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National Emission Standards for Hazardous Air Pollutants:
Ethylene Oxide Emissions Standards for Sterilization Facilities
Residual Risk and Technology Review Reconsideration
EPA-HQ-OAR-2019-0178
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The Environmental Protection Network (EPN) harnesses the expertise of more than 750 former Environmental Protection Agency (EPA) career staff and confirmation-level appointees from Democratic and Republican administrations to provide the unique perspective of former regulators and scientists with decades of historical knowledge and subject matter expertise.

EPN's comments follow on EPA's March 17, 2026, proposed reconsideration of its April 5, 2024, Revised National Emission Standards for Ethylene Oxide (EtO) Emissions from Commercial Sterilization Facilities, based on a Residual Risk and Technology Review (RTR). Because, as we show in these comments, the proposal is irretrievably flawed from both a legal and a public health perspective, EPA must rescind the proposal.

Introduction

The proposed repeal or weakening of significant provisions in EPA's 2024 Commercial Sterilizers National Emissions Standards for Hazardous Air Pollutants (NESHAP), if finalized, would constitute yet another blow to human health protection. If finalized, the rule would expose the communities where a reported 97 commercial sterilizers operate and 14 million Americans live to increased levels of carcinogenic EtO emissions resulting in increased levels of risks. This would be an especially perverse result for an agency whose explicit mission is to protect human health and the environment.

The proposal delivers this blow to human health protection via a comparably perverse interpretation of the Clean Air Act (CAA) – an interpretation that would bar EPA from acting to protect the public from the significantly increased cancer risk posed by EtO emissions. This new interpretation would also apply to hazardous air pollutants (HAPs) emitted from coke ovens, iron and steel facilities, and chemical manufacturing facilities, all of which would be curbed by rules adopted by the Biden EPA. It would also constrain EPA in the future from taking into account newly developed information about the health effects of any HAP from any type of industry EPA regulates under CAA Section 112.

The 2024 Commercial Sterilizers NESHAP was the culmination of a lengthy rulemaking process that included an updated risk assessment incorporating the results of EPA's extensive scientific review of its EtO cancer potency estimate completed in 2016.[1] That 2016 review used human data on cancers seen in sterilization workers to develop cancer potency estimates, a contrast to the rodent-based potency estimates used in earlier studies. This review found that EtO's potency was significantly higher than had previously been determined and, thus, when the revised estimate was used to evaluate human exposures in the Commercial Sterilization Facilities context, it resulted in higher estimated health risks than previously estimated. In 2006, EPA conducted a review of the risks posed by exposure to EtO via commercial sterilization facilities and concluded, based on the science available at the time, that EtO's risks were appropriately controlled under Section 112(f)(2) and, thus, no further action was required. After EPA

[1] "Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Final Report)" available at https://iris.epa.gov/document/&deid=329730

updated the science of EtO in the revised potency estimate described above, it found that people exposed to EtO faced a lifetime cancer risk 10-to-100 times greater than understood at the time EPA performed the 2006 residual risk review of EtO sterilization facilities. The finding prompted EPA's Office of Inspector General (OIG) to recommend in a May 6, 2021, report[2] that the Agency should conduct a new risk review of the existing standards for EtO under section 112(f)(2) in light of the new science. Taking full account of the updated science, EPA completed the risk review, incorporating the revised cancer potency estimates. The results indicated that, at baseline, an estimated 19,000 people living within 10 km of EtO sterilization facilities had attendant health risks of *greater than* 100 in 1 million, levels deemed unacceptable by EPA. . Thus the 2024 NESHAP review lead to new, tighter standards requiring reductions in EtO emissions that would ensure that these risks are reduced, such that no residents are exposed to levels above 100 in 1 million and that risks are reduced for other residents (i.e., those who are exposed to lower levels) as well. More detail is provided later in our comments.

EPA's March 2026 proposal, in contrast, makes the claim that the CAA ended EPA's authority to protect the public from EtO emissions at commercial sterilizers once it took action in 2006, that the 2016 scientific update and the 2021 Inspector General's recommendation must be deemed of no effect, and that 14 million Americans must be left exposed to elevated cancer risk all thanks to the proposal's newly discovered and counterintuitive reading of the CAA.

The proposal reaches this perverse result via an implausible interpretation of section 112(f)(2) of the CAA and by truncating the analytic record. Although the plain present tense language of 112(f)(2) contemplates periodic ongoing risk assessments and intersecting language in section 307(d) recognizes revisions of existing standards like the 2024 rule, the proposal claims to find a one-and-done limit on EPA's authority. It ignores the requirement that the standards "shall provide an ample margin of safety to protect public health" and that EPA "shall promulgate standards" whenever the technology-based standards "do not reduce lifetime excess cancer risks to the individual most exposed to emissions from a source in the category or subcategory to less than one in one million."

The proposal, meanwhile, presents a wholly insufficient record, discarding the 2024 residual risk assessment's findings of high baseline inhalation risk resulting from EtO exposure. Although the proposal would result in increases in EtO emissions, it provides no assessment of the health impacts of those increases.[3]

With this proposal, EPA seems to have lost sight entirely of the purpose the maximum achievable control technology (MACT) and the Residual Risk program must serve: to assure cancer risks to exposed populations from industrial facility air emissions are acceptable.

Instead, the proposal's objective appears to be not just to abandon that purpose but to find yet another way to delete EPA's legal authority to fulfill that purpose – and to justify the current EPA's ongoing rejection of its human and environmental health mission.

[2] https://www.epa.gov/sites/default/files/2021-05/documents/_epaoig_20210506-21-p-0129.pdf

[3] Public access to those findings is not even available on EPA's website; on March 13, 2026, EPA physically removed from its website pages describing the risks of EtO exposure as set forth in the 2024 rule and supporting documents.

In sum, we believe that the 2026 proposal is irretrievably flawed from both legal, procedural, and public health perspectives. The proposal not only misinterprets the CAA so as to negate consideration of any new risk assessment in the MACT and Residual Risk context, it unjustifiably discards the 2024 residual risk assessment and its findings of high baseline inhalation risk owing to EtO exposure. For these reasons, we urge that EPA rescind this proposal.

Legal Analysis and Rebuttal

The starting point in interpreting a statutory provision is always the text itself.[4] Section 112(f)(2) states as follows:

> (2) Emission standards
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> (A) If Congress does not act on any recommendation submitted under paragraph (1), the Administrator shall, within 8 years after promulgation of standards for each category or subcategory of sources pursuant to subsection (d), promulgate standards for such category or subcategory if promulgation of such standards is required in order to provide an ample margin of safety to protect public health in accordance with this section (as in effect before November 15, 1990) or to prevent, taking into consideration costs, energy, safety, and other relevant factors, an adverse environmental effect. Emission standards promulgated under this subsection shall provide an ample margin of safety to protect public health in accordance with this section (as in effect before November 15, 1990), unless the Administrator determines that a more stringent standard is necessary to prevent, taking into consideration costs, energy, safety, and other relevant factors, an adverse environmental effect. If standards promulgated pursuant to subsection (d) and applicable to a category or subcategory of sources emitting a pollutant (or pollutants) classified as a known, probable or possible human carcinogen do not reduce lifetime excess cancer risks to the individual most exposed to emissions from a source in the category or subcategory to less than one in one million, the Administrator shall promulgate standards under this subsection for such source category.
>
> (B) …
>
> (C) The Administrator shall determine whether or not to promulgate such standards and, if the Administrator decides to promulgate such standards, shall promulgate the standards 8 years after promulgation of the standards under subsection (d) for each source category or subcategory concerned. In the case of categories or subcategories for which standards under subsection (d) are required to be promulgated within 2 years after November 15, 1990, the Administrator shall have 9 years after promulgation of the standards under subsection (d) to make the determination under the preceding sentence and, if required, to promulgate the standards under this paragraph.

1. EPA's 2024 interpretation of §112(f)(2).

In 2024, EPA interpreted this provision as follows:

[4] *Environmental Defense Fund v. EPA*, 124 F.4th 1, 11 (D.C. Cir. December 2024) (""As with all questions of statutory interpretation, we start with the text." Pharm. Mfg. Rsch. Servs., Inc. v. FDA, 957 F.3d 254, 260 (D.C. Cir. 2020).")

(i) Subsection (f)(2) mandates an initial residual risk review and appropriate standard setting, to occur no later than 8 years after EPA promulgated HAP standards for a source category under §112(d). The subsection (d) standards are technology based, and the subsection (f) standards are risk based, designed to address health and environmental risks remaining after the technology standards are adopted.

(ii) Subsection (f)(2) authorizes EPA to conduct subsequent risk reviews and standard setting, in its discretion and if appropriate under the circumstances. EPA determined it was appropriate to conduct a risk review and set residual risk standards for EtO sources, given the updated IRIS assessment for EtO, which showed significantly increased cancer risk associated with exposure to EtO.[5]

EPA pointed to the text of this provision as supporting this reading. EPA noted the inherent or assumed authority of administrative agencies to revisit and revise prior actions under appropriate circumstances, as EPA was doing for EtO, and EPA noted that nothing in subsection (f)(2) prohibits EPA from taking this action. EPA also noted that this interpretation is consistent with past actions and statements in prior EPA rulemakings. EPA also pointed to the explicit reference in §307(d), a provision on rulemaking procedures, to the "promulgation or revision" of standards under subsection (f)(2). EPA explained this indicated Congress' awareness of EPA's authority to review and revise the residual risk standards.

2. EPA now proposes a contrary interpretation. EPA's proposed interpretation fails for several reasons, and it clearly is not the best reading of §112(f)(2).

EPA proposes that the initial review and standard setting for residual risks is the only one EPA has authority to conduct. Under the proposal, EPA has no authority and no discretion to conduct a subsequent residual risk review and standard setting, no matter how the circumstances may have changed over time. No matter how dangerous the pollutant, no matter how great the level of risk to the exposed public, EPA proposes that subsection (f)(2) provides no further authority for EPA to take action to prevent a risk Congress defined as unacceptable in subsection (f)(2) itself.

(a) EPA does not analyze the text of subsection (f)(2), its interpretation is atextual. As noted above, the text of the provision is always the starting point of statutory interpretation, and failure to analyze the text undercuts EPA's proposed interpretation.

(b) The text of subsection (f)(2) is best read as requiring an initial residual risk review and standard setting, and establishing the obligation and authority to review and revise the standards over time, if appropriate, to ensure they meet the criteria set by Congress for margin of safety and reduction in cancer risk.

The first sentence of subsection (f)(2)(A) clearly establishes a duty for an initial risk review and standard setting, with an eight-year deadline, if the technology-based standards do not protect with an ample margin of safety (conditioned on no Congressional action on the subsection (f)(1) report).

[5] EPA, "Summary of Public Comments and Responses for Risk and Technology Review for Ethylene Oxide Commercial Sterilization Facilities" February 2024. See pp. 227-235.

The second sentence states that emission standards under subsection (f) "shall provide" an ample margin of safety. The third sentence states that EPA "shall promulgate" standards if the technology-based standards promulgated under subsection (d) "do not reduce" cancer risk to the required level.

Both of these sentences use verbs in the present tense, which is typically interpreted as encompassing both the present and the future.[6] As such, the straightforward reading of these two sentences is that EPA must ("shall") conduct subsequent reviews and standard setting when the standards no longer provide the required margin of safety or reduction in cancer risk. These two sentences establish a duty on EPA to ensure that the standards meet the statutory criteria – the required margin of safety and the required reduction in cancer risk. The use of the present tense means this duty is ongoing, it is not frozen in time. Unlike the eight-year deadline for the initial residual risk review and standard setting, and unlike the eight-year review and revise cycle for the technology-based standards under subsection (d), Congress did not impose a statutory deadline, periodic or otherwise, for EPA to discharge this duty. Hence it is not the kind of non-discretionary duty found in the provisions that specify eight-year deadlines. That does not change the fact it is an ongoing duty EPA must meet.

For example, if EPA determines that the standards no longer provide the required margin of safety or reduction in cancer risk, then EPA must revise the standards. That is the import of the use of "shall" in the second and third sentences. This clearly authorizes EPA to conduct subsequent risk reviews and standard setting under appropriate circumstances. The 2024 rulemaking is one example of EPA implementing its authority to review and update the standards to ensure they meet the statutory criteria. It was fully authorized by subsection (f)(2).

What differs here is that there are no specific statutory deadlines defining when EPA is to determine whether the standards meet the required level of safety and reduction in cancer risk. The 2024 rulemaking is an example of EPA exercising its authority and implementing this provision – monitoring the science and other circumstances and taking action when appropriate, updating the standards to ensure they meet the required levels of safety and reduction in cancer risk. Logically, EPA should determine (formally or otherwise) whether the standards meet the required criteria when the technology-based standards are updated. However, there is no statutory deadline requiring EPA to act on such a periodic schedule.[7] At the same time, if EPA fails to keep up with the science and other circumstances, interested parties can petition EPA to take action and update the residual risk standards. EPA will have to respond to any such petition with a reasoned decision, grounded in subsection (f)(2)'s requirements, for granting or denying the petition.[8]

The second and third sentences of subsection (f)(2) use the phrasing "emission standards" and "standards," they do not say "such standards." Congress' failure to include this kind of reference to the initial review and standard setting when it referred to standards in the second and third sentence supports the view that Congress was not limiting or tying EPA's authority to a single, initial standard setting.

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[6] *Kennedy v. Braidwood Management, Inc.*, 2025 WL 1773628 (S. Ct. June 27, 2025).

[7] While there are no specific statutory deadlines for subsequent reviews, the close relationship between subsection (d) and subsection (f) standards and standard setting at the least strongly implies a need for EPA to act regularly. EPA's proposal improperly draws just the opposite conclusion.

[8] See *Massachusetts v. EPA*, 549 U.S. 497 (2007) (EPA's denial of a petition for rulemaking under Section 202(a) unlawful because EPA relied on reasons irrelevant to the statutory criteria).

The case law EPA properly relied upon in 2024 indicates administrative agencies typically have an inherent or assumed authority to revisit and revise prior actions under appropriate circumstances.

As discussed below, the explicit reference in §307(d)(1)(C) to "promulgation or revision" of residual risk emission standards is most naturally read the same way it is read for all of the other referenced provisions — a recognition by Congress that EPA has authority to revise the emission standards that have been promulgated.

In sum, the better reading of subsection (f)(2) is that EPA has the obligation and the authority to review and revise the standards over time, if appropriate, to ensure the standards meet the criteria established by Congress. As discussed below, EPA's arguments for its contrary interpretation are either wrong or of little weight.

(c) EPA's first justification or argument concerns the text of subsection (d) and what it implies about the meaning of subsection (f)(2). This appears to be EPA's main argument.

EPA points to Congress' imposition of a detailed, mandatory, eight-year review and revise cycle for technology-based standards under subsection (d) and contrasts it with the absence of the same or similar language for the residual risk standards in subsection (f)(2). From this absence of text EPA "infer[s] … that Congress did not authorize multiple risk reviews under section 112(f)(2)."[9]

This argument fails a basic logic test.

The case law EPA cites refers to a well-accepted tool for interpreting a statute. The logic of this tool is as follows: If Congress says A in one place but does not say A in another place, then it does not mean A in the second place. If Congress used A elsewhere, but left A out here, you could infer Congress meant to leave it out here. If the provision Congress put elsewhere is not here, then Congress did not intend that provision to apply here.

This tool and its logic have been used by courts when interpreting statutes in many different situations.

> Other statutes authorize the setting of tariffs. This statute does not refer to tariffs, so you do not have authority to set tariffs under this one. *Learning Resources, Inc. v. Trump*, 2026 WL 477534 (S. Ct. February 20, 2026).
>
> Other provisions in the statute mandate the release of information. This provision does not mandate release, so EPA may, but is not required, to disclose the information. *Environmental Defense Fund v. EPA*, 124 F.4th 1, 11 (D.C. Cir. December 2024).
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> Other provisions impose restrictions on the authority to remove an officer. This provision does not include those restrictions, so the authority to remove is not restricted in that manner. *Kennedy v. Braidwood Management, Inc.*, 2025 WL 1773628 (S. Ct. June 27, 2025).

[9] 91 FR 12700, 12712-713 (March 17, 2026).

> Other statutes use language that imposes a limitation on grantees. This statute does not include that language, so the limitation on grantees is not imposed here. *Medina v. Planned Parenthood South Atlantic*, 2025 WL 1758505 (S. Ct. June 26, 2025).

Here, Congress imposed a detailed, mandatory review and revise cycle, with eight-year deadlines, for the technology-based standards under subsection (d). Congress did not include a detailed, mandatory review and revise cycle, with periodic statutory deadlines, for the residual risk standards under subsection (f). Under the above logic, the absence of such a provision in subsection (f) would indicate that Congress did not intend to impose a mandatory review and revise cycle, with periodic statutory deadlines, for the residual risk standards. That is the proper inference to draw.

However, EPA goes much farther and draws a different and greater inference. EPA infers that the missing text means Congress also limited EPA to a one-time initial residual risk review and prohibited any subsequent risk reviews and standard setting by EPA.

This inference does not follow. The implication EPA draws (prohibiting any and all subsequent review and standard setting) is significantly different from and goes far beyond the scope of what Congress included in subsection (d) but left out of subsection (f) (mandating subsequent review on specified deadlines). It goes beyond the logic of this tool of statutory interpretation.

In a recent Toxic Substances Control Act (TSCA) case, the D.C. Circuit applied this tool of interpretation to determine that EPA had discretion to disclose certain information but was not mandated to disclose it. This was based on the presence in other provisions of language that required disclosure, but the absence of such language in the provision at issue.[10] The same approach applies here. The presence of mandatory, periodic eight-year review requirements in another provision, and the absence of such language in this provision, implies there is no mandatory review requirement with statutory deadlines in this provision. But the absence of the mandatory review text with statutory deadlines does not divest EPA of its authority to conduct subsequent reviews and standard setting, over time, when appropriate.

(d) EPA's second argument is that the 2024 interpretation causes major problems when considered in the context of the subsection (d) technology standards. EPA claims it would "effectively gut Congress's carefully articulated existing system" and would "disrupt[] the statutory scheme by eliminating the finality of residual risk reviews, undermining certainty for regulated industry and the public, and placing certain source categories on a different trajectory from the rest" and would be "inconsistent with CAA section 112(f) itself, which envisions potential further action from Congress."[11]

This is rhetoric without substance, assuming the very thing it needs to prove. It takes as a given that the proposed interpretation is right, e.g. eliminating the finality of initial risk reviews is only a disruption of the

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[10] *Environmental Defense Fund v. EPA*, 124 F.4th 1, 16 (D.C. Cir. December 2024) ("The best reading of the TSCA is that it permits, but does not require, the disclosure of all information that falls outside of the section 2613(a) prohibition on disclosure. Importantly, the TSCA does not contain a general requirement of disclosure for all non-confidential information. Instead, where Congress does require information to be disclosed, it states so expressly. … Such provisions suggest that, in the absence of an express mandate, EPA is not subject to a mandatory duty to disclose. See also id. § 2613(d) (listing information that "shall be disclosed" in specific circumstances). Thus, EPA is under no obligation to generally disclose all non-confidential information when not required to under one of the statute's express mandates.").

[11] 91 FR at 12713.

statutory scheme if the statutory scheme does not authorize reviews beyond the initial one. EPA presents no evidence of actual problems, and the small number of discretionary risk reviews over several decades show no sign of what EPA claims. Subsequent reviews do not interfere with future actions by Congress; Congress remains free to take any action it deems appropriate. Further discussion of this issue can be found below. This argument is of no merit.

Each of these claims needs to be addressed individually:

- Ad Hoc Basis: The 2024 Final Rule was clear that the motivation for revisiting risk for this source category is "additional information about the health risks of EtO that was not available at the 2006 RTR." Indeed, the 2006 rulemaking clearly pointed to the ongoing science review for this chemical and the possibility of revisiting the risk review. The basis is clear – and not *ad hoc*. It is in response to updated science and good science takes time.

  It is true that section 112(d)(6) provides for periodic technical reviews in light of "developments in practices, processes, and control technologies." No such similar provision is clearly stated in section 112(f)(2) to reflect advancements in science, which has occurred here for this chemical. EPA has, therefore, now taken the position that it cannot take action to protect human health – despite its clear mandate to do so under multiple sections of the law. EPA's record includes its own data showing the adverse effects of this chemical with maximum individual cancer risk more than 10 times the maximum "acceptable risk" benchmark of 100-in-1 million. For carcinogenic substances like EtO, EPA attempts to set emission standards within the 100- to 1-in-1 million range, while having to take into account cost and other relevant factors. EPA has failed to articulate how its proposed emissions standards are sufficiently protective of the public's health.

- Finality of Residual Risk Reviews: While section 112(f)(2) does require a one-time residual risk review, there is nothing in the statute that suggests any "finality" to EPA's ability to protect public health under the CAA. Furthermore, as noted in the April 5, 2024, Federal Register notice, the second residual risk review (conducted for the 2024 Final Rule) also encompasses certain area sources for which EPA did not evaluate residual risk previously. It goes on to note that although a risk review is not required for categories of area sources, it clearly does not prohibit such review. Indeed, the mere mention that "the Administrator shall not be required to conduct" such review reflects Congress's direction for EPA discretion on this matter. EPA also fails to recognize that unlike technology which changes over time, that the science of per unit health risks does not regularly change over time. Congress would not have required regular reviews based on changes in risk estimates since those do not happen with any reasonable frequency. The 10 year update of the EtO risk values shows how long it takes to update these values. The fact that Congress did not require something that does not happen on a reliable schedule is not proof that EPA does not have the ability to do it.

  It is also important to note that EPA's concern that the industry needs finality is negated by the Act's requirement that the standards be reevaluated every eight years, meaning that Section 112 standards never provide long term certainty to industry that the standards will not change over time. It makes no sense to claim that Congress was seeking long-term standard certainty for air toxics sources when it clearly wants the standards to be subject to change every 8 years.

- Undermining Certainty and Placing Certain Source Categories on a Different Trajectory: As initially flagged in the 2006 rulemaking, throughout the 10-year EPA science review process, and during the Agency's outreach actions following release of the 2014 National Air Toxics Assessment (NATA) (including extensive discussion with the affected industry), it was made clear that revised, tighter, not relaxed emission standards were needed for this source category. The industry has been on notice for 20 years that further emission reductions would be necessary for public health reasons. And, as noted in the 2024 Final Rule, "a number of facilities covered by this final rule have already implemented one or more of the controls that will be needed for compliance. Moreover, the EPA's own experience working with facility owners, as well as State and local agencies that have regulated EtO emissions from these facilities, confirms that "it is feasible for individual facilities to install the required controls well within the deadlines provided in this rule, and for multiple facilities to do so simultaneously."

In summary, as noted above (and stated clearly in the April 5, 2024, Federal Register notice) the "standard" for EPA's discretionary second residual risk review for this source category is "significant improvements to the science" which demonstrates that EtO is approximately 60 times more toxic than the Agency had understood when the first residual risk review was conducted 20 years ago. To ignore such information (along with Agency data showing that "approximately 23 of these facilities pose high lifetime cancer risks to surrounding communities, and some facilities pose exceptionally high risks that are among some of the highest for a CAA section 112(f)(2) risk assessment,") runs counter to the Agency's mission (and Congress' clear direction) to protect public health.

(e) EPA next argues that the 2024 rulemaking misreads and overreads past rulemakings in this area.[12] EPA's explanation is strained and unpersuasive. Further discussion of this can be found below. While this argument is not a baseless rhetorical flourish, it is an argument with little weight in determining the best reading of subsection (f)(2).

(f) EPA's final argument is a rebuttal of EPA's 2024 reliance in part on the fact Congress specifically referenced "promulgation or revision … of any … emission standard … under" subsection (f)(2) in section 307(d)(1)(C). Section 307(d) is a detailed provision that spells out procedural requirements for rulemakings under a wide number of CAA provisions. Setting emission standards under subsection (f)(2) is included in the list of these CAA provisions. In 2024, EPA pointed to this provision as indicating Congress understood that residual risk standards under subsection (f)(2) could be revised, typically in subsequent discretionary risk reviews.

EPA claims that the reference to subsection (f)(2) in 307(d) is consistent with its proposed interpretation. EPA argues that the reference to "revision" of subsection (f)(2) standards is quite limited in scope and refers solely to rulemakings to revise the initial, required standards either under the mandatory reconsideration provision in § 307(d)(7)(B) or on remand from judicial review of the initial standards.[13]

This is a stingy and inappropriately narrow interpretation of the reference to revision of standards under subsection (f)(2). Congress used the same phrasing "promulgation or revision" of standards throughout § 307(d)(1)(C), applying it to a long list of different CAA provisions. Typically, the multiple, identical use of a

[12] *Id.*
[13] *Id.*

phrase like this in a single statutory provision calls for giving it the same meaning every time it is used. EPA claims it means one thing for all the other times it is used in § 307(d)(1)(C) – any revision of the standards, whether the rulemaking is discretionary or mandatory, and whether it is on judicial remand or not. However, the one time it is used in reference to subsection (f)(2), the phrase has a very different and much narrower meaning. There is no indication Congress meant this kind of result, and EPA offers no specific support for this argument.

In addition, § 307(d)(7)(B) already addresses the rulemaking procedures required for mandatory reconsideration under that provision. Further, both rulemaking under the reconsideration provision and rulemaking on remand from a court would be seen as part of the initial risk review and standard setting. The reference to "revision" in §307(d)(1)(C) would appear to be superfluous if its scope was limited in the way EPA proposes. Interpretations that make a provision superfluous are to be avoided, not endorsed.[14]

EPA's proposed explanation for Congress' use of the phrase "promulgation or revision" of standards in reference to subsection (f)(2) is quite strained and unnatural, and appears to make the reference superfluous. It certainly is not the best reading of that provision. Instead, the reference is readily read to indicate a recognition by Congress that revisions of the residual risk standards could occur. That fits smoothly with EPA's 2024 interpretation of the residual risk provision.

3. Finally, but of great importance, EPA fails to discuss how its proposed interpretation relates to the public health and welfare objectives of the CAA. Subsection (f) makes clear that Congress recognized there could be important risks remaining after adoption of the technology-based standards under subsection (d). It determined that EPA should play a role in addressing those risks, with the objective of ensuring the public receives the appropriate margin of safety and reduction in risk of cancer. The issue here is determining the proper scope of the role Congress assigned to EPA.

EPA's 2024 interpretation establishes a typical role under the CAA. EPA monitors the situation over time, and as science and technology progress, if the facts show unacceptable risk (as defined in subsection (f)(2)) or facts are otherwise appropriate), EPA reviews and updates the applicable standards so they continue to meet the criteria set by Congress to assure safety from exposure to air toxics. This is a logical and typical path under the CAA for addressing the public health and welfare problems associated with long-term air pollution problems.

EPA's proposal assigns a totally different role to EPA. EPA reviews residual risk once, sets appropriate standards, and has no role after that. It doesn't matter what the future teaches us about the nature or degree of residual risk, including cancer risk. EPA can do nothing more under subsection (f)(2), the very provision Congress established to assure safety from exposure to air toxics.

It seems strange that Congress would be concerned enough about residual risk to public health and welfare to identify it as a problem, set up a regulatory structure to address it, but set it up in a way that EPA must address residual risk once, at one point in time, but never address it again. Prohibiting EPA from ever again

[14] *Est. of Levin v. Wells Fargo Bank, N.A.*, No. 23-7080, 2025 WL 2737588, p.12 (D.C. Cir. Sept. 26, 2025) ("Furthermore, regardless of whether the government's interpretation of "frozen" would reduce the license exception entirely to surplusage, or would simply render it implausibly narrow, that structural consideration cuts against its proposed interpretation. *See Mackey v. Lanier Collection Agency & Serv., Inc.*, 486 U.S. 825, 837, 108 S.Ct. 2182, 100 L.Ed.2d 836 (1988).").

reviewing and revising the residual risk standards, irrespective of what future circumstances tell us, is inconsistent with the fact Congress recognized residual risk as a public health and welfare problem that needed to be addressed. There are no indications Congress believed it was a one-time, short-term public health and welfare problem. Congress recognized that addressing the public health and environmental threats of air pollution was not a "one and done" proposition.[15] Multiple provisions that authorize, and in some cases require, that standards be updated to take account of scientific advances, support an interpretation of subsection (f)(2) that is empowering rather than constraining. EPA's proposed interpretation lacks an underlying logic that reasonably ties it to protection of public health and welfare from an air pollution problem Congress determined needed to be addressed and knew could change over time.

At the same time, there is an obvious public health and welfare logic in EPA's 2024 interpretation, consistent with statutory text, and with the Benzene NESHAP it codifies. Residual risk is a long-term problem and there is a public health and welfare value in EPA monitoring over time and taking appropriate action to address residual risk if future circumstances show it is needed. The 2024 rulemaking exemplifies this.

It's also worth nothing that EPA stated clearly and unequivocally in the 2006 Rule that it can revisit risk. In responding to a public comment on the proposed Rule (which claimed that there is no mechanism to revisit section 112(f) assessments), EPA stated:

> "We disagree with the commentor's assertion that there is no mechanism to revisit risks from the source category... We have the authority to revisit (and revise, if necessary) any rulemaking if there is sufficient evidence that changes which the affected industry or significant improvement in science suggest the public is exposed to significant increases in risks as compared to the risk assessment for the rulemaking (e.g., CAA section 301)."

EPA attempts to dismiss its prior, long-standing position by claiming that the 2024 Final Rule "overread" this statement and now should be read as a reference to section 112(d)(6) and, furthermore, that the statement "does not stand for the proposition that the Agency anticipated finalizing an entirely new residual risk review and associated standards nearly 20 years later." Based on the facts at hand, these claims are unfounded and, certainly, disingenuous.

First, the public comment and the Agency's response clearly point to its authority in revisiting risk reviews. There is no reference in the comment or response to technology reviews. It seems like the Agency is now trying to create (20 years later) a reading that is not supported by its own words.

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[15] Section 112 (f)(2) essentially codified EPA's Benzene NESHAP rule and the D.C. Circuit's en banc *Vinyl Chloride* opinion (*NRDC v. EPA*, 824 F. 2d 1146 (D.C. Cir. 1987). *See, e.g.* S. Rep. no. 101-228 (101st Congress, 1st session at 178, 181; A Legislative History of the Clean Air Act Amendments of 1990, S. Pet. 103-38 vol. 1 at 877. The Benzene NESHAP, and the underlying D.C. Circuit en banc opinion, require that standards for air toxics be established at levels that are safe (as determined under the Benzene NESHAP formulation). There is no hint in either the NESHAP rule or the court's opinion that the Agency's hands are tied once it makes an initial determination. Nor can there be. That would mean that it is permissible for the agency to leave in place standards that are unsafe. This does not make sense and is antithetical to the statutory text, its purpose and the history of subsection (f). Other provisions of § 112 likewise indicate the regulatory structure Congress adopted to address this air toxics pollution problem was intended to be responsive to changes over time, to be dynamic and not static. In addition to subsection (d), *see*, *e.g.*, subsections (b)(2) and (3) (changes over time to the initial list of HAPs), subsections (c)(5) and (9) (changes over time to the list of regulated source categories), subsection (l)(6) (withdrawal of prior approval of a State program), and subsection (r)(6) (changes over time to the initial list of HAPs subject to the accidental release provisions).

Second, concerning the 20-year timeframe, that reflects the deliberative, necessary process EPA went through to get the science right and to follow the law for this important source category – see **Table 1**, below. The lengthy time it took to finalize revised emission standard included a thorough science review (over a 10-year period involving two rounds of transparent peer review and public comment), detailed data collection for a complicated source category, coordination with other affected federal agencies (especially, the Food and Drug Administration), and engagement with communities located next to sterilization facilities. Many times, EPA explained to various groups – including its own OIG and congressional interests – the reasons why its regulatory process was taking so long.

EPA has not now nor anytime in the past 20 years attempted to rebut its claim made in the 2006 rulemaking that EPA has the necessary authority to revisit an existing emission standard. According to the statute, "the Administrator is authorized to prescribe such regulations as are necessary to carry out his functions under this chapter." Those functions include, as stated in CAA section 101, to "promote reasonable Federal, State and local governmental actions... for pollution prevention" and, furthermore, to "protect and enhance the quality of the Nation's air resources so as to promote public health and welfare and the productive capacity of the population."

EtO Carcinogenicity Value

The chief rationale for EPA's 2024 revision of the commercial sterilization facility standards, published in 2006 on the basis of an RTR review, was to re-assess the associated risks using an EtO carcinogenicity potency value that had been unavailable at the time of the original RTR. This new value – finalized in 2016 and made available in EPA's Integrated Risk Information System (IRIS) following extensive review by the public, the agency's Science Advisory Board (SAB), and EPA – had a significantly higher potency than that used in the 2006 RTR. When used in evaluating exposures of residents in the environs of these facilities, it was found, as noted below, that thousands of people have unacceptably high exposures, i.e., cancer risks greater than the minimally acceptable 100 in a million.

In its March 2026 proposal, EPA has provided no estimate, or even mention, of the real cancer risks posed to those citizens living close to these facilities. EPA should reaffirm the results of its 2024 assessment and acknowledge the high baseline estimated cancer risks resulting from EtO exposures identified in the 2024 rule and how the 2024 rule significantly mitigates these risks:

- Baseline: 19,000 people living within 10 km of EtO sterilization facilities with estimated risks of *greater than* 100 in 1 million.
    - Post 2024 rule controls: zero people.
- Baseline: 124,000 people living within 10 km of EtO sterilization facilities with estimated risks of g*reater than or equal to* 50 in 1 million.
    - Post 2024 rule controls: 170 people.[16]

As noted on EPA's website:

> "The DNA-damaging properties of EtO have been studied since the 1940s. EtO is known to be mutagenic in a large number of living organisms, ranging from bacteriophage to mammals, and it

[16] US EPA Regulatory Impact Analysis for the Final National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Commercial Sterilization and Fumigation Operations, EPA-452/r-24-011, March 2024, pp 4-9 – 4-13

> also induces chromosome damage. It is carcinogenic in mice and rats, including tumors of the lymphohematopoietic system, brain, lung, connective tissue, uterus, and mammary gland. In humans employed in EtO-manufacturing facilities and in sterilizing facilities, there is strong evidence of an increased risk of cancer of the lymphohematopoietic system and of breast cancer in females."[17]

It also should be noted that EtO is a germ cell mutagen which means that any DNA damage it suffers can be inherited if it survives the insult.

According to the American Cancer Society's 2024 and 2025 reports, **40% to 42% of men** and **39% to 40% of women** will be diagnosed with some form of cancer sometime during their lifetime.[18] In the United States, four out of 10 cancer cases are associated with modifiable (that is, non-genetic) risk factors.[19] So, EtO-associated cancer should be a concern (and was previously determined so by EPA) and, more importantly, is preventable. That's what the law is supposed to do – protect the health of the American public.

EPA's March 2026 proposal lacks any estimate of associated risks and discussion of the health disbenefits due to the foregone emission reductions associated with this proposed action. Page 12734 merely mentions that the proposed reconsideration will increase EtO emissions by almost 8 tons per year relative to the 2024 Final Rule. It goes on to say that the associated health effects of this emissions increase are discussed qualitatively in the Regulatory Impact Analysis. The meager 16-page RIA memo contains a mere seven sentences on the topic of the health effects of EtO exposure; mostly repeating the information cited above (e.g., carcinogenic to humans, increases risk to lymphoid cancer and female breast cancer, and mutagenic). There is no discussion of the adverse health effects and increased public health risk of the proposed foregone emission reduction of almost 8 tons per year. This demonstrates clearly that EPA has not considered the impact of its proposed action on public health. Consistent with how EPA has treated health effects caused by the increased pollution following multiple repeals of existing environmental protections since 2025, EPA has failed to analyze the health impacts of its actions and has given no value to the resulting disease and death.

The March 2026 proposal notes that EPA is soliciting comments on the information in comments on the 2016 EtO IRIS value provided in the context of other rulemaking proposals, including the January 2025 proposed Chemical Manufacturing Area Sources NESHAP (see Question 6 on Page 12715). That prior proposal recognizes that "EPA received numerous comments in favor of and opposed to the proposed listing and regulation of EtO from area sources that produce a material or family of materials described by NAICS code 325 (chemical manufacturing) and the Agency needs additional time to consider those comments before taking final action." The March 2026 proposal identifies five specific comments from four commenters. Of the four, the comments provided by the American Chemistry Council (ACC, 2025) and the Texas Commission of Environmental Quality (TCEQ, 2025) offered specific technical comment on EPA's assessment of EtO cancer risks, as supported by the IRIS risk assessment for EtO (EPA, 2016). Because the ACC and TCEQ 2025 comments overlap on many matters, it is efficient to discuss these comments jointly. A thorough presentation of our responses to these comments is provided in **Appendix A**. In sum, we believe that the ACC and TCEQ comments are flawed, and strongly encourage EPA to stick with its

[17] https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=329730
[18] American Cancer Society, Cancer Facts & Figures 2026.
[19] AACR Cancer Disparities Progress Report-2024.

2016 assessment and corresponding IRIS value for EtO. We wish to also note that EPA has previously responded to many comments on the IRIS assessment and EtO dose response including earlier submissions by ACC and TCEQ. Most content in their 2025 comments recapitulate and further opine on matters from earlier comments and corresponding EPA responses. A partial list of earlier EPA responses to comments regarding EtO cancer dose response matters is also provided in **Appendix A**.

Finally, on March 31, 2020, the Agency's OIG issued a Management Alert related to EtO in which the OIG stated that the EPA's mission statement includes working to ensure that "all parts of society…have access to accurate information sufficient to effectively participate in managing human health and environmental risk."[20] EPA's failure here to address (or even mention) the severe toxicity of this chemical and the risk it poses to neighboring communities is irresponsible and runs counter to the direction from its own OIG.

EPA should not walk away from its own well-established science; rather, it should reaffirm its 2016 EtO potency value and apply it in a well-documented risk assessment.

EPA's Reliance on Uncertainty as an Additional Reason for Rescinding Existing Standards
All regulatory decision-making involves some degree of uncertainty. Here, EPA is taking the position that "significant uncertainties regarding the magnitude of EtO's carcinogenic potency…would be an additional reason for rescinding the EtO standards in the 2024 Rule."[21] EPA has, however, provided little evidence of what makes the uncertainty here so "significant" that it is grounds for rescinding the existing emission standards for this source category.

First, EPA cites a memo[22] from its Office of Research and Development (ORD) that was prepared in 2019 in response to an inquiry from the Agency's Office of Air Quality Planning and Standards (OAQPS) about the dose-response selection for the IRIS EtO inhalation unit risk. Based on an examination of information in the Agency's 2016 EtO IRIS assessment, an ORD staff person synthesized the information on the range of model forms evaluated in the IRIS assessment and identified additional models examined that can reasonably contribute to quantitatively characterizing model and statistical uncertainty in cancer risks associated with environmental exposure to EtO. This non-peer-reviewed memo considered the well-documented impact of EtO on female breast cancer and lymphoid cancers.

On one hand, ORD reported that for the upper bound of unit risk estimate "(i)f all combination of models for both cancers are considered, then total cancer unit risk estimates range from approximately the same to 5 times lower than the IRIS recommended value." Furthermore, "[i]f all combinations of models for both cancers are considered, central estimates of total risk range from approximately equal to 3 times lower than the central estimates from the selected spline models."

On the other hand, EPA failed to note that ORD also stated clearly that

> "The IRIS unit risk should not be considered **a worst-case analysis**. Higher estimates of risk were obtained using some other models providing statistically appropriate fits to the data. While there

[20] https://www.epa.gov/sites/default/files/2020-03/documents/_epaoig_20200331-20-n-0128_0.pdf
[21] https://www.federalregister.gov/d/2023-06676/p-253
[22] Sensitivity of Ethylene Oxide Risk Estimates to Dose-Response Model Selection. Memorandum drafted by EPA's Office of Research and Development, docketed in the Miscellaneous Organic Chemical Manufacturing NESHAP Proposed Rule, 84 FR 69182 (Dec. 17, 2019).

were limitations with these models, and we have noted them in this analysis, it is likely that a comprehensive analysis of alternative models…would likely include some risk estimates higher than the chosen IRIS unit risk."[23] (emphasis added)

EPA, on the basis of no serious analysis, is now taking the position that all uncertainty is to always be assumed to only reduce risks. EPA needs to acknowledge that uncertainty goes both ways and that risks could be greater than the listed values. For example, EPA's analysis fails to take into account risks to future generations from germ cell mutations and the possible synergistic impact of EtO with other pollutants in the environment. It may be noted that during the first Trump administration, EPA regulated EtO emissions using the IRIS value after having provided due consideration to the alternative model estimates generated in the ORD memo to characterize uncertainties. Alternative estimates generated for an uncertainty analysis however cannot all be treated on the same footing. This is because model selection is based on the best statistical fit to the underlying data and a determination of which of the models with overall good fit better reproduces the data at lower exposure concentrations (the range of relevance).

It is unfortunate that EPA has not provided a full and fair presentation of the ORD memo – choosing only to selectively cite the "5 times lower" result. (EPA uses this result to make the ludicrous claim about the "safety" of this dangerous chemical.) Nowhere has EPA recognized the additional finding of "approximately the same" and "approximately equal," nor the finding that higher risk estimates are likely. This unbalanced presentation of the information undermines EPA's claims and is a clear indication of EPA's bias in taking this action.

The American Chemistry Council (ACC) and others have used the issue of endogenous production of EtO in arguing against the 2024 rule. Echoing these arguments, EPA makes the ridiculous statement that "(it) is known that EtO can be produced within the body (endogenously) via normal metabolic processes and that tobacco smoke is a source of EtO exposure." EPA's reason for even raising the contribution of endogenous and tobacco smoke EtO levels appears to create further unnecessary, unsubstantiated distraction. These arguments have been addressed at length within the main body as well in explicit response to comments in several EPA documents on EtO. The fact that there are other sources of a dangerous chemical is not a "get out of jail free card" to polluters to increase exposure from a hazardous chemical. If anything, it shows a reason for increased caution since the pollution is adding risk to an already significant body burden in the population.

It is important to recognize that the IRIS cancer potency estimate for EtO is used in the context of this rulemaking to estimate human health risks associated only with emissions from the commercial sterilization facilities themselves – these estimated risks do <u>not</u> consider any additional estimated potential risks that may exist from endogenous or ambient background levels of EtO in commercial sterilization facility environments. As discussed in EPA's response to comments on the 2020 NESHAP reconsideration, the occupational exposures in the National Institute for Occupational Safety and Health (NIOSH) study[24] represent workplace EtO levels and are in addition to any endogenous or broad population background exposures to which the workers may also have been exposed. Likewise, the risk estimates are computed with reference to individuals in the absence of occupational exposure – but these reference individuals would also have exposure to population background and endogenous EtO. Thus, endogenous exposures (and baseline

[23] Id.
[24] https://www.federalregister.gov/d/2022-27522/p-89.

population level risks that may result from these exposures) have been accounted for in development of the EtO IRIS dose-response assessment. Nonetheless, it is true that high and variable endogenous and background levels would lead to greater statistical uncertainty in attributing risks from low levels of marginal additional exposures to EtO. However, as explained in the response to comments section of the 2024 rule document, the cited measurements of endogenous and background levels were not reliable. Analyses funded by the ACC have relied on endogenous equivalents (not direct measurements) based on hemoglobin adducts formed by EtO. EPA has explained that individuals on whom these measurements were made were also exposed to ambient EtO. Furthermore, a recent paper by Lin *et al* (2025)[25] shows that it is not possible to explain the high background levels of N-(2-hydroxyethyl)valine (HEV) hemoglobin adducts observed in non-smokers in these studies and that endogenous EtO is much lower than inferred from measurements of these adducts.

Arguments pertaining to the impact of endogenous production of EtO also embed a fallacious or, at best, unsupported assumption that endogenous levels do not contribute to background rates of cancer. It is unknown how much the endogenous or background levels of EtO contribute to background rates. Indeed, the SAB peer review of the IRIS assessment had concluded that "based on the discussion presented in the assessment and considering the weight of evidence from human and animal studies, the SAB finds EPA's conclusion on endogenous exposure to EtO to be supported."

Finally, EPA references both its own 2016 updated assessment and the 2020 Texas Commission on Environmental Quality (TCEQ) assessment[26] – seeming to place the two on equal footing, which is an unsupportable conclusion. Based on the Agency's very deliberative 10-year process, which included two rounds of peer review and public comment (see milestones in Table 1 below), the Agency determined in 2016 that: (1) confidence in the hazard characterization of EtO as "carcinogenic to humans" is high, and (2) confidence in the updated unit risk estimate is high. EPA placed considerable weight on two studies of sterilization workers released in 2003 and 2004 by NIOSH. The NIOSH studies reported positive exposure-response trends for lymphohematopoietic cancer mortality particularly in males and for breast cancer mortality in females. A follow-up study issued in 2025 of these occupational exposures found further evidence that "EtO is a human breast carcinogen" and pointed out the "serious public health importance" of EtO exposures.[27]

EPA cites the above study (Kelly-Reif et al, 2025) as new evidence possibly triggering a need to reevaluate toxicity values. This study is a follow up of the prior NIOSH study and its results provide a stronger confirmation of the risks of breast cancer as well as the shape of the dose-response curve used in IRIS (i.e. a plateau-ing of the risk at higher exposures). These results reinforce the results of the IRIS assessment, suggesting the cancer potency may even be higher. Therefore, there is an urgent need to protect vulnerable populations, not delay regulation as EPA argues.

TCEQ's assessment, on the other hand, lacks both a sound scientific basis and credible peer review. In particular, the National Academies of Science, Engineering, and Math's March 2025 review[28] of TCEQ's Development Support Document concluded that the "lack of application of systematic review methods, the

[25] Lin YS, Thayer KA, White P, Morozov V, Persad AS. J Exposure Science & Environmental Epidemiology (2025).
[26] https://www.tceq.texas.gov/downloads/toxicology/dsd/final/eto.pdf
[27] Kelly-Reif K., Bertke S.J., Staynew L., Steensland K. "Exposure to Ethylene Oxide and Relative Rates of Female Breast Cancer Mortality: 62 Years of Follow-Up in a Large US Occupational Cohort", Environ Health Perspect, May 2025.
[28] https://www.nationalacademies.org/projects/DELS-BEST-23-01

exclusion of critical epidemiological data, the limitations in the modeling approach and use of unpublished validation data all contribute to a lack of confidence in TCEQ's risk assessment of ethylene oxide." Clearly, the robust EPA assessment and the deficient TCEQ assessment should not be considered comparable in any way and do not support EPA's latest claim that their differences are indicative of uncertainty in the science. The science was sound in EPA's 2016 assessment and is further supported by subsequent valid studies (e.g., the 2025 Keely-Reif paper).

It should be noted that in formulating its 2020 rule,[29] EPA granted reconsideration (and invited public comment) on using the TCEQ estimate as an alternative to the IRIS value. However, upon due consideration, EPA issued its final rule that rejected the TCEQ estimate and reaffirmed use of the IRIS value.

Even if EPA were to incorrectly decide it is not appropriate to rely on the 2016 EtO IRIS value, EPA must decide on some value and provide the rationale for its decision and allow comment on it. In this proposal, EPA provides no serious scientific analysis or evidence for rejection of the 2016 value. It is not enough for EPA to say some comments were received in another rulemaking.

Additionally, EPA misreads *Ass'n of Battery Recyclers, Inc. v. EPA*,[30] when it says that a technology review is not necessary. In fact, the case says just the opposite: "To the contrary, the statute directs EPA to "tak[e] into account developments in practices, processes, and control technologies."[31] This means that EPA must do an analysis of the developments in practices, processes, and control technologies before making any change to the 112(d)(6) standards. The existing analysis is out of date. EPA needs to provide that analysis and take comments on it.

EPA has Failed to Discuss the Burden Its Proposed Action Will Have on Neighboring Communities

For almost five years – from 2019 to 2023 – EPA conducted extensive outreach and communication with the people who live and breathe the air around commercial sterilization facilities. It's important to remind EPA about this engagement and its prior messaging to these communities and how they are relying on the federal government to protect their health.

In August 2018, EPA released its next version of the NATA - the Agency's tool that provides information on potential health risks from breathing air toxics. Among other things, the assessment found that more than 20 areas could have elevated cancer risks from long-term exposure to EtO. The elevated risks were driven by the EPA IRIS risk value for EtO that was updated in December 2016.

Following release of the NATA, EPA interacted with some communities and responded to multiple congressional interests. In written correspondence in Spring 2019, EPA laid out a dual approach to address EtO emissions around the county: (1) review and update CAA regulations for facilities that emit EtO, and (2) gather additional information on EtO emissions to help EPA evaluate opportunities to reduce EtO emissions as part of its regulatory review and help the Agency determine whether more immediate emission

[29] Reconsideration of the 2020 National Emission Standards for Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing Residual Risk and Technology Review, 87 Fed. Reg. 6466, 6467 (proposed Feb. 4, 2022).
[30] 716 F.3d 667 (D.C. Cir. 2013).
[31] 42 U.S.C. § 7412(d)(6)" Emphasis added.

reduction steps are necessary in particular locations. And in correspondence later in 2019, EPA also recognized that it was critical to actively engage with affected communities and reported that several EPA regional offices had conducted or participated in meetings with local elected officials and community groups. The Agency expressed its commitment to continue this engagement.

Over concerns about the pace and transparency of EPA's outreach efforts, the Agency's OIG issued its March 2020 Management Alert. The OIG recommended that the Agency provide residents in all communities near 25 high-priority EtO-emitting facilities with a forum for an interactive exchange of information with EPA or state personnel regarding health concerns related to exposure of EtO.

In May 2020, the Agency proposed to the OIG a two-part corrective action plan with milestones. Part 1 of the plan was to conduct additional, more-refined investigations of risk. Part 2 was to conduct outreach to affected communities. EPA noted that outreach had already occurred or was planned for many of these areas, and intended to coordinate outreach with the appropriate state air agencies in the other areas.

Although the Agency and the OIG exchanged several memos concerning the adequacy of the proposed plan, the Agency forged ahead with the plan and posted regular updates on its technical and outreach efforts for all of the areas of interest. For example, reports posted in January 2021 summarize in-person and virtual meetings with affected communities, interactions with congressional and community groups, and citations concerning shared materials. On its (former) website for this work, EPA also noted that it was generating new risk estimates for EtO sterilizers across the country as part of developing a proposed revision to the NESHAP for these facilities. EPA committed to share this information with the public as part of its upcoming proposed rule.

Following the collection of additional emissions-related data for sterilization facilities in 2020 and 2021 (e.g., two information collection requests, comments received in response to an Advance Notice of Proposed Rulemaking, and information obtained through a Small Business Advocacy Review panel) and completion of updated, more refined risk assessments, in Spring 2022, EPA reached out to state air agencies to describe a 3-phase approach for outreach, including a national launch, community engagement, and ongoing engagement with an emphasis on reliable communication of risks. The purposes of this risk communication were to: (1) inform residents about risks from EtO (and what EPA, state agencies and the facilities were doing about those risks), (2) increase community involvement in the rule-making process and increase partnership between communities, states, and facilities to lower risk, and (3) "increase trust that EPA is taking this issue incredibly seriously and is dedicated to making change." At that time, EPA identified 30 facilities associated with elevated risk (greater than 100-in-1-million) due to EtO and noted that many commercial sterilization facilities are located near residences and schools, and disproportionately impact communities of color and low-income communities.

In August 2022, EPA announced its plans to engage and inform communities, states, Tribes, Territories and stakeholders about up-to-date information on the risks posed by air emissions of EtO from commercial sterilizers. EPA committed to do everything it can to "share critical information on exposure risk to the people who need and deserve this information, and to take action to protect communities from pollution." EPA's phased outreach approach consisted of a national public webinar followed by community-specific engagements starting with communities where the risk is the highest. These engagements were largely led by EPA regional offices and state and local air agencies and continued over the following months.

In total, EPA and its state partners interacted with more than 50 communities across the country following release of its NATA in 2018 and in advance of its 2023 proposed rulemaking. In all of these interactions, federal and state governments expressed their concern about the toxicity of EtO, the need to achieve reductions in emissions of EtO to the outdoor air, and their intentions to use available authorities to protect the health of people living near commercial sterilizers. It is unclear what EPA's message to these same communities is now in light of the current proposed action. In particular, EPA estimates that the foregone benefit of this proposed action will be an additional almost 8 tons of EtO annually being emitted into the Nation's air. Over the course of a human lifetime, the extra EtO will further increase the cancer risk posed to these neighboring communities, a risk that CAN be quantified based upon currently available information. A question often posed by people living near these facilities is "am I safe"? EPA needs to provide an honest answer to these communities about whether its proposed action will ensure their safety from a public health standpoint.

EPA should also restore the 2024 rule's requirements for continuous emissions monitors (CEMS) and quarterly reporting for most commercial sterilizers that will provide communities, States, Tribes, and local governments, and EPA with data to ensure EtO emissions are not entering the outdoor air.

Finally, EPA's proposal lists a number of questions to solicit feedback on specific issues. Question 1 is whether the 2024 Final Rule and underlying interpretations have generated reliance interests which could support retaining an action that, in EPA's current opinion, is inconsistent with the best reading of the statute. On page 12705 of the proposal, EPA states that it does not believe that the standards or supporting interpretations adopted in the 2024 Final Rule have generated significant and reliance interests. The 2024 rulemaking was a direct response to the public outcry on EtO and, consequently, the public clearly has a reliance interest in EPA fixing a public health problem which the agency promised to do. EPA should, therefore, consider the interests of the neighboring communities in addressing EtO under the CAA.

EPA's Proposed Action Adversely Affects Children

In the 2026 proposal's discussion of Executive Order 13045: Protection of Children From Environmental Health Risks and Safety Risks, the Agency admits that "this action may have a disproportionate effect on children." EPN agrees that the environmental health and safety risks addressed by this action do present a disproportionate risk to children due to EtO being mutagenic (i.e., it can damage DNA). The complete lack in this proposal of any meaningful analysis of an acknowledged potential risk constitutes a substantive flaw. EPA should withdraw this proposal and, if it chooses to go forward with this action, include actual analysis of the expected increased risk to children from the increased EtO exposure that would result from weakening the rule's control requirements.

Aeration Room Vent Analysis

EPA states that the 2024 analysis for new aeration room vents (ARVs) was incorrect in selecting the 99.9% EtO reduction option because it was more cost effective than the 99.6% EtO reduction. EPA claims that "a new ARV could share and make use of ductwork, control devices, and other existing infrastructure for the ARVs already in place at the facility; therefore, the expected capital and annual costs for the 99.6% reduction option would be much lower than the estimate in the 2024 Final Rule."[32] EPA ignores the fact that its proposal makes clear that at least 50% of the facilities in 2024 already met the 99.9% reduction level. Considering all the public focus on sterilizers, it is quite likely that the number has climbed. EPA has not

[32] https://www.federalregister.gov/d/2026-05167/p-216

done any analysis since the 2024 review was completed of what the current level of controls are. EPA claims that the cost effectiveness has changed but again provides no data or analysis to support that conclusion. EPA also does not explain why it believes that the public should bear additional risks in all the cases where an existing facility that does not meet either the 99.6 or the 99.9% reduction level should not be required to meet the more cost effective 99.9% reduction level. Based on the proposal, they are the same 25% of all facilities or the same number as the 25% of facilities meeting the 99.6% level but not the 99.9% level. EPA also does not present any data to show why it believes that most or many or, for that matter, any "new" ARVs will be built at locations with 99.6% control levels. Similarly, EPA ignores the construction of completely new ARVs facilities. It seems highly unlikely that no new facilities will ever be built in the U.S. in the future. If EPA has any actual analysis that is more than hand waving, it needs to present that to the public for additional comment.

Medical Supply Chain Analysis

EtO is complicated and requires a fuller and more honest presentation to the public than EPA has provided in this proposal. EPA's announcement of the current action states: "EPA Releases Proposal for Commercial Sterilizers to Safeguard the Supply of Life-Saving Medical Tools." It is certainly true that "commercial sterilizers provide a critical benefit for the health of all" and "play a vital role in maintaining an adequate supply of sterilized medical devices for public health needs in the U.S.," as noted in the 2024 Final Rule. According to the FDA, more than 20 billion medical devices used in the U.S. every year are sterilized with EtO – approximately half of medical devices that need to be sterilized.

However, EPA's announcement provides a false, or at least utterly unsupported, sense of importance – it is noteworthy that EPA "was not able to quantitatively assess potential market impacts for this proposed rule." Indeed, the Agency merely speculates that "it is likely that this proposed reconsideration would reduce the risk of capacity constraints in the sterilization sector." EPA provides no real data here; thus, undermining its claim that the proposed action would actually "safeguard the supply of live-saving medical tools."

If EPA has any evidence that the existing standards make running sterilizers so uneconomical that facilities will be likely to close and will need to be replaced with imported sterilized medical devices, it needs to provide it to the public for comment. We see no reason to believe that is true. For example, one study showed that "device reprocessing, including maintenance, packaging, labor, and high-level disinfection, costs approximately $0.51 to $0.77 per instrument," while another study showed the "average cost of medical device reprocessing for one instrument was $0.34 to $0.47 in a tray and $0.81 to $0.84 for an instrument in a peel pack."[33] These low costs seem to show that reducing the costs of sterilization under the existing rules is not necessary to prevent an industry-wide risk of bankruptcy; especially when compared to the additional costs and risks of shipping sterilized equipment from overseas.

We would argue that the bigger risk to the commercial viability of sterilizers is public outrage over the risks they present. For example, as it says on EPA's website, "Sterigenics was a commercial sterilizer that used ethylene oxide (EtO) to sterilize medical equipment and other products in Willowbrook, Ill. It had been operating in Building 1 (7775 Quincy Street) since 1984 and in Building II (830 Midway) since 1999. The facility has not operated since the State of Illinois issued a seal order on February 15, 2019. On September 30, 2019, Sterigenics announced that it would be discontinuing operations at the Willowbrook facility."[34] We

[33] https://remmed.com/how-much-does-it-cost-to-reprocess-medical-devices/
[34] https://www.epa.gov/il/sterigenics-willowbrook-facility

would also point out that Sterigenics also had "to pay $408 million to settle hundreds of lawsuits over toxic gas emissions. The company agrees to settle more than 870 suits alleging that its Willowbrook plant released ethylene oxide gas. Last year, a jury awarded a cancer survivor $363 million."[35]

Conclusion

EPA's 2024 interpretation of section 112(f)(2) is well-reasoned and persuasive. Consistent with that interpretation and as discussed above, the better interpretation is that EPA has the obligation and authority to review and revise the standards over time, if appropriate, to ensure that they meet the criteria set by Congress for margin of safety, reduction in cancer risk, and safety from exposure to air toxics. Under this interpretation the 2024 rulemaking and standard setting was fully authorized under subsection 112(f)(2). EPA's proposed contrary interpretation is atextual, based on illogical arguments, arguments without evidence, arguments of little merit and weight, and a strained and unlikely interpretation of a related provision on procedures for rulemaking. It ignores the public health and welfare objectives of §112(f) and the CAA. EPA's current proposal is not the better reading of this provision, by far, and EPA should not adopt it.

Table 1. EPA Actions to address EtO following promulgation of 2006 rule

April 2006	Final decision on EtO Emissions Standards for Sterilization Facilities
June 2006	EPA publishes Health Assessment Document for EtO
Sept. 2006	EPA releases draft reassessment for 30-day public comment period
Jan. 2007	Peer review meeting of the SAB
Dec. 2007	SAB issues a final report on the review of the draft assessment of EtO
July 2011	EPA initiates Final Agency and an Interagency Science Discussion of a revised draft assessment of EtO
June 2012	EPA conducts further Agency review of a revised draft assessment of EtO
July 2013	EPA revises draft assessment and releases it for additional public review and comment
Dec. 2013	EPA hosts IRIS public science meeting to discuss draft assessment released for public comment
Aug. 2014	EPA submits draft assessment (revised in response to public comments) to SAB for extended peer review
Nov. 2014	SAB hosts a panel meeting for the SAB Chemical Assessment Advisory Committee

[35] https://chicago.suntimes.com/2023/1/9/23547780/sterigenics-to-pay-408-million-settle-hundreds-of-lawsuits-over-toxic-gas-emissions

Aug. 2015	SAB issues a final report on its review of the draft assessment of EtO
Oct. 2016	EPA submits a revised draft for final Agency Review and Interagency Science Discussion
Dec. 2016	EPA posts final Evaluation of the Inhalation Carcinogenicity of EtO to the IRIS database
2017	EPA conducts analyses using the updated IRIS value as part of the Agency's next NATA (i.e, 2014 NATA)
2018	August EPA releases 2014 NATA and, under the oversight of the Agency Office of Inspector General, initiates engagement with a number of EtO-impacted communities
2018-2019	EPA begins work on potential revisions to the EtO Emissions Standards for Sterilization Facilities. EPA also begins coordination with other federal agencies.
Dec. 2019	EPA issues Advance Notice of Proposed Rulemaking to solicit information that will aid in potential future revisions to EtO Emissions Standards. The notice includes discussion of the risks posed by EtO.
2020-2021	EPA convenes Small Business Advisory Review Panel as required by section 609(b) of the Regulatory Flexibility Act EPA issues two proposed Information Collection Requests - one in May 2020 and one in May 2021
May 2023	EPA proposes revised emission standards
April 2024	EPA finalizes revised emission standards

Appendix A. EPN Response to Question 6

In its March 2026 proposal, EPA solicited comment on the information provided by four commenters concerning the January 2025 proposed Chemical Manufacturing Area Source NESHAP (See Question 6 on Page 12715). Of the four, the comments provided by the American Chemistry Council (ACC, 2025) and the Texas Commission of Environmental Quality (TCEQ, 2025) offered specific technical comment on EPA's assessment of EtO cancer risks, as supported by the IRIS risk assessment for EtO (EPA, 2016).

These two organizations proposed that TCEQ's EtO cancer dose response assessment (TCEQ, 2020), which estimates much lower risks from EtO, should be used by EPA in replacement of the EtO IRIS Assessment. The ACC and TCEQ 2025 comments overlap on many matters, and it is efficient to discuss these comments jointly. EPA has previously responded to many comments on the IRIS assessment and EtO dose response including earlier submissions by these organizations. Most content in their 2025 comments recapitulate and further opine on matters from earlier comments and corresponding EPA responses. A partial list of earlier EPA responses to comments regarding EtO cancer dose response matters is also provided below. The present comments that follow examine some key matters and arguments raised in these 2025 comments.

A. The National Academies of Science, Engineering, and Medicine (NASEM, 2025) review of the TCEQ assessment

As the two commenters urge that EPA should utilize the TCEQ risk assessment for EtO (TCEQ, 2020), it is important to examine and consider the recent prominent review of the TCEQ assessment by NASEM (2025). TCEQ describes their EtO assessment as having undergone two peer reviews. The first review contracted with six scientific experts for their individual comments (a process that did not provide for public input and did not seek consensus amongst the reviewers). TCEQ then requested a much expanded second review of their by then "final" assessment by NASEM, the preeminent US science body often considered as providing "gold standard" science reviews. The NASEM assembled a review panel of 11 experts and developed a consensus report of their peer review. This process included meetings for public input and examination of the NASEM committee's draft review report by 11 additional independent scientists.

However, TCEQ's (2025) comments to EPA state, that they view the NASEM peer review of the TCEQ assessment as unsuitable for their use: "The Recent National Academies review of the TCEQ's EtO assessment cannot be used to judge the TCEQ's assessment because it contains numerous errors and misrepresentations and demonstrates a clear lack of expertise on the part of the review panel" (TCEQ, 2025, p.4). TCEQ states that the NASEM report focused on matters that "were not requested" of the Academy. However, scientific panels are widely expected to look critically at their assigned tasks and determine if additional matters need to be examined to complete an adequate review. The NASEM statement of work for Texas recognizes this, providing for NASEM to provide "[a]ny additional relevant comments or issues about the TCEQ's carcinogenic hazard and dose-response assessment of EtO" (NASEM,2025, p. 3). While TCEQ may not feel they obtained the product they sought from NASEM, the Academy's review does provide substantial advice on key areas that are at issue in EtO risk assessment. Thus the NASEM review is very relevant to EPA in considering commenters suggestions that EPA make use of the TCEQ assessment.

The following excerpts present NASEM comments on a number of key EtO risk assessment matters. It should be noted that while the TCEQ (2020) assessment contains much critique of the EPA IRIS (2016) assessment, the NASEM statement of work provided that the committee would not review either the IRIS assessment or the TCEQ Appendix commenting on the IRIS assessment (NASEM, 2025, p. 17). We have also added brief remarks in the current document to characterize how the NASEM recommendations to TCEQ compare with procedures that were used in the IRIS assessment.

1. Breast cancer hazard.

Texas concluded that there was a breast cancer hazard from EtO by utilizing prior reviews from EPA and International Agency for Research on Cancer (IARC) and two narrative reviews that reevaluated the epidemiologic literature. Per NASEM, "Reliance on these narrative reviews and other information led TCEQ to conclude that there was insufficient evidence for the determination of a breast cancer hazard" (NASEM, p.4).

NASEM did not agree with the TCEQ review process or conclusions:

> "The committee identified several flaws in TCEQ's analysis that may have been avoided had TCEQ performed a systematic review for the hazard assessment. The committee also found issues with the way TCEQ interpreted the epidemiological evidence. TCEQ inappropriately relied on analyses using an external reference group, as opposed to an internal reference group, for breast cancer because it concluded that the Healthy Worker Effect (HWE) was not relevant for this outcome. The committee does not agree with this decision. There is no compelling evidence that the healthy worker effect is not operating in cohort studies of ethylene oxide. Internal analyses are preferred in occupational cohort studies of long-term exposures and chronic disease endpoints to avoid potential bias due to the Heathy Hire Effect (one of the two components of HWE). Moreover, analyses of breast cancer incidence in the NIOSH studies of sterilizer workers showed significant exposure-response effects with occupational exposure using internal analyses in both categorical analyses and continuous cumulative exposure models. These findings were further supported by breast cancer mortality analyses" (NASEM, 2025, p.5).

NASEM made specific recommendations for the breast cancer hazard analysis that TCEQ (NASEM, 2025, pp. 7 and 8):

- "should evaluate all relevant human evidence for the hazard assessment of breast cancer, without exclusion of studies that did not present quantitative data that would be adequate for dose-response assessment";
- "should rely on the internal analyses from the breast cancer incidence study conducted by Steenland and colleagues"; and
- "should reevaluate all relevant animal and mechanistic evidence for breast cancer in reaching conclusions about the evidence for this cancer endpoint."

We note that the IRIS assessment was largely consistent with NASEM recommendations to TCEQ regarding breast cancer, as it: (1) Included thorough reviews of available human cancer studies (See IRIS Appendix A. Critical Review of Epidemiological Evidence and IRIS Chapter 3. Hazard Identification). The

IRIS assessment did not present a formal systematic review, but did emphasize examination of the quality of essential content in the epidemiological studies. The IRIS review included human cancer studies with and without dose-response data; (2) IRIS placed greater weight on the internal analyses of EtO's carcinogenic effects in occupational populations. (3) IRIS included substantial review of animal cancer bioassay and mechanistic data as supporting its findings on human cancer hazards including breast cancer.

2. Dose-response modeling for human cancer risk.

Broadly, NASEM advised that "The [TCEQ] model selection criteria and the approach to validate the selected model were inadequate and inconsistent with best practice" (NASEM, p. 9). Specifically:

- TCEQ "should evaluate flexible, nonlinear models (e.g., cubic splines). TCEQ should prioritize selecting a model that best fits the dose-response curve at the lowest end of the exposure distribution rather than a model that best fits occupationally relevant levels of the exposure-response curve or the entire exposure range" (NASEM, p. 9),
- "Despite evidence from modeling of ethylene oxide epidemiologic data categorically that the exposure-response function may not be linear across all levels of exposure, TCEQ considered linear dose-response models as consistent with its guidance." (TCEQ 2015)… Given the observed shape of the dose-response association for analyses modeling ethylene oxide categorically, flexible, nonlinear models may provide insight into model selection for the epidemiologic data. For lymphoid cancers, categorical dose-response analyses indicate a nonlinear association (i.e., supralinear, steeper at the lowest end of the exposure-response curve). This is an important consideration since the URF ultimately will be used for environmental ethylene oxide exposures, which occur at the lower end of the exposure distribution relative to occupational exposures experienced in the NIOSH cohort. TCEQ did not prioritize selecting a model that best fits the lowest end of the exposure-response function (NASEM, p.36);
- "TCEQ relied on statistical significance testing when interpreting effect estimates and dismissed clear evidence of exposure-response in categorical analyses, including as occurring with appropriate internal reference groups. Given the extensive deficiencies in statistical significance testing, current best practice is to consider the magnitude, direction, precision, and consistency of effect estimates, especially those derived from studies with relatively small sample or case sizes (Greenland et al. 2016; Lash et al. 2021; Savitz et al. 2024). These considerations are also standard practice in systematic review" (NASEM p. 27); [This comment addresses both hazard and dose-response comparisons.]
- "Model parsimony should not be prioritized over this consideration [using models responsive to low-dose data]. Of the two models, the two-piece spline model may better reflect the supralinear dose-response shape at the lowest end of the exposure distribution. TCEQ guidance states that the MOA must be considered in model selection, and the considered two-piece spline model is not at odds with this guidance. TCEQ also can consider, as feasible, evaluating model fit in a subset of the chosen data that is restricted to the lower end of the exposure distribution. Such approaches have been used to inform low-dose extrapolation when associations are attenuated at the highest exposure levels. Attenuation of the association at the highest exposure levels is not unexpected in occupational studies, further underscoring the need to prioritize model selection based on fit at the lowest exposure levels (Stayner et al. 2003)." (NASEM, p. 37).

We note that the EPA IRIS assessment: (1) Selected spline models as its preferred modeling method as that approach was responsive to the shape of the cancer response at lower-dose in the NIOSH sterilization

worker cancer study. EPA chose to utilize the two-piece linear spline model for this purpose, given the numbers of specific cancer cases observed, after also considering models with more parameters (e.g., the cubic spline model). EPA received positive Science Advisory Board (SAB) review on these choices; (2) EPA also examined evidence showing high sensitivity of the log-linear Cox model preferred by TCEQ to the observations in the most highly exposed workers; (3) The two-piece spline model allowed for predictions of a steeper dose-response at low doses as compared to high doses, the pattern that was indicated by the categorical analysis of the NIOSH data. However, note that this model form is flexible enough to also allow predictions of fully linear patterns as well as patterns with steeper response at high dose response when the data so indicate; (4) As with TCEQ, the IRIS assessment made use of p-value results as an indicator of model fit. NASEM's discussion of deficiencies in statistical significance testing could suggest less emphasis on these results for model selection. The NASEM committee commented that its view, the Akaike Information Criterion (AIC) statistics calculated did not indicate the better fitting of the IRIS and TCEQ models (NASEM, p37). The IRIS assessment also noted that it was following advice of its SAB review in de-emphasizing AIC results for EtO model selection. (5) EPA and TCEQ have differed regarding calculating and interpreting p-values and AIC statistics. The results of TCEQ's NASEM review and the EPA IRIS and SAB review indicate that these statistics should not be determinative of EtO dose-response model choice. The ability of a model to be responsive to lower dose worker cancer data is discussed by NASEM as an essential consideration. The IRIS choice of modeling the cancer data with a two-piece linear spline model aligns with NASEM (and SAB) review recommendations.

3. <u>TCEQ approaches for "reality-checks" on model results</u>.

    - "TCEQ should use internal cross-validation and should not attempt to validate models built using NIOSH data with Union Carbide Corporation data. TCEQ should not use general population rates to model expected cancer rates given bias due to the Healthy Hire Effect" (NASEM, p. 9).
    - NASEM discusses the potential to use HEV hemoglobin adducts as a marker of EtO exposure and effects. NASEM discusses potential advantages of DNA adducts: "To conduct a risk assessment more accurately, the relative contribution of endogenously versus exogenously derived mutagenic DNA adducts and subsequent mutation rates would therefore be valuable" (NASEM, p. 40), and note this as a data gap.
    - The NASEM review concludes: "The committee supports TCEQ's conclusion that endogenous production of ethylene oxide may not inform the dose-response curve and derivation of the URF for ethylene oxide present in ambient air (NASEM, p. 40)." The NASEM report does not evaluate confidence in estimates of "EtO inhalation equivalents" associated with background adduct levels as used by TCEQ. It appears that the NASEM committee may have prepared further discussion of adduct based inferences than is now available. Somewhat concerningly, a footnote states that the NASEM report was "changed after release of the report to remove content that was beyond the scope of the committee's review."

The EtO IRIS assessment does not contain analyses such presented by TCEQ in their "reality-check" calculation on worker tumor risks (which NASEM found to be problematic). Later, EPA's response to comment documents have detailed the problems EPA has seen in these TCEQ calculations.

The IRIS assessment includes a review of potential processes for formation of endogenous EtO in the human body - processes that involve inhalation or internal formation of ethylene and its conversion to EtO. The IRIS assessment emphasized that its purpose was estimating risks from assessed exposures to inhaled EtO. That is estimation of risks from direct EtO exposures, while recognizing there would be some level of endogenous exposure that can contribute to a baseline source for both workers and members of the general population. The IRIS assessment is consistent with NASEM's conclusion. Thus the conclusions of the IRIS assessment are consistent with the NASEM statement, that presence of endogenous sources may not inform risk assessment for EtO in ambient air (EPA response to comment documents - and recent research - have addressed the need for validation of the assumption that background measurements of hemoglobin adducts can be converted into equivalent concentrations of inhaled EtO.)

B. Claimed statistical errors in IRIS Assessment

Both ACC (2025) and TCEQ (2025) devote much space to stating what they perceive as statistical errors in the IRIS assessment. The terms "error" or "flawed" are used dozens of times in these comments. While this can be understood as editorial indulgence, and the matters raised have been addressed in prior EPA response to comment documents, it is appropriate to review the issue here.

EPA has explained why these comments are themselves in error on multiple occasions. Specifically for the final sterilizer emissions rule EPA stated: "Arguments that the EPA's fit statistics should be "corrected" rest on an incorrect statement that the EPA utilized a statistically optimized (maximum likelihood) estimate of the knot value. However, the IRIS assessment clearly indicates that the 1600 ppm-day knot value was not the maximum likelihood estimate of the knot for the lymphoid cancer model ... instead the maximum likelihood knot was 100 ppm-days (IRIS Appendix D, pg. D-60). EPA judged the 1600 ppm-day model as providing a better visual fit to the lower dose data on lymphoid cancer than the maximum likelihood knot of 100 ppm-days. EPA did not use a maximum likelihood knot value in the IRIS assessment" (EPA RTC, 2024, p. 62).

Re-review of key matters concerning the spline model and knot selections:

1. This discussion focuses on an aspect of the characterization of the fit of EPA's two-piece linear spline model. In this model, the dose-response pattern consists of two linear segments which intersect at a specific cumulative dose level termed the "knot" value. In the IRIS EtO assessment, a specific fixed knot dose was selected for the preferred cancer dose response model - selected at 1600 ppm-days for the lymphoid cancer assessment that is the focus of these comments. EPA selected 1600 ppm-day knot value after examining a range of potential knot values. While EPA graphed model likelihood estimates for a range of potential knot values, EPA did not select the maximum likelihood value of this parameter as the preferred knot. EPA's judgment was that use of the maximum likelihood knot of 100 ppm-day did not suit the needs of the assessment. Considerations included: (1) the better visual-fit for the 1600 ppm-day value per the above quote from the IRIS assessment, (2) a dearth of data for workers developing cancer at or below doses of 100 ppm-days as compared with 1600 ppm-days; and (3) EPA's view that the lower-dose line segment if based on the 100 ppm-day knot was problematically steep. The selection of the 1600 ppm knot value supported the assessment goal of biological reasonableness. The model based on 1600 ppm-days yielded a relatively high likelihood (it was described as having a local maximum likelihood value) and this

model also aligned with results from other continuous model fits and categorical response estimates that also indicated that risks increased more rapidly at lower versus higher doses.

Thus, the IRIS approach utilized judgement: First in developing inhalation unit risk estimates for EtO in an approach using a fixed knot value, and second in the selection of a knot substantially greater than the maximum likelihood estimate for this parameter.

2. EPA's subsequent risk calculations used to estimate the upper bound unit risk (IUR) were made using this fixed knot value. This is important because if the knot value had instead been varied in the dose response model fitting, higher central risk estimates and bounds would have resulted. The assessment also calculated p-values and AIC statistics using the lymphoid cancer model with the fixed 1600 ppm-day value.

3. EPA's draft IRIS assessment reviewed by the SAB laid out this approach to modeling with the knot value for the SAB and public commenters. Specifically, Figure D-3a showed EPA examination of how model likelihood estimates varied with the knot choice. Then Table D3-d shows p-value calculations were made using two degrees of freedom - i.e., treating the knot value treated as fixed. (At the time of the 2014 draft, EPA preferred a different modeling approach for bottom line risk estimates for lymphoid cancer which used a linear regression of categorical risk ratios. Nonetheless, the details of the approach of fitting two-piece spline models were presented in 2014.)

4. The SAB's advice to EPA supported the approach to two-piece spline modeling presented in the draft: "Thus, models with very few estimated parameters should be favored in cases where there are only a few events in the dataset. To elaborate further, in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example." ACC's comments (2025, p. 12) opine that this SAB advice was ambiguous, however, SAB was addressing actual implementation of spline modeling presented in the draft. The spline modeling in the final EPA assessment maintained the same approach.

5. With this recapitulation as background, the claim by ACC and TCEQ of "major errors" in the IRIS assessment statistics is simply due to the fact that when EPA calculated p-values and AIC parameters it treated the knot value as fixed as discussed above. The TCEQ (2020) assessment calculated what they termed "corrected" p-values and AIC statistics (using a degree of freedom increased by one unit). These "corrected values" for p-value and AIC were then somewhat larger and comparable to values obtained using the log-linear Cox model preferred by ACC and TCEQ.

6. The "corrected" values put forward by commenters are themselves in error. Firstly, both the p-values methodology presented and the calculation of AIC measures explicitly require use of maximum likelihood values and the suggested recalculation does not use maximum likelihood values. Secondly the proposed recalculation presumes a full degree of freedom will accrue for a parameter that was not fully optimized and in fact importantly bounded away from values that would have yielded greater likelihoods and higher risk estimates. This approach inappropriately over credits the effective model flexibility present in a restricted model (as reflected by assumed degrees of freedom).

7. Technical note: The statistical issues underlying (but not mentioned) in comments about "correct" estimates are complex and subtle. In EPA's approach to the knot estimation in the IRIS assessment, the accepted values for knot estimates are essentially bounded away from lower values that can provide more optimal fits. There is research on methods for precise likelihood based estimation for this type of situation. Specifically, see the seminal paper by White and Liang (1987). [P. White, S.G. and K.-Y. Liang (1987)]. This paper developed approaches to characterize the distributions of maximum likelihood estimates when parameters are on the boundary of the allowable parameter space. One result is that distributions for maximum likelihood estimates for bounded parameters can often be expressed as mixtures of chi-squared distributions. That is when estimating a distribution for a parameter like the knot that is not allowed to reach low values, the statistical distribution is *not* a simple chi-squared distribution as stated by TCEQ and ACC.

8. TCEQ has emphasized that statistical experts engaged in the first peer review of their EtO assessment agreed with TCEQ's correction of p-values and AIC statistics. However, it is not clear that these reviewers were actually aware of the judgement based process used in IRIS to select a preferred knot value. The charge for these reviewers did not ask them to review the IRIS assessment, and TCEQ materials they received incorrectly stated that the IRIS assessment had used the maximum likelihood estimate for the knot. It is speculation to infer what advice TCEQ would have received if their reviewers had received correct information.

9. NASEM's advice to TCEQ strongly cautioned against over-reliance on statistical testing (and hence p-values) in favor of an integrative approach to data evaluation and model characterization. TCEQ's initial peer review also advised against reliance on the calculated p-values as indicators of model fit [Comments from "reviewer #6", a statistical expert]. SAB advised EPA to deemphasize the use of AIC statistics for characterizing model fit, advice that EPA followed in the IRIS assessment. In particular, both SAB and NASEM stressed the importance of utilizing models that can provide local fits to the lower dose data.

10. In this light, it is highly misleading for ACC to describe arguments about precise estimation of p-values and AIC statistics as being of "high consequence" to EPA's application of the spline model to assess cancer risks from EtO (ACC, 2025, p. 4). On the contrary, the most salient matters in EPA's choice of the spline model were the model's ability to provide more local fits in the low exposure range (per SAB, 2015, summary letter to EPA) and the consistency of spline model estimates with of other continuous models (e.g log-dose) and categorical estimates of cancer risk indicative of steeper responses at lower compared with higher dose levels. The inability of the log-linear ("standard") Cox model to meet these needs are likewise key reasons not to rely on that model in EtO risk assessment.

C. <u>Comparing rate ratios estimated from continuous models and categorical estimates</u>

Comments in 2025 repeat a claim that magnitude of risk estimates from different models and categorical risk estimates cannot be compared. EPA MON RTC (2020), p 89, addressed this statement: "A commenter suggested that the visual fit was based on how closely a model overlaid the categorical (rather than individual) data points. Specifically, the commenter broadly contends that it is not appropriate to compare the categorical estimates of relative risk for EtO with relative risk predictions from continuous models. In this regard the EPA notes that: (1) Plotting of fits of models in comparison with categorical breakouts of the

data is a very useful and commonly used tool in epidemiology as it allows examination of the behavior of the parametric continuous models versus unstructured information on disease within ranges of the independent variable (exposure); (2) The categorical response predictions and continuous model fits were appropriately developed from the same individual level data on cancer; (3) The categorical and continuous results compared utilize the same referent group – individuals who have no estimated exposure after taking into account the lag period of the modeling; (4) Both categorical and continuous model results are utilizing proportional hazard methodology to estimate the relative risk of worker exposures compared to the same reference group and this relative risk is a well-defined quantity. Thus, the categorical and continuous relative risk estimates should be in general agreement within the statistical variability of model fitting and may reasonably be compared."

Subsequent comments on these matters:

A 2025 commenter objects to descriptions of the continuous modeling results as showing risks in comparison to controls or a referent group (ACC, 2025, p. 5). The commenter is correct in that continuous modeling uses the full set of data for estimation of all the model parameters. To meet the commenter's urge for more academic wording, EPA's observation (3) above can be just as well stated using the words "reference condition" (instead of "referent group") to refer to cancer rates in workers in the absence of attributable workplace exposure to EtO. The thrust of EPA's 2020 conclusions remains the same. Both the categorical models and continuous models are estimating risk ratios for workers with defined exposures to EtO as compared to risks that occur in the cohort in the absence of workplace exposures.

A commenter states that the SAB (2015) advised EPA against making comparisons between categorical and continuous risk estimates for the NIOSH cohort. This is not correct. Upon examining the SAB report, there was not advice against comparing categorical versus continuous modeling results. In fact, SAB itself makes such a comparison in their important comment that for lymphoid cancer, "The cubic spline, two-piece linear splines, categorical, and log-exposure models all suggest that the risk rises rapidly with a small amount of exposure and then rises much more gradually for even higher exposures" (SAB, 2025, p. 14). Instead SAB's disagreement with the EPA review draft concerned a different matter about using categorical results as inputs for further modeling: "The SAB does not agree with the conclusion that the linear regression of the categorical results is a preferable model over the other, better-fitting models using individual-level exposure data (SAB, 2025, p. 14)." Based on this advice, EPA did not select an estimate based on the regression of categorical results in the final IRIS assessment.

A commenter highlights phrasing of a marginal note in some IRIS graphs of dose-response modeling results, e.g., IRIS Figure 4-3, namely "Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis. They are, however, comparable in terms of general shape."

We would agree that this marginal text in the IRIS graph is not easy to follow. Taking a closer look, the bottom line statement that different risk estimates should be "comparable in terms of general shape" does capture a key point of making the visual comparisons of the results. However, the wording that different models "are not strictly comparable to each other in terms of RR values" is not explained in the assessment properly and is thus confusing to readers. Furthermore, the statements about having "different implicitly estimated baselines" for different models (also not explained in the assessment text) is questionable. The key

point about the conditional likelihood calculations used in Cox-type regression models for internal risk estimates is that baseline risks are not – and do not need to be – estimated to develop valid estimates of risk ratios. And while, in a cohort study, further analyses might be done to estimate baseline risks, the Cox model analysis does not estimate such baselines either explicitly or implicitly. Thus comparisons as in Figure 4-3 examine estimates of risk ratios across different analyses stand as valid in their own right and are independent of any further analyses to estimate baseline risks. As addressed in the EPA RTC, the different models seek to estimate risk ratios for workers receiving EtO exposures relative to workers without attributable exposure. There is certainly statistical noise in any such comparisons, but the principle of making these comparisons is compelling.

Some brief historical digging indicates the origin of the marginal text in these figures. The quoted marginal note was inserted into IRIS figures following the IRIS public comment draft of July 2013.[36] The ACC commented on this draft including submission of the Valdez-Flores and Sielken (2013) paper which they supported. The IRIS 2014 revised draft responded to comment on the 2013 draft and states: "Discussion of the new Valdez-Flores and Sielken (2013) study has been added to Appendix J (Section J.3.1). In light of issues raised by Valdez-Flores and Sielken (2013), text was added to the assessment clarifying the model comparisons in some of the figures of Chapter 4 [page L-7]." The IRIS authors responsiveness to comment is to be appreciated, except that the work in Valdez-Flores and Sielken (2013) does not substantiate that paper's statements that the estimated rate ratios cannot be compared between categorical and continuous risk models or between different continuous models. These authors' statements about differences in "implicit estimate of the underlying background hazard rate", do not provide a reason why the *rate ratios* (RRs) as estimated in Cox regression (and related methods) cannot validly be compared. Comparisons between continuous and categorical models are likewise reasonable as long as they are generating RRs compared to the same reference condition - and for EPA analysis of EtO, both are compared (as noted in the EPA 2020 response to comments) to the reference condition of workers without attributable EtO exposure.

Valdez-Flores and Sielken (2013) refer to a respected historical text (Breslow and Day, 1980. See p. 229) which discusses how alternate choices can be made for the definition of the exposure level used as the reference condition in proportional hazards modeling. They use an example where intakes other than zero could be used as a reference condition for tobacco use. The magnitude of estimated RRs would then differ to reflect that choice of a baseline tobacco intake. These observations are correct and noncontroversial. Breslow and Day (1980) then state that it is the shape but not the magnitude of the modeled risk ratios that matter. Unfortunately, Breslow and Day (1980) do not further explain their thinking or substantiate this wording. Note that Breslow and Day (1980) addresses the analysis of case-control studies - which are a fundamentally different study design than the NIOSH "cohort study" of cancer deaths. And unlike cohort studies, case control studies do not allow direct estimation of disease rates in the controls or the exposed workers. It is unclear what role this plays with their remark.)

[36] https://iris.epa.gov/document/&deid=2395860

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