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EPN Comments on Proposed Interim Decision and Draft Risk Assessment Addendum for Ethylene Oxide

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Founded in 2017, the Environmental Protection Network (EPN) harnesses the expertise of more than 550 former Environmental Protection Agency (EPA) career staff and confirmation-level appointees from Democratic and Republican administrations to provide the unique perspective of former regulators and scientists with decades of historical knowledge and subject matter expertise.

On April 13, 2023, EPA published two Federal Register notices, each of which described proposals to update and amend the regulatory status of ethylene oxide (EtO) under two different statutes, the 1996 update of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA, known as the Food Quality Protection Act (FQPA)) and the Clean Air Act (CAA).

It is understandable and appropriate that these two sets of proposed actions were issued simultaneously, as the decisions considered and made under FQPA will inform the decisions considered and made under the CAA and *vice versa*. The situation is made even more complex because two other federal regulatory agencies (the Food and Drug Administration (FDA) and the Occupational Safety and Health Administration (OSHA)) have roles to play as well.

Furthermore, EtO is the focus of attention in several other CAA actions: the recently-issued decision on reconsideration of the 2020 rule for the Miscellaneous Organic Chemical Manufacturing sector (the MON rule) as it pertains to its use of the 2016 EtO Integrated Risk Information System (IRIS) hazard assessment; the April 2023 proposal for amendments to the New Source Performance Standards (NSPS) and National Emission Standards for Hazardous Air Pollutants (NESHAP) that apply to the Synthetic Organic Chemical Manufacturing Industry (SOCMI) source category; and a forthcoming review of the 2007 NESHAP for Hospital Ethylene Oxide Sterilizers.

In spite of all these moving parts, EPN intends to focus this set of comments on the Office of Pesticide Programs' (OPP) Proposed Interim Registration Review Decision, acknowledging that there may be instances in which the Office of Air Quality Planning and Standards' (OAQPS) proposal to amend the NESHAP for Commercial Sterilization Facilities will warrant comment.

Background

Ethylene oxide (EtO) is a flammable, colorless gas with many industrial uses, primarily in the making of other chemicals used in a wide variety of products. One category of use is as a pesticide, specifically as a sterilant/fumigant, regulated as such under both subcomponents of FQPA (FIFRA and FFDCA). Current registrations encompass treatment of new and reusable medical devices and equipment in commercial sterilization and healthcare facilities, including hospitals; treatment of dried herbs, spices and vegetables in commercial sterilization facilities; several niche uses: museum, library, and archival materials, cosmetics, and musical instruments; and beekeeping equipment in North Carolina.

In 2016, EPA updated its 1990 IRIS assessment. As first determined more than two decades earlier, EPA found that carcinogenic potential was the health effect of greatest concern and declared it to be a probable/likely carcinogen based upon animal bioassay data. EPA now classifies EtO as "Carcinogenic to Humans" by the inhalation route and has derived a new inhalation unit risk estimate based upon data from human epidemiology studies. Both OPP and OAQPS have relied upon the 2016 IRIS hazard assessment for the hazard component of their respective human health risk assessments. Both programs determined that acceptable risk thresholds currently are or may be exceeded for several subpopulations: workers who handle EtO or the containers where it is used in the commercial (and hospital/ healthcare) sterilization facilities; individuals who work in those facilities but do not handle the sterilant or the containers it is used in (occupational bystanders); and individuals who live near (residential bystanders) or spend significant time at non-residential sites near such facilities (non-residential bystanders).

Looming over the efforts of both programs is the reality that it is likely that even if/when all of the proposed mitigation measures are put into place, neither program will be able to determine whether or not those measures yield a level of risk considered, as a matter of policy, acceptable for each subpopulation of concern. "OPP generally seeks to reduce the risk to less than 1×10^{-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 1×10^{-4} (100 in 1 million) may be used for occupational exposures."[1] OAR generally uses the 100 in 1 million as its benchmark for all subpopulations.

However, based upon new information made available only after the original 1990 IRIS assessment was published, the Inhalation Unit Risk (IUR) was revised in the 2016 IRIS assessment. The reassessment resulted in the conclusion that EtO was 60 times more risky now than estimated in 1990. With that conclusion came the realization that the exposure dose(s) of EtO that would equate to the acceptable risk threshold(s), depending upon the subpopulation of concern, would be reduced by 60-fold as well. The result of this change is that the sentinel dose(s) fall below the Limit of Detection (LOD) and Limit of Quantification (LOQ). So, at the moment, the relevant doses cannot be measured, and one cannot tell if the desired goal has been reached. This conundrum will be with us throughout the current regulatory process unless there are unanticipated breakthroughs in analytical chemistry.

Comments

The continued use of EtO as a sterilant of medical devices and equipment and dried herbs, spices, and vegetables poses a particular set of challenges for EPA. Given the updated IRIS cancer hazard assessment, the projected risks to workers far exceed acceptable risk thresholds. Projected risks for occupational, residential, and non-residential bystanders are problematic as well. At the moment, absent significant benefits, EtO would not meet the FIFRA standard for continued registration based upon those projected risks. On the other hand, EtO remains a critical component for assuring the safety of much of the supply of medical devices and equipment used in the modern medical care arena. Furthermore, it is key to avoiding illness from foodborne pathogens on dried herbs, spices, and vegetables. Thus, even though no quantitative risk-benefit analysis has been conducted during this round of registration review, the long-held position that EtO's benefits outweigh its risks still appears to hold.

[1] Ethylene Oxide, Proposed Interim Registration Review Decision, Case Number 2275, March 2023. p 14

We have used the outline presented in the draft Proposed Interim Decision (PID) to structure our responses/comments to each of the actions EPA is proposing to take to mitigate risks from EtO exposure.

A. Proposed Risk Mitigation and Regulatory Rationale

Termination of some uses

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. However, given the availability of less risky, lower cost, easily available alternatives, use of EtO has fallen out of favor. Thus, the impact expected if registration of these uses is terminated is little to none. Approval of the uses will be ended.

While it is mandated during the registration review process to update and modify, if necessary, the use profile for every pesticide, it should be noted that this action with EtO will do virtually nothing to reduce the current health risk from EtO exposure. However, hopefully, it should inhibit its return as a sterilant in these settings, as a registrant would have to through the whole registration process once again. For this reason, it is a wise decision.

EPN comment: We concur with this proposal.

Beekeeping Equipment (in NC only)

The state of North Carolina has been granted approval under Section 24(c) of FIFRA to operate one facility that uses EtO for the sterilization of beekeeping equipment to control American foulbrood (AFB) disease in the state. As with the commercial and healthcare sterilization facilities, EtO use in this facility poses potentially unacceptable risks to its workers and to non-occupational bystanders. A number of less risky chemical and non-chemical alternatives to EtO have become available that successfully deal with AFB disease. EPA is proposing to cancel the use of EtO in this setting, which will lead to a measure of risk reduction as EtO has not yet been abandoned as the pesticide of choice.

EPN comment: We concur with this proposal.

To expedite the cancellation process, 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.

EPN comment: We concur with this proposal.

Spices

Effective non-EtO alternatives exist for some of the dried herb, spice, and vegetable products for which EtO sterilization is currently allowed. The agency is considering a phased cancellation of the use of EtO on

specific spices/commodities, unless the registrant(s) provide documented evidence that only EtO can produce successful sterilization outcomes. Registrants seeking to maintain approvals on commodities for which viable alternatives do exist will be asked to submit requests for voluntary cancellation of EtO.

Employing this approach should lead to reduced EtO use overall, and thus less exposure and risk to workers (both hands-on and bystander), residential, and non-residential bystanders in and near the subset of commercial sterilization facilities that handle most of the spice sterilization tasks.

While at this time one cannot predict the exact amount of reduction in the EtO environmental load that will occur as a consequence of implementing this approach, it is likely to be beneficial to those both within and around those facilities.

EPN comment: EPN heartily encourages the agency to transition *consideration* of a phased cancellation into an *actionable* effort, on the expectation that viable alternatives exist for many commodities and it is in the public's best interest to facilitate the shift.

Proposed EtO Use Rate Reduction

Medical Devices

Pages 47-49: This section on EtO use rate reduction in a sterilization chamber treating medical devices and equipment warrants some further discussion concerning the establishment of the maximum rate/concentration to be allowed in the chamber.
EPA states that it understands that many facilities are using much higher concentrations of EtO than what is required for sterility assurance—oftentimes even double the amount required and as high as 700 mg/L. The agency also understands that "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)."[2]

New cycle: EPA is proposing that the EtO concentration for new cycles must be no greater than 500 mg/L, and that the sterilization validation process specific to the concentration used is reviewed by FDA. It is seeking public comment on the feasibility of a 2-year compliance timeline for use rate reduction through reduced concentrations of new cycles.

EPN comment: EPN assumes that the 500 mg/L maximum rate eventually will apply to everything, including the subset of medical devices once or still requiring a higher rate such as the surgical kits containing a mixed variety of devices which are pre-packaged. It is not clear from the background material whether or not any of these devices are already in the new cycle mode.

If our assumption is correct that 500 mg/L maximum would apply to everything, we could support a two-year timeframe for transition to the 500 mg/L upper limit for all new cycle products. That said, we would expect to see as many of the optimizations put into place as is feasible, and every attempt made to titer the rate to as low as possible while still achieving effective sterilization.

[2] Ethylene Oxide, Proposed Interim Registration Review Decision, Case Number 2275, March 2023. p 48

Existing cycle: EPA is proposing a 5-year compliance timeframe to redesign cycles, devices, or packaging and for review by FDA under applicable device authorities to actuate the 500 mg/L limit for existing cycles.

EPN comment: In this instance, EPN would argue for shortening that five-year timeframe to no more than four years. This position is not based so much on the knowledge that this would be feasible but because of the urgency to reduce the risk to both workers and bystanders to as low as possible as quickly as possible.

We also feel that if products cannot meet the 2-year new cycle or 4-year existing cycle criteria, they should be excluded from the market. There should be no exceptions. Furthermore, potential new medical devices and equipment that cannot be successfully sterilized at or below the 500 mg/L limit should not be approved for use. There is discussion in the OPP draft Proposed Interim Decision that the federal task force and relevant stakeholders are (supposedly) working diligently to find alternatives to EtO for use in the sterilization/fumigation settings. But we are not aware of any commitment to develop medical devices and equipment that are not dependent upon EtO in the first place. One might wish to begin thinking about dependence upon EtO as a disqualifying criterion for approval.

Record-keeping requirements: EPN comment: In the short term while adaptation to the 500 mg/L limit is underway, all of the record-keeping requirements that EPA has proposed should be implemented.

And, to reiterate our position, if the 500 mg/L limit cannot be made viable for a particular set of devices or other products within the time frames for the new or existing cycles, those products should be phased out or removed from, or never introduced into the market.

Cycle Calculation Approach: No comments

Cycle Design Optimization & Half Cycle Approach: No comments

Spices

Sterilization of spices is not driven by standardized methods as it is for medical devices. While there are some shared requirements with regard to the physical elements of the sterilization chamber, including the proposed application rate upper limit of 500 mg/L, other aspects are company-, chamber-, pathogen-, and spice-specific. Those specifics can be found on the label.

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, potentially lower than what is on the current label, but never exceeding 500 mg/L. EPA would like to establish a new upper limit which is lower than 500 mg/L while maintaining food safety standards.

EPN comment: EPA proposes no firm timeframe for establishing a new upper limit. EPN offers the recommendation of 2 years, citing similarities in the circumstances surrounding the new cycle mode for medical devices: useful data should already exist from the registration process. Registrants should have already established the rate(s) needed for their product(s); otherwise, the registration should not have been approved. New studies would be needed only if current registrations are dependent upon rates above the

500 mg/L limit. If results indicate failure to achieve successful pathogen control at or below 500 mg/L, then alternative methods must be developed or the product registration canceled. And vigorous efforts must be continued to find EtO alternatives. The spice industry does not have the luxury of redesigning their products with new chemistry as does the medical device industry.

Proposed Mitigation for Residential Bystander Risk

"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."[3]

EPN comment: No comment.

Proposed Mitigation for Non-Residential Bystander Risk

EPN comment: No comment.

Proposed Mitigation for Occupational Risk

Engineering Controls for Healthcare Facilities

Prompted by the significant change in the hazard assessment's conclusions with regard to EtO's carcinogenic potential and even though OAR is not currently proposing to update and amend the NESHAP for hospitals and other healthcare facilities, OPP is proposing to impose additional engineering controls in these settings to enhance the protection of workers and others who are present in those environments. During the last round of re-registration for EtO, as articulated in the 2008 Reregistration Eligibility Decision document (RED), EPA required that sterilization with EtO in healthcare settings must be performed in all-in-one systems.
In an effort to further reduce exposure and risk to both workers and bystanders, EPA is retaining this requirement and now proposing several additional measures:

- The all-in-one devices must be located in a containment area that is physically separate from all other work areas of the healthcare facility.
- The sites housing the all-in-one systems must be kept at negative pressure to prevent EtO emissions from the containment site.
- The exhaust from the all-in-one devices must be directed through dedicated exterior ventilation stacks via a system separate from that for the rest of the facility in which the sterilization system is located.
- The exhaust duct must terminate away from areas where people walk or work, located at least 25 feet away from the building air intake source and in compliance with existing codes.
- Already-available auxiliary abatement accessories must be added to the all-in-one system, if that step has not already been taken. Assuming that they are properly installed and maintained, this is claimed to reduce EtO emissions more than 99%.

EPN comment: While EPN cannot comment on the cost of compliance with implementation of the

[3] Ethylene Oxide, Proposed Interim Registration Review Decision, Case Number 2275, March 2023. p 53

engineering controls, we are supportive of completion as soon as possible but no later than the proposed two-year timeline.

Respirator Use

EPA also is soliciting 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.

EPN comment: Given that the agency will not be able to determine if the risk targets are attained with the proposed mitigation measures due to deficiencies in the analytical chemistry, use of respirators should be mandated in healthcare facilities for employees who are unloading EtO sterilization equipment and/or products from the sterilization chamber and for any occupational bystanders who enter the space where the sterilization chamber is located while unloading is underway.

Engineering Controls for Commercial Sterilization Facilities

EPA is proposing to require the following engineering controls in Commercial Sterilization Facilities:

- 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).

EPN Comments: EPN agrees that control efforts in these five areas could/should result in the reduction of EtO levels within these facilities. We support each of the proposed actions.
The switch to the use of netting rather than plastic surrounding pallets of treated medical devices makes sense, for the reason stated. All of the proposed engineering controls should be implemented expeditiously, in all existing facilities, not just in new ones. It is the existing facilities that are fostering the unacceptably risky environments within and around their sites. We would expect any new sites would start out with the proposed controls in place and, thus, would not present the same problems as the existing ones.

Lowered Action Limit for Commercial Sterilization Facilities

"EtO product labels currently cite the OSHA permissible exposure limit (PEL) of 1 ppm to trigger the requirement that EtO handlers in commercial sterilization facilities wear a respirator." The current risk assessment, based upon the 2016 IRIS assessment, makes it clear that the 1 ppm trigger is not sufficiently protective. Thus, EPA will remove the OSHA PEL from the product labels and replace it with 10 ppb as the trigger (which, unfortunately, also is not sufficiently protective but, currently, is the best available technologically quantifiable EtO concentration of ambient air for real time measurements).

EPA proposes that the relevant label changes shall be made within 2 years.

EPA Comments: We support all of the proposed actions and the two-year timeline for compliance associated with lowering the trigger level from 1 ppm to 10 ppb.

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

New Respirator Requirement for EtO Handlers

The Agency is proposing to add specified personal protective equipment (PPE) respirator requirements to mitigate risks at points when the potential for exposure is the greatest to workers involved in the EtO commercial sterilization process. The label changes will include relevant associated fit tests, training, and medical evaluation requirements.

A data call-in (DCI) also will be issued to gather monitoring data in accordance with the OPPTS guideline 875.1400 Inhalation Exposure Indoor, requiring a protocol (to be approved by EPA) before monitoring for the study begins. The goal would be to assure monitoring is done for workers at specific sites within the facility, performing specific tasks and, presumably, wearing the specified type of respirator.

EPN Comments: We agree with all of the proposed actions with regard to PPE requirements and indoor air monitoring.

EPA also plans 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. While lowering the trigger level from 1 ppm to 10 ppb is a 100-fold reduction, it still doesn't achieve a measurement equal to or lower than the desired risk threshold target which is approximately another 100-fold lower (0.19 ppb). The agency proposes a two-year time frame for compliance with this request.

EPN Comments: Availability of a credible analytical method for measuring indoor air EtO at levels at or near EPA's target risk level (0.19 ppb) is a critical piece in the decision-making process and, thus, has urgency associated with it. We agree with all of the proposed actions to be taken, including the two-year time frame, although it would be preferred if that timeline could be shortened.

Training Requirements

Commercial Sterilization Facilities Training Requirements

EPA currently requires 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 agency is not proposing any significant changes to the training curriculum, but wants to ensure that the employees are made fully aware of the potential health risks, particularly in light of the revision of the carcinogenicity risk estimates and response protocol following the reduction in the trigger level from 1 ppm to 10 ppb.

Healthcare Facilities Training Requirements

Training is currently recommended, *but not required*, for personnel who work with EtO sterilization devices in healthcare facilities. EPA is proposing to make the training *obligatory*. As with Commercial Sterilization Facilities, special emphasis should be placed upon the potential health risks, particularly in light of the revision of the carcinogenicity risk estimates. EPA also is proposing that registrants ensure that both types

of facilities maintain records on employee training. EPA will require that the requisite label changes will be made within 60 days of promulgation.

EPN Comments: We agree with all of the actions proposed with regard to employee training.

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.

EPN Comments: We agree with all of the proposed changes as specified in Appendix B.

B. Environmental Justice

EPN Comments: EPN lauds the agency's efforts to determine whether there are any communities and persons, including minority, low-income, and indigenous populations who may be disproportionately impacted by exposure to EtO, both within and around facilities.

The discussion in this section of the PID is focused solely on the potential for differential risks based upon differences in exposures. While exposure is a key factor, it is not the only one that can lead to differentiated responses.

What effort has the agency extended to determine which, if any, other factor(s) may be playing a role? In particular, the agency should ask and answer the question of whether or not the exposure-impacted subpopulations also reflected a differential response in cancer rates, especially of the tumor types observed in the epidemiology studies that form the basis of the risk assessment (lymphopoietic and breast).

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."[4]

"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."[5]

EPN Comments: We agree will all of the proposed actions, with the caveat that there may be some additional tolerances that can be removed if a registrant shows that a non-EtO alternative is now their preferred approach and moves to cancel the EtO registration for that commodity, as discussed earlier in the draft PID.

[4] Ethylene Oxide, Proposed Interim Registration Review Decision, Case Number 2275, March 2023, p 66
[5] *Ibid*.

D. <u>Additional EPN Comments</u>

We recommend that, in its final regulatory decision for EtO pesticide products, EPA should inform registrants that compliance with the labeling requirements will be enforced using the misbranding authority in FIFRA. The agency's decision should make the affirmative finding that the presence of the additional and revised labeling text on EtO products' labeling is necessary to ensure the protection of public health, as defined in FIFRA sec. 2(q). The agency should also set a deadline after which the absence of such labeling text would render the products "misbranded" and subject to enforcement actions under FIFRA secs. 12 and/or 13.