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EPA-HQ-OAR-2019-0178

Attn: Brian Langloss, POC

Office of Air and Radiation

U.S. Environmental Protection Agency

**RE: Docket ID EPA-HQ-OAR-2019-0178: U.S. Environmental Protection Agency (EPA) Proposed National Emission Standards for Hazardous Air Pollutants—Ethylene Oxide Emissions Standards for Sterilization Facilities Residual Risk and Technology Review Reconsideration**

Dear Mr. Langloss:

The Advanced Medical Technology Association (“AdvaMed”) submits the following comments on the U.S. Environmental Protection Agency’s (EPA’s or Agency’s) reconsideration of the National Emission Standards for Hazardous Air Pollutants (“NESHAP”) - Residual Risk and Technology Review for Ethylene Oxide published in the Federal Register on March 17, 2026 (“Reconsideration”).

AdvaMed is the largest association representing companies that develop lifesaving, life-enhancing medical technology innovations for patients nationwide and around the world. We represent more than 650 companies supplying the sterile devices upon which Americans depend. Our members create and manufacture IV tubing, blood sample kits, surgical tools, heart valves, pacemakers, syringes, catheters, and much more serving patients in every healthcare setting. Many of AdvaMed’s members use and rely on ethylene oxide (EtO) as an essential infection prevention measure to sterilize the critical equipment they develop and manufacture used in surgeries, testing, and other life-changing medical care.

The medtech industry is committed to protecting and improving public health. We welcomed the prior issuance of the updated NESHAP standards and appreciated EPA’s efforts in its development. Even before the rule was finalized in 2024, many facilities had already implemented significant investments in advanced controls and abatement technology to reduce emissions and support ongoing process improvements. We have also worked with EPA and the Food and Drug Administration (FDA) to ensure our facilities have remained operational while installing



technologies to meet new standards. As EPA's regulatory work advances, we continue to place the highest priority on the safety of our communities, employees, and the millions of patients we serve.

Further, the medtech industry has consistently reinforced that rulemaking must be scientifically sound and grounded in the best, most current available science. We have long supported updates to emissions standards as knowledge and technology have evolved. While we supported issuance of the 2024 rulemaking, many scientific, technical, and legal questions have remained after its issuance, particularly around the residual risk assessment used. Consequently, these issues are not new that are now being formally examined through the reconsideration process. Our comments will cover several areas previously raised in our feedback to the docket.

It is also important to note that fulfilling the responsibility of the ample provision of sterile medical technology is not only critical and an ethical obligation from manufacturers to customers, but it is also a regulatory requirement. FDA requirements for safe, effective medical technology ensure the sterility of products reaching patients. The medtech industry has worked in partnership for decades with the FDA and EPA in achieving product sterility for patients while also protecting the health of employees at sterilization facilities and the communities around those facilities.

EtO sterilized devices can be found in many healthcare procedures from a standard blood draw during an annual physical to a complex surgical procedure such as an open-heart surgery. EtO sterilization is crucial for preventing infection in patients. Medical device sterilization represents a tiny fraction of commercial use of EtO, representing only half of 1 percent of all commercial use, yet it sterilizes half, or 20 billion, of all medical devices used in the U.S. every year.

As EPA itself recognizes, it is the only effective, viable sterilization method for many medical devices. For these sensitive and intricate devices, there is no existing alternative method for sterilization. EtO allows for the sterilization of many critical medical technologies and devices that otherwise would be destroyed or unsafe by other sterilization methods as they would not be able to ensure sterilization without affecting the integrity and function of the device. Disruption to critical sterilization of medtech would prevent the use of many lifesaving technologies that have advanced medical care over the past 50 years.

Millions of surgeries, outpatient and inpatient, hospitalizations, childbirth, and much more demand a wide array of sterile medtech. The criticality of sterilization for medtech to U.S. healthcare and ensuring our national security is a public health imperative. The supply chain underpinning those procedures is vital, and any disruptions could cause delays in care.

It is important to consider that EtO sterilization of medical devices takes many forms. In the first place, some manufacturers sterilize their own devices in-house, while others contract with commercial sterilizers or other manufacturers. Notably, the proposed reconsideration therefore



affects not only sterilization facilities within the source category, but medical device manufacturers who do not use EtO themselves.

Additionally, sterilization facilities are not all designed and engineered in the same manner. AdvaMed member companies vary in many ways, including with respect to products and packaging, cycle design, equipment, facility design and configurations, process, and geographies. As EPA notes, these are not uniform operations—there is no “one-size-fits-all” approach to the medical technology industry. Thus, ensuring flexibility to meet the needs of the diverse products and processes to ensure innovation and technological advancements is essential to prevent any delays in lifesaving, life-enhancing, and timely patient care.

Furthermore, EtO sterilization facilities are already at capacity in the U.S. because of high demand for sterile medtech in our healthcare system. Thus, taking even a few facilities offline, or abrupt or otherwise infeasible implementation, could jeopardize the timely provision of medtech and cause delays in patient care. FDA has shared this view. For many years, the EPA has recognized these critical factors by allowing additional time as authorized under the Clean Air Act (CAA) to ensure facilities can plan, access and deploy technologies, and remain operational while meeting rigorous standards. Notably, disruptions in the ability to sterilize medtech domestically could shift critical medical supply chains overseas, threatening our national sterile infrastructure. In short, patient care, public health preparedness, and national security all depend on a stable, domestic sterilization infrastructure.

An essential consideration in any rulemaking is adopting standards that are implementable in practice and grounded in the best available science. The medtech industry is committed to transforming lives by improving health outcomes, which includes environmental stewardship of the process for sterilizing the medical technologies critical for serving patients around the clock in our healthcare system.

Our membership places the highest priority on the safety of our communities, employees, and millions of patients we serve, and we support reasonable and balanced science-based regulations. We continue to stand ready as a collaborative and cooperative stakeholder in responding to implementation of requirements across a variety of regulations and initiatives that help supply the American people with the most innovative medical technology in the world while protecting community members and employees.

We appreciate the opportunity to provide our technical comments and thank the Agency for its efforts in the reconsideration. We provide further comments below related to questions posed in the Federal Register notice.



## Specific Comments

### **I. The Residual Risk Assessment warrants reconsideration, particularly as it does not provide a realistic assessment of ethylene oxide risk [Proposed Rule generally; Risk Assessment and Analyses (Q-4 to Q-5)]**

AdvaMed appreciates EPA's decision to reconsider aspects of its regulatory approach to EtO, including the residual risk assessment that underpins several elements of the prior proposal. We support the reconsideration as an important opportunity to ensure that the Agency's final regulatory decisions are grounded in sound science and accurately reflect real-world conditions.

Notwithstanding EPA's reconsideration, AdvaMed's underlying concerns with the residual risk assessment remain unchanged. Like many stakeholders, we continue to believe that the residual risk assessment relies on assumptions and modeling choices that materially overstate health risks from EtO emissions. In particular, the assessment appears to arrive at an inaccurately and unjustifiably low inhalation unit risk value by applying a model that does not appropriately account for background levels of EtO that occur naturally and ubiquitously in the environment and in human biology.

As EPA notes, EtO is present in ambient air from a wide range of sources unrelated to commercial sterilization and is also produced endogenously by normal human metabolic processes. Yet the current residual risk assessment does not adequately reconcile modeled risk estimates with these well-documented background levels or with observed disease incidence in the general population.

AdvaMed remains concerned that the modeling approach used in the residual risk assessment—particularly the reliance on steep low-dose extrapolation—produces risk estimates that are not supported by the weight of epidemiological, toxicological, and biological evidence. Multiple independent scientific reviews have identified similar issues, including concerns that the selected model overpredicts risk at low exposure levels and yields results that are inconsistent with real-world population data. These concerns have been raised by state regulators, academic experts, and advisory bodies, underscoring that they are not unique to the medical technology sector.

A more comprehensive discussion of these scientific issues is covered in the attached expert report prepared by toxicologist Dr. Lucy Frasier, Ph.D., DABT, which synthesizes and explains the most significant concerns with EPA's 2016 EtO IRIS assessment along with a supplemental review of recent studies related to dose-response models and human exposure. That report details the limitations of the current modeling approach, including its failure to meaningfully integrate background exposure and its divergence from established risk-assessment best practices.

As we have long stated, a residual risk assessment that does not reasonably align modeled risk with observed population-level health outcomes risks undermining confidence in the regulatory



foundation of the rule. We therefore support EPA's reconsideration of the residual risk assessment and ensuring that any final regulatory determinations reflect a balanced, scientifically grounded evaluation of risk.

**II. The proposed emission standards for aeration room vents are appropriate considering low inlet concentration and practical limitations of the technology and should take into account manufacturer-guaranteed levels of EtO reduction. [Q-7 to Q-8]**

AdvaMed appreciates EPA's review of the proposed emission reduction levels for new aeration room vents (ARVs) at facilities using at least 10 tons per year of EtO. As previously commented, the total amount of residual EtO making its way to the ARV is typically small, sometimes even below the detectible limit. Further, as EPA knows, industry continually strives to reduce the amount of residual EtO on products and packaging before moving them to the aeration room. These cycle and process elements reduce the amount of EtO present at every downstream stage and at the facility overall. At these low inlet concentrations, percent-reduction requirements become increasingly difficult to achieve, even when overall emissions are lower. In effect, standards based solely on destruction efficiency can penalize facilities that have already reduced EtO at the source, without delivering meaningful additional public health benefit. Essentially, the more EtO present in the aeration room, the easier it will be to comply.

Further, at these low concentrations EPA's proposed approach will ensure emission reduction requirements at levels that do not exceed the practical capabilities of available measurement methods. Otherwise, the standards will operate at or very near the lower limits of detection for EtO, where reliable measurement is highly sensitive to ambient conditions such as humidity, temperature, altitude, and air density. At these levels, some approved or proposed test methods do not consistently achieve the necessary detection thresholds or produce reproducible results. This creates compliance uncertainty that is unrelated to actual emissions performance and undermines confidence in compliance determinations. In this context, EPA would advance both regulatory clarity and environmental protection by aligning emission standards with what can be reliably measured using proven methods under real-world operating conditions.

Finally, as part of its reconsideration, EPA should consider manufacturer (or vendor)-guaranteed performance levels when evaluating appropriate emission reduction requirements for new ARVs. Control equipment vendors design, test, and warrant their systems based on demonstrated, repeatable performance across a range of operating conditions. Those guaranteed reduction levels reflect the technological limits of control systems when inlet concentrations are low. When vendors cannot guarantee or make claims with the ARV destruction and removal efficiency set forth in the 2024 rule, this leaves manufacturers in an untenable position. Incorporating manufacturer guarantees into EPA's assessment of feasible emission reduction levels would better align regulatory standards with commercially available technology, ensure emissions



controls remain robust and enforceable, and avoid imposing requirements that are technically unattainable or unverifiable in practice. Consistent with our longstanding comments, the proposed updates to ARV will address some of these key considerations.

**III. Flexibility in compliance option, including parametric monitoring and performance testing or continuous emissions monitoring systems, should be provided to allow for demonstration of compliance across diverse sterilization operations. [Q-9 to Q-10]**

AdvaMed continues to believe that all facilities should be provided the flexibility to demonstrate compliance with the Commercial Sterilization Facilities NESHAP either through parametric monitoring combined with performance testing or through the use of continuous emissions monitoring systems (or CEMS). This flexible framework has been in place for years, is well understood by regulated facilities, and has proven effective in ensuring compliance while accommodating diverse sterilization operations.

Building flexibility into the monitoring and testing provisions of the NESHAP is critical given the significant variation across sterilization facilities in size, configuration, equipment, and processes. Not all EtO sterilization facilities are designed or engineered in the same manner. Consequently, how one site achieves acceptable air emission control may not work for another site. Providing compliance options ensures that facilities can select the monitoring approach for their operations while achieving EPA's environmental protection objectives.

Parametric monitoring has long been an accepted and reliable component of the existing compliance framework under Subpart O. By tracking operating parameters that are directly correlated with emissions control performance, parametric monitoring provides continuous assurance that control systems are functioning as intended under normal operating conditions. This approach is especially well suited to batch processes and low-concentration environments.

At the same time, AdvaMed recognizes that EtO CEMS can be an appropriate compliance tool and facilities should retain the option to use CEMS for their diverse sterilization facilities. Preserving both compliance pathways—rather than prescribing a single monitoring one-size-fits all method—allows the rule to function effectively across facilities of varying complexity and scale.

As EPA conducts its review, AdvaMed reiterates its support for a flexible monitoring framework that permits compliance through either parametric monitoring and performance testing or EtO CEMS. AdvaMed previously submitted a proposal for parametric monitoring to EPA, which was included as an appendix to our comments. As described there, this approach provides the



flexibility necessary to accommodate diverse and complex facility configurations while allowing companies to demonstrate emissions control and conduct ongoing monitoring to ensure operations remain within established parameters.

**IV. Feasibility and overall implementation should be considered in the evaluation of permanent total enclosure requirements as a compliance option. [Q-11 to Q-13]**

AdvaMed has consistently raised concerns that EPA has significantly underestimated the costs and practical challenges associated with implementing permanent total enclosures (PTEs) across a diverse population of sterilization facilities. Those concerns remain unchanged. Based on our review of the proposed reconsideration, it also appears that facilities may still be required—depending on state implementation—to comply with PTE requirements. EPA states that “the proposed change would not affect the permitting process for any state” and that states may continue to make case-by-case determinations regarding whether PTE is required for a given facility. This aspect of the proposal warrants greater clarity, particularly given the differing challenges PTE requirements impose across facilities of different size, configuration, and complexity.

From both a technical and economic perspective, we have noted that PTE may not be achievable or cost-effective for many facilities. Medical device manufacturers and commercial sterilization facilities have already invested millions of dollars in primary emissions control technologies that capture the vast majority of EtO emissions. By contrast, PTE requirements would necessitate substantially higher capital investment to address only a small fraction of remaining fugitive emissions. Notably, the cost for compliance with PTE requirements of the NESHAP, especially at facilities with both manufacturing and sterilization operations, has proven to be extremely costly and disruptive to manufacturing operations that must meet stringent clean-room requirements.

Implementing a PTE with routing to a control device requires significant facility alterations. In many cases, the area where products are packaged may be on the opposite side of a facility from the sterilization activities and existing control system. In these circumstances, the Group 2 room may need to be relocated within a facility before construction of a PTE can even begin. In other cases, facilities may not be able to relocate natural draft openings or exhaust points to comply with Method 204 requirements, necessitating a broad redesign of the facility. These changes require significant time and coordination and may be incompatible with the physical realities of existing facilities.

Further, the steps required to implement PTE are complex and sequential: site evaluation to inform design, engineering and design, state and local permitting, fabrication and construction, installation, commissioning and validation, and updates to operating and maintenance procedures. Even where some tasks can proceed in parallel, others cannot, resulting in long



implementation timelines and extended downtime. The associated costs include not only design and construction but also testing, validation, lost capacity during installation, and ongoing operational impacts.

At the same time, EPA has underestimated the costs of implementation. Real-world experience from AdvaMed members demonstrates that actual PTE implementation costs are far higher—often orders of magnitude higher—than EPA’s estimates. Vendor quotes have ranged from approximately \$10 million to \$25 million per facility. In at least one case, the cost of PTE installation translated to roughly \$100,000 per pound of EtO emissions reduced. These figures far exceed EPA’s estimate of approximately \$100 million in total costs across commercial sterilization facilities.

Notably, room air emissions have historically been unregulated in part because EtO concentrations in Group 1 and Group 2 room areas are extremely low and, in many cases, at or near non-detectable levels. These low concentrations are difficult to measure reliably and challenge the practical ability to demonstrate high percentage reductions when measurements approach the limits of detection. Against this backdrop, the high outlay to create a PTE where even feasible and additional abatement infrastructure that could handle the required airflow appears disproportionate to the limited emissions reductions that could realistically be achieved.

Finally, we appreciate EPA’s consideration that a one-size-fits-all solution may not work optimally with diverse and varied facility designs, workflows, and operational constraints. Facilities differ widely in how sterilization, aeration, packaging, and distribution functions are configured and co-located. In some cases, the scope and cost of retrofitting existing facilities to accommodate PTE requirements would be so extensive that constructing a new facility may be more economical than renovating the existing one.

For these reasons, we appreciate EPA’s effort to conduct its review as part of the reconsideration and to seek greater clarity regarding how state permitting authorities may apply these requirements in practice. We concur that flexibility should be considered in ensuring that facilities of varying size, configuration, and complexity can continue to operate safely, ensure compliance, and maintain the reliable supply of critical sterile medical technologies

**V. Additional clarification through technical corrections and clear definitions could assist regulated entities and permitting authorities in practical implementation of the proposed requirements. [Q-14 to Q-15, Q-17]**

AdvaMed has consistently raised that clear and understandable technical provisions are key to ensuring that the standards are implemented as intended, reflects real-world operations, and avoids unintended consequences. Ambiguity increases the risk of uncertainty and inconsistent implementation. Notably, we concur that the definition of “operating day” should relate to when



sterilization operations are active (when sterilizer, aeration, or post-sterile product areas are in operation with ETO in use or sterile product is actively in aeration or post-sterilization storage) rather than broadly sweeping to an entire facility, including operations unrelated to sterilization. Similarly, clarity would also be helpful in ensuring understanding of what is defined as “sterilization operation.”

In that vein, we continue to support technical updates that support practical implementation and reflect the capabilities of available technologies rather than one-size-fits-all solutions. For example, we agree with the technical edit proposed to indicate that CEMS measurement points need not be equidistant so long as the response times are similar. Technology can be configured to accommodate both line length and time sharing. As long as the technology is capable of accounting for these variables, this should be acceptable.

**VI. An adequate timeline for compliance should be considered for facilities consistent with authorities and timelines permitted under CAA to ensure sufficient predictability and continuity of the healthcare supply chain. [Q-20]**

AdvaMed has long supported issuance of the EtO NESHAP and recognized the importance of rigorous regulation that protects communities while ensuring a stable supply of lifesaving technologies for patients. Rulemaking must take care importantly not to disrupt the critical medical device supply chain that doctors and patients rely on.

The medtech industry has also reiterated that supply chain and capacity impacts would be grave if we have an insufficient or overly condensed implementation period. There are complex facilities and no two are alike. Time is critical to ensure planning, upgrades and reconfiguration can be done that meet process safety management obligations safely and are operationally possible with minimal impact to the healthcare supply chain. As we have previously commented, AdvaMed had requested that EPA adjust the proposed compliance schedule so that existing facilities have at least 4 to 5 years from the effective date of the final NESHAP before any new standards take effect. Essentially and at a minimum, this would represent the CAA’s 3-year compliance schedule plus a statutorily permitted 1-year blanket extension at a minimum to allow existing facilities time to come into compliance, address compliance questions with state agencies, and provide additional time flexibility for addressing supply chain considerations. This is necessary considering the wide scope of changes necessitated and assumes that provisions are reasonable and technically feasible. Such predictability is critical as uncertainty risks failure of the supply chain.

EPA itself has long recognized the significance of sufficient implementation time as an essential aspect of implementation of updated standards for commercial sterilizer facilities. In issuance of the 2024 final rule, EPA acknowledged the importance of time to implement the regulation while safeguarding the supply chain and ensuring our national capacity for sterile medical



technologies. The Agency in its 2024 rulemaking increased the time to the maximum allowed under the CAA along with citing the availability of waiver authorities for an additional two years to support implementation. The following year, the Administration executed such authorities under the CAA to implement the waiver process through provision of the presidential waiver authorities. Notably, waivers are an extension of time for compliance—not an exemption from regulation. All standards must be met following the time period for implementation and facilities are expected to come into full compliance. Without reasonable transition time for, facilities would otherwise all be forced to go offline at the same time with serious implications for U.S. healthcare, which could result in disruption to the availability of medical devices and adversely affect the public health. Sterilization is already at capacity in the U.S. and various stakeholders, including U.S. EPA, FDA, Small Business Administration, and many healthcare institutions, physician groups, and industry organizations have all raised concerns that efforts should be made to ensure that medical technologies remain available and there is no disruption to the medtech supply chain for patients.

With this in mind and amidst the reconsideration, we would respectfully request adequate time be provided following issuance of the final standards given the complexity and time requirements for safe implementation. Ideally, this can be accomplished through establishing a compliance deadline of two years from the date of issuance of final amendments. This could be accomplished through clearly outlining the implementation timeline in the final action so that all facilities can ensure the updates can be done safely with minimal impact to the supply chain.

## **VII. Flexibility and coordinated implementation of the EtO NESHAP will help maintain U.S. sterilization capacity. [Q-21]**

We appreciate EPA's recognition of the importance of maintaining the infrastructure necessary to support safe and effective sterilization of medical devices relied upon throughout the U.S. healthcare system. Notably, the proposed amendments do not eliminate or unwind the EtO NESHAP framework. Many of the EtO emission limits and underlying requirements will remain in place and unchanged, and the pollution control technologies expected to be installed under the revised rule will be similar, if not identical, to those required under the 2024 final rule.

The proposed revisions provide additional flexibility in how facilities may demonstrate compliance and more closely align regulatory expectations with the capabilities of existing and demonstrated technologies. Even with this added flexibility, facilities will still be required to undertake significant capital investments and operational upgrades to meet the revised standards. Installation of these controls is expected to result in temporary reductions in sterilization capacity as upgrades are carefully scheduled around ongoing operations to ensure worker safety and product quality.

For these reasons, we continue to recommend that EPA allow sufficient implementation time so that required upgrades can be completed safely and in a manner that minimizes disruption to the



healthcare supply chain. While it remains uncertain whether the proposed amendments will reduce the number of facility closures, construction and retrofitting activities, particularly those associated with Group 2 room air emission controls, will still require substantial facility re-design and construction. These activities will result in manufacturing downtime and may affect the volume of medical devices that can be produced at facilities.

Given these realities, we strongly encourage EPA to continue close coordination with the FDA to anticipate and mitigate potential production disruption, curtailment, and site closures to the greatest extent possible. Such coordination remains essential to ensuring that implementation of the EtO NESHAP continues to protect public health and the environment while also preserving patient access to sterile medical devices.

### VIII. Conclusion

AdvaMed appreciates EPA's undertaking of the reconsideration and its focus on protecting human health and the environment while also considering the importance of safeguarding our U.S. healthcare supply chain and national security. We value our longstanding collaboration with EPA and FDA, which has advanced significant progress in reducing ethylene oxide exposure while recognizing the importance of rigorous environmental protection and safeguarding of the public health. As EPA considers the path forward, it is critical that any final standards remain flexible, achievable with existing technologies and compliance timeline, and applicable across the wide range of facility designs and sterilization processes subject to subpart O. Clear, predictable, and science-based requirements are essential to ensuring effective implementation while ensuring the reliable supply of the lifesaving and life-enhancing medical technologies on which patients depend. AdvaMed and its members look forward to continued constructive engagement to advance these shared public health goals.

Sincerely,

*Khaterah Calleja*

Khaterah Calleja  
Senior Vice President  
Technology & Regulatory Affairs

(Enclosure)

Attachment: Dr. Lucy Frasier, Ph.D., DABT, Comments on the U.S. Environmental Protection Agency's Proposed Amendments to the National Emission Standards for Hazardous Air Pollutants (NESHAP); Ethylene Oxide Emissions Standards for Sterilization Facilities Residual Risk and Technology Review Reconsideration (May 11, 2026).





May 11, 2026

VIA E-MAIL

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**Re: Comments on the US Environmental Protection Agency’s National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Emissions Standards for Sterilization Facilities Residual Risk and Technology Review Reconsideration**

Dear Ms. Calleja,

This letter responds to the Advanced Medical Technology Association’s (AdvaMed’s) request for expert analysis in connection with the United States (US) Environmental Protection Agency’s (EPA’s) *National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Emissions Standards for Sterilization Facilities Residual Risk and Technology Review Reconsideration*. I reviewed the risk assessments<sup>1</sup> reflected in the 2024 revision to the Commercial Sterilization Facilities National Emission Standards for Hazardous Air Pollutants (NESHAP), which was based on a residual risk and technology review (RTR). My feedback is intended to supplement previous analyses included in AdvaMed’s 2023 docket comments.

The comments in this letter focus on the following science-based questions on which EPA specifically solicited comment: I) Question 4: New or updated information relevant to dose-response model selection; and II) Question 5: New or updated studies on human exposure to EtO, including information on occupational, background, or endogenous exposures not yet considered by the Agency.

The *Residual Risk Assessment for the Commercial Sterilization Facilities Source Category in Support of the 2022 Risk and Technology Review Proposed Rule*<sup>2</sup> that underlies the NESHAP proposal does not

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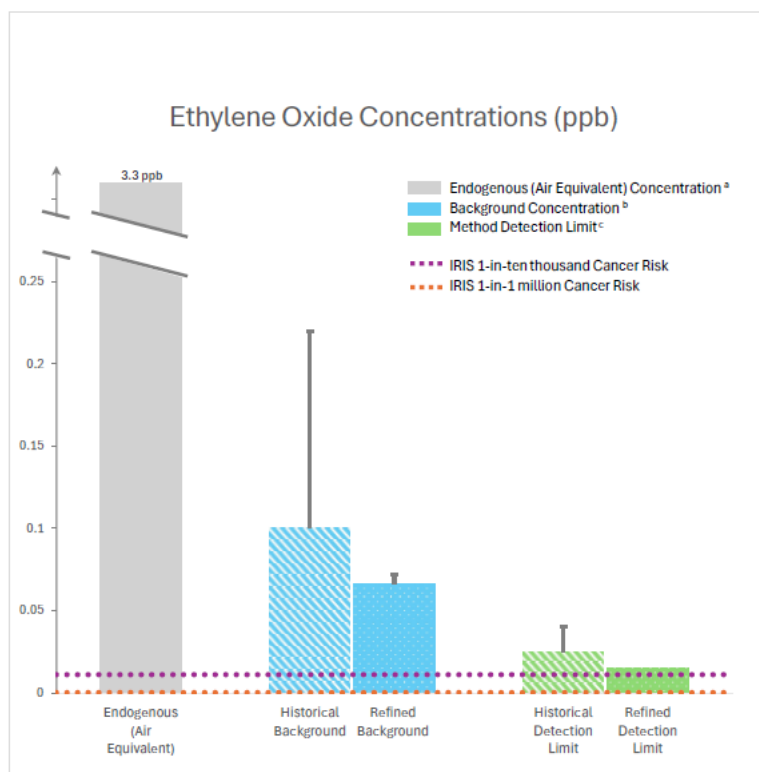
<sup>1</sup> EPA (2022). US Environmental Protection Agency. Residual Risk Assessment for the Commercial Sterilization Facilities Source Category in Support of the 2022 Risk and Technology Review Proposed Rule; EPA (2023). US Environmental Protection Agency. Addendum to “Draft Human Health and Ecological Risk Assessment in Support of Registration Review” - Inhalation Exposure Risk Assessment in Support of Registration Review. March 27.

<sup>2</sup> EPA (2022). Residual Risk Assessment for the Commercial Sterilization Facilities Source Category in Support of the 2022 Risk and Technology Review Proposed Rule. p. 16. December.

provide a realistic assessment of the health and environmental risks that remain after implementation of the NESHAP or whether the continued use of EtO as a sterilant poses an unreasonable risk when based on the 2016 IRIS value.

There are at least two different *practical* issues with EPA’s 2016 IRIS value, which are illustrated in **Figure 1** and discussed below.

**FIGURE 1: PRACTICAL ETO COMPARISONS**



**FIGURE NOTES**

- a. Kirman et al. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, 22(4), 597.
- b. Historical Method TO-15 (diagonal stripes): National Air Toxics Trends Stations and Urban Air Toxics Monitoring Program stations October 1, 2018 – March 31, 2019. [https://www.epa.gov/sites/default/files/2019-11/documents/data\\_summary\\_stations.pdf](https://www.epa.gov/sites/default/files/2019-11/documents/data_summary_stations.pdf); Refined Method TO-15A (dotted): Kirman et al. (2025)
- c. Historical Method TO-15 (diagonal stripes): Willowbrook, IL Ethylene Oxide Concentrations in Outdoor Air [ug/m3] - 24 Hour Samples. <https://www.epa.gov/il/outdoor-air-monitoring-willowbrook-community>; Refined Method TO-15A (dotted): Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. *ACS Es&t Air*, 1(8), 747-754.

First, EtO levels reflect a stressor to which humans are expected to have evolved and adapted over millions of years. This likely means that there is an EtO level (in the range of endogenous EtO production) below which DNA damage, a precursor to cancer, does not occur (because biological defenses prevent it).<sup>3</sup>

<sup>3</sup> Tates, A. D., P. J. Boogaard, F. Darroudi, A. T. Natarajan, M. E. Caubo, and N. J. van Sittert (1995). Biological effect monitoring in industrial workers following incidental exposure to high concentrations of ethylene oxide. *Mutation Research*, 329:63–77; Tompkins, E. M., K. I. McLuckie, D. J. Jones, P. B. Farmer, and K. Brown (2009). Mutagenicity of DNA adducts derived from ethylene oxide exposure in the pSP189 shuttle vector replicated in human Ad293 cells. *Mutation Research*, 678:129–37.

The **gray bar in Figure 1** represents the **endogenous EtO** air equivalent estimated by Kirman et al. (2025),<sup>4</sup> the derivation of which is discussed in Section II B (i) of this letter. Analyses of the National Institute of Occupational Safety and Health (NIOSH) cancer data have suggested increases in male lymphohematopoietic cancer in the highest cumulative exposure groups *only*, which is consistent with exceeding biological repair mechanisms only at high exposures. Smoking has not been associated with any of the various lymphohematopoietic cancers, despite the fact that EtO is a component of tobacco smoke and DNA adducts attributable to EtO are more than an order of magnitude higher in smokers (i.e., smokers are exposed to much higher EtO levels).<sup>5</sup> This also supports the notion that there is an exposure level below which EtO-induced cancer does not occur. However, regardless of whether EtO can be demonstrated to have a true threshold dose-response, low exposures to external (exogenous) EtO in air are much lower than endogenous EtO levels, as reflected by endogenous air equivalents, implying no detectable increase in risk due to EtO exposures from ambient air.<sup>6</sup>

The **blue bars in Figure 1** represent **background EtO** concentrations in ambient air (the diagonal stripe bar represents historical measurements via EPA Method TO-15<sup>7</sup> and the dotted bar represents refined measurements via EPA Method TO-15A<sup>8</sup>). Based on the 2016 IRIS value, the EtO air concentration corresponding to a **1-in-10 thousand** (100-in-1 million) target cancer risk is represented by the **purple dotted line** and the **1-in-1 million** target cancer risk is represented by the **red dotted line**. As **Figure 1** illustrates, the background EtO concentrations to which everybody across the US is exposed are considerably higher than air concentrations corresponding to EPA's IRIS value. Specifically, background concentrations range from approximately 10 times to more than 100 times the concentrations corresponding to EPA's targeted cancer risks based on the 2016 IRIS value. This implies that further restricting EtO emissions is unlikely to materially affect ambient background concentrations, regardless of how stringent EtO regulations become.

**Analytical detection limits** *potentially* achievable for EtO in air samples are represented by the **green bars in Figure 1**. The detection limits range from *approximately* 0.015 ppb (refined EPA Method TO-

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<sup>4</sup> Kirman et al. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, 22(4), 597.

<sup>5</sup> CR Kirman, AA Li, PJ Sheehan, JS Bus, RC Lewis & SM Hays (2021) Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management, *Journal of Toxicology and Environmental Health, Part B*, 24:1, 1-29.

<sup>6</sup> Kirman, C.R.; Hays, S.M. (2017). Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. *Regulatory Toxicology and Pharmacology*, 91, 165–172; Kirman, C. R., Li, A. A., Sheehan, P. J., Bus, J. S., Lewis, R. C., & Hays, S. M. (2021). Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management. *Journal of Toxicology and Environmental Health, Part B*, 24(1), 1-29; Kirman, C. R., Sheehan, P. J., Li, A. A., Bus, J. S., Su, S. H., Dopart, P. J., ... & Reiss, R. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, 22(4), 597.

<sup>7</sup> National Air Toxics Trends Stations and Urban Air Toxics Monitoring Program stations October 1, 2018 – March 31, 2019. [https://www.epa.gov/sites/default/files/2019-11/documents/data\\_summary\\_stations.pdf](https://www.epa.gov/sites/default/files/2019-11/documents/data_summary_stations.pdf)

<sup>8</sup> Kirman et al. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, 22(4), 597.

15A) to 0.040 ppb (historical EPA Method TO-15) in specialized/optimized systems designed to detect trace concentrations.<sup>9</sup> As shown in **Figure 1**, detection limits for EtO air samples have consistently been higher than the air concentrations corresponding to EPA's IRIS value (~ two times to more than 100 times the IRIS value, depending on the target cancer risk level). Therefore, reductions in air concentrations potentially resulting from use of the 2016 IRIS value to regulate EtO emissions are unlikely to be confirmable because the analytical methods for EtO are incapable of detecting small changes against the backdrop of relatively high background levels.

The 2016 IRIS value implies very high cancer risks at low concentrations because the approach EPA used to develop the 2016 IRIS value assumes that a supra-linear relationship exists between low-level exposure, the formation of DNA lesions, and subsequent conversion into mutations, even though measurable increases in mutagenic events are only associated with relatively high EtO doses. However, recent studies that examine the plausibility of the different dose-response models that have been applied to the NIOSH cancer data for deriving an EtO IUR support a single-sloped dose-response model as biologically plausible, not the supra-linear dose-response model used in deriving the 2016 IRIS value.

The 2016 IRIS value is highly impractical as a basis for regulation because compliance with a level below widespread background levels cannot be demonstrated. The scientific debate surrounding the 2016 IRIS value is not merely academic; it has enormous regulatory and economic consequences.

#### **I. NEW STUDIES DO NOT SUPPORT THAT EtO IS A HIGHLY POTENT CARCINOGEN WITH A STEEP RISK AT LOW CONCENTRATIONS (QUESTION 4)**

In cancer risk assessment, observational data can be fit using different dose-response models with equivalent statistical validity, resulting in widely varying risk estimates. Estimating health effects associated with long-term exposure to low levels of air pollution based on occupational data representing high exposure levels presents key methodological challenges,<sup>10</sup> including the fact that dose-response relationships estimated within a traditional regression framework cannot simply be *assumed* to represent causal relationships and can be highly sensitive to model choice for both the shape of the dose-response curve and the adjustment for confounding.

The Science Advisory Board (SAB)<sup>11</sup> has advised EPA that any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data.<sup>12</sup> Because EtO is produced endogenously (internally), it is expected that detoxification processes and DNA repair enzymes are present in the human body and have evolved to

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<sup>9</sup> EPA (2021a). US Environmental Protection Agency. Effect of Canister Type on Background Ethylene Oxide Concentrations. May 7, 2021. <https://www.epa.gov/sites/default/files/2021-05/documents/ord-eto-canister-background-memo-05072021.pdf>; EPA (2021b). U.S. Environmental Protection Agency. Technical Note: The Ethylene Oxide (EtO) Canister Effect. May 25, 2021. <https://www.epa.gov/sites/default/files/2021-05/documents/technical-note-on-eto-canister-effect-052521.pdf>; Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. *ACS Es&t Air*, 1(8), 747-754.

<sup>10</sup> Dominici F, Schwartz J, Di Q, Braun D, Choirat C, Zanobetti A (2019). Assessing Adverse Health Effects of Long-Term Exposure to Low Levels of Ambient Air Pollution: Phase 1. Health Effects Institute (HEI), Report No. 200.

<sup>11</sup> EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. Appendix I, p. I-9.

<sup>12</sup> EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. Appendix I, p. I-2 and I-3.

efficiently detoxify and/or repair DNA adducts in the range produced inside the body. This suggests a no more than linear low-dose response component near the endogenous range with a transition to a steeper dose-response slope at some point above the endogenous range, where the body can no longer effectively detoxify EtO and/or repair the EtO-induced DNA damage. This describes a sub-linear dose-response, not the supra-linear dose-response model used by EPA. EPA made the following acknowledgements in its 2016 IRIS evaluation:

“EPA considers it highly plausible that the dose-response relationship over the endogenous range is sublinear (e.g., that the baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work more effectively for lower levels of endogenous adducts), that is, that the slope of the dose-response relationship for risk per adduct would increase as the level of endogenous adducts increases.”<sup>13</sup>

“The EPA is not aware of a mechanistic explanation for the shape of the exposure-response relationship in the NIOSH cohort...”<sup>14</sup>

Thus, it appears that EPA did not seriously consider biological plausibility in selecting the dose-response model used to derive the 2016 IRIS value. The debate surrounding the linearity of low-dose effects related to genotoxicity and cancer has been ongoing for decades.<sup>15</sup> New studies published after the 2024 Commercial Sterilizer final rule that inform the shape of the EtO dose-response are discussed in Sections A and B, below.

#### A. Valdez-Flores’ (2025) Updated Mortality Study

Using analyses of a 10-year update of the Union Carbide Corporation (UCC) worker cohort as an external dataset, Valdez-Flores et al (2025)<sup>16</sup> examined the plausibility of the different dose-response models that have been applied by EPA and other regulatory agencies to the NIOSH cancer data to derive IUR (inhalation unit risk) factors for EtO. Despite relying on the same study of sterilization workers that was conducted by NIOSH, EPA and the Texas Commission on Environmental Quality (TCEQ) derived EtO cancer risk estimates from the NIOSH data that differed by more than three orders of magnitude, even though both used linear (non-threshold) extrapolation. EPA<sup>17</sup> used a steep two-piece linear spline Cox Proportional Hazards (CPH) model, while TCEQ (2020)<sup>18</sup> applied a nearly linear single sloped standard (log-linear) CPH model to the NIOSH mortality study. The slopes for both models are essentially linear at the lower exposure levels, but the slope of the EPA two-spline model is very steep.

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<sup>13</sup> EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. p. 4-95. (emphasis added).

<sup>14</sup> EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. Appendix I, p. I-29.

<sup>15</sup> Klapacz, J., Pottenger, L. H., Engelward, B. P., Heinen, C. D., Johnson, G. E., Clewell, R. A., ... & Andersen, M. E. (2016). Contributions of DNA repair and damage response pathways to the non-linear genotoxic responses of alkylating agents. *Mutation Research/Reviews in Mutation Research*, 767, 77-91.

<sup>16</sup> Valdez-Flores, C., Li, A. A., Bender, T. J., & Teta, M. J. (2025). Use of updated mortality study of ethylene oxide manufacturing workers to inform cancer risk assessment. *Risk Analysis*, 45(9), 2822-2837.

<sup>17</sup> EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. December, 2016.

<sup>18</sup> TCEQ (2020). Texas Commission on Environmental Quality. Ethylene Oxide Carcinogenic Dose-Response Assessment. May 2020.

Steenland et al.'s (2004) evaluation of the NIOSH cohort found no statistically significant excesses in males and females combined for all lymphohematopoietic cancers. However, a statistically significant exposure–response relationship was observed in males for all lymphohematopoietic cancers combined, but *only at the highest cumulative dose*. Steenland et al.(2004) did not, however, find a statistically significant exposure-response relationship in females (the slope was negative). Hence, Steenland et al. (2004) analyzed male and female lymphoid cancer separately. Valdez-Flores' (2025) analyses of the NIOSH study data were generally consistent with those of Steenland et al (i.e., increased lymphoid cancer mortality in males only at the highest exposure category). However, analyses of the updated UCC cohort by Valdez-Flores et al. (2025) did not indicate any statistically significant excess lymphohematopoietic cancer mortality.

EPA's conclusion that the NIOSH study supports a steep risk at low exposures is based primarily on the fact that, of the large number of curve-fitting models and lag times assessed, the only one that produced a statistically significant positive slope for lymphoid cancer mortality in males was the supra-linear log cumulative exposure model with a 15 year lag. Another rationale given by EPA for using the supra-linear model was “visual fit” of a few non-parametric categorical rate ratios (to surmise the shape of continuous models), even though visual fit models are subjective and depend on how data are presented. EPA (2016)<sup>19</sup> combined male and female lymphoid cancers to estimate the cancer potency of EtO in its final risk assessment, despite evidence of differences in exposure-response patterns in men and women in the NIOSH cohort, as acknowledged by Steenland et al. (2004). According to Valdez-Flores et al. (2025), when combined with male data, the female data in the low exposure region erroneously alters the perception of the slope as a steep exposure response. Moreover, Valdez-Flores et al. (2025) indicate that neither model had a superior visual fit to the data when the data were normalized along the y-axis and different implicitly estimated baseline risks were accounted for. Valdez-Flores et al.'s 2025 analyses of the updated UCC cohort did not identify any exposure-response trends, did not support an increased risk of lymphohematopoietic cancer, and provide no indication of a steep slope at low exposures, as concluded by EPA. Based on their combined analyses of the NIOSH and UCC cohort studies, Valdez-Flores et al. (2025) concluded that there is no evidence that EtO is a highly potent carcinogen consistent with a steep increase in risk at low exposures and that the standard CPH model more plausibly describes the relationship between EtO exposures and lymphoid mortality in both the NIOSH and UCC cohorts.

#### B. Gollapudis' (2026) EtO Genotoxicity Dose-Response Investigation

The initiating event for EtO-induced mutagenicity and carcinogenicity is its reaction with the nucleophilic centers of DNA.<sup>20</sup> Therefore, the dose-response associated with EtO-induced genetic damage is relevant to determining which dose-response models are biologically plausible for deriving EtO cancer risks. To this end, Gollapudi et al. (2026)<sup>21</sup> investigated EtO-induced genetic damage to inform the

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<sup>19</sup> EPA (2016). US Environmental Protection Agency. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide. EPA/635/R-16/350Fa. December, 2016.

<sup>20</sup> Walker VE, Fennell TR, Upton PB, et al. Molecular dosimetry of ethylene oxide: formation and persistence of 7-(2-hydroxyethyl)guanine in DNA following repeated exposure of rats and mice. *Cancer Research*, 1992;52: 4328–34; Li F, Segal A, Solomon JJ. In vitro reaction of ethylene oxide with DNA and characterization of DNA adducts. *Chemico-Biological Interactions*, 1992;83:35–54.

<sup>21</sup> Gollapudi, B. B., Bus, J. E., Cassidy, P., Weinberg, J. T., Bemis, J. C., Torous, D. K., ... & Li, A. A. (2026). Investigation of Ethylene Oxide Genotoxicity Dose-Response to Inform Cancer Risk Assessment. *bioRxiv*, 2026-03.

biological plausibility of the various dose-response models (the log-linear CPH and 2-piece linear spline) that have been applied to the NIOSH cancer data. EtO is an alkylating agent that is capable of reacting with cellular macromolecules, including hemoglobin and DNA to produce several adducts including the major DNA adduct N7-2-hydroxyethylguanine (N7-HEG), which although not mutagenic, is a useful biomarker of exposure, and O<sup>6</sup>-2-hydroxyethylguanine (O<sup>6</sup>-HEG), which is a minor but mutagenic DNA adduct.<sup>22</sup> The scientific literature on EtO-induced DNA damage indicates that relatively high exposure concentrations and longer exposure durations are required to elicit genotoxic responses in experimental *in vivo* systems.<sup>23</sup>

Gollapudi et al. (2026) investigated the shape of the dose-response for the induction of *Pig-a* mutations and micronuclei (a reporter for cytogenetic damage) in erythrocytes, as well as other endpoints specific to a mutagenic mode of action, in mice. An exposure-dependent increase in the formation of both hemoglobin and N7-HEG DNA adducts was observed at all concentrations of EtO evaluated but mutagenic O<sup>6</sup>-HEG adducts were only detected in mice exposed to greater than 50 ppm EtO. The dose-response slopes for both adducts increased disproportionately *only* at higher EtO concentrations (i.e., ≥ 50 ppm), presumably after all detoxification and repair capacities were saturated. The shape of the observed dose-response for genetic damage was linear throughout the range of exposure, supporting a single-sloped dose-response model as biologically plausible. Importantly, the most abundant N7-HEG adduct, a biomarker of the critical target (i.e., DNA) showed no indication of a dose response pattern with an initial steeper linear slope that plateaus at higher concentrations, thus providing no evidence for the hypothesized 2-piece supra-linear spline dose-response model used in deriving the 2016 IRIS value for these endpoints and concentrations (0.05 to 200 ppm).

DNA repair capacity in humans is similar, if not better, than that of mice,<sup>24</sup> including O<sup>6</sup>-methylguanine-DNA methyltransferase, which is a highly conserved repair protein involved in the direct repair pathway of the pro-mutagenic O<sup>6</sup>-HEG and other O<sup>6</sup>-guanine alkyl adducts.<sup>25</sup> Moreover, EtO Physiologically-Based Pharmacokinetic (PBPK) modeling indicates that concentrations of EtO in blood are similar in mice and humans at EtO exposures less than 100 ppm, which suggests that EtO absorption,

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<sup>22</sup> van Sittert, N. J., Boogaard, P. J., Natarajan, A. T., Bates, A. D., Ehrenberg, L. G., & Törnqvist, M. A. (2000). Formation of DNA adducts and induction of mutagenic effects in rats following 4 weeks inhalation exposure to ethylene oxide as a basis for cancer risk assessment. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 447(1), 27-48; Kirman, C. R., & Hays, S. M. (2017). Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. *Regulatory Toxicology and Pharmacology*, 91, 165-172.

<sup>23</sup> Gollapudi, B. B., Su, S., Li, A. A., Johnson, G. E., Reiss, R., & Albertini, R. J. (2020). Genotoxicity as a toxicologically relevant endpoint to inform risk assessment: A case study with ethylene oxide. *Environmental and Molecular Mutagenesis*, 61(9), 852-871; Donner, E. M., Wong, B. A., James, R. A., & Preston, R. J. (2010). Reciprocal translocations in somatic and germ cells of mice chronically exposed by inhalation to ethylene oxide: implications for risk assessment. *Mutagenesis*, 25(1), 49-55.

<sup>24</sup> MacRae, S. L., Croken, M. M., Calder, R. B., Aliper, A., Millholland, B., White, R. R., ... & Vijg, J. (2015). DNA repair in species with extreme lifespan differences. *Aging (Albany NY)*, 7(12), 1171.

<sup>25</sup> Klapacz, J., Pottenger, L. H., Engelward, B. P., Heinen, C. D., Johnson, G. E., Clewell, R. A., ... & Andersen, M. E. (2016). Contributions of DNA repair and damage response pathways to the non-linear genotoxic responses of alkylating agents. *Mutation Research/Reviews in Mutation Research*, 767, 77-91; Roy, R., Shiota, S., Kennel, S. J., Raha, R., Wronski, M. V., Brent, T. P., & Mitra, S. (1995). A comparative study of the biochemical properties of human and mouse recombinant O<sup>6</sup>-methylguanine-DNA methyltransferases. *Carcinogenesis*, 16(2), 405-411.

distribution, metabolism and excretion are similar across the species.<sup>26</sup> These results provide a biologically plausible basis for selection of a statistical dose-response model for EtO human cancer risk assessment that is rooted in the widely accepted mode of action key events (i.e., mutation and cytogenetic damage) for EtO mutagenicity. The mode of action data derived from mice in this study and others collectively support selection of a single-sloped linear (CPH) dose response model for risk assessment of EtO carcinogenicity. Moreover, the following information argues against the biological plausibility of the 2-piece linear spline dose-response model: 1) EtO does not require metabolic activation for mutagenicity, which could lead to saturation at higher concentrations (and a plateau in the dose-response curve); 2) the highest exposure level in this study (i.e., 200 ppm) is twice the tumorigenic level in the carcinogenicity study using the same strain of mice;<sup>27</sup> and 3) no genotoxicity was detected at lower exposure levels, possibly as a result of efficient detoxification/DNA repair.

The dose response pattern for genetic damage, which is the first key event of the mutagenic mode of action for the carcinogenicity of EtO, supports the biological plausibility of a single-slope linear CPH, rather than the 2-piece spline supra-linear model for the derivation of inhalation unit cancer risk for EtO.

## II. NEW OR UPDATED STUDIES ON HUMAN EXPOSURE TO ETO NOT YET CONSIDERED BY THE AGENCY (QUESTION 5)

Human exposure studies published or updated since release of the final 2024 Commercial Sterilizer NESHAP are discussed in Sections A, B, and C, below.

### A. New or Updated Studies Suggesting Stronger Associations between EtO and Breast Cancer May be Biased as a Result of Inappropriate or Inadequate Control for Healthy Worker Survivor Effect (Question 5a)

The NIOSH cohort consisted of male and female workers employed in 14 commercial sterilizers across the US from the 1940's to the 1980's. Breast cancer incidence in female workers was evaluated by Steenland et al. (2003)<sup>28</sup> and breast cancer mortality was evaluated by Steenland et al. (2004).<sup>29</sup> The breast cancer incidence study (Steenland, 2003),<sup>30</sup> which was based on a cohort of 7,576 women in which a total of 319 breast cancers were observed, found no overall increase in breast cancer incidence (by comparison to the US general population) but an increased risk of breast cancer was observed for those in the highest cumulative exposure group in internal analyses (by comparison to randomly selected controls from a pool of women within the cohort that survived without breast cancer).<sup>31</sup> The breast cancer mortality study

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<sup>26</sup> Fennell, T. R., & Brown, C. D. (2001). A physiologically based pharmacokinetic model for ethylene oxide in mouse, rat, and human. *Toxicology and applied pharmacology*, 173(3), 161-175.

<sup>27</sup> NTP (1987). National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Ethylene Oxide (CAS No. 75-21-8) in B6C3F1 Mice (Inhalation Studies). Natl Toxicol Program Tech Rep Ser. 1987 Nov.

<sup>28</sup> Steenland, K., Whelan, E., Deddens, J., Stayner, L., & Ward, E. (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes & Control*, 14, 531-539.

<sup>29</sup> Steenland, K., Stayner, L., & Deddens, J. (2004). Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occupational and Environmental Medicine*, 61(1), 2-7.

<sup>30</sup> Steenland, K., Whelan, E., Deddens, J., Stayner, L., & Ward, E. (2003). Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes & Control*, 14, 531-539.

<sup>31</sup> Authors suspected that some breast cancer cases were not captured due to incomplete response and lack of complete coverage by state cancer registries. Some women did not have interviews and did not live in states with cancer registries. In addition, cancer registries were available in only nine of the 11 states in which plants were located, and often for limited periods of time.

(Steenland et al., 2004),<sup>32</sup> which consisted of 9,885 women in which a total of 103 breast cancer deaths were observed, similarly found no overall excess mortality for breast cancer. However, external analyses (compared to breast cancer mortality in the general US population) found a statistically significant 2-fold increase in deaths from breast cancer for women in the highest cumulative EtO exposure group and internal analyses found a statistically significant 3-fold increase in deaths from breast cancer in women with the highest cumulative EtO exposure group (20-year lag).

i. *Kelly-Reiff et al. (2025) Breast Cancer Mortality Update of NIOSH Cohort*

A breast cancer mortality update of the NIOSH cohort was published by Kelly-Reiff et al. (2025),<sup>33</sup> with an additional 23 years of follow-up and 181 deaths from breast cancer<sup>34</sup> in the cohort of 7,549 women with more than one year of employment. This update of the NIOSH breast cancer cohort failed to observe an overall increase in breast cancer mortality in external analyses in which breast cancer mortality was compared to rates in US female population and failed to show a statistically significant increase in breast cancer deaths for any exposure category. However, statistically significant increases in breast cancer mortality were observed for most exposure categories in internal analyses (when breast cancer mortality rates were compared to rates in unexposed women in the cohort), including in a sub-cohort with data on risk factors for breast cancer (20-year lag).<sup>35</sup> The authors concluded that greater weight should be given to findings from internal analyses because Standard Mortality Rate (SMR) by exposure level are not directly comparable and are subject to biases from the Healthy Worker Effect. Use of the general population as a reference can cause underestimation of the risk of cancer in working populations if there is a Healthy Worker Effect. There are two components of the Healthy Worker Effect: 1) “*Healthy Worker Hire Effect*” and 2) “*Healthy Worker Survivor Effect*”. The Healthy Worker Hire Effect can occur because less healthy individuals are less likely to seek, gain, or retain employment.<sup>36,37</sup> Bias introduced by the Healthy Worker Hire Effect can be avoided by using comparison groups within the cohort (internal referents). The Healthy Worker Survivor Effect is more difficult to deal with and may introduce bias in exposure-response relationships because short-term workers are often less healthy than long-term workers and may leave the workforce for reasons related to the disease under study.<sup>38</sup>

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<sup>32</sup> Steenland, K., Stayner, L., & Deddens, J. (2004). Mortality analyses in a cohort of 18,235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occupational and Environmental Medicine*, 61(1), 2-7.

<sup>33</sup> Kelly-Reiff, K., Bertke, S. J., Stayner, L., & Steenland, K. (2025). Exposure to ethylene oxide and relative rates of female breast cancer mortality: 62 years of follow-up in a large US occupational cohort. *Environmental Health Perspectives*, 133(5), 057013.

<sup>34</sup> A 75% increase from the 103 deaths reported by Steenland et al. (2004).

<sup>35</sup> Sub-cohort of 5,132 women employed for at least one year, for whom investigators collected information on risk factors for breast cancer (via interview) in the late 1990s (the same cohort used in internal analyses in the Steenland et al. (2003) incidence study).

<sup>36</sup> Kirkeleit, J., Riise, T., Bjørge, T., & Christiani, D. C. (2013). The healthy worker effect in cancer incidence studies. *American Journal of Epidemiology*, 177(11), 1218-1224.

<sup>37</sup> The general population also includes persons with chronic diseases and disabilities and persons otherwise out of the active worker population; therefore worker populations may have a lower risk of disease than the general population.

<sup>38</sup> Stayner, L., Steenland, K., Dosemeci, M., & Hertz-Picciotto, I. (2003). Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. *Scandinavian Journal of Work, Environment & Health*, 317-324.

Even with the increase in the follow-up period (23 additional years for a total follow time of greater than 60 years) in the NIOSH breast cancer mortality update by Kelly-Reiff et al. (2025), an attenuation in risk (by comparison to the earlier breast cancer mortality study of Steenland et al., 2004) was not observed, arguing against a Healthy Worker Survivor Effect for breast cancer.<sup>39</sup> Despite this contrary evidence, Kelly-Reiff attempted to account for the possibility of a Healthy Worker Survivor Effect<sup>40</sup> (previously hypothesized by Park [2020]<sup>41</sup>),<sup>42</sup> by matching cases and internal referents on duration of employment. By using internal reference groups, theoretically any risk differences observed between the groups could be assumed to be due to differences in their specific workplace EtO exposures. Similar to Park's findings, matching on duration of employment substantially increased SMRs across all exposure categories, most of which were statistically significant, although breast cancer mortality did not increase consistently with dose. Although the Kelly-Reiff (2025) study reports stronger associations between workplace EtO exposure and breast cancer mortality, it may not indicate a stronger association because the study does not clearly indicate dose-dependency and, more importantly, failed to describe how the internal referent group was chosen. Several researchers<sup>43</sup> have suggested that if work status is both a mediator and a confounder of the exposure-outcome relationship, as appears to be the case with EtO exposure and breast cancer mortality,<sup>44</sup> adjustment by employment duration may result in a biased estimate of the dose-response and more sophisticated methods (i.e., g-methods) may be needed to adequately control for the HWSB.

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<sup>39</sup> Kirkeleit, J., Riise, T., Børge, T., & Christiani, D. C. (2013). The healthy worker effect in cancer incidence studies. *American Journal of Epidemiology*, 177(11), 1218-1224; Gridley, G., Nyren, O., Dosemeci, M., Moradi, T., Adami, H. O., Carroll, L., & Zahm, S. H. (1999). Is there a healthy worker effect for cancer incidence among women in Sweden?. *American Journal of Industrial Medicine*, 36(1), 193-199.

<sup>40</sup> Healthy worker survivor bias can occur in occupational studies because of the tendency for unhealthy individuals to leave the workforce earlier, accruing less exposure than their healthier counterparts. This bias can result in attenuation of the estimated effects of exposures on health outcomes (i.e., can bias results towards the null).

<sup>41</sup> Park, R. M. (2020). Associations between exposure to ethylene oxide, job termination, and cause-specific mortality risk. *American Journal of Industrial Medicine*, 63(7), 577-588.

<sup>42</sup> Park (2020) observed a statistically significant negative effect of EtO exposure on employment duration.

<sup>43</sup> Robins, J. (1987). A graphical approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. *Journal of Chronic Diseases*, 40, 139S-161S; Chevrier, J., Picciotto, S., & Eisen, E. A. (2012). A comparison of standard methods with g-estimation of accelerated failure-time models to address the healthy-worker survivor effect: application in a cohort of autoworkers exposed to metalworking fluids. *Epidemiology*, 23(2), 212-219; Naimi, A. I., Cole, S. R., Hudgens, M. G., Brookhart, M. A., & Richardson, D. B. (2013). Assessing the component associations of the healthy worker survivor bias: occupational asbestos exposure and lung cancer mortality. *Annals of Epidemiology*, 23(6), 334-341; Buckley, J. P., Keil, A. P., McGrath, L. J., & Edwards, J. K. (2015). Evolving methods for inference in the presence of healthy worker survivor bias. *Epidemiology*, 26(2), 204-212.

<sup>44</sup> Park, R. M. (2020). Associations between exposure to ethylene oxide, job termination, and cause-specific mortality risk. *American Journal Of Industrial Medicine*, 63(7), 577-588; Picciotto, S., Kelly-Reiff, K., Eisen, E. A., Stayner, L. T., & Costello, S. (2026). How to identify the healthy worker survivor effect empirically and how to interpret results from published studies: the NIOSH ethylene oxide cohort as a case study. *American Journal of Epidemiology*, kwag052.

ii. *Picciotto et al. (2026) Evaluation of Healthy Worker Survivor Effect in NIOSH Cohort*

A 2026 publication by Picciotto et al.<sup>45</sup> evaluated whether a Healthy Worker Survivor Effect is operating in the NIOSH cohort by assessing whether length of employment, which is influenced by prior EtO exposure,<sup>46</sup> is a confounder of lymphohematopoietic or female breast cancer mortality. The Picciotto et al. study (2026) was co-authored by some members of the group that conducted the NIOSH EtO breast cancer mortality update by Kelly-Reiff et al. (2025) and concluded that previously published estimates of lymphohematopoietic cancer and female breast cancer mortality in the NIOSH cohort are underestimated because of the failure to adjust for the Healthy Worker Survivor Effect. Although this recent study acknowledges that the conditioning on exposure duration does not eliminate potential bias associated with the Healthy Worker Survivor Effect, and that complete adjustment for the Healthy Worker Survivor Effect requires the use of sophisticated g-computation, it stopped short of doing those computations, stating that they are not currently possible.

Picciotto et al. (2026) claims that the presence of a Healthy Worker Survivor Effect lends credibility to the supra-linear dose-response curve that has been assumed for EtO, although the presence of a Healthy Worker Survivor Effect does not provide information on the shape or steepness of the exposure response curve. Another possible explanation for the apparent supra-linear curve is exposure misclassification, which is known to be a problem with the NIOSH cohort since workers accumulated person-years at risk beginning in January 1940 but the only measured exposure data were from 1976 to 1985. Depending on the amount of exposure measurement error, the true trend may not be discernible, or it might disappear entirely, obscuring a “real” relationship; hence, it is possible to be misled by the statistical analyses that are the cornerstone of epidemiology studies.

Picciotto et al. (2026) conclude that the true effects in higher exposure groups are almost certainly stronger than previously estimated. However, it is not the effects observed in the highest occupational exposure groups that are important for estimating community risks due to EtO exposure. Instead, lower exposure levels, which are less affected by the potential presence of a Healthy Worker Survivor Effect, are important for estimating the risk of cancer from exposure to EtO in ambient air. At this point, the extent and direction of bias introduced by conditioning on length of employment in the Kelly-Reiff et al. (2025) breast cancer mortality update of the NIOSH cohort is unclear.

B. A New Study on Background EtO Exposure Uses Updated Biomarker Data and More Recent and Improved Monitoring Data to Provide Options for Identifying What Level Constitutes a Substantial Difference from Background (Question 5b)

People are continuously exposed to EtO, not only because EtO is ubiquitous in outdoor air, but also because it is produced naturally by the human body. DNA adducts attributable to EtO have been detected in lymphocytes isolated from people not knowingly in contact with any exogenous source of EtO.<sup>47</sup> The biological importance of endogenous EtO DNA alkylation has been understood for decades and

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<sup>45</sup> Picciotto, S., Kelly-Reif, K., Eisen, E. A., Stayner, L. T., & Costello, S. (2026). How to identify the healthy worker survivor effect empirically and how to interpret results from published studies: the NIOSH ethylene oxide cohort as a case study. *American Journal of Epidemiology*, kwag052.

<sup>46</sup> Park, R. M. (2020). Associations between exposure to ethylene oxide, job termination, and cause-specific mortality risk. *American Journal Of Industrial Medicine*, 63(7), 577-588.

<sup>47</sup> Wu KY, Scheller N, Ranasinghe A, et al. (1999). A gas chromatography/electron capture/negative chemical ionization high-resolution mass spectrometry method for analysis of endogenous and exogenous N7-

has resulted in questioning of current regulatory procedures for assessing the risk of minute EtO doses.<sup>48</sup> EPA's dose-response model for EtO does not take this observation into account and, therefore, overestimates EtO's cancer potency.

EPA's low-dose IUR is an unrealistic value that is well below the background levels of EtO found in ambient air across the entire US. Based on the 2016 evaluation of EtO's cancer potency published in the Integrated Risk Information System (IRIS), EPA has concluded that long-term continuous residential exposure (24 hours a day, 7 days a week, for 70 years) to 0.011 ppb of EtO potentially increases the risk of developing cancer by 1-in-10 thousand (100-in-1 million),<sup>49</sup> despite the fact that the only studies that correlate EtO to increased cancer have involved EtO exposures orders of magnitude higher.<sup>50</sup> By comparison, historical monitoring data for EtO across the US have reported background levels of EtO generally in the range of 0.1 to 0.2 ppb, 10 times the air concentration corresponding to EPA's acceptable risk level,<sup>51</sup> although more recent monitoring<sup>52</sup> (discussed later) has produced slightly lower ambient background concentrations for EtO (but still well above EPA's targeted cancer risk levels). This risk-based air concentration (0.011 ppb) is also below current detection limits for EtO in ambient air, which range

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(2-hydroxyethyl)guanine in rodents and its potential for human biological monitoring. *Chemical Research in Toxicology*, 18:722–9; Zhao C, Hemminki K. (2002). The in vivo levels of DNA alkylation products in human lymphocytes are not age dependent: an assay of 7-methyl- and 7-(2-hydroxyethyl)-guanine DNA adducts. *Carcinogenesis*, 23: 307–10; Yong LC, Schulte PA, Kao CY, et al. (2007). DNA adducts in granulocytes of hospital workers exposed to ethylene oxide. *American Journal of Industrial Medicine*, 50:293–302.

<sup>48</sup> Bolt, H. M. (1996). Quantification of endogenous carcinogens: the ethylene oxide paradox. *Biochemical Pharmacology*, 52(1), 1-5.

<sup>49</sup> EPA (2023). US Environmental Protection Agency. Ethylene Oxide Proposed Interim Registration Review Decision Case Number 2275P. Docket Number EPA-HQ-OPP-2013-0244. March 28. p. 75.

<sup>50</sup> Steenland, K., Stayner, L., and Deddens, J. (2004). Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occupational and Environmental Medicine*, 61(1): 2-7; Stayner, L., Steenland, K., Greife, A., Hornung, R., et al. (1993). Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. *American Journal of Epidemiology*, 138(10): 787-798.

<sup>51</sup> Sheehan, P. J., Lewis, R. C., Kirman, C. R., Watson, H. N., Winegar, E. D., & Bus, J. S. (2021). Ethylene oxide exposure in US populations residing near sterilization and other industrial facilities: Context based on endogenous and total equivalent concentration exposures. *International Journal of Environmental Research and Public Health*, 18(2), 607; Lewis, R.C. Sheehan, P.J. DesAutels, C.G. Watson, H.N. and Kirman, C.R. (2022). Monitored and modeled ambient air concentrations of ethylene oxide: Contextualizing health risk for potentially exposed populations in Georgia. *International Journal of Environmental Research and Public Health*, 19(6): 3364-3379. DOI: 10.3390/ijerph19063364; CR Kirman, AA Li, PJ Sheehan, JS Bus, RC Lewis & SM Hays (2021) Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management, *Journal of Toxicology and Environmental Health, Part B*, 24:1, 1-29; ATSDR (2022). Agency for Toxic Substances Disease Registry. Toxicological Profile for Ethylene Oxide. See Table 5-8; GA DNR (2022). Georgia Department of Natural Resources. Environmental Protection Division. Ethylene Oxide Monitoring Report. Table 16. <https://epd.georgia.gov/document/document/ethylene-oxide-monitoring-report-appendices51222pdf/download>.

<sup>52</sup> Kirman, C. R., Sheehan, P. J., Li, A. A., Bus, J. S., Su, S. H., Dopart, P. J., ... & Reiss, R. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, 22(4), 597.

from 0.015<sup>53</sup> to 0.04 ppb.<sup>54</sup> Not only does this make identifying health-significant contributions from sources of EtO nearly impossible to discern, it also renders the 2016 IRIS value highly impractical as a basis for regulation because compliance with a level below widespread background levels cannot be demonstrated.<sup>55</sup>

EPA has responded that the 2016 IRIS value is intended to predict *extra risk* (i.e., risk above background) and that background environmental and/or endogenous levels of EtO are not integral to the development of the estimates of extra risk. However, taking background levels of EtO in ambient air into account need not involve changing EPA policy on deriving IURs. Instead, background EtO in the environment could be used in making risk management decisions without specifically incorporating it into the EPA's IRIS value. EPA could develop an approach like that used by EPA in characterizing risks from soil contaminants that are also attributable to background sources under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and by many state-based Resource Conservation and Recovery Act (RCRA) clean-up programs.<sup>56</sup>

According to EPA's CERCLA guidance, "In general, the presence of high background concentrations of hazardous substances, pollutants, and contaminants found at a site is a factor that should be considered in risk assessment and in making risk management decisions." This recommendation is based on knowledge and experience that contamination at a site may also originate from other sources, including natural and/or anthropogenic sources not attributable to the specific site release(s) under investigation. In these circumstances, EPA recommends that these constituents be considered in the risk assessment, particularly when their concentrations exceed risk-based concentrations. In cases where background levels are high or present health risks, this information may be important to the public and information on background levels is important to risk managers because the CERCLA program, generally, does not clean up to concentrations below natural or anthropogenic background levels.<sup>57</sup> In other words, under CERCLA and many state risk-based soil cleanup programs, the risk-based cleanup goals are not themselves altered based on background concentrations, but regulated entities are not required to remediate to levels that are below background. The situation with EtO is somewhat different since air regulations regulate how much of a chemical can be emitted before the fact, rather than attempting remediation after the fact. Based on this line of thinking, in circumstances where the EtO levels emitted from a particular entity do not cause a meaningful increase in EtO above background levels, no further emission reductions should be required since they are unlikely to materially affect risk from ambient exposure. Under such an approach, the IRIS value would not be used directly to set emission limits. This approach would be much more practical given that the 2016 IRIS value is lower than background and current detection limits.

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<sup>53</sup> Willowbrook, IL Ethylene Oxide Concentrations in Outdoor Air [ug/m3] - 24 Hour Samples.

<https://www.epa.gov/il/outdoor-air-monitoring-willowbrook-community>.

<sup>54</sup> Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. *ACS Es&t Air*, 1(8), 747-754.

<sup>55</sup> Rietjens, I. M., Michael, A., Bolt, H. M., Siméon, B., Andrea, H., Nils, H., ... & Gerhard, E. (2022). The role of endogenous versus exogenous sources in the exposome of putative genotoxins and consequences for risk assessment. *Archives of Toxicology*, 96(5), 1297-1352.

<sup>56</sup> EPA (2002). US Environmental Protection Agency. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites. EPA 540-R-01-003 OSWER 9285.7-41 September.

<sup>57</sup> EPA (2002). US Environmental Protection Agency. Guidance for Comparing Background and Chemical Concentrations in Soil for CERCLA Sites. Appendix B: Policy Considerations for the Application of Background Data in Risk Assessment and Remedy Selection. EPA 540-R-01-003 OSWER 9285.7-41 September.

i. Kirman et al. (2025) Characterization of Background Exposures to EtO

Background EtO exposures, including endogenous (inside the body) levels, can provide an important reality check to inform the biological plausibility of dose-response models for EtO. EtO forms adducts on the terminal valine of hemoglobin, N-(2-hydroxyethyl)-valine (HEV), which are more stable than EtO DNA adducts, readily measurable in erythrocytes, and are widely accepted as a biomarker for EtO exposure.<sup>58</sup> Although not a direct measure of EtO exposure, the National Health and Nutrition Examination Survey (NHANES) HEV data have been used to support evaluations of EtO exposure. To address concerns<sup>59</sup> about whether EtO hemoglobin adduct-based total equivalent (TE) and endogenous equivalent (EE) methods represent a valid biomarker of total and endogenous EtO exposures, Kirman et al. (2025)<sup>60</sup> updated and refined their overall background EtO assessment based on new data and information developed since their previous analyses<sup>61</sup> and performed an enhanced validation of the TE (total equivalent) method coupled with refined analytical measurements of EtO background concentrations in ambient air.

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<sup>58</sup> ATSDR (2022). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Ethylene Oxide. August. <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=734&tid=133>; ATSDR (2024). Clinician Brief: Ethylene Oxide. <https://www.atsdr.cdc.gov/environmental-medicine/hcp/clinicianbriefeto/>; Eckert E, Bader M, Drexler H, Hartwig A, MAK Commission (2024). Ethylene oxide – Addendum: re-evaluation of the EKA. Assessment Values in Biological Material – Translation of the German version from 2024. MAK Collect *Occupational Health and Safety*, 9(3):Doc070. [https://doi.org/10.34865/bb7521e9\\_3ad](https://doi.org/10.34865/bb7521e9_3ad); WHO (1985). World Health Organization International Programme on Chemical Safety. Environmental Health Criteria 55: Ethylene Oxide. <https://iris.who.int/server/api/core/bitstreams/77f970ff-3414-417a-92af-2091bee55b5e/content>; IARC (2008). World Health Organization International Agency for Research On Cancer. Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 97: 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide), pp. 246 – 247 and 252 – 253. <https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/1-3-Butadiene-Ethylene-Oxide-And-Vinyl-Halides-Vinyl-Fluoride-Vinyl-Chloride-And-Vinyl-Bromide--2008>; ECHA (2018). CLH report Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Substance Name: Ethylene oxide, oxirane. [https://echa.europa.eu/documents/10162/2842450/clh\\_rep\\_ethylene\\_oxide\\_6789\\_en.pdf/4e5b7970-8517-02ef-c757-8f62097fbc10?version=1.0&t=1519730746121&download=true](https://echa.europa.eu/documents/10162/2842450/clh_rep_ethylene_oxide_6789_en.pdf/4e5b7970-8517-02ef-c757-8f62097fbc10?version=1.0&t=1519730746121&download=true).

<sup>59</sup> EPA (2020). US Environmental Protection Agency. Summary of Public Comments and Responses for the Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review. <https://www.regulations.gov/document/EPA-HQ-OAR-2019-0178-1494>.

<sup>60</sup> Kirman, C. R., Sheehan, P. J., Li, A. A., Bus, J. S., Su, S. H., Dopart, P. J., ... & Reiss, R. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, 22(4), 597.

<sup>61</sup> Kirman, C.R.; Hays, S.M. (2017). Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. *Regulatory Toxicology and Pharmacology*, 91, 165–172; Kirman, C. R., Li, A. A., Sheehan, P. J., Bus, J. S., Lewis, R. C., & Hays, S. M. (2021). Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management. *Journal of Toxicology and Environmental Health, Part B*, 24(1), 1-29.

## 1. Confirmed Linear Relationship between EtO Exposure and HEV Adducts

Several worker biomonitoring studies have found that HEV adduct levels rise roughly in proportion to measured airborne EtO<sup>62</sup> and animal inhalation studies show linearity over low-to-moderate exposure ranges as well.<sup>63</sup> Moreover, in a recent re-evaluation (based on more recent studies on the correlation between external and internal exposure of EtO in the air and its hemoglobin adduct [HEV]) of EtO exposure equivalents (EKA)<sup>64</sup> and biological reference value (BAR)<sup>65</sup> for HEV developed by Deutsche Forschungsgemeinschaft (DFG or German Research Foundation), the EKA were confirmed and extended to a lower exposure range using linear extrapolation. To further support the validity of the single-slope linear relationship between EtO exposure and HEV biomarker burden, Kirman et al. (2025) evaluated multiple lines of evidence. First, a linear regression analysis of HEV measurements in workers with known exposures to EtO provided empirical support for the linear relationship at moderate to high exposure levels. Second, it was determined that the linear relationship between EtO exposure and HEV is also supported by theoretical predictions from different EtO PB/PBPK models.<sup>66</sup> And lastly, linear regression of HEV measurements in US smokers (from NHANES) supported the conclusion that the relationship between exogenous EtO exposures (via tobacco smoke) and HEV is linear because the line continued downward in a monotonic fashion from moderate HEV levels in US smokers to low HEV levels in non-smokers. While the available occupational and controlled inhalation laboratory studies, as well as evaluations performed by other international regulatory agencies support the linear relationship between EtO exposures and HEV, there is greater uncertainty at lower EtO levels because of background (endogenous + exogenous) adduct formation (e.g., endogenous ethylene metabolism to EtO, cigarette smoke) and, therefore, the observed relationship may not appear strictly linear at low ambient EtO levels. Despite some uncertainty at low exposure levels, the best supported interpretation of the available evidence is that the relationship between EtO and HEV is approximately linear.

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<sup>62</sup> Angerer, J., Bader, M. & Krämer, A. Ambient and biochemical effect monitoring of workers exposed to ethylene oxide. *International Archives of Occupational Environmental Health*, **71**, 14–18 (1998); Boogaard, P. J., Rocchi, P. S. J., & Van Sittert, N. J. (1999). Biomonitoring of exposure to ethylene oxide and propylene oxide by determination of hemoglobin adducts: correlations between airborne exposure and adduct levels. *International Archives of Occupational And Environmental Health*, **72**(3), 142-150; van Sittert, N. J., Beulink, G. D., van Vliet, E. W., & van der Waal, H. (1993). Monitoring occupational exposure to ethylene oxide by the determination of hemoglobin adducts. *Environmental Health Perspectives*, **99**, 217.

<sup>63</sup> Walker, V. E., MacNeela, J. P., Swenberg, J. A., Turner Jr, M. J., & Fennell, T. R. (1992). Molecular dosimetry of ethylene oxide: formation and persistence of N-(2-hydroxyethyl) valine in hemoglobin following repeated exposures of rats and mice. *Cancer Research*, **52**(16), 4320-4327; Walker, V. E., Fennell, T. R., Upton, P. B., MacNeela, J. P., & Swenberg, J. A. (1993). Molecular dosimetry of DNA and hemoglobin adducts in mice and rats exposed to ethylene oxide. *Environmental Health Perspectives*, **99**, 11.

<sup>64</sup> Eckert E, Bader M, Drexler H, Hartwig A, MAK Commission (2024). Ethylene oxide – Addendum: re-evaluation of the EKA. Assessment Values in Biological Material – Translation of the German version from 2024. MAK Collect *Occupational Health and Safety*, **9**(3):Doc070. [https://doi.org/10.34865/bb7521e9\\_3ad](https://doi.org/10.34865/bb7521e9_3ad).

<sup>65</sup> Eckert E, Bader M, Drexler H, Hartwig A, MAK Commission (2022). Ethylene oxide – Addendum: Derivation of BAR. Assessment Values in Biological Material – Translation of the German version from 2022. MAK Collect *Occupational Health and Safety*, **7**(1):Doc018. [https://doi.org/10.34865/bb7521e7\\_1ad](https://doi.org/10.34865/bb7521e7_1ad).

<sup>66</sup> Eckert E, Bader M, Drexler H, Hartwig A, MAK Commission (2024). Ethylene oxide – Addendum: re-evaluation of the EKA. Assessment Values in Biological Material – Translation of the German version from 2024. MAK Collection, *Occupational Health and Safety*, **9**(3):Doc070. [https://doi.org/10.34865/bb7521e9\\_3ad](https://doi.org/10.34865/bb7521e9_3ad); Filser, J.G.; Klein, D. A. (2018). Physiologically based toxicokinetic model for inhaled ethylene and ethylene oxide in mouse, rat, and human. *Toxicology Letters*, **286**, 54–79; Eckert, E., Bader, M., Drexler, H., & Hartwig, A. (2024).

2. *Recently Measured Background EtO Concentrations Using Updated EPA Methods Are Lower than Previously Reported, but Still Well Above EPA's Targeted Cancer Risk Levels*

Concerns that have been raised about the quality and reliability of ambient monitoring data for characterizing ambient background EtO concentrations include: 1) high method detection limits (relative to monitored concentrations);<sup>67</sup> and 2) the potential for monitored concentrations to be biased high as a result of (a) possible EtO growth inside canisters with certain inner surface lining characteristics used to sample ambient air; and (b) inadequately cleaned canisters.<sup>68</sup> Kirman et al. (2025) performed a comprehensive analysis of ambient background EtO concentrations based on data from 2019–2023 but primarily relied on 2021–2023 samples collected with EPA's new refined methods and canister cleanliness criteria, which are designed to maximize sensitivity and minimize bias, to characterize ambient background concentrations. Based on method refinement and stringent cleaning and certification criteria, these more recent measurements of EtO background concentrations made with EPA Methods TO-15 and TO-15A in accordance with the EPA's May 2021 Technical Note<sup>69</sup> are lower than levels previously reported, although still well above air concentrations corresponding to EPA's targeted cancer risks (i.e., 100-in-1 million and 1-in-1 million). Kirman et al. (2025) reported representative background EtO concentrations from samples collected subsequent to EPA's refined methods and canister cleanliness criteria (2021 – 2023) of 0.066 – 0.077 ppb (0.12 – 0.13  $\mu\text{g}/\text{m}^3$ ), depending on which EPA Method was used (TO-15 or TO-15A). Previously reported representative background concentrations collected prior to method refinement and implementation of cleanliness criteria<sup>70</sup> ranged from 0.1 to 0.22 ppb (0.185  $\mu\text{g}/\text{m}^3$  – 0.397  $\mu\text{g}/\text{m}^3$ ) and averaged 0.165 ppb (0.23  $\mu\text{g}/\text{m}^3$ ).<sup>71</sup>

3. *More Recent Total Equivalent and Endogenous Equivalent Estimates are of High Quality and Provide EtO Exposure Comparisons for Identifying Levels that Constitute a "Substantial Difference" from Background (Question 5c)*

The more recent TE (total equivalent) and (endogenous equivalent (EE) estimates provided by Kirman et al. (2025) are considered to be of higher quality since they rely on: 1) high-quality updated

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<sup>67</sup> EPA (2020). US Environmental Protection Agency. EPA's Work to Understand Background Levels of Ethylene Oxide. <https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/epas-work-understand-background-levels-ethylene-oxide>; Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. *ACS Es&t Air*, 1(8), 747-754.

<sup>68</sup> EPA (2021a). US Environmental Protection Agency. Effect of Canister Type on Background Ethylene Oxide Concentrations. May 7, 2021. <https://www.epa.gov/sites/default/files/2021-05/documents/ord-eto-canister-background-memo-05072021.pdf>; EPA (2021b). U.S. Environmental Protection Agency. Technical Note: The Ethylene Oxide (EtO) Canister Effect. May 25, 2021. <https://www.epa.gov/sites/default/files/2021-05/documents/technical-note-on-eto-canister-effect-052521.pdf>; Yelverton, T. L., Hays, M. D., & Rice, J. (2024). Ethylene oxide: An air contaminant of concern. *ACS Es&t Air*, 1(8), 747-754.

<sup>69</sup> EPA (2021b). US Environmental Protection Agency. Technical Note: The Ethylene Oxide (EtO) Canister Effect. May 25, 2021. <https://www.epa.gov/sites/default/files/2021-05/documents/technical-note-on-eto-canister-effect-052521.pdf>.

<sup>70</sup> Sheehan, P. J., Lewis, R. C., Kirman, C. R., Watson, H. N., Winegar, E. D., & Bus, J. S. (2021). Ethylene oxide exposure in US populations residing near sterilization and other industrial facilities: Context based on endogenous and total equivalent concentration exposures. *International Journal of Environmental Research and Public Health*, 18(2), 607.

<sup>71</sup> EPA (2020). US Environmental Protection Agency. Ethylene Oxide Ambient Concentrations at National Air Toxics Trends Stations and Urban Air Toxics Monitoring Program stations October 1, 2018 – March 31, 2019. [https://www.epa.gov/sites/default/files/2019-11/documents/data\\_summary\\_stations.pdf](https://www.epa.gov/sites/default/files/2019-11/documents/data_summary_stations.pdf).

datasets (CDC’s HEV data from NHANES); 2) more recent EPA air monitoring data for EtO that maximize sensitivity and minimize bias); and 3) a verified continuously linear relationship between HEV and EtO exposure from low-ppb to high-ppm exposures. The TE and EE EtO concentrations provided in Kirman et al. (2025) provide EtO exposure comparisons that can be used to identify what level constitutes a “substantial difference” from background EtO,<sup>72</sup> analogous to EPA’s approach for soil remediation.<sup>73</sup>

C. PBPK Models Based on HEV Adducts in Highly Exposed Occupational Cohorts Do Not Necessarily Accurately Portray the Relationship between Ethylene and Circulating EtO, Despite Fitting Observed EtO HEV Data (Question 5c)

i. *Lin et al. (2025) Ethylene Exposure and Endogenous EtO Levels*

A recently published study (Lin et al., 2025)<sup>74</sup> authored by US EPA staff examined the role of ethylene in endogenous EtO production in people without a history of occupational exposure to ethylene or smoking. Exhaled ethylene was used as an exposure metric and HEV adduct measurements, accompanied by pharmacokinetic analysis, was used to estimate a quantitative relationship between ethylene and endogenous EtO. Understanding the role of ethylene in endogenous EtO formation is relevant because Kirman and colleagues<sup>75</sup> have argued that the majority of hemoglobin adducts (HEV) observed in the non-smoking US population derive from the oxidation of endogenous ethylene to EtO.

To assess the extent to which endogenous EtO is influenced by total ethylene dose from both endogenous and exogenous sources, Lin et al. (2025) performed two distinct pharmacokinetic analyses, including: 1) application of the 2018 PBPK model by Filser and Klein,<sup>76</sup> incorporating endogenous ethylene sources as part of the ethylene exposure input; and 2) use of a simplified model to characterize the kinetic profile of exhaled ethylene to explore the relationship between ethylene exposure and endogenous EtO rates and reactions.

Using the Filser and Klein model, the study reported that exhaled ethylene levels largely mirror inhaled (exogenous) ethylene concentrations, which was interpreted to mean that the contribution from endogenous ethylene production was minimal. Assuming a lower endogenous ethylene production rate,

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<sup>72</sup> For example, 1) multiples of the mean background level, 2) multiples of the standard deviation for background levels, and 3) percentiles for the distribution of background levels.

<sup>73</sup> EPA (2002). US Environmental Protection Agency. Role of Background in the CERCLA Cleanup Program. OSWER 9285.6-07P. <https://www.epa.gov/risk/role-background-cercla-cleanup-program>.

<sup>74</sup> Lin, Y. S., Thayer, K. A., White, P., Morozov, V., & Persad, A. S. (2026). Uncovering the connection: ethylene exposure and endogenous ethylene oxide levels in humans. *Journal of Exposure Science & Environmental Epidemiology*, 36(2), 361-374.

<sup>75</sup> Kirman, C.R.; Hays, S.M. (2017). Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. *Regulatory Toxicology and Pharmacology*, 91, 165–172; Kirman, C. R., Li, A. A., Sheehan, P. J., Bus, J. S., Lewis, R. C., & Hays, S. M. (2021). Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management. *Journal of Toxicology and Environmental Health, Part B*, 24(1), 1-29; Kirman, C. R., Sheehan, P. J., Li, A. A., Bus, J. S., Su, S. H., Dopart, P. J., ... & Reiss, R. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, 22(4), 597.

<sup>76</sup> Filser, J. G., & Klein, D. (2018). A physiologically based toxicokinetic model for inhaled ethylene and ethylene oxide in mouse, rat, and human. *Toxicology Letters*, 286, 54-79.

in the absence exogenous ethylene exposure, the Filser and Klein PBPK model predicted lower exhaled ethylene levels and lower HEV adduct estimates. This was interpreted to suggest that the influence of endogenous ethylene is greater in the absence of exogenous ethylene and diminishes with higher external ethylene exposure. The authors concluded that the low exhaled ethylene concentrations from studies identified in the literature review involving inhalation of purified air (i.e., minimal ambient ethylene) suggest limited internal contribution from endogenous processes like lipid peroxidation and methionine oxidation and that the results collectively corroborate the predictions of their pharmacokinetic analysis. Using an alternative kinetic approach and assumptions consistent with the Filser Klein model, similar estimates of exhaled ethylene were predicted and the pharmacokinetic simulations were concluded to imply that neither internal ethylene production, nor typical environmental ethylene exposure levels significantly impacted circulating endogenous EtO levels. According to this evaluation, the average 70 kg adult is expected to have a background of 3.47 pmol HEV/g globin, which includes endogenous ethylene production and nominal ambient ethylene exposure; and 2) only about 17.5% of background HEV adducts (i.e., 3.47/20 pmol/g HEV) reported for non-smokers can be attributed to endogenous and exogenous ethylene exposure combined. This conclusion is in contrast to conclusions drawn by Kirman and colleagues,<sup>77</sup> that the majority of background EtO exposure (~93%) is associated with endogenous metabolism of ethylene to EtO. Lin et al. argue that background levels of ethylene in ambient air are too low to produce the EE levels estimated by Kirman and colleagues based on linear extrapolation of occupational HEV data to background HEV levels in the US population and that internal ethylene production cannot account for this level of EtO production (ultimately leading to HEV adduct formation).

The PBPK models used in these evaluations contain numerous parameters, some of which were determined by curve fitting (optimized) and others that were obtained from *in vitro* studies. The optimized parameter estimates are conditional on the values that have been assumed for the fixed parameters (those based on empirical research), many of which may contain a certain degree of inaccuracy and/or imprecision, as with any experimental result.<sup>78</sup> Values used as input parameters in these models are often chosen because when used, the models produce values that approximate those observed in the scientific literature. However, the fact that a PBPK model produces HEV values that are close to observed values does not necessarily mean that the PBPK model accurately depicts the relationship between ethylene or EtO exposure and the HEV body burden. Lin et al. nevertheless conclude that while ethylene may produce the same hemoglobin adducts (HEV) as EtO exposures, their analyses indicate that neither external nor internal ethylene exposures can explain observed levels of background HEV adducts, despite the fact that

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<sup>77</sup> Kirman, C.R.; Hays, S.M. (2017). Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. *Regulatory Toxicology and Pharmacology*, 91, 165–172; Kirman, C. R., Li, A. A., Sheehan, P. J., Bus, J. S., Lewis, R. C., & Hays, S. M. (2021). Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management. *Journal of Toxicology and Environmental Health, Part B*, 24(1), 1-29; Kirman, C. R., Sheehan, P. J., Li, A. A., Bus, J. S., Su, S. H., Dopart, P. J., ... & Reiss, R. (2025). Characterization of Background Exposures to Ethylene Oxide in the United States: A Reality Check on Theoretical Health Risks for Potentially Exposed Populations near Industrial Sources. *International Journal of Environmental Research and Public Health*, 22(4), 597.

<sup>78</sup> Tsamandouras, N., Rostami-Hodjegan, A., & Aarons, L. (2015). Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data. *British Journal of Clinical Pharmacology*, 79(1), 48-55.

metabolism of endogenously produced ethylene to EtO has been cited as the major source for background endogenous EtO levels for decades.<sup>79</sup>

Even *if* the etiology of endogenous EtO is not yet completely understood, endogenous EtO exposures are still much higher than exogenous exposures to EtO in air.

### III. CONCLUSION

- New studies that inform the shape of the EtO dose-response curve do not support that EtO is a highly potent carcinogen with a steep risk at low concentrations.
- New or updated studies *potentially* suggesting stronger associations between EtO and breast cancer are likely biased as a result of inappropriate or inadequate control for the healthy worker survivor effect.
- An updated study on background EtO exposure uses updated biomarker data and more recent air monitoring data to provide options for identifying what EtO level constitutes a substantial difference from background.
  - While recently measured background EtO concentrations using updated EPA methods are lower than previously reported, they are still well above EPA's targeted cancer risk levels.
- PBPK models based on HEV adducts in highly exposed occupational cohorts do not necessarily accurately portray the relationship between ethylene and circulating endogenous EtO levels, despite fitting observed EtO HEV adduct data.
  - Even *if* the etiology of endogenous EtO is not yet completely understood, endogenous EtO exposures are still much higher than exogenous exposures to EtO in air.
- Ambient EtO concentrations to which everybody across the US is exposed, as well as currently achievable analytical detection limits, are considerably higher than air concentrations corresponding to EPA's 2016 IRIS value.
  - This implies that further restricting EtO emissions on the basis of predicted risk is unlikely to materially affect ambient concentrations or produce demonstrable health benefits.

Sincerely



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<sup>79</sup> Ehrenberg, L., & Törnqvist, M. (1995). The research background for risk assessment of ethylene oxide: aspects of dose. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 330(1-2), 41-54; Filser, J. G., & Klein, D. (2018). A physiologically based toxicokinetic model for inhaled ethylene and ethylene oxide in mouse, rat, and human. *Toxicology Letters*, 286, 54-79; Segerbäck, D. (1983). Alkylation of DNA and hemoglobin in the mouse following exposure to ethene and ethene oxide. *Chemico-Biological Interactions*, 45(2), 139-151.