# Ethylene Oxide

# Proposed Interim Registration Review Decision
# Case Number 2275

## March 2023

Approved by: _____

Anita Pease
Director
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Date: 03/28/2023

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## Table of Contents

# I. INTRODUCTION

**Executive Summary**

As a pesticide,[1] EtO is primarily used as a sterilant for medical devices and equipment, and it is highly valuable because it is a penetrative gas that has a high throughput capacity, is effective at a wide range of temperatures, and is compatible with a broad range of materials. EtO is used on approximately 50% of all sterilized medical devices, annually, including an estimated 95% of all surgical kits. Presently, there are no viable alternatives to EtO for the sterilization of certain medical devices and equipment. The absence of EtO for use on medical devices and equipment would cause widespread disruption to the availability of sterile medical devices. In the U.S. EtO is also used during the processing and reconditioning of dried herbs and spices to reduce foodborne pathogens of concern such as *Salmonella* and *Escherichia coli*.

EtO is a known carcinogen. The registered pesticidal uses of EtO pose inhalation risks to workers inside commercial sterilization facilities, healthcare facilities, and to those treating beekeeping equipment in North Carolina. EtO also has the potential to pose inhalation risks to communities near facilities where EtO is used. Therefore, EPA is proposing mitigation to address inhalation risk concerns, including the termination of certain uses, a use rate reduction through reduced concentrations, a series of engineering controls within commercial sterilization facilities and healthcare facilities, respiratory protection requirements for commercial sterilization facilities, monitoring, training, and recordkeeping requirements, as well as establishing an action limit based on the current lowest technologically measurable (i.e.,

[1] Ethylene Oxide (EtO) is a flammable, colorless gas that is primarily used to make other chemicals that are used in making a range of products, including antifreeze, textiles, plastics, detergents, and adhesives. This Proposed Interim Decision (PID), in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) focuses only on the regulation of the pesticidal uses for EtO. Other activities involving EtO, including manufacturing, may be regulated under other statutes and/or by other agencies.

quantifiable)limit. Additionally, at the time this Proposed Interim Decision is released for public comment, EPA's Office of Air and Radiation (OAR) is concurrently releasing for public comment their Proposed Rulemaking for EtO commercial sterilizers, *National Emission Standards for Hazardous Air Pollutants (NESHAP): Ethylene Oxide Emissions Standards for Sterilization Facilities Residual Risk and Technology Review*.[2] OAR is proposing to revise the NESHAP for commercial sterilization facilities by both amending existing standards and establishing additional standards, in order to reduce EtO emissions to residential communities.

This document is the Environmental Protection Agency's (EPA or the Agency) Proposed Interim Registration Review Decision (PID) for ethylene oxide, henceforth referred to as EtO (PC Code 042301, case 2275). In a registration review decision under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Agency determines whether a pesticide continues to meet FIFRA's registration standard.[3] Where appropriate, the Agency may issue an interim registration review decision before completing a registration review.[4] Among other things, the interim registration review decision may determine that new risk mitigation measures are necessary, lay out interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment and completing the registration review.[5] For more information on EtO, see EPA's public docket for this chemical's registration review case (EPA-HQ-OPP-2013-0244) at www.regulations.gov.

FIFRA[6] mandates the continuous review of existing pesticides. All pesticides distributed or sold in the United States must be registered by EPA based on scientific data showing that they will not cause unreasonable adverse effects to human health or to the environment when used as directed on product labeling. In 2006, the Agency began implementing the registration review program. EPA generally reviews each registered pesticide every 15 years. Through the registration review program, the Agency intends to verify that all registered pesticides continue to meet the registration standard as the ability to assess and reduce risk evolves and as policies and practices change. By periodically re-evaluating pesticides as science, public policy, and pesticide-use practices change, the Agency ensures that the public can continue to use products in the marketplace that do not present unreasonable adverse effects. For more information on the registration review program, see http://www.epa.gov/pesticide-reevaluation.

EtO was first registered as a pesticide in the U.S. in 1966. Because it was registered before 1984, it was subject to reregistration and a Reregistration Eligibility Decision was completed by EPA in 2008. There is currently one technical registrant—ARC Specialty Products of Balchem Corporation.

In addition to the registration review of EtO as a pesticide under FIFRA, the Agency also conducts a periodic review of air emission standards for air pollutants, including EtO, through

[2] EPA-HQ-OAR-2019-0178.
[3] Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) § 3(g), 7 U.S.C. § 136a(g); 40 C.F.R. § 155.57.
[4] 40 C.F.R. §§ 155.56, 155.58.
[5] 40 C.F.R. § 155.56.
[6] As amended by the Food Quality Protection Act (FQPA) of 1996, Pub. L. No. 104-170, 110 Stat. 1489 and by the Consolidated Appropriations Act, 2023, Pub L. No. 117-328, § 711, 136 Stat. 4459 (2022).

the National Emission Standards for Hazardous Air Pollutants (NESHAP) under the Clean Air Act. At the same time as the issuance of this Office of Pesticide Programs (OPP) Proposed Interim Decision for EtO, the Office of Air and Radiation (OAR) is proposing updates to the emission standard for EtO in Proposed National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Commercial Sterilization and Fumigation Operations (EPA-HQ-OAR-2019-0178). The proposed requirements set forth in each Agency action are complementary in that they are intended to reduce public health risks from EtO exposure. The OAR proposed rulemaking focuses on reducing EtO emissions released outside the facilities for residential bystanders of commercial sterilization facilities. OPP's proposed mitigation measures for sterilizations and other facilities that use EtO will also reduce EtO exposure to people outside the facilities, including residential and non-residential bystanders (i.e., those who go to work or school near facilities), as well as reduce risks to workers exposed to EtO inside the facilities. OPP's mitigation applies to all commercial sterilization facilities in the U.S. OPP is also proposing mitigation to healthcare facilities, and all niche uses of EtO (i.e., beekeeping equipment; museum, library, and archival materials, cosmetics; and musical instruments). Conversely, OAR's mitigation is focused only for the commercial sterilizers source category. At the time of OAR's assessment on commercial sterilizers, 23 out of 85 facilities were identified as high risk. See Appendix F.

The Agency is issuing a PID for EtO so that it can move forward with aspects of the registration review and propose risk mitigation (see Appendices A and B). EPA is currently working with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (the Services) to improve the consultation process for federally listed threatened and endangered (listed) species for pesticides under the Endangered Species Act (ESA).[7] The Agency has not yet fully evaluated EtO's risks to federally listed species. However, EPA will complete its listed-species assessment and any necessary consultation with the Services before completing the registration review of EtO. Before completing registration review, EPA will also complete endocrine screening for EtO under the Federal Food, Drug, and Cosmetic Act (FFDCA).[8] For more information on the listed-species assessment and the endocrine screening for the EtO registration review, see Appendices C and D. The EtO Registration Review case thus cannot be considered complete until the Agency assesses the aforementioned ESA assessment and endocrine screening; however, EPA will require mitigation to address risks to EtO following the publication of the Interim or Final Decision, even if EPA has not yet completed its ESA obligations.

EPA has highlighted specific areas in the PID where additional information is needed. The Agency welcomes comments on all aspects of the PID.

This document is organized in six sections:

- *Introduction* (summarizing the registration review milestones and responding to public comments);
- *Use and Usage* (discussing how and where EtO is used);

[7] Endangered Species Act (ESA) § 7, 16 U.S.C. § 1536.
[8] Federal Food, Drug, and Cosmetic Act (FFDCA) § 408(p), 21 U.S.C. § 346a(p).

- *Scientific Assessments* (summarizing EPA's risk and benefits assessments, updating or revising previous risk assessments, and discussing risk characterization);
- *Interagency Considerations* (discussing EPA's coordination with OSHA and FDA on EtO regulation);
- *Proposed Interim Registration Review Decision* (presenting EPA's proposed decision, registration rationale, and any mitigation measures to address risks of concern); and
- *Next Steps and Timeline* (discussing how and when EPA intends to complete registration review).

## A. Summary of EtO Registration Review Timeline

On September 25, 2013, the Agency formally initiated registration review for EtO with the opening of the registration review docket for the case.[9] The following summary highlights the docket opening and other significant milestones that have occurred thus far during the registration review of EtO:

- September 2013 – EPA posted the EtO *Preliminary Work Plan* (PWP) (September 25, 2013) to the public docket for a 60-day public comment period. Along with the PWP, the following documents were also posted in the ethylene oxide registration review docket (EPA-HQ-OPP-2013-0244):
  - *Ethylene Oxide (ETO): Review of Human Incidents* (May 8, 2013)
  - *BEAD Chemical Profile for Registration Review: Ethylene Oxide (ETO) (042301) (September 25, 2013)*

- April 2014 – EPA posted the EtO *Final Work Plan* (FWP) (April 4, 2014) to the public docket. The Agency received 12 comments on the PWP. Public comments on the PWP did not change the schedule, risk assessment needs, or anticipated data requirements in the FWP. In the FWP, EPA corrected the anticipated Registration Review schedule and noted that no additional data were needed outside of what was required in the PWP. After the PWP public comment period closed, the Agency received additional information from the Ethylene Oxide Sterilization Association, Inc. that was considered in the risk assessment phase of registration review. This additional information can be found in docket EPA-HQ-OPP-2013-0244 at www.regulations.gov.

- October 2014 – EPA issued a generic data call-in (GDCI) for EtO to obtain data needed to conduct the registration review risk assessments (GDCI-042301-1428). The registrants submitted all required data except the non-guideline study Monitoring Data on Fumigated Commodities (required for the spice use only). The registrants submitted a waiver request for this study (MRID 50384901) on September 8, 2017. However, this waiver request was denied on July 17, 2018, due to a lack of information related to potential exposures within the various channels of trade after fumigation, dissipation of EtO beyond the facility, and the analytical method used to measure air concentrations.[10] The Agency has

[9] 40 C.F.R. § 155.50.
[10] Ethylene Oxide (EtO): Response to registrant's inhalation exposure monitoring requirements waiver request. Decision Number 533138. June 21, 2018.

been coordinating with the Ethylene Oxide Task Force (EOTF) to fulfill this data requirement and is awaiting a protocol submission by EOTF. Accordingly, all data requirements have not been satisfied. For more information, see Sections III.A. and III.B.

- November 2020 – EPA posted the *Ethylene Oxide (EtO) Draft Human Health and Ecological Risk Assessment in Support of Registration Review* (2020 DRA) for a 60-day public comment period. The Agency received 15 comments from 10 commenters. After the DRA public comment period closed, the Agency received additional submissions from the Ethylene Oxide Task Force and the American Chemistry Council. The Agency determined that the submissions included information that had already been considered during development of the DRA. All comments can be found in the docket for the EtO case. The Agency has summarized and responded to these comments in Appendix E. The comments did not change the risk assessments or registration review timeline for EtO.

- March 2023 – The Agency has completed the PID for EtO. The PID is posted to the docket for a 60-day public comment period. Along with the PID, the following documents are also posted to the EtO docket.

    - Response to Public Comments for the Ethylene Oxide (EtO) Draft Risk Assessment (DRA). March 27, 2023.
    - Ethylene Oxide (EtO). Addendum to "Draft Human Health and Ecological Risk Assessment in Support of Registration Review" - Inhalation Exposure Risk Assessment in Support of Registration Review. March 27, 2023.
    - Review of MRID 50231101. Ethylene Oxide Exposures for Ethylene Oxide Sterilization Plant Workers Submitted in Response to the Registration Review GDCI for EtO. March 23, 2023.
    - Food and Drug Administration Center for Devices and Radiological Health (FDA-CDRH) Medical Device Benefits Statement. March 15, 2023.
    - Ethylene Oxide (EtO) Spice Sterilizing Facilities. Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA) responses to questions from Office of Pesticide Programs (OPP), Environmental Protection Agency (EPA). December 20, 2022.
    - Ethylene Oxide (PC# 042301): Use, Usage, Benefits, and Impacts of Cancellation. December 1, 2022.
    - Ethylene Oxide (EtO): Response to registrant's ambient air monitoring requirements waiver request. October 12, 2022.
    - Letter from Dr. Girvin Liggans, Acting Deputy Director for Plant Derived Foods, Office of Food Safety, Center for Food Safety and Applied Nutrition, Food and Drug Administration to Edward Messina, Director, Office of Pesticide Programs, Environmental Protection Agency. August 18, 2022.
    - Email Response to FDA and EPA Questions. Shannen Kelly, American Spice Trade Association (ASTA) to Aparna Tatavarthy, Office of Food Safety, Center for Food Safety and Applied Nutrition, Food and Drug Administration. August 12, 2022.

- Ethylene Oxide (EtO): Summary of Hazard and Science Policy Council (HASPOC) Meeting on June 9th, 2022: Recommendations on the Need for a Special Acute Inhalation Toxicity Study. June 14, 2022.
- Overview of Application Methods and Factors, Use, Usage, and Benefits of Commodity and Structural Fumigants: Phosphine [(066500) including Aluminum Phosphide (066501) and Magnesium Phosphide (066504)], Propylene Oxide (042501), Sulfur Dioxide (077601), Sodium Metabisulfite (111409), Sulfuryl Fluoride, (078003), Ethylene Oxide (042301), and Methyl Bromide (053201). October 5, 2020.
- Letter from Laura Shumow, Executive Director, American Spice Trade Association (ASTA) to Susan Bartow, Pesticide Re-evaluation Division, Office of Pesticide Programs, Environmental Protection Agency. June 25, 2020.
- Ethylene Oxide (ETO): Response to registrant's inhalation exposure monitoring requirements waiver request. June 21, 2018.
- Ethylene Oxide (ETO): Review of MRID 50231103 "Supplemental Information on Ethylene Oxide Industry Usage and Product Use Information." July 19, 2018.
- Ethylene Oxide: Revised Response to Data Waiver Requests Submitted by the Ethylene Oxide Task Force. March 9, 2018.
- Ethylene Chlorohydrin: Summary of Hazard and Science Policy Council (HASPOC) Meeting of January 21, 2016. Recommendations on the Requirement for a Chronic/Cancer Study. June 16, 2016.
- Ethylene Oxide: Response to Data Waiver Requests Submitted by the Ethylene Oxide Task Force. January 21, 2016.
- Ethylene Oxide/Ethylene Chlorohydrin: Summary of Hazard and Science Policy Council (HASPOC) Meeting of April 11, 2013. Recommendations on the need for multiple toxicology studies. May 14, 2013.

### B. EtO Special Review

As discussed above, through the registration review of EtO, EPA will determine whether EtO continues to meet the standard for registration under FIFRA – i.e., does not cause unreasonable adverse effects on the environment. Based on this determination, the Agency also intends to initiate termination of its Special Review of EtO. The Special Review process predates, and is distinct from, the registration review and reregistration processes. EPA may initiate the Special Review process if EPA determines that the use of a pesticide may pose significant risks. EtO entered EPA's Special Review process in 1978 based on concern for potential developmental toxicity, mutagenicity, and neurotoxic effects in workers who are exposed to EtO. A Position Document 1 (PD1) was published in the Federal Register on January 27, 1978, to announce the initiation of the Special Review.[11] In the early 1980s, the carcinogenicity of EtO became of concern and was included for consideration in the Special Review.

To terminate the Special Review of a chemical substance, EPA must publish first a Notice of Preliminary Determination, followed by a Notice of Final Determination, addressing the Agency's determination of whether the use of a pesticide causes unreasonable adverse effects to

[11] 43 Fed. Reg. 3,801.

human health or the environment. On October 29, 2008, the Agency announced in the Federal Register the availability of Position Document 2/3 (PD 2/3). PD 2/3 presented the Agency's preliminary determination to terminate the Special Review of EtO after publication of the Reregistration Eligibility Decision (RED).[12] The Agency has not published a final determination terminating the Special Review of EtO, and since publication of the preliminary determination has received additional data about EtO which EPA has incorporated into the human health assessment for the registration review of EtO.

However, because through registration review EPA will be making a determination as to whether the use of EtO causes unreasonable adverse effects to human health or the environment – the same purpose for which Special Review is undertaken, EPA intends to initiate termination of the Special Review of EtO pursuant to the Agency's Special Review regulations based on the outcome of registration review. Following the publication of the ID or Final Decision, EPA will publish the Notice of Preliminary Determination, then publish the Notice of Final Determination after the public comment period on the Notice of Preliminary Determination. EPA will continue to review the registration of EtO as part of the ongoing registration review process.

### C. Summary of Public Comments on the Draft Risk Assessments and Agency Response

During the 60-day public-comment period for the EtO Draft Risk Assessment (November 20, 2020 to January 19, 2021), the Agency received 15 public comments from 10 commenters. After the DRA public comment period closed, additional comments were submitted by the American Chemistry Council (ACC) and the Ethylene Oxide Task Force (EOTF) on March 19, 2021. The comments submitted by ACC and the EOTF were determined to be similar to comments received from the Louisiana Chemical Association (LCA) and are addressed in the EPA's responses to those commenters. Comments were submitted by representatives from government, non-profit groups, and industry as summarized below:

- United States Department of Agriculture (USDA)
- Harris County, Texas
- Earthjustice, on behalf of Air Alliance Houston et al.
- University of California, San Francisco (UCSF) et al.
- North Carolina State University
- Louisiana Chemical Association (LCA)
- The Ethylene Oxide Sterilization Association (EOSA)
- Ethylene Oxide Task Force (EOTF)
- The American Chemistry Council (ACC)
- Elite Spice, Inc.

The Agency has summarized and responded to all substantive comments and comments of a broader regulatory nature in Appendix E and in the *Response to Public Comments for the*

[12] 73 Fed. Reg. 64,318.

*Ethylene Oxide (EtO) Draft Risk Assessment (DRA)*. The Agency thanks all commenters for participating and has considered all comments in developing this PID.[13]

## II. USE AND USAGE

EtO was first registered as a pesticide in the U.S. in 1966. Because it was registered before 1984, it was subject to reregistration, and a RED was completed by EPA in 2008. There is currently one technical registrant—ARC Specialty Products of Balchem Corporation.

There are 16 registered FIFRA Section 3 products containing EtO as an active ingredient (a.i.), and one FIFRA section 24(c) registration for the use of EtO in beekeeping in North Carolina. 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 1 below presents a summary of the registered antimicrobial and conventional uses of EtO.

**Table 1. Summary of EtO Registered Uses**

| EPA Reg. No. | % a.i. | Packaging (EtO Content) | Use Site |
|---|---|---|---|
| 36736-2 | 100 | Bulk Cylinder | Medical or laboratory items, pharmaceuticals, and aseptic packaging, (21 CFR 201.1(d)(5)), whole and ground spices or other seasoning materials (40 CFR 180.151), artifacts, archival material, library objects, cosmetics and musical instruments. |
| 36736-3 | 80 | Bulk Cylinder | Medical or laboratory items, pharmaceuticals, and aseptic packaging, (21 CFR 201.1(d)(5)), whole and ground spices or other seasoning materials (40 CFR 180.151), artifacts, archival material, library objects, cosmetics and musical instruments. |
| 36736-4 | 10 | Bulk Cylinder | Medical or laboratory items, pharmaceuticals, and aseptic packaging, (21 CFR 201.1(d)(5)), whole and ground spices or other seasoning materials (40 CFR 180.151), artifacts, archival material, library objects, cosmetics and musical instruments. |
| 36736-5 | 20 | Bulk Cylinder | Medical or laboratory items, pharmaceuticals, and aseptic packaging, (21 CFR 201.1(d)(5)), whole and ground spices or other seasoning materials (40 CFR 180.151), artifacts, archival material, library objects, cosmetics and musical instruments. |
| 36736-6 | 12 | Bulk Cylinder | Medical or laboratory items, pharmaceuticals, and aseptic packaging, (21 CFR 201.1(d)(5)), whole and ground spices or other seasoning materials (40 CFR 180.151), artifacts, archival material, library objects, cosmetics and musical instruments. |
| 36736-7 | 8.5 | Bulk Cylinder | Medical or laboratory items, pharmaceuticals, and aseptic packaging, (21 CFR 201.1(d)(5)), whole and ground spices or other seasoning materials (40 CFR 180.151), artifacts, archival material, library objects, cosmetics and musical instruments. |
| 36736-8 | 100 | Technical registration[14] | Medical/lab items; pharmaceuticals; packaging; spices; seasonings; artifacts, archival material, library objects |
| 69340-2 | 97 | Ampule (18.15 g) | Surgical instruments; hospital instruments; hospital critical equipment; heat labile materials; oral and inhalation equipment; diagnostic |

[13] *Response to Public Comments for the Ethylene Oxide (EtO) Draft Risk Assessment (DRA).* Decision Number: 569904. EPA-HQ-OPP-2013-0244.
[14] A technical product is a registered pesticide product that is solely used to formulate other pesticide products.

**Table 1. Summary of EtO Registered Uses**

| EPA Reg. No. | % a.i. | Packaging (EtO Content) | Use Site |
|---|---|---|---|
| | | | instruments/equipment; hospital critical rubber/plastic items; hospital materials; first aid equipment; veterinary hospital instruments; veterinary hospital critical equipment; human face gear; contact lens. |
| 69340-4 | 96 | Cartridge (5 to 14 g) | 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 instruments; veterinary hospital critical equipment; human face gear; contact lens. |
| 69340-5 | 90 | Cartridge (4.5 g) | 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 instruments; veterinary hospital critical equipment; human face gear; contact lens. |
| 69340-6 | 96 | Cartridge (10.5 g) | 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 instruments; veterinary hospital critical equipment; human face gear; contact lens. |
| 69340-7 | 97 | Ampule (17.6 g) | 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 instruments; veterinary hospital critical equipment; human face gear; contact lens. |
| 69340-9 | 97 | Cartridge (17.6 g) | 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 instruments; veterinary hospital critical equipment; human face gear; contact lens. |
| 7182-1 | 100 | Cartridge (100 to 170 g) | Medical equipment and supplies, musical instruments, library/museum artifacts, and cosmetics. |
| 73711-5 | 100 | Ampule (100 to 170 g) | Medical or laboratory items, pharmaceuticals, and aseptic packaging, cosmetics, and artifacts, archival material or library objects. |
| 89514-1 | 100 | Bulk Cylinder | Medical or laboratory items, pharmaceuticals, and aseptic packaging, cosmetics, spices or other seasoning materials, artifacts, archival material or library objects, musical instruments. |
| NC140003 | 8.5 | Bulk Cylinder (parent label) | Special Local Need for beekeeping equipment in North Carolina. The parent label is 36736-7. |
| Note: All End Use Products (EPs) and technical products are formulated as pressurized gas. | | | |

EtO is registered for sterilization of medical devices and equipment (including veterinary equipment), laboratory items, pharmaceuticals, and aseptic packaging. EtO is registered to reduce the microbial load on dried herbs and spices, processed vegetables that have been dried or dehydrated, archival and museum materials, musical instruments, and cosmetics. Additionally, EtO is registered for use under a special local needs registration in North Carolina for use on beekeeping equipment contaminated with American foulbrood (AFB) or other pests.

EPA's Office of Air and Radiation's Office of Air Quality Planning and Standards (OAR OAQPS) estimates that the overall EtO usage as a pesticide (sterilant) in the U.S. is 14 million

pounds annually[15]. As a pesticide, the majority of EtO usage in the U.S. is for sterilization of medical equipment. Usage of EtO for dried herb and spice fumigation is the second most common use pattern and represents approximately 5 - 6% of the total EtO used within the U.S. The American Spice Trade Association (ASTA) reports that the spice industry uses approximately 800,000 pounds of EtO on an annual basis in the U.S.[16]. For beekeeping equipment, the use of EtO is limited via a FIFRA section 24(c) registration to one facility in North Carolina, and the amount of EtO used pursuant to this registration is likely to be low. The Agency expects the total EtO usage for other registered use sites—musical instruments, cosmetics, museum, library, and archival materials—to be very low or zero. There are 97 commercial sterilization facilities using EtO in the U.S. (86 commercial sterilization facilities that are currently in operation and 11 research and development facilities); five of the facilities treat only dried herbs and spices, four facilities treat both medical devices and dried herbs and spices, and the remaining 88 facilities treat only medical devices. EtO also is used to treat medical equipment in healthcare facilities such as hospitals, veterinarian offices, and dental offices.

Antimicrobial Uses: EtO is primarily used as a sterilant for new, single use, and reusable medical devices and equipment (21 C.F.R. § 201). EtO is used to sterilize 50% of all sterilized medical devices, annually, including an estimated 95% of all surgical kits[17, 18, 19, 20]. The other registered antimicrobial uses of EtO include the fumigation/sterilization of artifacts, archival material, library objects, cosmetics, and musical instruments. The antimicrobial products are packaged as bulk cylinders for use in tractor trailer-sized chambers in commercial sterilization facilities or as cartridges for use in oven-sized chambers in healthcare 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

[15] Usage information was collected for the year for which the most recent information was available at each facility, ranging from 2005 to 2019, and was compiled from a number of sources including Clean Air Act Section 114 Information Collection Request for Chemical Manufacturers, EPA, state, or local government inspection reports, company reports, and facility usage logs.
[16] American Spice Trade Association (ASTA). 2020. ASTA's reply to EPA questions regarding ethylene oxide use on spices. Email from Laura Shumow, Executive Directors, ASTA to Susan Bartow, Pesticide Re-Evaluation Division, Office of Pesticide Programs, Environmental Protection Agency. June 25, 2020.
[17] Gamma Industry Processing Alliance (GIPA). 2017. A Comparison of Gamma, E-beam, X-ray and Ethylene Oxide Technologies for the Industrial Sterilization of Medical Devices and Healthcare Products. Found at http://gipalliance.net/wp-content/uploads/2013/01/GIPA-WP-GIPA-iia-Sterilization-Modalities-FINAL-Version-2017-October-308772.pdf. Accessed August 2021.
[18] Federal Advisory Committee Act (FACA). 2019. General Hospital and Personal Use Devices Panel of the Medical Devices Advisory Committee Meeting Announcement, FDA Executive Summary - EtO. https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-6-7-2019-general-hospital-and-personal-use-devices-panel-medical-devices-advisory-committee#event-materials. Accessed August 2021.
[19] Ethylene Oxide Task Force (EOTF). 2020. Ethylene Oxide Benefits Statement submitted by B&C Consortia Management, L.L.C. on behalf of the EOTF. EOTF email to EPA regarding benefits of ethylene oxide for medical devices. Email sent from Lisa Campbell, Partner, Bergeson & Campbell PC to Jessica Bailey, Antimicrobial Division, Office of Pesticide Programs, Environmental Protection Agency. May 6, 2020.
[20] B&C Consortia Management, LLC. 2014. Registration Review of Ethylene Oxide Stakeholder Meeting presentation. Docket ID: EPA-HQ-OPP-2013-0244-0018. https://www.regulations.gov/document/EPA-HQ-OPP-2013-0244-0018. Accessed July 2022.

medical devices and the acceptable levels of residual EtO and ethylene chlorohydrin left on a device after it has undergone EtO sterilization.[21] These standards help ensure levels of EtO on medical devices are within safe limits for patient use. These standards also ensure devices meet sterility assurance levels.[22]

Conventional Uses: EtO is a commodity fumigant/sterilant registered for use to reduce pathogen load (such as *Salmonella* and *Escherichia coli*) on dried herbs and spices, processed vegetables that have been dried or dehydrated, and /or other seasoning materials. ASTA estimates that approximately 40% of dried spices in the U.S. are treated with EtO each year.[23] There are eight products currently registered for treatment of dried herbs, dried spices, dried vegetables, and seasoning materials. All of these products are 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. The maximum application rate for treatment of dried herbs and spices, dried vegetables, and other seasonings is 500 mg/L (or 31.22 lb a.i./1,000 $ft^3$) in a sealed chamber.

# III. SCIENTIFIC ASSESSMENTS

## A. Human Health Risks

The Agency has summarized the human health sections of the 2020 DRA and 2023 DRA Addendum below. The Agency used the most current science policies and risk assessment methodologies to prepare the risk assessment and addendum in support of the registration review of EtO. For additional details on the 2020 DRA and 2023 DRA Addendum, see *Ethylene Oxide (EtO) Draft Human Health and Ecological Risk Assessment in Support of Registration Review* and *Ethylene Oxide (EtO). Addendum to "Draft Human Health and Ecological Risk Assessment in Support of Registration Review" - Inhalation Exposure Risk Assessment in Support of Registration Review* in EPA's public docket (EPA-HQ-OPP-2013-0244).

Definition of terms

For purposes of the registration review of EtO, EPA is using the following definitions for describing the different groups of individuals exposed to EtO:

- *Occupational handler*: A person who is directly involved in EtO sterilization, in commercial sterilization facilities, healthcare facilities or beekeeping operations. This

[21] Ethylene chlorohydrin is a reaction product of EtO. See ANSI AAMI ISO 10993-7:2008(R)2012.
[22] For additional information on sterilization for medical devices, please see: https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/ethylene-oxide-sterilization-medical-devices.
[23] American Spice Trade Association (ASTA). 2020. ASTA's reply to EPA questions regarding ethylene oxide use on spices. Email from Laura Shumow, Executive Directors, ASTA, to Susan Bartow, Pesticide Re-Evaluation Division, Office of Pesticide Programs, Environmental Protection Agency. June 25, 2020.

employee, for example, would be loading or unloading sterilization or aeration chambers/areas.

- *Occupational bystander*: A person who, by nature of their employment, could be exposed to EtO. This includes employees within a facility or area where EtO is used, but who do not directly handle EtO (for example, employees in control rooms or storage warehouses). This also includes persons employed at other workplaces nearby facilities or areas where EtO is used, who would spend a significant amount of time at that location (e.g., 8 hours per day, 5 days per week). An occupational worker who is employed nearby a facility in another workplace may also be referred to as a "non-residential bystander" (see below).

- *Non-residential bystander*: A person who may be exposed to EtO who does not live near a facility or area where EtO is used, but who may otherwise spend a significant amount of time near the facility. For example, children in schools or daycares who typically spend several hours per day and five days per week in that location.

- *Residential bystander*: A person who may be exposed to EtO who lives nearby a facility or area where EtO is used.

***Risk Summary and Characterization***

Under the Federal Insecticide Fungicide and Rodenticide Act, OPP applies a "no unreasonable risk" standard for both dietary and non-dietary exposures in making a risk management decision. To help initially identify chemicals which may pose such unreasonable risks, OPP considers whether the risks from a chemical exceed a specified level of concern. If a given risk exceeds this level, OPP decides what further action, if any, is needed. OPP generally seeks to reduce the risk to less than $1 \times 10^{-6}$ (1 in 1 million) for both occupational and residential exposures. In some cases, when it is not possible to mitigate to this level of risk and benefits of the pesticide are high, a risk target of up to $1 \times 10^{-4}$ (100 in 1 million) may be used for occupational exposures.

As explained in the following sections, The EtO concentration at which the cancer risk equals a certain target level ($1 \times 10^{-4}$ or $1 \times 10^{-6}$) was back calculated from the inhalation unit risk (IUR) for adults. OPP generally seeks to reduce the risk to less than $1 \times 10^{-6}$ (1 in a million) for both occupational and residential exposures. At that level, OPP generally considers risks to be negligible and would not pursue additional risk mitigation measures. In the case of EtO given its high benefits, for occupational exposures, OPP also examines risks in the range of $1 \times 10^{-4}$ (100 in 1 million) to determine whether benefits of use outweigh the risks and whether mitigation is appropriate to reduce those risks. For EtO, risks exceed 100 in 1 million; however, the corresponding benefits outweigh the risks, as explained in Section V.D. For occupational bystanders employed in commercial sterilization facilities, healthcare facilities, and beekeeping equipment treatment areas, EPA is establishing a risk threshold of 100 in 1 million. For occupational bystanders employed in workplaces (i.e., non-residential bystanders) nearby EtO treatment facilities, EPA is establishing a risk threshold of 1 in 1 million. Calculations in all scenarios indicate EtO concentrations would have to be extremely low in order to meet either risk threshold. As explained in the following sections, this calculation indicates that if the EtO

exposure for workers in contract sterilization facilities in these areas does not exceed 0.19 ppb as an 8-hour time-weighted average (TWA), the cancer risk will not exceed 1 x $10^{-4}$ (100 in 1 million). If the EtO exposure for workers employed in nearby workplaces (i.e., not the commercial sterilization facility) does not exceed 0.0019 ppb, the cancer risk will not exceed 1 x $10^{-6}$ (1 in 1 million). This calculation of 0.0019 ppb is relevant to both the antimicrobial and conventional uses of 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 (introduces an alkyl radical to) 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. For workers 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 in the qualitative 2020 *Ethylene Oxide Draft Risk Assessment* differ in conclusions concerning the association of EtO exposure with breast cancer. However, the 2023 DRA Addendum includes a quantitative risk assessment based on the 2016 EPA Integrated Risk Information System (IRIS) cancer assessment, which includes breast cancer risk.

Neurotoxicity is also observed in repeat dose toxicity studies with EtO in experimental animals and from exposure in humans. Peripheral neuropathy, impaired hand-eye coordination and memory loss have been reported in workers exposed to EtO for longer periods.

OPP collaborated with the Office of Research and Development's (ORD) and Office of Air and Radiation (OAR) during their assessment process of EtO to further inform the cancer evaluation characterization and ongoing work 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, and federal agencies such as the Occupational Safety and Health Administration (OSHA) and the Food and Drug Administration (FDA). See Section IV.

In the 2020 *Ethylene Oxide Draft Risk Assessment,* OPP presented multiple perspectives on cancer evaluations for EtO but did not choose a single value for risk extrapolation, nor did OPP provide a critical review of the available approaches. In the 2020 DRA, OPP recognized that, despite several years of study by EPA and various stakeholders, there are different approaches for addressing the cancer dose-response assessment for EtO. Nevertheless, based on the range of cancer inhalation unit risks (IUR) provided in the qualitative assessment, OPP believed that additional mitigation of EtO exposure would be necessary to address cancer risk from inhalation exposure to EtO.

In the 2023 DRA Addendum, OPP updated a portion of the EtO risk characterization by providing a quantitative risk assessment that used the inhalation unit risk (IUR) value from the 2016 EPA IRIS cancer assessment to assess inhalation cancer risk to workers and bystanders. The 2016 IRIS assessment went through "unusually extensive processes for the consideration of

public comment and external peer review," and is considered by ORD to be the "best available scientific information regarding cancer risks from EtO." Further, since the publication of the 2020 DRA, EPA has repeatedly expressed favorable views of the IRIS assessment, including in comparison to the other EtO cancer inhalation risk characterization approaches cited in the 2020 DRA.[24] Therefore, the 2023 DRA Addendum updates the EtO 2020 DRA for the human health inhalation risk assessment using the IUR values from the IRIS Assessment to characterize the cancer risk from inhalation exposure.[25]

For the conventional dried spice fumigation use of EtO, the assessment included EtO and its reaction products ethylene bromohydrin (EBH), ethylene chlorohydrin (ECH), and ethylene glycol (EG). Formation of EBH and ECH results 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. The 2020 DRA primarily focused 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. EPA has concluded that dietary risks from exposures to EtO and its reaction products in food and drinking water are not of concern. The 2023 DRA Addendum did not change OPP's conclusions about residues.

*Dietary (Food + Water) Risks*

In the 2020 DRA, EPA did not identify any dietary risks of concern for EtO or ECH. A quantitative dietary assessment was not conducted for EtO since sterilization studies[26] show that EtO residues disappear rapidly after sterilization and are unlikely to be found in spices available for consumption. EtO residues are expected to be present on commodities immediately after the fumigation process (e.g., 24 hours) and may be present as the commodity enters the channels of trade; therefore, a tolerance for EtO is needed and was established with 2005 residue data for the single chamber fumigation process required on product labels. However, the EtO residues are expected to completely dissipate by the time the commodity is available for consumption (e.g., 2 months)[27][28] and thus a quantitative dietary assessment for EtO was not conducted. Because exposures to residues of EtO in food and drinking water are expected to be minimal to none, no dietary risks are expected.

[24] US EPA, 2021a. EPA Should Conduct New Residual Risk and Technology Reviews for Chloroprene- and Ethylene Oxide-Emitting Source Categories to Protect Human Health, Report No. 21-P-0129, US EPA Office of Inspector General, May 6, 2021.
[25] 87 Fed. Reg. 77, 985 (Dec. 21, 2022).
[26] MRID 46625301. Magnitude of the Residue of Ethylene Oxide and Ethylene Chlorohydrin in/on Spices. Wright, M. (2005). Study sponsored by American Spice Trade Association. 829 p.
[27] MRID 46625301. Magnitude of the Residue of Ethylene Oxide and Ethylene Chlorohydrin in/on Spices. Wright, M. (2005). Study sponsored by American Spice Trade Association. 829 p.
[28] Memorandum. *Ethylene Oxide. Case 2275. Results of Trade Practices Survey on Spices & Anticipated Residues for Dietary Exposure Assessment*. Leung Cheng, Health Effects Division. March 26, 1997.

ECH is a reaction product formed during the EtO fumigation. ECH residues are present on commodities immediately after the fumigation process and when the commodities are available for consumption. Therefore, both tolerances and a dietary assessment are needed for ECH. 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). EPA did not conduct a quantitative acute dietary risk assessment as toxicological effects attributable to a single dose were not present (i.e., no acute endpoint identified). In addition, a separate cancer dietary risk assessment was not conducted because the chronic assessment adequately accounts for all chronic toxicity, including potential carcinogenicity. The conservative chronic dietary risk assessment assumed 100% of registered dried spices were treated with EtO post-harvest, and that the ECH residues on such crops reflected tolerance-level residues.[29] All processing factors were set to 1 since drying procedures are performed prior to sterilization. No residues were 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 because EtO is a volatile gas and its use in sterilization chambers is unlikely to result in EtO residues in groundwater or surface water. Moreover, residential exposures to ECH are not expected because ECH is a reaction product that forms on the surface of the treated commodity during EtO fumigation. ECH is not volatile and will remain on the commodity; therefore, the only relevant exposure pathway is through dietary sources. 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 U.S. population was 2.7% cPAD. The 2023 DRA Addendum did not change OPP's conclusions about dietary risks.

*Commercial Sterilization Facilities: Residential Bystander Exposures and Risks*

There is the potential for EtO exposure to children and adults who live near sterilization facilities. These exposures are also being addressed by the proposed OAR rulemaking.[30] The EtO average daily concentration at which the cancer risk is 1 x $10^{-6}$, and therefore not considered by OPP to be of concern for non-occupational exposures, was back calculated from the IUR for lifetime exposure. This is assuming continuous exposure (i.e., 24 hours a day for seven days a week) for a 70-year lifetime starting at birth. This calculation indicates that if the average daily concentration in these areas does not exceed 0.00011 ppb (0.11 ppt), the cancer risk will not exceed 1 x $10^{-6}$ (1 in 1 million). This is below the limit of detection (LOD) of 20-90 ppt for EtO in ambient air.

*Commercial Sterilization Facilities: Non-Residential Bystander Exposures and Risks (Daycare Centers and Schools)*

[29] 40 CFR §180.151.
[30] US EPA, 2022. Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review. FR Doc. 2022-01923, Filed: 02/03/2022.

Non-residential bystander exposures can occur at a variety of facilities such as daycare centers, schools, retail establishments, restaurants, gyms, swimming pools, music studios, movie theatres, etc., that are between the fence line of a sterilization facility and the nearest residence. Exposures to children attending daycare centers and schools are protective of other non-residential bystander exposures because they occur more frequently and with a longer daily duration. In addition, EtO is a mutagen that requires the use of age dependent adjustment factors (ADAFs) to assess childhood exposures. The EtO concentration at which the cancer risk equals $1 \times 10^{-6}$ was back calculated from the IUR assuming children attend daycare 8 hours per day for 240 days per year for 6 years and school for 6 hours a day for 180 days per year for 12 years near a sterilization facility. These calculations indicate that the cancer risk is $1 \times 10^{-6}$ (1 in 1 million) for children who attend daycare and school where the average daily EtO concentration is 0.0012 ppb (1.2 ppt). This is below the LOD of 20-90 ppt for EtO in ambient air.

To get a better understanding of how the back-calculated concentrations that exceed risks of concern for non-residential bystanders (e.g., children who attend school) relate to concentrations around facilities, the air concentrations developed by the Office of Air and Radiation (OAR) in their recent proposed rulemaking were considered.[31] Air concentrations were modeled around each sterilization facility and annual average air concentrations were derived by OAR. The model results indicate that there is a potential for EtO concentrations to exceed the level of 1.2 ppt that corresponds to a cancer risk of $1 \times 10^{-6}$ for children in schools/daycares that are in non-residential areas near sterilization facilities. This is below the LOD of 20-90 ppt for EtO in ambient air.

*Health Care Facilities: Residential and Non-Residential Bystander Exposures*

Since 2010, healthcare sterilization facilities have been required to utilize all-in-one sterilizers (i.e., materials are treated and aerated in the same chamber to reduce worker exposure) in accordance with the EtO RED.[32] These facilities sterilize material in oven-sized chambers using 4.5 to 170 grams of EtO per load (in comparison, EtO usage is much smaller in healthcare facilities compared to commercial sterilization facilities, where fumigation takes place in tractor trailer sized chambers). The exhaust from the chambers is typically routed to an air pollution control device and the room air is typically ventilated though an exhaust stack to minimize exposures as recommended in the American National Standard Institute/Association for the Advancement of Medical Instrumentation (ANSI/AAMI) standard ST41.[33] Given this information, exposures to residential and non-residential bystanders near health care facilities are expected to be minimal, but the exact concentrations are not known and therefore the risks were not quantitatively assessed in the 2020 DRA or 2023 DRA Addendum. It is known, however, that the exposures that would result in a cancer risk of 1 in 1 million are the same as those calculated for contract sterilization facilities (i.e., 0.11 ppt for residential areas and 1.2 ppt for

[31] See OAR's residual risk assessment for the commercial sterilization facilities source category document in support of the 2022 Risk and Technology Review Proposed Rule. This document is currently an internal draft and will be posted to Regulations.Gov for Docket Number: EPA-HQ-OAR-2019-0178 when it is finalized.
[32] Reregistration Eligibility Decision for Ethylene Oxide. March 31, 2008.
[33] ANSI/AAMI, 2018. American National Standard: Ethylene Oxide Sterilization in Health Care Facilities: Safety and Effectiveness. ANSI/AAMI ST41:2008/(R)2018. American National Standards Institute/Association for the Advancement of Medical Instrumentation (ANSI/AAMI). 2018.

children in schools and daycares). EPA-OPP does not have monitoring data from health care facilities to confirm potential exposure concentrations to bystanders. The NESHAP for Hospital Ethylene Oxide Sterilizers addresses EtO emissions from hospitals where EtO is used, and OAR plans to evaluate the risks from hospital sterilizers in an upcoming regulatory review of this NESHAP.

*Beekeeping Equipment Fumigations in North Carolina: Residential and Non-Residential Bystander Exposures and Risks*

For the FIFRA section 24(c) beekeeping equipment fumigation use in North Carolina, there is the potential for both residential and non-residential non-occupational bystander exposure. A quantitative residential non-occupational bystander assessment, assuming someone lives near a fumigation chamber for a full lifetime (24 hours/day for four or eight exposure days per year for 70 years of exposure per lifetime), was conducted using the Probabilistic Exposure and Risk Model for Fumigants (PERFUM)[34]. This assessment would be protective of any non-residential exposures which would have a shorter exposure duration (e.g., 35 working years vs. 70 lifetime years). Two application rates were modeled as provided on the product label: 28.3 lb. ai/1,000 $ft^3$ and 46.5 lb. ai/1,000 $ft^3$. The concentration distribution output from PERFUM for various percentiles ($50^{th}$, $75^{th}$, $80^{th}$, $85^{th}$, and $90^{th}$) was used to calculate cancer risk estimates assuming four or eight exposure days (24 hrs./day) per year and 70 years of exposure per lifetime. The IRIS inhalation unit risk for environmental exposures for a full lifetime [$5.0 \times 10^{-3}$ per $\mu g/m^3$ ($9.15 \times 10^{-3}$ per ppb)] was used to estimate cancer risks.

The distances from the fumigation chamber at which the cancer risk estimates are less than $1 \times 10^{-6}$ increase from lower to higher percentiles. For example, at the $75^{th}$ and $80^{th}$ percentiles, the distance from the fumigation chamber at which the cancer risk is less than $1 \times 10^{-6}$ is only 10 meters, while at the $90^{th}$ percentiles, distances of 300 meters or more are necessary to reach cancer risk estimates less than $1 \times 10^{-6}$. A specific percentile has not been selected for regulation (and correspondingly a buffer distance from the fumigation chamber has not been established) since the Agency is proposing to terminate the use of EtO on beekeeping equipment in North Carolina (see Section V.A for details).

*Occupational Bystander and Occupational Post Application Risk*

OPP considers the potential for exposure to occupational bystanders who work in non-processing areas of treatment facilities, healthcare facilities, or beekeeping equipment treatment areas; in downstream facilities such as warehouses where the treated product is shipped and stored; or in other workplaces that are near the treatment facilities, healthcare facilities, or beekeeping equipment treatment areas.

To get a better understanding of how the back-calculated EtO concentrations that exceed risks of concern for occupational bystanders (adults who work near sterilization facilities) relate to

[34] US EPA, 2019. User's Guide for the Probabilistic Exposure and Risk model for FUMigants PERFUM Version 3.0. Prepared by Exponent, 1800 Diagonal Road, Suite 500 Alexandria, VA 22314. Sponsored by US EPA, OPP, Health Effects Division (HED). October 28, 2019.

concentrations around facilities, the air concentrations modeled by the Office of Air and Radiation (OAR) in their recent proposed rulemaking were considered.[35] Air concentrations were modeled around each sterilizing facility and annual average air concentrations were derived by OAR. The model results indicate that there is a potential for EtO concentrations to exceed the level of 0.0019 ppb (1.9 ppt) that corresponds to cancer risk of 1 x $10^{-6}$ for adults who work near facilities modeled by OAR.

*Aggregate Risks*

In an aggregate assessment conducted to support the safety of EtO tolerances, EPA considers the combined pesticide exposures and risks from three major sources: food, drinking water, and residential / non-occupational exposures. In the context of discussing the FFDCA aggregate assessment, EPA is using the term "residential" to reflect the FFDCA requirement to consider non-occupational sources of exposure to the pesticide chemical residue. The Agency sums the exposures from these sources and compares the aggregate exposure to quantitative estimates of hazard. EPA considers the route and duration of exposure when assessing aggregate risks.

*EtO*
EPA did not conduct a quantitative aggregate assessment for EtO, although it has determined that exposures to EtO will not result in aggregate risks of concern for purposes of supporting the EtO tolerances. EPA has concluded that dietary risks from exposures to EtO in food and drinking water are not of concern. This conclusion is based on residue data showing that there is no expectation of residues of EtO on food when consumed. Although residue data show that there are residues on food treated with EtO following fumigation, for 24 hours, the available data indicates that most spices are not available for purchase until at least 2 months after treatment, at which time, extrapolated residues indicate no residues of EtO on food.[3637] Moreover, EPA does not expect any residues in drinking water, because EtO is a volatile gas and its use in sterilization chambers is unlikely to result in EtO residues in groundwater or surface water.

Under EPA's General Principles for Performing Aggregate Exposure and Risk Assessments, EPA considers many factors in determining whether to aggregate exposures. For example, EPA's guidance says that exposure scenarios should not be combined when there are different toxicological effects via different routes of exposure. Moreover, EPA may consider the temporal nature of exposure to residues and the likelihood of co-occurrence of those exposures.

Although there may be some residues of EtO in or on food soon after treatment, EPA does not expect consumption of those spices while parent EtO residues persist. At the time of consumption of treated food commodities, there will be no residues of parent EtO in or on

[35] See OAR's residual risk assessment for the commercial sterilization facilities source category document in support of the 2022 Risk and Technology Review Proposed Rule. This document is currently an internal draft and will be posted to Regulations.Gov for Docket Number: EPA-HQ-OAR-2019-0178 when it is finalized.
[36] MRID 46625301. Magnitude of the Residue of Ethylene Oxide and Ethylene Chlorohydrin in/on Spices. Wright, M. (2005). Study sponsored by American Spice Trade Association. 829 p.
[37] Memorandum. *Ethylene Oxide. Case 2275. Results of Trade Practices Survey on Spices & Anticipated Residues for Dietary Exposure Assessment*. Leung Cheng, Health Effects Division. March 26, 1997.

food.[38, 39] At that time, there is no co-occurrence of residues in or on food with any potential residential exposures; therefore, there cannot be an additive effect. The FFDCA requires aggregation to ensure that residues in or on food are safe; if people are not being exposed to residues in or on their food, then there is no risk from exposures on food with which to aggregate risks from other exposures.

Based on the lack of dietary risk and the nonadditive nature of any negligible residues on food with residential exposures, EPA concludes that the aggregate risk from exposure to EtO consists only of exposures to residues on food, of which there are none at the time of consumption. Therefore, aggregate risk does not exceed the Agency's level of concern.

*EtO Reaction Products*

For the reaction products of EtO (ECH and EG), there are no water or non-dietary residential exposures; the only exposure route is through food. Thus, the aggregate risk from exposure to ECH is equal to the risk from dietary exposure alone; a separate aggregate assessment was not conducted for ECH or EG. Since dietary exposure alone does not exceed EPA's risks of concern, aggregate exposure does not exceed the Agency's level of concern.

*Cumulative Risks*

EPA has not made a common-mechanism-of-toxicity finding for EtO and any other substance. EtO does not appear to produce a toxic metabolite produced by other substances. Therefore, EPA has premised this PID and the underlying risk assessments on the belief that EtO does not have a common mechanism of toxicity with other substances.

*Occupational Handler Risks*

Antimicrobial Uses in Commercial Sterilization Facilities. The cancer risks for the antimicrobial uses were calculated using the arithmetic mean of the submitted exposure data for commercial sterilizer and healthcare facilities. Since these facilities operate on a continuous basis, the submitted exposure data were assumed to represent a 35-year occupational exposure between ages 20 and 55 years (8 hours per day, 40 hours per week). The cancer risks for the exposure were, therefore, estimated using the table in the 2016 IRIS assessment titled "Extra Risk Est. for Total Cancer Incidence for Occupational Exposure Levels" found in the IRIS cancer assessment (and referenced in table 9 of the 2020 DRA). The Maximum Likelihood [Risk] Estimate (MLE) and upper-bound cancer risk estimates range from $4 \times 10^{-2}$ (1 in 25) to $1 \times 10^{-1}$ (1 in 10), depending upon which facility type and cancer risk estimate are considered. The upper-bound cancer risks are approximately twice the MLE cancer risks. For commercial sterilization facilities, the MLE cancer risk is 1 in 17 and the upper bound cancer risk is 1 in 10. EPA expects the mitigation in Section V.A. to reduce exposures from commercial sterilization facilities.

[38] MRID 46625301. Magnitude of the Residue of Ethylene Oxide and Ethylene Chlorohydrin in/on Spices. Wright, M. (2005). Study sponsored by American Spice Trade Association. 829 p.
[39] Memorandum. *Ethylene Oxide. Case 2275. Results of Trade Practices Survey on Spices & Anticipated Residues for Dietary Exposure Assessment*. Leung Cheng, Health Effects Division. March 26, 1997.

Antimicrobial Uses in Healthcare Facilities. In healthcare facilities, the MLE cancer risk is 1 in 25 and the upper bound cancer risk is 1 in 12. Since 2010, health care sterilization facilities have been required to operate on an all-in-one basis in accordance with the EtO Reregistration Eligibility Decision[12]. These facilities sterilize material in oven-sized chambers using 4.5 to 170 grams of EtO per load. The exhaust from the chambers is typically routed to an air pollution control device and the room air is typically ventilated though an exhaust stack (ANSI/AAMI, 2018). Given this information, exposures to residential and non-residential bystanders near health care facilities are expected to be minimal, but the exact concentrations are not known and therefore the risks were not quantitatively assessed in the 2020 DRA or 2023 DRA Addendum. It is known, however, that the exposures that would result in a cancer risk of 1 in 1 million are the same as those calculated for contract sterilization facilities (i.e., 0.11 ppt for residential areas and 1.2 ppt for children in schools and daycares). EPA-OPP does not have monitoring data from health care facilities to confirm potential exposure concentrations to bystanders. The NESHAP for Hospital Ethylene Oxide Sterilizers addresses EtO emissions from hospitals where EtO is used, and OAR plans to evaluate the risks from hospital sterilizers in an upcoming regulatory review of this NESHAP. Recognizing that risks to bystanders from healthcare facilities were not quantitatively assessed, EPA expects the mitigation proposed in Section V.A., abatement devices, to reduce exposures, and therefore any risks, to bystanders.

Conventional Uses in Commercial Sterilization Facilities. The cancer risks for the use of EtO on dried herbs and spices (i.e., conventional uses) in commercial sterilization facilities were calculated using the arithmetic mean of the submitted exposure data for the commercial spice facilities. Since these facilities operate on a continuous basis, the submitted exposure data were assumed to represent a 35-year occupational exposure between ages 20 and 55 years. Since the exposure is less than 0.1 ppm, the cancer risks were calculated using the formulas listed in Section 4, page 111 of the IRIS assessment.[40]

Submitted exposure data from commercial sterilization facilities indicate that some of the workers did not wear respirators during the time that they were monitored when they were doing activities for which a respirator was not required. Therefore, when calculating exposures, respiratory protection factors were only applied to concentrations measured during activities when a respirator was worn. Concentrations measured during activities when no respirator was worn (and is not required to be worn according to the product labels) were not adjusted for any respiratory protection factors. Cancer risks range from $3 \times 10^{-2}$ (1 in 36) for the MLE to $6 \times 10^{-2}$ (1 in 16) for the upper bound.

Beekeeping Equipment Use in North Carolina. Monitoring data specific to the beekeeping equipment fumigation use are not available; however, based on the label directions and requirements for the Special Local Need (SLN) beekeeping equipment use (related to EPA Reg. # 36736-7), it is anticipated that the ASTA monitoring data for the commercial spice facilities would be protective of the beekeeping use and was used as a surrogate. Cancer risks for the beekeeping equipment use were calculated using the arithmetic mean of the submitted exposure

[40] US EPA, 2016. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, (CASRN 75-21-8), In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-16/350Fa. NCEA, ORD, US EPA, Washington, DC. December 2016.

data for the commercial spice facilities. To account for the differences in potential exposure between workers in an indoor commercial spice sterilization facility and workers fumigating beekeeping equipment in an outdoor chamber, the activities reported were limited to those that would likely occur during outdoor beekeeping equipment fumigation (see Appendix A in the 2023 DRA Addendum for details). Since the beekeeping fumigation exposures are considered "intermittent occupational exposures," a lifetime average concentration (LAC) was calculated, assuming either four or eight exposure days per year, and then the cancer risks were calculated using the LAC and the adult specific IUR of $5.5 \times 10^{-3}$ per ppb. Cancer risks range from $2 \times 10^{-4}$ (1 in 5,000) when assuming four exposure days per year to $4 \times 10^{-4}$ (1 in 2,500) when assuming eight exposure days per year. These risk estimates, which also assume that self-contained breathing apparatus (SCBA) PPE is in use, exceed the Agency target of $1 \times 10^{-4}$ for occupational risks.

***Human Incidents and Epidemiology***

EPA reviewed EtO incidents reported to the Incident Data System (IDS). As of EPA's latest search on December 1, 2022, the IDS showed nine medium- to high-severity incidents from March 1, 2008 to December 1, 2022. Six of these incidents were in an international setting using a U.S. EPA-registered product in Barbados, Sri Lanka, Korea (two), Taiwan, and Thailand. Two incidents, which occurred in the U.S., involved a spill and a misuse of the product, which were associated with acute symptoms such as headache, light-headedness, and racing heart. The remaining incident in the U.S. described a hospital employee who was diagnosed with leukemia after six years of employment. Although EtO is a known carcinogen, it is not possible to determine if the cancer in this incident was caused by EtO exposure and/or some other factor(s) based on the available information. The Agency intends to monitor human incidents for EtO and will conduct additional analyses if necessary.[41]

***Tolerances***

EtO is registered for uses that result in residues in or on food. Generally, a tolerance or tolerance exemption must cover the residues, or the affected food is considered adulterated.[42] EPA has determined that the Agency established most of the necessary tolerances for residues resulting from EtO's legal use.

The Agency has established tolerances for EtO and the EtO reaction product, ethylene chlorohydrin (ECH), under 40 C.F.R. § 180.151. However, during the risk assessment process, EPA determined that revisions to the tolerances and tolerance expressions are necessary. EtO and ECH tolerances need to be revised for several commodities to reflect updated commodity definitions. The 2020 DRA notes that the tolerance expressions for EtO and ECH need to be updated per current practice concerning tolerance expressions. In the 2020 DRA, the Agency determined that the EtO tolerance for walnuts needs to be revised to reflect the lower residues resulting from the required single chamber process. The 2020 DRA also states an ECH tolerance

[41] OSHA additionally has publicly available information on EtO incidents and enforcement, which can be accessed at https://www.osha.gov/data
[42] 21 U.S.C. §§ 342, 346(a).

for walnuts needs to be established based on the documented level of quantification (LOQ). However, the Agency is not aware of current EtO use on walnuts and none of the EtO products are currently labeled for use on walnuts. Based on the information currently before EPA, the use of EtO on walnuts is unlikely to meet the standard for registration under FIFRA because (1) the lack of usage of EtO on walnuts suggests that there are alternatives (e.g., nonchemical, propylene oxide [PPO]) available for the fumigation of walnuts and (2) the occupational cancer risk estimates for EtO use in commercial sterilization facilities exceed the Agency's threshold of 1 x $10^{-4}$. Therefore, the Agency intends to exercise its authority under the FFDCA to revoke the walnut tolerance. Tolerance changes will be proposed through a separate rulemaking process.

No tolerance changes are anticipated for international harmonization. Codex has not set Maximum Residue Limits (MRLs) for EtO or ECH. Canada has not set MRLs for walnut 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. For more information on tolerances, see Section V.C, below.

***Human Health Data Needs***

The human health database for EtO is not considered complete. Although not all human health data requirements have been completely met, EPA has determined that available data were sufficient to conduct the 2020 HHRA and the 2023 DRA Addendum and are sufficient to support this PID. Based on the occupational risk estimates for EtO, EPA believes that further mitigation of EtO exposure is required. The Agency intends to continue working with the registrants to satisfy the data requirements under the existing DCI notice (GDCI-042301-1428).

One data requirement is still outstanding and will be used to inform future risk assessments. The following study is outstanding for the EtO GDCI-042301-1428:

- Non-Guideline Study Monitoring Data on Fumigated Commodities

This study is required to evaluate emission rates for EtO from treated commodities/materials and the potential for occupational exposure due to those emissions in the channels of trade after fumigation activities are complete. The registrants submitted a waiver request for this study (MRID 50384901) on September 8, 2017. However, this waiver request was denied on July 17, 2018, due to a lack of information related to potential exposures within the various channels of trade after fumigation, dissipation of EtO beyond the facility, and the analytical method used to measure air concentrations.[43]

Further, EPA proposes that registrants submit OCSPP GLN 875.1400 Inhalation Exposure Indoor for worker monitoring data for both the medical device sterilization and spice fumigation uses. To quantify the effect of mitigation on worker exposure in commercial sterilization facilities, EPA proposes to issue a Data Call-In (DCI) for OCSPP GLN 875.1400 Indoor Inhalation and require a protocol before monitoring begins. Based on non-specificity and lacking

[43] Ethylene Oxide (EtO): Response to registrant's inhalation exposure monitoring requirements waiver request. Decision Number 533138. June 21, 2018.

detail of previously submitted worker monitoring data in commercial sterilization facilities treating medical devices, EPA proposes to require, through a DCI, air monitoring of the occupational handlers specifically involved in fumigation activities (e.g., loading and unloading chambers, routine maintenance, product transfer), documentation of what activities each worker did while monitored, and whether they were wearing a respirator or not (and what type) for all commercial sterilization facilities. For non-handlers in the facility (e.g., office workers, warehouse workers), EPA proposes to also require air monitoring data through a DCI. The Agency proposes that registrants follow the OSHA Method 1010 as the monitoring method.[44] EPA proposes that the DCI to be issued would require registrants to submit this data following implementation of all mitigation. The Agency would issue a DCI to establish a timeline for submitting these data.

To reduce worker exposure, EPA is proposing that respirator requirements be based on a technologically measurable (i.e., quantifiable) EtO concentration of ambient air for real time measurements, which by the Agency's understanding is 10 ppb. See Section V.A.

## B. Ecological Risks

The Agency assessed ecological risks in the 2020 DRA, which are summarized below. EPA did not reassess ecological risks as part of the 2023 DRA Addendum, which focused on human health risks. The Agency used the most current science policies and risk assessment methodologies to prepare a risk assessment in support of the registration review of EtO.[45] For additional details on the 2020 DRA, see *Ethylene Oxide (EtO) Draft Human Health and Ecological Risk Assessment in Support of Registration Review* in EPA's public docket (EPA-HQ-OPP-2013-0244).

The EPA is currently working with its federal partners and other stakeholders to improve the consultation process for federally-listed species and their designated critical habitats. The Agency has not yet fully evaluated EtO's risks to listed species. However, EPA will complete its listed-species assessment and any necessary consultation with the Services before completing the EtO registration review. See Appendix C for more details. As such, potential risks for non-listed species only are described below.

### *Risk Summary and Characterization*

The Agency assessed ecological risks in the 2020 DRA, which are summarized below. All ecological data requirements were waived as part of a waiver response dated March 9, 2018, as explained below. EPA did not reassess ecological risks as part of the 2023 DRA Addendum.

[44] OSHA Method 1010 (revised 2014) can be found at https://www.osha.gov/sites/default/files/methods/osha-1010.pdf.

[45] The 2020 Eco DRA only addresses potential risks to species not listed under the Endangered Species Act. EPA is working with its federal partners and other stakeholders to implement a Revised Method (EPA-HQ-OPP-2019-0185-0054) for assessing potential risk to listed species and their designated critical habitats. The Agency will complete EtO's listed-species assessment once EPA has fully implemented the scientific methods necessary to complete listed species' risk assessments. For more details, see Appendix C.

EtO sterilization is performed indoors in vacuum or gas tight chambers. Sterilization in large- and medium-sized commercial sterilization facilities must follow National Emissions Standards for Hazardous Air Pollutants (NESHAP) requirements for emissions control. Approximately 1% of the EtO used for sterilization is used in medium-sized facilities and approximately 0.1% of the EtO used for sterilization is used in small-sized facilities.[46] Exposures to EtO from large- and medium-sized facilities with controls achieving greater than or equal to 99% reduction in emissions—consistent with the applicable NESHAP requirements for emissions control at the time of the OPP ecological assessment—are not of concern.[47, 48] Therefore, with approximately 99% of sterilization occuring in large- and medium-sized facilities with emissions controls achieving greater than or equal to 99% emissions reductions, any exposure to wildlife from the use of EtO will likely be limited, with the possible exception of the aforementioned low percentage of small-sized facilities that are not subject to the NESHAP requirements for emissions controls and may not achieve 99% emissions reductions. OPP notes that OAR is proposing updates to the NESHAP for the Commercial Sterilization Facilities source category to require more stringent controls for EtO emissions. OPP expects that these more stringent emissions controls and OPP's proposed rate reductions (if finalized) will further reduce exposure to nontarget species.

For both the spice and medical uses in small-sized commercial sterilization facilities, terrestrial organisms in the vicinity or downwind of a treatment vent may be at risk from EtO vapor exposure due to the fugitive emissions. 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. For aquatic organisms, risks are not expected due to limited exposure potential since uses of EtO are not expected to create a significant pathway for deposition, runoff, or leaching into water bodies. EPA has determined that emissions of EtO uses from small-sized facilities may present risks of concern to birds, mammals, honey bees, or plants when considering currently available data; however, emissions of EtO uses from large- and medium-sized facilities (after controls achieving ≥ 99% reduction in emissions) do not present risks of concern to non-target organisms.[49, 50] In the absence of toxicity studies, there is greater uncertainty regarding risk near EtO commercial sterilization facilities that either have no or limited (< 99% reduction) emission controls, which was the NESHAP requirement at the time of the OPP ecological assessment. In those cases, especially for those facilities without emission controls, risk cannot be precluded for terrestrial organisms in adjacent areas around EtO treatment facilities. OPP notes that OAR is proposing updates to the NESHAP for the Commercial Sterilization Facilities source category to require more stringent controls for EtO

[46] The size of the facility is determined by the amount of EtO emitted in accordance with section 112 of the Clean Air Act. See https://www.epa.gov/stationary-sources-air-pollution/ethylene-oxide-emissions-standards-sterilization-facilities
[47] Ethylene Oxide: Revised Response to Data Waiver Requests Submitted by the Ethylene Oxide Task Force. March 9, 2018.
[48] Ethylene Oxide (EtO). Draft Human Health and Ecological Risk Assessment in Support of Registration Review. November 3, 2020.
[49] Ethylene Oxide: Revised Response to Data Waiver Requests Submitted by the Ethylene Oxide Task Force. March 9, 2018.
[50] Ethylene Oxide (EtO). Draft Human Health and Ecological Risk Assessment in Support of Registration Review. November 3, 2020.

emissions. OPP expects that these more stringent proposed emissions controls and rate reductions (if finalized) will further reduce exposure to nontarget species.

***Ecological Incidents***

EPA reviewed EtO incidents reported to the Incident Data System (IDS). As of EPA's latest search on January 18, 2023, IDS showed zero incidents reported from March 1, 2008 to January 18, 2023. The Agency intends to monitor ecological incidents for EtO and will conduct additional analyses if necessary.

***Ecological and Environmental Fate Data Needs***

The ecological and environmental fate dataset for EtO is considered complete. The Agency does not anticipate any further data needs for EtO as part of this registration review cycle.

EPA did not identify a risk concern for acute exposure of adult honeybees to EtO. However, chronic risks to adult honeybees and acute risks to larval honeybees have not been defined at this time based on current available information. Additional data may be necessary to fully evaluate risks to non-target terrestrial invertebrates, especially pollinators, based on the *Guidance for Assessing Pesticide Risks to Bees* (June 2014).[51]

The ecological and environmental fate data requirements in GDCI-042301-1428 included GLN 850.4150 Vegetative Vigor, Non-guideline study Honeybee Acute Vapor Exposure, and Non-guideline study Avian Acute Inhalation Toxicity. On June 10, 2015, EPA received waiver requests for all three data requirements from the Ethylene Oxide Task Force (EOTF) (MRIDs 49648401, 49648402, and 49688601). In May 2017, EOTF submitted information to fulfill the Product Use Information data requirement (GLN 875.1700) which was also considered when evaluating the ecological data requests. EtO sterilization is performed indoors in vacuum or gas tight chambers. Approximately 1% of the EtO used for sterilization is used in medium-sized facilities and approximately 0.1% of the EtO used for sterilization is used in small-sized facilities. Exposures to EtO from large- and medium-sized commercial sterilization facilities with controls achieving greater than or equal to 99% reduction in emissions—consistent with the applicable NESHAP requirements (according to section 112 of the Clean Air Act) for emissions control at the time of the OPP ecological assessment—are not of concern. Therefore, with approximately 99% of sterilization occuring in large- and medium-sized facilities with emissions controls achieving greater than or equal to 99% emissions reductions, any exposure to wildlife from the use of EtO will likely be limited with the possible exception of the aforementioned low percentage of small-sized facilities that are not subject to the NESHAP requirements for emissions controls and may not achieve 99% emissions reductions. Consequently, EPA waived the data requirements GLN 850.4150 Vegetative Vigor; Non-guideline study Honeybee Acute Vapor Exposure; and Non-guideline study Avian Acute Inhalation Toxicity on March 9, 2018.[52] OPP notes that OAR is proposing updates to the NESHAP for the Commercial Sterilization

[51] https://www.epa.gov/sites/production/files/2014-06/documents/pollinator_risk_assessment_guidance_06_19_14.pdf.
[52] Ethylene Oxide: Revised Response to Data Waiver Requests Submitted by the Ethylene Oxide Task Force. (Orrick, 2018).

Facilities source category to require more stringent controls for EtO emissions. OPP expects that these more stringent emissions controls (if finalized) will further reduce exposure to nontarget species.

### C. Benefits Assessment

EtO is primarily used as a sterilant for new, single use, and reusable medical devices and equipment. EtO is highly valuable in the industrial sterilization setting – or any setting that has the objective of destroying, inactivating, or physically removing all microorganisms to meet defined sterility assurance standards – because it is a penetrative gas that has a high throughput capacity, is effective at a wide range of temperatures, and is compatible with a broad range of materials. EtO is used on approximately 50% of all sterilized medical devices, annually, including an estimated 95% of all surgical kits. A key benefit of EtO is its ability to sterilize medical devices in their final packaging as it is able to penetrate palletized materials, cardboard, and other cellulosic packaging material. Presently, there are no viable alternatives to EtO for the sterilization of certain medical devices and equipment because gamma irradiation and e-beam irradiation, the next most commonly employed methods for medical device sterilization, cannot be used on certain materials. Other technologies (e.g., hydrogen peroxide, chlorine dioxide, vaporized peracetic acid) are limited due to issues with material compatibility, scalability, and because they lack accepted validation measures for sterility assurance. The absence of EtO for use on medical devices and equipment would cause widespread disruption to the availability of sterile medical devices including feeding tubes used in neonatal intensive care units, drug-eluting cardiac stents, catheters, shunts, and other implantable devices.

In the U.S., EtO is used during the processing and reconditioning of dried herbs and spices to reduce food safety pathogens of concern such as *Salmonella* and *Escherichia coli*. The presence of moisture alone may be sufficient for the development of pathogens such as *Salmonella* and keeping moisture out of dried herbs and spices can be challenging during processing, handling, shipping, and storage activities. Additionally, most spices are imported from overseas, which creates more opportunity for pathogens to be introduced due to differing sanitation and food handling practices and regulations. EtO is advantageous as it has minimal impact on the desirable characteristics of an herb or spice including its aromatics, color, flavor, or texture. There are a few alternatives to EtO for the sanitization of dried herbs and spices from pathogens and filth; however, alternatives may not be viable for every situation, pathogen, or consumer market. The absence of EtO for use on dried herbs and spices may result in an increased rejection of imported spices, an increased prevalence of foodborne illnesses from an increased risk of pathogens being present among imported dried herbs and spices, and, potentially, disruptions in product availability.

EtO is also registered for niche uses in beekeeping to manage American foulbrood on equipment (in North Carolina only); the preservation of library, museum, and archival materials against bacteria, fungi, and insects; on musical instruments to prevent the transmission of human diseases, and for the sterilization of cosmetics. For the beekeeping equipment, the use of EtO is limited via a FIFRA section 24(c) registration to one facility in North Carolina. There are alternative chemical, cultural, and mechanical controls available to manage American foulbrood disease on beekeeping equipment. EtO is no longer used for treatment of museum, library, or

archival materials due to concerns over human health risks associated with off-gassing from treated materials. Alternatives for the museum, library, and archival materials include freezing, anoxia (oxygen deprivation), and irradiation. For the musical instrument uses, other disinfectant products are available for use that are more practical, low cost, and easily accessible. EPA expects that EtO is likely no longer used in the cosmetics industry. Gamma irradiation is a viable alternative for cosmetics. Therefore, in these use sites, EtO provides minimal benefits based on the availability of alternatives and/or limited to no current EtO usage. The absence of EtO for use on these use sites is unlikely to impact these industries.

For more information on the benefits of EtO, see *Ethylene Oxide (PC# 042301): Use, Usage, Benefits, and Impacts of Cancellation* and the letter from Dr. Girvin Liggans to Edward Messina (dated August 18, 2022)[53] in this docket (EPA-HQ-OPP-2013-0244).

### D. Alternatives for Medical Device Sterilization and Spice Fumigation

As described above, the Agency estimates that EtO use results in cancer risks of concern to occupational handlers as well as risks to occupational and non-occupational bystanders. However, EPA recognizes that EtO products are registered for uses which are extremely beneficial and have no currently registered alternatives that can completely replace EtO. Under its Reduced Risk Policy, OPP encourages the submission of applications for pesticides which offer a reduced risk alternative and will give priority consideration to the review of such applications. The registration of such a reduced risk alternative pesticide would allow OPP to achieve greater risk reduction.[54] Even though there is one registered alternative active ingredient for spice fumigations (propylene oxide) and there are no registered alternative pesticide active ingredients for medical device sterilization, there are a variety of alternative sterilization methods described below. However, the current field of alternatives are insufficient to completely replace EtO for reasons described below.

*Medical Devices*

Some medical devices can only be sterilized with EtO. However, there are several alternative methods used to sterilize medical devices: gamma irradiation, X-ray sterilization, electron beam sterilization, and steam; as well as alternative sterilization methods in development including vaporized hydrogen peroxide, nitrogen dioxide, chlorine dioxide, and vaporized peracetic acid.

Despite the availability of alternative sterilization methods, EPA understands the limitations of alternative sterilization methods for use with medical devices due to their lack of compatibility with materials and/or packaging; and also due to their lack of scalability or capacity, application method, and/or lack of validation measures for sterility assurance or efficacy data. See Section III.C. and *Ethylene Oxide (PC# 042301): Use, Usage, Benefits, and Impacts of Cancellation* in this docket. Despite these limitations, EPA is seeking to pursue identifying alternatives to EtO sterilization as a long-term risk reduction strategy.

[53] Letter from Dr. Girvin Liggans, Acting Deputy Director for Plant Derived Foods, Office of Food Safety, Center for Food Safety and Applied Nutrition, Food and Drug Administration to Edward Messina, Director, Office of Pesticide Programs, Environmental Protection Agency. August 18, 2022.
[54] https://www.epa.gov/pesticide-registration/conventional-reduced-risk-pesticide-program.

FDA's Center for Devices and Radiological Health (CDRH) assures that patients and providers have timely and continued access to safe, effective, and high-quality medical devices. Before most sterile medical devices are on the market, FDA reviews premarket submissions such as premarket approval applications (PMAs) and premarket notifications (referred to as 510(k)s) to determine if the sterility information is consistent with the sterility assurance under which the device is labeled and intended for use (e.g., in accordance with internationally agreed upon voluntary consensus standards that FDA recognizes). See Section IV.B. for more information on FDA's jurisdiction over recognizing sterilization modalities and verifying sterility assurance for medical devices.

As part of interagency collaboration, EPA-OPP and FDA-CDRH have held discussions on pursuing alternatives to EtO sterilization and have identified regulatory and logistical limitations in prescribing which sterilization modality must be used on specific medical devices. These regulatory and logistical limitations, and additional background regarding FDA's regulatory oversight over medical devices, are described below:

- Given that medical device material makeup varies from manufacturer to manufacturer (even for the same device type), it is not possible to prescribe which types of medical devices must use which sterilization modality, due to material compatibility issues. For example, catheters from different manufacturers could be made from different materials, some of which may or may not be compatible with alternative sterilization modalities.

- The FFDCA authorizes FDA to exercise regulatory oversight over medical devices, including through its implementing regulations.[55] In the context of devices labeled as sterile, the FFDCA does not authorize FDA to require sponsors/manufacturers of these devices to provide a justification as to why a certain sterilization modality is used to support marketing authorization rather than another. Rather, the information provided to FDA as support for a device sterilization claim must show that the selected sterilization method for a subject device conforms to the labeling and intended use of the device, which may include any applicable FDA-recognized consensus standards or an equivalent sterilization method. A more detailed description of FDA's regulatory oversight in this space is provided below.

    - With respect to devices that are intended to be sterilized using EtO, sponsors may choose to reference certain FDA-recognized standards that include EtO exposure potential information based on the applicable standards and their allowable limits for residual EtO.[56] Accordingly, information related to the EtO exposure potential of a subject device, both during the manufacturing and sterilization process and at the time the device is used by an end user (such as a healthcare professional or patient), is generally reviewed and compared to any applicable International

[55] FD&C Act Section 501 *et seq*.; 21 CFR Part 800 *et seq*.
[56] ANSI AAMI ST41:2008/(R)(2018); ISO 10993-7, 2nd Ed. 2008-10-15. Additionally, depending on the premarket submission pathway, there may be other applicable regulations that further contextualize how sponsors should submit sterilization data.

Standards defining allowable limits of EtO residuals and exposures.

- As part of FDA's regulatory oversight, FDA is also required to evaluate whether a subject device, prior to its introduction in the market, offers a reasonable assurance of safety and effectiveness upon the imposition of certain regulatory controls.[57] Fundamental to this evaluation is, among other things, the weighing of any probable benefits to health from the use of a device against any probable risks of injury or illness from such use (i.e., analyzing clinical risks and clinical benefits for a given device).[58] For example, if EtO as a device sterilizing agent poses a cancer exposure risk to an end user or to manufacturing or sterilization staff, FDA is obligated to review that information, together with other probable risks, against the probable benefits offered by the finished sterile device. If FDA determines that the probable benefits from use of the device outweigh the probable risks of such use, this specific risk information alone would be unlikely to lead FDA to conclude that a device should not be cleared or approved.

- Separately, since the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115),[59] Congress has directed FDA to take a least burdensome approach to medical device premarket evaluation in a manner that eliminates unnecessary burdens that may delay the marketing of beneficial new products, while maintaining the statutory requirements for clearance and approval. In practice, FDA defines least burdensome to refer to the minimum amount of information necessary to address regulatory questions in line with the statutory and regulatory requirements applicable to a subject device, and encourages industry to refer to least burdensome principles in compiling information for premarket review by the FDA.[60] Consequently, if certain information was not provided in a premarket submission, but that information is not needed to support a determination that the device meets the applicable

[57] See FFDCA Section 513(a)(1).
[58] The safety and effectiveness of a device is determined, among other things, by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use" FFCDA Section 513(a)(2)(C)). To aid this process, sponsors submit valid scientific evidence, which FDA reviews to determine whether "the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device" FFCDA Section 513(a)(3)(A).
[59] Congress enacted additional least burdensome provisions to the FFCDA through the FDA Safety and Innovation Act (Public Law 112-144) and the 21st Century Cures Act (Public Law 114-255).
[60] See, e.g., FFCDA Section 513(i)(1)(D)(i) ("Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly."); FFCDA Section 513(a)(3)(D)(ii) ("Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."); see also FDA Guidance entitled "The Least Burdensome Provisions: Concept and Principles," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.

statutory and regulatory standards for marketing authorization, FDA does not request such information.

- EPA's authority under FIFRA does not allow for OPP to prescribe on pesticide product labels FDA's process for validation assessment of sterilization modalities for medical devices. As noted above, FDA's role in this regard under the FFCDA and its implementing regulations is to evaluate whether the sterilization data (irrespective of method) submitted for premarket review is adequate to support a claim that a subject device is sterile as part of the overall benefit/risk assessment carried out on all FDA-regulated devices.

Despite these limitations, EPA still seeks to pursue identifying alternatives to EtO sterilization as a long-term risk reduction strategy and will continue to collaborate with FDA on their work through the *Innovation Challenge: Identify New Sterilization Methods and Technologies*. See Section IV.B for more information on the steps FDA is taking to identify alternatives to EtO sterilization.

*Spices*

Spices or herbs discussed in this document refer only to the dried forms, not fresh forms, of herbs and/or spices. Limiting the use of EtO to specific dried herbs and spices where its use is deemed critical for food safety and where alternative treatment methods are not available also would result in fewer EtO applications overall, and thus less exposure to workers (including handlers and occupational bystanders), residential bystanders, and non-residential bystanders. There are several alternatives used to treat dried herbs and spices: irradiation, heat, steam, and propylene oxide. However, these alternatives may not be viable for every spice, spice form (e.g., dried leafy-type, ground/powdered), spice blend, or target pathogen[61]. See Section III.C. and *Ethylene Oxide (PC# 042301): Use, Usage, Benefits, and Impacts of Cancellation* in this docket.

Pesticides can be used to treat food commodities in the U.S. if the commodity is listed on the product label (i.e., the pesticide is registered for use on the commodity), and there is an established tolerance or tolerance exemption for the pesticide on the commodity. As stated on the EtO product labels, EtO is currently registered to reduce the microbial load on various whole and ground spices (except basil), dried vegetables, and seasonings. Tolerances are established for EtO and ECH for various dried herbs and spices, dried vegetables, and walnuts (see Table 2 for all commodities with EtO and ECH tolerances). Seasonings are blends of dried herbs and spices. If a seasoning/spice blend is treated with EtO, it can only include commodities identified in Table 2.

**Table 2. Current Commodities with Tolerances for EtO and ECH in the U.S.**

| Herbs (crop subgroup 19A) | Spices (crop subgroup 19B) | Other food commodities in 40 CFR § 180.151 |
|---|---|---|
| Angelica | Allspice | Licorice, roots |

[61] American Spice Trade Association (ASTA). 2020. ASTA reply to EPA questions regarding ethylene oxide use on spices. Email from Laura Shumow, Executive Directors, ASTA, to Susan Bartow, Pesticide Re-Evaluation Division, Office of Pesticide Programs, Environmental Protection Agency. June 25, 2020.

| | | |
|---|---|---|
| Balm | Anise (seed) | Peppermint, tops, dried |
| Borage | Anise, star | Sesame seed |
| Burnet | Annatto (seed) | Spearmint, tops, dried |
| Camomile[A] | Caper (buds) | Vegetable, dried[D] |
| Catnip | Caraway | Walnut[E] |
| Chervil (dried) | Caraway, black | |
| Chive | Cardamom | |
| Chinese chive | Cassia (buds) | |
| Clary | Celery (seed) | |
| Coriander (leaf) | Cinnamon | |
| Costmary | Clove (buds) | |
| Culantro (leaf) | Coriander (seed) | |
| Curry (leaf) | Culantro (seed) | |
| Dillweed | Cumin | |
| Horehound | Dill (seed) | |
| Hyssop | Fennel, common | |
| Lavender | Fennel, Florence (seed) | |
| Lemongrass | Fenugreek | |
| Lovage (leaf) | Grains of paradise | |
| Marigold | Juniper (berry) | |
| Marjoram (*Origanum spp.*)[B] | Lovage (seed) | |
| Nasturtium | Mace | |
| Parsley (dried) | Mustard (seed) | |
| Pennyroyal | Nutmeg | |
| Rosemary | Pepper, black[C] | |
| Rue | Pepper, white | |
| Sage | Poppy (seed) | |
| Savory (summer and winter) | Saffron | |
| Sweet bay | Vanilla | |
| Tansy | | |
| Tarragon | | |
| Thyme | | |
| Wintergreen | | |
| Woodruff | | |
| Wormwood | | |

A – Camomile includes both German and Hungarian (46694 Federal Register / Vol. 74, No. 175 / Friday, September 11, 2009).
B – Oregano is covered by the preferred term marjoram (46694 Federal Register / Vol. 74, No. 175 / Friday, September 11, 2009).
C – Also includes pink peppercorns (46694 Federal Register / Vol. 74, No. 175 / Friday, September 11, 2009).
D – Dried vegetables include capsicums, ginger, horseradish, paprika, garlic, onion, turmeric, and arrowroot (46694 Federal Register / Vol. 74, No. 175 / Friday, September 11, 2009).
E – Walnut is not listed on current product labels.

Based on discussions with industry and FDA, EPA understands the limitations of the alternative treatment methods due to compatibility with spices and/or their packaging, scalability, and lack of validation measures or efficacy data. Despite these limitations, due to the inhalation risk estimates associated with the use of EtO, EPA still seeks to identify alternatives to EtO spice treatments, as well as specific spices where EtO use is critical for food safety. The Agency is

soliciting comments on the specific commodities in Table 2 for which there is a critical need for the use of EtO and for which there are no viable alternatives to EtO (e.g., steam, irradiation, or propylene oxide cannot be used for pathogen control on a particular spice, spice form, or spice blend). Any commodities without documented support for continued treatment with EtO will be considered for a phased-out cancellation to reduce exposure to workers (including handlers and occupational bystanders), residential bystanders, and non-residential bystanders. The Agency intends to include language in the Interim Decision (ID) stating that registrants should submit requests to voluntarily terminate uses on these commodities (see Section V.A.).

Based on information submitted to the Agency, EPA understands that the following spices often have high pathogen loads— black pepper, paprika, celery seed, coriander, turmeric, and thyme[62, 63]. The Agency is seeking public comment on alternative treatment options for those spices and target pathogens (e.g., *Salmonella*, *E. coli*.). In addition, the Agency would like to know if there are other commodities that typically have high pathogen loads for which there are not efficacious treatment options besides EtO. The Agency is also seeking information regarding the importance of EtO to spice blends (e.g., seasonings) and the specific spices in the blends for which EtO fumigation is critical.

None of the EtO products are currently labeled for use on walnuts and the Agency is not aware of current EtO use on walnuts. Based on the information currently before EPA, the use of EtO on walnuts is unlikely to meet the standard for registration under FIFRA because (1) the lack of usage of EtO on walnuts suggests that there are alternatives available for the fumigation of walnuts (e.g., nonchemical, PPO) and (2) the occupational cancer risk estimates for EtO use in commercial sterilization facilities exceed the Agency's threshold of $1 \times 10^{-4}$. Therefore, the Agency intends to exercise its authority under the FFDCA to revoke the walnut EtO tolerance. Tolerance changes will be proposed through a separate rulemaking process.

# IV. INTERAGENCY CONSIDERATIONS

The federal government has taken an all-agency approach to addressing concerns about the use of EtO since the establishment of the Ethylene Oxide Interagency Task Force in February 2020. Members of the Task Force include EPA Office of Pesticide Programs (EPA-OPP), EPA Office of Air and Radiation (EPA-OAR), EPA Office of Research and Development (EPA-ORD), the Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry (CDC-ATSDR), the Occupational Safety and Health Administration (OSHA), the Food and Drug Administration Center for Food Safety and Applied Nutrition (FDA-CFSAN), and the Food and Drug Administration Center for Devices and Radiological Health (FDA-CDRH). Members meet monthly to discuss the on-going regulatory concerns for EtO. In particular, for the regulation of the pesticidal registrations of EtO, OPP is working closely with OSHA and

[62] EOTF email to EPA regarding benefits of ethylene oxide for medical devices. Email sent from Lisa Campbell, Partner, Bergeson & Campbell PC to Jessica Bailey, Antimicrobial Division, Office of Pesticide Programs, Environmental Protection Agency. May 6, 2020.
[63] American Spice Trade Association (ASTA). 2017. Clean, Safe Spices, Guidance from the American Spice Trade Association, 2017 Update. https://www.astaspice.org/food-safety-technical-guidance/best-practices-and-guidance/clean-safe-spices-guidance-document/. Accessed September 2020.

FDA on the registration review risk mitigation to address risks to workers and nearby communities, as discussed below. EPA thanks all federal partners for their collaboration.

### A. Occupational Safety and Health Administration (OSHA)

OSHA standards are issued pursuant to the OSH Act and are found in title 29 of the Code of Federal Regulations (CFR). There are separate standards for general industry, construction, maritime and agriculture activities, as well as general standards applicable to a number of sectors (e.g., OSHA's Respiratory Protection standard). OSHA has numerous standards that could apply to pesticidal uses of chemicals, including the OSHA standard 29 CFR 1910.1047 Ethylene Oxide.[64]

OSHA sets legally enforceable limits on the concentrations of hazardous chemicals in the air in a workplace, referred to as permissible exposure limits (PELs), to protect workers against the health effects of exposure to such chemicals (29 CFR 1910 Subpart Z, 1915 Subpart Z, 1926 Subparts D and Z). Under section 6(a) of the OSH Act, OSHA was permitted an initial two-year window after the passage of the Act to adopt "any national consensus standard and any established Federal standard." 29 U.S.C. 655(a). OSHA used this authority in 1971 to establish PELs that were adopted from federal health standards originally set by the Department of Labor through the Walsh-Healy Act, pursuant to which approximately 400 occupational exposure limits were selected based on the American Conference of Governmental Industrial Hygienists (ACGIH) 1968 list of Threshold Limit Values (TLVs). In addition, about 25 exposure limits recommended by the American Standards Association (now called the American National Standards Institute (ANSI)) were adopted as PELs.

Following the two-year window provided under section 6(a) of the OSH Act for adoption of national consensus and existing Federal standards, OSHA has issued health standards following the requirements in section 6(b) of the Act. OSHA has established approximately 30 PELs under section 6(b)(5) as part of comprehensive substance-specific standards that include additional requirements for protective measures such as establishment of regulated areas, exposure assessment, medical surveillance, and training.

With few exceptions, OSHA's PELs have not been updated since they were first established starting in 1971. At this time, the EtO PEL was established at 50 ppm, based on the 1968 ACGIH TLV. The PEL for EtO has not been revised since 1984, when it was set at 1 ppm. Yet, in many instances, scientific evidence has accumulated suggesting that the current limits are not sufficiently protective. As stated on OSHA's annotated PELs webpage, OSHA has recognized that many of its PELs are outdated and inadequate for ensuring protection of worker health.[65] In addition, health standards issued under section 6(b)(5) of the OSH Act must reduce significant risk only to the extent that it is technologically and economically feasible. OSHA's legal requirement to demonstrate that its 6(b)(5) standards are technologically and economically feasible often precludes OSHA from imposing exposure control requirements sufficient to ensure that the chemical substance no longer presents a significant risk to workers. In sum, the great majority of OSHA's chemical standards are outdated or do not eliminate significant risk as

[64] https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1047.
[65] https://www.osha.gov/annotated-pels.

defined by the Supreme Court's interpretation of the OSH Act[66]. They would, in either case, be unlikely to address unreasonable adverse effects to workers within the meaning of FIFRA, which allows EPA to consider more sensitive endpoints and working populations than OSHA's risk evaluations typically contemplate.

OSHA, under limited circumstances, has cited the General Duty Clause for worker exposure to hazardous chemicals that are not sufficiently addressed under 29 CFR 1910 Subpart Z, 1915 Subpart Z, 1926 Subparts D and Z. To prove a violation of the General Duty Clause, OSHA must prove employer or industry recognition of the hazard, that the hazard was causing or likely to cause death or serious physical harm, and a feasible method was available to eliminate or materially reduce the hazard. In rare situations, OSHA has cited employers for violation of the General Duty Clause where exposures were below a chemical-specific OSHA PEL. In such situations, OSHA must demonstrate that the employer had actual knowledge that the PEL was inadequate to protect its employees from death or serious physical harm. Because of the heavy evidentiary burden on OSHA to establish violations of the General Duty Clause, it is not frequently used to cite employers for employee exposure to chemical hazards.

Thus, it is appropriate that EPA conduct risk assessments and, where it finds risks of concern to workers, develop risk mitigation measures to address risks from the pesticidal uses of chemicals that OSHA also regulates, and it is expected that EPA's findings and requirements may sometimes diverge from OSHA's. However, it is also appropriate that EPA consider the chemical standards that OSHA has already developed, so as to limit the compliance burden to employers by aligning risk management approaches required by the agencies, where alignment will ensure that the use of a pesticide will not cause unreasonable adverse effects on the environment, including to workers.

When developing mitigation measures to address risks of concern to workers, EPA will: 1) strive for consistency with applicable OSHA requirements and industry best practices, including appropriate application of the hierarchy of controls (e.g., elimination, substitution, engineering controls, administrative controls, PPE), when those measures would address risks of concern to workers; 2) ensure the EPA requirements apply to all potentially exposed workers; and 3) develop occupational risk mitigation measures to address any risks of concern identified by EPA.

EPA's risk assessment on EtO has found risks of concern to workers associated with the registered uses of EtO, even when the applicable OSHA requirements are being met. EPA has, therefore, developed risk mitigation measures beyond those included in OSHA's standards.

In the *Reregistration Eligibility Decision for Ethylene Oxide* (2008), OPP required registrants to implement label amendments for respirator requirements and air monitoring requirements based on the OSHA PEL of 1 ppm. Since 2008, there have been considerable updates to the scientific database on EtO exposure and risk, including the 2016 IRIS assessment on EtO, OPP's 2020 EtO DRA, and OPP's 2023 EtO DRA Addendum. EPA thus considers the OSHA PEL of 1 ppm to no longer ensure that the use of EtO will not cause unreasonable adverse effects, including effects to workers, as required under FIFRA and is therefore proposing to require that registrants amend

[66] Am. Petroleum Inst., 448 U.S. at 655.

their EtO labels to no longer include the OSHA PEL. See Section V.A. for details on worker mitigation and Appendix B for EtO product label requirements.

EPA understands that OSHA's EtO PEL has not been updated since it was established in 1984, and that health standards issued under section 6(b)(5) of the OSH Act must reduce significant risk only to the extent that it is technologically and economically feasible.[67] OSHA's legal requirement to demonstrate that its 6(b)(5) standards are technologically and economically feasible often precludes OSHA from imposing exposure control requirements sufficient to ensure that the chemical substance no longer presents a significant risk to workers. Therefore, in lieu of revising the EtO PEL of 1 ppm, EPA will work with OSHA to revise the following parts of OSHA standard *29 CFR 1910.1047 Ethylene Oxide* to align more with updated scientific assessments on EtO:

- Engineering controls and work practices provision (29 CFR 1910.1047(f)(1))
- Hazard communication (29 CFR 1910.1047(j)(1))
- Classifying the hazards of EtO (29 CFR 1910.1047(j)(1)(ii))
- Signage and labels (29 CFR 1910.1047(j)(2)(i)) and 1047(j)(2)(ii))[68]

EPA will also work with OSHA to revise the OSHA Safety and Health Topics Webpage for Ethylene Oxide to acknowledge EPA's publications.[69]

***Alternative Exposure Limits***

Internationally, an 8-hour worker exposure limit of 1 ppm for EtO is generally accepted, with few exceptions. In Israel, for example, the exposure limit is 1 ppm for men, but 0.75 ppm for women.[70] In Germany, 1 ppm is the workplace exposure concentration corresponding to the proposed tolerable cancer risk, while 0.1 ppm is the workplace exposure concentration corresponding to the proposed preliminary acceptable cancer risk.[71] The German Committee on Hazardous Substances (Ausschuss für Gefahrstoffe, or AGS) sets risk-based limits for carcinogens based on social policy wherein there are "acceptable" and "tolerable" risks. For occupational lifetime cancer risks, acceptable risk in Germany is 4 in 100,000, which may be exceeded if specific measures are complied with; and tolerable risk is 4 in 1,000, which may not be exceeded.[72] The European Union EtO exposure limit of 1 ppm is a regulatory limit, which takes into account market availability of biocidal products while ensuring a high level of protection for human and animal health and the environment, and was established in 2017.[73] The

[67] https://www.federalregister.gov/citation/49-FR-25734.
[68] https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1047.
[69] https://www.osha.gov/ethylene-oxide.
[70] GESTIS International Limit Values. https://limitvalue.ifa.dguv.de/.
[71] The MAK Collection for Occupational Health and Safety 2019, Vol 4, No 3. A. Hartwig, MAK Commission, DOI: 10.1002/3527600418.mb7521d0067.
[72] Occupational Limit Values (Arbeitsplatzgrenzwerte – AGW). https://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/limit-values-germany-(ags)/index.jsp?query=webcode+e786799.
[73] Directive (EU) 2017/2398 of the European Parliament and of the Council of 12 December 2017 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at

EU also has a risk-based limit of 3 ppb, based on extrapolation from a mouse study in 2021. In this study, exposure monitoring data from four EtO commercial sterilization facilities in Europe were compared to the derived minimal effect level (DMEL) of 3 ppb and showed that even the lowest monitoring value exceeded the DMEL by 400%; therefore, no acceptable worker risk was shown.[74]

In the U.S., there is a recommended exposure limit (REL) from the National Institute for Occupational Safety & Health (NIOSH) set at 0.1 ppm.[75] As this is a recommended limit only, it is not enforceable. The purpose of NIOSH RELs is to provide guidance to OSHA for forming enforceable regulations.[76]

It is EPA's understanding that certain sterilization facilities in the U.S. may utilize a lower exposure limit than what is required by OSHA to set company-specific risk policies. EPA requests public comment on facilities that utilize lower exposure limits than the OSHA PEL, and what practices these facilities use to achieve and measure these lower limits.

***Training Requirements***

*Commercial Sterilization Facilities for Medical Devices and Spices*

OSHA's standard for EtO, 1910.1047(j)(3)(iii) *Information and Training* states that employee training shall include at least:

- Methods and observations that may be used to detect the presence or release of EtO in the work area (such as monitoring conducted by the employer, continuous monitoring devices, etc.);
- The physical and health hazards of EtO,[77] which must include at a minimum cancer; reproductive effects; mutagenicity; central nervous system; skin sensitization; skin, eye, and respiratory tract irritation; acute toxicity effects; and flammability per 1910.1047(j)(1)(ii);
- The measures employees can take to protect themselves from hazards associated with EtO exposure, including specific procedures the employer has implemented to protect employees from exposure to EtO, such as work practices, emergency procedures, and personal protective equipment to be used; and
- The details of the hazard communication program developed by the employer, including an explanation of the labeling system and how employees can obtain and use the appropriate hazard information.

work (Text with EEA relevance) can be found at https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=uriserv:OJ.L_.2017.345.01.0087.01.ENG

[74] Norwegian Environment Agency, Oslo, Norway. 2021. Regulation (EU) NO 528/2012 Concerning the making available on the market and Use of Biocidal Products, Ethylene Oxide. EC Number 200-849-9. CAS Number 75-21-8.

[75] https://www.cdc.gov/niosh/npg/npgd0275.html.

[76] https://www.cdc.gov/niosh/npg/pgintrod.html.

[77] This includes all classified hazards as per 1910.1200, and at a minimum include at a minimum Cancer; reproductive effects; mutagenicity; central nervous system; skin sensitization; skin, eye and respiratory tract irritation; acute toxicity effects; and flammability as per 1910.1047(j)(1)(ii).

For information on EPA's current and proposed training requirements, see Section V.A.

### B. Food and Drug Administration (FDA)

**Medical Devices**

FDA's Center for Devices and Radiological Health (CDRH) assures that patients and providers have timely and continued access to safe, effective, and high-quality medical devices.[78] Before most sterile medical devices are on the market, FDA reviews submissions to determine if the sterility information is consistent with the sterility assurance under which the device is labeled and intended for use (e.g., in accordance with internationally agreed upon voluntary consensus standards that FDA recognizes).

For EtO sterilization, 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 (ECH) left on a device after it has undergone EtO sterilization. FDA also inspects industrial facilities that sterilize medical devices and medical device manufacturing facilities to make sure that they have validated sterilization processes that meet FDA-recognized standards. State health departments inspect healthcare facilities that use EtO to sterilize medical devices.

FDA actively works with sterilization experts, medical device manufacturers, and other government agencies to advance innovative ways to sterilize medical devices with lower levels of EtO and employ new agents or alternatives, while maintaining device safety and effectiveness in order to prevent potential medical device shortages.[79] In May and November 2019, FDA engaged the infection control community at the Healthcare Infection Control Practices Advisory Committee (HICPAC) and General Hospital and Personal Use Panel of the Medical Devices Advisory Committee meetings, respectively, to update the public on FDA's work and engagement with industry on sterilization modalities with devices that are normally sterilized using EtO.[80]

On July 15, 2019, FDA announced two public innovation challenges to encourage development of new approaches to medical device sterilization, which could include identifying alternatives to EtO sterilization methods or strategies to reduce EtO emissions:

- Challenge 1: Identify New Sterilization Methods and Technologies.
- Challenge 2: Reduce Ethylene Oxide Emissions.

On November 25, 2019, FDA announced that 46 applications were received, and 12 participants were selected for the challenges. Details on the progress of innovations are described below.

[78] https://www.fda.gov/about-fda/fda-organization/center-devices-and-radiological-health.
[79] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-steps-agency-taking-prevent-potential-medical-device.
[80] https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-6-7-2019-general-hospital-and-personal-use-devices-panel-medical-devices-advisory-committee.

**Innovation Challenge 1: Identify New Sterilization Methods and Technologies**

The goal of this challenge is to identify safe and effective sterilization methods or technologies for medical devices that do not rely on EtO and that meet these criteria:

- Compatibility: The method or technology is compatible with a large cross section of materials used to manufacture or fabricate medical devices as well as packaging materials or sterile barriers. The materials, devices, and barriers of particular interest are those that are compatible with EtO sterilization.

- Scalability and High Throughput: The method or technology should have the potential to be scalable and allow for the effective sterilization of large volumes of devices.

FDA selected four participants and five submissions for this challenge: NovaSterilis's Supercritical Carbon Dioxide Sterilization; Noxilizer's Nitrogen Dioxide Sterilization; STERIS's Accelerator-Based Radiation Sterilization; STERIS's Vaporized Hydrogen Peroxide Sterilization; and TSO3 (Stryker)'s Vaporized Hydrogen Peroxide-Ozone Sterilization. Participants selected for this challenge are working directly with FDA to accelerate the development and review of these innovative technologies.

**Innovation Challenge 2: Reduce Ethylene Oxide Emissions**

The goal of this challenge is to develop strategies or technologies to reduce emissions to as close to zero as possible from the EtO sterilization process. Innovative strategies may entail changing current sterilization processes or workflow, such as changes in the supply chain, transportation of medical devices, or procedures in the sterilization site. Strategies may also include making alterations to EtO process waste to reduce emissions.

The strategies or technologies may allow for the:

- Use of lower levels of EtO while maintaining assurance that devices are safely and effectively sterilized.
- Capture of EtO emissions and/or transformation to harmless byproducts.
- Detection, measurement, tracking, and containment of fugitive emissions to prevent or minimize emissions into the sterilization facility or environment.
- Safe use of EtO while minimizing harmful exposure (such as toxicity and carcinogenicity) to sterilization workers and nearby communities.

FDA selected eight participants for this challenge: Abbott's Enhanced EtO Cycle Design and Processes; Andersen Scientific's Use of EtO-Flexible Chamber Technology; Becton Dickinson and Company's Enhanced EtO Cycle Design and Processes; DMB Apparatebau's Reduced Sterilant Concentration; Medtronic's Enhanced EtO Cycle Design and Processes; Sterigenics's Enhanced EtO Cycle Design and Processes; STERIS's Enhanced EtO Cycle Design and Processes; and Taiwan Advanced Sterilization Technologies Inc.'s Abatement Strategy.

Participants selected for this challenge are working directly with FDA to accelerate the development and review of innovative technology.

Through FDA's Innovation Challenge 2, some industry participants have already implemented their optimized cycle designs, reducing EtO use by a significant amount. Per an FDA statement, early observations suggest that some facilities have cut emissions ranging from 20-35%, with the potential to impact millions of devices. In general, participating manufacturers are targeting an EtO concentration that is 11-66% less than the typical concentration range.[81]

**Expediting Approvals for Changes to Sterilization Processes**

Typically, for premarket application (PMA) approved devices, if a medical device manufacturer changes the method, process, or the facility identified in its original PMA submission for sterilizing its devices, the manufacturer generally needs to submit a PMA supplement so that FDA can review these changes and determine if the sterility information remains consistent with the sterility assurance under which the device is labeled and approved for use (e.g., in accordance with internationally agreed-upon voluntary standards that FDA recognizes). For manufacturers that are 510(k) holders, sterilization method, process or site modifications can be assessed as recommended in the FDA guidance document: "Deciding When to Submit a 510(k) for a Change to an Existing Device" for determination on whether the sterilization modifications would trigger the need for resubmission.[82]

On November 26, 2019, FDA announced the Ethylene Oxide Sterilization Master File Pilot Program for sterilization facilities and PMA holders. The EtO Pilot Program seeks to help ensure patient access to safe medical devices while encouraging new, innovative ways to sterilize medical devices that reduce the potential impact of EtO on the environment and on the public health while providing a regulatory approach that would address potential device shortages. The EtO Pilot Program is voluntary and is intended to allow companies that sterilize single-use medical devices using fixed chamber EtO to submit a Master File when making certain changes between sterilization sites or when making certain changes to sterilization processes that utilize reduced EtO concentrations. Under this voluntary program, manufacturers ("Pre-Market Application (PMA) holders") of Class III devices subject to premarket approval that are affected by such changes may, upon FDA's permission, reference the Master File submitted by their sterilization provider in a post approval report in lieu of submission of a premarket approval application (PMA) supplement.[83,84] The EtO Sterilization Master File Pilot Program for PMA holders includes the following participants: Boston Scientific (accepted March 18, 2020);

[81] https://www.fda.gov/news-events/press-announcements/fda-continues-efforts-support-innovation-medical-device-sterilization.
[82] https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/ethylene-oxide-sterilization-medical-devices.
[83] https://www.federalregister.gov/documents/2019/11/26/2019-25631/center-for-devices-and-radiological-health-ethylene-oxide-sterilization-master-file-pilot-program.
[84] Device classification depends on the intended use of the device and also upon indications for use. A discussion of the meaning of intended use is contained in The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notification [510(k)]. In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.

Becton, Dickinson & Company (accepted September 11, 2020); Steris Corporation (accepted October 25, 2021); Oscor, Inc. (accepted December 17, 2021); and Medtronic, Inc. (accepted February 17, 2022).[85]

On May 20, 2022, FDA announced its 510(k) Sterility Change Master File Pilot Program. The 510(k) Sterility Pilot Program is voluntary and is intended to give interested companies that terminally sterilize single-use devices using certain sterilization methods a pathway to submit a Master File for FDA's review. This voluntary pilot program seeks to encourage industry to consider new, innovative ways to sterilize devices that reduce the potential impact of EtO on the environment and on public health, while ensuring consistent patient access to safe devices and providing a framework for future regulatory approaches that would help address potential device shortages related to EtO sterilization. FDA will accept a Master File into the 510(k) Sterility Pilot Program when it determines, among other things, that there is not a likelihood that switching from a fixed chamber EtO sterilization method to the sterilization method described in the Master File could significantly affect the safety or effectiveness of a 510(k)-cleared device that meets the product definition in the Master File. If a Master File is accepted into the 510(k) Sterility Pilot Program, manufacturers of 510(k)-cleared devices may choose to reference the Master File in internal documentation in support of a justification for not submitting a new premarket notification. The 510(k) Sterility Change Master File Pilot Program is open to all current 510(k) holders, and up to nine eligible sterilization providers may be selected for participation in the 510(k) Sterility Pilot Program.[86]

**Spices**

FDA also is an important federal partner with respect to EtO fumigation of spices. FDA's Center for Food Safety and Applied Nutrition (CFSAN) protects and promotes public health by 1) modernizing methods to find, track, and eliminate harmful pathogens and other hazards, 2) evaluating the safety of new ingredients for food and the safety of new color additives, 3) strengthening manufacturing practices, 4) ensuring properly labeled food, dietary supplements, and cosmetics, 5) fostering good nutrition and effective food safety practices, 6) investigating causes of foodborne illness outbreaks, and 7) targeting unsafe products.[87] Passage of the Food Safety Modernization Act (FSMA) in 2011 expanded FDA's authority under the Federal Food, Drug, and Cosmetic Act to ensure the food supply in the United States is safe. FDA's authority covers domestically grown and produced food as well as food and ingredients imported from abroad, except for meat; poultry; Siluriformes fish, including catfish; and certain egg products for which the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture (USDA) is responsible. FDA is responsible for ensuring that food, including spices, is not adulterated or misbranded. Foods, including spices, can be adulterated for reasons such as they contain pathogens or pesticide residues such as EtO or ECH at unsafe levels, or because they are produced under unsanitary conditions.

[85] https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/ethylene-oxide-sterilization-medical-devices#MasterFile.
[86] https://www.federalregister.gov/documents/2022/05/20/2022-10925/medical-devices-510k-sterility-change-master-file-pilot-program.
[87] https://www.fda.gov/about-fda/center-food-safety-and-applied-nutrition-cfsan/what-we-do-cfsan

Many spices are imported into the U.S.[88,89] FDA has an import safety program that has traditionally consisted of inspecting foreign facilities that import food into the U.S. and inspecting shipments at the port of entry. FSMA also established prevention-based programs to ensure the safety of imported foods before they reach the U.S.[90] These include the Foreign Supplier Verification Program and the Voluntary Qualified Importer Program, as well as accrediting third-party certification bodies to conduct food safety audits of foreign food entities. The Foreign Supplier Verification Program requires importers to verify the safety of the food they import, and FDA inspects importers to make sure they are doing so. The Voluntary Qualified Importer Program involves expedited review of food from eligible importers that meet rigorous standards.

**Treatment (including reconditioning) of spices for pathogen control**

Herbs and spices can contain pathogens of public health significance. Spices may be treated for pathogen reduction as a preventive measure to control pathogens, due to the confirmed presence of a pathogen, such as *Salmonella*, or due to the appearance of adulteration. The primary treatment options for pathogen reduction on dried herbs and spices are EtO, steam, and irradiation; propylene oxide (PPO) also is used occasionally. When FDA detains spice shipments for pathogens, a reconditioning proposal to bring the product into compliance can be submitted by the responsible firm to FDA. The reconditioning proposal must identify the proposed treatment option and treatment location. If the reconditioning proposal is accepted by FDA, the spices are then sent to the facility for treatment. After the treatment process, the manufacturer or importer of the lot will generally provide testing results of the treated lot for FDA review to verify that the treatment was effective, and the product is safe. [91]

Of the reconditioning proposals submitted to FDA for imported spices and herbs from 2015-2019, half of the reconditioning proposals were for EtO treatment. The other half proposed alternative treatment methods (e.g., irradiation, steam, propylene oxide). A review of spice reconditioning proposal applications from 2019-2022 revealed that there were 34 total submissions including resubmissions (there were 14 original submissions), and approximately 36% (5 of the 14 original submissions) of the proposed treatments were for EtO.[92] The other reconditioning proposals were for heat treatment, steam sterilization or irradiation (gamma or infrared drum). Some examples of spices that were submitted for reconditioning by EtO

[88] FDA Center for Food Safety and Applied Nutrition (FDA CFSAN). 2017. Draft Risk Profile: Pathogens and Filth in Spices. Center for Food Safety and Applied Nutrition, Food and Drug Administration. U.S. Department of Health and Human Services. https://www.fda.gov/media/108126/download. Accessed August 2021.
[89] American Spice Trade Association (ASTA). 2020. ASTA reply to EPA questions regarding ethylene oxide use on spices. Email from Laura Shumow, Executive Directors, ASTA, to Susan Bartow, Pesticide Re-Evaluation Division, Office of Pesticide Programs, Environmental Protection Agency. June 25, 2020.
[90] https://www.fda.gov/food/cfsan-risk-safety-assessments/questions-answers-improving-safety-spices.
[91] *Ethylene Oxide (EtO) Spice Sterilizing Facilities*. Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA) responses to questions from Office of Pesticide Programs (OPP), Environmental Protection Agency (EPA). December 20, 2022.
[92] Letter from Dr. Girvin Liggans, Acting Deputy Director for Plant Derived Foods, Office of Food Safety, Center for Food Safety and Applied Nutrition, Food and Drug Administration to Edward Messina, Director, Office of Pesticide Programs, Environmental Protection Agency. August 18, 2022.

treatment were thyme, thyme leaves and black pepper. Reconditioning proposals are generally for whole spices or single spice powders.[93]

FDA also may inspect commercial sterilization facilities. Firms are not required to submit process control validation data to FDA, but FDA will review data during inspections. Regardless of the facility location and type, FDA's review of reconditioning proposals ensures that each treatment process for microbial reduction is effective. In addition, when a manufacturing/processing facility is subject to the requirements for hazard analysis and preventive controls in the Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food (PCHF) regulation in 21 CFR part 117 and is using a certain process for pathogen reduction as a preventive control, it must validate the process to ensure it is adequate for controlling the identified hazards (21 CFR 117.160(a)).[94]

The ASTA developed documents to assist sterilization facilities in developing validations for fumigations of herbs and spices entitled, *General Protocol for the Validation of Microbiocidal Processes on Pathogen Contaminated Spices and Culinary Herbs (2001) and Validation of Microbial Reduction Processes for Spices (2013).* These documents may assist commercial sterilization facilities with complying with portions of the PCHF regulation as mandated by FSMA. FDA is in the process of developing its own guidance, *Hazard Analysis and Risk-Based Preventive Controls for Human Food; Chapter 16: Validation of Process Controls; Draft Guidance for Industry*. EPA is not aware of any new technologies that are available for spice microbial remediation. New technologies can take up to ten years to be implemented because research and validation are required.[95]

# V. PROPOSED INTERIM REGISTRATION REVIEW DECISION

## A. Proposed Risk Mitigation and Regulatory Rationale

EtO is a known carcinogen. EtO is also a critical tool for the medical sterilization market and is beneficial when used on spices to control microbes which may cause food-borne illnesses. The registered uses of EtO pose inhalation risks to workers inside commercial sterilization facilities, healthcare facilities, and to those treating beekeeping equipment in North Carolina. EtO also has the potential to pose inhalation risks to communities near facilities where EtO is used. See Section III.A.-B. above. Therefore, EPA is proposing mitigation to address inhalation risk concerns. The Agency finds that mitigation of inhalation risk concerns is necessary for use of EtO to meet the FIFRA standard for continued registration. To help address these concerns, EPA is proposing the termination of certain uses, a use rate reduction through reduced concentrations,

[93] *Ethylene Oxide (EtO) Spice Sterilizing Facilities*. Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA) responses to questions from Office of Pesticide Programs (OPP), Environmental Protection Agency (EPA). December 20, 2022.
[94] *Ethylene Oxide (EtO) Spice Sterilizing Facilities*. Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA) responses to questions from Office of Pesticide Programs (OPP), Environmental Protection Agency (EPA). December 20, 2022.
[95] *Ethylene Oxide (EtO) Spice Sterilizing Facilities*. Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA) responses to questions from Office of Pesticide Programs (OPP), Environmental Protection Agency (EPA). December 20, 2022.

a series of engineering controls within commercial sterilization facilities and healthcare facilities, respiratory protection requirements for commercial sterilization facilities, monitoring, training, and recordkeeping requirements

The Agency discussed risk mitigation options with sterilization industry representatives, (including the Ethylene Oxide Task force (EOTF), Steris, the American Spice Trade Association (ASTA), and AdvaMed), as well as USDA, OSHA, and FDA. The Agency also discussed the proposed mitigation measures associated with the beekeeping equipment use in North Carolina with the North Carolina Department of Agriculture and Consumer Services (NCDACS).

***Proposed Termination of Uses***

EPA proposes to terminate the following uses of EtO:

- Museum materials
- Library materials
- Archival materials
- Cosmetics
- Musical instruments
- Beekeeping equipment

Use of EtO by Commercial Sterilization Facilities for Museum, Library, and Archival Materials, Cosmetics, and Musical Instruments

EtO is registered for use to treat museum, library, and archival materials, as well as cosmetics and musical instruments, in commercial sterilization facilities. For occupational handlers at commercial sterilization facilities, cancer risk estimates are estimated from $4 \times 10^{-2}$ (1 in 25 workers) to $1 \times 10^{-1}$ (1 in 10 workers). Cancer risks of concern are also anticipated for occupational and non-residential and residential bystanders. Because there are viable EtO alternatives available for these uses, continued registration of EtO provides minimal benefits. Alternatives for the museum, library, and archival materials include freezing, anoxia (oxygen deprivation), and irradiation. EtO is no longer used for treatment of museum, library, or archival materials due to concerns over human health risks associated with off-gassing from treated materials.[96] Gamma irradiation is a viable alternative for cosmetics and EtO is likely no longer used in the cosmetics industry. For the musical instrument uses, other disinfectant products are available for use that are more practical. These products are low cost and easily accessible as compared to EtO sterilization in commercial sterilization facilities. For additional information, see Section III.C and *Ethylene Oxide (PC# 042301): Use, Usage, Benefits, and Impacts of Cancellation* in this docket. Therefore, EPA proposes that these uses be terminated.

[96] Email communication between Jessica Johnson, Head of Conservation, Museum Conservation Institute, Smithsonian Institution and Jessica Bailey, Antimicrobial Division, Office of Pesticide Program, Environmental Protection Agency. March 18, 2021.; Email communication between Lindsey Oakley, Director of Heritage Science Research and Testing, U.S. National Archives and Records Administration and Jessica Bailey, Antimicrobial Division, Office of Pesticide Program, Environmental Protection Agency. March 30, 2021.; Email communication between Hayes Robinson III, Associate Director, Environmental Management Division, Office of Safety, Health and Environmental Management at the Smithsonian Institution and Jessica Bailey, Antimicrobial Division, Office of Pesticide Program, Environmental Protection Agency. March 18, 2021.

There is low to no impact expected as a result of the termination of these uses. For more information on the alternatives to EtO and impacts of termination of these uses, see *Ethylene Oxide (PC# 042301): Use, Usage, Benefits, and Impacts of Cancellation* in this docket.

Beekeeping Equipment (in NC only)

EtO is approved for the treatment of beekeeping equipment in North Carolina under FIFRA section 24(c) SLN registration NC140003. EtO is used for the sterilization of beekeeping equipment to control American foulbrood (AFB) disease in the state. The North Carolina Department of Agriculture and Consumer Services (NCDACS) currently operates one treatment chamber in the Raleigh, NC area for this purpose. There is the potential for non-occupational bystander exposure for people who live near the treatment chamber (residential non-occupational bystanders) or who spend significant time in the area for non-work-related activities (e.g., school, daycare, shopping) (non-residential non-occupational bystanders).

The distances from the fumigation chamber at which the cancer risk estimates are less than 1 x $10^{-6}$ increase from 10 meters to 300 meters or more depending on the percentile considered (e.g., 75$^{th}$ and 90$^{th}$ respectively). A specific percentile has not been selected for regulation (and correspondingly a buffer distance from the fumigation chamber has not been established) since the Agency is proposing to terminate the use of EtO on beekeeping equipment in North Carolina.

There also is the potential for occupational exposure for people who operate the treatment chamber in NC. Cancer risks range from 2 x $10^{-4}$ (1 in 5,000) when assuming 4 exposure days per year to 4 x $10^{-4}$ (1 in 2,500) when assuming 8 exposure days per year. These risk estimates also assume that self-contained breathing apparatus (SCBA) PPE is in use. These cancer risk estimates exceed the Agency target of 1 x $10^{-4}$ for occupational risks. For more information, see section III. A above and *Ethylene Oxide (EtO). Addendum to "Draft Human Health and Ecological Risk Assessment in Support of Registration Review" - Inhalation Exposure Risk Assessment in Support of Registration Review* in this docket.

Beekeepers have several chemical and non-chemical alternatives to EtO for preventing and disinfecting beekeeping equipment of AFB. Chemical control alternatives include antibiotics such as terramycin, tylan (tylosin), or lincomix soluble powder. Non-chemical control tactics include cultural and mechanical/physical controls. Examples of cultural controls include practices such as purchasing several new frames for hives each year, sanitizing hands with alcohol-based hand sanitizer and wearing non-leather gloves when working with a hive, sanitizing equipment/tools with isopropyl alcohol, irradiation, or autoclave prior to working with a hive and/or between seasons, and hive placement. Examples of mechanical controls include fire scorching small equipment with a blowtorch followed by a bleach spray, or the burning or destruction of infected colonies and equipment. Beekeepers can also sanitize infected equipment including frames by boiling infected materials in sodium hydroxide (lye), although this may involve culling the hive if the equipment is in use.

Given that the risk estimates for this use assume the use of the highest level of respiratory protection (SCBA) and, nonetheless, exceed the Agency target of 1 x $10^{-4}$ for occupational risks,

and that there are alternative control methods for AFB in place in the other states that are feasible in North Carolina, the Agency proposes that the benefits of the use do not outweigh the risk. Therefore, the Agency has determined that the use of EtO for disinfecting beekeeping equipment does not meet the FIFRA standard and proposes that the use be terminated.

There is low to no impact expected from the proposed termination of the use to sterilize beekeeping equipment in North Carolina (the only state with this registered use). There are alternative chemical, cultural, and mechanical controls available to manage American foulbrood, a contagious disease that affects honeybees. For more information on the impacts of the cancellation of this use, see *Ethylene Oxide (PC# 042301): Use, Usage, Benefits, and Impacts of Cancellation* in this docket.

EPA proposes that the registrants submit requests to voluntarily terminate the uses of EtO for museum materials, library materials, archival materials, cosmetics, musical instruments, and beekeeping equipment as soon as practicable, but no later than 60 days from the publication of the Interim or Final Decision. EPA will specify the timing for submission of such requests at a later date.

Spices

Limiting the use of EtO to specific dried herbs and spices where its use is deemed critical for food safety and where alternative treatment methods are not available could result in fewer EtO applications overall, and thus less exposure to workers (including handlers and occupational bystanders), non-residential bystanders, and residential bystanders. Because of the estimated occupational and bystander risks associated with the use of EtO to fumigate spices, the Agency is soliciting comments on the specific commodities in Table 2 for which there is a critical need for the use of EtO and for which there are no viable alternatives to EtO (e.g., steam, irradiation, or propylene oxide cannot be used for pathogen control on a particular spice, spice form, or spice blend). The Agency is considering a phased cancellation of specific spices/commodities without documented support for continued treatment with EtO. The Agency intends to include language in the ID stating that registrants should submit requests to voluntarily terminate uses on these commodities. When the Agency receives requests from registrants to voluntarily cancel a pesticide registration or terminate a use, the Agency is required to publish an FRN regarding the cancellation request and take public comment (see 7 U.S.C. § 136d(f)(1)).

***Proposed EtO Use Rate Reduction***

Medical Devices

A sterilization cycle is defined as "treatment in a sealed chamber, which includes air removal, conditioning (if used), injection of ethylene oxide, inert gas (if used), exposure to ethylene oxide, removal of ethylene oxide and flushing (if used), and air/inert gas admission."[97] A sterilization calculation includes validated parameters such as pressure, concentration, temperature, humidity,

[97] International Standard ISO 11135. Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routing control of a sterilization process for medical devices. 2014.

and exposure time. Assessment of cycle validation from FDA includes specifications for products, load configuration, packaging, and sterility assurance level.

Based on discussions with industry and FDA, it is the Agency's understanding that many sterilization facilities sterilize medical devices using much higher concentrations of EtO than what is required for sterility assurance – specifically, the Agency has been informed that double the necessary concentration is often used on some devices. Furthermore, it is the Agency's understanding, through discussions with industry, that the current EtO concentration may be as high as 700 mg/L for medical device sterilization. The increased application rate is related to the way in which facilities sterilize large quantities of mixed devices in order to meet demand. For example, if a few devices in a large mixed load require 700 mg/L, then all of the devices will be sterilized at that rate, even those that may need less EtO to ensure sterility. Surgical kits are an example, which are pre-packaged in order to be quickly sent to operating rooms and contain a variety of devices which require differing levels of EtO for sterilization. Batching devices in mixed loads also helps to reduce the total number of EtO cycles run. More EtO runs may be needed to meet device demand and could result in the need for additional chambers, staff, and possibly more EtO.

Based on further discussions with industry, the majority of new sterilization cycles are able to use 500 mg/L or less, if a variety of optimizations are put into place, at the time the device itself is designed (e.g., device design, packaging, and sterilization parameters). For existing cycles, the majority of devices are sterilized at concentrations higher than 500 mg/L, and a reduction of this concentration limit across the industry would require extensive cycle experimentation and redesigning of devices, as well as cycle validation and review.

EPA proposes that the EtO concentration for new cycles must be less than or equal to 500 mg/L, and that the sterilization validation process specific to the concentration used is reviewed by FDA. EPA seeks public comment on the feasibility of a 2-year compliance timeline for use rate reduction through reduced concentrations of new cycles.

In order to limit the EtO concentration to 500 mg/L for existing cycles, EPA proposes a 5-year compliance timeframe to redesign cycles, devices, or packaging and be reviewed by FDA under applicable device authorities. EPA seeks public comment on the feasibility of a 5-year compliance timeline for use rate reduction of existing cycles.

EPA anticipates this use rate reduction through reduced concentrations would reduce risks for all exposure scenarios, given that currently most cycles exceed 500 mg/L. If a sterilization cycle requires more than 500 mg/L, due to the device design, EPA proposes to require registrants ensure that facilities maintain records that include a justification for the increased application rate. Specifically, this justification would demonstrate the necessary calculations for determining the application rate, through either the Cycle Calculation Approach (described below), or other approaches found in ISO 11135 (described below). EPA further proposes to require registrants ensure that facilities maintain records for the amount of EtO used regardless of whether the amount used is less than or greater than 500 mg/L. All records would need to be available upon request to any local, state, tribal, or federal pesticide enforcement personnel. Records would be required to be maintained for two years from the date of sterilization.

If a device has historically used more than 500 mg/L unnecessarily, there are several methods for decreasing EtO concentration limits while ensuring sterility, including the cycle calculation approach and cycle design optimization (e.g., with the use of the half cycle approach), as described below.

*Cycle Calculation Approach*

The International Organization for Standardization (ISO) is a worldwide federation of national standards bodies that set a standard for medical device sterilization using EtO titled *ISO 11135:2014 Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*. This standard specifies requirements for the development, validation and routine control of an EtO sterilization process for medical devices in both the industrial and healthcare facility settings.[98] Compliance with the requirements ensures that validations conducted following this international standard will provide products that meet the defined requirements for sterile products with a high degree of confidence.[99] The sterilization/fumigation cycle parameters are prescribed by the device manufacturer. Device manufacturers must also validate sterilization methods they select to facilitate FDA review of sterility information as part of the premarket review process for devices.

Manufacturers and applicators (i.e., end users) may, for example, follow the *Cycle Calculation Approach* to determine the precise amount of EtO necessary to sterilize medical devices. According to ISO Standard 11135, for the cycle calculation approach, the lethality of the process on disease-causing microbes can be determined by either direct enumeration, the fraction-negative method, or both. Once the inactivation of a known number of microorganisms has been confirmed, the sterilization facility would determine the extent of treatment for the sterilization process by extrapolation to a known predicted probability of a surviving microorganism. This method consists of exposing internal process challenge devices to the experimental cycle, removing the challenge and testing for survivors.[100] This information can be used to calculate the cycle necessary to deliver the defined sterility assurance level for the product. The recommended number of biological indicators or process challenge devices can be based on the product volume to be sterilized. Further guidance on the *Cycle Calculation Approach* can be found in *ISO*

[98] According to ISO 11135:2014, "In terms of the initial condition of medical devices, medical device manufacturers generally sterilize large numbers of similar medical devices that have been produced from virgin material. Health care facilities, on the other hand, must handle and process both new medical devices and reusable medical devices of different descriptions and with varying levels of bioburden. They are therefore faced with the additional challenges of cleaning, evaluating, preparing and packaging a medical device prior to sterilization. In this International Standard, alternative approaches and guidance specific to health care facilities are identified as such."
[99] The development, validation and routine control of a sterilization process comprises a number of activities; calibration, maintenance, product definition, process definition, installation qualification, operational qualification and performance qualification. See ISO 11135:2014.
[100] Process challenge devices, or PCD's, are defined as items designed to constitute a defined resistance to a sterilization process and used to assess performance of the process.

*14161:2009 Sterilization of health care products — Biological indicators — Guidance for the selection, use and interpretation of results*.[101]

EPA acknowledges that this approach could increase the overall number of cycles that need to be run since each device, under the Cycle Calculation Approach, will need its own cycle. This could make it difficult for sterilization providers to maximize their output and could reduce overall device availability for patients, as it is rare that a chamber can be completely filled with one particular product. Due to these limitations, FDA and industry continue to research and implement additional methods for use rate reductions through reduced concentrations that use a more conservative ISO 11135 approach while optimizing cycle designs, as described below.

*Cycle Design Optimization & Half Cycle Approach*

EPA understands that most sterilization facilities employ a very conservative method for medical device sterilization, the *Half Cycle Approach*. According to ISO Standard 11135, the Half Cycle Approach is a total of three consecutive experiments resulting in total inactivation of the biological indicators, wherein the cycle time is halved compared to the full cycle. Due to its relative ease of use and the conservative sterility assurance level obtained, this method is commonly used to demonstrate total inactivation of the biological indicators at a half-cycle exposure time. As compared to the half cycle, running a full cycle may lead to a process supporting a sterility assurance level that is higher than the device specification.[102]

There are methods to reduce the amount of EtO used during the Half Cycle Approach, and these are currently being pursued by the FDA's "Innovation Challenge 2" participants (see Section IV.B.). EPA and FDA share the same goal of reducing the overall amount of EtO used by optimizing cycle design, through the optimization of various specifications such as dwell times, pressure, and humidity, as well as the reduction in the amount of paper packaging which is known to absorb EtO. Through FDA's Innovation Challenge 2, some industry participants have already implemented their optimized cycle designs, reducing EtO use by a significant amount. Per an FDA statement, early observations suggest that some facilities have cut emissions ranging from 20-35%, with the potential to impact millions of devices. In general, manufacturers are targeting an EtO concentration that is 11-66% less than the typical concentration range.[103]

EPA proposes that sterilization facilities use the least amount of EtO needed to meet sterility assurance through cycle design optimization, taking into consideration that sterilization cycles often include mixed loads of different medical devices which require different levels of EtO concentrations. Industry has already demonstrated the ability to optimize dwell times, pressure, and humidity, as well as the reduction in the amount of paper packaging through FDA's Innovation Challenges.

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[101] ISO 14161:2009. Sterilization of health care products — Biological indicators — Guidance for the selection, use and interpretation of results.
[102] ISO 11135:2014 *Sterilization of health-care products — Ethylene oxide — Requirements for the development, Validation and routine control of a sterilization process for medical devices.* Publication date: 2014-07. Technical Committee: ISO/TC 198 Sterilization of health care products.
[103] https://www.fda.gov/news-events/press-announcements/fda-continues-efforts-support-innovation-medical-device-sterilization.

EPA plans to collaborate with FDA on innovating improvements to EtO sterilization for medical devices as a way to reduce potential impacts to the supply chain of critical medical devices. By reducing the overall concentration of EtO permitted to be used in sterilization processes while following standards for sterility assurance, risks to workers, non-residential bystanders, and residential bystanders would be reduced. Reducing the application rate of EtO would result in less EtO exposure.

For new cycles, use rate reduction through reduced concentrations of 500 mg/L or less should be minimally impactful from a facility standpoint for most commercial sterilization facilities; however, new cycle validations and potentially additional staff and/or chambers may be needed to implement reduced concentrations. By encouraging use of the Cycle Calculation Approach or cycle optimization for concentrations over 500 mg/L, EPA strives to direct the user community to a more efficient use of EtO.

For existing cycles, the Agency acknowledges that there would be impacts to many commercial sterilization facilities from implementation of use rate reduction through reduced concentrations for medical device sterilization. Reduction of the amount of EtO used in sterilization processes for medical devices may have high impacts to the customers of commercial sterilization facilities. Reducing the concentration of EtO used in sterilization processes would result in some cost savings by reducing the amount (and cost) of EtO applied as well as reducing the amount of time a product spends in off-gassing and allowing the product to be released more quickly. However, using less EtO may also result in the need for longer sterilization times. Additionally, it would also require medical device manufacturers and other customers to recalculate and revalidate the sterilization methods, including the concentration of EtO used and duration in the chamber, for each specific product sterilized by EtO. Updating processes while guaranteeing sterilization would result in increased labor and validation costs for customers of commercial sterilization facilities. Additionally, technicians at EtO commercial sterilization facilities and employees at FDA may have increased workload initially due to an increase in validation tests needed to review new methodologies used to sterilize products. Validation tests may also take time from the sterilization chamber schedule that was previously scheduled for another product which could result in temporary delays in the supply of sterilized medical devices.

The Agency seeks public comment on how long is necessary for registrants to implement label amendments requiring facilities to use less than or equal to 500 mg/L, taking into account the compliance timeframes, impacts to the sterilization process and/or supply chain, costs on users of EtO and customers of commercial sterilization facilities, or any other relevant impacts or factors. EPA is proposing that this change be implemented within 5 years for existing cycles, and within 2 years for new cycles.

The Agency is also soliciting alternative proposals for reducing the amount of EtO used in commercial sterilization facilities.

Spices

The Agency is also interested in reducing the concentration of EtO used to fumigate spices. ISO standard 11135 described above does not apply to spice treatments and there are no other ISO standards in place for spice treatments as there are for sterilization of medical devices. The spice treatment process is specified on the FIFRA product labels as follows:

> "This product may not be used on or in any form of basil.
>
> After August 1, 2008, this product may only be applied to or on spices, dried vegetables or seasonings utilizing an EtO sterilization method that uses a single sterilization chamber to precondition and aerate with an alternating vacuum and aeration purging procedure. If you wish to employ an alternative method to that described below, you must contact the Environmental Protection Agency Office of Pesticide Programs for instruction on how to receive authorization.
>
> Place spices in the treatment chamber. Assure that the mixture of ethylene oxide and air is compatible with the chamber design, then, introduce into the chamber a concentration of Ethylene Oxide not to exceed 500 mg/L, with a dwell time not to exceed 6 hours. Then evacuate the gas from the chamber using a sequence of not less than 21 steam washes (injections and evacuations) between 1.5 PSIA (27" Hg) and 5.0 PSIA (20" Hg) while maintaining a minimum chamber temperature of 115°F."

Based on discussions with FDA and ASTA, it is the Agency's understanding that the actual EtO concentration used (and validated) to treat spices in commercial sterilization facilities is company-, chamber-, pathogen-, and spice-specific. The Agency is seeking public comment on examples of efficacious EtO treatments for pathogen control at rates lower than the maximum label rate, and how often facilities have completed EtO validations for EtO concentrations that are less than 500 mg/L. The Agency is interested in establishing an alternative method for the product labels that uses a lower rate of EtO. EPA encourages facilities and interested stakeholders to work with the Agency to develop a new method at a lower rate that is effective for pathogen control and continues to meet the dietary safety standards (e.g., acceptable residues of EtO and ECH).

***Proposed Mitigation for Residential Bystander Risk***

Bystander exposures around commercial sterilization facilities are considered "residential" if the exposures occur where people live (i.e., their homes).

At the time of this Proposed Interim Decision, EPA's Office of Air and Radiation (OAR) is concurrently releasing their Proposed Rulemaking for EtO commercial sterilizers, *National Emission Standards for Hazardous Air Pollutants (NESHAP): Ethylene Oxide Emissions Standards for Sterilization Facilities Residual Risk and Technology Review*.[104] OAR is proposing to revise the NESHAP for commercial sterilization facilities by both amending existing standards and establishing additional standards for this source category, exercising authority under multiple provisions of section 112 of the Clean Air Act (CAA). In December 2016, the EPA's Integrated

[104] EPA-HQ-OAR-2019-0178.

Risk Information System (IRIS) Program issued its final, updated EtO toxicological assessment, which indicated that EtO is a far more potent carcinogen than EPA had understood at the time of the previous risk and technology review for this source category. For the risk assessment for this proposed rulemaking, EPA applies the revised updated cancer risk value. There are 85 commercial sterilization facilities in this source category, many of which are located near residences, schools, and other public facilities. Many of these facilities are also located in communities with environmental justice concerns. OAR has determined that approximately 23 of these facilities pose elevated lifetime cancer risks to the surrounding communities, some of which are exceptionally high.

OAR is proposing mitigation to reduce EtO emissions from commercial sterilizers to residential populations.[105, 106] Specifically, OAR is proposing that emission sources in existing and new facilities reduce emissions by a certain percentage or to a specific pound per hour, depending on the emission source, EtO usage per year, and whether the facility is existing or new.[107] OPP notes that OAR is proposing, similar to OPP's proposal, that under certain scenarios, facilities use less EtO per cycle while maintaining sterility assurance.

While the OAR and OPP proposals are based on different statutory authorities and mandates, they complement each other in their shared objective of preventing the use of more EtO than necessary to achieve sterility. In this Proposed Interim Decision, OPP is relying on OAR's proposed mitigation to address residential bystander risks from inhalation exposure to EtO through the emissions reductions that would result from action proposed to be taken by OAR under the authority of the Clean Air Act. OPP believes that the emissions limits proposed by OAR would significantly reduce residential and non-residential bystander exposure without causing adverse impacts to the U.S. supply of sterilized medical devices needed for a variety of medical procedures. Additionally, OPP's proposal for use rate reduction through reduced concentrations for all medical devices in all facilities will result in reduced emissions overall and would, therefore, be expected to reduce risk to residential bystanders.

Compliance with both Agency actions, the OPP decision and the OAR rulemaking, will impose costs on commercial sterilization facilities. While the requirements set forth in each Agency action may be complementary in that they may both reduce public health risks from EtO exposure, the costs to commercial sterilization facilities to comply with both Agency actions are additive in some respects. The *Regulatory Impact Analysis for the Proposed National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Commercial Sterilization and Fumigation Operations* (EPA-HQ-OAR-2019-0178) provides estimates of the cost to industry to comply with the proposed OAR rule.[108] As is typical of the Registration Review process under

[105] The Proposed Rulemaking from OAR is based on risk to residential areas only. OPP's analysis and proposed mitigation includes residential, non-residential, and worker exposure.
[106] At the time of OAR's assessment on commercial sterilizers, 23 out of 85 facilities were identified that exceeded a 100 in 1 million risk threshold. See Appendix F.
[107] Emission sources in sterilization facilities include: sterilization chamber vents, aeration room vents, chamber exhaust vents, Group 1 room air emissions (emissions from indoor EtO storage, EtO dispensing, vacuum pump operations, and pre-aeration handling of sterilized material), and Group 2 room air emissions (emissions from post-aeration handling of sterilized material).
[108] OAR did not include discussion of the PID and its potential costs – or costs of both actions – in the regulatory impact analysis (RIA) for the commercial sterilizer proposed rule.

FIFRA, OPP did not conduct a cost analysis for the proposed mitigation in this PID. However, OPP is specifically requesting public comment on the costs of the proposed mitigation measures included in this PID.

***Proposed Mitigation for Non-Residential Bystander Risk***

Bystander exposures around commercial sterilization facilities are considered "non-residential" if the exposures occur at locations other than homes where people may spend a significant amount of time (i.e., daycare centers, schools).

Emissions controls proposed by OAR to address risks from residential exposure to EtO would also reduce exposure to non-residential bystanders. See *Proposed Mitigation for Residential Bystander Risk* above.

***Proposed Mitigation for Occupational Risk***

**Engineering Controls for Healthcare Facilities**

Healthcare facilities such as hospitals, dental offices and veterinary facilities are expected to use significantly smaller volumes of EtO than commercial sterilization facilities. Exposure scenarios in healthcare facility settings differ significantly from commercial sterilization exposure scenarios because in health care facilities, EtO sterilization is intermittent, and devices are typically used soon after sterilization (i.e., not stored for shipping). As of the 2008 RED, sterilization is required to be performed in all-in-one systems. However, given the low concentration at which EtO may present inhalation cancer risks of concern, EPA now believes additional risk mitigation measures are needed. To reduce exposure to EtO in healthcare facilities, EPA is proposing to require the following engineering controls:

*Physical separation of EtO sterilization spaces*

EPA proposes to require that all-in-one EtO sterilization devices be located in a containment area that is physically separate from all other work areas of the healthcare facility.

*Negative air pressure*

EPA proposes that the rooms containing all-in-one EtO sterilization devices must have a negative pressure in comparison to the rest of the healthcare facility. This ensures that air will not flow from the room with a higher EtO concentration through the rest of the healthcare facility.

*Ventilation of EtO through exterior ventilation stacks*

EPA proposes that all exhaust from all-in-one EtO healthcare facility sterilization devices be directed through exterior ventilation stacks. This would ensure that there is minimal EtO

exposure for workers and bystanders within healthcare facilities. EPA's proposal would require EtO exhaust to be vented to a dedicated exhaust ventilation system composed of local exhaust ducts that serve the sterilizer area only (i.e., the area containing the all-in-one sterilization device, EtO ampules, etc.) and route EtO directly to the outside of the building by maintaining a net suction on all of the exhaust ductwork.[109] The exhaust duct would also be required to terminate away from areas where people walk or work, and the duct would be required to be located at least 7.6 meters (25 feet) away from the building air intake source and be engineered according to existing codes.[110]

*Abatement Devices*

EPA proposes that additional abatement devices be required to be used along with all-in-one EtO sterilization devices in healthcare settings. Both all-in-one sterilization device manufacturers offer accessory abatement devices that reduce EtO emissions by more than 99%.[111,112] By requiring that all EtO sterilization devices are used with dedicated abator systems, EtO levels would be kept to a minimum both within healthcare facilities and in their outgoing emissions. Abatement devices will reduce risks to workers inside healthcare facilities. Recognizing that risks to bystanders from healthcare facilities were not quantitatively assessed, EPA expects abatement devices to reduce exposures, and therefore any risks, to bystanders as well.

The Agency acknowledges that there would be impacts to healthcare facilities from implementation of engineering controls. Through discussions with industry leaders, the Agency determined that some engineering control measures described in this section may already be common practice while others would impose costs from retrofitting existing facilities to meet the new standards proposed. The cost of retrofitting includes the costs of new equipment, installation, operation and maintenance, and the loss of revenues associated with any necessary downtime required for installation.

The Agency seeks public comment on the cost and time necessary for registrants to implement label amendments requiring the implementation of the proposed engineering controls. EPA is proposing that these engineering controls be implemented within 2 years.

In addition to the proposed engineering controls, EPA is seeking public comment on the feasibility of respirator use (supplied airline respirators or self-contained breathing apparatus respirators) in healthcare facilities for employees who are unloading EtO sterilization equipment from the sterilization chamber.

**Engineering Controls for Commercial Sterilization Facilities**

According to OSHA's hazard prevention principles, the first and best strategy is to control the hazard at its source. Engineering controls do this, unlike other controls that generally focus on

[109] https://www.cdc.gov/niosh/docs/89-115/default.html.
[110] ANSI/AAMI ST41:2008/(R)2018 Section 3.9.2.6: Exhaust Ducts (pg. 15).
[111] https://multimedia.3m.com/mws/media/1427940O/3m-steri-vac-sterilizer-gs-series-safety-summary.pdf.
[112] https://www.sterility.com/gas-abatement-equipment-eto-abator-sterility/.

reducing exposures to the employee exposed to the hazard, such as the use of PPE. Under these principles, the work environment and the job itself should be designed to eliminate hazards or reduce exposure to hazards.[113] The National Institute for Occupational Safety and Health (NIOSH) states that well-designed engineering controls can be highly effective in protecting workers.

To reduce exposure to EtO at commercial sterilization facilities, EPA is proposing to require the following engineering controls:

- Air pressure gradient so that air is always flowing from low-EtO concentration to high-concentration spaces.
- Separation of office and sterilization area HVAC systems.
- Ventilation of storage areas.
- Automation of movement of sterilized and aerated materials.
- All-in-one processing (combination sterilizers).[114]

*Air pressure gradient*

EPA proposes to require that the indoor air pressure gradient in commercial sterilization facilities using EtO is continuously flowing from low-EtO concentration to high-concentration spaces. Under this proposal, areas where EtO is processed must have slightly negative pressure compared to non-processing areas, which must have positive pressure. The highest level of negative pressure would have to be in the sterilization chamber. The negative pressure is caused when the exhaust fan airflow is less than the supply fan airflow. The air is discharged through the exhaust duct to outside the building.

*HVAC systems*

EPA proposes the HVAC systems in commercial sterilization facilities be separated. EtO processing areas would have to have separate HVAC systems from non-processing areas, such as office space and control rooms.

*Ventilation*

EPA proposes to require that commercial sterilization facilities that use EtO have adequate ventilation in spaces where EtO-sterilized product is stored. EPA is soliciting public comment on the number of air exchanges per hour that would adequately ventilate product storage areas. Understanding that not all EtO could be removed from post-sterile product areas, due to the absorbent nature of pallets, cardboard, and packaging, EPA proposes any storage area be properly ventilated. EPA is soliciting public comment on the use of netting rather than plastic surrounding pallets of treated medical devices to increase aeration and prevent EtO from becoming trapped in plastic wrap or other packaging.

[113] https://www.osha.gov/sites/default/files/2018-12/fy11_sh-22318-11_Mod_3_HazardPrevention.pdf.
[114] All-in-one systems would only be required in facilities that do not sterilize pressure sensitive devices.

*Automation*

In traditional EtO treatment configurations, sterilization and aeration are performed in two separate chambers. In these systems, employees may transfer post-treatment materials from the sterilization chamber to the aeration chamber via forklift. EPA is aware that in some sterilization facilities, post-treatment materials are instead transferred via enclosed conveyor system, to reduce employee exposure. EPA proposes that all EtO commercial sterilization facilities with a traditional sterilization configuration implement an enclosed conveyor to transport sterilized materials from the sterilization chamber to the aeration chamber.

Additionally, EPA proposes that all EtO commercial sterilization facilities implement an enclosed conveyor to transport aerated materials from aeration chamber/room to storage/shipping areas, in both traditional sterilization (multi-chamber) scenarios and all-in-one sterilization (single chamber) scenarios. This would apply to both medical device sterilization and spice fumigation processes. EPA is seeking public comment on the feasibility and cost of a conveyor system from the aeration area to the storage/shipping area of EtO commercial sterilization facilities.

*All-in-one processing*

All-in-one processing (also known as single chamber processing or combination sterilizers) is defined as EtO sterilization chambers where the sterilization and aeration occur within the same chamber, thereby eliminating product transfer from a separate sterilization chamber to an aeration chamber.

Since August 1, 2008, EtO products applied to or on spices, dried vegetables or seasonings have been required to utilize an EtO sterilization method that uses a single sterilization chamber to pre-condition and aerate with an alternating vacuum and aeration purging procedure. As of February 28, 2010, a single chamber process has been required for EtO treatment in hospitals and healthcare facilities.

For commercial sterilization facilities treating medical devices, it is the Agency's understanding that there are instances where an all-in-one sterilization chamber could be utilized, rather than the traditional sterilization configuration wherein sterilization and aeration are performed in two separate chambers. However, EPA also understands that there are certain pressure-sensitive devices that cannot be sterilized in all-in-one systems. Further, EPA acknowledges that there could be capacity constraints on the volume of medical devices that could be sterilized in all-in-one systems, which typically have a longer processing time within the chamber.

The Agency is proposing to require all-in-one sterilization systems in commercial sterilization facilities that do not sterilize pressure sensitive devices.[115] EPA further proposes that registrants ensure facilities keep records that document there are pressure sensitive devices being sterilized and are therefore unable to be processed in all-in-one systems, if applicable. All records would

[115] Pressure sensitive devices could include, for example, any device with a cap and plug, or other configuration which changes in pressure could result in shattering or otherwise compromising the elements of the device.

need to be available upon request to any local, state, tribal, or federal pesticide enforcement personnel. Records would be required to be maintained for two years from the date of sterilization. If an all-in-one system is not feasible, the facility would be required to implement a covered conveyor systems as described above.

The Agency acknowledges that there would be impacts to commercial sterilization facilities from implementation of engineering controls. Through discussions with industry leaders, the Agency determined that some facility-level engineering control measures described in this section may already be common practice while others would impose significant costs to retrofit existing facilities to meet the new proposed engineering controls. The cost of retrofitting would include the costs of new equipment, installation, operation and maintenance, and the loss of revenue associated with any necessary downtime required for installation. EPA also acknowledges the corresponding potential impacts on the supply chain of sterilized medical devices related to the costs and potential downtime of sterilizing equipment.

The Agency seeks public comment on the cost and time necessary for registrants to implement label amendments requiring the proposed engineering controls. EPA is proposing that these changes be implemented within 3 years following the publication of the Interim or Final Decision. EPA is also seeking public comment on whether to implement each of the aforementioned engineering controls for all existing facilities, or for only new facilities. EPA further seeks public comment on whether these engineering controls would require state or local permits before the renovations could take place, and the timing associated with that permitting process. Finally, the Agency seeks public comment on potential impacts on the supply chain of sterilized medical devices related to the potential downtime of sterilizing equipment during renovation.

**Lowered Action Limit for Commercial Sterilization Facilities**

As noted in Section IV.A., EtO product labels currently cite the OSHA PEL of 1 ppm to trigger the requirement that EtO handlers in commercial sterilization facilities wear a respirator. Since the publication of the RED in 2008, there have been considerable updates to the scientific database on EtO exposure and risk, including the 2016 IRIS assessment on EtO, OPP's 2020 EtO Draft Risk Assessment (DRA), and 2023 EtO DRA Addendum. EPA thus considers the OSHA PEL of 1 ppm to no longer ensure that the use of EtO will not cause unreasonable adverse effects, including effects to workers, as required under FIFRA, and is, therefore, proposing to require registrants to amend the EtO labels to no longer include the OSHA PEL. EPA understands that OSHA's EtO PEL has not been updated since it was established in 1984, and that health standards issued under section 6(b)(5) of the OSH Act must reduce significant risk only to the extent that it is technologically and economically feasible.[116] OSHA's legal requirement to demonstrate that its 6(b)(5) standards are technologically and economically feasible often precludes OSHA from imposing exposure control requirements sufficient to ensure that the chemical substance no longer presents a significant risk to workers.

[116] https://www.federalregister.gov/citation/49-FR-25734.

To reduce worker exposure, EPA is proposing that respirator requirements be based on a technologically measurable (i.e., quantifiable) EtO concentration of ambient air for real time measurements, which by the Agency's understanding is 10 ppb, using either gas chromatograph systems, Fourier Transform Infrared Spectroscopy (FTIR), or mass spectrometers. Facilities would be required to monitor both processing and non-processing areas, for which the monitoring system would have a visual and audio alarm to alert employees when 10 ppb air concentration is exceeded. Therefore, in addition to the respirator requirements described in the following section, EPA proposes that Self Contained Breathing Apparatus (SCBA) or supplied airline respirators be required when EtO concentrations in a sterilization facility exceed 10 ppb, and proposes adding any associated fit test, training, and medical evaluation requirements. Understanding that respirator use for all employees may not be feasible, if EtO levels exceed 10 ppb, EPA is also proposing to require that employees would have the option to vacate the premises until the levels return to below 10 ppb.

The Agency proposes that facilities maintain records of indoor EtO concentration levels. EPA further proposes that facilities maintain records of employee respirator wear time and/or evacuation time. All records would need to be available upon request to any local, state, tribal, or federal pesticide enforcement personnel. Records would be required to be maintained for two years from the date of sterilization.

EPA requests public comment on the feasibility of real time monitoring to a 10 ppb level (i.e., the lowest quantifiable level), as well as the possible impacts on the daily operations of commercial sterilization facilities from requiring respirators at the 10 ppb level.

It is EPA's understanding that certain commercial sterilization facilities may already utilize a lower exposure limit than what is required by OSHA (1 ppm) to set company-specific risk policies. EPA requests public comment on facilities that utilize lower exposure limits than the OSHA PEL, and what practices these facilities use to achieve these lower limits.

EPA understands that the supply of monitoring systems may be limited, and so the compliance timeframe may be affected by equipment availability. The Agency seeks public comment on the cost and how long is necessary for registrants to implement label amendments requiring compliance with this respirator requirement and the corresponding monitoring and recordkeeping requirements. EPA is proposing that this change be implemented within 2 years.

**Personal Protective Equipment for Commercial Sterilization Facilities and Data Call-In Requirement**

*New Respirator Requirement for EtO Handlers:* The Agency proposes to require the addition to EtO product labels of a respirator statement to mitigate potential inhalation exposure risks to workers involved in the EtO commercial sterilization process and proposes adding any associated fit test, training, and medical evaluation requirements[117] for the following:

[117] Pursuant to 40 C.F.R. pt. 170, EPA requires fit testing (29 C.F.R. § 1910.134), training (29 C.F.R. § 1910.134(k)(1)(i)-(vi)), and medical evaluations (29 C.F.R. § 1910.134)—conducted in accordance with the cited OSHA regulations—for all handlers that are required to wear respirators and whose work falls within the scope of the WPS. Label Review Manual at Ch. 10, App. A, https://www.epa.gov/pesticide-registration/label-review-manual.

- Supplied air/airline (SAR) respirators or self-contained breathing apparatus (SCBA) respirators (full facepiece) for employees connecting and disconnecting EtO containers from sterilization process equipment.

- SAR or SCBA (full facepiece) for employees unloading processed products from the sterilization chamber, whether at the end of a cycle for an all-in-one process, or, for a conventional process, prior to moving product to the aeration area.

- SAR or SCBA (full facepiece) for employees loading and unloading product from the aeration area.

- SAR or SCBA (full facepiece) for employees removing validation test materials from processed product at any time prior to the completion of aeration.

- SAR or SCBA (full facepiece) for employees opening process lines or equipment that may contain EtO (e.g., for repairs or routine maintenance tasks).

Current PPE requirements are triggered by the OSHA PEL of 1 ppm, which EPA determined is not protective based on the Agency's updated risk analysis, and thus are not sufficient to ensure that the use of EtO will not cause unreasonable adverse effects to workers. The new respirator requirements outlined above are anticipated to reduce inhalation risk to workers involved with the EtO sterilization process at points when the potential for exposure is highest. To quantify the effect of mitigation on worker exposure in commercial sterilization facilities, EPA proposes to issue a Data Call-In (DCI) for OCSPP GLN 875.1400 Inhalation Exposure Indoor, requiring a protocol before monitoring for the study begins. Based on previously submitted worker monitoring data that lacked specificity and detail, EPA proposes to require, through a DCI air monitoring of the handlers specifically involved in activities related to the sterilization/fumigation (e.g., loading and unloading chambers, routine maintenance, product transfer, etc), documentation of the activities each worker performed while monitored, and whether they were wearing a respirator (and what type of respirator). For non-handlers in the facility (e.g., office workers, warehouse workers), EPA also proposes to require, through a DCI, air monitoring data to monitor their exposures. The Agency proposes that registrants follow the OSHA Method 1010 as the monitoring method.[118] EPA proposes that the DCI to be issued would require registrants to submit these data following implementation of all mitigation.

EPA further proposes to issue a DCI for data on commercially available technologies that can monitor below 10 ppb in real time, while also documenting other instruments that can quantify levels around 0.19 ppb, which is the Agency's concentration of concern for worker exposure. This includes the air inside of EtO commercial sterilization facilities, as well as warehouses that store sterilized devices. It is the Agency's understanding that current measurement technology is able to measure down to 10 ppb, which is the lowest quantifiable level. Since EPA's assessment

[118] OSHA Method 1010 (revised 2014) can be found at https://www.osha.gov/sites/default/files/methods/osha-1010.pdf.

shows that risks to workers are not of concern where workers are exposed at a level of 0.19 ppb, the Agency proposes that the DCI to be issued would require registrants to submit data to demonstrate the advancements in technologies that are capable of monitoring EtO levels as close to this level as possible. The Agency proposes issuing a DCI for the development of lower measurement methodologies/technologies on a two-year timeframe. The Agency is soliciting comments on the feasibility of a two-year DCI timeframe. Once these data become available, the Agency may promptly initiate the next cycle of Registration Review.

Requiring a respirator and any associated fit testing, training, and medical evaluation could impose a cost on handlers or employers. Per Agency discussions with industry leaders, use of the SCBA or SAR systems may already be standard industry practice for the performance of several of the tasks for which a SCBA or SAR system is proposed to be required; therefore, the overall impacts from this requirement are expected to be low. However, use of a SCBA or SAR system may not currently be part of current practice for some of the tasks at some facilities, meaning that facilities would need to purchase additional SCBA or SAR systems. Prices for an industrial-use SCBA system range from $2,300 to $9,300 depending on the duration of air supply needed (30 or 60 minutes), cylinder pressure, tank material (typically aluminum or carbon fiber), and mask size[119, 120, 121]. In addition to the original SCBA system purchase, replacement air cylinders range in price from $600 to $3,500[122, 123, 124]. Facilities may also opt to purchase on-site tank air cylinder fill stations to refill cylinders on site instead of purchasing additional replacements. Complete SAR systems range from $1,500 to $4,100 depending on hose length, air pump horsepower, and mask size[125, 126, 127]. SCBA or SAR systems can only be used by a single person that has been fit for the system, so these costs are per user. Facilities with multiple users would have to incur these costs for every individual they employ that may require the system. Additional costs may also arise from the maintenance of SCBA or SAR systems and necessary replacement parts. Applicators may also incur additional costs of training and fit testing.

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[119] AirGas. 2022. Respiratory Protection, https://www.airgas.com/Safety-Products/Respiratory-Protection/category/177. Accessed December 2022.
[120] Fisher Science. 2022. Atmosphere-Supplying Respirators. https://www.fishersci.com/us/en/browse/90411025/atmosphere-supplying-respirators. Accessed December 2022.
[121] Grainger. 2022. Respiratory Protection. https://www.grainger.com/category/safety/respiratory-protection. Accessed December 2022.
[122] AirGas. 2022. Respiratory Protection, https://www.airgas.com/Safety-Products/Respiratory-Protection/category/177. Accessed December 2022.
[123] Fisher Science. 2022. Atmosphere-Supplying Respirators. https://www.fishersci.com/us/en/browse/90411025/atmosphere-supplying-respirators. Accessed December 2022.
[124] Grainger. 2022. Respiratory Protection. https://www.grainger.com/category/safety/respiratory-protection. Accessed December 2022.
[125] AirGas. 2022. Respiratory Protection, https://www.airgas.com/Safety-Products/Respiratory-Protection/category/177. Accessed December 2022.
[126] Fisher Science. 2022. Atmosphere-Supplying Respirators. https://www.fishersci.com/us/en/browse/90411025/atmosphere-supplying-respirators. Accessed December 2022.
[127] Grainger. 2022. Respiratory Protection. https://www.grainger.com/category/safety/respiratory-protection. Accessed December 2022.

EPA's 2023 DRA Addendum assumes National Institute for Occupational Safety and Health (NIOSH) protection factors[128] in estimating the inhalation risks and the risk reduction associated with different respirators.[129] If the respirator does not fit properly, EPA's proposed PPE mitigation for EtO may not reduce risks and thus the use of EtO may result in unreasonable adverse effects for the pesticide handler and others involved in the sterilization process.

**Training Requirements**

*Commercial Sterilization Facilities Training Requirements*

In commercial sterilization facilities, labels on EtO products registered by EPA require safety and awareness training for all employees including office staff. Information and training must be provided to all employees in the facility at the time of initial assignment and annually thereafter. The safety training must include, at a minimum, the following information:

- The most recent monitored ambient levels of EtO in the facility.[130]
- The potential health effects from the levels of EtO in the facility.
- The emergency response plan and how to respond in an emergency.
- The availability of the Material Safety Data Sheet and other materials related to the health hazards of exposure to EtO.[131]

EPA proposes that the registrants ensure that the requirements to train employees on the potential health effects from the levels of EtO in the facility and the availability of materials related to the health hazards of exposure to EtO be reflective of the occupational risks expected based on the 2016 IRIS IUR, and not be based on the OSHA PEL. Specifically, the Maximum Likelihood Exposure (MLE) cancer risk for EtO handlers for medical devices is 1 in 17, and the upper bound cancer risk for EtO handlers for medical devices is 1 in 10. The MLE cancer risk for EtO handlers for spices is 1 in 36, and the upper bound cancer risk for EtO handlers for spices is 1 in 16. See section III.A.

*Healthcare Facilities Training Requirements*

In healthcare facilities, training is currently recommended for personnel who work with EtO sterilization devices by the Association for the Advancement of Medical Instrumentation (AAMI) in their EtO Standard (ANSI/AAMI ST41:2008/(R)2018). It is common industry practice that healthcare facilities follow the guidelines in the AAMI Standard – Personnel Considerations. Specifically, ANSI/AAMI ST41 states: Education and training materials and information are available from the sterile processing vendors, associations and journals; in

[128] NIOSH protection factors assume that respirators are used according to OSHA's standards.
[129] Proper fit and use of respirators is essential to accomplish the protections respirators are intended to provide. Respirator fit tests are currently required by the Occupational Safety and Health Administration (OSHA) for other occupational settings to ensure proper protection. 29 C.F.R. § 1910.134.
[130] The most recent monitored ambient levels would be available to the employees by real time monitoring. See section V.A.
[131] EtO Reregistration Eligibility Decision. 2008.

addition, OSHA has education materials available for loan.[132] Personnel may receive in-service training for all new instrumentation, devices and equipment. All orientation, on-the-job and in-service training may be documented.[133]

Similar to the training requirements for commercial sterilization facilities, EPA proposes to require registrants ensure employees be trained on the potential health effects from the levels of EtO in the healthcare facility and the availability of materials related to the health hazards of exposure to EtO, and that training be reflective of the occupational risks expected based on the 2016 IRIS value. Specifically, the Maximum Likelihood Exposure (MLE) cancer risk for EtO handlers in healthcare facilities is 1 in 25, and the upper bound cancer risk for EtO handlers in healthcare facilities is 1 in 12. See section III.A.

EPA proposes a requirement for registrants to ensure that commercial sterilization and healthcare facilities maintain records on employee training. Specifically, documentation of the training materials provided to employees upon assignment and annually thereafter, and records of the dates individual employees are trained must be kept. All records would need to be available upon request to any local, state, tribal, or federal pesticide enforcement personnel. Records would be required to be maintained for the duration that the trainee is employed, or for two years from the date of training if the trainee leaves the place of employment before two years.

EPA proposes that the registrants submit label amendments to implement the aforementioned training requirements within 60 days.

***Label Consistency and Clarification***

The Agency is proposing to require several label changes for consistency and clarification as specified in Appendix B. These label changes are directionally correct with respect to reducing the amount of EtO exposure to workers and to those near commercial sterilization facilities that use EtO.

- Current EtO labels contain general/undefined terms for use on dried herbs and spices and the language used is not consistent within the product labels. Specifically, the *Directions for Use* section of the labels say, "This product may be used only…to reduce microbial load on cosmetics, whole and ground spices or other seasoning materials (see 40 CFR 180.151)..." The same section also states, "After August 1, 2008, this product may only be applied to or on spices, dried vegetables or seasonings…"

  To clarify the acceptable use sites on the product labels, the Agency is proposing to standardize the label language within each label (and as a result across all the labels) to reflect registered uses. The Agency proposes to require that registrants amend EtO product labels to specifically identify the dried herbs, dried spices, and dried vegetables on the label for which EtO use is registered following the receipt of documentation regarding the specific commodities in Table 2 for which there is current critical use of

[132] https://www.osha.gov/etools/hospitals/central-supply/hazardous-chemicals
[133] ANSI/AAMI ST41:2008/(R)2018. Page 20.

EtO and for which there are no viable alternatives to EtO. The Agency intends to include language in the Interim Decision (ID) stating that registrants should submit requests to voluntarily terminate uses on those specific spices/commodities not identified.

In addition, the phrase "other seasoning materials" on the labels is vague and undefined. The Agency proposes deleting the use of "other seasoning materials" since this is a blend of the dried commodities specified in the newly added list of dried herbs, spices, and vegetables on the label.

- Currently, EtO product labels contain references to the OSHA Permissible Exposure Limit (PEL), OSHA Excursion Limit (EL), and the OSHA regulations at 29 CFR 1910.1047 which establish the OSHA PEL and EL levels. However, since the establishment of the OSHA PEL and EL in 1984, there have been considerable updates to the scientific database on EtO exposure and risk, including the 2016 IRIS assessment on EtO, OPP's 2020 EtO DRA, and OPP's 2023 EtO DRA Addendum. EPA thus considers the OSHA PEL of 1 ppm and the EL of 5 ppm to no longer adequately address worker risk under the requirements of FIFRA and is therefore proposing to require registrants to amend the EtO labeling to no longer include references to the OSHA PEL, EL, or the OSHA regulations that define them (i.e., 29 CFR 1910.1047). The removal of these references to the OSHA regulations from the EtO product labels would not alter the obligations of employers subject to these OSHA regulations.

- Current labels do not clearly specify the type of facility in which an EtO product is intended to be used. Since the application rate and method for sterilization in healthcare settings compared to commercial sterilization settings differ greatly (e.g., in small oven sized systems versus large chambers), the Agency is proposing to clarify which products are intended to be used in which settings. EPA is proposing to require that the following statement be added to EtO product labels: "This product is intended only for use in commercial sterilization facilities. This product may not be used in healthcare facilities (hospitals, veterinary facilities, dental offices, etc.)."

  The Agency also is proposing to clarify which products are intended to be used in healthcare facilities by requiring that the following statement be added to EtO product labels: "This product is intended only for use in single chamber sterilization/aeration devices in healthcare facilities (e.g., hospitals, veterinary facilities, dental offices, etc.)."

### B. Environmental Justice

EPA seeks to achieve environmental justice, the fair treatment and meaningful involvement of all people, regardless of race, color, national origin, or income, in the development, implementation, and enforcement of environmental laws, regulations, and policies. Throughout the registration review process, EPA has sought to include all communities and persons, including minority, low-income, and indigenous populations who may be disproportionately overburdened by the exposure to EtO.

EPA's Office of Air and Radiation (OAR) conducted an in-depth Environmental Justice analysis as part of the *National Emission Standards for Hazardous Air Pollutants (NESHAP): Ethylene Oxide Emissions Standards for Sterilization Facilities Residual Risk and Technology Review*.[134] OAR examined the potential for the 97 facilities that were assessed to pose concerns to environmental justice (EJ) communities both in the baseline and under the control options considered in their proposal. Overall, the results of this proximity demographic analysis indicate that the percent of the population living within 10 km of the 97 facilities that is Hispanic or Latino is substantially higher than the national average, driven largely by the seven facilities in Puerto Rico. The baseline proximity analysis indicates that the proportion of other demographic groups living within 10 km of commercial sterilizers is closer to the national average. The baseline risk-based demographic analysis, which focuses on those specific locations that are expected to have higher cancer risks as identified by OAR (defined by OAR for the purpose of this analysis as cancer risks greater than or equal to 1-in-1 million, greater than or equal to 50-in-1 million, and greater than 100-in-1 million), suggests that African Americans are disproportionally represented at the higher risk levels. The post-control risk-based demographic analysis focuses on how the options considered in OAR's proposed regulatory action would affect the distribution of risks identified in the baseline. The post-control options from OAR's proposed rulemaking show a substantial reduction in the number of individuals at each risk level, as well as a significant reduction in the proportion of individuals that are African American that experience higher risk levels from facilities in this source category. OAR projects that the majority of the individuals that would remain at risk after implementation of the proposed standards are Hispanic or Latino, driven largely by the sterilization facilities in Puerto Rico. These three distinct but complementary analyses indicate the potential for EJ concerns associated with this source category in the baseline, as well as the substantial benefits OAR's proposed standards would have in reducing EtO emissions and associated health risks in communities with EJ concerns.

OPP has identified risks to workers handling EtO or who may be exposed to EtO within the facilities where it is used. Because people tend to live and work within their community, individuals who would be employed in these facilities could be disproportionally drawn from the Hispanic or Latino communities, as identified by OAR, since many facilities are located in Puerto Rico.

Additionally, according to the 2021 U.S. Bureau of Labor Statistics, people working in warehousing and storage, such as those who would be employed in these facilities, moving materials into and out of chambers for fumigation, could be disproportionally drawn from communities of concern. The national average of employed persons working in warehousing and storage are about 22% Black or African American and 36% Hispanic or Latino.[135]

The Agency requests information on any other groups or segments of the population who, as a result of their proximity and exposure to pesticides, unique exposure pathway (e.g., as a result of cultural practices), location relative to physical infrastructure, exposure to multiple stressors and cumulative impacts, lower capacity to participate in decision making, or other factors, may have

[134] EPA-HQ-OAR-2019-0178.
[135] U.S. Bureau of Labor Statistics. Household Data Annual Averages: Employed persons by detailed industry, sex, race, and Hispanic or Latino ethnicity. 2022. Accessed January 19, 2023. https://www.bls.gov/cps/cpsaat18.htm.

unusually high exposure to EtO compared to the general population or who may otherwise be disproportionately affected by the use of EtO as a pesticide.

### C. Tolerance Actions

The Agency plans to exercise its FFDCA authority to update the tolerance expressions to appropriately cover the metabolites and degradates of EtO and the EtO reaction product, ethylene chlorohydrin (ECH), and to specify the residues to be measured for each commodity for enforcement purposes. EPA anticipates amending the tolerance expressions 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.
>
> (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.

The Agency also plans to exercise its FFDCA authority to modify certain commodity definitions associated with the tolerances for EtO and ECH and to revoke the EtO tolerance for walnuts, as summarized in Table 3, below. The tolerances listed in Table 3 only include those for which changes are recommended.

**EtO**. EPA is proposing to revise the commodity definitions for Peppermint, dried leaves; and Spearmint, dried leaves. In addition, EPA proposes to revise the commodity definition for Herb and spice group 19, dried leaves (except basil), although depending on what information is submitted to the Agency concerning the importance of EtO for treatment of various dried herbs and spices, EPA would propose to remove tolerances for those herbs and spices for which uses may be cancelled. Ultimately, tolerances would remain for only those herbs and spices for which it is determined that use on those commodities does not present unreasonable adverse effects and that are safe. These revisions would not substantively change the established tolerance of 7 ppm for each of these commodities, as listed in 40 C.F.R. § 180.151. The 2020 DRA recommended that the EtO tolerance for walnuts be revised to reflect the lower residues resulting from the single chamber process required for the treatment of spices, dried vegetables or seasonings with EtO. However, the Agency is not aware of current EtO use on walnuts and none of the EtO products are currently labeled for use on walnuts. In addition, based on the information currently before EPA, the use of EtO on walnuts is unlikely to meet the standard for registration under FIFRA because (1) the lack of usage of EtO on walnuts suggests that there are alternatives (e.g., nonchemical, PPO) available for the fumigation of walnuts and (2) the occupational cancer risk estimates for EtO use in commercial sterilization facilities exceed the Agency's threshold of 1 x $10^{-4}$. The Agency does not believe this tolerance is necessary and intends to take action under the FFDCA to revoke the walnut tolerance, rather than revise it consistent with the recommendation in the 2020 DRA.

**ECH**. EPA is proposing to revise the commodity definitions for Peppermint, dried leaves; and Spearmint, dried leaves. In addition, EPA proposes to revise the commodity definition for the Herb and spice group 19, dried leaves (except basil), although depending on what information is submitted to the Agency concerning the importance of EtO for treatment of various dried herbs and spices, EPA would propose to remove tolerances for those herbs and spices for which uses may be cancelled. Ultimately, ECH tolerances would remain for only those herbs and spices for which it is determined that EtO fumigations do not present unreasonable adverse effects and are safe. These revisions would not substantively change the established tolerance of 940 ppm for each of these commodities, as listed in 40 C.F.R. § 180.151. The 2020 DRA recommends that an ECH tolerance for walnuts be established based on the documented level of quantification (LOQ). However, the Agency is not aware of current EtO use on walnuts and none of the EtO products are currently labeled for use on walnuts. The Agency intends to take action under the FFDCA to revoke the EtO walnut tolerance and does not propose to establish an ECH tolerance for walnuts.

**Table 3. Summary of Anticipated Tolerance Actions (40 C.F.R. § 180.151)**

| Commodity | Established Tolerance (ppm) | Anticipated 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 | |
| **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 | remove | Walnut use is not on current product labels and occupational risk estimates of concern. |
| **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 | |
| **Peppermint, dried leaves** | -- | 940 | Commodity definition revision. |
| Peppermint, tops, dried | 940 | remove | |
| **Spearmint, dried leaves** | -- | 940 | Commodity definition revision. |
| Spearmint, tops, dried | 940 | remove | |

### D. Proposed Interim Registration Review Decision

The Agency is issuing this PID in accordance with 40 C.F.R. §§ 155.56 and 155.58. The Agency has made the following proposed interim decision: (1) EPA proposes that registrants submit OCSPP GLN 875.1400 Inhalation Indoor Exposure data and a special study on commercially

available technologies that can measure below 10 ppb in real time; and (2) EPA proposes that EtO does not meet the registration standard without changes to the affected registrations and their labeling. EPA proposes that the mitigation specified in Sections V and Appendix B are sufficient to address certain concerns. EPA intends to reevaluate EtO more frequently than the typical 15-year registration review timeframe, based on new data that becomes available after issuance of the Interim or Final Decision.

FIFRA requires that a pesticide "will not generally cause unreasonable adverse effects on the environment" before EPA can register the pesticide. "Unreasonable adverse effects on the environment" is defined by FIFRA to be "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits." To determine whether there are any unreasonable risks under FIFRA from the registration of a product, EPA's Office of Pesticide Programs conducts a risk-benefit analysis. The Agency weighs the benefits (e.g., sterilization of medical devices) of the use of a pesticide against the potential ecological and human health risks and proposes a decision about the use of a pesticide considering these factors. Risk-benefit analysis is conceptually equivalent to more traditional benefit-cost analysis (BCA) conducted elsewhere in the Agency. Risk-benefit analysis and benefit-cost analysis need not exhaustively quantify costs in monetary terms. EPA guidance advises that "benefits and costs that cannot be quantified should be presented qualitatively."[136] The Office of Management and Budget's Circular A-4, which defines good regulatory analysis and standardizes the way benefits and costs of Federal regulatory actions are measured and reported, advises that "if you are not able to quantify the [cost or benefit] effects, you should present any relevant quantitative information along with a description of the unquantified effects."[137] Through implementation of risk-benefit analysis, OPP meets the FIFRA section 2(bb) mandate by taking into account the "economic, social, and environmental costs and benefits of the use of any pesticide." EPA is specifically requesting public comment on the cost of the proposed mitigation measures and will include this information as part of the Interim or Final Decision.

The Agency conducted a DRA in 2020, as well as a detailed Addendum to the DRA in 2023. In these risk assessments, EPA identified inhalation risks for workers and nearby communities from continuing to register EtO. For occupational handlers at commercial sterilization and healthcare facilities, cancer risk estimates are estimated from $4 \times 10^{-2}$ (1 in 25) to $1 \times 10^{-1}$ (1 in 10). Cancer risks of concern are also anticipated for occupational, residential, and non-residential bystanders. Although an ESA determination has not yet been completed for EtO, any exposure to wildlife from the use of EtO will likely be limited, given the current and upcoming emissions controls from OAR's NESHAP. These risks are not quantified in dollars, but they represent the Agency's assessment of risk from the use of EtO. To help address these risks, EPA is proposing the termination of certain uses, a use rate reduction through reduced concentrations, a series of engineering controls within commercial sterilization facilities and healthcare facilities, respirator protection requirements for commercial sterilization facilities, training requirements, monitoring

[136] Environmental Protection Agency (EPA). 2010. Guidelines for preparing economic analyses. Accessed online on January 6, 2023 at: https://www.epa.gov/environmental-economics/guidelines-preparing-economic-analyses.
[137] Office of Management and Budget (OMB). 2003. Executive Office of the President, OMB Circular A-4, Regulatory Analysis.

requirements, and recordkeeping requirements, as well as requiring data from the registrants. These proposed mitigation measures would reduce risks to workers and residential and non-residential bystanders. EPA has not conduced a quantitative analysis of the risk reduction that would result from these measures; however, the proposed required monitoring data after implementation of mitigation would provide the Agency with information on risk reduction. After this information is obtained, EPA can re-initiate registration review of EtO and take further action if necessary. Since the risk reduction is not quantitatively assessed, and since the air concentrations need to be very low to meet risk thresholds, the Agency is taking an approach of "as low as reasonably achievable" (ALARA) for EtO use and application. Under FIFRA, cancellation is an option for achieving risk reduction; however, in the case of EtO, using the "ALARA" approach would result in a reasonable level of reduction, considering the benefits of EtO and the current unavailability of alternatives, particularly for medical device sterilization.

EPA expects inhalation cancer risks of concern to remain for workers inside sterilization and healthcare facilities, and residential and non-residential bystanders, even after the implementation of the proposed mitigation.[138] Ambient air data are normally used to provide context for the exposures and risks that are being assessed. In the case of EtO, however, there are risks of concern for levels that are below the levels of detection and/or quantification for the methods that are used to measure EtO in ambient air. To achieve a residential population cancer risk that is less than 1 in 1 million, for example, the lifetime average EtO concentration would need to be less than 0.11 ppt. This level is less than the detection limit of 20-90 ppt and this detection limit can only be achieved under optimum conditions.[139] EPA is proposing to require registrants to submit data on commercially available technologies that can monitor below 10 ppb in real time.

The Agency has determined that despite these risks, EtO remains a critical pesticide for certain uses. EPA is also proposing to determine that continuing to register EtO provides extensive benefits to public health, as it is critical for the sterilization of new and reusable medical devices, instruments, and equipment. Industrial EtO sterilization has a high throughput capacity, broad material compatibility, low cost, and effective bactericidal, sporicidal, and virucidal activity. EtO is used to sterilize 50 percent of all sterilized medical devices, or 20 billion devices, annually. EPA has investigated alternatives to EtO for sterilizing medical devices, including engaging in discussions with FDA about pursuing alternatives to EtO. EPA understands that, while there are alternative sterilization methods for some medical devices, there are currently no available alternatives—pesticidal or non-pesticidal—for some devices due to challenges such as material compatibility, scalability, and capacity. Therefore, if commercial sterilization and healthcare facilities no longer had access to EtO to sterilize medical devices, the result would likely be a disruption to the medical device supply chain, which could in turn result in a nationwide public health crisis. There is also a public health benefit to continuing to register EtO for spice fumigation. The threat of food-borne contamination from pathogens such as *Salmonella* and

[138] OPP notes that for residential bystander risk, even though OAR and OPP have different thresholds for when residential cancer risks are considered to be of concern (100 in a million and 1 in a million, respectively), OPP believes that the emissions controls proposed by OAR would significantly reduce bystander exposure without causing adverse impacts to the U.S. supply of sterilized medical devices needed for a variety of medical procedures.
[139] Ethylene Oxide (EtO). Addendum to "Draft Human Health and Ecological Risk Assessment in Support of Registration Review" - Inhalation Exposure Risk Assessment in Support of Registration Review.

*Escherichia coli*, and the potential for serious illness from exposure to these pathogens, is a concern for the Agency, food manufacturers, and the general public. EtO is used in the U.S. during the processing of herbs and spices to reduce microbial activity. As with medical devices, EPA has investigated the availability of alternatives to EtO in spice fumigation, including discussing potential alternatives with FDA. EPA understands that while alternatives may be available to treat certain spices, EtO may be the only viable option for the treatment of certain spices and spice forms. See Section III.C. Therefore, EPA is proposing to determine that the risk from the use of EtO that is expected to remain following implementation of the proposed mitigation measures would be outweighed by the significant public health benefits of the continued use of EtO.

During registration review, EPA considers whether a pesticide registration "continues to satisfy the FIFRA standard for registration."[140] Here, EPA proposes that EtO does not meet the FIFRA registration standard without the changes to the affected registrations and their labeling described in Section IV.A and Appendices A and B.

EPA has determined that there is no human dietary risk from registered uses of EtO that is inconsistent with the FFDCA safety standard. An aggregate assessment for EtO was not conducted since there are no food or drinking water exposures to EtO. For the reaction products of EtO (ECH and EG), there are no water or non-dietary residential exposures; the only exposure route is through food. Thus, an aggregate assessment was not conducted for ECH or EG. For more information, see *Ethylene Oxide (EtO) Draft Human Health and Ecological Risk Assessment in Support of Registration Review* (2020 DRA) in this docket.

EPA concludes that there is a reasonable certainty that no harm will result from dietary exposure to EtO or ECH. Therefore, the EtO and ECH residues are safe. EPA intends to leave the tolerances in place (except for the walnut tolerance) as well as make several non-substantive modifications, as EPA's analysis indicates that such actions would be safe.

In this PID, the Agency is not making any human health or environmental safety findings associated with the Endocrine Disruptor Screening Program (EDSP) screening of EtO. Similarly, the Agency is not making a complete endangered species finding, though the proposed mitigation is expected to reduce the extent of environmental exposure and may reduce risk to listed species whose range or critical habitat co-occur with the use of EtO. The Agency will complete a listed-species assessment and any necessary Endangered Species Act (ESA) Section 7 consultation with the Services, and make an EDSP determination before issuing a final registration review decision for EtO. For more information, see Appendices C and D.

[140] 40 C.F.R. § 155.40(a); 7 U.S.C. § 136a(c)(5); *see also* 7 U.S.C. §§ 136(bb) (defining "unreasonable adverse effects on the environment" as encompassing both "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide" [FIFRA's risk-benefit standard] and "a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the [FFDCA safety standard]"). In a PID, EPA sets out a proposed interim decision that includes EPA's "proposed findings with respect to the FIFRA standard for registration and describe the basis for such proposed findings." 40 C.F.R. §§ 155.56, 155.58(b)(1).

## E. Data Requirements

EPA proposes that registrants submit worker monitoring data as outlined in OSCPP GLN 875.1400 Inhalation Exposure Indoor. To quantify the effect of mitigation on worker exposure in commercial sterilization facilities, EPA proposes to issue a Data Call-In (DCI) for OCSPP GLN 875.1400 Inhalation Exposure Indoor data and require a protocol before monitoring for the study begins. Based on previously submitted worker monitoring data that lacked specificity and detail, EPA proposes to require, through a DCI, badge monitoring of the handlers specifically involved in activities related to the sterilization/fumigation (e.g., loading and unloading chambers, routine maintenance, product transfer, etc), documentation of the activities each worker performed while monitored, and whether they were wearing a respirator (and what type of respirator was worn). For non-handlers in the facility (e.g., office workers, warehouse workers), EPA proposes to also require air monitoring data, through a DCI, to monitor their exposure to EtO. The Agency proposes that registrants follow the OSHA Method 1010 as the monitoring method.[141] EPA proposes that the DCI to be issued would require registrants to submit following implementation of all mitigation. The Agency will issue a DCI to establish a timeline for submitting these data.

EPA further proposes to issue a DCI for methods to improve measurement technologies inside of EtO commercial sterilization facilities, as well as warehouses that store sterilized devices. It is the Agency's understanding that current measurement technology is able to measure down to 10 ppb, which is the lowest quantifiable level. Since EPA's assessment shows that risks to workers are not of concern where workers are exposed at a level of 0.19 ppb, the Agency proposes that the DCI to be issued would require registrants to submit data to demonstrate the advancements in technologies that are capable of monitoring EtO levels as close to this level as possible. The Agency proposes issuing a DCI to collect data on commercially available technologies that can monitor below 10 ppb in real time, on a two-year timeframe. The Agency is soliciting comments on the feasibility of a two-year DCI timeframe. Once these data become available, the Agency may promptly initiate the next cycle of Registration Review.

## F. Summary of Proposed Recordkeeping Requirements

*Application Rates*

EPA proposes that the EtO application rate must be less than or equal to 500 mg/L while still meeting FDA sterility requirements. If sterilization of a device requires more than 500 mg/L, due to the device design, EPA proposes to require facilities maintain records for a justification for the increased application rate. Specifically, this justification would demonstrate the necessary calculations for determining the application rate, through either the Cycle Calculation Approach, or other approaches found in ISO 11135. EPA further proposes a facility recordkeeping requirement for the amount of EtO used regardless of whether the amount used is less than or greater than 500 mg/L. All records would need to be available upon request to any local, state, tribal, or federal pesticide enforcement personnel. Records would be required to be maintained for two years from the date of sterilization.

[141] OSHA Method 1010 (revised 2014) can be found at https://www.osha.gov/sites/default/files/methods/osha-1010.pdf.

*Pressure Sensitive Devices*

The Agency is proposing to require all-in-one sterilization systems in commercial sterilization facilities that do not sterilize pressure sensitive devices. EPA further proposes that registrants ensure facilities keep records that show there are pressure sensitive devices being sterilized, and are, therefore, unable to be processed in all-in-one systems, if applicable. All records would need to be available upon request to any local, state, tribal, or federal pesticide enforcement personnel. Records would be required to be maintained for two years from the date of sterilization.

*Indoor EtO Concentrations and Corresponding Worker Protection Measures*

To reduce worker exposure, EPA is proposing that respirator requirements be based on a technologically measurable (i.e., quantifiable) EtO concentration of ambient air, which by the Agency's understanding is 10 ppb for real time measurements.[142] Understanding that respirator use for all employees may not be feasible, if EtO levels exceed 10 ppb, EPA is also proposing to require that employees would have the option to vacate the premises until the levels return to below 10 ppb. The Agency proposes that facilities maintain records of indoor EtO concentration levels, including the daily average concentration, and minimum and maximum concentrations. EPA further proposes that facilities maintain records of employee respirator wear time and/or evacuation time. All records would need to be available upon request to any local, state, tribal, or federal pesticide enforcement personnel. Records would be required to be maintained for two years from the date of sterilization.

*Employee Training*

EPA proposes a requirement for commercial sterilization and healthcare facilities to maintain records on employee training. Specifically, what training materials are provided to employees upon assignment and annually thereafter, and records of the dates individual employees are trained. All records would need to be available upon request to any local, state, tribal, or federal pesticide enforcement personnel. Records would be required to be maintained for the duration that the trainee is employed, or for two years from the date of training if the trainee leaves the place of employment before two years.

## G. Summary of Public Comment Requested

In addition to general areas on which persons may wish to comment, there are some areas identified in this PID which the Agency specifically seeks comments and information. Interested stakeholders are encouraged to include additional information on the following topics, and the Agency welcomes comments on all aspects of the proposed mitigation.

<u>Use Rate Reduction through Reduced Concentrations for Medical Device Sterilization</u>

[142] The limit of quantification (LOQ) of 10 ppb is for real-time instruments. These instruments respond within minutes to changes in EtO levels. The OSHA method for air sampling has a limit of detection (LOD) of 1 ppb for a 4-hour sample. See OSHA Method 1010 (revised 2014) which can be found at https://www.osha.gov/sites/default/files/methods/osha-1010.pdf.

EPA proposes that the EtO concentration must be less than or equal to 500 mg/L while still meeting FDA sterility requirements. For existing cycles, EPA proposes a 5-year compliance timeframe to limit the EtO concentration to 500 mg/L. EPA seeks public comment on the feasibility of a 5-year compliance timeline for use rate reduction through reduced concentrations of existing cycles. EPA proposes a 2-year compliance timeframe to limit the EtO concentration to 500 mg/L for new cycles and seeks public comment on the feasibility of a 2-year compliance timeline for use rate reduction through reduced concentrations of new cycles. EPA also seeks public comment on alternative limits that may differ from 500 mg/L.

Commercial Sterilization Facilities Engineering Controls (Medical Device and Spice Use)

*All-in-one systems*

The Agency is seeking additional information on the feasibility of all-in-one processing (combination sterilizers) for the treatment of medical devices by commercial sterilization facilities. With all-in-one systems, sterilization and aeration occur in the same chamber. EPA understands that all-in-one systems may not be appropriate for use to sterilize pressure-sensitive materials. Additionally, each all-in-one processing chamber is utilized for a greater amount of time when compared to traditional sterilization configurations, potentially limiting the throughput in a facility. EPA seeks public comment on feasibly of upgrading facilities to use all-in-one systems, and the potential impacts on the medical device supply chain.

*Ventilation of product storage areas and product packaging*

EPA is soliciting public comment on the number of air exchanges per hour that would adequately ventilate product storage areas. The Agency is also soliciting public comment on the use of netting rather than plastic surrounding pallets of treated medical devices to increase aeration and prevent EtO from becoming trapped in plastic wrap or other packaging.

*Automation via covered conveyor for transported aerated materials to shipping/storage areas*

In traditional EtO treatment configurations, sterilization and aeration are performed in two separate chambers. In these systems, employees may transfer post-treatment materials from the sterilization chamber to the aeration chamber via forklift. EPA is aware that in some sterilization facilities, post-treatment materials are instead transferred via enclosed conveyor systems, to reduce employee exposure. EPA is seeking public comment on the feasibility of reconfiguring existing EtO commercial sterilization facilities to use an enclosed conveyor system from the aeration area to the storage/shipping area. Note that in facilities that have all-in-one systems, EPA is proposing automation via covered conveyor from the aeration area to the shipping and storage area.

*Other engineering and process controls not proposed as part of this PID*

It is EPA's understanding that there are other methods and controls available that could reduce worker exposure to EtO that are not included in this PID. The Agency seeks further information

on all engineering controls and/or work practices that would result in lowered EtO exposure for workers (for example, internal capture and emissions controls like dry beds or filters, increased air turns and cascade pressure systems, or others). In multi-chamber systems, process controls like minimizing the time and transfer length that is taken from the sterilization to aeration area, or the elimination of a staging area, may reduce worker exposure. As EPA is proposing automation in these areas, the Agency seeks information on the comparative exposure reductions of the aforementioned process controls.

*Implementation time and cost for all engineering controls*

EPA recognizes implementation of the proposed engineering controls would require a longer timeframe than typically provided by the Agency for the implementation of risk mitigation measures, given the limited availability of new equipment, increased demand, and the potential for disrupting the supply chain if facilities need to close to make these upgrades. EPA is seeking public comment on a reasonable timeframe for registrants to submit label amendments to implement the proposed engineering controls, as well as cost information. EPA further seeks public comment on whether these engineering controls would require state or local permits before the renovations could take place, and the timing associated with that permitting process. Finally, the Agency seeks public comment on potential impacts on the supply chain of sterilized medical devices related to the potential downtime of sterilizing equipment during renovation.

*Engineering controls for existing (all or subset) versus new facilities*

EPA is seeking public comment on whether to implement the engineering controls proposed in this PID to be for all existing facilities, a subset of existing facilities, or for only new facilities.

Personal Protective Equipment (Medical Device and Spice Use)

*Respiratory protection logistical limitations*

EPA recognizes there are logistical limitations to Self-Contained Breathing Apparatus (SCBA) respirators and Supplied Air Respirators. The typical maximum wear time for a SCBA respirator is 45 minutes before the cylinder must be changed. Supplied air systems are affixed to walls with a hose running to the supplied air respirator worn by the sterilization worker. While this system provides an unlimited supply of air which eliminates the need to change cylinders, the hose can limit worker mobility. EPA seeks public comment on facility layout and typical employee work shifts, as it relates to the proposed personal protective equipment requirement in Section V.A.

*Technologies for Worker Monitoring and Respirator Requirement*

This PID proposes that all workers (including both handlers and occupational bystanders) in commercial sterilization facilities be required to wear respirators when EtO concentrations in the facilities exceed 10 ppb. EPA requests public comment on the feasibility of continuous, real-time monitoring to a 10 ppb level inside of commercial sterilization facilities and the possible impacts of the daily operations of commercial sterilization facilities. EPA understands that the supply of monitoring systems may be limited, and so the compliance timeframe may be affected by

equipment availability. The Agency seeks public comment on the cost and how long is necessary for registrants to implement label amendments requiring compliance with this respirator requirement and the corresponding monitoring and recordkeeping requirements. EPA is proposing that this change be implemented within 2 years.

Alternative Sterilization Methods for Medical Devices

Some medical devices can only be sterilized with EtO. However, there are several FDA-recognized methods used to sterilize medical equipment: gamma irradiation, X-ray sterilization, electron beam sterilization, and steam; as well as the alternative sterilization methods in development including hydrogen peroxide, vaporized hydrogen peroxide, nitrogen dioxide, chlorine dioxide, and vaporized peracetic acid. EPA understands there are limitations of comparable sterilization methods due to compatibility with materials and/or packaging, scalability or capacity, and lack of validation measures or efficacy data. EPA seeks public comment on more information about the existing limitations of available alternatives. EPA also seeks public comment on existing and emerging alternative methods for medical device sterilization that are scalable and could most effectively replace EtO.

Technologies to Lower Detection Limits for Ambient Air

When assessing risks from exposure to a pesticide, EPA normally uses ambient air data to provide context for the exposures and risks that are being assessed. In the case of EtO, however, there are risks of concern for levels of EtO that are below the levels of detection for the methods that are used to measure EtO in ambient air. To achieve a residential population cancer risk that is less than $1 \times 10^{-6}$, for example, the lifetime average EtO concentration would need to be less than 0.11 ppt. This level is less than the detection limit of 20-90 ppt and this detection limit can only be achieved under optimum conditions. EPA's Office of Research and Development (ORD) is actively working in this area to improve sampling methods for ambient levels of EtO.[143] EPA seeks public comment on advancements in technologies to lower detection limits for EtO.

OSHA's Permissible Exposure Limit (PEL)

EPA understands that OSHA's EtO PEL has not been updated since it was established in 1984, and that health standards issued under section 6(b)(5) of the OSH Act must reduce significant risk only to the extent that it is technologically and economically feasible.[144] Given that EPA has identified risks for workers at levels below the OSHA PEL, EPA does not consider the current OSHA PEL to be protective of workers. EPA is seeking public comment to determine if facilities have voluntarily set lower exposure limits to better protect workers.

Environmental Justice

The Agency requests information on any other groups or segments of the population who, as a result of their proximity and exposure to pesticides, unique exposure pathway (e.g., as a result of

[143] Ethylene Oxide (EtO). Addendum to "Draft Human Health and Ecological Risk Assessment in Support of Registration Review" - Inhalation Exposure Risk Assessment in Support of Registration Review.
[144] https://www.federalregister.gov/citation/49-FR-25734.

cultural practices), location relative to physical infrastructure, exposure to multiple stressors and cumulative impacts, lower capacity to participate in decision making, or other factors, may have unusually high exposure to EtO compared to the general population or who may otherwise be disproportionately affected by the use of EtO as a pesticide.

Healthcare Facilities

*Healthcare facilities engineering controls*

EPA is proposing to require the following engineering controls in healthcare facilities: physical separation of EtO sterilization spaces; negative air pressure in rooms containing EtO sterilization devices; ventilation of EtO exhaust through exterior ventilation stacks; and abatement devices to capture excess EtO. The Agency seeks public comment on the cost and time necessary for registrants to implement label amendments requiring the implementation of the proposed engineering controls. EPA is proposing that these engineering controls be implemented within 2 years.

*Respirator use in healthcare facilities*

EPA is seeking public comment on the feasibility of respirator use (supplied airline respirators or self-contained breathing apparatus respirators) in healthcare facilities for employees who are unloading EtO sterilization equipment from the sterilization chamber.

Spice Fumigation Use

*Use Rate Reduction for Spice Treatments*

The EtO product labels provide detailed use directions, including a maximum use rate, for the EtO use on herbs and spices. The Agency is seeking public comment on examples of efficacious EtO treatments for pathogen control at rates lower than the maximum label rate, and how often facilities have completed EtO validations for EtO concentrations that are less than 500 mg/L. The Agency is interested in establishing an alternative method for the product labels that use a lower rate of EtO. EPA encourages facilities and interested stakeholders to work with the Agency to develop a new method at a lower rate that is effective for pathogen control and continues to meet the dietary safety standards (e.g., acceptable residues of EtO and ECH).

*Alternative fumigation methods for spices*

Because of the estimated occupational and bystander risks associated with the use of EtO to fumigate spices, the Agency is considering a phased cancellation of specific spices/ commodities without documentation showing that alternatives are not viable and the need for EtO is critical to food safety. The Agency intends to include language in the ID stating that registrants should submit requests to voluntarily terminate uses on commodities for which there are viable alternatives (see Section III.D). When the Agency receives requests from registrants to voluntarily cancel a pesticide registration or terminate a use, the Agency is required to publish an FRN regarding the cancellation request and take public comment (see 7 U.S.C. § 136d(f)(1)).

There are several alternatives to EtO that are used to treat herbs and spices for pathogen control. These are irradiation, heat, steam, and propylene oxide. However, EPA understands that these alternatives may not be viable for every spice, spice form (e.g., leaf, ground), spice blend, or target pathogen. EPA seeks public comment on specific spices/commodities listed in Table 2 (see section III.D. above) for which EtO use is deemed critical for food safety and for which there are no viable alternatives to EtO (e.g., steam, irradiation, or propylene oxide cannot be used for pathogen control on a particular spice, spice form, or spice blend). The information provided should include why the alternative methods are not effective and include the amount of a commodity treated with EtO (lbs./year). All information provided should be specific and detailed.

Based on information submitted to the Agency, EPA understands that the following spices often have high pathogen loads: black pepper, paprika, celery seed, coriander, turmeric, and thyme.[145] [146] The Agency is seeking public comment on alternative treatment options for those spices and target pathogens (e.g., *Salmonella*, *E. coli*). In addition, the Agency would like to know if there are other commodities that typically have high pathogen loads for which there are not efficacious treatment options besides EtO. The Agency is also seeking information regarding the importance of EtO to spice blends (e.g., seasonings) and the specific spices in the blends for which EtO fumigation is critical.

# VI. NEXT STEPS AND TIMELINE

## A. Proposed Interim Registration Review Decision

A Federal Register Notice will announce the availability of the EtO PID and open a 60-day comment period. The Agency may issue an Interim Registration Review Decision (ID) for EtO after the close of this comment period, as long as the Agency would not have reason to change the proposed interim decision in Section IV.D, above. The Agency may make a final registration review decision for EtO without previously issuing an ID. However, a final registration review decision for EtO will only be made after EPA completes (1) an endangered species determination and any necessary consultation with the Services, and (2) an EDSP determination.

EPA is proposing that registrants would submit label amendments within 60 days after the decision. The Agency would review such label amendments as expeditiously as feasible and is proposing that products distributed by registrants would have to bear the revised labeling within the timeframes outlined in the mitigation section of this PID after EPA has approved the revised labeling. For certain mitigation measures, the time period exceeds 12 months for compliance,

[145] American Spice Trade Association (ASTA). 2017. Clean, Safe Spices, Guidance from the American Spice Trade Association, 2017 Update. https://www.astaspice.org/food-safety-technical-guidance/best-practices-and-guidance/clean-safe-spices-guidance-document/. Accessed September 2020.
[146] Ethylene Oxide Task Force (EOTF). 2020. Ethylene Oxide Benefits Statement submitted by B&C Consortia Management, L.L.C. on behalf of the EOTF. EOTF email to EPA regarding benefits of ethylene oxide for medical devices. Email sent from Lisa Campbell, Partner, Bergeson & Campbell PC to Jessica Bailey, Antimicrobial Division, Office of Pesticide Programs, Environmental Protection Agency. May 6, 2020.

taking into consideration the costs, impacts to the supply chain, and other logistical elements. As noted throughout the PID, EPA is seeking public comment on compliance timelines of the proposed mitigation measures.

## Appendix A: Summary of Proposed Actions for EtO

| Registration Review Case #: 2275<br>PC Code: 042301<br>Chemical Type: Fumigant<br>Chemical Family: Oxirane<br>Mode of Action: Alkylation | | | | | | |
|---|---|---|---|---|---|---|
| Affected Population(s) | Source of Exposure | Route of Exposure | Duration of Exposure | Potential Risk(s) of Concern | Proposed Actions | Comment |
| Occupational handler | Air | Inhalation | Lifetime | Cancer | • Delete uses for which alternatives exist.<br>• Reduce application rate.<br>• Require engineering controls for automation, air pressure gradient, HVAC systems, and ventilation.<br>• Require SCBA or supplied air respirators for specific tasks and when EtO concentrations exceed 10 ppb.<br>• Real time indoor air monitoring to the lowest technologically measurable (i.e., quantifiable) level (10 ppb). | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | • Recordkeeping requirements of application rates, types of devices sterilized (noting pressure-sensitive devices), indoor EtO concentrations and corresponding worker protection measures, and employee training. | |
| Occupational bystander | Air | Inhalation | Lifetime | Cancer | • Delete uses for which alternatives exist.<br>• Reduce application rate.<br>• Require engineering controls for automation, air pressure gradient, HVAC systems, and ventilation.<br>• Require SCBA or supplied air respirators for specific tasks and when EtO concentrations exceed 10 ppb.<br>• Real time indoor air monitoring to the lowest technologically measurable (i.e., quantifiable) level (10 ppb). | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | • Recordkeeping requirements of application rates, types of devices sterilized (noting pressure-sensitive devices), indoor EtO concentrations and corresponding worker protection measures, and employee training. | |
| By-standers (residential and non-residential) | Air | Inhalation | Lifetime | Cancer | • Delete uses for which alternatives exist.<br>• Reduce application rate.<br>• Emissions reductions as would be required per OAR's Proposed EtO Emissions Standards for Sterilization Facilities.[147] | |

[147] EPA-HQ-2019-0178.

## Appendix B: Proposed Labeling Changes for EtO Products

| Description | Proposed Label Language for EtO Products[148] | Placement on Label |
|---|---|---|
| **Technical and Manufacturing Use Products** | | |
| **Use Deletion** | Remove the following use sites: Museum materials, Library materials, Archival materials, Cosmetics, Musical instruments, Beekeeping equipment. | Directions for Use |
| **Spice Use Definition/Identification :** Specifying allowable spices and herbs from Crop Group 19 | Deletions are shown with a strikethrough and insertions are shown with an underline.<br><br>"As A Sterilant and Fumigant Gas<br><br>…<br><br>This product may be used only to sterilize medical or laboratory items, pharmaceuticals, and aseptic packaging, (see 21 CFR 201.1(d)(5)), or to reduce microbial load on ~~cosmetics, whole and ground spices or other seasoning materials (see 40 CFR 180.151) and artifacts, archival material or library objects~~ [LIST OF SPICES]." | Directions for Use |
| **End Use Products** | | |
| **Use Deletion** | Remove the following use sites from the label: Museum materials, Library materials, Archival materials, Cosmetics, Musical instruments, Beekeeping equipment. | Directions for Use |
| **Spice Use Definition/Identification :** Specifying allowable | Deletions are shown with a strikethrough and insertions are shown with an underline. | Directions for Use |

[148] Unless otherwise specified, the proposed requirements are effective 60 days from the publication of the Interim / Final Decision.

| | | |
|---|---|---|
| spices and herbs from Crop Group 19 | "As A Sterilant and Fumigant Gas<br><br>This product may be used only to sterilize medical or laboratory items, pharmaceuticals, and aseptic packaging, (see 21 CFR 201.1(d)(5)), or to reduce microbial load on ~~cosmetics, whole and ground spices or other seasoning materials (see 40 CFR 180.151) and artifacts, archival material or library objects~~ [LIST OF SPICES]."<br><br>"This product may only be applied to or on ~~spices, dried vegetables or seasonings~~ [LIST OF SPICES] utilizing an ETO sterilization method that uses a single sterilization chamber for pre-conditioning, sterilization and aeration …" | |
| **Removal of OSHA 1 ppm Permissible Exposure Limit (PEL) and 5 ppm Excursion Limit (EL)** | Remove OSHA citations for 1 ppm Permissible Exposure Limit (PEL) and 5 ppm Excursion Limit (EL) (OSHA 29 CFR 1910.1047). | Directions for Use |
| **Use Rate Reduction through Reduced Concentrations for Medical Device Sterilization** | "As of [2 years from the publication of the Interim / Final Decision] commercial sterilization facilities are required to limit the application rate to less than or equal to 500 mg/L for new cycles. As of [5 years from the publication of the Interim / Final Decision] commercial sterilization facilities are required to limit the application rate to less than or equal to 500 mg/L for existing cycles.<br><br>The sterilization/fumigation cycle parameters are prescribed by the equipment manufacturer. Safety and efficacy must be validated by FDA and are the responsibility of the user." | Directions for Use |
| **Engineering Controls in Commercial Sterilization Facilities:** Air Pressure Gradient | "To reduce exposure to EtO at commercial sterilization facilities, EPA requires the following engineering control by [2 years from the publication of the Interim / Final Decision]:<br><br>Air pressure gradient so that air is continuously flowing from low-EtO concentration to high-concentration spaces. Non-processing areas must have | Directions for Use |

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| | positive pressure compared to slightly negative pressure of processing areas. The highest level of negative pressure must be in the sterilization chamber." | |
| **Engineering Controls in Commercial Sterilization Facilities:** HVAC Systems | "To reduce exposure to EtO at commercial sterilization facilities, EPA requires the following engineering control [2 years from the publication of the Interim / Final Decision]:<br><br>Separation of office and sterilization area HVAC systems. Non-processing areas, such as office space and control rooms, must have separate HVAC systems from EtO processing areas." | Directions for Use |
| **Engineering Controls in Commercial Sterilization Facilities:** Ventilation of Storage Areas | "To reduce exposure to EtO at commercial sterilization facilities, EPA requires the following engineering control [by 2 years from the publication of the Interim / Final Decision]:<br><br>Adequate ventilation of EtO-sterilized product storage spaces. All storage areas must be properly ventilated since not all EtO could be removed from post-sterile product areas, due to the absorbant nature of pallets, cardboard, and packaging." | Directions for Use |
| **Engineering Controls in Commercial Sterilization Facilities:** Automation of movement of sterilized and aerated materials via covered conveyor. | "To reduce exposure to EtO at commercial sterilization facilities, EPA requires the following engineering control [by 2 years from the publication of the Interim / Final Decision]:<br><br>All EtO medical device sterilization facilities with a traditional multi-chamber sterilization configuration must utilize an enclosed conveyor to transport sterilized materials from the sterilization chamber to the aeration chamber.<br><br>Additionally, all EtO medical device and spice sterilization facilities must utilize an enclosed conveyor to transport aerated materials from the aeration chamber/room to storage/shipping areas, in both traditional sterilization scenarios (multi-chamber) and all-in-one sterilization (single chamber) scenarios." | Directions for Use |
| **Engineering Controls in Commercial Sterilization Facilities:** All-in-one processing | "To reduce exposure to EtO at commercial sterilization facilities, EPA requires the following engineering control [by 2 years from the publication of the Interim / Final Decision]: | Directions for Use |

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| (combination sterilizers) where feasible. | For the sterilization of medical devices by commercial sterilization facilities, all-in-one processing (combination sterilizers) where sterilization and aeration occur in the same chamber is required if the facility does not sterilize pressure sensitive devices.<br><br>EtO products applied to or on [LIST OF SPICES] are required to use an EtO sterilization method that uses a single sterilization chamber for pre-conditioning, sterilization and aeration.<br><br>A single chamber process is required for EtO treatment in hospitals and healthcare facilities." | |
| **Physical separation of EtO sterilization spaces in Healthcare Facilities** | "All EtO single chamber sterilization/aeration devices in healthcare facilities (hospitals, veterinary facilities, dental offices, etc.) must be located in a containment area that is physically separate from all other work areas of the healthcare facility by [2 years from the publication of the Interim / Final Decision]." | Directions for Use |
| **Use of Abatement Devices in Healthcare facilities** | "Healthcare facilities (hospitals, veterinary facilities, dental offices, etc.) using EtO single chamber sterilization/aeration devices must utilize an abatement device in order to reduce EtO emissions. Refer to sterilization device manufacturer for information on abatement devices by [2 years from the publication of the Interim / Final Decision]." | Directions for Use |
| **Venting of Healthcare Facilities** | "All EtO sterilizers in healthcare facilities (hospitals, veterinary facilities, dental offices, etc.) must be vented out of the workplace to the outside atmosphere. A separate exhaust duct to the outside is required. The exhaust duct should terminate away from areas where people walk or work. The duct should be located at least 7.6 meters (25 feet) away from the building air intake source and must be engineered according to existing codes by [2 years from the publication of the Interim / Final Decision]." | Directions for Use |
| **Pressure Differential in Healthcare Facilities** | "EtO sterilization areas must be kept at a negative pressure differential compared to the ambient air pressure of the healthcare facility (hospitals, veterinary facilities, dental offices, etc.) by [2 years from the publication of the Interim / Final Decision]." | Directions for Use |

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| **Specification of Use Site for Healthcare Facility Products** | "This product is intended only for use in single chamber sterilization/aeration devices in healthcare facilities (*e.g.*, hospitals, veterinary facilities, dental offices, etc.)." | Directions for Use |
| **Specification of Use Site for Commercial Sterilization Facilities** | "This product is intended only for use in commercial sterilization facilities. This product is not intended for use in healthcare facilities (hospitals, veterinary facilities, dental offices, etc.)." | Directions for Use |
| **Updated Respirator Language for Commercial Sterilization Facilities**[149] | "To reduce exposure to EtO at commercial sterilization facilities, supplied air/airline (SAR) respirators or self-contained breathing apparatus (SCBA) respirators (full facepiece) be worn by all workers in a commercial sterilization facility by workers engaged in the following tasks, regardless of the EtO concentration in the facility:<br>• Connecting and disconnecting EtO containers from sterilization process equipment.<br>• Unloading processed products from the sterilization chamber, whether at the end of a cycle for an all-in-one process, or, for a conventional process, preparatory to moving product to the aeration area.<br>• Loading and unloading product from the aeration area.<br>• Removing validation test materials from processed product at any time prior to the completion of aeration.<br>• Opening process lines or equipment that may contain EtO (e.g., for repairs or routine maintenance tasks. | In the Personal Protective Equipment (PPE) within the Precautionary Statements |

[149] Task-based respirator use is required 60 days from the publication of the Interim / Final Decision. The concentration-based respirator use is required 2 years from the publication of the Interim / Final Decision, taking into account the time needed for facilities to update their monitoring systems.

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| | Additionally, if not vacating the premises, SAR or SCBA respirators must be worn by all employees when EtO concentrations in the facility exceed 10 ppb by [2 years from the publication of the Interim / Final Decision]." | |
| **Decrease Action Level** | "Commercial sterilizer facilities must continuously monitor, in real time, down to a minimum of 10 ppb by [2 years from the publication of the Interim / Final Decision]. Monitoring areas include processing and non-processing (i.e. office spaces, control rooms, warehouses, etc,) areas. This data must be made available to all employees in real time." | Directions for Use |
| **Respirator Fit Testing Requirements for Non-WPS Uses** | **"Respirator fit testing, medical qualification, and training**<br>Using a program that conforms to OSHA's requirements (see 29 CFR Part 1910.134), employers must verify that any worker who uses a respirator is:<br>• Fit-tested and fit-checked,<br>• Trained, and<br>• Examined by a qualified medical practitioner to ensure physical ability to safely wear the style of respirator to be worn. A qualified medical practitioner is a physician or other licensed healthcare professional who will evaluate the ability of a worker to wear a respirator. The initial evaluation consists of a questionnaire that asks about medical conditions (such as a heart condition) that would be problematic for respirator use. If concerns are identified, then additional evaluations, such as a physical exam, might be necessary. The initial evaluation must be done before respirator use begins. Handlers must be reexamined by a qualified medical practitioner if their health status or respirator style or use conditions change.<br><br>Upon request by local/state/federal/tribal enforcement personnel, employers must provide documentation demonstrating how they have complied with these requirements." | In the Personal Protective Equipment (PPE) within the Precautionary Statements |
| **Training Requirements in Commercial Sterilization Facilities** | "**For Commercial Sterilization Facilities:** Employees must be trained upon assignment and annually thereafter on the potential health effects from the levels of EtO in the facility and the availability of materials related to the health hazards of exposure to EtO. Specifically, the Maximum Likelihood Exposure (MLE) cancer risk for EtO handlers for medical devices is 1 in 17, and the upper bound cancer risk for EtO handlers for medical devices is 1 in 10. The MLE | Directions for Use under the heading "Training Requirements" |

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| | cancer risk for EtO handlers for spices is 1 in 36, and the upper bound cancer risk for EtO handlers for spices is 1 in 16." | |
| **Training Requirements in Healthcare Facilities** | "**For Healthcare Facilities:** Employees must be trained upon assignment and annually thereafter on the potential health effects from the levels of EtO in the healthcare facility and the availability of materials related to the health hazards of exposure to EtO. Specifically, the Maximum Likelihood Exposure (MLE) cancer risk for EtO handlers in healthcare facilities is 1 in 25, and the upper bound cancer risk for EtO handlers in healthcare facilities is 1 in 12." | Directions for Use under the heading "Training Requirements" |
| **Recordkeeping Requirements** | "**Recordkeeping Requirements:** All records must be maintained for two years from the date of sterilization, or in the case of training materials, 2 years from the date of training. Records must be made available upon request to any local, state, tribal, or federal pesticide enforcement personnel.<br><br>Application Rates: Facilities must maintain records for the amount of EtO used. If sterilization of a device requires more than 500 mg/L, due to the device design, facilities must maintain records for a justification for the increased application rate. Specifically, this justification would demonstrate the necessary calculations for determining the application rate, through either the Cycle Calculation Approach, or less conservative approaches found in ISO 11135.<br><br>Indoor EtO Concentrations and Corresponding Worker Protection Measures: Facilities must maintain records of indoor EtO concentration levels, and records of employee respirator wear time and/or evacuation time.<br><br>Employee Training: Facilities must maintain records on training materials provided to employees upon assignment and annually thereafter, and records of the dates individual employees are trained." | Directions for Use under the heading, "Recordkeeping Requirements" |

# Appendix C: Listed-Species Assessment

This Appendix provides general background about the Agency's assessment of the effects of pesticides on listed species and designated critical habitats under the Endangered Species Act (ESA).

*Developing Approaches for ESA Assessments and Consultation for FIFRA Actions*

In 2015, EPA, along with the Services—the U.S. Fish and Wildlife Service (FWS) and the National Marine Fisheries Service (NMFS)—and the United States Department of Agriculture (USDA) (referred to as "the agencies") released their joint Interim Approaches[150] for assessing the effects of pesticides to listed species. The agencies jointly developed these Interim Approaches in response to the 2013 National Academy of Sciences' recommendations that discussed specific scientific and technical issues related to the development of assessments of pesticides' effects to listed species. Since that time, the agencies have been continuing to work to improve the approaches for assessing effects to listed species. After receiving input from the Services and USDA on proposed revisions to the interim method and after consideration of public comments received, EPA released an updated *Revised Method for National Level Listed Species Biological Evaluations of Conventional Pesticides* ("Revised Method") in March 2020.[151]

The agencies also continue to work collaboratively through a FIFRA Interagency Working Group (IWG). The IWG was created under the 2018 Farm Bill to recommend improvements to the ESA section 7 consultation process for FIFRA actions and to increase opportunities for stakeholder input. This group is led by EPA and includes representatives from NMFS, FWS, USDA, and the Council on Environmental Quality (CEQ). The IWG outlines its recommendations and progress on implementing those recommendations in reports to Congress.[152]

*Consultation on Chemicals in Registration Review*

EPA initially conducted biological evaluations (BEs) using the interim method on three pilot chemicals representing the first nationwide pesticide consultations (final pilot BEs for chlorpyrifos, malathion, and diazinon were completed in January 2017). These initial pilot consultations were envisioned as the start of an iterative process. Later that year, NMFS issued a final biological opinion for these three pesticides. In 2019, EPA requested to reinitiate formal consultation with NMFS on malathion, chlorpyrifos and diazinon to consider new information that was not available when NMFS issued its 2017 biological opinion. EPA received a final malathion biological opinion[153] from FWS in February 2022 and a final biological opinion from

[150] https://www.epa.gov/endangered-species/interim-approaches-pesticide-endangered-species-act-assessments-based-nas-report.
[151] https://www.epa.gov/endangered-species/revised-method-national-level-listed-species-biological-evaluations-conventional.
[152] https://www.epa.gov/endangered-species/reports-congress-improving-consultation-process-under-endangered-species-act.
[153] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.

NMFS on malathion, chlorpyrifos and diazinon in June 2022.[154] The Agency plans to implement both biological opinions according to the 18-month timeframes specified in the biological opinions.

In 2020, EPA released draft BEs for the first two chemicals conducted using the 2020 Revised Method—carbaryl and methomyl. Subsequently, EPA has used the Revised Method to complete final BEs for carbaryl, methomyl, atrazine, simazine, glyphosate, clothianidin, imidacloprid, and thiamethoxam. EPA is currently in consultation with the Services on these active ingredients.

*EPA's New Actives Policy and the 2022 Workplan*

In January 2022, EPA announced a policy[155] to evaluate potential effects of new conventional pesticide active ingredients to listed species and their designated critical habitat and initiate consultation with the Services, as appropriate, before registering these new pesticides. Before the Agency registers new uses of pesticides for use on pesticide-tolerant crops, EPA will also continue to make effects determinations. If these determinations are "likely to adversely affect", the Agency will not register the use unless it can predict that registering the new use would not have a likelihood of jeopardizing listed species or adversely modifying their designated critical habitats. EPA will also initiate consultation with the Services as appropriate.

In April 2022, EPA released a comprehensive, long-term approach to meeting its ESA obligations, which is outlined in *Balancing Wildlife Protections and Responsible Pesticide Use*.[156] This workplan reflects the Agency's most comprehensive thinking to date on how to create a sustainable ESA-FIFRA program that focuses on meeting EPA's ESA obligations and improving protection for listed species while minimizing regulatory impacts to pesticide users and collaborating with other agencies and stakeholders on implementing the plan.

On November 16, 2022, EPA released the *ESA Workplan Update: Nontarget Species Mitigation for Registration Review and Other FIFRA Actions*.[157] As part of this update, EPA announced its plan to consider and include, as appropriate, a menu of FIFRA Interim Ecological Risk Mitigation intended to reduce off-target movement of pesticides through spray drift and runoff in its registration review and other FIFRA actions. These measures are intended to reduce risks to nontarget organisms efficiently and consistently across pesticides with similar levels of risks and benefits. EPA expects that these mitigation measures may also reduce pesticide exposures to listed species.

[154] https://www.epa.gov/endangered-species/biological-opinions-available-public-comment-and-links-final-opinions.
[155] https://www.epa.gov/newsreleases/epa-announces-endangered-species-act-protection-policy-new-pesticides.
[156] https://www.epa.gov/endangered-species.
[157] https://www.epa.gov/system/files/documents/2022-11/esa-workplan-update.pdf.

## Appendix D: Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, sub-chronic 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 most recent registration decision for EtO, the 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 §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 § 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. The Agency has reviewed all of the assay data received for the List 1[158] chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. A second list of chemicals identified for EDSP screening was published on June 14, 2013,[159] 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. EtO is not on either list. 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, visit the EPA website.[160]

EPA's EDSP is actively pursuing the application of new approach methods (NAMs) to create a more efficient and robust screening program. In October 2020, EPA underwent a reorganization and the EDSP was moved to the Office of Pesticide Programs. This reorganization provides

[158] See https://www.regulations.gov/document/EPA-HQ-OPPT-2004-0109-0080 for the Final First List of Chemicals for Tier 1 Screening in the EDSP.
[159] See https://www.regulations.gov/document/EPA-HQ-OPPT-2009-0477-0074 for the Final Second List of Chemicals for Tier 1 Screening in the EDSP.
[160] https://www.epa.gov/endocrine-disruption.

better alignment of the EDSP with the procedures and methods used by the program offices. On July 28, 2021, the Office of Inspector General (OIG) released its new report on the EDSP and made ten recommendations. EPA looks forward to working with stakeholders and the scientific community to accelerate the implementation of this important program into pesticide risk assessments and decision making.

In this PID, EPA is making no human health or environmental safety findings associated with the EDSP screening of EtO. Before completing this registration review, the Agency will make an EDSP FFDCA §408(p) determination.

# Appendix E: Summary of Public Comments on the Draft Risk Assessments and Agency Responses

During the 60-day public-comment period for the EtO Draft Risk Assessment (November 20, 2020 to January 19, 2021), the Agency received 15 public comments from 10 commenters. After the DRA public comment period closed, the Agency received additional information from the Ethylene Oxide Task Force and the American Chemistry Council that was considered in the risk assessment phase of registration review. Comments were submitted by representatives from government, non-profit groups, and industry as summarized below:

- United States Department of Agriculture (USDA)
- Harris County, Texas
- Earthjustice, on behalf of Air Alliance Houston et al.
- University of California, San Francisco (UCSF) et al.
- North Carolina State University
- Louisiana Chemical Association (LCA)
- The Ethylene Oxide Sterilization Association (EOSA)
- Ethylene Oxide Task Force (EOTF)
- The American Chemistry Council (ACC)
- Elite Spice, Inc.

The Agency has summarized and responded to all substantive comments and comments of a broader regulatory nature below and in the *Response to Public Comments for the Ethylene Oxide (EtO) Draft Risk Assessment (DRA)*. The Agency thanks all commenters for participating and has considered all comments in developing this PID.[161]

## Extension Requests on Public Comment Period

**Comment:** EPA received requests to extend the DRA public comment period by 60 days from the American Chemistry Council (ACC), the Ethylene Oxide Task Force (EOTF), Earthjustice, the Ethylene Oxide Sterilization Association (EOSA), Elite Spice, and the Harris County Environmental Division.[162]

**EPA Response:** The request for extension was denied for all parties, as EPA plans to move toward mitigation for EtO as efficiently as possible. However, OPP informed all requestors that comments submitted after the close of the official comment period may be considered at any point during the registration review of EtO.

## Industry's Information Submitted Outside the Public Comment Period

[161] *Response to Public Comments for the Ethylene Oxide (EtO) Draft Risk Assessment (DRA).* Decision Number: 569904. EPA-HQ-OPP-2013-0244.

[162] See comments EPA-HQ-OPP-2013-0244-0024, EPA-HQ-OPP-2013-0244-0025, EPA-HQ-OPP-2013-0244-0026, EPA-HQ-OPP-2013-0244-0027, and EPA-HQ-OPP-2013-0244-0033 in EtO docket EPA-HQ-OPP-2013-0244 at www.regulations.gov.

**Comment:** The Ethylene Oxide Task Force (EOTF) notified the Agency that they intended to provide further input on the EtO DRA after the close of the public comment period, and EOTF provided this further input on March 19, 2021. The submission included information on new publications and new analyses on key points of the risk assessment. The Agency received several comments from other industry groups supporting EOTF's plan to submit more detailed comments on the EtO DRA, including the American Chemistry Council (ACC), Elite Spice, Louisiana Chemical Association, and the Ethylene Oxide Sterilization Association (EOSA).[163]

**EPA Response:** The Agency thanks EOTF and ACC for their supplemental submission on March 19, 2021. However, the comments have been considered and were determined to be similar to comments received from the TCEQ and the LCA and are addressed in the EPA's responses to those commenters.

**Request to Make Publicly Available the Exponent White Paper and Slide Presentation**

**Comment:** Earthjustice et al., LCA, and the University of California's San Francisco Program on Reproductive Health and the Environment urged EPA to make publicly available the Exponent White Paper, *Cancer Risk Estimates for Ethylene Oxide Based on Epidemiological and Biological Weight-of-Evidence*, which was cited in the EtO DRA. Earthjustice et al. also requested Exponent's slide presentation to the Agency on June 16 and 18, 2020 be made publicly available.[164]

**EPA Response:** EPA has made available the Exponent White Paper, *Cancer Risk Estimates for Ethylene Oxide Based on Epidemiological and Biological Weight-of-Evidence*. This document can be found at www.regulations.gov in EtO docket EPA-HQ-OPP-2013-0244 under document ID EPA-HQ-OPP-2013-0244-0042. Exponent's slide presentation to the Agency on June 16 and 18, 2020 can be found at www.regulations.gov in EtO docket EPA-HQ-OPP-2013-0244 under document ID EPA-HQ-OPP-2013-0244-0029.

**Request to Make Publicly Available EOTF's Mitigation Proposal from February 2020**

**Comment:** The Louisiana Chemical Association (LCA) stated that the Draft Risk Assessment states that further mitigation of EtO exposure is required and that detailed mitigation will be proposed in the forthcoming Proposed Interim Decision. A mitigation proposal submitted by the EOTF to OPP in February 2020 is cited, but the proposal is not available in the docket for review.

**EPA Response:** The initial mitigation proposal submitted by the Ethylene Oxide Task Force (EOTF) in February 2020 was a preliminary draft and was shared with EPA to show industry's on-going efforts in examining possible mitigation methods. Discussions with EOTF since February 2020 have refined this mitigation plan. EPA would like to minimize public confusion by not posting draft information in the public docket in advance of the PID, as these documents

[163] See comments EPA-HQ-OPP-2013-0244-0031, EPA-HQ-OPP-2013-0244-0034, EPA-HQ-OPP-2013-0244-0035, EPA-HQ-OPP-2013-0244-0036, and EPA-HQ-OPP-2013-0244-0037 at www.regulations.gov.
[164] See comments EPA-HQ-OPP-2013-0244-0027, EPA-HQ-OPP-2013-0244-0038, and EPA-HQ-OPP-2013-0244-0039 at www.regulations.gov.

are not fully reflective of OPP's final mitigation plans. All documentation of mitigation discussions will be made available upon publication of the PID. LCA and all public stakeholders will have the opportunity to review and comment on any mitigation proposal for EtO during the public comment period of the Proposed Interim Decision (PID). These public comments will be taken into consideration before the Agency finalizes the mitigation for EtO.

**Environmental Justice**

**Comment:** Earthjustice et al. expressed concern over environmental justice issues for communities located in the surrounding areas of EtO sterilization facilities. Earthjustice et al. stated that, "the people facing health threats from ethylene oxide are disproportionately communities of color and low-income, and the National Environmental Justice Advisory Council has urged EPA to protect public health by following the best available science on this chemical," citing the May 3, 2019 letter from the National Environmental Justice Advisory Council to former EPA Administrator, Andrew Wheeler.[165,166]

**EPA Response:** OPP recognizes that there are certain EtO commercial sterilization facilities that impact communities with environmental justice concerns. OPP is collaborating with EPA's Office of Air and Radiation (OAR) in their ongoing efforts to address environmental justice concerns for EtO. Mitigation measures to address environmental justice by OAR in their EtO Commercial Sterilizers Rulemaking are included in OPP's registration review on EtO. See Section V.B. of this document for detailed information on how OPP will address environmental justice concerns for EtO.

**Request to Reevaluate the Need for Mitigation**

**Comment:** The Louisiana Chemical Association (LCA) requested that OPP reevaluate the need for mitigation after the consideration of public comments on the DRA.[167]

**EPA Response:** EtO is a known human carcinogen. Based on the cancer inhalation unit risks from assessments published by EPA's Office of Research and Development Integrated Risk Information System (ORD/IRIS), EPA has identified risks of concern to workers and residential and non-residential bystanders, and mitigation of EtO inhalation exposure is required to address those concerns. These measures are intended to mitigate risks to both workers within EtO sterilization facilities, as well as the communities surrounding the EtO sterilization facilities. Detailed mitigation can be found in Section V.A. of this document and are available for 60-day public comment upon publication of this PID.

**FIFRA and FFDCA Standards**

**Comment:** Earthjustice et al. stated that EPA must assess the health risks presented by EtO's pesticide uses and ensure they meet the FFDCA and FIFRA standards.[168]

[165] https://www.epa.gov/environmentaljustice/nejac-letter-regarding-ethylene-oxide.
[166] See comment EPA-HQ-OPP-2013-0244-0027 at www.regulations.gov.
[167] See comment EPA-HQ-OPP-2013-0244-0035 at www.regulations.gov.
[168] See comment EPA-HQ-OPP-2013-0244-0038 at www.regulations.gov.

**EPA Response:** The Agency agrees with Earthjustice's statement. The 2020 DRA and 2023 DRA addendum assessed human health risk. EPA did not identify dietary risks of concern. EPA identified inhalation cancer risks of concern and is proposing that EtO does not meet the standard for registration under FIFRA without the implementation of mitigation measures sufficient to address these risks, as described in this PID.

**Incompleteness of the 2020 DRA**

**Comment:** The Louisiana Chemical Association (LCA) stated that certain components of the DRA were not completed at the time the document was released for public comment, specifically, the non-occupational bystander inhalation exposure and environmental justice evaluations, and the common mechanism of toxicity finding. LCA asserted that no final risk assessment should be issued until the public has adequate opportunity for review and comment of these components.[169]

**EPA Response:** OPP is publishing a DRA Addendum with this PID, which characterizes risks to workers and non-residential bystanders based on the EPA IRIS value for EtO. OAR's proposed NESHAP rule will address non-occupational bystander risks and will include an environmental justice evaluation. There will be a public comment period for this proposed rule. Additionally, OPP's PID includes an environmental justice evaluation (Section V.B), and a common mechanism of toxicity finding (Section III.A) and is subject to a public comment period.

**Beekeeping Equipment Use**

**Comment:** USDA[170] and North Carolina State University (NCSU) submitted comments detailing the use and benefits of EtO for disinfecting beekeeping equipment contaminated with the honeybee pathogen, *Paenibacillus larvae* (the causative agent in American foulbrood), and other bee pathogens. NCSU stated that beekeeping and the associated pollination services add significantly to the agricultural production of North Carolina, and they consider EtO to be essential to maintaining a healthy beekeeping industry. NCSU noted that alternative control measures, such as burning or boiling equipment in lye, are more expensive and present higher risks to beekeepers. NCSU requested renewal of the EtO product registered for the beekeeping equipment use.

**EPA Response:** EPA thanks USDA and NCSU for their comments and has taken them into consideration in this PID and in the document *Ethylene Oxide (PC# 042301): Use, Usage, Benefits, and Impacts of Cancellation* (December 1, 2022). The anticipated occupational inhalation cancer risk posed by the use of EtO on beekeeping equipment in NC is higher than the Agency's threshold for occupational risk ($1 \times 10^{-4}$) and the Agency has determined that the benefits of the use do not outweigh that risk. Therefore, the Agency has determined that the use

[169] See comment EPA-HQ-OPP-2013-0244-0035 at www.regulations.gov.
[170] See comment EPA-HQ-OPP-2013-0244-0030 at www.regulations.gov.

of EtO for disinfecting beekeeping equipment does not meet the FIFRA standard and proposes that the use be terminated.

**Use of EtO on Spices**

**Comment:** USDA and Elite Spice, Inc.[171] submitted comments on the spice use of EtO. USDA submitted comments regarding the value of EtO in ensuring food safety. They stated that EtO is used to fumigate both domestically produced and imported spices for the purpose of eliminating pathogenic microbial contaminants such as *Salmonella* and *E. coli* that pose serious risks to human health.

USDA also commented on the human health risk assessment and ecological risk assessments. In their comments on the human health risk assessment, USDA discussed the approach taken in the dietary, aggregate, bystander, and occupational analyses and generally agreed with the assumptions used in them. Similarly, USDA commented on the ecological risk assessment, and confirmed label information and the process used for treating spices. USDA stated that existing label mitigations make exposure to non-target organisms unlikely. USDA also noted that they would be willing to facilitate additional outreach to agricultural stakeholders on the feasibility and practicality of any mitigation measures currently under consideration by EPA to address human health or ecological risks.

Elite Spice, Inc. provided comments on the benefits of EtO. They noted that EtO products are critically important to the U.S. food industry, including spice and seasoning manufacturers, to mitigate pathogen contamination. They further noted that there are a limited number of acceptable and effective treatment methods to address this serious food safety concern.

In addition, Elite Spice, Inc. stated that they support the comments submitted by the EOTF and urged EPA to carefully consider those comments and revise the DRA and PID in accordance with them. They requested that EPA continue to permit the use of EtO for the treatment of spices and to ensure any new emissions control requirements are not overly burdensome.

**EPA Response:** EPA thanks USDA and Elite Spice for their comments and has taken them into consideration in this PID and in the documents *Ethylene Oxide (PC# 042301): Use, Usage, Benefits, and Impacts of Cancellation* and *Response to Public Comments for the Ethylene Oxide (EtO) Draft Risk Assessment (DRA)* (December 1, 2022, and March 27, 2023, respectively).

The Agency agrees that the use of EtO for fumigating certain dried herbs and spices is important for pathogen control and that alternatives to EtO may not be viable for every spice, spice form, spice blend, target pathogen, or consumer market. Despite these limitations, due to the inhalation cancer risk estimates associated with the use of EtO, EPA still seeks to identify alternatives to EtO spice treatments as well as specific spices where EtO use is critical for food safety. The Agency is soliciting comments on the specific commodities for which there is current critical use of EtO and for which there are no current viable alternatives to EtO (e.g., heat, steam, irradiation, or propylene oxide cannot be used for pathogen control on a particular spice, spice form, or spice

[171] See comment EPA-HQ-OPP-2013-0244-0034 at www.regulations.gov.

blend). Any commodities without documented support for continued treatment with EtO will be considered for a phased-out cancellation.

The Agency disagrees with the points raised by EOTF in their comments. Since the publication of the 2020 DRA, and in contexts other than the registration review of EtO, EPA has continued to consider the best approach for characterizing the cancer risk associated with inhalation exposure to EtO. While there are some uncertainties associated with all of the approaches in characterizing the cancer risk (as discussed in the 2020 DRA), the EPA has determined that the 2016 IRIS assessment should be used to characterize the cancer risk associated with inhalation exposure to EtO.

As for new emissions control requirements, those requirements are under the purview of EPA's Office of Air and Radiation and are included in their proposed rulemaking on commercial EtO sterilizers under Section 112 of the Clean Air Act (CAA). See public docket EPA-HQ-OAR-2019-0178 at www.regulations.gov for details.

**EPA's Use of Industry Analysis**

**Comment:** Earthjustice et al. and the University of California San Francisco Program on Reproductive Health and the Environment expressed concern that EPA should not be citing assessments conducted by industry for the Agency's risk assessment. Earthjustice et al. stated, "OPP treats ethylene oxide's cancer risk level as an open question, presenting EPA's own 2016 IRIS cancer risk value alongside competing values calculated by the Texas Commission on Environmental Quality (TCEQ) and an industry consulting firm that are up to 3,500 times less protective. […] OPP cannot now equate EPA's 2016 IRIS value with the industry-supported analyses that fail to follow same rigor as the IRIS external peer-review process."[172] The University of California San Francisco Program on Reproductive Health and the Environment stated that the DRA "presents multiple approaches for cancer risk estimation without critical analysis, treating them as if they are equally valid, which they are not. […] The TCEQ and EOTF assessments do not reflect any new data or hypotheses that were not available to the Office of Research and Development's Integrated Risk Information System (ORD/IRIS) or the Science Advisory Board (SAB) at the time of its 2016 assessment, merely analyses and approaches that were rejected by ORD/IRIS and the SAB."[173]

**EPA Response:** Since the publication of the 2020 DRA, and in contexts other than the registration review of EtO, EPA has continued to consider the best approach for characterizing the cancer risk associated with inhalation exposure to EtO. While there are some uncertainties associated with all of the approaches in characterizing the cancer risk (as discussed in the 2020 DRA), the EPA has determined that the 2016 IRIS assessment should be used to characterize the cancer risk associated with inhalation exposure to EtO. Therefore, OPP is publishing a DRA Addendum with this PID, which quantifies risks posed by EtO using EPA's ORD/IRIS 2016 IUR value.

[172] See comment EPA-HQ-OPP-2013-0244-0038 at www.regulations.gov.
[173] See comment EPA-HQ-OPP-2013-0244-0039 at www.regulations.gov.

# Appendix F: Explanation of Office of Air and Radiation and Office of Pesticide Programs Cancer Risk Thresholds

***EPA Clean Air Act (CAA) Residual Risk Evaluations***

Section 112 of the Clean Air Act (CAA) instructs EPA to regulate hazardous air pollutants (also known as "air toxics") by setting limits on the amount of pollution that industrial sources can emit to the air, rather than by setting ambient standards, which are limits on the amount of a pollutant that is allowed in the outdoor air. CAA section 112 establishes a two-stage regulatory process for setting emission standards for hazardous air pollutants (HAP). The first stage involves EPA establishing technology-based standards, either maximum achievable control technology (MACT) emission standards or generally available control technology standards (GACT). The second stage involves EPA evaluating these standards to determine whether additional requirements are needed to address any remaining risk associated with HAP emissions. This second stage is referred to as the "residual risk review."

EPA conducts residual risk reviews for sources of HAP in each industrial source category (e.g., Petroleum Refineries, Taconite Iron Ore Facilities, Aerospace Manufacturing Facilities, etc.) subject to MACT standards in order to address any remaining or "residual" risk from HAP emissions. Specifically, section 112(f)(2) of the CAA requires the EPA to determine whether promulgation of additional standards or revised standards is needed for a source category to provide an ample margin of safety to protect public health or to prevent an adverse environmental effect.

The approach incorporated into the CAA and used by the EPA to evaluate residual risk and to develop standards under CAA section 112(f)(2) is a peer-reviewed two-step approach.[174,175] In the first step, the EPA determines whether risks are acceptable. This determination ''considers all health information, including risk estimation uncertainty, and includes a presumptive limit on maximum individual lifetime [cancer] risk (MIR) 1 of approximately 1 in 10 thousand.'' (54 FR 38045, September 14, 1989). If risks are unacceptable, the EPA must determine the emissions standards necessary to reduce risk to an acceptable level without considering costs.

In the second step of the residual risk approach, the EPA considers whether the emissions standards provide an ample margin of safety to protect public health ''in consideration of all health information, including the number of persons at risk levels higher than approximately 1 in 1 million, as well as other relevant factors, including costs and economic impacts, technological feasibility, and other factors relevant to each particular decision.'' *Id.* The EPA must promulgate emission standards necessary to provide an ample margin of safety to protect public health or determine that the standards being reviewed provide an ample margin of safety without any revisions. After conducting the ample margin of safety analysis, we consider whether a more

[174] U.S. EPA. *Risk and Technology Review (RTR) Risk Assessment Methodologies: For Review by the EPA's Science Advisory Board with Case Studies – MACT I Petroleum Refining Sources and Portland Cement Manufacturing*, June 2009. EPA-452/R-09-006. https://www3.epa.gov/airtoxics/rrisk/rtrpg.html.

[175] Recommendations of the SAB Risk and Technology Review Methods Panel are provided in their report, which is available at: https://yosemite.epa.gov/sab/sabproduct.nsf/4AB3966E263D943A8525771F00668381/$File/EPA-SAB-10-007-unsigned.pdf.

stringent standard is necessary to prevent, taking into consideration costs, energy, safety, and other relevant factors, an adverse environmental effect.

The EPA conducts a risk assessment that includes estimates of:

- Maximum individual cancer risk (MIR) posed by the HAP emissions from each source in the source category at residential locations.
- Hazard index (HI) for chronic exposures to HAP with potential to cause chronic (or long-term) noncancer health effects at residential locations, and
- Hazard quotient (HQ) for acute exposures to HAP with the potential to cause noncancer health effects off-site and at locations that may be accessible to the public (*e.g.,* roadways and public buildings).

The MIR is defined as the cancer risk associated with a lifetime of exposure (i.e., 70 years) at the highest concentration of HAP where people are likely to live (i.e., residential locations). The HQ is the ratio of the potential exposure to the HAP to the level at or below which no adverse effects are expected; the HI is the sum of HQs for HAP that affect the same target organ or organ system. The risk assessment also provides estimates of the distribution of cancer risks within the exposed populations, cancer incidence and an evaluation of the potential for adverse environmental effects.

***Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Risk Assessment***

For OPP, the level of concern, for a given endpoint, refers to a predetermined quantified level above which OPP believes more detailed consideration of the risks of a pesticide is necessary. When it appears that the use of a pesticide may pose risks greater than the level of concern, OPP will first attempt to refine its risk assessment to obtain a more accurate characterization of the risk. If the level of concern is still exceeded, OPP will consider a variety of measures for reducing the risk to a level at or below the level of concern. In general, OPP will use a tiered approach to reduce risks starting with the quickest and least expensive means. This may be accomplished through discussions with registrants who voluntarily agree to risk reduction measures; through required risk reduction in a Reregistration Eligibility Decision document or Interim or Final Registration Review Decision document; or other means. If OPP believes that these actions will not result in sufficient risk reduction, it may initiate a special review or take regulatory action under FIFRA.

OPP considers dietary and non-dietary cancer risks of $10^{-6}$ and less to be negligible, and thus it would not typically pursue risk reduction measures for such negligible risks. OPP does not allow dietary risks to exceed $10^{-6}$, or non-dietary risks to exceed $10^{-4}$, except in those cases where it has determined that benefits exceed the risks. OPP examines non-dietary risks in the $10^{-5}$ to $10^{-4}$ range to determine whether the benefits of use outweigh the risks and will seek ways to mitigate unacceptable risks. OPP's policy allows for the consideration of a wide range of factors in making a risk management decision for non-dietary risks. These factors may include: risk to individuals, number of people exposed, weight of scientific evidence regarding carcinogenicity, lower risk alternatives, and benefits associated with the pesticide under review. In general, OPP tolerates less risk to individuals as the size of the exposed population increases. Therefore, for the largest exposed populations, including residents and pesticide handlers, OPP seeks to reduce

the individual risks to the greatest extent feasible, preferably to $10^{-6}$ or less. The goal is to ensure that there is a minimum level of protection from exposure to pesticides for workers, residents, bystanders and vulnerable populations, particularly children. OPP strives to ensure that this policy is consistently applied to all pesticide program decisions.

*Risks greater than $10^{-4}$*. It is OPP's intent, generally, not to grant new registrations or allow the continued registrations of existing uses which have non-dietary cancer risks greater than $10^{-4}$ (e.g., $10^{-3}$), because such risks, based on the program's experience, typically outweigh benefits and thus will cause unreasonable adverse effects.[176] If risk reduction measures do not reduce the risk below the level of concern, OPP may initiate Special Review or take regulatory action under FIFRA. As is the case for EtO, OPP recognizes there may be currently registered high risk uses which are very beneficial and have no currently registered alternatives.

*Risks Between $10^{-6}$ and $10^{-4}$*. OPP evaluates pesticides with risks in this range and seeks ways to reduce individual cancer risks to the greatest extent feasible, preferably to $10^{-6}$ or less. OPP will require, as appropriate, additional protective clothing or equipment or changes in application methods, taking benefits into account, through the reevaluation and registration processes, as follows:

> Applications for new registrations. In considering applications for new registrations with non-dietary cancer risks, OPP carefully examines those uses with potential risks in the $10^{-6}$ to $10^{-4}$ range to seek ways of reducing those risks before registration occurs. Also, OPP recognizes there may be currently registered high risk uses which are very beneficial and have no currently registered alternatives. In such a case, under its Reduced Risk Policy, OPP encourages the submission of applications for pesticides which offer a reduced-risk alternative, and will give priority consideration to the review of such applications. The registration of such a reduced-risk alternative pesticide might affect the risk/benefit balance for the currently registered higher-risk chemical, allowing OPP to achieve greater risk reduction.
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> Reregistration and Registration Review. For those chemicals subject to reregistration and registration review, OPP carefully examines those uses with estimated risks in the $10^{-6}$ to $10^{-4}$ range to seek ways of cost-effectively reducing risks.
>
> Ongoing examination of chemicals through reevaluation. OPP monitors registered pesticides with risks greater than $10^{-6}$ to look for opportunities to reduce risks further, including requiring technology changes and changes in application methods. For example, advances in technology have had a major effect on reducing exposure to pesticide handlers. Examples include: closed-loading systems, enclosed cabs offering respiratory protection, containers which limit spilling, and water soluble packaging. OPP encourages these technological improvements as they become available and requires them in appropriate cases.

[176] For EtO, the benefits are considered to exceed the risks for medical device sterilization and spice fumigation. See Section III.C for a full description on EtO benefits.

*Risks Below $10^{-6}$*. Generally, OPP does not seek risk reduction below this level unless it is cost-effective.[177]

[177] Memorandum, 1996. *Non-Dietary Cancer Risk Policy*. Daniel M. Barolo, Director Office of Pesticide Programs.