Assessment of Uncertainty

In October of 2019, the EPA ORD's Center for Public Health and Environmental Assessment (CPHEA) published a memo with the subject heading, "*Sensitivity of ethylene oxide risk estimates to dose-response model selection*" in response to an inquiry from OAR about dose-response selection for the 2016 IRIS EtO inhalation unit risk estimate (USEPA, 2019). Note: the IRIS 2019 alternative model discussions do not change IRIS's original IUR recommendations presented in the IRIS 2016 evaluation. The memo utilized recommendations of the SAB to review multiple modeling results presented in the 2016 IRIS assessment in order to identify reasonable dose-response modeling approaches compared to the selected two-piece linear spline model used in the 2016 IRIS assessment. According to IRIS (2019), "It is important to note that this analysis relies entirely on results and equations presented in the final EtO IRIS assessment [i.e., IRIS's 2016 assessment]."

"Alternative modeling results for female breast cancer incidence from the IRIS assessment are summarized here…" "Models using a square root of dose transformation fit the data without need for a spline modeling approach, achieved the best (lowest) AIC scores, and provided appropriate visual fit to the categorical data over the full dose range. The two square root of dose models implemented in the IRIS assessment would lead to unit risk estimates for EtO inhalation roughly 3-10 times higher than the selected two-piece spline model. However, the IRIS assessment did not prefer these models, noting that the slopes for square-root of dose models become increasingly steep at low-dose and thus unit risk estimates are dependent on the choice of the point of departure leading to an additional modeling uncertainty. The square root of dose models are supralinear in the low dose region and thus contrast with the two-piece spline models that are linear over the lower dose range of the data. Accordingly, the square root models are not suggested as desirable alternative models. The additional models fit using a log transform of dose did not fit as well as the square root models and showed a more marked pattern of low-dose supra-linearity and are also not deemed useful as candidate alternative models." (USEPA 2019, page 4)

"A linear model of risk using cumulative EtO dose was examined and provided a statistically significant global fit to the data and a roughly appropriate fit to the categorical data (the reader is referred to USEPA (2016) Figure 4-7); however, the agreement with the categorical data is poorer in the low-dose region. For the present analysis, the linear model is retained as a potentially useful, but marginally supported, alternative model." (USEPA 2019, page 4)

"The log-linear (standard Cox) cumulative dose regression model also provides a statistically significant fit to the global data set but shows notably worse agreement with the plateauing shape of the categorical rates. IRIS also provided a sensitivity analysis of behavior of the log- linear model where the data for women having the highest 5% of EtO doses are removed from the fit (the reader is referred to USEPA (2016) Appendix D, Figure D-4). The predicted breast cancer risks increase strongly when these high dose data points are removed. Additionally, further data plots for this review indicated that while the log linear model increased roughly linearly over most of the dose range, model predictions, particularly using the upper bound slope estimate, curve sharply upwards at the highest doses - a behavior not indicated by the observed data. Accordingly, this model (which would provide a unit risk estimate 13-fold lower than the recommended two-piece spline model) is not recommended as a reasonable alternative model." (USEPA, page 5)

Table 10 below summarizes the IURs associated with selected models considered in the 2016 IRIS assessment as presented in the 2019 memo. These estimates are not adjusted for ADAF factors for early life sensitivity to mutagenic carcinogens. As discussed in the USEPA (2016) assessment and the 2019 memo, these factors should be applied in estimating cancer risks involving early life exposure to EtO. For the total risk estimates based on the linear spline models used in USEPA (2016) and discussed in the 2019 memo, the ADAF adjusted full-life risk estimates are 1.5 (9.1/6.1) times higher than the unadjusted values.

Table 10. Evaluation of Inhalation Unit Risk Estimates for selected dose-response models considered in the 2016 IRIS assessment (as summarized in the 2019 Memo).

Source	Cancer Type	Inhalation Unit Risk (IUR)		Comment
		$(\mu g/m^3)^{-1}$	$(ppm)^{-1}$	
USEPA (2019)	Lymphoid (worker F/M) Log-linear spline, individual data	1.0E-3	1.9 (a)	IRIS EtO Assessment Modeling Comparisons and Assessment of Uncertainty memo (USEPA 2019)
	Lymphoid (worker F/M) Linear regression, categorical data	5.3E-4	0.97 (b)	
	Breast (worker F) Linear regression, categorical data	5.0E-4	0.91 (c)	
	Breast (worker F) Linear model, individual data	2.1E-4	0.38 (d)	
	Total (worker F)	1.3E-3	2.4 (a+c)	
	Total (worker F)	6.6E-4	1.2 (b+d)	

To convert unit risk estimates to $(ppm)^{-1}$, multiply the $(\mu g/m^3)^{-1}$ estimates by 1,830 $(\mu g/m^3)/ppm$

[e]These (upper-bound) unit risk estimates are intended for use in ADAF calculations and less-than-lifetime adult exposure scenarios (U.S. EPA, 2005b). Note that these are not the same as the unit risk estimates derived directly from the human data in USEPA (2016) Section 4.1 under the assumption that relative risks (RRs) are independent of age. See USEPA (2016) Section 4.4 for the derivation of the adult-based unit risk estimates.

6.3.3.2.4 Texas Council on Environmental Quality's (TCEQ) Cancer Inhalation Evaluation

Because EtO is emitted in Texas and has been determined to be a carcinogen, the TCEQ analyzed the NIOSH occupational cohort data (lymphoid cancer mortality) using a Cox proportional hazards model to derive a unit risk factor (URF) (equivalent to an IUR) and an effect screening level (ESL) for EtO as part of its permitting program (i.e., the ESL is used to determine limits for proposed air permits in Texas).

According to the TCEQ, the human epidemiological data available for deriving a URF are from two occupational cohorts (Union Carbide Corporation (UCC) and National Institute for Occupational Safety and Health (NIOSH)). The TCEQ based its preferred dose response estimates upon the results of the NIOSH study alone. TCEQ did not adopt the IRIS inhalation unit risk value for several reasons discussed in TCEQ 2020, and instead calculated their own unit risk value.

In summary, TCEQ indicated the following rationale on why they did not select the IRIS IUR value and instead derived their own estimate:

"The TCEQ determined that USEPA's use of an overall supra-linear dose-response model to derive their URF: 1) is not justified by the MOA data (which support a no-more-than linear dose-response); 2) is not consistent with predicted population risk from endogenous EtO for lymphoid cancer; and 3) statistically significantly over-estimates the number of lymphoid cancer deaths in the cohort from which the dose-response model was derived. Therefore, the TCEQ found that USEPA's EtO inhalation URF is not adequately supported by scientific data (consistent with Vincent et al. 2019) and the TCEQ did not adopt it for this evaluation." (TCEQ 2020, page 3)

"Supra-linear models are generally not biologically plausible and tend to grossly overestimate low-dose risks. Therefore, sufficient mechanistic or biological data are required to support the application of a supra-linear model (i.e., the steep lower-dose component) for low-dose extrapolation (TCEQ 2015). USEPA (2016) provides no solid mechanistic or biological foundation for adopting an overall supra-linear dose-response model, particularly its steep slope in the range of interest (e.g., typical environmental levels). In fact, *USEPA acknowledges the lack of mechanistic data to support the biological plausibility of a supra-linear dose-response,* stating *"the EPA is not aware of a mechanistic explanation"* and citing *"insufficient information to elucidate a basis"* (pp. I-29 and I-34 of USEPA 2016). Indeed, all the relevant considerations (e.g., MOA, normal endogenous background levels) discussed in various sections of this DSD consistently support the conclusion that there is a lack of data to adequately support the application of a supra-linear model with its steep low-dose slope to extrapolate to significantly lower (e.g., ambient air) EtO doses." (TCEQ 2020, pages 5-6)

"The TCEQ determined that the use of Cox proportional hazards models to derive a URF for inhalation EtO cancer risk: 1) is justified by the MOA data showing EtO to be a direct-acting carcinogen whose effects, particularly at doses near the endogenous range, would be buffered by cellular repair mechanisms; 2) is consistent with population background risk considering background internal EtO levels (i.e., does not overestimate population risk for lymphoid cancer mortality); and 3) accurately estimates the number of lymphoid cancer deaths in the cohort from which the dose-response model was derived. Therefore, the TCEQ's ADAF-adjusted URF for EtO has a sound

scientific basis and will be adopted for review of air concentration data and for use in air permit reviews." (TCEQ 2020, page 5)

"The knot values, *being statistically estimated / optimized based on the NIOSH data*, clearly do not conform to the USEPA SAB's notion of potentially fixing some parameters *not estimated from the data* in the interest of parsimony (see p. 12 of SAB 2015)." (TCEQ 2020, page 58). "Thus, it appears the degrees of freedom (df) were inappropriately reduced for the spline models (i.e., *df=k*, the number of additional parameters estimated for this model with zero-slope with cumulative exposure), which was not inconsequential. Among other consequences, this:

- Inappropriately decreased the p-value for adequate statistical fit, incorrectly implying that the linear two-piece spline model with a knot at 1,600 ppm x days for lymphoid cancer fit the data statistically better than other models in Table 4-6 of USEPA (2016); and
- Inappropriately decreased the Akaike Information Criterion (AIC) for the spline models, which did not allow for an appropriate comparison of model fit among models for either lymphoid cancer or breast cancer incidence." (TCEQ 2020, page 59).

Lymphoid cancer mortality was chosen by TCEQ as the critical cancer endpoint using a 15-year EtO exposure lag, with the mortality for NIOSH males being higher than for males and females combined, to calculate an ADAF-unadjusted URF of 0.0025 per ppm (1.4E-6 per $\mu g/m^3$) and an ADAF-adjusted URF (as presented in Table 11) of 0.0041 per ppm (2.3E-6 per $\mu g/m^3$). Breast cancer was not used by TCEQ as a key cancer endpoint for EtO (in contrast to IRIS) based on TCEQ's conclusion that there is insufficient evidence that EtO exposure leads to breast cancer (TCEQ 2020).

The estimates of unit risk calculated by TCEQ as shown in Table 11 are approximately three orders of magnitude lower than the estimates calculated by IRIS discussed above.

Table 11. TCEQ EtO Evaluation of Inhalation Unit Risks

Source	Cancer Type	Inhalation Unit Risk (IUR)		Comment
		$(\mu g/m^3)^{-1}$	$(ppm)^{-1}$	
TCEQ (2020)	Lymphoid (human M)	2.3E-6	0.0041	ADAF adjusted

To convert unit risk estimates to $(ppm)^{-1}$, multiply the $(\mu g/m^3)^{-1}$ estimates by 1,830 $(\mu g/m^3)$/ppm

6.3.3.2.5 Ethylene Oxide Task Force (EOTF) Submission of Exponent's Inhalation Cancer Evaluation

In 2020, the Ethylene Oxide Task Force submitted a document titled, *"Cancer Risk Estimates for Ethylene Oxide Based on Epidemiological and Biological Weight of Evidence"* (MRID 51258401). EOTF bases their analyses on the "standard [Cox proportional hazards] model" which was also examined but not preferred in the IRIS assessment and USEPA (2019) [where it is termed the log-linear model]. According to EOTF (2020, page 11), "…the main emphasis of this report is to demonstrate the superiority of the standard [Cox proportional hazards] CPH model to the supralinear 2-piece spline model based on a thorough analysis of the available epidemiological and biological evidence." Unlike IRIS 2016 and TCEQ, the EOTF 2020 has not been peer reviewed.

According to the EOTF, "The epidemiology, mode of action (MoA), and animal data for ETO support the use of the standard CPH model and do not support use of a supralinear 2-piece spline slope. For example, combining rat carcinogenicity data for ethylene and ETO together with dose-dependent DNA adduct formation provides critical MoA insight that indicates the assumption of a supralinear exposure-response is highly implausible. Despite the fact that both models do not yield statistically significant slope estimates, selection of the CPH model is preferred based on MoA considerations, which indicate that the exposure-response is no more than linear overall." (EOTF 2020, page 11)

"As a biologically-based reality check for the one-in-a-million risk-specific concentrations (1/M RSC) of 0.1 ppt estimated by IRIS and the 245 ppt estimated in this report, we evaluated endogenous levels of ETO. Our bodies produce ETO through normal metabolic processes, which can be quantitated as hemoglobin adduct N-(2-hydroxyethyl)-valine (HEV) levels that are approximately equivalent to inhaling ETO air concentrations of 1,900 ppt ± 1,300 ppt (Kirman and Hays, 2017). These HEV levels predominately reflect endogenous levels with only a small contribution from exogenous background ambient levels. The IRIS 1/M RSC of 0.1 ppt is implausible because it is not only 19,000 ppt times below the endogenous levels but is also a miniscule fraction of the inter-individual variability of endogenous ETO levels. The epidemiology and animal data for ETO further confirm that a small fractional increase is unlikely to contribute significant extra risk in endogenously exposed populations. While our proposed 1/M RSC of 245 ppt derived using the CPH model is also below endogenous levels and is well-within human variability, the value is much more scientifically plausible as a conservatively protective level for possible regulatory action." (EOTF 2020, page 12)

"As an additional reality check, the ability of the supralinear 2-piece spline and the CPH models to predict lymphoid mortalities were compared. The standard CPH model accurately predicts the observed lymphoid mortalities in the study cohort while the supralinear 2-piece spline model over predicts the number of mortalities 95% of the time (TCEQ 2019). The estimates based upon an external referent group are valid because there is no healthy worker effect (HWE) for lymphoid mortalities (Kirkeleit et al. 2013). Furthermore, benchmark dose analysis of mutagenicity data from chronic inhalation rodent studies provides converging evidence that a 1/M RSC of 245 ppt based on the CPH model is protective of cancer risks." (EOTF 2020, page 13)

The document submitted by the EOTF proposed an ADAF-adjusted IUR of 2.3×10^{-6} $(\mu g/m^3)^{-1}$ for lymphoid cancer mortality. The estimate of the ADAF unadjusted IUR is presented in Table 12 for lymphoid mortality and is identical to the TCEQ value. The IUR is approximately three orders of magnitude lower (i.e., less potent) than the estimates calculated by IRIS discussed above. The difference in the risk estimates by IRIS and the EOTF is based primarily on the use of a two-piece linear spline model by IRIS, and the use of the log-linear Cox proportions hazard model by the EOTF, using the same NIOSH epidemiological study and data set. In addition, whereas the IRIS assessment based the cancer risk on the lymphoid mortality and breast cancer incidence of the NIOSH study, the EOTF adopted TCEQ's approach and based the cancer risk on lymphoid mortality. EOTF did not include breast cancer "…due to substantial incomplete ascertainment of breast cancer incidence reported by Steenland et al. (2003)" and "also considering the Steenland et al (2004) conclusion that the evidence is only suggestive for breast cancer mortality compared to lymphoid mortality." (EOTF 2020, page 12).

Table 12. EOTF EtO Evaluation of Inhalation Unit Risks.

Source	Cancer Type	Inhalation Unit Risk (IUR)		Comment
		$(\mu g/m^3)^{-1}$	$(ppm)^{-1}$	
EOTF (2020)	Lymphoid (human M)	2.3E-6	0.0042	ADAF Adjusted

To convert unit risk estimates to $(ppm)^{-1}$, multiply the $(\mu g/m^3)^{-1}$ estimates by 1,830 $(\mu g/m^3)$/ppm

6.3.3.2.6 Summary of Cancer Inhalation Evaluations

EPA/OPP has provided a brief overview of information on the approaches (summarized in Table 13) to the cancer dose-response assessment for EtO from the 2008 RED, ORD/IRIS 2016 evaluation and their 2019 memorandum discussing sensitivity of EtO risk estimates to dose-response model selection, TCEQ (2020), and EOTF (2020). While the 2008 RED was based on animal data, the other evaluations were based on the same NIOSH occupational cohort data. The TCEQ (2020) and EOTF (2020) used similar approaches, which differed from the IRIS 2016 assessment in terms of statistical approach used, the assumptions, and the type and degree of peer review (note: EOTF 2020 has not been peer reviewed). These key differences lead to cancer values that differ by three orders of magnitude.

Approaches using human versus animal data have different strengths and associated uncertainties. For example, using the laboratory animal data requires extrapolation from animals to humans and from high to low dose. However, the laboratory animal studies are simpler to interpret as the level of exposure to EtO is well characterized. In contrast, although the epidemiology studies consider humans in occupational settings, there remains significant uncertainties in the assumptions used to estimate the exposure levels to the subjects from decades ago.

This document presents the results of the EPA IRIS assessment dose response for cancer risks based on the available epidemiological data. OPP also presents current dose response results developed by TCEQ and EOTF that utilize the same database. There are differences in the approach in these other assessments that lead to estimation of much lower risks than does the IRIS assessment. For the needs of this assessment, OPP has decided it does not need to develop a detailed evaluation of EtO quantitative risk assessment issues and OPP has not selected a single value for extrapolating risk. Instead, based on the body of qualitative and quantitative risk information provided in the present document, EPA believes that further mitigation of EtO exposure is required. The EOTF, who represent EtO registrants, submitted a mitigation proposal to OPP in February 2020. Mitigation options range from emissions abatement technologies, parameter monitoring, respiratory protective equipment, and the elimination of minor uses such as artifacts, archival materials, and library objects. Detailed mitigation will be proposed in the Proposed Interim Decision following the publication of this DRA.

Table 13. Summary of the ORD/IRIS, TCEQ, and EOTF EtO Inhalation Unit Risks.

Source	Cancer Type	Inhalation Unit Risk (IUR) ADAF-unadjusted		Comment
		$(\mu g/m^3)^{-1}$	$(ppm)^{-1}$	
EPA RED (2008)	Lung adenomas/carcinomas in mice (M)	2.22E-05	0.040	Continuous exposures (24-hrs/day, 7 days/week
	Brain tumors in rats (M)	2.67E-06	0.0048	
EPA/IRIS (2016)	Lymphoid (human F/M)	2.6E-3	4.76	Not intended for use with continuous lifetime exposure levels above 40 $\mu g/m^3$ (22 ppb or 0.022 ppm).
	Breast (human F)	7E-4	1.28	
	Total (human F)	3E-3	5.49	
USEPA (2019)	Lymphoid (worker F/M) Log-linear spline, individual data	1.0E-3	1.9 (a)	Note: The values in the IRIS 2019 memorandum were derived from the IRIS 2016 evaluation to provide alternative model comparisons as described above in Section 6.3.3.2.3; the IRIS recommended values are still based on the IRIS 2016.
	Lymphoid (worker F/M) Linear regression, categorical data	5.3E-4	0.97 (b)	
	Breast (worker F) Linear regression, categorical data	5.0E-4	0.91 (c)	
	Breast (worker F) Linear model, individual data	2.1E-4	0.38 (d)	
	Total (worker F)	1.3E-3	2.4 (a+c)	
	Total (worker F)	6.6E-4	1.2 (b+d)	
TCEQ (2020)	Lymphoid (human M)	1.4E-6	0.0025	See Table 11 for ADAF-adjusted values
EOTF (2020)	Lymphoid (human M)	1.4E-6	0.0025	See Table 12 for ADAF-adjusted values

To convert unit risk estimates to $(ppm)^{-1}$, multiply the $(\mu g/m^3)^{-1}$ estimates by 1,830 $(\mu g/m^3)$/ppm;
To convert air concentrations from ppb to $\mu g/m^3$ divide ppb by 1.83 ug/m^3 /ppb (i.e. 1 ppb = 1.83 ug/m^3)
Note: The IURs are not adjusted for ADAF factors for early life sensitivity to mutagenic carcinogens. As discussed in the USEPA (2016) assessment, these factors should be applied in estimating cancer risks involving early life exposure.

6.3.4 Occupational Exposure Limits for Ethylene Oxide (EtO)

Occupational exposure limits have been established for EtO by the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH) and the California Division of Occupational Safety and Health (Cal/OSHA). These limits are summarized in Table 14. The limits are expressed as 8-hour time weighted averages (TWAs) which represents the average exposure during an 8-hour workday or as short-term exposure limits (STELs) which represents the exposure of a 10- or 15-minute period within the workday.

The permissible exposure limits (PELs) established by OSHA and Cal/OSHA are regulatory limits. These limits can be enforced by measuring worker exposures and fines can be issued when measured

exposures exceed the PEL. The recommended exposure limits (RELs) and the Threshold Limit Values (TLVs) established by NIOSH and ACGIH are recommended limits. These limits cannot be enforced.

The OSHA PEL was established in 1984 and the OSHA STEL was established in 1988. These values were based upon health effects knowledge and sterilization process engineering knowledge that was available at that time and they represent a compromise between what is necessary to prevent adverse health effects and what is feasible in the sterilization process. The NIOSH RELs and the ACGIH TLV were based solely on health effects and do not consider feasibility. Like the OSHA PEL and STEL, the NIOSH REL and STEL, which were established in 1983 and the ACGIH TLV, which was most recently updated in 1984, are outdated because they do not include the more recent epidemiology studies reported in Steenland (2003) and Steenland (2004).

OSHA Permissible Exposure Limit (PEL) and Short-Term Exposure Limit (STEL)

The OSHA PEL of 1 ppm was established as a final rule in 29 CFR 1910.1047 (Federal Register 49:25734 of 6/22/1984). The previous PEL was 50 ppm. On page 25775, OSHA states that, "O*ccupational exposure to EtO presents an excess cancer risk of 634 to 1,093 deaths per 10,000 employees exposed at the current OSHA limit of 50 ppm (TWA). The final rule, which sets an 8-hour TWA of 1 ppm, will achieve a 98 percent reduction in cancer mortality risk, for an excess of 12 to 23 deaths per 10,000 employees. OSHA believes that the remaining risk at the 1 ppm limit is still significant, but that the 1 ppm limit reduces the risk to the extent feasible."*

The final rule for EtO (29 CFR 1910.1047) was amended in 1988 to include a 15-minute excursion limit (Federal Register 53:114 of April 6, 1988). This limit was meant to reduce average long-term exposures caused by short term (i.e. 15 minute) high exposure events that occur within the workday. In the federal register, OSHA stated that, *"To the extent an excursion limit reduces average long-term exposures, then the cancer deaths prevented by adoption of an excursion limit represent the primary benefit derived from this action."*

NIOSH Recommended Exposure Limit (REL)

The NIOSH REL of <0.1 ppm for the 8 Hour TWA was first recommended in Current Intelligence Bulletin #35 Ethylene Oxide Evidence of Carcinogenicity (NIOSH, 1981) and the STEL of 5 ppm was included in a 1983 reprint of this bulletin. These limits were recommended to assist OSHA in its effort to update the PEL. The REL for the 8-hour TWA was listed as <0.1 ppm, because an exact limit that would prevent cancer incidence could not be determined and it was recommended that exposures be reduced to a level *as low as reasonably achievable* (ALARA).

ACGIH Threshold Limit Value (TLV)

The ACGIH TLV was reduced to the current value of 1 ppm as an 8-hour TWA in 1984 (ACGIH, 2001). This limit is intended to, "*Minimize potential oncogenic risk and the risk from potential, non-neoplastic adverse effects on lungs, liver, kidneys, endocrine system, blood forming elements, and the central nervous system (CNS). This value should also reduce the risk of human chromosomal damage and reduce the risk of potential reproductive and developmental toxicity."* The ACGIH did

not set a STEL but instead refers to its excursion exposures policy (now listed as Peak Exposures) which recommends that 15-minute TWA exposures not exceed 5 times the TLV.

California OSHA PEL

The California OSHA PEL is 1.0 ppm and the STEL is 5.0 ppm as listed in section 5220 of Title 8 of the California Code of Regulations. This section was filed on January 16, 1985 (https://www.dir.ca.gov/title8/5220.html).

Table 14. Ethylene Oxide Occupational Exposure Limits

Organization	8-hour TWA (ppm)	STEL (ppm)	Action Level[1] (ppm)
Occupational Safety and Health Administration (OSHA)	1 (PEL[2])	5 (PEL STEL[3])	0.5
National Institute for Occupational Safety and Health (NIOSH)	< 0.1 (REL[4])	5 (REL STEL[5])	NA
American Conference of Governmental Industrial Hygienists (ACGIH)	1 (TLV[6])	NA	NA
California Division of Occupational Safety and Health (Cal/OSHA)	1	5	0.5

TWA = Time Weighted Average, STEL = Short Term Exposure Limit,
PEL = Permissible Exposure Limit, REL = Recommended Exposure Limit, TLV = Threshold Limit Value
NA = Not Applicable

[1]Action Level: Concentration as an 8-hour time-weighted average, above which the employer must initiate certain compliance activities such as periodic employee exposure monitoring and medical surveillance;
[2] PEL: The employer shall ensure that no employee is exposed to an airborne concentration of EtO in excess of the PEL as an 8-hour time-weighted average (8-hour TWA);
[3] PEL STEL: The employer shall ensure that no employee is exposed to an airborne concentration of EtO in excess of the STEL as averaged over a sampling period of 15 minutes.
[4] REL = Recommended exposure limit, established by NIOSH. The REL of <0.1 ppm is based on the limit of detection.
[5] The NIOSH REL-STEL is based on a sampling period of 10 minutes.
[6] TLV = Threshold limit value, Established by ACGIH in 1984.

6.4 Safety Factor for Infants and Children (FQPA Safety Factor)[3]

OPP recommends that the 10X FQPA Safety Factor be reduced to 1X for all exposure scenarios including that for the degradate ECH. The toxicology database for EtO and its degradate ECH is complete and exposure analyses are unlikely to underestimate exposure to EtO and its degradate ECH.

6.4.1 Completeness of the Toxicology Database

The toxicology database for EtO and its degradate ECH is considered complete for evaluating and characterizing toxicity, assessing children's susceptibility under FQPA 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. Based on a WOE approach, considering all the available hazard and exposure data for ECH, the HASPOC recommended that rabbit and rodent developmental toxicity studies be

[3] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

waived at this time for ECH (TXR # 0058035, J. Leonard, 05/14/2020). For a listing of the available toxicity studies for ECH, see Appendix A and for EtO see USEPA 2007 (D338729).

6.4.2 Evidence of Neurotoxicity

There is no evidence of neurotoxicity in the existing database for the degradate ECH. There was no evidence of neurotoxicity for PCH, a chemical very structurally similar to ECH, in the subchronic and chronic toxicity studies. Evidence of neurotoxicity was evident in the EtO database, as discussed below.

In an acute neurotoxicity study (MRID 44256402), groups of ten Sprague-Dawley rats/sex were exposed to 0, 100, 300, or 500 ppm EtO for six hours by whole body inhalation and observed for 14 days. Evidence of neurotoxicity was observed at doses of 300 ppm and above, and included drooping eyelids or half-closed eyes, low arousal level and no response to an approaching object. No effects were found on fore- and hind-limb grip strengths, landing foot splay, or reflex assessments. Motor activity was decreased in 300 ppm males and 500 ppm males and females. No microscopic lesions were described for the brain, spinal column, or peripheral nerves from any control or high dose animal.

In a subchronic neurotoxicity study (MRID 44359401), groups of 15 Sprague-Dawley rats/sex were exposed to 0, 25, 50, 100, or 200 ppm EtO for six hours/day, five days/week for 14 weeks (at least 65 exposures) by whole body inhalation. There was a 25% decrease in hind limb grip strength at 200 ppm. There were no treatment-related effects on motor activity. One male exposed to 100 ppm was found dead during the recovery period (4 weeks after termination of exposure).

Neurological effects in animals have also been reported in several subchronic and chronic toxicity studies. In a subchronic study (Snellings et al.1984a) reported altered gait and decreased locomotor activity at 50 ppm in B6C3F1mice (30/sex/group) exposed to EtO at concentrations of 0, 10, 50, 100 or 250 ppm for 6h/day, 5d/week for 10 or 11weeks. At 250 ppm, effects on various reflexes (righting, tail pinch and toe pinch) were noted. IPCS (2003) summarized neurological findings observed in several subchronic and chronic studies. Poor coordination of the hindquarters was observed in rats and mice following exposure to EtO at 450 ppm for 7-8 weeks. Awkward or ataxic gait, paralysis and atrophy of the muscles of the hindlimbs, (accompanied in some cases by pathological evidence of axonal degeneration of myelinated fibers in nerves of the hind legs) were reported in rats and mice exposed to EtO at 250-500 ppm. Paralysis of the hind limbs and atrophy of the leg muscles have been reported in rabbits and monkeys following exposure to ≥ 202 ppm (IPCS, 2003). Demyelination of the sciatic nerve was reported in cynomolgus monkeys exposed to 50 and 100 ppm EtO for 2 years (MRID 42159401).

Peripheral neuropathy, impaired hand-eye coordination and memory loss have been reported in case studies of chronically exposed workers at estimated average exposure levels as low as 3 ppm (with possible short-term peaks as high as 700 ppm) (ATSDR, 1990).

6.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

For the degradate 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. HASPOC recommended that rabbit and rodent developmental toxicity studies be waived for ECH at this time for (TCHXR # 0058035, J. Leonard, 05/14/2020).

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. Although there is no acceptable rabbit developmental toxicity study submitted for EtO, the preliminary evidence suggests that no developmental effects were seen up to 150 ppm in rabbit fetuses. Based on the available data, rodents appear to be more sensitive for developmental effects compared to rabbits.

6.4.4 Residual Uncertainty in the Exposure Database

Currently OPP is waiting for OAR to complete their EtO assessment for bystanders as discussed below in Section 13. OPP anticipates OAR to complete this assessment during the mitigation phase of the registration review process. There are no residual uncertainties in the dietary exposure database. The dietary exposure analyses are unlikely to underestimate exposure as they incorporated tolerance-level ECH residues and 100% crop treated.

6.5 Endocrine Disruptor Screening Program

As required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for EtO, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), EtO is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[4] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[5]

7.0 Residue Chemistry

The nomenclature, registration numbers, PC Code, and chemical structure of EtO and its degradates are listed in Appendix B.

Spice/Herb/Walnut Sterilization Studies

Two spice sterilization studies were previously reviewed by HED and form the basis for current tolerances and the current dietary assessment. The 1994 study provided residue data reflecting traditional sterilization methods for spices, herbs, walnuts, and dried vegetables at the following time intervals: 0 day, 2 weeks, and 2 months after fumigation (D316652, J. Stokes, 12-JUL-2005). Residue data were reported for EtO and its metabolites ECH, EBH, and ETG. Relatively high residues were found in this study. An improved sterilization process, EtO Express, was used for the second study conducted in 2005 involving 29 herbs and spices (D321143, J. Stokes, 25-JAN-2006). Residue data for EtO and ECH were reported at the following time intervals: 0 day, 24 hours, and 72 hours. Current tolerances are based on the EtO Express residue data collected 24 hours after fumigation, while dietary assessments are based on ECH residues collected at the 72-hour interval. These time intervals are considered health protective as information from the spice industry indicates that treated spices will not enter commerce within 24 hours of treatment nor will treated spices be available for purchase within 72 hours of treatment. All domestic spice sterilization work now uses the EtO Express method; thus it is appropriate to base tolerances and dietary estimates on the results of the EtO Express sterilization study (D330820, J. Stokes, 12-JUL-2006).

[4] See https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[5] https://www.epa.gov/endocrine-disruption

8.0 Dietary Exposure

A summary of parent and reaction products included in the risk assessment and tolerance expression is provided in Table 14. These selections have not changed from those presented in the EtO Reregistration Eligibility Document (B. Daiss, D316675, 01/26/2006).

Table 13. Compounds to be included in the Risk Assessment and Tolerance Expression

Source		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plant	Primary Crop	ethylene chlorohydrin, ethylene glycol	EtO ethylene chlorohydrin
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Not Applicable	Not Applicable
	Poultry	Not Applicable	Not Applicable
Drinking Water		Not Applicable	Not Applicable

While the tolerance for EtO is retained for regulatory compliance purposes, 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. ECH and ethylene glycol (EG) are the predominant residues based on spice sterilization residue data showing persistently significant levels of these compounds following fumigation treatments. Based on similar residue levels in sterilization studies, and the lower toxicity of EG (see Section 6.2.2), EPA considers dietary assessments of ECH to be protective for residues of EG and has conducted the dietary assessment for ECH alone. The spice sterilization study data indicate that ethylene bromohydrin (EBH) is also a reaction product of the EtO sterilization process. However, EBH residues are negligible relative to ECH residues. Therefore, EBH was not assessed separately.

8.1 Description of Residue Data Used in Dietary Assessment

Ethylene Chlorohydrin
Acute and cancer analyses were not conducted as toxicological effects attributable to a single dose were not identified and the chronic assessment adequately accounts for all chronic toxicity, including potential carcinogenicity.

A drinking water exposure assessment was not conducted because the Environmental Fate and Effects Division (EFED) expects that uses of EtO for indoor food and nonfood uses will result in insignificant exposure to drinking water resources (E. Odenkirchen, D279672, 12/12/01).

The chronic dietary assessment was unrefined as it used tolerance-level residues and assumed 100% crop treated. All processing factors were set to 1 since drying procedures are performed prior to sterilization.

8.2 Percent Crop Treated Used in Dietary Assessment

The analysis assumed 100% crop treated.

8.3 Acute Dietary Risk Assessment

An acute dietary risk assessment is not required as a single-dose effect was not identified for ECH.

8.4 Chronic Dietary Risk Assessment

A food only chronic dietary risk assessment was conducted using DEEM-FCID (ver. 3.16) which incorporates food consumption data from the U.S. Department of Agriculture's (USDA) National Health and Nutrition Examination Survey, What We Eat in America, NHANES/WWEIA (2003-2008). The chronic exposure estimates do not exceed HED's level of concern (100% cPAD, chronic population adjusted dose); children 3-5 years old was the most highly exposed subpopulation at 6.6% cPAD; while that for the US Population was 2.7% cPAD. Table 15 is a summary of the chronic exposure and risk estimates.

Table 14. Summary of Chronic Dietary (Food Only) Exposure and Risk for ECH

Population Subgroup	Chronic Dietary[1]	
	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.022181	2.7
All Infants (<1 year old)	0.031311	3.8
Children 1-2 years old	0.053012	6.5
Children 3-5 years old	**0.054327**	**6.6**
Children 6-12 years old	0.033506	4.1
Youth 13-19 years old	0.019023	2.3
Adults 20-49 years old	0.019509	2.4
Adults 50-99 years old	0.015785	1.9
Females 13-49 years old	0.018555	2.3

[1] Subgroup in bold had the highest dietary exposure.

8.5 Cancer Dietary Risk Assessment

A cancer dietary assessment was not conducted as the chronic assessment adequately accounts for all chronic toxicity, including potential carcinogenicity.

9.0 Residential Exposure

There are no uses of EtO resulting in direct residential applications; therefore, residential handler and post-application exposures from residential uses are not expected (see Sections 12 and 13 for discussion of ambient and bystander EtO exposure potential).

10.0 Aggregate Exposure and Risk Assessment

In accordance with the FQPA, OPP must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. An aggregate assessment for EtO was not conducted since there are no food, drinking water or residential exposures to EtO. For the metabolites of EtO (ECH and EG), the only exposure route is through food. Therefore, an aggregate assessment for ECH and EG is not needed.

11.0 Non-Occupational Spray Drift Exposure and Risk Estimates

A spray drift assessment was not completed for EtO. The application practices for EtO are not reflected in the standard spray drift assessment as outlined in the Residential SOP Addenda 1: *Consideration of Spray Drift*[6]. Therefore, spray drift exposures have not been quantitatively assessed.

12.0 Ambient EtO Air Concentrations (Non-Point Sources of EtO)

EtO can be found in the outdoor air in areas away from specific industrial sources of EtO. Ambient EtO air monitoring data are available from locations that are not associated with specific industrial sources. Detailed monitoring data are available in EPA's Air Quality System (AQS), which houses outdoor air quality data collected by EPA, state, local, and tribal air pollution control agencies across the country (see (https://www.epa.gov/aqs). Additionally, annual summaries by geographic location may be found as part of annual air toxics data available at https://www.epa.gov/outdoor-air-quality-data/monitor-values-report-hazardous-air-pollutants

In addition, EPA recently provided the following summary:

> ### Update on EPA's work to measure background ethylene oxide
>
> **September 30, 2020 –**As EPA pursues its mission to protect public health and the environment, addressing ethylene oxide remains a major priority for the Agency. As part of its work, EPA is continuing to examine ethylene oxide monitoring data from monitoring sites in the National Air Toxics Trends Stations (NATTS) and the Urban Air Toxics Monitoring Program (UATMP), which are not focused on specific industrial sources. While we have not seen significant change in background concentrations over the past 18 months, we are learning more about things that might affect background ethylene oxide monitoring results. Learn more here.
>
> - EPA's Work to Understand Background Levels of Ethylene Oxide (PDF)

From the available EtO data within the Air Quality System (AQS), the ambient data from NATTS and UATMP sites for October 2018 through March 2020 are available in a summarized tabular format. Annual summaries by geographic location may be found as part of annual air toxics data available at https://www.epa.gov/outdoor-air-quality-data/monitor-values-report-hazardous-air-pollutants. In addition, for users wishing to work with raw data files, the ambient EtO data from all sites are continuously uploaded into the AQS which is available to the public.

Despite the small number of samples from a small number of locations, the available data provide support that EtO is present at lower, yet detectable levels at locations away from specific industrial sources of EtO. However, as EPA and its state and local air agency partners have become more experienced in monitoring EtO at low levels, the Agency has discovered issues that may affect monitoring results that are near the method detection limit. While EPA has high confidence in the

[6] https://www.regulations.gov/document?D=EPA-HQ-OPP-2013-0676-0003

results of EtO monitoring results immediately *downwind* of facilities, where results have generally been well above the level of EtO that the current monitoring method can detect, the Agency is less confident in the accuracy of values that are near the method detection limit.

There is also the potential for inhalation exposure to EtO via ambient air. EtO in ambient air from the 27 NATTS and UATMP sites monitored between October 2018 through March 2020 are summarized in Table 16. The average ambient EtO concentrations from these 27 sites during this particular timeframe range from 0.069 to 0.686 µg/m^3.

Table 15. EtO Ambient Air Concentrations

State	City	Network	Mean ($\mu g/m^3$)	Median ($\mu g/m^3$)	Std. Dev. ($\mu g/m^3$)	Min ($\mu g/m^3$)	Max ($\mu g/m^3$)	N
			0.241	**0.194**	**0.253**	**0**	**6.104**	**1314**
AZ	Phoenix	UATMP	0.307	0.274	0.121	0	0.488	35
AZ	Phoenix	NATTS	0.365	0.334	0.218	0	1.188	77
CO	Grand Junction	NATTS	0.288	0.257	0.181	0	0.708	59
FL	Valrico	NATTS	0.090	0.082	0.033	0.041	0.193	36
FL	St. Petersburg	UATMP	0.097	0.092	0.030	0.054	0.205	36
FL	Pinellas Park	NATTS	0.108	0.101	0.042	0.047	0.256	36
GA	Decatur	NATTS	0.686	0.295	1.506	0.042	6.104	15
IL	Schiller Park	UATMP	0.309	0.293	0.206	0	0.962	73
IL	Northbrook	NATTS	0.262	0.238	0.245	0	1.082	89
KY	Ashland	UATMP	0.284	0.230	0.223	0.085	0.663	6
KY	Grayson	NATTS	0.218	0.189	0.174	0	0.864	79
KY	Smithland	UATMP	0.306	0.293	0.174	0	0.828	27
KY	Calvert City	UATMP	0.295	0.232	0.275	0	1.424	30
MA	Boston	NATTS	0.069	0.069	0.017	0.034	0.094	14
MI	Dearborn	NATTS	0.220	0.203	0.141	0	0.731	50
MO	St. Louis	NATTS	0.229	0.214	0.152	0	0.846	73
NJ	Camden	UATMP	0.292	0.268	0.194	0	0.920	73
NJ	East Brunswick	UATMP	0.317	0.305	0.210	0	0.884	70
NJ	Chester	UATMP	0.282	0.270	0.201	0	0.816	70
NJ	Elizabeth	UATMP	0.278	0.253	0.218	0	0.706	62
NY	Bronx	NATTS	0.120	0.112	0.047	0.057	0.250	42
NY	Rochester	NATTS	0.125	0.117	0.064	0.050	0.397	45
RI	Providence	NATTS	0.082	0.065	0.058	0.043	0.268	14
UT	Bountiful	NATTS	0.235	0.203	0.227	0	0.796	73
WA	Seattle	NATTS	0.139	0.139	0.118	0	0.679	70
WA	Lacy	UATMP	0.203	0.184	0.187	0	0.769	47
WI	Horicon	NATTS	0.013	0	0.048	0	0.175	13

a. UTAMP = Urban Air Toxics Monitoring Program and NATTS = National Air Toxics Trends Stations

13.0 Non-Occupational Bystander Exposure

Although there are no direct residential applications of EtO, those who live or work near sites where EtO fumigation occur (i.e., defined herein as "bystanders") are potentially exposed via inhalation to EtO emissions that travel off-site.

EtO is a listed hazardous air pollutant (HAP) under Clean Air Act (CAA) section 112(b). Within EPA, the responsibility for developing the CAA emission standards and other requirements applicable to the commercial sterilizer and fumigation operations source category rests with the Office of Air and Radiation's (OAR) Office of Air Quality Planning and Standards (OAQPS). Therefore, OPP is collaborating with OAQPS in their efforts to assess and mitigate EtO emissions from EtO fumigation facilities. OAQPS efforts can be viewed in the following link: https://www.epa.gov/newsreleases/epa-moves-forward-suite-actions-address-ethylene-oxide#:~:text=Ethylene%20oxide%20is%20one%20of,pollutants%20regulated%20by%20the%20EPA.&text=Ethylene%20oxide%20also%20is%20used,risk%20value%20for%20ethylene%20oxide

> *"EPA has been taking steps to address ethylene oxide emissions after EPA's National Air Toxics Assessment, issued in 2018, found that ethylene oxide emissions may be contributing to potentially elevated cancer risk in some areas around the country. Since then, EPA has been taking a two-pronged approach to evaluate these emissions. First, the agency is reviewing existing Clean Air Act regulations for industrial facilities that emit ethylene oxide. Second, because the process for revising our regulations takes time, EPA is gathering additional information on ethylene oxide emissions and is working with state and local air agencies to determine whether more immediate emission reduction steps may be warranted. By working with our state and local partners, we seek to identify opportunities to achieve early emission reductions.*
>
> *In addition to the proposed RTR* [risk and technology] *for the MON* [Miscellaneous Organic Chemical Manufacturing]*, EPA is also reviewing the NESHAP* [National Emission Standards for Hazardous Air Pollutants] *for Ethylene Oxide Commercial Sterilization and Fumigation Operations. EPA intends to issue* [*] *an Advance Notice of Proposed Rulemaking (ANPRM) to outline potential approaches and gather comments and data. The ANPRM will seek information on several key topics, including possible approaches to calculate and control fugitive emissions; potential improvements to EtO monitoring technologies; and process differences between types of sterilization facilities. EPA also will issue a survey under Clean Air Act section 114 to gather information from several commercial sterilization companies on facility characteristics, control devices, work practices and costs for emission reductions. Our efforts are intended to inform a potential future proposed rule for ethylene oxide commercial sterilizers in the coming months."* [*] The public comment period for the ANPRM closed on February 10, 2020, and EPA received 98 comments, all of which will be considered during the NESHAP review.

OAR is currently in the process of reviewing information collected under CAA section 114 from commercial sterilization companies on facility characteristics, control devices, work practices and costs for emission reductions collected. OPP will continue to work with OAQPS

during their assessment and review of this information. OPP plans to work collaboratively with OAQPS during the risk mitigation phase of the Registration Review process.

14.0 Occupational Exposure

There is potential for occupational handler inhalation exposure from the registered uses of EtO. At this time, OPP is characterizing the worker inhalation exposure data available for EtO. Occupational dermal exposures are not expected given the high vapor pressure of EtO and based on the delivery systems used (which include pressurized cylinders).

OPP has obtained personal breathing zone (PBZ) air monitoring data from registrant submitted studies (see Section 14.1) and from the OSHA website (see Section 14.2) for sterilization plant workers, health care facilities and workers involved in the treatment of spices. These PBZ air monitoring data represent observational monitoring during routine workdays and are expressed as 8-hour time weighted average (TWA) air concentrations when compared to the OSHA PEL-TWA of 1.0 ppm or as 15-minute TWAs when compared to the OSHA PEL-STEL of 5 ppm.

14.1 Occupational Exposure Data Submitted to EPA

A summary of available exposure data that was submitted to EPA is presented in Table 17.

Antimicrobial Uses - Sterilization Plants: Data from a sterilization plant worker study (MRID 50231101) was submitted and those values in Table 17 are the derived values that include the use of respiratory protection that reduces exposure by a protection factor of 1,000 when the respirators are worn. The study contains 1,273 samples. These data were collected using 3M badges, and only data with a reporting time of 210 minutes or more were used. The study report indicates that this was done because OSHA defines full-shift sampling "as a minimum of the total time of the work shift less one hour (e.g., seven hours of an 8-hour work shift or nine hours of a ten-hour work shift)," and samples from periods of at least half a day (i.e., 420 / 2) were considered to reflect TWA exposures. The sample times ranged from 210 to 420 minutes for four samples, 420 to 480 minutes for 1,121 samples and 480 to 772 minutes for 148 samples.

The reported TWA EtO concentrations for all 1,273 workers ranged from 0.002 ppm to 4.6 ppm. Of the 1,273 worker badge samples, 367 samples (28.8%) were reported as <LOD or yielded an estimated exposure below the LOD. According to OSHA Method 49 for Ethylene Oxide, the detection limit and reliable quantitation limit are both 0.03ug/sample. Based on the 3M badge airflow rate of 49.3 mL/minute, this equates to an air concentration of 0.7 ppb (0.0007 ppm) for an 8-hour air sample and 22.0 ppb (0.02 ppm) for a 15-minute sample. These limits are based on validation data which indicated an average recovery of 94.6% (SD = 2.9) for six badge samples spiked with 0.03 µg of EtO.

Of the 1,273 data rows, respirators were not worn at any time during monitoring for 662 workers. Respirators were worn at all times for 6 workers and respirators were worn part of the time for the remaining 605 workers. The geometric mean and average TWA ETO exposures for the workers wearing a respirator at any time during sampling were 0.061 ppm and 0.18 ppm, respectively. The geometric mean and average TWA ETO exposures for workers who did not wear a respirator at any time during sampling were 0.14 ppm and 0.27 ppm, respectively.

Antimicrobial Uses - Health Care Facilities: The 3M Health Care Facility data (MRID 50231102) were presented at a May 15, 2015 meeting at the U.S. Food and Drug Administration (FDA). These data were used in an analysis conducted by 3M to compare the OSHA/IMIS data from prior years to employee badge data from health care facilities for fiscal year 2012. Comparison of arithmetic means, 75th and 90th percentiles and maximum exposures demonstrates that EtO exposures have been reduced in recent years. The 2012 badge data (with an arithmetic mean of 0.12 ppm) demonstrate that hospitals and other health care facilities are currently achieving EtO exposure levels well below the OSHA 8-hour TWA of 1.0 ppm. In fact, more than 90 percent of the 647 observations are at least 5-fold below the OSHA TWA. Reductions in EtO exposures are attributed by 3M to process changes mandated by EPA and the introduction of engineering controls. These data are the actual exposures and have not been modified to account for respiratory protection. The lowest value was not reported and is assumed to be 0.0007 ppm, which is the limit of detection/quantification for an 8-hour badge sample.

Conventional Uses (Spice Sterilization Facilities and Beekeeping): In support of the use of EtO for the sterilization of spices, the ASTA submitted exposure monitoring of two (2) workers at each of two (2) facilities (MRID 47338301; D347717). Each worker was monitored for 10 days at facilities that ASTA claim treat the majority of spices in the United States. The Agency believes the data – representing a total of 40 EtO exposure-days – are a reasonable representation of EtO exposure throughout the spice industry.

Air concentrations were collected utilizing a continuous monitoring instrument (BW Technologies, Inc. GasAlert Extreme) set to record EtO exposure throughout the day with a limit of detection (LOD) of 0.1 ppm. Results submitted to the Agency included the following:

- 5-minute instantaneous readings (e.g., 0.2 ppm at 7:05 AM, 0.1 ppm at 7:10 AM, etc.);
- 15-minute rolling averages;
- 8-hour rolling averages;
- Activity specific information corresponding to each 5-minute reading;
- "Yes/No" indication for respiratory protection (a PF50 MSA Ethylene Oxide Gas Mask – NIOSH Certification TC 14G-0202) worn during time of reading; and,
- 8-hour TWA results from a ChemChip™ Ethylene Oxide Personal Monitor by Assay Technologies, Inc.

The Agency utilized the 15-minute rolling averages provided to calculate 5-minute averages for each exposure-day. A reduction factor of 98% (the quantitative reduction in exposure based on a PF50 respirator) was then applied to those 5-minute averages where a respirator was worn, and daily averages were calculated. For results showing no exposure (i.e., non-detects), ½ the LOD (0.1 ppm) was used as is standard HED practice; unless EtO was detected, breaks and lunch were not included.

Additionally, MRID 50231101 indicates, *"whereas most of the data were obtained from facilities that sterilized medical equipment, badge data were obtained from two facilities which treat spices exclusively and from at least one other facility which treated both medical equipment and spices on days when badge monitoring was conducted."*

Based on information provided at the time of the EtO RED (March 2008), the beekeeping use of EtO is limited to a state-managed facility in North Carolina. The North Carolina Department of Agriculture and Consumer Affairs (NCDA&CS) uses 2 vacuum tight chambers designed for use with EtO. Both chambers are located outdoors. Based on the label directions and requirements for the SLN beekeeping use (related to EPA Reg. # 36736-7), it is anticipated that the ASTA monitoring data would also be representative of the beekeeping use. In addition, information submitted to the Agency for EtO sterilization of beekeeping equipment in North Carolina indicated that use is approximately 40 times per year (electronic mail correspondence from Dan Hopkins, NC Dept. of Agriculture to Susan Bartow, EPA/OPP/SRRD; 2/7/2008), as opposed to a potential year round operation like the spice treatment facilities. Therefore, it is assumed that estimated exposures for the spice industry would be protective of the treatment of beekeeping equipment with EtO.

Table 16. EtO Occupational Exposure Data Submitted to EPA.

Data Source	Number of Facilities Monitored	Number of Air Samples Collected	EtO Air Concentration (ppm)		
			Range	Geometric Mean	Arithmetic Mean
Sterilization & Spice Plant Worker Exposure Study (MRID 50231101)	25	1273	0.002 to 4.6	0.093	0.23
3M Health Care Facility Data (MRID 50231102)	More than 34	647	0.0007 to 10.1	0.073 (50th Percentile)	0.12
ASTA Worker Exposure Study (MRID 47338301; D347717)	2 (2 workers at each facility)	40	0.015 – 0.858	0.048	0.076

MRID 50231101. Ethylene Oxide Exposures for Ethylene Oxide Sterilization Plant Workers, Acta Group, 3/31/2017. The ETO air concentrations reflect the use of PF1000 respiratory protection.
MRID 50231102. Supplemental Information on State Controls Affecting Ethylene Oxide Emissions, Targeted Monitoring Data near Operating Chambers, and Monitoring Data from Health Care Facilities. Acta Group, 3/31/2017. Includes data from passive EtO monitors in health care facilities across 33 states and Puerto Rico in 2012. The ETO air concentrations do not reflect the use of respiratory protection.
MRID 47338301. Render, C. 2008. Ethylene Oxide Worker Exposure Study. Sponsored by the American Spice Trade Association (ASTA). The ETO air concentrations reflect the use of PF50 respiratory protection.

14.2 Occupational Exposure Data Available from OSHA

Occupational exposure data for EtO are available as Chemical Exposure Health Data from https://www.osha.gov/opengov/healthsamples.html. Data for the years 2008 through 2019 were downloaded and screened to eliminate area samples, bulk samples and blank values leaving only personal breathing zone samples. Data were also deleted for industries, such as chemical manufacturing, that are not relevant for FIFRA registered uses. The remaining data are summarized in Table 18. Numerical results were calculated for the samples reported as non-detect (ND) by dividing the detection limit of 0.03 µg/sample for the method used (OSHA, 2012) by the sample air volume. Given that the OSHA PEL is 1 ppm for the 8 hour TWA (i.e. PEL-TWA) and 5 ppm for the 15 minute short term exposure limit (i.e. PEL-STEL), the data for EtO include both samples of up to 480 minutes that were collected for comparison to the PEL-TWA and samples of less than 30 minutes for comparison to the PEL STEL.

The combined sample TWA values reported in Table 18 for each facility inspection are the time weighted average (TWA) for all the samples collected during that inspection. These TWAs were

calculated for each facility rather than for each worker because the identity of the worker associated with each sample is not included in the chemical exposure health data. Combined sample durations that are greater than 480 indicate that more than one worker was sampled during the inspection. For example, the combined sample duration of 3150 minutes for the 21 samples collected during Inspection #315303131 suggests that at least 7 seven workers were sampled. It also is likely that multiple samples were collected on each worker sampled at a particular facility because the PEL of EtO is expressed both as an 8-hour TWA and as a STEL. For some of the inspections listed in Table 18, the upper end of the range of results includes samples that were collected to evaluate the PEL-STEL. This is particularly true for Inspection #1192822 which includes a result of 19.5 ppm. This result of 19.5 ppm and next highest result of 4.4 ppm were from 19-minute samples that were taken to evaluate the STEL of 5 ppm. The remaining results are from samples of approximately 240 minutes in duration that were collected to evaluate the PEL-TWA of 1 ppm.

Table 17. OSHA EtO Data for EPA Registered Uses (2008 through 2019)

OSHA Inspection Number	Year	Industry	Number of Samples	Range of Results (ppm EtO)	Combined Sample Duration[A] (Minutes)	Combined Sample TWA[B] (ppm EtO)
Medical Equipment Production and Sterilization Facilities						
315303131 1192822	2011 2017	Medical Equipment Wholesale	21 15	0.05 to 0.74 0.048 to 19.5	3150 2903	0.22 1.5
1169775	2016	Scientific and Technical Consulting[C]	8	0.0008 to 0.026	2074	0.0013
314845975 810881 1013403	2011 2013 2015	Surgical and Medical Equipment Manufacturing	4 6 6	0.005 to 0.18 0.005 to 0.85 0.02 to 2.4	350 603 906	0.11 0.43 1.4
317586501	2014	Surgical Equipment and Supplies Manufacturing	11	0.001 to 0.60	1065	0.23
1400790	2019	Surgical and Medical Equipment Manufacturing	13	0.001 to 0.23	2280	0.15
Health and Veterinary Care Facilities						
312835390 310770896 315129924 1147145 312226533	2009 2009 2011 2016 2008	Health Care Facilities	4 4 3 5 6	0.003 to 0.02 0.0008 to 0.89[D] 0.005 to 0.03 0.001 to 0.02 0.009 to 0.02	217 460 99 445 150	0.0061 0.031 0.010 0.0037 0.013
1007452 1276007	2015 2017	Veterinary Care Facilities	2 2	0.02 and 0.02 0.006 and 0.002	30 75	0.022 0.0089
Non-Medical Facilities						
1241931	2017	Spice and Extract Manufacturing	5	0.002 to 0.16[E]	472	0.082

A. The combined sample duration is the duration of all of the samples taken during the inspection.
B. The combined TWA is the TWA of all of the samples taken during the inspection.
C. This facility does sterilization protocol development and testing.
D. Only one sample was above non-detect. This sample was collected for 15 minutes.
E. The highest result of 0.16 ppm is from a 240 minute sample.

15.0 Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, OPP estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant.

For its proposed rulemaking for EtO commercial sterilization, OAR will examine the potential for any environmental justice issues that might be associated with sterilization facilities by performing a demographic analysis, which is an assessment of risks to individual demographic groups of the populations living within 5 km and within 50 km of the facilities. In the analysis, OAR will evaluate the distribution of cancer and noncancer risks from the facilities across different demographic groups within the populations living near facilities.

16.0 Cumulative Risk Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for EtO or ECH with any other substances. For the purposes of this assessment, therefore, EPA has not assumed that the EtO has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[7] and conducting cumulative risk assessments (CRA)[8]. During Registration Review, the agency will utilize this framework to determine if the available toxicological data for the EtO suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

[7] *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity* (USEPA, 1999)
[8] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002)

17.0 Ecological Risks

Under ambient environmental conditions, EtO released to air is expected to be persistent resulting in potential inhalation exposure of terrestrial wildlife. The ecotoxicity data available for EtO is limited, however, EtO is expected to be toxic to terrestrial animals via the inhalation route of exposure (see USEPA 2013 for more details). Chemicals that are released down-the-drain can typically take from a few to several hours to reach waste-water treatment plant (WWTP) intakes following their discharge and from several hours to roughly a day following their discharge down-the-drain to subsequently be discharged from wastewater treatment plants to surface water. Since uses of EtO are not expected to have a significant component that is available for runoff or leaching, aquatic exposures are not expected. Therefore, for both the spice and commercial sterilization uses, due to the toxicity of EtO to non-target organisms and the potential for exposure, terrestrial animals in the vicinity or downwind of a treatment vent may be at risk. For aquatic organisms, risks are not expected due to limited exposure potential. Therefore, at this time and based on the available information, the Agency is not able to make a 'no effects' determination for Federally listed species or their designated critical habitats.

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Appendix A. Toxicity Profile Tables for ECH and EG

Toxicity Profile for ECH

Table A.1. Ethylene Chlorohydrin – Acute Toxicity			
Study/ Species	**MRID or Publication**	**Results**	**Classification**
870.1100 Acute Oral, Rats	Lawrence et al. 1971a	Oral LD_{50} = 71.3 mg/kg (m) (95% C.L. 57.8-88.6)	Category II
Acute Oral, Mice	Lawrence et al. 1971a	Oral LD_{50} = 81.4 mg/kg (m) (95% C.L. 66.4-99.7)	Category II
870.1200 Acute Dermal, Rabbits	Lawrence et al. 1971a	LD_{50} = 67.8 mg/kg (m&f) (95% C.L. 41.2-111.7)	Category I
Acute Dermal, Rats	NTP, 1985	LD_{50} = 410 mg/kg (f); LD_{50} = Between 360-480 mg/kg (m)	Category II
Acute Dermal, Mice	NTP, 1985	LD_{50} = 1324 mg/kg (m), 1858 mg/kg (f)	Category II
870.1300 Acute Inhalation, Mice	NIOSH, 1975 (As reported in NTP, 1985)	LC_{50} = 117 ppm (0.39 mg/L) Duration not known	Category II
Acute Inhalation, Rats	Carpenter et al. 1949 (As reported in NTP, 1985)	LC_{50} = 32 ppm (0.11 mg/L) Duration not known	Category II
Acute Inhalation, Guinea pigs	NIOSH, 1977 (As reported in NTP, 1985)	LC_{50} = 918 ppm (3.0 mg/L) Duration not known	Category IV
870.2400 Primary Eye Irritation, Rabbits	Lawrence et al. 1971a	Severe Irritation	Category undetermined Inadequate observation period
870.2500 Primary Skin Irritation, Rabbits	Lawrence et al. 1971a	Marked Irritation	Category undetermined Inadequate observation period
870.2600 Dermal Sensitization, Guinea pig	Lawrence et al. 1971b	No Sensitization	
870.6200 Acute Neurotoxicity, Rats	No Study Identified	-	-

Table A.2. Ethylene Chlorohydrin – Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
Developmental/Reproduction Toxicity			
Developmental Toxicity CD-1 mice	Courtney et al. 1982	Doses: 0, 50, 100, 150 mg/kg GD 6-16 (gavage)	**Maternal NOAEL: 100 mg/kg/day** **Maternal LOAEL: 150 mg/kg/day** Based on 75% mortality of dams. Note: the remaining 25% mice at the HDT were not pregnant **Developmental NOAEL: 100 mg/kg/day**

Table A.2. Ethylene Chlorohydrin – Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
			Developmental LOAEL: 150 mg/kg/day based on increased incidence of 14th rib. **Unacceptable/nonguideline**
Developmental Toxicity CD-1 mice	Courtney et al. 1982	**Doses:** 0, 16, 43, 77, 227 mg/kg/day (drinking water)	**Maternal and Developmental NOAEL: 227 mg/kg/day (HDT)** **Maternal and Developmental LOAEL: Not Established** **Unacceptable/nonguideline**
Developmental Toxicity Rabbit	No Study identified	-	-
870.3800 Two-Generation Reproduction Study, Rats	48794601	Doses: 0, 400, 1200, or 2400/3200 ppm in the diet. The 2400 ppm diet was increased to 3200 ppm beginning at week 6 for females and week 12 for males. The dietary levels corresponded to 0, 27.3, 82.4, and 160.6 mg/kg bw/day for P males, 0, 31.3, 95.8, and 209.6 mg/kg bw/day for P females,	**Parental NOAEL: 82.4 mg/kg/day (males) /95.8 mg/kg/day (females).** **Parental LOAEL: 160.6 mg/kg bw/day (males)** based on decreased body weights (P and F1 during pre-mating), increased liver weight and decreased spleen (P and F1), kidney weights (P and F1), and adrenal gland (F1) weights. **Parental LOAEL: 209.6 mg/g/day (females**) based on decreased body weights (P during lactation and F1 during pre-mating, gestation, and lactation), clinical signs (emaciation, lethargy, piloerection, hunched posture) in P females during lactation and decreased ovary (P and F1), uterus/cervix/oviduct (P and F1), adrenal gland (F1), pituitary (P and F1), spleen and kidney weights (P and F1), increased liver weights (P and F1) and atrophy of the uterus, vagina and cervix. **Offspring NOAEL: 82.4 mg/kg/day (males)/95.8 mg/kg/day (females).** **Offspring LOAEL: 160.6 mg/kg bw/day (males)/209.6 mg/g/day (females)** based on decreased bodyweight (F1 and F2 generation), decreased spleen and thymus weights, and increased incidence of runts (F1 and F2 generation). **Reproductive NOAEL: 95.8 mg/kg/day.** **Reproductive LOAEL: 209.6 mg/kg bw/day** based on a decrease in the total number of follicular counts in the P and F1 generation, decreased ovary, uterus/cervix/oviduct weights for both P and F1 generations, and delayed sexual maturation. **Acceptable/Guideline**
Subchronic Oral Toxicity			
Subchronic (13 weeks) Albino Rats (FDRL strain)	Oser et al. 1975	Doses: 0, 30, 45, 67.5 mg/kg/day Gavage	**NOAEL: 45 mg/kg/day** **LOAEL: 67.5 mg/kg/day** Decreased mean body weight in males (34%) and decreased survival in males and females (32% in the HDT vs 100% in control males and 24% in the HDT vs 96% in control females); Labored breathing in animals that died earlier (~3 weeks) at the high dose. Gross and histological changes in animals that died at the high dose (~3 weeks). Dark liver, lungs and hemorrhagic adrenal and pituitary glands; subacute myocarditis, colloid depletion in the thyroid, fatty liver, thyroid congestion and a high incidence of congestive pulmonary changes.

Table A.2. Ethylene Chlorohydrin – Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
			Minimum data reporting **Unacceptable/Non-Guideline**
Subchronic (13 weeks), Beagle Dogs	Oser et al. 1975	Doses: 0, 600, 900, 1350 ppm gavage Mean chemical intake: 0, 13.3, 18.4, 18.3 mg/kg (m) 0, 16.9, 20.3, 19.3 mg/kg (f)	**NOAEL: 18.4 mg/kg/day** **LOAEL: Not Established** No treatment related effects. The chemical intake in the mid and high doses were not different from each other due to emesis and decreased body weight; Limited data reporting. **Unacceptable/Non-Guideline**
Subchronic (13 weeks) Monkeys	Oser et al. 1975	Doses: 0, 30, 45, 62.5 mg/kg/day Gavage	**NOAEL: 62.5 mg/kg/day (HDT)** **LOAEL: Not Established** No treatment related effects. Note: Limited findings reported. **Unacceptable/Non-Guideline**
Subchronic Dermal Toxicity			
Subchronic (14 days) Rats	NTP, 1985	Doses: 0, 20, 30, 40, 60, 80 mg/animal dermal, each day 0, 114/147, 172/222, 226/313, 339/451, 442/611 (m/f)	**NOAEL: 313 mg/kg/day** **LOAEL: 451 mg/kg/day** 60% mortality in females, decreased body weight gain (↓41%) **Acceptable/Non-Guideline**
Subchronic (14 days) CD-1 Mice	NTP, 1985	Doses: 0, 2.5, 5, 10, 20, 30, 45, 60 mg/animal, dermal, each day 0, 92/109, 174/225, 344/435, 741/847, 1095/1376, 1411/1875 (m/f)	**NOAEL: 1095 mg/kg/day** **LOAEL: 1411 mg/kg/day** 60% mortality in males and females, decreased body weight in males. **Acceptable/Non-Guideline**
Subchronic (13 weeks) Rats	NTP, 1985	Doses: 0, 62, 125, 250, 500, 1000 mg/kg 5d/week, dermal	**NOAEL: 125 mg/kg/day** **LOAEL: 250 mg/kg/day** 10% mortality in males and 30% mortality in females **Acceptable/ Non-Guideline**
Subchronic (13 week) CD-1 Mice	NTP, 1985	Doses: 0, 5, 10, 20, 30, 45 mg/animal 5d/week, dermal 0, 192/227, 385/455, 769/909, 1154/1304, 1731/1957	**NOAEL: 385 mg/kg/day** **LOAEL: 769 mg/kg/day** 10-30% mortality in one week **Acceptable/ Non-Guideline**
Combined Chronic Carcinogenicity - dermal			
870.4300 Combined Chronic Toxicity/ Carcinogenicity F344 Rats	NTP, 1985	Doses: 0, 50, 100 mg/kg/day dermal, 5d/week	**NOAEL: 100 mg/kg/day** **LOAEL: Not Established** No change in survival or body weight gain. No evidence of carcinogenicity

Table A.2. Ethylene Chlorohydrin – Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
			Acceptable/Non-Guideline
870.4300 Combined Chronic Toxicity/ Carcinogenicity CD-1 Mice	NTP, 1985	Doses: 0, 7.5, 15 mg/animal Dermal, 5d/week 0, 253, 630 mg/kg –Wk 1 0, 180, 411 mg/kg –Wk 100 Average 0, 216, 520 mg/kg/day	**NOAEL: 216 mg/kg/day** **LOAEL: 520 mg/kg/day** Low survival at high dose; NTP concluded no evidence of carcinogenicity . **Acceptable/Non-Guideline**
Mutation/Genotoxicity			
	NTP, 1995	-	Positive for mutagenicity in bacteria and the mutagenicity was enhanced in the presence of rat liver S9 extract. Negative for the mutagenicity tests using mammalian cell cultures (in vitro) or rodents (in vivo). However, in one test, ECH induces DNA repair in human fibroblasts in vitro. Negative for dominant-lethal mutations or heritable translocations in the mouse
Metabolism			
	Grunow and Altmann, 1982, as cited in NTP, 1985	-	Limited evidence suggests that ECH is rapidly absorbed in rats and majority of the administered radioactivity (77-80%) was eliminated in urine within 24 hours of ingestion and less than 5% of the administered radioactivity in total is excreted in feces and in expired air. Peak levels of radioactivity were found in blood 1 hour after administration and the radioactivity was reduced to 50% after approximately 4 hours. About 90% of the radioactivity in the urine was in the form of thiodiacetic acid and thionyldiacetic acid

Toxicity Profile for EG

Table A.3. Ethylene Glycol Acute Toxicity			
Study/Species	**MRID or Publication**	**Results**	**Classification**
Acute Toxicity			
870.1100 Acute Oral Fischer 344 Rats Wistar Rats Mice Mice Guinea-pigs Dogs Cats	 Clark et al. 1979 (HSDB, 2005) Richardson 1973 (ATSDR, 1997) Schuler et al. 1984 (HSDB, 2005) IPCS, 2002 IPCS, 2002 IPCS, 2002 IPCS, 2002	 LD_{50} = 4000 mg/kg/day (f) LD_{50} = ~12, 900 mg/kg/day (m) LD_{50} = >11, 090 mg/kg/day LD_{50} = 6610 mg/kg/day LD_{50} = 5500-8350 mg/kg/day LD_{50} = 5500 mg/kg/day LD_{50} = 1650 mg/kg/day	 Category III Category IV Category IV Category IV Category IV Category IV Category III
870.1200 Acute Dermal, Rabbits	IPCS, 2002	LD_{50} = 10600 mg/kg/day	Category IV
870.1300 Acute Inhalation, Rats and Mice	IPCS, 2002	LC_{50} = >200 mg/m^3	Category II

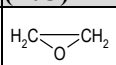
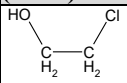
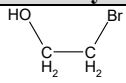
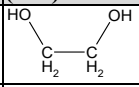
Table A.3. Ethylene Glycol Acute Toxicity			
Study/Species	**MRID or Publication**	**Results**	**Classification**
870.2400 Primary Eye Irritation, Rabbits	IPCS, 2002	Minimal conjunctival irritation without permanent corneal damage	-
870.2500 Primary Skin Irritation, Rabbits and Guinea pigs	IPCS, 2002	Mild dermal irritation	-
870.2600 Dermal Sensitization, Guinea pigs	No study identified	-	-

Table A.4. Ethylene Glycol Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
Developmental/Reproduction Toxicity			
Developmental Toxicity CD-1 Rats	Neeper-Bradley et al. 1990 and 1995 (NTP-CERHR 2004)	Doses: 0, 150, 500, 1000, 2500 mg/kg/day. (GD6-15), 25/group	**Maternal NOAEL: 1000 mg/kg/day** **Maternal LOAEL: 2500 mg/kg/day** Increased liver and kidney weights and water intake. **Developmental NOAEL: 500 mg/kg/day** **Developmental LOAEL: 1000 mg/kg/day** Reduced fetal body weight, increased incidence of litters with skeletal malformations (duplicated or missing ribs, centra and arches and poor ossification). At the HDT, increased litter incidences for total malformations, and external, visceral and skeletal malformations. The malformations included gastroschisis, hydrocephaly, lateral ventricle dilation, umbilical hernia, and malformations of the ribs and vertebrae. **Acceptable/Non-Guideline**
Developmental Toxicity CD Rats	Price et al. 1985 (NTP-CERHR 2004)	Doses: 0, 1250, 2500, 5000 mg/kg/day. (GD 6-15) gavage, 27-29/group	**Maternal NOAEL: Not Established** **Maternal LOAEL: 1250 mg/kg/day** Decreased maternal body weight , increased kidney weight, water intake and post implantation loss per litter, decreased liver weight and number of live fetuses per litter at the HDT **Developmental NOAEL: Not Established** **Developmental LOAEL: 1250 mg/kg/day** Increased incidence of litters with visceral malformations. Increased incidence of litters with skeletal malformations at 2500 mg/kg/day. Decreased fetal body weight per litter and increased number of malformed fetuses per litter and increased litter incidence for skeletal, visceral and external malformations at the HDT. Malformations involved varying degrees of skeletal dysplasia, and clefts of the face, lip or palate. **Acceptable/Non-Guideline**
Developmental Toxicity Fischer 344 Rats	Maronpot et al. 1983 (NTP-CERHR 2004)	Doses: 0, 40, 200, 1000 mg/kg/day. (GD 6-15) diet, ~20/group	**Maternal NOAEL: 1000 mg/kg/day (HDT)** 17.1.1.1.1 Maternal LOAEL: Not Established **Developmental NOAEL: 1000 mg/kg/day** **Developmental LOAEL: Not Established** **Acceptable/Non-Guideline**
Developmental Toxicity CD-1 Mice	Price et al. 1984 and 1985 (NTP-CERHR 2004)	Doses: 0, 750, 1500, 3000 mg/kg/day. (GD 6-15) gavage, 23-25/group	**Maternal NOAEL: 750 mg/kg/day** **Maternal LOAEL: 1500 mg/kg/day** Decreased maternal body weight and decreased liver weight, Increased post implantation loss /litter at the HDT **Developmental NOAEL: Not Established** **Developmental LOAEL: 750 mg/kg/day** Increased malformed fetuses/litter, and percentage of litters with malformed fetuses (mostly skeletal malformations) and decreased fetal weight. Similar effects at 1500 mg/kg/day.

Table A.4. Ethylene Glycol Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
			Acceptable/Non-Guideline
Developmental Toxicity CD-1 Mice	Neeper-Bradley et al. 1995 and Tyl and Frank, 1989 (NTP-CERHR 2004)	Doses: 0, 50, 150, 500, 1500 mg/kg/day. (GD 6-15)	**Maternal NOAEL: 1500 mg/kg/day (HDT)** **Maternal LOAEL: Not Established** **Developmental NOAEL: 500 mg/kg/day** **Developmental LOAEL: 1500 mg/kg/day** Reduced fetal body weight, increased incidence of total malformations, fused ribs and arches, poor ossification in thoracic and lumbar centra and 14th rib. **Acceptable/Non-Guideline**
Developmental Toxicity New Zealand white Rabbits	Tyl et al. 1993 (NTP-CERHR 2004)	Doses: 0, 150, 500, 1000, 2000 mg/kg/day. (GD 6-19)	**Maternal NOAEL: 1000 mg/kg/day** **Maternal LOAEL: 2000 mg/kg/day** 42% mortality, three early deliveries, one spontaneous abortion and renal lesions which include intraluminal oxalate, epithelial necrosis, tubular dilatation and degeneration **Developmental NOAEL: 2000 mg/kg/day (HDT)** **Developmental LOAEL: Not Established** **Acceptable Non-Guideline**
Three-Generation Reproduction Study, Fischer 344 Rats	DePass, 1986a and Woodside et al. 1974 (NTP-CERHR 2004)	Doses: 0, 40, 200, 1000 mg/kg/day Diet	**Systemic/Reproductive/Offspring NOAEL: 1000 mg/kg/day** **Systemic/Reproductive/Offspring LOAEL: Not Established** **Acceptable Non-Guideline**
Two-Generation Reproduction Study, CD-1 Mice	Lamb et al. 1985, Morrissey et al. 1989 (NTP-CERHR 2004)	Doses: 0, 0.25, 0.5, 1.0% in drinking water (w/v) Equivalent to 0, 410, 840 and 1640 mg/kg/day	**Systemic NOAEL: 1640 mg/kg/day (HDT).** **Systemic LOAEL: Not Established** **Reproductive NOAEL: 840 mg/kg/day** **Reproductive LOAEL: 1640 mg/kg/day** Decreased number of F1 litters per fertile F0 pair **Offspring NOAEL: 840 mg/kg/day** **Offspring LOAEL: 1640 mg/kg/day** Decreased number of F1 pups/litter and mean F1 pup weight, skeletal effects in F1 pups. **Acceptable/Non-Guideline**
Subchronic Oral Toxicity			
Subchronic 16 weeks, Wistar Rats	Gaunt et al. 1974 (IPCS, 2002)	Doses: 0, 35, 71, 180, 715 mg/kg/day (m); 0, 38, 85, 185, 1128 mg/kg/day (f)	**NOAEL: 180 mg/kg/day (male)** **LOAEL: 715 mg/kg/day (male)** Increased urinary excretion of oxalate and increased incidence for kidney histopathological effects. The changes include dilation, degeneration, protein casts, and deposition of calcium oxalate crystals in nephrons. **Acceptable/Non-Guideline**
Subchronic 90 days Sprague-Dawley Rats	Robinson et al., 1990 (IPCS, 2002)	Doses: 0, 0.25-2.0 % (w/v) in drinking water Equivalent Doses: 205-3130 mg/kg/day (m); 0, 600-5750 mg/kg/day (f)	**NOAEL: 407 mg/kg/day (males)** **LOAEL: 950 mg/kg/day (males)** Decreased body weight and kidney histopathological effects **Acceptable/Non-Guideline**
Subchronic 13 weeks Fischer 344 Rats	Melnick, 1984 (IPCS, 2002)	Doses: 0, 165, 325, 640, 1300 or 2600 mg/kg/day, diet	**NOAEL: 640 mg/kg/day** **LOAEL: 1300 mg/kg/day.** Reduced body weight and kidney histological effects **Acceptable/Non-Guideline**
Combined Chronic Carcinogenicity			
Combined Chronic Toxicity/Carcinogenicity, 2 years, Fischer 344 Rats,	DePass et al 1986b	Doses: 0, 40, 200, 1000 mg/kg/day	**NOAEL: 200 mg/kg/day (males)** **LOAEL: 1000 mg/kg/day (males)** Mortality by 12 months, decreased body weight, changes in clinical chemistry and hematological parameters, organ weight changes, and

Table A.4. Ethylene Glycol Subchronic, Chronic Toxicity Studies			
Study/Species	**MRID or Publication**	**Doses**	**Results/Classification**
		30 rats/sex/group	renal histopathological effects in males. Oxalate nephrosis was the primary cause of death in males. **Acceptable/Non-Guideline**
CD-1 Mice, 2 years	DePass et al 1986b	Doses: 0, 40, 200, 1000 mg/kg/day 20 mice/sex/group	**NOAEL: 1000 mg/kg/day** **LOAEL: Not Established** **Acceptable/Non-Guideline**
B6C3F1 Mice Diet, 2 Years	NTP, 1993 (IPCS, 2002)	Doses: 0, 1500, 3000, 6000 mg/kg/day (m); 0, 3000, 6000, 12000 mg/kg/day (f)	**NOAEL: Not Established** **LOAEL: 1500 mg/kg/day** Arterial medial hyperplasia in lungs in females. High dose mice and mid dose males had hyalin degeneration in the liver. Mid and high dose mice had transient kidney damage. No evidence of carcinogenicity at the doses tested **Acceptable/Non-Guideline**
Mutagenicity/Genotoxicity			
	IPCS, 2002		Mutagenicity tests in bacteria and mammalian cells are consistently negative. The chromosomal aberrations tests in Chinese hamster ovary cells and DNA damage in rat hepatocytes are negative. The in vivo genotoxicity tests are also negative for dominant lethal mutations in rats and chromosomal aberrations of bone marrow cells in mice exposed to ethylene glycol.

Appendix B. Physical/Chemical, Fate and Transport Properties of EtO and Major Reaction Products

Common name	Ethylene Oxide (EtO)	Ethylene chlorohydrin (ECH)	Ethylene bromohydrin (EBH)	Ethylene Glycol (EG)
Chemical structure				
Molecular Formula	C_2H_4O	C_2H_5ClO	C_2H_5BrO	$C_2H_6O_2$
Molecular Weight, grams/mole	44.053	80.514	124.965	62.068
IUPAC name	Oxirane	2-chloroethanol	2-bromoethanol	Ethane-1,2-diol
CAS name	Oxirane	2-chloroethanol	2-bromoethanol	Ethylene glycol
CAS #	75-21-8	107-07-3	540-51-2	107-21-1
PC Code	042301	600502	NA	042203, 800009
Melting point, degrees Celsius (°C)	-111.6	-89	-80	-12.9
Boiling point, °C	10.4	130	150 (EPISuite v4.10)	195
Density or specific gravity, grams/liter (g/L) at 25 °C	1.80	1.2015-1.2025	1.494 at 20 °C	1.1155
Water solubility, at 20°C	Not available	Not available	Not available	Not available
Vapor pressure, at 25° C	1255 mm Hg (EPISuite v4.10)	7.18 mm Hg (EPISuite v4.10)	2.06 mm Hg (EPISuite v4.10)	0.0609 mm Hg (EPISuite v4.10)
Henry's Law Constant at 25 °C (atm-m^3/mole)	1.48E-04 (Conway et al 1983)	7.61E-07 (EPISuite v4.10)	4.12E-07 (EPISuite v4.10)	1.31E-07 (EPISuite v4.10)
Dissociation constant, pKa	NA	NA	NA	NA
Soil Adsorption Coefficient (Koc), L/kg	4.662 (EPISuite v4.10)	3.39 (EPISuite v4.10)	4.374 (EPISuite v4.10)	0.2239 (EPISuite v4.10)
Sludge Adsorption, % removal	1.65 (EPISuite v4.10)	1.76 (EPISuite v4.10)	1.76 (EPISuite v4.10)	1.75 (EPISuite v4.10)
Log Octanol/water partition coefficient (Log K_{ow}) at 25 °C	-0.30 (EPISuite v4.10)	0.112 (EPISuite v4.10)	0.23 (EPISuite v4.10)	-1.20 (EPISuite v4.10)
Bioaccumulation Factor, L/kg-ww	Not available	Not available	Not available	Not available
UV/VIS absorption spectrum	Not applicable, non-conjugated molecule	Not applicable, non-conjugated molecule	Not applicable, non-conjugated molecule	Not applicable, non-conjugated molecule
Half-life in air (days)	39 (EPISuite v4.10)	Not available	Not available	Not available
Activated Sludge Biodegradation, % removal	Not available	Not available	Not available	Not available

CAS = Chemical Abstracts Service; IUPAC = International Union of Pure and Applied Chemistry; NA = not applicable; UV = ultraviolet light; VIS = visible light

Appendix C. International Residue Limit Status Sheet.

Ethylene Oxide (042301)

Summary of U.S. Tolerances and Maximum Residue Limits					
Residue Definition					
U.S. - 40 CFR 180.151: ethylene oxide and ethylene chlorohydrin					
Canada - ethylene oxide and ethylene chlorohydrin					
Codex – none					
Commodity	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*				
	U.S. Established	U.S. Recommended	Canada	Codex	Mexico
180.151 (a)(1) ethylene oxide					
Herb and spice group 19, dried leaves, except basil	7	7	7		
Licorice, roots	7	7			
Peppermint, dried leaves	7	7			
Sesame, seed	7	7	7		
Spearmint, dried leaves	7	7			
Vegetable, dried	7	7			
Walnut	50	7			
180.151 (a)(2) ethylene chlorohydrin					
Herb and spice group 19, dried leaves, except basil	940	940	940		
Licorice, roots	940	940			
Peppermint, dried leaves	940	940			
Sesame, seed	940	940	940		
Spearmint, dried leaves	940	940			
Vegetable, dried	940	940			
Walnut	--	100			
Completed using BCGlobal MRL, 02-SEP-2020.					