

BEFORE THE
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDE PROGRAMS

COMMENTS OF THE ETHYLENE OXIDE STERILIZATION ASSOCIATION AND
ETHYLENE OXIDE TASK FORCE
ON OPP'S PROPOSED INTERIM DECISION AND DRAFT RISK ASSESSMENT
ADDENDUM FOR ETHYLENE OXIDE

	)	
Registration Review; Pesticide Dockets	)	
Opened for Review and Comment	)	EPA-HQ-OPP-2013-0244
(88 Fed. Reg. 22447	)	
(Apr. 13, 2023)	)	
	)	

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I. INTRODUCTION

The Ethylene Oxide Sterilization Association (EOSA) and the Ethylene Oxide Task Force (EOTF) jointly submit these comments to the United States Environmental Protection Agency (EPA) in response to the April 13, 2023, notice of availability of the Proposed Interim Decision and Draft Risk Assessment Addendum for Ethylene Oxide (EtO) (PID).¹

EOSA is comprised of the leading experts of the medical device manufacturing and sterilization industry. In addition to medical device manufacturers, EOSA members include manufacturers of emissions control equipment, ethylene oxide sterilizers, and ethylene oxide detection systems. EOSA members also include many contract sterilization providers, sterilization consultants, environmental consultants, and registrants.

The diversity of EOSA member companies provides EOSA a broad view of the overall implications of these proposed regulatory actions. The highly knowledgeable subject matter experts within EOSA are uniquely capable of assessing the issues and complications posed by the NESHAP and PID proposals on the sterilization process, the sterilization facilities, the economics of sterilization, the safety of sterilization facilities, and the security of the supply chain of critical medical devices. No other organization has EOSA's breadth or depth of expertise in the matters presented by the EPA's proposals.

The EOTF, which is comprised of ARC Specialty Products Balchem Corporation and Sterigenics U.S., LLC, are EtO registrants.

EOSA and EOTF incorporate by reference the comments submitted by EOSA in response to the April 13, 2023, notice of availability of the Proposed National Emission Standards for Hazardous Air Pollutants (NESHAP) for the Commercial Sterilization Facilities source category, Docket No. Docket: EPA-HQ-OAR-2019-0178.²

As a preliminary matter, it is critical to emphasize that the comment period provided is wholly insufficient to allow adequate comment on the sweeping changes that the PID proposes on so many issues fundamental to and vital if sterilization facilities are to continue to be able to provide sterilized medical devices that are essential to U.S. patients and safe spaces to U.S.

¹ 88 Fed. Reg. 22447 (April 13, 2023) (*Federal Register* notice announcing the availability of the U.S. Environmental Protection Agency's (EPA) Proposed Interim Decision (PID) and Draft Risk Assessment (DRA) Addendum for ethylene oxide (EtO), available at <https://www.federalregister.gov/documents/2023/04/13/2023-07727/pesticide-registration-review-proposed-interim-decision-and-draft-risk-assessment-addendum-for>.

² 88 Fed. Reg. 22790 (April 13, 2023) (*Federal Register* notice announcing the availability of the U.S. Environmental Protection Agency's (EPA) National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Emission Standards for Sterilization Facilities Residual Risk and Technology Review (NESHAP), available at <https://www.govinfo.gov/content/pkg/FR-2023-04-13/pdf/2023-06676.pdf>.

consumers. Indeed, it is not possible even to identify all of the issues that must be addressed, let alone adequately comment on them and propose alternative solutions, in the time period provided. The brevity of the comment period on proposals of the breadth contained in the PID has deprived EOSA, EOTF, and their members of an adequate opportunity to comment. This is of overwhelming concern given the vast number of critical issues posed in the PID, many of which could dramatically adversely affect public health.

EOSA and EOTF are committed to working with EPA to address these issues and reserves all rights to supplement these comments to address the many issues that EOTF and EOSA are not able to identify and/or address fully or adequately, if at all, in the insufficient time period provided. Based on the review of the PID that EOSA and EOTF have been able to complete to date, fundamental technical errors, omissions, and/or misunderstandings in EPA's assessment and preliminary determinations in the PID have been identified, but this review is far from complete.

It is essential to address all of these issues, both those identified in these comments and those that will be the subject of supplementary submission, given the critical need for EtO in the sterilization of certain medical devices and equipment for which no viable alternative exists. Without wholesale changes the proposals, if implemented, many would drastically and adversely disrupt safe, available, healthcare in the United States.

It is important to note in this regard that EPA has also issued a proposed NESHAP rulemaking addressing the same facilities that the PID requirements affect, and the breadth of that proposal is of a similar scope and with analogous enormously significant adverse potential consequences to the ability to continue to sterilize critical medical devices and to ensure the safety of spices. It is impossible to comment adequately on the PID without a full consideration of the NESHAP proposals, and vice versa, given that some of them overlap with, conflict with, or render impossible requirements proposed by the other. EOSA and EOTF have worked tirelessly since the PID and NESHAP were proposed, as have many others in the industry, to review and address the complexity of scientific and technical issues raised in these documents, particularly considering the enormous adverse implications both domestic and internationally of the current proposals. Without wholesale revisions, as noted, the availability of sterilized medical devices and spices is at an enormous risk of being crippled, and the comment period provided is wholly insufficient to allow an adequate comment to be made.

It is important also to note that critical proposals made in the PID would affect significantly requirements that are under the Food and Drug Administration's (FDA) jurisdiction for particular medical devices. These jurisdictional issues must be adequately resolved, particularly given the enormous potential impact the proposals would have on public health.

EPA must ensure that its decisions do not violate applicable legal requirements under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the Administrative Procedure Act (APA), the Federal Food, Drug, and Cosmetic Act (FFDCA), or EPA's own policies. To do this, it is essential that additional time for comment be provided, and that EPA carefully consider the comments that are submitted on these highly critical issues and revise the PID accordingly. The law and EPA's own policies require EPA to do.

II. DISCUSSION

Outlined below are some of the issues that EOSA and EOTF have identified to date; this is far from a comprehensive summary for the reasons noted. Attached to this document are the following:

- Attachment 1 - Technical comments that EOSA and EOTF are able to provide to date on the questions on which EPA specifically requested comment in the PID. EOSA and EOTF reserve all rights to supplement these comments as they are able to complete their review, both to identify additional critical issues and to propose alternatives to EPA's proposals.
- The following attachments prepared by Exponent and the American Chemistry Council (ACC) which address the enormous errors in the risk assessment that drives much of the proposed mitigation, based on a wildly overstated potential risk:
 - Attachment 2 - Exponent's Response to EPA's Proposed Interim Decision for Ethylene Oxide;
 - Attachment 3 - A copy of comments recently submitted by ACC to the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) regarding its draft cancer Inhalation Unit Risk factor (IUR) for EtO that also address these enormous and critical errors;
 - Attachment 4 - A copy of comments recently submitted by ACC to OEHHA regarding its No Significant Risk Level (NSRL) for EtO that additionally addresses these enormous and critical errors; and
 - Comments that ACC is preparing for submission to the EPA-HQ-OAR-2022-0730 on July 7, 2023, are incorporated by reference in these comments, as they also address these critical issues.

By way of example, among the issues identified to date are the following; as stated, this is not intended to be a comprehensive list given that lack of adequate review time:

- Compliance timelines for all mitigation measures are not feasible.
- Reduced EtO concentrations are not possible to achieve in any guaranteed time frame, if at all, and would not achieve EPA's objectives.

- Requiring all-in-one systems is infeasible and would cause enormous and severe adverse impacts on the availability of medical devices essential to U.S. healthcare; an exception for facilities sterilizing pressure sensitive devices is wholly insufficient to address the concerns this proposal raises.
- Due to the numerous factors that can impact EtO concentrations in different facilities, there is no specific number of air exchanges per hour that can or should be established to properly ventilate storage areas.
- Requiring covered conveyors to move sterilized product from chamber to Aeration, and also from aeration to storage/shipping areas is impossible for the vast majority of existing sterilization facilities. Such a requirement would cripple the availability of medical device sterilization capacity, including facility shut downs, and thus the availability of needed sterilized medical devices, with minimal, if any, benefits to workers.
- Existing systems cannot reliably monitor to 10 parts per billion (ppb) and this proposed arbitrary requirement would trigger the facility shutdowns and consequent disastrous effect on the availability of sterilized medical devices described above and in the appended comments.
- Healthcare facilities have been following AAMI ST41 for over twenty years. New proposed requirements included in PID for many healthcare facilities, including small facilities, dentist, plastic surgeon, and veterinarian' offices, however, are not feasible and will have a significant adverse impact on patient health and on the economic viability of these facilities. Healthcare facilities should be permitted to continue following AAMI ST41.

Among the issues that EOSA and EOTF plan to address in supplemental submissions, due to the inadequacy of the comment period, are potential alternatives for some of EPA's proposed mitigation measures, as well as issues EOSA and EOTF were not able to address more fully in the appended technical comments. Examples of issues on which EOSA and EOTF plan to make supplement submissions include the following:

- Feasible compliance timelines
- Pallet configurations
- State or local permit issues
- SCBA requirements
- EtO concentration limit for new cycles
- Engineering controls proposed for facilities

- Technologies for EtO detection and measurement
- Respirator use /employee evacuation
- Employee training and recordkeeping
- ACH (air change per hour)
- Pressure sensitive devices
- Cost issues

EOSA and EOTF urge EPA to address the critical procedural and substantive errors identified in this submission and in EOSA's and EOTF's 's planned forthcoming submissions before preparing the Interim Decision. EOSA and EOTF believe the issues are of such a magnitude and so fundamentally affect the proposed requirements that EPA should consider issuing an amended PID for comment. Regardless, and as already noted, EOSA and EOTF reserve all rights to supplement these comments, including the attachments.

EOSA and EOTF support the comments submitted by the American Spice Trade Association (ASTA) regarding the PID. As EOSA and EOTF have stated and ASTA agrees, EPA has proposed several mitigation measures that are not achievable and/or are unnecessarily burdensome, including but not limited to the ability to conduct real time ambient air EtO monitoring, the 10 ppb proposed action level and the proposed automation requirements, including the proposed requirement for covered conveyors. EOSA and EOTF further support ASTA's comments and reasoning as to why EPA should not revoke tolerances on commodities for which uses of EtO may be cancelled. Moreover, although EPA has not provided any stakeholder, including EOSA, EOTF or ASTA, sufficient time to respond to the complex issues being raised in the PID, EOSA and EOTF support ASTA's comments regarding the commodities it has been able to identify, to date, where due to food safety risks and lack of viable alternatives, the use of EtO remains critical for the food safety of those commodities.

III. EOSA AND EOTF HAVE NOT BEEN AFFORDED THE PROCESS DUE TO THEM AND EPA HAS UNLAWFULLY DEPRIVED EOSA AND EOTF OF THEIR NOTICE AND COMMENT RIGHTS

Although far from complete, EOSA and EOTF continue their efforts to review the PID, including identifying significant factual errors, significant technical and feasibility issues, and other critical matters, and to provide appropriate and meaningful comment to EPA on these issues. The 60-day comment period originally provided by EPA, which is the *minimum* time provided in EPA's regulations to comment on any proposed registration review decision,³ is wholly insufficient for a proposal of this magnitude and the enormous and severe adverse effects

³ 40 C.F.R. § 155.58(a) (requires EPA to provide *at least* 60 calendar days to comment on the proposed decision).

it will cause if implemented. EOSA and EOTF have been deprived of an adequate opportunity to comment, for these reasons. This is particular concern given the complexity of the issues that the PID raises for EOSA and EOTF members, and the hugely significant adverse effect the proposal will have on the supply of sterile healthcare products, and on the availability of spices. To ensure an adequate opportunity to comment meaningfully on the PID, EOSA and EOTF had each requested that EPA extend the comment period by 120 days. Instead of extending the comment period to an adequate duration, EPA provided a meager 15-day extension.

Compounding the issues posed by the brevity of the comment period for such a complex and sweeping proposal, is the fact that EPA simultaneously released for comment its National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Emissions Standards for Sterilization Facilities Residual Risk and Technology Review, which proposes an equally complex and sweeping set of changes. It is impossible to comment adequately on the PID without a full consideration of the NESHAP proposals, given that some of them overlap with, conflict with, or render impossible requirements proposed by the other, and the brevity of the overlapping comment period for both makes it even more impossible to comment adequately on either proposal. EOSA, EOTF, and related stakeholders have been denied comment period on both rules; the comment period provided was wholly insufficient for each of them and combined, it is even more insufficient.

It is a basic due process right for the government to provide adequate notice and an opportunity to be heard before depriving an individual of a protected interest.⁴ Furthermore, the APA requires agencies to adhere to notice and comment procedures to ensure the public has an opportunity to participate meaningfully in the rulemaking process. After providing notice of a proposed rule by publication in the *Federal Register*, the agency must provide interested persons with an opportunity to comment on the proposed rule through the submission of “written data, views, or arguments.”⁵ For example, in *Synthetic Organic Chemical Manufacturers Association v. Brennan*, the court remanded Department of Labor standards where the agency did not give interested parties adequate time to comment in publishing a proposed rule before the advisory committee submitted its final report on the rule.⁶

⁴ See, e.g., *Mathews v. Eldridge*, 424 U.S. 319, 333 (1976); *Cleveland v. Board of Education v. Loudermill*, 470 U.S. 532, 546 (1985); *James Madison Ltd By Hecht v. Ludwig*, 82 F.3d 1085, 1099 (D.C. Cir. 1996), *cert. denied* 117 S. Ct. 737 (1997).

⁵ APA § 553(b)-(c).

⁶ 506 F.2d 385, 388-89 (3d Cir. 1974), *cert. denied sub nom. Oil, Chem. & Atomic Workers Int'l Union*, 423 U.S. 830 (1975). See also *Chemical Waste Mgmt., Inc. v. EPA.*, 976 F.2d 2, 28 (D.C. Cir. 1992) *cert. denied sub nom. Chemical Mfrs. Ass'n v. EPA*, 507 U.S. 1057 (1993); *Horsehead Resource Dev. v. Browner*, 16 F.3d 1246, 1267-68 (D.C. Cir. 1994), *cert. denied sub nom. Cement Kiln Recycling Coalition v. Browner*, 513 U.S. 816 (1994) (“[I]nsightful comments may be reflective of notice and may be adduced as evidence of its adequacy”).

As the court stated in *Florida Power & Light Co. v. United States*, an agency's "notice must not only give adequate time for comments, but also must "provide sufficient factual detail and rationale . . . to permit interested parties to comment meaningfully." ⁷ For the public to have a "meaningful opportunity" to comment, there must be "enough time with enough information to comment and for the agency to consider and respond to the comments." ⁸ In determining whether an agency has provided "enough time" to comment, important considerations may include whether commenters have a "meaningful opportunity to submit data and written analysis," whether the duration of the comment period is warranted based upon the importance of the underlying issues, or whether interested persons identified substantive challenges if provided additional, or adequate, time to comment. ⁹ Here, the issues are of critical importance and EOSA and EOTF have stated the significant challenges it faces to respond meaningfully in the time provided.

Following an adequate comment period, EPA must, in turn, consider and respond to relevant, significant issues raised in these comments. ¹⁰ In addition to providing stakeholders with the opportunity to be heard and in satisfying the requirements of the APA, notice and comment procedures help to ensure that agency decisions are based upon all relevant information. The opportunity for interested parties, such as experts in the field and those affected by the proposed action, to communicate information that EPA may have overlooked and to offer informed criticisms or comments for EPA's consideration, will lead to better-informed agency decision-making. ¹¹ EPA thus should have its own incentives to ensure that interested parties have

⁷ 846 F.2d 765, 771 (D.C. Cir. 1988), *cert. denied* 490 U.S. 1045 (1989).

⁸ *Prometheus Radio Project v. FCC*, 652 F.3d 431, 450 (3d. Cir. 2011) (citing [Rural Cellular Ass'n v. FCC](#), 588 F.3d 1095, 1101 (D.C. Cir. 2009)).

⁹ *Id.* at 453; *N.C. Growers' Ass'n v. United Farm Workers*, 702 F. 3d 755, 769 (4th Cir. 2012) (holding that an agency's "exceedingly short" 10-day comment period was inadequate and unwarranted "based on the important interests underlying" the regulation); *Florida Power & Light*, 846 F.2d at 772 (finding a comment period to be of sufficient duration where petitioner was not harmed by its brevity, noting that petitioners did identify substantive challenges that "differ in kind from the original comments" raised in comments); *Omnipoint Corp. v. FCC*, 78 F.3d 620, 630 (D.C. Cir. 1996) (noting that the petitioner did not "identify any substantive challenges it would have made had it been given additional time" to comment).

¹⁰ [Citizens to Preserve Overton Park, Inc. v. Volpe](#), 401 U.S. 402 (1971).

¹¹ *Horsehead Resource Dev. v. Browner*, 16 F.3d at 1268; *Spartan Radiocasting Co. v. FCC*, 619 F.2d 314 (4th Cir. 1980); *National Tour Brokers Ass'n. v. United States*, 591 F.2d 896 (D.C. Cir. 1978) (The purpose of the notice-and-comment procedure is both "to allow the agency to benefit from the experience and input of the parties who file comments . . . and to see to it that the agency maintains a flexible and open-minded attitude towards its own rules") (*quoted by Chocolate Mfrs. Asso. v. Block*, 755 F.2d 1098 (4th Cir. 1985)).

sufficient time to comment meaningfully on the PID. As explained, the comment period is insufficient for interested parties to have sufficient time to review and comment meaningfully on the significant issues in the PID, and therefore, public comments will be more limited than if EPA provided sufficient time.

Agency actions that fail to address fundamental issues raised by parties entitled to protection have also been found to violate “basic concepts of fair play.”¹² EPA cannot make a reasoned, “principled” assessment of the uses and risk mitigation measures of EtO without giving stakeholders a full and complete opportunity to comment and fully considering the information provided. This process failure is extremely serious and represent an arbitrary and capricious denial of due process.

IV. TO MAKE DEFENSIBLE REGISTRATION REVIEW DECISIONS, EPA IS OBLIGATED TO FOLLOW LEGAL REQUIREMENTS AND SCIENTIFIC PRINCIPLES THAT IT HAS IGNORED OR MISAPPLIED IN THE EtO PID

A. EPA Has Ignored Or Not Considered Adequately Or Appropriately the Applicable Legal Requirements

Under applicable legal requirements, EtO meets the FIFRA standards for registration. FIFRA Section 3(g) requires EPA to review existing pesticide registrations every 15 years to determine whether they continue to meet the statutory standard for registration.¹³ Under FIFRA Section 3(c)(5), EPA must register a pesticide if it determines that, when considered with any restrictions imposed:

- a. Its composition is such as to warrant the proposed claims for it;
- b. Its labeling and other materials required to be submitted comply with the requirements of this subchapter;
- c. It will perform its intended function without unreasonable adverse effects on the environment; and

¹² *Wellford v. Ruckelshaus*, 439 F.2d 598, 602 (D.C. Cir. 1971) (“We are troubled by the possibility that the Secretary failed to give petitioner’s allegations [made in a petition to suspend use of a pesticide] the careful consideration to which they were entitled . . .”); *see also EDF v. Hardin*, 428 F.2d 1093, 1100 (D.C. Cir. 1970) (court directed EPA to provide detailed explanation for failure to take action to suspend DDT in face of “impressive evidence presented by petitioners.”).

¹³ FIFRA § 3(g)(1)(A), 7 U.S.C. § 136(g)(1)(A).

- d. When used in accordance with widespread and commonly recognized practice, it will not generally cause unreasonable adverse effects on the environment.¹⁴

The term “unreasonable adverse effects on the environment” is defined by FIFRA Section 2(bb) as one of two circumstances: “(1) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with” the food tolerance standard set forth in FFDCA Section 408.¹⁵

With regard to the first criteria, there is no question that the composition of EtO products warrant the claims made for them. With regard to the remaining criteria, and as discussed in detail below, if EPA had reviewed and relied upon all available relevant, defensible data, and had properly conducted the EtO analysis under the Integrated Risk Information System (IRIS), along with the critical analysis of the benefits of EtO products, it would have determined that EtO products, with reasonable and achievable risk mitigation measures, do not cause “unreasonable adverse effects on the environment” and are eligible for registration. Instead, EPA has ignored or not considered adequately or appropriately, relevant data or best available data and is proposing risk mitigation measures that either cannot be implemented, and even if it is assumed that some could be implemented, many of those could be implemented in the proposed timeframes. Moreover, many will not achieve EPA’s desired objectives and will instead devastate the availability of safe, sterilized medical devices, an enormous risk to public health, as discussed in the attachments. EPA thus has ignored the standards applicable to a determination of whether an “unreasonable adverse effect on the environment” exists. EPA’s failure to consider relevant data and best available data has resulted in a risk/benefit analysis that grossly overestimates risk with unreasonable, unachievable, risk mitigation measures.

1. EPA Cannot Ignore the Best Available Data and Science, and the 2016 IRIS Assessment Is Clearly Not the Best Available Nor Does It Accurately Reflect the Data and Science Available

FIFRA Section 3(c)(2) states that EPA “shall publish guidelines specifying the kinds of information which will be required to support the registration of a pesticide and shall revise such guidelines from time to time.”¹⁶ FIFRA’s implementing regulations state that “[d]ata requirements will be revised from time to time to keep up with policy changes and technology. Revisions to this part will be made in accordance with the Administrative Procedure Act (5 U.S.C.

¹⁴ FIFRA § 3(c)(5), 7 U.S.C. § 136a(c)(5).

¹⁵ FIFRA § 2(bb), 7 U.S.C. § 136(bb).

¹⁶ FIFRA § 3(c)(2), 7 U.S.C. § 136a(c)(2).

551 *et seq.*).¹⁷ In a 2005 proposed rule to update and revise data requirements for conventional pesticides, EPA makes several statements demonstrating its need to ensure that data requirements and guidelines are updated so that its risk assessments and regulatory decisions are based upon sound science.¹⁸

In fact, on innumerable occasions over the years, EPA has emphasized its policy of basing its decisions on the best available, sound science.¹⁹ Indeed, EPA is under a legal obligation to follow this policy and to base the EtO PID on the best available data and science inasmuch as it has not provided, much less attempted to provide, a rational explanation for departing from this established policy.²⁰

¹⁷ 40 C.F.R. § 158.85(a).

¹⁸ 70 Fed. Reg. 12276, 12279 (Mar. 11, 2005) (noting that Pesticide Assessment Guidelines describe acceptable protocols, test conditions, and data reporting guidelines to ensure that EPA’s regulatory decisions are based on sound scientific data); *id.* at 12313 (noting that EPA considers animal welfare considerations in developing health effects data, “consistent with the essential need to conduct scientifically sound chemical hazard/risk assessments in support of the Agency’s mission”).

¹⁹ See, e.g., EPA, *EPA 2006-2011 Strategic Plan: Charting our Course* (May 2006 Draft) at Cross-Goal Strategy Best Available Science (EPA “utilizes the best available scientific theories, data, and models . . . to meet its mission to protect the environment and safeguard public health), available at http://www.epa.gov/cfo/plan/06strat_plan.pdf; EPA, *Peer Review and Peer Involvement at the U.S. Environmental Protection Agency* (Jan. 31, 2006) at 1 (“EPA strives to ensure that the scientific and technical bases of its decisions . . . are based upon the best current [scientific] knowledge”), available at http://www.epa.gov/peerreview/pdfs/peer_review_policy_and_memo.pdf; EPA, *Guidelines for Carcinogen Risk Assessment* (Mar. 2005) at 1-7 (“[T]hese cancer guidelines adopt a view of default options that is consistent with EPA’s mission to protect human health while adhering to the tenets of sound science.”), available at <http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=116283>; EPA, *An Examination of EPA Risk Assessment Principles and Practices* (March 2004) at 72 (“it is EPA’s practice to base decisions on the best available science”), available at <http://www.epa.gov/OSA/pdfs/ratf-final.pdf>; EPA, *The State of Sound Science at the U.S. Environmental Protection Agency* (Summer 2003) at 6 (referring to EPA’s “use of the best available scientific and technical information”), available at <http://www.epa.gov/OSA/pdfs/soundscience-062603.pdf>; EPA, *U.S. Environmental Protection Agency Fiscal Year 2000 Annual Report* (Mar. 2001) at cover letter and II-32 (EPA will use “the best available science in the review of new and existing pesticides” and base its “policies and decisions on sound science and meaningful peer review”).

²⁰ See, e.g., *Chelsea Indus., Inc. v. NLRB*, 285 F.3d 1073, 1075-76 (D.C. Cir. 2002) (“[an] agency acts unreasonably if it departs from established policy without giving a reasoned explanation for the change”); *National Conservative Political Action Comm. v. FEC*, 626 F.2d 953, 959 (D.C. Cir. 1980) (“Agencies are under an obligation to follow their own

In addition to its longstanding policy calling for the use of the best available science, EPA's guidelines under the Information Quality Act (IQA)²¹ affirm that "EPA is dedicated to the collection, generation, and dissemination of high quality information," and make clear that EPA's conduct of a risk assessment "involves a 'weight-of-evidence' approach that considers all relevant information"²² Objectivity with respect to risk assessments is ensured by, *inter alia*, EPA's use of "the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer-reviewed science and supporting studies."²³ EPA defines "best available" data as the best data that is available "at the time [the] assessment is made."²⁴

On January 9, 2006, OMB built upon the federal government-wide IQA guidelines by issuing its *Proposed Risk Assessment Bulletin*, which is intended "to enhance the technical quality and objectivity of risk assessments prepared by federal agencies by establishing uniform,

regulations, procedures, and precedents, or provide a rational explanation for their departures").

²¹ Congress enacted the IQA to ensure the consistency and quality of information disseminated by federal agencies. The statute required the Office of Management and Budget (OMB) to develop federal government-wide guidelines that "provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies," and called upon individual agencies to issue their own guidelines "ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by the agency." 44 U.S.C. § 3516, note. OMB issued the final version of the government-wide IQA guidelines in early 2002, *see* 67 Fed. Reg. 8452 (Feb. 22, 2002), and EPA issued its IQA guidelines later that year. *See* EPA, *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity, of Information Disseminated by the Environmental Protection Agency* (Oct. 2002) (IQA Guidelines), available at https://www.epa.gov/sites/default/files/2020-02/documents/epa-info-quality-guidelines_pdf_version.pdf.

²² IQA Guidelines at 10, 21.

²³ *Id.* at 22. Elsewhere in its IQA Guidelines, EPA explains its intent "to use all relevant information, including peer reviewed studies, studies that have not been peer reviewed, and incident information; evaluate that information based on sound scientific practices as described in [EPA's] risk assessment guidelines and policies; and reach a position based on careful consideration of all such information" *Id.* at 26.

²⁴ *Id.* at 23.

minimum standards.”²⁵ The RA Bulletin states that federal agency risk assessments “should use the best available data and should be based on the weight of the available scientific evidence.”²⁶ It further provides that “direct real-world data” must be relied upon when they are available.²⁷ EPA stated, in the context of how EPA will conduct future registration reviews of pesticides, that it will, in accordance with the IQA, follow its guidance regarding the quality of information that it relies upon for regulatory decisions.²⁸

Thus, EPA must utilize and rely upon the best available scientific data in its risk assessment and PID for EtO. EPA states in the PID that the “2016 IRIS assessment went through ‘unusually extensive processes for the consideration of public comment and external peer review,’ and is considered by ORD to be the ‘best available scientific information regarding cancer risks from EtO.’” Despite EPA’s statements on this issue, as the Exponent documents attached as Attachments 2 and 3 demonstrate clearly, as well as the forthcoming Exponent comments on the

²⁵ OMB, *Proposed Risk Assessment Bulletin* (Jan. 9, 2006) at 3 (RA Bulletin), available at https://obamawhitehouse.archives.gov/sites/default/files/omb/assets/omb/inforeg/proposed_risk_assessment_bulletin_010906.pdf.

²⁶ *Id.* at 14, citing The Presidential/Congressional Commission on Risk Assessment and Risk Management, *Framework for Environmental Health Risk Management: Final Report, Volume 1* (1997) at 38 (“Because so many judgments must be made based on limited information, it is critical that *all* reliable information be considered. Risk assessors and economists are responsible for providing decision-makers with the best technical information available or reasonably attainable, including evaluations of the weight of the evidence that supports different assumptions and conclusions.”), available at <http://www.riskworld.com/Nreports/1997/risk-rpt/pdf/EPAJAN.PDF>.

²⁷ *Id.* at 6; see also National Research Council, *Science and Judgment in Risk Assessment* (1994) at 90 (“Over time, the choice of defaults should have decreasing impact on regulatory decision-making. As scientific knowledge increases, uncertainty diminishes. Better data and increased understanding of biological mechanisms should enable risk assessments that are less dependent on default assumptions and more accurate as predictions of human risk. . . . Risk assessors and managers must be receptive to new scientific information about the character and magnitude of the toxic effects of a chemical substance.”), available at <http://fermat.nap.edu/catalog/2125.html>; The Presidential/Congressional Commission on Risk Assessment and Risk Management, *Risk Assessment and Risk Management in Regulatory Decision-Making: Final Report, Volume 2* (1997) at iv (“Agencies should continue to move away from using the hypothetical . . . toward more realistic assumptions based on available scientific data”), available at <http://www.riskworld.com/Nreports/1997/risk-rpt/volume2/pdf/v2epa.PDF>.

²⁸ 71 Fed. Reg. 45719 (Aug. 9, 2006).

proposed rule for the Hazardous Organic NESHAP (HON),²⁹ EPA, in fact, did not comply with its IQA obligations.

EPA is well aware of EOSA's views that the IRIS risk value, upon which all of EPA's regulatory actions and statements are based, does not represent the best available science on the risk of EtO. The issues with the IRIS risk value, as discussed in detail in the Exponent attachments referenced above include the following:

- The value is based entirely on a National Institute for Occupational Safety and Health (NIOSH) study where there was barely a cancer signal; only after a convoluted mathematical reanalysis of the data did the high risk estimate appear.
- The NIOSH study has a poor exposure assessment with inadequate information to accurately know the exposure for periods where workers were in the industry.
- EPA used improper statistical methods to evaluate the fit of its dose-response model and used a misleading figure to justify it.
- EPA's inclusion of breast cancer from the NIOSH study is improper based on under-ascertainment.
- The higher potency estimate for lymphoid cancers is inconsistent with the fact that smokers have high EtO exposures yet do not have elevated lymphoid cancers.
- Another large epidemiologic study, the Union Carbide Corporation study, had higher exposures yet saw no increase in cancer.
- The EPA potency estimate and steep slope at low doses is inconsistent with the large levels of endogenous EtO exposure and with available toxicokinetic and mechanistic data.

2. EPA Cannot Ignore Relevant Data

FIFRA Section 4(g)(1) provides that EPA, in taking "appropriate regulatory action" under the reregistration provisions, "*shall* conduct a thorough examination of all data submitted under this section concerning [the pesticide active ingredient] . . . and of *all other available data*

²⁹ 88 Fed. Reg. 25080 (Apr. 25, 2023) (proposed rule for "New Source Performance Standards for the Synthetic Organic Chemical Manufacturing Industry and National Emission Standards for Hazardous Air Pollutants for the Synthetic Organic Chemical Manufacturing Industry and Group I & II Polymers and Resins Industry"). Comments must be submitted by July 7, 2023. 88 Fed. Reg. 41369 (June 26, 2023).

found by the Administrator to be *relevant*.”³⁰ FIFRA thus requires EPA to consider all relevant data in support of registration.

In addition, EPA’s regulations implementing FIFRA require that EPA, when considering a registration under FIFRA Section 3(c)(5), “review[] all relevant data in the possession of the Agency.”³¹ EPA similarly has stated:

Universally accepted scientific principles require that all relevant information, not an arbitrarily selected subset of the information, be considered in making risk/benefit decisions. The Agency has consistently adhered to this principle. The Agency rejects any interpretation of the statute that would limit the scope of the information reviewed or compromise the integrity of its scientific decision-making process.³²

Moreover, under APA, EPA is required to “examine the relevant data and articulate a satisfactory explanation for its action including a ‘rational connection’ between the facts found and the choice made.”³³ As the Supreme Court explained in *Motor Vehicle Mfrs. Ass’n*, an agency action is arbitrary and capricious if, *inter alia*, the agency has “entirely failed to consider an important aspect of the problem [or] offered an explanation for its decision that runs counter to the evidence before the agency.”³⁴ Courts applying this administrative law precept have held EPA actions to be arbitrary and capricious where, for example, EPA relied upon generic studies in the

³⁰ FIFRA § 4(g)(1), 7 U.S.C. § 136a-1(g)(1) (emphasis added).

³¹ 40 C.F.R. § 152.112(b). *See also* FFDCA § 408(b)(2)(D), 21 U.S.C. § 346a(b)(2)(D) (FFDCA Section 408(b)(2)(D), as amended by the Food Quality Protection Act (FQPA), requires that EPA consider, among other relevant factors, “(i) the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue; (ii) the nature of any toxic effect shown to be caused by the pesticide chemical . . . in such studies; [and] (iii) available information concerning the relationship of the results of such studies to human risk”).

³² 49 Fed. Reg. 30884, 30902 (Aug. 1, 1984).

³³ *Motor Vehicle Mfrs. Ass’n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (quoting *Burlington Truck Lines, Inc. v. U.S.*, 371 U.S. 156, 168 (1962)).

³⁴ *Id.*

face of conflicting “detailed and specific” scientific evidence,³⁵ and where EPA’s final decision ran counter to the evidence before EPA.³⁶

Particularly instructive is the case of *Chemical Manufacturers Ass’n v. EPA*, where the court reviewed EPA’s designation of a hazardous air pollutant, methylene diphenyl diisocyanate (MDI), as a high-risk pollutant.³⁷ EPA based its designation on the application to MDI of a generic air dispersion model. The court, observing that it “must reverse the agency’s application of the generic air dispersion model as arbitrary and capricious if there is simply no rational relationship between the model and the known behavior of the hazardous air pollutant to which it is applied,” flatly rejected EPA’s use of the model rather than actual, proffered data on MDI.³⁸ The court explained that “EPA has not pointed to any record evidence that shows a rational relationship between the generic air dispersion model and the physical properties of MDI, even in the face of the specific scientific evidence to the contrary adduced by the [petitioner].”³⁹ Other appellate courts have similarly held that an agency decision is unlawful if the agency ignored or failed to give adequate consideration to relevant information in its possession.⁴⁰

³⁵ See *Tex Tin Corp. v. EPA*, 992 F.2d 353, 354-55 (D.C. Cir. 1993) (National Priorities List decision under the Comprehensive Environmental Response, Compensation, and Liability Act); see also *Columbia Falls Aluminum Co. v. EPA*, 139 F.3d 914, 923 (D.C. Cir. 1998) (finding arbitrary and capricious EPA’s use of a Resource Conservation and Recovery Act (RCRA) treatment standard that bore no correlation to actual disposal conditions).

³⁶ See *Sierra Club v. EPA*, 346 F.3d 955, 961-63 (9th Cir. 2003) (EPA Clean Air Act determination inconsistent with actual wind data), *cert. denied*, *Imperial County Air Pollution Control District v. Sierra Club*, 542 U.S. 919 (2004).

³⁷ 28 F.3d 1259 (D.C. Cir. 1994).

³⁸ *Id.* at 1265.

³⁹ *Id.*; see also *Sierra Club v. EPA*, 356 F.3d 296, 307 (D.C. Cir. 2004) (modeling would be arbitrary and capricious if EPA failed to “ensure consistency with real-world observations”); *Appalachian Power Co. v. EPA*, 249 F.3d 1032, 1053 (D.C. Cir. 2001) (stating that “model assumptions must have a ‘rational relationship’ to the real world”) (citation omitted); accord *Edison Elec. Inst. v. EPA*, 2 F.3d 438, 446-47 (D.C. Cir. 1993) (rejecting EPA’s application of the RCRA Toxicity Characteristic Leaching Procedure (TCLP) generic mismanagement scenario to mineral wastes due to the absence of evidence demonstrating that such wastes actually are exposed to the conditions simulated by the TCLP).

⁴⁰ See, e.g., *Love v. Thomas*, 858 F.2d 1347, 1358-63 (9th Cir. 1988) (EPA’s dinoseb suspension found to be arbitrary and capricious because EPA failed to evaluate information in its possession about the impacts on Pacific Northwest agriculture); *NCAMP v. Thomas*, 809 F.2d 875, 882-83 (D.C. Cir. 1987) (EPA’s reversal of position on an ethylene dibromide tolerance under the FFDCA found to be arbitrary and capricious due to EPA’s failure to give appropriate consideration to the relevant factors); *Public Citizen Health*

Here, by disregarding specific, highly relevant data in favor of models and other less relevant information that clearly contradict these data when assessing potential risks posed by EtO uses, EPA has violated its legal obligations. EPA's failure to consider highly relevant data, and the impact that failure has had on its proposed decisions in the EtO PID include the issues discussed in the attachments to this document. Key examples of how the IRIS review disregards important sources of data include:

- The Union Carbide Corporation (UCC) study has higher exposures than the NIOSH study that EPA relied upon and the authors also had exposure measurements from the early periods of the cohort, unlike NIOSH. Despite this, EPA improperly dismissed the null findings in this study.
- Several papers document the large levels of endogenous exposure to EtO but EPA improperly dismisses this important line of evidence that shows the implausibility of high risks at low exposures.
- EPA did not consider numerous studies that show no risk of lymphoid cancers for smokers, despite smokers having high EtO exposures.
- EPA improperly dismisses the risk assessment done by the Texas Commission on Environmental Quality (TCEQ), which came to very different conclusions about EPA over the same body of information.

Likewise, EPA also has inappropriately or inadequately considered how certain proposed risk mitigation measures will create catastrophic shortages of sterilized medical devices, given that EPA is proposing these measures despite EPA acknowledging that the loss of EtO would have a severe impact on medical device sterilization capacity and device supply, triggering “widespread disruption to the availability of sterile medical devices” and a “nationwide public health crisis.”⁴¹ In *Love v. Thomas*, the court determined EPA's decision to suspend the use of the pesticide dinoseb was arbitrary and capricious, an abuse of discretion, and not in accordance with FIFRA because EPA failed to evaluate information in its possession about potentially disastrous and unique impacts of the suspension on agriculture in the Pacific Northwest.⁴²

Research Group v. Tyson, 796 F.2d 1479, 1507 (D.C. Cir. 1986) (remanding the Occupational Safety and Health Administration's decision not to promulgate a short-term exposure limit because the agency “entirely failed to consider an important aspect of the problem”); *Gulf S. Insulation v. CPSC*, 701 F.2d 1137, 1146 (5th Cir. 1983) (finding the U.S. Consumer Product Safety Commission's (CPSC) exclusive reliance on a rat study inadequate to support its rule where the agency ignored a body of available epidemiologic studies, and stating that “[t]o make precise estimates, precise data are required”).

⁴¹ PID at 3, 28, 69.

⁴² *Love v. Thomas*, 858 F.2d at 1358-1363.

3. EPA Has Acknowledged EtO's Essential Benefits, Yet Its Proposed Risk Mitigation Measures Threaten EtO's Continued Availability

EPA acknowledges that it cannot make a determination that a pesticide causes “unreasonable adverse effects on the environment” without “taking into account the economic, social, and environmental costs and benefits of the use of any pesticide.” EPA also states in its final rule setting forth procedural regulations for registration review that EPA would weigh the benefits of a pesticide more favorably when there is a lack of viable alternatives:

[W]hen there are risks of concern for a pesticide, FIFRA requires EPA to weigh those risks against the benefits of that pesticide to determine whether the risks are unreasonable. Benefits are the advantages that accrue to the pesticide users or society in general, such as increased production, decreased production costs, pest-free homes, or disease-vector control. The magnitude of those benefits often depends on the availability of alternative pest control measures, whether chemical, biological or cultural. Benefits are, in general, expected to be higher when there are no viable alternatives.⁴³

In the PID, EPA acknowledges that EtO is “highly valuable” and that “there are no viable alternatives to EtO for the sterilization of certain medical devices and equipment.”⁴⁴ EPA states further: “The absence of EtO for use on medical devices and equipment would cause widespread disruption to the availability of sterile medical devices.”⁴⁵ With regard to the spice industry, EPA recognizes EtO's importance “during the processing and reconditioning of dried herbs and spices to reduce foodborne pathogens of concern such as Salmonella and Escherichia coli.”⁴⁶

Considering the current essential need for EtO, EPA must review EOSA, EOTF, and other comments regarding certain risk mitigation measures that are impossible to implement or may be possible but at costs and in timeframes that will jeopardize the availability of EtO for these critical sterilization uses. There also are mitigation measures proposed that will not achieve the objectives EPA seeks with regard to exposure reductions and must be removed or revised. In short, the risk mitigation measures in the PID must be wholly reconsidered, in conjunction with wholesale reconsideration of reliance on the IRIS factor, so that EPA can instead conduct a

⁴³ 71 Fed. Reg. at 45725.

⁴⁴ PID at 3.

⁴⁵ *Id.* at 3, 28.

⁴⁶ *Id.*

reasonable cost-benefit analysis and then propose measures that are appropriate for a potential risk that is supported by the data and science, and that this industry can implement while ensuring the steady availability of sterilized medical devices and equipment.

4. EPA Failed to Meet Its Commitment to Transparency and the Collection, Generation, and Dissemination of High Quality Information

It is inconsistent with FIFRA, APA, defensible science, EPA's stated commitment to transparency,⁴⁷ and common sense to issue a PID when EPA has not provided a transparent record of the bases for EPA's conclusions for review by relevant stakeholders. Moreover, it is inconsistent with the IQA and EPA's IQA Guidelines, which affirm that "EPA is dedicated to the collection, generation, and dissemination of high quality information."⁴⁸

EPA has failed its commitment to transparency and has denied the public the right to review and comment here. The proposed NESHAP also lacks transparency that affects the ability of stakeholders to comment adequately, for example, EPA does not provide transparency on its mass limit calculation method, nor does it provide any defensible, reasonable basis for its assumptions. EPA has failed to meet its commitment to transparency and has denied stakeholders an adequate opportunity to comment by not making available for review this critical information.

EPA also may have violated IQA, APA, and FIFRA by not timely making available documents critical to the evaluation of EtO, but EOSA and EOTF have not been provided an adequate opportunity to review fully and determine whether it has all of the relevant documents.

⁴⁷ See, e.g., 71 Fed. Reg. at 45720 ("The registration review program established by this regulation is intended to ensure that all pesticide registrations are systematically reviewed in a manner that is based on sound science and provides for public participation, transparency and efficiency to protect public health and the environment"); Environmental Protection Agency 2005 Annual Performance Plan and Congressional Justification at IV-13, IV-32 through IV-33 ("Additional program requirements and priorities within FQPA include: . . . Transparency of our regulatory decisions The Agency has worked extensively with stakeholders through the Pesticide Program Dialogue Committee (PPDC) and the Committee to Advise on Reassessment and Transition (CARAT) to ensure transparency in decision-making and a fuller understanding of the implications for growers, producers and the public."), available at <http://www.epa.gov/ocfo/budget/2005/g04final.pdf>; see also EPA's Office of Science Policy Update (Feb. 2004) at 1 ("The public launch of the Science Inventory is another example of open, transparent government," said Steve Johnson"), available at <http://www.epa.gov/osp/recent/0402qrt.pdf>; Office of Environmental Information FY2003 Program and Highlights (Oct. 2003) at 7 ("Quality and transparent information is critical to EPA's ability to make sound decisions.").

⁴⁸ IQA Guidelines at 10.

B. Medical Devices and Sterilization of Medical Devices Are Regulated by FDA and EPA Must Ensure Its Proposals Are Within EPA Jurisdiction

It is critically important to note that medical device sterilization process and sterility assurance are strictly regulated by FDA. EPA should not propose specific regulatory requirements that are under FDA purview, to avoid conflicting regulatory requirements, especially in the context here, where these regulations affect the ability to ensure sterile medical devices used on U.S. patients across the U.S. As FDA states on its website:

How Does the FDA Help Ensure that Medical Devices Sterilized with Ethylene Oxide Are Safe?

Before most sterile medical devices are on the market, the FDA reviews premarket submissions to determine if the sterility information (for example, the method the manufacturer is choosing to sterilize their device and validation activities used to show that the device can be effectively sterilized) is in accordance with internationally agreed upon voluntary consensus standards that the FDA recognizes. An important element of our regulatory framework is a robust standards program. The FDA encourages medical device sponsors to use FDA-recognized voluntary consensus standards in their submissions, as conformity to relevant standards streamlines regulatory review and fosters quality. [Learn more about the FDA's Recognized Standards Program.](#)

For ethylene oxide sterilization, two voluntary consensus standards (ANSI AAMI ISO 11135:2014 and ANSI AAMI ISO 10993-7:2008(R)2012) describe how to develop, validate, and control ethylene oxide sterilization processes for medical devices and the acceptable levels of residual ethylene oxide and ethylene chlorohydrin left on a device after it has undergone ethylene oxide sterilization. These standards help ensure levels of ethylene oxide on medical devices are within safe limits since long-term and occupational exposure to ethylene oxide has been linked to cancer. [Learn more about the risks of ethylene oxide on the National Institutes of Health web page on ethylene oxide.](#)

If a medical device manufacturer changes the method, process, or the facility identified in its original PMA submission for sterilizing its devices, the manufacturer generally needs to submit a PMA supplement so that the agency can review these changes and determine if they also meet internationally agreed-upon voluntary standards that the FDA recognizes. For manufacturers that are 510(k) holders, sterilization method, process or site modifications can be assessed with the FDA guidance document: “[Deciding When](#)

to Submit a 510(k) for a Change to an Existing Device” for determination on whether the sterilization modifications would trigger the need for resubmission.

EPA cannot propose risk mitigation measures that would prevent medical devices from meeting the standards necessary to ensure safe patient use. EPA also must address the concerns with the need for manufacturers to submit PMA or 501(k) supplements and the enormous and impossible challenges these processes would pose, which are discussed in Attachment 1.

Moreover, as discussed in the appended technical comments, the 1 in 10 risk estimated by EPA for sterilizer workers based on the IRIS value is completely absurd and the proposed inclusion of a risk statement as part of worker training is arbitrary, without basis, misleading, and could lead to unintended and unnecessary adverse consequences. This proposal raises First Amendment commercial speech concerns.⁴⁹

Please contact Lisa M. Campbell at lcampbell@lawbc.com or (202) 557-3802 if there are any questions.

⁴⁹ Nat’l Ass’n of Wheat Growers v. Becerra, 468 F. Supp. 3d 1247, 1258-59, 1264-65 (E.D. Cal. 2020) (entering a permanent injunction against enforcement of a requirement under Proposition 65 to provide a warning that glyphosate is a substance known to cause cancer when it was not demonstrated that the warning is “purely factual and uncontroversial” and thus violated the First Amendment prohibition against compelled commercial speech).

Attachment 1

Technical Comments Identified to Date on United States Environmental Protection Agency (EPA) Proposed Interim Decision and Draft Risk Assessment Addendum for Ethylene Oxide (PID)¹

¹ 88 Fed. Reg. 22447 (April 13, 2023) (*Federal Register* notice announcing the availability of the U.S. Environmental Protection Agency's (EPA) Proposed Interim Decision (PID) and Draft Risk Assessment (DRA) Addendum for ethylene oxide (EtO) (PID), available at <https://www.federalregister.gov/documents/2023/04/13/2023-07727/pesticide-registration-review-proposed-interim-decision-and-draft-risk-assessment-addendum-for>.

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INTRODUCTION

The Ethylene Oxide Sterilization Association (EOSA) and the Ethylene Oxide Task Force (EOTF) jointly submit these comments to the United States Environmental Protection Agency (EPA) in response to the April 13, 2023, notice of availability of the Proposed Interim Decision and Draft Risk Assessment Addendum for Ethylene Oxide (EtO) (PID).

As noted in the document to which this is an attachment, EOSA and EOTF incorporate by reference the comments submitted by EOSA in response to the April 13, 2023, notice of availability of the Proposed National Emission Standards for Hazardous Air Pollutants (NESHAP) for the Commercial Sterilization Facilities source category, Docket No. Docket: EPA-HQ-OAR-2019-0178.²

EOSA is comprised of the leading experts of the medical device manufacturing and sterilization industry. In addition to medical device manufacturers, EOSA members include manufacturers of emissions control equipment, ethylene oxide sterilizers, and ethylene oxide detection systems. EOSA members also include many contract sterilization providers, sterilization consultants, environmental consultants, and registrants. The diversity of EOSA member companies provides EOSA a broad view of the overall implications of these proposed regulatory actions. The highly knowledgeable subject matter experts within EOSA are uniquely capable of assessing the issues and complications posed by the NESHAP and PID proposals on the sterilization process, the sterilization facilities, the economics of sterilization, the safety of sterilization facilities, and the security of the supply chain of critical medical devices. No other organization has EOSA's breadth or depth of expertise in the matters presented by the EPA's proposals.

EOSA and EOTF have worked extensively with to identify and address the many issues posed by the PID. As noted in the document to which this is an attachment, the comment period provided was wholly inadequate to provide comment. Accordingly, the comments below do not identify all issues that the PID poses, nor do they address potential alternatives that may help to address EPA concerns. As noted in the document to which this is attached, EOSA and EOTF are committed to working with EPA to address the concerns noted and plans to submit supplements to these comments to identify issues not yet identified due the short time period for comment, to address more fully some of those identified, and to address potential alternatives. EPA's PID for ethylene oxide (EtO) as proposed will have an enormous negative impact on public health because as currently structured, it will cause medical devices shortages and hamper the availability to provide safe spice products. EtO is critical and essential to sterilize essential medical devices and equipment for which no viable alternative exists. Implementation of many of the proposed requirements in the PID would significantly disrupt safe healthcare in the United States.

² 88 Fed. Reg. 22790 (April 13, 2023) (*Federal Register* notice announcing the availability of the U.S. Environmental Protection Agency's (EPA) National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Emission Standards for Sterilization Facilities Residual Risk and Technology Review (NESHAP), available at <https://www.govinfo.gov/content/pkg/FR-2023-04-13/pdf/2023-06676.pdf>.

Among the many issues of grave concern to EOSA and EOTF, based on what EOSA and EOTF have been able to identify to date in the brief amount of time they have had to review the PID, are the following, and this is far from an exhaustive list:

- The elimination or significant restriction on the use of EtO as a sterilant could immediately compromise the U.S. healthcare system's ability to provide a consistent and safe supply of sterile healthcare products to medical care providers and their patients, causing a public health crisis. A lack of sterile medical supplies to operating rooms would result in delayed or even canceled procedures, which would pose grave risk to those in urgent medical need. Medical supplies sterilized with EtO are used in nearly every surgical procedure performed and have also been critical for the global treatment options during the pandemic. Especially given the serious flaws in EPA's Integrated Risk Information System (IRIS) analysis for EtO, restricting or eliminating the use of EtO would jeopardize the medical device supply in the U.S., for no appreciable health benefit to sterilization workers, the public, or anyone else.
- As discussed in more detail below, EPA has denied EOSA and EOTF the minimal amount of time to comment adequately and meaningfully on the PID and the proposed NESHAP, which propose sweeping and extremely restrictive measures on a wide swath of issues that are critical to the ability of industry to operate. Despite the relentless efforts that the industry has undertaken since the PID was published, it is impossible to provide meaningful input for many of the proposed measures included in the PID given the extremely inadequate comment period. For these reasons, EOSA and EOTF reserve all rights to supplement these comments. EPA should not proceed until it has additional information regarding adverse impacts, costs, and timelines, and has an opportunity to revise its proposal and allow comment on the revision. This is essential to avoid potentially catastrophic consequences to industries dependent on EtO sterilization.
- Many of EPA's proposed engineering controls included in the PID for commercial sterilization facilities and health care facilities pose serious and considerable issues that must be addressed. Some of the proposed requirements, such as the proposed automation via covered conveyor for transported aerated materials to shipping/storage areas, are not feasible for the vast majority of existing sterilization facilities, would provide limited-to-no benefits in terms of worker exposure to EtO, and would result in the need for reconstruction of existing facilities, if they could be implemented at all. The result of imposing this and other requirements would be a severe adverse impact on medical device sterilization capacity and device supply,

triggering “widespread disruption to the availability of sterile medical devices” and a “nationwide public health crisis.”³

- EPA’s proposal to set 10 parts per billion (ppb) as the action level in EtO commercial sterilization facilities is unachievable and must be changed. Currently available technologies cannot reliably or realistically detect, let alone quantify, ambient air EtO levels in facilities down to 10 ppb. Implementing this action level and the associated requirements given these facts will inevitably cause unnecessary work force panic and retention issues, facility shutdowns, and significant medical device supply chain shortages.
- It is impossible for the industry to meet EPA’s proposed requirements for a 2-year and a 5-year compliance implementation timeframe to limit the EtO concentration to 600 milligrams per liter (mg/L), let alone the 500 mg/L proposed, for new cycles and existing cycles, respectively, without severely impacting the medical device supply. First, there is no guarantee that such work to limit concentrations will be successful, and many efforts to date demonstrate this. Moreover, sterilization cycle development/modification and the necessary validation/revalidation is a rigorous process requiring sterilizers to follow strictly the approved protocol(s)/method(s) and regulatory requirements, take into consideration the product type and packaging design, and be able to meet the product sterility and performance requirements. Given the large number of existing cycles (in the thousands) that currently are in place, it could take decades or longer to have the cycles revalidated, and that assumes that efforts to design the cycles are successful. Of enormous importance, given these facts, is that EtO concentration reduction does not correlate to reduced EtO residue or fugitive emissions. Additional information is provided below addressing the reasons why EPA’s proposal will not achieve its desired objective of lower worker exposure.
- EPA must eliminate any mandatory requirement for All-In-One (AIO) processing from the mitigation measures. EPA acknowledges that AIOs would be required only in facilities that do not sterilize pressure sensitive devices (a term with no corresponding EPA definition, and which should be defined clearly in the manner discussed below) but this does not address all the circumstances when AIO should not be required. It is imperative that performance criteria be used to achieve less emission and lowered worker exposure. As discussed in detail below, and considering that EtO sterilization facilities are currently operating very near or at capacity, any requirement to change to AIO processing will cause serious healthcare supply issues, resulting in potentially devastating effects on the entire

³ PID at 3, 28, 69.

healthcare system by creating significant shortages of life-improving, life-sustaining, and life-saving devices.

- Air Exchange per Hour (ACH) is a facility-specific factor and EPA should not implement a set standard that will unnecessarily cripple the facility design and process without achieving any benefit for worker exposure. Although ACH has been used historically as a guideline for the amount of air needed to provide ventilation to an area, this measurement has been used largely as a rule-of-thumb and provides a means of estimating the cubic feet per minute of air either supplied or exhausted to maintain the desired environment.
- Self-contained breathing apparatus (SCBA) for workers should be required only for workers performing specified activities in areas in commercial sterilization facilities. An example of an activity that could be assessed for potential SCBA requirements is connecting and disconnecting EtO containers from the sterilization process equipment.
- Healthcare facilities have been following AAMI ST41 for over twenty years. New proposed requirements included in the PID for many healthcare facilities, including small facilities, dentist, plastic surgeon, and veterinarian' offices, however, are not feasible and will have a significant adverse impact on patient health and on the economic viability of these facilities. Healthcare facilities should be permitted to continue following AAMI ST41.
- There are currently no effective alternatives to EtO for certain spices and spice-related categories. EtO's use is essential until effective alternatives exist. EPA proposes several actions in the PID that are either not achievable or that would significantly impact the industry's ability to supply safe, clean spices to the U.S. population. Moreover, and in any event, since exposure to EtO and ethylene chlorohydrin (ECH) residues from the consumption of spices does not pose a public health risk,⁴ EPA should not propose any revocation of any tolerance for herbs, spices, and dried vegetables, as they are essential for global trade.

Among the issues that EOSA and EOTF plan to address in supplemental submissions, due to the inadequacy of the comment period, are potential alternatives for some of EPA's proposed mitigation measures, as well as issues EOSA and EOTF were not able to address more fully in the appended technical comments. Examples of issues on which EOSA and EOTF plan to make supplement submissions include the following:

⁴ PID at 16.

- Feasible compliance timelines
- Pallet configurations
- State or local permit issues
- SCBA requirements
- EtO concentration limit for new cycles
- Engineering controls proposed for facilities
- Technologies for EtO detection and measurement
- Respirator use /employee evacuation
- Employee training and recordkeeping
- ACH (air change per hour)
- Pressure sensitive devices
- Cost issues

COMMENTS

I. EPA'S PROPOSED EtO CONCENTRATION REDUCTION CANNOT BE IMPLEMENTED IN EPA'S TIMEFRAMES AND WILL NOT ACHIEVE LOWER WORKER EXPOSURES

On page 73, EPA proposes that the EtO concentration must be less than or equal to 500 mg/L while still meeting FDA sterility requirements. For existing cycles, EPA proposes a 5-year compliance timeframe to limit the EtO concentration to 500 mg/L. EPA seeks public comment on the feasibility of a 5-year compliance timeline for use rate reduction through reduced concentrations of existing cycles. EPA proposes a 2-year compliance timeframe to limit the EtO concentration to 500 mg/L for new cycles and seeks public comment on the feasibility of a 2-year compliance timeline for use rate reduction through reduced concentrations of new cycles. EPA also seeks public comment on alternative limits that may differ from 500 mg/L.

It is impossible for the industry to meet EPA's proposed requirements for a 2-year and a 5-year compliance timeframe to limit the EtO concentration to 600 mg/L, let alone the 500 mg/L proposed, for new cycles and existing cycles, respectively, without severely impacting and devastating the medical device supply. First, **there is no guarantee that such work to limit concentrations will be successful, and many efforts to date demonstrate this.** Moreover, sterilization cycle development/modification and necessary validation/revalidation is a rigorous process requiring sterilizers to follow strictly the approved protocol(s)/method(s) and regulatory requirements, take into consideration the product type and packaging design, and be able to meet the product sterility and performance requirements. Given the large number of existing cycles (in the thousands) that currently are in place, it could take decades or longer to have the cycles revalidated, and that assumes that efforts to design the cycles are successful. Of enormous importance, given these facts, is that EPA's proposal will not achieve the desired objective of lower worker exposure.

It is critical to emphasize that EOSA is uniquely qualified to comment on these important issues, given that EOSA is comprised of the leading experts of the medical device manufacturing and sterilization industry. As noted earlier, in addition to medical device manufacturers, EOSA members include manufacturers of emissions control equipment, ethylene oxide sterilizers, and ethylene oxide detection systems. EOSA members also include many contract sterilization providers, sterilization consultants, environmental consultants, and registrants. The diversity of EOSA member companies provides EOSA a broad view of the overall implications of these proposed regulatory actions. The highly knowledgeable subject matter experts within EOSA are uniquely capable of assessing the issues and complications posed by the NESHAP and PID proposals on the sterilization process, the sterilization facilities, the economics of sterilization, the safety of sterilization facilities, and the security of the supply chain of critical medical devices. No other organization has EOSA's breadth or depth of expertise in the matters presented by the EPA's proposals.

It is also critically important to note that medical device sterilization process and sterility assurance are strictly regulated by the U.S. Food and Drug Administration (FDA). EPA must not propose specific regulatory requirements that are under FDA purview. It is also essential to avoid conflicting regulatory requirements.

A. Concentration Reduction Does Not Correlate to Reduced EtO Residues or Fugitive Emissions

The proposed 500 mg/L usage limit does not dictate final product and load EtO residues, and mandating a general limit on EtO will result in longer cycle times and loss of capacity while not significantly addressing EPA's concerns with EtO. EtO concentration is one of many variables (*e.g.*, vacuum depth, gas washes, temperature, material density) that impact sterility and EtO residues. Reducing gas concentration alone may not equate to reduced residues or reduced fugitive emissions if other cycle parameters such as exposure time need to be increased, resulting in more absorption of EtO, to ensure the required sterility assurance level is achieved. Test cycles have been run where the amount of EtO used was reduced by 50 percent or more but did not result in reduction of fugitive emissions or employee exposure.

B. The Validation Effort and Timelines Will Impact Sterilization Capacity

The amount of effort needed to undertake validation of reduced EtO concentration cycles for existing cycles is significant. Validation is a complex process requiring chamber time, research and development (R&D), validation, testing resources, and potential product and packaging design changes. Tying up these resources will correspondingly reduce resources available for product development and innovation, and more importantly, limit the availability of critically needed sterile medical devices. The same challenges exist for new cycles as for existing cycles and two years is not sufficient time for manufacturers to redesign new products, even if it is assumed that a manufacturer had completed much of the necessary development process of a redesign. Given the timelines for device development and regulatory approval, any requirement for **new** cycles to meet a 600 mg/L maximum concentration (with exception processes as discussed below) would take a minimum of 10 years, and likely much more time, to implement.

In addition to the large number of cycles required for validation, there is a multi-step process to obtain regulatory approval. Five years is a wholly insufficient, and indeed impossible, timeframe in which to revalidate and comply with the reduced EtO concentration requirement for existing cycles. This is particularly true for companies with large numbers of existing cycles, for example, contract sterilizers, or where product or packaging redesign is required to achieve the reduced EtO concentration requirement. Customers and/or device industries own the products and process, not the contract sterilizers. Cycle parameters are included as part of contract sterilization contracts and would require renegotiation. The quantity of regulatory resubmissions associated with revalidating at a lower EtO concentration, both domestically and worldwide, may overwhelm regulatory authorities. This also will very likely increase the time needed to comply with a reduced EtO concentration limit, if it is assumed for the sake of argument that such a limit could be achieved, which is not at all certain.

This loss of EtO sterilization capacity, due to validation efforts and longer cycle times, and its enormous adverse impact on the availability of sterilized products, must be considered, in addition to risks of medical device supply chain shortage and hospital acquired infections. For all of these reasons, any requirement to revalidate **existing** cycles – in any timeframe – to meet a cycle concentration limit would have immense adverse impacts on the medical device supply chain and would significantly reduce innovation and new product development, while not providing reductions in residues, fugitive emissions, or worker exposure.

It is again critical to emphasize that EOSA is uniquely qualified to comment on these important issues, given that EOSA is comprised of the leading experts of the medical device manufacturing and sterilization industry. As noted earlier, in addition to medical device manufacturers, EOSA members include manufacturers of emissions control equipment, ethylene oxide sterilizers, and ethylene oxide detection systems. EOSA members also include many contract sterilization providers, sterilization consultants, environmental consultants, and registrants. The diversity of EOSA member companies provides EOSA a broad view of the overall implications of these proposed regulatory actions. The highly knowledgeable subject matter experts within EOSA are uniquely capable of assessing the issues and complications posed by the NESHAP and PID proposals on the sterilization process, the sterilization facilities, the economics of sterilization, the safety of sterilization facilities, and the security of the supply chain of critical medical devices. No other organization has EOSA's breadth or depth of expertise in the matters presented by the EPA's proposals.

C. An Exception Process Is Needed

Many products may not be able to achieve their required sterility assurance level using a reduced EtO concentration. Reducing EtO concentrations below 600 mg/L will not be viable, for example, for products with shallow vacuum cycles, products with complex geometry, or where the required sterility assurance level has been difficult to obtain during validation. If sterility assurance cannot be achieved below any mandatory uniform EtO concentration limit, product and or packaging redesign will be required to allow the required sterility assurance level to be achieved, and there is no guarantee that such redesign efforts would be successful. Alternatively, companies may choose to move product manufacturing and sterilization to a jurisdiction outside the U.S. that does not have an EtO concentration limit, which may significant

adversely affect the reliability of the supply chain and the availability of needed medical devices in the United States, or may discontinue the product. In both cases medical device supply shortages will occur.

It is essential for clear exceptions to be provided for products requiring more than any mandatory uniform EtO concentration limit. Justification for the increased application rate can be documented and maintained by the manufacturer or the sterilizer.

D. EtO Concentration: Calculation vs. Measurement

EPA has not specified whether the EtO concentration limit is as measured in-chamber or calculated using temperature and the differential pressure of the EtO injected. EtO concentration as measured in-chamber varies dependent on the ratio of EtO in the chamber headspace versus absorbed into the load in addition to product and packaging greatly impacting absorption rate. EPA must use the EtO concentration as calculated using temperature and EtO differential pressure, as this calculation will be consistent amongst all sterilization cycles.

EPA must not set an EtO concentration limit, for all of the reasons discussed in these comments and previously with EPA. EPA must instead allow performance-based standards, in a manner that allows industry sufficient time to work to achieve these standards while still meeting the required sterility assurance.

II. REQUIRING ALL-IN-ONE SYSTEMS IS UNACHIEVABLE AND IMPRACTICABLE

On page 73, the Agency is seeking additional information on the feasibility of all-in-one processing (combination sterilizers) for the treatment of medical devices by commercial sterilization facilities. With all-in-one systems, sterilization and aeration occur in the same chamber. EPA understands that all-in-one systems may not be appropriate for use to sterilize pressure-sensitive materials. Additionally, each all-in-one processing chamber is utilized for a greater amount of time when compared to traditional sterilization configurations, potentially limiting the throughput in a facility. EPA seeks public comment on feasibility of upgrading facilities to use all-in-one systems, and the potential impacts on the medical device supply chain.

Conventional three phase processing (TPP) occurs where the entire sterilization process is performed in three separate and distinct areas ((pre)conditioning room/cell/chamber, sterilization chamber, and aeration room/cell/chamber). This type of processing is practiced by the majority of the sterilization industry. In general, the average sterilization chamber time typically ranges from eight to 16 hours.

In contrast, AIO processing is carried out with all three phases being performed in the sterilization chamber. The typical process takes about 16-32 hours of time in the sterilization chamber. Since the sterilization chamber time is much longer, this type of processing is practiced to a much lesser degree.

EPA must not implement the AIO processing requirements:

- AIO processing takes much longer in the sterilization chamber than TPP cycles. A requirement to switch to AIO processing would therefore have a direct, severe impact on chamber capacity. Since U.S. based EtO sterilization facilities have very little if any additional capacity, a conversion to AIO processing would lead to an immediate, significant reduction in capacity by roughly fifty percent (50%), which will result in catastrophic shortages in sterile healthcare products.
- If implementation of AIO processing is required, industry will lack the ability to be responsive to meet critical and timely needs in the event of any medical crisis, let alone another pandemic.
- In the majority of instances where the (pre)conditioning and aeration phases of the process with AIO are performed in the sterilization chamber, the temperature is generally higher for both of these phases than it would be if TPP processing was used. With this difference in mind, entire sterilization processes would have to be validated anew, and many products would then be subject to regulatory approval. This process takes many years to complete in the vast majority of instances and is very expensive. Any requirement to undertake it will exacerbate the existing capacity crisis even further. It is important to note in addition that where the products at issue would not withstand these higher temperatures, the products may well need to be redesigned, which could make this effort take even longer. In these cases, if redesign is not feasible or achievable, critical products would not only be unavailable, but could be discontinued altogether, which would even more severely impact public health.
- Since the sterilization chamber time for AIO processing versus TPP is much longer, if the proposed requirement were implemented, the number of sterilization chambers would have to at least double for the industry to handle the same volume. This also would take many years to complete, if it is possible to do so at all, be very costly, and would result in significant increases in the cost of healthcare. In addition, much of the existing equipment (*e.g.*, chambers, control systems) cannot perform AIO processing. To obtain all of the necessary equipment and/or build new equipment to meet this requirement would require decades and great expense, if it is possible at all.
- All of the steps necessary to convert to AIO processing cannot be accomplished in EPA's proposed 36-month timeframe. Capacity would instantly be cut by at least 50 percent. EOSA and EOTF estimate that to complete the process of switching to AIO processing so there is enough AIO processing equipment would take decades or more, if it can be done at all. In the meantime, there will be a crushing shortage of medical devices.

- The extraordinary amount of work that would be required to switch to AIO processing in the short timelines that EPA provides would stifle R&D efforts for product improvements, innovation, and the creation of new products.
- Expansion of existing facilities to accommodate the requirement for more EtO chambers to perform AIO processing is not feasible in most instances, and certainly not in any foreseeable timeframe.
- Considering the tremendous difficulty of meeting the proposed EPA regulations, along with public pressure, most expansion of the EtO sterilization industry will occur outside the U.S. The serious issue of a critical healthcare device shortage cannot be understated. In addition, this will likely lead to healthcare manufacturing companies choosing not to expand in the U.S., and/or moving out of our country, which will lead to device shortages, increased dependence on a foreign supply chain that does not currently, or for the foreseeable future, exist with adequate capacity for critical devices, loss of jobs, and increased healthcare costs.

In summary, any mandatory requirement for AIO processing must be eliminated from the mitigation measures. Instead, it is imperative that performance criteria be permitted for industry to achieve less emission and lowered worker exposure. This PID proposal is unachievable and impracticable as any requirement to purchase and/or convert, validate, and use AIO processing will cause serious healthcare supply issues, resulting in potentially devastating effects on the entire healthcare system by creating significant shortages of life-improving, life-sustaining, and life-saving devices. This is particularly the case given that the EtO sterilization facilities are currently operating very near or at capacity.

III. EPA SHOULD NOT SPECIFY A MANDATORY LEVEL OF AIR EXCHANGES AND INSTEAD ALLOW FACILITIES TO ACHIEVE THE AIR CONCENTRATION THROUGH A PERFORMANCE-BASED APPROACH THAT WOULD BE CUSTOMIZED BY EACH FACILITY

On page 73, EPA is soliciting public comment on the number of air exchanges per hour that would adequately ventilate product storage areas. The Agency is also soliciting public comment on the use of netting rather than plastic surrounding pallets of treated medical devices to increase aeration and prevent EtO from becoming trapped in plastic wrap or other packaging.

Although ACH have been used historically as a guideline for the amount of air needed to provide ventilation to an area, this measure has largely been used as a rule-of-thumb and provides means of estimating the cubic feet per minute of air either supplied or exhausted to

maintain the desired environment.^{5,6} For example, certified cleanrooms such as those certified to ISO 14644, require several factors to be considered, with air changes being only one of those factors. Regardless, specifying a specific ACH, or by extension the cubic feet per minute of air to be moved through the space, and not considering the differences between each facilities' spaces, will result in inefficiencies and will not likely achieve the desired objective of lower worker exposure.

A standard ACH specification is not appropriate for sterilization facilities since variations in room design, air mixing, air flow within the space, and release rate of the contaminant impact the concentration in the space. It is expected that the amount of exhaust ventilation needed will be significantly different for different facilities. Setting an average or minimum ACH does not result in any benefit and will instead result in unnecessary use of energy if the target concentration were already achieved. Prescription of these metrics is unnecessary if facilities are meeting emissions and exposure standards. EPA must not specify a mandatory level of air changes and instead allow facilities to achieve the air concentration through a performance-based approach that would be customized by each facility.

Moreover, an ACH requirement, would prevent a facility from having the ability to implement the Permanent Total Enclosure requirement in the proposed NESHAP since a fixed ACH will not allow for the required static pressure differentials to be feasibly maintained between various areas of the building in many facilities.

EtO can be released in an appropriate manner from palletized products with vented plastic wrap and netting alternatives; netting should not be required.

Depending on the commercial sterilization, various types of product containment are used, including stretch wrap, vented wrap, netting and corner boards and straps, and it is not useful to require one type over the other. Furthermore, wrapping and banding are used to stabilize loads during transport, processing, and storage. Requiring one kind of product containment may compromise worker safety if loads become unstable during any point of a cycle.

In summary, ACH is a facility-specific factor. EPA must not implement a set standard that will unnecessarily cripple the facility design and process, particularly when doing so will not achieve any benefit for lower worker exposures. This comment is pertinent to both on-site and off-site storage areas and warehouses.

⁵ Industrial Ventilation, a manual of Recommended Practice for Design, by American Conference of Governmental Industrial Hygienist. 2013.

⁶ User Manual ANSI/ASHRAE Standard 62.1, by the American Society of Heating, Refrigerating and Air-Conditioning Engineers. 2019.

IV. EPA'S PROPOSED AUTOMATION VIA COVERED CONVEYOR FOR TRANSPORTED AERATED MATERIALS TO SHIPPING/STORAGE AREAS IS NOT FEASIBLE

On page 73, in traditional EtO treatment configurations, sterilization and aeration are performed in two separate chambers. In these systems, employees may transfer post-treatment materials from the sterilization chamber to the aeration chamber via forklift. EPA is aware that in some sterilization facilities, post-treatment materials are instead transferred via enclosed conveyor systems, to reduce employee exposure. EPA is seeking public comment on the feasibility of reconfiguring existing EtO commercial sterilization facilities to use an enclosed conveyor system from the aeration area to the storage/shipping area. Note that in facilities that have all-in-one systems, EPA is proposing automation via covered conveyor from the aeration area to the shipping and storage area.

A requirement for covered conveyors to move sterilized product from chamber to aeration, and also from aeration to storage/shipping area, is not feasible for the vast majority of existing sterilization facilities. Moreover, it would provide limited-to-no benefits in terms of worker exposure to EtO and would result in the need for reconstruction of existing facilities with a severe impact on medical device sterilization capacity and device supply. This would also likely cause significant offshoring of the medical device sterilization and manufacturing industries.

The layout of the vast majority of existing sterilization facilities precludes the use of conveyor automation. Most existing facilities were constructed multiple years or even decades ago, and were explicitly designed, in accordance with longstanding industry standards, practices, and building/safety codes, for movements of product via forklift from chamber to aeration and aeration to warehouse. The layout of a typical facility includes complex floorplan configurations with multiple walls, corridors and turns that simply do not allow material movement by conveyor without facility redesign, meaning tearing down and rebuilding substantial portions of the facility. Additionally, in most facilities, especially the large number of contract facilities that sterilize a wide variety of devices under one roof (the significant majority of EtO medical device sterilization takes place in facilities like this), the vast number of permutations of product flow options between sterilization chamber and aeration room, and aeration room to warehouse, provides additional significant, insurmountable challenges that preclude material movement by conveyor – it is simply not possible to accommodate the large number of combinations of material flow with a conveyor system and without the flexibility of product movement by forklift. The level of facility rebuild needed to comply with this requirement would, *at best*, disrupt the operations of most medical device sterilization facilities for substantial periods of time (months or years), causing large impact on throughput that would result in substantial medical device supply disruption for extended periods. However, even this highly unfavorable “best case” scenario may not be possible for a variety of reasons, including the huge costs required, impact on facility operation, as well as lack of approval for facility redesign/construction by local building authorities (a very important yet seldom acknowledged factor that would essentially make it impossible for facilities to make required changes if the local building authorities refuse to issue permits). With those factors in mind, alternate likely scenarios include permanent closure of a large number of sterilization facilities in the U.S., and the resulting offshoring of the critical medical device sterilization

industry (and likely the medical device manufacturing industry would follow as well for logistical reasons).

Especially in light of the enormous difficulties and impacts on facility operation and medical device supply outlined above, it is also critical to note the limited-to-zero benefits that enclosed conveyor systems provide in an EtO sterilization facility. Employees who transport products are already using respiratory personal protective equipment (PPE) as a preventative measure to prevent potential exposure to any fugitive emissions while transporting pallets of sterilized product. Additionally, task-specific use of PPE/respirators, including the use of respirators when driving forklifts into sterilization chambers and aeration rooms, would effectively preclude employee exposures when making product transfers via forklift. The capacity loss, medical device shortages, and likely relocation of some portion of the medical device manufacturing and sterilization industries resulting from a requirement for covered conveyors would be triggered but provide minimal if any level of additional EtO exposure reduction.

As discussed, for the vast majority of existing facilities, enclosed conveyors would require a complete redesign and rebuild of the facility. To illustrate why trying to retrofit an existing sterilization facility with covered conveyors instead of forklifts to transfer product, the following items are examples of some of the difficulties and challenges that must be taken into consideration:

- Many chamber doors swing open on hinges and do not roll/slide open (like a sliding door), preventing connection to a conveyor system. In many cases these are huge steel doors weighing thousands of pounds, on a chamber large enough to process multiple pallets or even truckloads of product at a time. In many cases, each chamber is different from the others in the facility so the new rolling/sliding doors would need to be made specifically for each chamber. Since this is not part of the manufacturer's design, the feasibility of producing these roller doors, and who would do so, is highly uncertain, if not impossible.
- Facility 'blast doors' that are often part of chamber room design, pose similar issues. These doors swing open in many cases in a similar manner to the chamber doors themselves. Roll-open blast doors may not even be capable of meeting specific anti-blast requirements.
- Even if it is possible, which is far from certain, automating and changing out chamber and blast doors is a major project in and of itself that involves significant facility downtime.
- Another major issue is the fact that products can move in many different directions when exiting a given sterilization chamber in a facility. The many permutations of flow from multiple chambers to multiple aeration room options creates a situation where doing this via automated conveyor is impossible, even without the further major obstacles of facility walls and other physical barriers in the way. Existing facilities can have multiple

chambers and dozens of entrances to aeration rooms, in many cases on multiple levels, resulting in hundreds of product flow combinations that are only feasible with forklift movements and cannot be done via conveyors.

- Similar flow/configuration barriers exist with moving product from aeration room to warehouse/storage using a conveyor system. The complex and varied product flow options, cross-flow, building codes and reclassification, safety protocol and fire hazard issues, and the required control systems make it impossible to automate these movements with a conveyor system.
- Chambers that are ASME rated would need to be modified and may not be able to be recertified.
- Many facilities are covered under the Occupational Safety and Health Administration's (OSHA) Product Safety Management (PSM). Adding conveyors and modifying a facility will require complete process hazard analysis revalidation. This will add considerable time and could result in the need to make further changes that may or may not be feasible under that standard.
- Adding conveyors (covered or not) in an existing facility will result in emergency access and egress issues. Walkways with unimpeded access to an emergency exit will be blocked due to the fact that facilities were not designed with the significant space a conveyor takes up. Simply adding doors or access points is not possible in an area that has been designed to meet the building and safety codes of a sterilization facility.
- If additional rooms are needed, such as Secondary Aeration rooms, automation is even more complex and requires a much longer implementation time, if implementation is even possible, which is highly doubtful.
- After automation is in place, personnel training, additional maintenance activities, and possible downtimes will affect processes and will require a longer lead time, which in turn will severely and adversely impact medical device supply during this process.

In summary, due to the configuration of the vast majority of existing sterilization facilities, the implementation of enclosed conveyors to automate material handling between chambers and aeration is not feasible, and is in fact impossible, without huge facility redesign and reconstruction, which would certainly cause large amounts of downtime and severely interrupt the supply of medical devices. It also could very well cause the offshoring of the medical device sterilization, and medical device production, industries – both of which are critical to the U.S., to ensure critical medical devices are available in the U.S. without interruption, to the U.S. economy

and to this industry's ability to respond to pandemics and other national emergencies. Additionally, the major disruptions that would result from such a requirement must be considered in light of the fact that they would create minimal to no level of additional EtO exposure reduction versus existing best practices and the wearing of specified PPE when driving forklifts into chambers and aeration rooms. EPA must remove the proposed requirements for covered conveyor systems from its risk mitigation measures.

V. EPA MUST ALLOW FACILITIES TO CHOOSE OTHER ENGINEERING AND PROCESS CONTROLS TO ACHIEVE PERFORMANCE-BASED GOAL

On page 73, it is EPA's understanding that there are other methods and controls available that could reduce worker exposure to EtO that are not included in this PID. The Agency seeks further information on all engineering controls and/or work practices that would result in lowered EtO exposure for workers (for example, internal capture and emissions controls like dry beds or filters, increased air turns and cascade pressure systems, or others). In multi-chamber systems, process controls like minimizing the time and transfer length that is taken from the sterilization to aeration area, or the elimination of a staging area, may reduce worker exposure. As EPA is proposing automation in these areas, the Agency seeks information on the comparative exposure reductions of the aforementioned process controls.

EtO sterilization is a highly regulated industry, and sterilizers must follow strict building codes, fires code, local, state, and national regulatory requirements, as well as OSHA standards for employee health and safety and exposure monitoring. The industry is and has been committed to evaluating ways to reduce further potential worker exposure, but has not had sufficient time to determine whether some of the proposed PID changes are feasible, or to fully consider and comment on the potential options. As noted above in general, EOSA and EOTF plan to supplement these comments to address these issues, among many others.

With that caveat, as a preliminary comment, engineering controls and/or work practices that may be used and/or implemented broadly across many sterilization facilities, provided they do not conflict with existing facility design, engineering requirements, or best practices, and/or other regulatory requirements, may include the following examples:

- Requirements for nitrogen purge of piping prior to disconnection that allows for thorough purging of EtO from pipelines using nitrogen before breaking the line connection. This reduces the potential for EtO emission and exposure while disconnecting the EtO lines during drum changes.
- Measures to reduce transfer time for pallets being moved from sterilization to aeration areas, including the elimination of any unnecessary staging areas, could potentially be implemented as a mitigation measure, to reduce any potential off-gassing from pallets of sterilized product in a facility.

Some additional overall preliminary comments regarding cascading air flow systems and use of dry beds for internal capture of facility air are noted below. These are examples of engineering controls that may be used by some facilities, but not all facilities, due to unique facility design. It is important to emphasize that these examples could not be implemented as mandatory measures for all, but they could be used among a menu of options that facilities could select from to achieve a performance-based goal:

- For permanent total enclosure (PTE) controls, requiring cascading air flows or ACH are not necessary or feasible for the vast majority of facilities. It is imperative to allow options for control of EtO levels within the facility while minimizing fugitive emissions that facilities can select among to ensure feasibility and efficacy in achieving the intended reductions given the unique properties and characteristics of individual facilities and their operations.
- Discharging from a dry bed or other emission control devices to the interior of a facility should not be mandated due to significant potential exposure issues with potential byproducts. Additionally, building codes and standards may not allow the exhaust of an emissions capture system into a facility. National Fire Protection Association (NFPA) 55 Fire code and the International Fire Code (IFC) require certain ventilation rates per ft² in potentially flammable environment.
- Any requirement for air to be drawn into the chamber area is not pulling air into the highest concentration area. The highest continuous EtO concentrations generally occur in the Aeration Room, which should be under the most negative pressure, instead of the Chamber Room as indicated in the PID. The highest peak EtO concentration areas vary by facility.

Similar to any requirements for covered conveyor automation, the engineering controls discussed above are highly complex, and requirements for specific engineering controls have the potential to render a facility inoperable if the requirements are not feasible in a given facility. When designing engineering controls and considering other methods to reduce EtO concentration and worker exposure, it is critical to take entire existing facility design and airflow into consideration, and to implement requirements that are workable in a given facility. For the reasons explained in this section and in many parts of EOSA and EOTF's comments, EPA must allow performance-based requirements, instead of mandating a list of specific engineering/facility design requirements.

VI. EPA MUST RECONSIDER THE IMPLEMENTATION TIMELINE AND COST ESTIMATES FOR ALL PROPOSED ENGINEERING CONTROLS

On page 74, EPA recognizes implementation of the proposed engineering controls would require a longer timeframe than typically provided by the Agency for the implementation of risk mitigation measures, given the limited availability of new equipment, increased demand, and the potential for disrupting the supply chain if facilities need to close to make these upgrades.

EPA is seeking public comment on a reasonable timeframe for registrants to submit label amendments to implement the proposed engineering controls, as well as cost information. EPA further seeks public comment on whether these engineering controls would require state or local permits before the renovations could take place, and the timing associated with that permitting process. Finally, the Agency seeks public comment on potential impacts on the supply chain of sterilized medical devices related to the potential downtime of sterilizing equipment during renovation.

The engineering controls proposed in the PID for commercial sterilization facilities and health care facilities must be comprehensively reconsidered and revised. Some of the proposed requirements, including the proposed automation via covered conveyor for transported aerated materials to shipping/storage areas, are not feasible for the vast majority of existing sterilization facilities. These controls also would provide limited-to-no benefits in terms of worker exposure to EtO, while requiring reconstruction of existing facilities. The result will be that one of EPA's goals to reduce worker exposure will not be met and instead there will be a severe impact on medical device sterilization capacity and device supply affecting medical care providers and their patients. Requiring these controls also will likely cause significant offshoring of the medical device sterilization and manufacturing industries, impacting jobs and health care costs.

Engineering controls and/or work practices that potentially may be used and implemented broadly across many sterilization facilities, provided they do not conflict with existing facility design, engineering requirements or best practices, and/or other regulatory requirements may include the examples listed below, with the exceptions noted and in general exceptions for such issues as conflicts with existing facility design, engineering requirements or best practices and/or other regulatory requirements.

- Requirements for nitrogen purge of piping prior to disconnection that allows for thorough purging of EtO from pipelines using nitrogen before breaking the line connection. This reduces the potential for EtO emission and exposure while disconnecting the EtO lines during drum changes.
- Measures to reduce transfer time for pallets being moved from sterilization to aeration areas, including the elimination of the unnecessary staging areas, could potentially be implemented as a mitigation measure, to reduce any potential off-gassing from pallets of sterilized product in a facility.

Like any requirements for covered conveyor automation, the engineering controls discussed above are highly complex, and requirements for specific engineering controls have the potential to render a facility inoperable if the requirements are not feasible in a given facility. When designing engineering controls and considering other methods to reduce EtO concentration and worker exposure, it is critical to take entire existing facility design and airflow into consideration, and to implement requirements that are workable in a given facility. For the reasons explained in these comments, EPA must allow performance-based requirements, and must not mandate specific engineering/facility design requirements.

As EPA acknowledges, for the engineering controls that may be used and implemented broadly across many sterilization facilities, cost and timeline projection should take into consideration numerous factors, including but not limited to the limited availability of the new equipment, increased demand and associated longer equipment lead time and technical support for the entire industry, unique facility layout/design and product process for certain facilities, required revalidation after implementation of engineering control, state and local permit requirements for certain changes.

Additionally, the PID proposals do not address the impacts of the international regulatory approvals that would be required by its proposed changes. EPA proposes a 5-year compliance timeframe to redesign cycles, devices, or packaging for the proposed EtO concentration limit of 500 mg/L in order to provide time for review by the FDA. In addition to all of the other reasons discussed in these comments regarding the impossibility of this timeframe, or the changes themselves, it is important also to note that this timeframe ignores the fact that medical device supply chains are global in nature, and there are multiple international regulatory authorities who must also approve the redesign of cycles, devices, or packaging to accommodate the proposed change. Five years is wholly insufficient time to obtain regulatory approvals from all domestic and international regulatory agencies, particularly if all medical device companies are applying for such changes at the same time, thus leading to global disruption in the supply of sterile medical devices, even if it is assumed for the sake of argument that these changes could be made.

It is again critical to emphasize that EOSA is uniquely qualified to comment on these important issues, given that EOSA is comprised of the leading experts of the medical device manufacturing and sterilization industry. As noted earlier, in addition to medical device manufacturers, EOSA members include manufacturers of emissions control equipment, ethylene oxide sterilizers, and ethylene oxide detection systems. EOSA members also include many contract sterilization providers, sterilization consultants, environmental consultants, and registrants. The diversity of EOSA member companies provides EOSA a broad view of the overall implications of these proposed regulatory actions. The highly knowledgeable subject matter experts within EOSA are uniquely capable of assessing the issues and complications posed by the NESHAP and PID proposals on the sterilization process, the sterilization facilities, the economics of sterilization, the safety of sterilization facilities, and the security of the supply chain of critical medical devices. No other organization has EOSA's breadth or depth of expertise in the matters presented by the EPA's proposals.

As noted elsewhere, given the extremely inadequate comment period provided by EPA for both PID and NESHAP, despite industry's relentless efforts, it is impossible to provide at this time an accurate cost and timeline estimates for the engineering controls that may be implemented more broadly.

VII. EPA MUST NOT PROCEED WITH THE PROPOSED SCBA USE

On page 74, EPA recognizes there are logistical limitations to Self-Contained Breathing Apparatus (SCBA) respirators and Supplied Air Respirators. The typical maximum wear time for a SCBA respirator is 45 minutes before the cylinder must be changed. Supplied air systems are affixed to walls with a hose running to the supplied air respirator worn by the sterilization

worker. While this system provides an unlimited supply of air which eliminates the need to change cylinders, the hose can limit worker mobility. EPA seeks public comment on facility layout and typical employee work shifts, as it relates to the proposed personal protective equipment requirement in Section V.A.

EPA's proposed PPE trigger of 10 ppb would require SCBA or evacuation readiness at all times in the entire facility and continuous SCBA usage in all post sterilization locations at all times, including shipping and loading/unloading processes. This will result in operators wearing SCBAs for more than four hours per day. This is not feasible and must be revised. SCBAs should be used only during specified activities in commercial sterilization facilities. An example of an activity that could be assessed for potential SCBA requirements is connecting and disconnecting EtO containers from the sterilization process equipment.

EPA's proposed timeline of 60 days for implementation of even tasked-based SCBA use is not possible, however, and must be extended. The vast majority of facilities will need to order more SCBAs and filling equipment. Lead times, especially considering the increase in demand, could far exceed 60 days. Additionally, modifications to SCBAs may be required in order for personnel to be able to use SCBA for certain tasks. For example, a typical SCBA with the tank mounted on the employee's back cannot be used while the employee is driving a stand-up fork truck. The SCBA must be modified so that the tank can be mounted elsewhere. These modifications are complex and time-consuming and require recertification of the SCBA before use. A compliance timeline of no less than two years, and likely more time, is essential to ensure all facilities can obtain and customize SCBA and corresponding equipment in order to enable use.

It is, as stated, infeasible and impracticable to require, as the PID proposes, SCBA for more than the activities above. Moreover, doing so poses significant safety issues. Among the issues posed are the examples below:

- Despite maximum wear time of a SCBA being 45 to 60 minutes, in practice this time can be cut in half dependent on the amount of physical exertion and health of the individual. Sterilization processing area workers may have to replace SCBA tanks up to 20 times over an eight-hour shift where six hours may be spent in the sterilization processing area. This will significantly increase the number of tanks required for the task and reduce the work productivity and thus throughput of the facility and available sterilized medical devices, which will be further worsened by the requirement of monitoring the areas used to fill the tanks.
- Supplied air lines are not possible because the sterilization processing areas may be over the 10 ppb limit which would require respirator protection upon entry. These areas are large and require long distances of line. Many tasks also are required to perform in close quarters where a supplied airline is not possible. Supplied airlines are not possible for forklift work either.
- Employees must undergo medical clearance before they are allowed to use a SCBA per OSHA's regulations at 29 C.F.R. § 1910.134(e). Medical

clearance must take into consideration the time of use of the respirator and the employee's overall fitness, cardiovascular health, and pulmonary health. While many employees can meet the requirements of fitness and health for short duration SCBA use, many will not be able to meet the requirements for extended usage. The physical limitations of SCBA usage are acknowledged in some countries in respiratory protection usage standards. For example, Germany's regulations (BGR 190) require 30 minutes recovery after every 60 minutes of SCBA usage and requires a mandatory rest day after two days of usage with continuous breaks. Enforcement of unnecessary SCBA use does not help to improve, and may well be detrimental to, overall worker health and safety, and will cause increased down time due to required recovery phase after SCBA use, as well as the downtime necessary to maintain a large number of SCBA. The proposed SCBA requirements would cause impossible challenges in both recruiting and retaining workers at facilities, which will result in significant risks to the capacity to provide needed sterilized medical devices.

- Under OSHA, positive pressure SCBAs have an assigned protection factor (APF) of 10,000. The APF limits the concentration at which one can enter. This is calculated by multiplying the APF by the permissible exposure limit (PEL) or short-term exposure limit (STEL) to achieve the maximum use concentration (MUC). An occupational PEL of 10 ppb results in a MUC of 100 ppm, which is not feasible for situations such as emergencies, drum changes, potential/temporary entrances into the aeration room, or process maintenance work where exposures above 100 ppm may occur.
- SCBAs are restrictive by their nature; they limit peripheral vision, add bulk weight to the operator, and create equipment snag risks. Requiring SCBA usage at all times, particularly in shipping and loading areas, will create a significant, undue adverse risk where an operator may become crushed, ensnared, or caught between a forklift and product or equipment, or automations such as covered conveyor. Currently, companies limit operator SCBA usage and limited transfer situations. Adding several hours of SCBA usage fatigue in areas that are more open will inevitably result in more incidents or injuries.

In summary, only the task-specific use of SCBA discussed above for workers performing specified activities in commercial sterilization facilities should be required. EPA's proposed PPE trigger of 10 ppb would require SCBA or evacuation readiness at all times in the entire facility and continuous SCBA usage in all post sterilization locations at all times, including shipping and loading/unloading processes, poses unnecessary and significant risks with few if any benefits, and some significant disadvantages, to the workers at issue. For these reasons EPA must not proceed with the requirement it has currently proposed.

VIII. EPA'S PROPOSED REQUIREMENT FOR ALL WORKERS IN COMMERCIAL STERILIZATION FACILITIES TO WEAR RESPIRATORS WHEN EtO CONCENTRATION IN THE FACILITIES EXCEED 10 PPB IS NOT FEASIBLE.

On page 74, this PID proposes that all workers (including both handlers and occupational bystanders) in commercial sterilization facilities be required to wear respirators when EtO concentrations in the facilities exceed 10 ppb. EPA requests public comment on the feasibility of continuous, real-time monitoring to a 10 ppb level inside of commercial sterilization facilities and the possible impacts of the daily operations of commercial sterilization facilities. EPA understands that the supply of monitoring systems may be limited, and so the compliance timeframe may be affected by equipment availability. The Agency seeks public comment on the cost and how long is necessary for registrants to implement label amendments requiring compliance with this respirator requirement and the corresponding monitoring and recordkeeping requirements. EPA is proposing that this change be implemented within 2 years

Sterilization facilities operate under very strict federal, state, and local regulations and safety codes. Currently, facilities use a number of controls to achieve compliance, including engineering controls (local exhaust ventilation with abatement controls), administrative controls (limiting entry to areas which could potentially contain levels above the PEL), and PPE controls (SCBA use). It is well established that any area with the potential to go above the current PEL requires there to be some form of control in place. EPA's proposed PPE trigger of 10 ppb would require SCBA or evacuation readiness at all times in the entire facility and continuous SCBA usage in all post sterilization locations at all times, including shipping and loading/unloading processes, which poses enormous issues. It is impossible to implement, and, even if it could be implemented, would cause severe reductions in the availability of sterilized medical devices, due to the reductions in throughput that would occur, and/or complete facility shutdown for most if not all sterilization facilities. Among the issues posed are the following:

- Most existing monitoring systems in facilities cannot achieve a limit of detection (LOD) of 10 ppb, let alone a limit of quantitation (LOQ) of 10 ppb to reliably quantify EtO concentration in facilities. Current Gas Chromatograph (GC) monitoring equipment with flame ionization detector or photoionization detector with multiple sampling ports and manifold have method detection limits (MDL) around 50 ppb or greater with a few claiming to be at 10 ppb. It is critically important to note that this is the minimum detectable limit for certain circumstances, not a repeatable measurement with accuracy and precision that is required for any reliable measurement method. Similarly, other common measurement units, which use sensor modules, cannot repeatedly or reliably provide accurate data until measuring closer to 200 ppb. This leaves only two other options that are even remotely potentially feasible for the industry to use, Fourier-transform infrared spectroscopy (FTIR) and Cavity ring-down spectroscopy (CRDS). Both of these options, however, have their own significant limitations when doing multi-port area sampling and thus are not viable methods for achieving EPA's proposed requirement.

- One significant issue with FTIR and CRDS is the potential for interferences. Both technologies are prone to bias from relative humidity, gas and particle interferences such as methane, and photochemical reaction of EtO with OH radicals such as hydrogen peroxide. Unlike a continuous emission monitoring system (CEMS) application, there is greater variation of these potential interferences for an entire facility.
- Another significant issue is that it is well known that EtO will embed in the hundreds of feet of sampling lines and in filter units at the end of sampling ports. The ability to flush and purge these lines to ensure no carryover close to the MDL is not practically possible.
- For example, these units are prone to drift at lower detection levels. The precision required will mean that reference unit checking (similar to a Relative Accuracy Test Audit (RATA)), regular zero calibration and high-level reference gas testing protocols, and specialized equipment such as a mini-thermal oxidizers on FTIRs will be required to ensure drift does not occur.
- Additionally, multi-port (non-ambient and non-CEMS) systems present unique challenges. FTIR and CRDS have not been consistently proven to be able to span quickly between different ports with vastly different concentrations, (e.g., 10 ppb vs. 100 ppm), and they are not a direct occupational option to be worn on a person. The limited usage of these systems and the unreliable results at or near 10 ppb deployed haphazardly will inevitably result in unnecessary actions and concerns that are not related to true results, but because of measurement instrument variation and error. EPA states in its proposed NESHAP that due to uncertainty of measurement at the LOD, EPA is applying a 3x multiplicative factor, which increased the value to 30 ppb.⁷

EPA must consider all of these issues and revise the PID accordingly. EPA must also consider, accuracy, precision, and bias as outlined in the National Institute for Occupational

⁷ 88 Fed. Reg. 22790, 22815 (Apr. 13, 2023) (in the proposed NESHAP, EPA states it is applying “a multiplication factor of 3 to the RDL of 10 ppbv, which yields a workable-in-practice lower measurable value of 30 ppbv”).

Safety and Health's (NIOSH) Guidelines for Air Sampling and Analytical Method Development and Evaluation occupational sampling.

It is also important to note that, in general, when considering instrument sensitivity, a LOD is referenced. To implement a detection method reliably in facilities, however, a LOQ must be considered; otherwise the results will not be accurate, repeatable, and reliable. Typically, LOQ will be found at a higher concentration than LOD, but how much higher depends on the specifications for bias and imprecision used to define it.⁸ For the EtO analytical methods discussed above, it is clear that none of the existing technologies can reliably reach a LOQ of 10 ppb. In fact, the data show that a LOQ of 200 ppb is more likely.

Even with the most sensitive and reliable systems, and even if it could be assumed that they are implementable on the scale EPA proposes, obtaining and deploying such systems in the extremely brief timeframe that EPA has proposed is not possible for the industry. There are currently long lead times for these technologies of several months at a minimum. Should the entire sterilization industry, manufacturing/processing, warehouses, and healthcare facilities all be vying to purchase these limited options, even assuming the limitations outlined above were not at issue, it will inevitably lead to a significantly large backlog. The cost of these systems as a stand-alone item is in the six-figure range per unit. Installing new systems, tubing and sampling ports, calibrating, validating, and troubleshooting these devices requires specialized technicians who are also limited in availability. Most locations will need to integrate the systems with Human Machine Interfaces (HMIs) or include the system in their local networks. Locating sampling ports also presents a unique challenge. Unlike a CEMS that has clear protocol for stack sampling locations, sampling ports in occupational ambient settings are prone to location bias. For example, a port just above an off-gassing product or in an eddy main report will result in a much higher reading than the average value of mixed air within a room. Likewise, results can skew low if the sampling port is clogged or blocked. Area monitoring is not acceptable for means of actual occupational monitoring but may only be used for precautionary purposes. Any mandatory precautionary area monitoring must be accompanied by a standard protocol that is yet to be developed, if this can be done at all. Any mistake or issue that occurs in any one of these steps can create significant setbacks including premature evacuations of areas that may not present a hazard, generalized panic, and risk of employee loss and retention concerns. Furthermore, the proposal also states that audible and visual alarms must be present at all times when above 10 ppb. Audible alarms will inevitably lead to sensory fatigue and unnecessary fear and confusion.

Moreover, the additional requirements proposed in EPA's NESHAP proposed rulemaking make it even more impossible for facilities to comply with these proposed requirements. Indeed, some of the proposed NESHAP requirements contradict PID proposals. A few examples are listed below:

- Facilities would be required to limit and optimize airflows to comply with the requirement for monitoring down to 10 ppb, which will be at odds with

⁸ Armbruster, D.A. and Pry, T. Limit of Blank, Limit of Detection and Limit of Quantitation. Clin. Biochemi Rev. 2008 Aug; 29 (Suppl 1): S49-52.

NESHAP proposed requirements. Ventilation to obtain PTE seldom results in optimized ventilation for workers. Exhaust air that must be abated is limited by the abatement equipment's finite capacity. Air exchanges will be limited by system balancing, including the proper cascade of air as dictated by facility layout, volume, and natural draft openings (NDO).

- Biogenic sources of EtO exist in levels in nature and in that case, EtO is a byproduct of incomplete combustion. This fact also contributes to the frequently high standard deviations/errors for concurrent ambient sampling. Additionally, if an external influence such as a local controlled burn or diesel exhaust is somehow introduced or re-entrained into the facilities makeup airflow stream, that factor will introduce further errors and issues to the proposed continuous, real-time monitoring to a 10 ppb level inside of commercial sterilization facilities. Imposing these requirements, given these issues will inevitably create additional unnecessary significant disruption of essential sterilization operations at sterilization facilities that will adversely and severely impact the supply of sterilized medical devices.
- The reliability of any monitoring that would claim to measure down to 10 ppb is an enormous concern regarding the viability and the potential significant adverse consequences of EPA's proposal to require a 10 ppb action level for employees to vacate premises.

The limitations outlined above with regard to the proposed 10 ppb limit also preclude the ability to meet EPA proposed request for a Data Call-In (DCI) for OCSPP GLN 875.1400.

Moreover, the proposed DCI would require EPA to review every protocol and sampling event conducted by every sterilizer, manufacturer, processor, and health care facility, which will put enormous additional burdens on both facilities and EPA.

In summary, EPA's proposal of setting 10 ppb as the action level in EtO commercial sterilization facilities must be eliminated. It is impossible to reliably detect, let alone quantify, ambient air EtO levels in facilities down to 10 ppb, based on currently available technologies. Implementing this action level and the associated requirements given these facts will inevitably cause unnecessary work force panic and retention issues, facility shutdown, and significant medical device supply chain shortage.

Any such changes would have to be implemented subsequent to other proposed requirements in PID and NESHAP, particularly those impacting air flow and emission control. It is critical again to emphasize that EOSA is uniquely qualified to comment on these important issues, given that EOSA is comprised of the leading experts of the medical device manufacturing and sterilization industry. As noted earlier, in addition to medical device manufacturers, EOSA members include manufacturers of emissions control equipment, ethylene oxide sterilizers, and ethylene oxide detection systems. EOSA members also include many contract sterilization providers, sterilization consultants, environmental consultants, and registrants. The diversity of

EOSA member companies provides EOSA a broad view of the overall implications of these proposed regulatory actions. The highly knowledgeable subject matter experts within EOSA are uniquely capable of assessing the issues and complications posed by the NESHAP and PID proposals on the sterilization process, the sterilization facilities, the economics of sterilization, the safety of sterilization facilities, and the security of the supply chain of critical medical devices. No other organization has EOSA's breadth or depth of expertise in the matters presented by the EPA's proposals.

In any event, any proposed limit should not be a ceiling limit. EPA should propose, depending on the factors noted:

- a value of no less than 0.5 ppm eight-hour time weight average (TWA) with compliance required in two to three years or more; and/or
- a value of no less than 0.25 ppm TWA with compliance required in five to ten years or more.

IX. ALTERNATIVE STERILIZATION METHODS FOR MEDICAL DEVICES CANNOT REPLACE EtO

On page 75, some medical devices can only be sterilized with EtO. However, there are several FDA-recognized methods used to sterilize medical equipment: gamma irradiation, X-ray sterilization, electron beam sterilization, and steam; as well as the alternative sterilization methods in development including hydrogen peroxide, vaporized hydrogen peroxide, nitrogen dioxide, chlorine dioxide, and vaporized peracetic acid. EPA understands there are limitations of comparable sterilization methods due to compatibility with materials and/or packaging, scalability or capacity, and lack of validation measures or efficacy data. EPA seeks public comment on more information about the existing limitations of available alternatives. EPA also seeks public comment on existing and emerging alternative methods for medical device sterilization that are scalable and could most effectively replace EtO.

Since its discovery as a uniquely effective sterilant in the 1930s, EtO has played an essential role in the sterilization of healthcare products that protect the general public from serious infections that result from non-sterile medical devices. Decades later, EtO is now used to sterilize more than 20 billion healthcare products each year in the United States alone, including PPE, diagnostic testing kits, heart valves, pacemakers, surgical kits, gowns, drapes, ventilators, syringes, bandages, and catheters. This number represents more than 50 percent of all healthcare products sterilized annually. EtO sterilization is critical to ensuring the delivery of safe, sterile healthcare products to medical care providers and their patients and is crucial to a functioning and effective healthcare system and to the patients who rely on it.

Hundreds of thousands of medical, pharmaceutical, hospital, and laboratory processes rely on EtO to sterilize devices and equipment to protect millions of patients from the real risks of infectious diseases caused by bacteria, viruses, and fungi. For the majority of these healthcare products, EtO sterilization is the most effective and efficient, and often the only viable, sterilization technology. The extensive material compatibility and nature of EtO allows for the

sterilization of many critical healthcare products and devices that would otherwise be destroyed and rendered unusable by other sterilization methods. Currently, alternatives to EtO sterilization are quite limited; for example, many cannot be scaled to handle the required industry volume, many cannot adequately penetrate into complex device geometries to adequately sterilize all surfaces, and many result in medical products being damaged and unusable due to materials of construction incompatibilities.

For all of the reasons discussed above, “replacing EtO” cannot be EPA’s goal, nor is it possible in the foreseeable future. All known sterilants have disadvantages associated with their use, such as inhalational toxicity, contact toxicity, corrosion, or other damage to devices. EtO continues to be one of the primary methodologies for sterilization of medical devices for good reason: its ability to sterilize devices that are not amenable to processing with other technologies (*e.g.*, steam, radiation, corrosive sterilants). Industry has been and continues to work on developing new ways and methods to use EtO in ways that further reduce potential risk and that are more efficient; these important efforts should not be discouraged or blocked by regulation, especially when there are no viable alternatives to EtO for critical uses available.

The medical device industry and sterilization facilities have, for many years, continued to explore a number of alternative sterilization modalities, including e-beam, x-ray, chlorine dioxide, vaporized peracetic acid (VPA), self-sterilizing packaging, nitrogen dioxide, nitric oxide, and hydrogen peroxide. Despite an enormous effort to find alternatives, what the device industry has learned to this point, which EPA acknowledges in the PID, is that no technology offers a replacement for EtO. Conversion from EtO to irradiation modalities (gamma, e-beam and x-ray) often requires change of materials to more costly radiation-compatible materials which means that the device(s) essentially needs to go back to R&D for redesign. This is a lengthy and highly regulated process that can involve repeat of Design Verification testing, biocompatibility testing, shelf-life testing, packaging redesign and testing, and a 510K or pre-market approval (PMA) submission to, and approval by, FDA. For companies that manufacture and sell hundreds, or thousands, of different devices, the amount of required work, even if success were assumed, which it cannot be, to meet these regulatory requirements would be overwhelming, and would overwhelm FDA and other regulators, including international regulatory agencies that also must approve devices before they can be used in other countries. Moreover, in many cases, the range of materials that are compatible with radiation-based sterilization methods is more limited, resulting in devices that cannot adequately perform their intended function. Conversion from EtO to other gaseous sterilants also likely requires conversion to alternate materials, repeat of Design Verification, repeat of biocompatibility, and a 510k or PMA submission to, and approval by, FDA. In addition, many alternative gaseous sterilants cannot penetrate into complex medical devices (down long lumens and into mated surfaces) as effectively as EtO can. This means these gases cannot effectively sterilize many types of devices. Another limitation of the alternative gas sterilant is the scalability factor. While EtO can penetrate large loads of medical devices in pallets, alternative gas sterilant is limited to much smaller quantities. Additionally, many alternative gaseous sterilants are not compatible with cellulosic materials, such as corrugated boxes. Products need to be sterilized in their primary packaging. This means that the sterilization process needs to be incorporated into production, before the boxing and palletization process, which requires secondary packaging in a clean environment or the risk of recontamination. This all could require

major modifications to running medical device manufacturing plants, creating a huge impact on processing capacity and the supply of sterilized medical devices.

In summary, based on the significant existing limitations of available EtO alternatives discussed above, the elimination or significant restriction of the use of EtO as a sterilant would immediately compromise the U.S. healthcare system's ability to provide a consistent and safe supply of sterile healthcare products to medical care providers and their patients, causing a public health crisis. A lack of sterile medical supplies to operating rooms would result in delayed or even canceled procedures, which would pose grave risk to those in urgent medical need. Medical supplies sterilized with EtO are used in nearly every surgical procedure performed and have also been critical for the global treatment options during the pandemic. Especially given the serious flaws in EPA's IRIS analysis for EtO, restricting or eliminating the use of EtO would jeopardize the medical device supply in the United States, with no appreciable, if any, health benefit to sterilization workers, the public, or anyone else.

X. EPA SHOULD NOT PROPOSE TO SET A LOWER EXPOSURE LIMITS FOR FACILITIES

On page 75, EPA understands that OSHA's EtO PEL has not been updated since it was established in 1984, and that health standards issued under section 6(b)(5) of the OSH Act must reduce significant risk only to the extent that it is technologically and economically feasible.¹⁴⁴ Given that EPA has identified risks for workers at levels below the OSHA PEL, EPA does not consider the current OSHA PEL to be protective of workers. EPA is seeking public comment to determine if facilities have voluntarily set lower exposure limits to better protect workers

Any such changes would have to be implemented subsequent to other proposed requirements in PID and NESHAP, particularly those impacting air flow and emission control. It is critical again to emphasize that EOSA is uniquely qualified to comment on these important issues, given that EOSA is comprised of the leading experts of the medical device manufacturing and sterilization industry. As noted earlier, in addition to medical device manufacturers, EOSA members include manufacturers of emissions control equipment, ethylene oxide sterilizers, and ethylene oxide detection systems. EOSA members also include many contract sterilization providers, sterilization consultants, environmental consultants, and registrants. The diversity of EOSA member companies provides EOSA a broad view of the overall implications of these proposed regulatory actions. The highly knowledgeable subject matter experts within EOSA are uniquely capable of assessing the issues and complications posed by the NESHAP and PID proposals on the sterilization process, the sterilization facilities, the economics of sterilization, the safety of sterilization facilities, and the security of the supply chain of critical medical devices. No other organization has EOSA's breadth or depth of expertise in the matters presented by the EPA's proposals.

In any event, any proposed limit should not be a ceiling limit. EPA should propose, depending on the factors noted:

- A value of no less than 0.5 ppm eight-hour TWA with compliance required in two to three years or more; and/or

- A value of no less than 0.25 ppm TWA with compliance required in five to ten years or more.

NIOSH's long-term EtO exposure study did not note any elevated risk for any cancer or diseases compared to the general U.S. population. It was only noted that very high exposure levels may lead to increased risk, which supports the concept of a non-linear dose curve risk approach. Previous studies were conducted on workers who encountered much higher concentrations of EtO historically; over recent years the industry has become more efficient and effective in reducing EtO usage and exposure. There are also no known increases in mortality or disease amongst those who work with EtO currently. Many of these facilities have been in operations for many decades and have followed OSHA occupational monitoring and medical monitoring guidelines.

The proposed 10 ppb limit also does not account for concept of short-term exposure, which is particularly problematic when accounting for SCBA protection factors. In effect, EPA is proposing a ceiling limit to EtO, not a time weighted average value PEL. A TWA value would allow for variations in concentration accounting for the working eight- hour average and are appropriate for chronic risks. Ceiling limits are not for chronic risk and are reserved for acute risks.

Utilizing the IRIS inhalation unit risk (IUR) as a basis for occupational exposure limits creates an enormously unrealistic risk assessment and risk management approach. It also creates undue and impossible to meet regulatory burdens, both technologically and economically. Measuring down to 10 ppb for more than eight hours **at the breathing zone of the worker performing their task(s)** is currently not feasible. Methodologies, such as badges and sorbent tubes do not have LOQ close to this level that can account for bias and imprecision. This is crucially important when considering occupational exposure limits at time-weighted averages as it could mean the difference between SCBA usage, compliance/non-compliance, and labor needs.

XI. EPA'S EFFORTS TO ACHIEVE ENVIRONMENTAL JUSTICE GOALS MUST BE BASED ON RELEVANT AND BEST AVAILABLE DATA

On page 75, the Agency requests information on any other groups or segments of the population who, as a result of their proximity and exposure to pesticides, unique exposure pathway, location relative to physical infrastructure, exposure to multiple stressors and cumulative impacts, lower capacity to participate in decision making, or other factors, may have unusually high exposure to EtO compared to the general population or who may otherwise be disproportionately affected by the use of EtO as a pesticide.

EPA's efforts to achieve environmental justice goals must be based on relevant and best available data. The following scholarly articles review current knowledge regarding EtO potential exposure and toxicity. They demonstrate significantly lower concern for residential and non-residential bystander risk than EPA's assessment and must be considered in any consideration of environmental justice issues.

- CR Kirman, AA Li, PJ Sheehan, JS Bus, RC Lewis & SM Hays (2021) Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management, *Journal of Toxicology and Environmental Health, Part B*, 24:1, 1-29, DOI: 10.1080 / 10937404. 2020.1852988.
- Kirman CR, Sweeney LM, Teta MJ, et al. Addressing nonlinearity in the exposure-response relationship for a genotoxic carcinogen: cancer potency estimates for ethylene oxide. *Risk Anal.* 2004;24(5):1165-83. doi:10.1111/j.0272-4332.2004.00517.
- Lynch HN, Kozal JS, Russell AJ, Thompson WJ, Divis HR, Freid RD, Calabrese EJ, Mundt KA. Systematic review of the scientific evidence on ethylene oxide as a human carcinogen. *Chem Biol Interact.* 2022 Sep 1;364:110031. doi: 10.1016/j.cbi.2022.110031. Epub 2022 Jun 30. PMID: 35779612.
- G.M. Marsh, K.A. Keeton, A.S. Riordan, E.A. Best, S.M. Benson, Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis, *Int. Arch. Occup. Environ. Health* 92 (7) (2019) 919–939.
- Sheehan PJ, Lewis RC, Kirman CR, Watson HN, Winegar ED, Bus JS. Ethylene Oxide Exposure in U.S. Populations Residing Near Sterilization and Other Industrial Facilities: Context Based on Endogenous and Total Equivalent Concentration Exposures. *Int J Environ Res Public Health.* 2021 Jan 12;18(2):607. doi: 10.3390/ijerph18020607. PMID: 33445726; PMCID: PMC7828163.
- C. Valdez-Flores, R.L. Sielken, M.J. Teta, Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide, *Regul. Toxicol. Pharmacol.* 56 (3) (2010) 312–320.
- M.J. Vincent, J.S. Kozal, W.J. Thompson, A. Maier, G.S. Dotson, E.A. Best, K.A. Mundt, Ethylene oxide: cancer evidence integration and dose-response implications, *Dose Response* 17 (4) (2019), 1559325819888317.

Moreover, in the case of EtO, environmental justice concerns must be balanced against the vast population, including those of minority, low-income, and indigenous populations, that will face significant adverse consequences to their health if safe, sterilized medical devices are not available. Likewise, and as EPA has also recognized, the “public health benefit to continuing to register EtO for spice fumigation [against] [t]he threat of food-borne contamination from pathogens such as *Salmonella* and *Escherichia coli*, and the potential for serious illness from exposure to these pathogens, is a concern for the Agency food manufacturers, and the general

public.”⁹ These facts must be considered as part of an assessment of environmental justice issues given the disproportionate impact that may occur if needed sterilization is not available.

XII. EPA SHOULD NOT PROPOSES THAT STERILIZATION FACILITIES USE THE LEAST AMOUNT OF EtO NEEDED TO MEET STERILITY ASSURANCE THROUGH CYCLE DESIGN OPTIMIZATION

Page 50, EPA proposes that sterilization facilities use the least amount of EtO needed to meet sterility assurance through cycle design optimization.

EPA must revise the proposed requirements on optimizing cycles to minimize EtO use, and supplemental comments will address this issue. It is important to note, however, that even if it is assumed that for certain products, the required sterility assurance level may be able to be achieved using very low concentrations of EtO, this would result in shortages of sterilized medical devices if the cycle length necessary to achieve sterility at the lower concentration is significantly longer, as the amount of medical devices that can be sterilized in a given time period will be dramatically impacted. It is also critically important to note that medical device sterilization process and sterility assurance are strictly regulated by the FDA. EPA should not propose specific regulatory requirements that may affect the ability of any particular device to meet the requirements necessary for FDA purposes.

Moreover, validating a process to use the least amount of EtO is a significant and complex process itself, and greatly increases the scope of validation effort and the timeline necessary, if the validation is even possible, which is likely impossible for many and far, far from certain for others. It would involve adjustment of every cycle parameter (e.g., vacuum depth, conditioning, temperature, EtO concentration, dwell times), and require an iterative process to identify the optimal combination of parameters to use the ‘least’ amount of EtO needed to meet sterility assurance. Using the least amount of EtO can cause significant issues for cycle validation, reducing margins for errors, requiring significantly longer validation time, and may require product design modification.

It is again critical to emphasize that EOSA is uniquely qualified to comment on these important issues, given that EOSA is comprised of the leading experts of the medical device manufacturing and sterilization industry. As noted earlier, in addition to medical device manufacturers, EOSA members include manufacturers of emissions control equipment, ethylene oxide sterilizers, and ethylene oxide detection systems. EOSA members also include many contract sterilization providers, sterilization consultants, environmental consultants, and registrants. The diversity of EOSA member companies provides EOSA a broad view of the overall implications of these proposed regulatory actions. The highly knowledgeable subject matter experts within EOSA are uniquely capable of assessing the issues and complications posed by the NESHAP and PID proposals on the sterilization process, the sterilization facilities, the economics of sterilization, the safety of sterilization facilities, and the security of the supply chain of critical

⁹ PID at 69-70.

medical devices. No other organization has EOSA's breadth or depth of expertise in the matters presented by the EPA's proposals.

As discussed elsewhere in these comments, EPA must instead allow a performance-based standards.

Additionally, for cycles which are close to the limit of the required Sterility Assurance Level (SAL), normal bioburden fluctuations could lead to some sterilization loads not reaching the required SAL, which could result in significant unintended public health consequences. Discussions of the validation method must remain within FDA and not the subject of EPA regulation that cannot adequately account for FDA requirements that are device specific. Also, any validation method, including the half-cycle method, should be allowed if it allows the necessary requirements to be met.

XIII. EPA'S PROPOSED REQUIREMENTS FOR HEALTHCARE FACILITIES ARE NOT FEASIBLE

On page 76, EPA is proposing to require the following engineering controls in healthcare facilities: physical separation of EtO sterilization spaces; negative air pressure in rooms containing EtO sterilization devices; ventilation of EtO exhaust through exterior ventilation stacks; and abatement devices to capture excess EtO. The Agency seeks public comment on the cost and time necessary for registrants to implement label amendments requiring the implementation of the proposed engineering controls. EPA is proposing that these engineering controls be implemented within 2 years.

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

On page 85 Appendix B, "All EtO single chamber sterilization/aeration devices in healthcare facilities (hospitals, veterinary facilities, dental offices, etc.) must be located in a containment area that is physically separate from all other work areas of the healthcare facility by [2 years from the publication of the Interim / Final Decision]."

"Healthcare facilities (hospitals, veterinary facilities, dental offices, etc.) using EtO single chamber sterilization/aeration devices must utilize an abatement device in order to reduce EtO emissions. Refer to sterilization device manufacturer for information on abatement devices by [2 years from the publication of the Interim / Final Decision]."

"All EtO sterilizers in healthcare facilities (hospitals, veterinary facilities, dental offices, etc.) must be vented out of the workplace to the outside atmosphere. A separate exhaust duct to the outside is required. The exhaust duct should terminate away from areas where people walk or work. The duct should be located at least 7.6 meters (25 feet) away from the building air intake source and must be engineered according to existing codes by [2 years from the publication of the Interim / Final Decision]."

“EtO sterilization areas must be kept at a negative pressure differential compared to the ambient air pressure of the healthcare facility (hospitals, veterinary facilities, dental offices, etc.) by [2 years from the publication of the Interim / Final Decision].”

This comment is pertinent to all healthcare facilities specific requirements proposed in the PID, including physical separation of the sterilization area, use of abatement devices in healthcare facilities, venting of healthcare facilities, and pressure differential in healthcare facilities. Except for the requirement of the abatement devices, the three proposed requirements have been required in AAMI ST41 for over twenty years for hospital-based systems and large healthcare facilities. Requiring these for small healthcare facilities, such as dentist, plastic surgeon, and veterinarian’ offices, however, is not feasible and will have a significant adverse economic impact. It also is important to note that many of these healthcare facilities cannot meet the proposed abatement requirements.

It is important to note that most small practices use an AIO process for EtO sterilization.

XIV. EPA SHOULD NOT PROPOSE SCBA USE IN HEALTHCARE FACILITIES

On page 76, EPA is seeking public comment on the feasibility of respirator use (supplied airline respirators or self-contained breathing apparatus respirators) in healthcare facilities for employees who are unloading EtO sterilization equipment from the sterilization chamber.

The use of SCBA is not warranted nor is it practical for healthcare facility employees who are unloading EtO sterilization equipment from the sterilization chamber because adequate controls are already in place via FDA guidance documents, and device manufacturers instructions for use (IFU).

The EtO sterilization cycles used in healthcare facilities are FDA cleared as safe and effective per FDA guidance on *Premarket Notification [510(k)] Submissions for Sterilizers Intended for Use in Health Care Facilities Infection Control Devices Branch division of General and Restorative Devices*, March 1993 / Addendum September 1995. The removal of EtO from rigid chamber EtO sterilization systems with automatic cycles used in healthcare facilities employ three distinct phases during every sterilization cycle for EtO removal: (1) EtO Removal phase (first vacuum after EtO exposure), (2) Flushing phase (a series of vacuums and air flushes) and (3) Aeration phase (heated air flushing through the chamber and load while under a vacuum). The EtO Removal phase and the Flushing phase effectively removes EtO from the free chamber space and the free space within packaging. The Aeration phase effectively removes EtO off gassing from the packaging and device materials.

The use of SCBA is not warranted because remaining EtO in the free chamber space is safely and effectively removed by the EtO Removal and Flushing phases for many hours (in most cases 12 hours) before the healthcare operator unloads the chamber. Aeration effectively removes EtO off gassing from the packaging and device materials. The data supporting the safe and effective EtO aeration parameters is a data set that is required and reviewed by FDA before the device is cleared for use and reprocessing in U.S healthcare facilities. The required safe and

effective EtO aeration parameters are required to be documented in the device manufacturers IFU of the subject medical device.¹⁰

Since 2010, healthcare sterilization facilities have been required to utilize AIO sterilizers. Per FDA guidelines, all healthcare facilities must follow the device manufacturers IFU for aeration before the device is unloaded from the sterilization chamber. Since FDA has cleared the manufacturer's EtO aeration parameters as safe and effective and healthcare facilities are required to ensure the device remains in aeration until the aeration parameters are satisfied, supplied airline respirators or SCBA are not warranted in healthcare facilities.

In addition, the use of SCBA is not practical for healthcare facility employees who are unloading EtO sterilization equipment from the sterilization chamber.

Based on the current guidance documents per FDA and EPA to use utilize AIO sterilizers, when the EtO sterilization cycle has completed successfully and the required aeration parameters are satisfied per the device manufacturers IFU, the devices removed from the EtO chamber must be safe to handle and safe for use, therefore SCBA are not required.

XV. EtO USE AS SPICE FUMIGATION REMAINS CRITICAL AND EPA SHOULD NOT PROPOSE NEW CHANGES

On page 76, the EtO product labels provide detailed use directions, including a maximum use rate, for the EtO use on herbs and spices. The Agency is seeking public comment on examples of efficacious EtO treatments for pathogen control at rates lower than the maximum label rate, and how often facilities have completed EtO validations for EtO concentrations that are less than 500 mg/L. The Agency is interested in establishing an alternative method for the product labels that use a lower rate of EtO. EPA encourages facilities and interested stakeholders to work with the Agency to develop a new method at a lower rate that is effective for pathogen control and continues to meet the dietary safety standards (e.g., acceptable residues of EtO and ECH).

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

¹⁰ FDA, *Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff* Document, issued on: March 17, 2015, Appendix E of this guidance was updated on June 9, 2017.

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

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

EOSA and EOTF support the comments submitted by the American Spice Trade Association (ASTA) regarding the PID. As EOSA and EOTF have stated, and ASTA agrees, EPA has proposed several mitigation measures that are not achievable or unnecessarily burdensome, including but not limited to the ability to conduct real time ambient air EtO monitoring 10 ppb and the proposed automation requirements, particularly covered conveyors. EOSA and EOTF further support ASTA's comments and reasoning as to why EPA should not revoke tolerances on commodities for which uses of EtO are cancelled. Moreover, although EPA has not provided any stakeholder, including EOSA, EOTF, or ASTA, sufficient time to respond to the complex issues being raised in the PID, EOSA and EOTF support ASTA's comments regarding the commodities it has been able to identify, to date, where due to food safety risks and lack of viable alternatives, the use of EtO remains critical for the food safety for those commodities.

XVI. EPA MUST NOT IMPLEMENT THE PROPOSED TRAINING REQUIREMENTS

On page 87 Appendix B, for Commercial Sterilization facilities: Employees must be trained upon assignment and annually thereafter on the potential health effects from the levels of EtO in the facility and the availability of materials related to the health hazards of exposure to EtO. Specifically, the Maximum Likelihood Exposure (MLE) cancer risk for EtO handlers for medical devices is 1 in 17, and the upper bound cancer risk for EtO handlers for medical devices is 1 in 10. The MLE cancer risk for EtO handlers for spices is 1 in 36, and the upper bound cancer risk for EtO handlers for spices is 1 in 16."

Employees must be trained upon assignment and annually thereafter on the potential health effects from the levels of EtO in the HCF and the availability of materials related to health hazards of exposure to EtO. Specifically, the Maximum Likelihood Exposure (MLE) cancer

risk for EtO handlers in HCF is 1 in 25, and the upper bound cancer risk for EtO handlers in HCF is 1 in 12."

The 1 in 10 risk estimated by EPA for sterilizer workers is completely absurd for numerous reasons:

- It is all based on a NIOSH study where there was barely a cancer signal; only after a convoluted mathematical reanalysis of the data did the high-risk estimate come out.
- The NIOSH study has a poor exposure assessment with inadequate information to accurately know the exposure for periods where workers were in the industry.
- EPA used improper statistical methods to evaluate the fit of its dose-response model and used a misleading figure to justify it.
- EPA's inclusion of breast cancer from the NIOSH study is improper based on under-ascertainment.
- The higher potency estimate for lymphoid cancers is inconsistent with the fact that smokers have high EtO exposures yet do not have elevated lymphoid cancers.
- Another large epidemiologic study, the Union Carbide Corporation study, had higher exposures yet saw no increase in cancer.
- The EPA potency estimate and steep slope at low doses is inconsistent with the large levels of endogenous EtO exposure and with available toxicokinetic and mechanistic data.

The regulation proposes that training of workers using EtO must include a risk statement. This required language is without basis, is misleading, and could lead to unintended and unnecessary adverse consequences. The requirement should not be implemented as proposed for these reasons.

XVII. EPA SHOULD NOT IMPLEMENT THE PROPOSED RECORDKEEPING REQUIREMENTS

On page 88 Appendix B, Recordkeeping Requirements: All records must be maintained for two years from the date of sterilization, or in the case of training materials, 2 years from the date of training. Records must be made available upon request to any local, state, tribal, or federal pesticide enforcement personnel.

Application Rates: Facilities must maintain records for the amount of EtO used. if sterilization of a device requires more than 500 mg/L, due to the device design, facilities must maintain records for justification for the increased application rate. Specifically, this justification would

demonstrate the necessary calculations for determining the application rate, through either the Cycle Calculation Approach, or less conservative approaches found in ISO 11135.

Indoor EtO Concentrations and Corresponding Worker Protection Measures: Facilities must maintain records of indoor EtO concentration levels, and records of employee respirator wear time and/or evacuation time.

Employee Training: Facilities must maintain records on training materials provided to employees upon assignment and annually thereafter, and records of the dates individual employees are trained.

EOSA and EOTF have not had an adequate opportunity to provide comment on the proposed recordkeeping requirements, many of which are not possible or feasible given comments on the issues elsewhere in this document concerning the significant issues posed by requirements that would be the subject of the recordkeeping. As noted, EOSA and EOTF reserve all rights to supplement these comments on these and all issues in the PID.

Please contact Lisa M. Campbell at lcampbell@lawbc.com or (202) 557-3802 if there are any questions.

Attachment 2

Exponent's Response to EPA's Proposed Interim Decision for Ethylene Oxide

TITLE:

Response to EPA's Proposed Interim Decision for Ethylene Oxide

DATA REQUIREMENTS:

Not Applicable

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DATE:

June 27, 2023

PROJECT IDENTIFICATION:

1708342.000 - 8038

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Executive Summary

The U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) released its Proposed Interim Decision (PID) for ethylene oxide (EO) on April 11, 2023 (U.S. EPA, 2023) and released a related human health risk assessment on the same day (U.S. EPA, 2023b). These comments were prepared with support from the Ethylene Oxide Task Force (EOTF), which members include companies that use EO to sterilize medical devices.

The human health risk assessment estimates lifetime cancer incidence risks for sterilizer workers as high as 1 in 10. The EPA potency factor assumes risks for lymphoid and breast cancer. The estimated risks for sterilizer workers greatly exceed EPA's target of 1 in 10,000 for occupational exposures and are implausibly high for numerous reasons.

The EPA potency estimate is based on two epidemiology studies of 18,235 workers exposed to EO mostly in sterilizer facilities. The mortality and breast cancer incidence studies were conducted by the National Institute of Occupational Safety & Health (NIOSH) (Steenland et al., 2003; 2004). There were no mortality excesses or breast cancer incidence excesses with general population comparisons. In fact, there was a statistically significant deficit of breast cancer incidence attributable by the authors to under ascertainment. Due to non-participation in the interview substudy of the incidence study, there were additional missing cases. The only statistically significant finding for lymphoid cancer and the fully-ascertained breast cancer **mortalities** were for workers exposed to >13,500 ppm-days, which is massively higher than exposures in facilities today.

Despite the original author's conclusions, the EPA performed a complex dose-response analysis assuming a linear two-piece spline model with a knot at 1,600 ppm-day. The result was a substantial dose-response slope at low concentrations that is biologically implausible. There are several reasons why the EPA model is implausible and uncertain:

- The exposure assessment for the NIOSH cohort is highly uncertain because there is no exposure data prior to 1978 and most of the cohort (>80%) started work before then.
- EPA justifies the fit of its model using a misleading figure where it compares the model fit of its preferred to other competing models by comparing the exposure-response fit to categorical (grouped) estimates along the y-axis, contrary to the correct warning in the footnotes of the figure.
- EPA uses improper statistics to justify its exposure-response fit, including not considering the loss of a degree of freedom in estimating the location of the knot.

- EPA's cancer slope is also based on breast cancer incidence data which do not meet quality criteria for quantitative risk assessment use because of (a) the sizeable number of missing cases with high potential of missing short term employees with lower cumulative exposures and (b) the unavailability of these data to independently examine the impact of these missing cases.

An alternative exposure-response model was developed by the Texas Commission on Environmental Quality (TCEQ) using a standard Cox Proportional Hazards model based on lymphoid cancer mortalities. The TCEQ dose-response model, using the same NIOSH study, estimates risk that are 2,000-fold lower than estimated by EPA.

Calculations are presented in this document that show how the EPA Integrated Risk Information System (IRIS) potency estimate substantially overestimates the number of lymphoid cancer mortalities in the NIOSH study. The excess cancers (above population background) were estimated using the EPA and TCEQ models. There were 53 lymphoid mortality cases in the NIOSH cohort. Based on life table data, the predicted cancer cases would be 50.4, leaving 2.6 excess cases that might be associated with EO. This approach used to predict cancer deaths from the model is essentially the same well-accepted approach used in IRIS (EPA, 2016a, Section 4.7). IRIS (2016a) estimated extra risk for various occupational exposure levels by applying the IRIS model to the general population background cancer rates in the life-table program. The predictions for excess cases for the TCEQ and EPA models are:

- TCEQ central-tendency estimate: 2.03 excess cases, which is 78% of the predicted number of cases.
- TCEQ upper-bound estimate: 8.6 excess cases, which is 330% of the predicted number of cases.
- EPA central tendency estimate: 41.3 excess cases, which is 1,588% of the predicted number of cases.
- EPA upper-bound estimate (IRIS value): 90.7 excess cases, which is 3,488% of the predicted number of cases.

Thus, the TCEQ central estimate closely predicts the excess cases, and the TCEQ upper-bound is about 3-fold higher. Using the TCEQ upper-bound would be public health protective. On the other hand, the EPA model vastly overestimates the excess cases. Additional analyses in this report as well as ACC (2023) comments to OEHHHA shows the TCEQ model has superior fit across the full exposure-response range, including low cumulative exposures below the knot.

One counterpoint raised by EPA is that there may be a Healthy Worker Effect (HWE) or other potential differences between the general population and the NIOSH worker cohort, such that fewer of the observed cases would be background cases and thus more may be excess cases.

However, there is little evidence for a HWE in the NIOSH cohort,¹ and the epidemiologic literature has shown that a HWE is predominately related to workers with shorter follow-up and non-cancer causes (Monson, 1986; Fox and Collier, 1976; IARC, 1999). Despite the lack of a HWE in the NIOSH cohort, TCEQ provided a sensitivity analysis using a conservatively high HWE as a surrogate for possible unknown health-related differences between the NIOSH and general population, that might favor worker health. This analysis still shows that the TCEQ exposure-response model better predicts the observed lymphoid deaths compared to the IRIS model overall and locally below the knot.

EPA's IRIS estimate is also inconsistent with several other lines of evidence that serve as important reality checks for selection of the EPA's steep model:

- Smokers are exposed to high levels of EO, yet they do not have elevated lymphoid cancer rates.
- Another large epidemiologic study, the Union Carbide Corporation (UCC) study, shows no elevation in lymphoid cancer and EPA improperly dismisses it.
- EO is formed endogenously at substantial levels, and it is implausible that a chemical formed at high, natural endogenous levels would result in a high cancer risk at much lower concentrations.
- Available data on EO toxicokinetics and DNA adduct formation contradict the biological plausibility of a steep exposure-response at low concentrations, and the estimated high potency of EO is inconsistent with its weak genotoxic potential.

EOTF fully endorses and adopts the recent American Chemistry Council (ACC) comments to the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) Draft Cancer Inhalation Unit Risk Factor (IUR) for EO (ACC, 2023). These ACC comments provide updated responses to the IRIS assessment that take into consideration the most recent EPA (2022) response to public comments on the MON² as well as to evaluations by OEHHA (2023). As described in detail in ACC (2023), the following are the key reasons why the standard log-linear CPH model should be applied to lymphoid mortality data:

1. The single slope CPH model, which is linear at lower exposures and gradually increases at higher exposure is much more consistent with the epidemiological evidence including (a) lack of statistical significance at lower cumulative exposures

¹ "The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposures versus non-exposed comparisons." (Steenland et al., 2004).

² EPA (2022) Summary of public comments and responses for the reconsideration of the 2020 national emission standards for hazardous air pollutants: Miscellaneous organic chemical manufacturing residual risk and technology review.

for both the internal and external categorical analyses, and (b) the overall weak cancer weight-of-evidence including absence of cancer findings in the Union Carbide Corporation Cohort.

2. The CPH model is a no-threshold model that is linear at exposures of interest (e.g. at the POD of 1/100 extra risk).
3. The CPH model is statistically comparable (p-values and AIC) to the IRIS model, neither of which stand out due to weak cancer signal.
4. The CPH model better predicts the observed NIOSH data overall and locally (below the knot) when compared with the IRIS model.
5. While EPA's potency estimate technically only applies to exposures above endogenous levels, it is implausible that a chemical would be a potent carcinogen at levels that the body produces through natural processes. The key assumptions in extrapolating the exposure-response relationships at lower exposures are scientifically valid and are now corroborated by independent data sets on smoking.

In addition, EOTF concludes that breast cancer incidence is not an appropriate endpoint for quantitative risk assessment because the published data indicate a high potential for underascertainment of cases with shorter duration employment and, therefore, lower cumulative exposures. Furthermore, NIOSH does not allow access to breast cancer incidence data to allow independent analyses. EOTF emphasizes that if human data are used, lymphoid mortality is the most appropriate endpoint for quantitative risk assessment because the weight-of-evidence for breast cancer is weak. However, if EPA feels compelled to include breast cancer, then breast cancer **mortality** is more appropriate for quantitative risk assessment purposes because breast cancer mortality is fully ascertained (e.g. no missing data) and is publicly accessible. Based on EPA IRIS (EPA, 2016a, Table 4-11) application of the standard CPH model for breast cancer mortality, the central and lower-bound unit risk estimates for the cancer slope factor are 0.019³ and 0.035⁴ per ppm respectively, at the POD of 1/100⁵ extra risk not including the EPA's age-dependent adjustment factor (ADAF). This is in contrast to the application of the 2-piece spline model for the under-ascertained breast cancer incidence of 0.72⁶ and 1.5⁷ per ppm for the central estimate and upper bound (see also EPA, 2016a, Table 4-15, not including ADAF).

³ EPA IRIS (EPA, 2016a) Table 4-11 EC01(ppm) = 0.5305, not including ADAF

⁴ EPA IRIS (EPA, 2016a) Table 4-11 LEC01 (ppm) = 0.285, not including ADAF

⁵ Note: EPA IRIS provided no justification for applying the POD of 1/100 extra risk. An appropriate POD should be selected to ensure it is appropriately in the lower range of the experimental data.

⁶ EPA IRIS (2016) Table 4-15 EC01(ppm) = 0.0138, not including ADAF

⁷ EPA IRIS (2016) Table 4-15 LEC01(ppm) = 0.00675, not including ADAF

These EPA IRIS (2016a) results are presented for modeling comparison purposes identical to the EPA (2019⁸) approach for model comparisons. Further analysis would be needed to ensure the PODs are at the low-end of the observable range of exposures and to adjust for the USEPA ADAF (TCEQ, 2020a).

In summary, EOTF urges EPA OPP to adopt the TCEQ model based on the standard CPH model for lymphoid mortality to derive a more biologically plausible, statistically sound and conservatively protective cancer slope that is more consistent with the epidemiological evidence. EOTF's full rationale is detailed in recently submitted comments by the ACC Ethylene Oxide Panel to OEHHA, which EOTF fully endorses and includes as an integral part of EOTF's comments on the OPP Draft PID for EO (ACC, 2023). This report provides additional analyses focused on the implausibility of the EPA OPP's human health risk assessment estimates of lifetime cancer incidence risks for sterilizer workers to be as high as 1 in 10. At a minimum, this report can aid risk assessors in understanding the uncertainties in the EPA's estimated risks of cancer using new data and analysis that was not adequately addressed by EPA IRIS (2016a) nor EPA's recent responses to public comments (EPA, 2022).

⁸ EPA (2019) ORD Memo from Kristina A. Thayer to Peter Tsirigotis: EtO Assessment-Modeling Comparisons and Assessment of Uncertainty. For comparison purposes, this analysis appropriately did not include the ADAF

Introduction

The U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) released its Proposed Interim Decision (PID) for ethylene oxide (EO) on April 11, 2023 (U.S. EPA, 2023a). It also released a related human health risk assessment on the same day (U.S. EPA, 2023b). These comments were prepared with support from the Ethylene Oxide Task Force (EOTF), which members include companies that use EO to sterilize medical devices.

The human health risk assessment estimates exposures and associated cancer risks for a variety of occupations, including workers in EO sterilizer facilities. The estimated lifetime cancer risks were 1 in 10 to 1 in 17 for sterilizer workers, and 1 in 12 to 1 in 25 for healthcare workers. These risks greatly exceed EPA's target of 1 in 10,000 for occupational exposures.

The cancer risks were estimated using the potency value from EPA's Integrated Risk Information System (IRIS) risk assessment of available data on carcinogenicity. The EOTF and others, including the American Chemistry Council (ACC), have submitted comments on the validity of the IRIS potency estimate. (EPA, 2016a; 2016b). These comments echo many of the same criticisms of the IRIS assessment and also focus on the large occupational risks estimated by EPA.

The IRIS potency estimate is based on a reanalysis of the National Institute of Occupational Safety & Health (NIOSH) epidemiologic study of sterilizer workers (Steenland et al., 2003; 2004). While the original study only found a weak signal for lymphoid and breast cancers, EPA estimated a exposure-response model with a steep slope at low concentrations using a supralinear spline model where the exposure-response levels off after a knot at 1,600 ppm-days.

EOTF (2021 a,b) has questioned the validity of the IRIS potency estimate on several grounds, including improper interpretation of the NIOSH epidemiologic study of sterilizer workers, inadequate consideration of other, contrary epidemiologic data, and a lack of biological plausibility.

Until recently, EPA had only applied the IRIS value to estimate risks for bystanders living near facilities using EO for sterilization, for which exposures are much lower than for workers in the sterilizer facilities. EOTF (2021 a,b) has argued that EPA's risk estimates for bystanders were unrealistically high. The current risk assessment estimates risk for workers and takes the IRIS potency estimate to a completely unrealistic conclusion that the lifetime cancer risks for sterilizer workers are in the range of 1 in 10.

The comments that follow show that the IRIS potency estimate is inconsistent with the weak cancer signal of EO and that the 1 in 10 estimate is thoroughly inconsistent with the available scientific data.

An alternative analysis was conducted by the Texas Commission on Environmental Quality (TCEQ). TCEQ analyzed the same NIOSH dataset but derived a potency 2,000-fold lower than estimated by IRIS. Like the IRIS model, the TCEQ model is a no-threshold model, is linear at the exposures of interest (e.g. at or below the point of departure of 1 in 100 extra risk) and are not statistically significantly different from the null hypothesis. The key differences in the TCEQ analysis compared to EPA IRIS are:

- TCEQ used a standard Cox Proportional Hazard model with a 15-year lag, whereas EPA used a linear two-piece spline model with a 15-year lag.
- TCEQ included only lymphoid cancers because it concluded that EO exposure was not causally associated with breast cancer.

TCEQ emphasized mode-of-action information as the primary guiding principle for selecting exposure response models, whereas EPA considers MOA data from animals to be uninformative in selecting models based on human data. If the TCEQ potency were applied, the working lifetime risks at 0.2 ppm would be within EPA's acceptable level of concern of 1 in 10,000. In these comments, we show that the TCEQ exposure-response model is more consistent with the NIOSH dataset and the larger body of data. While EOTF agrees that the weight of evidence for breast cancer is weak, EOTF provides a more correct alternative to addressing breast cancer for quantitative risk assessment by selecting the fully ascertained mortality data rather than the substantially under ascertained incidence data.

Evaluation of IRIS Potency Derived from NIOSH Study

NIOSH Study Provides Only a Weak Cancer Signal

The IRIS potency estimate is based on the NIOSH epidemiologic studies of 18,235 workers exposed to ethylene oxide, mostly in sterilizer facilities (Steenland et al., 2003; 2004). The study found limited evidence of a exposure-response for lymphoid cancer mortality in males and breast cancer incidence in females. EPA obtained the raw data from the NIOSH study and conducted its own reanalysis in collaboration with Drs. Steenland and Deddens. Through coordinated efforts with the American Chemistry Council Ethylene Oxide Panel, we have been able to evaluate lymphoid mortality summary data, but the breast cancer incidence data has not been made available by NIOSH for privacy reasons.

Considering the dramatic estimates as high as 1 in 10 for lifetime cancer risk, it is important to consider that the original study does not describe the results as providing compelling evidence of cancer risk. Quoting from the abstract conclusions of the original study by Steenland et al. (2004):

“There was little evidence of any excess cancer mortality for the cohort as a whole, with the exception of bone cancer based on small numbers. Positive exposure-response trends for lymphoid tumours were found for males only. Reasons for the sex specificity of this effect is not known. There was also some evidence of a positive exposure-response relationship for breast cancer mortality.” (emphasis ours)

Steenland et al. (2003) was similarly cautious about the breast cancer incidence findings:

“Our data suggest that ETO is associated with breast cancer, but a causal interpretation is weakened due to some inconsistencies in exposure-response trends and possible biases due to non-response and incomplete cancer ascertainment.”

The internal categorical analysis, as presented by the original authors, provide important perspective on the potency of EO at lower exposures. The only statistically significant finding for the internal categorical analysis of lymphoid cancer mortality was in males and only in the highest exposure category of >13,500 ppm-day. Similarly, the internal categorical analyses of female breast cancer mortality and incidence were only statistically significant in the highest exposure categories of >13,500 ppm-days and >14,620 ppm-days, respectively (Steenland et al.,

2003; 2004). These results hardly suggest a cancer risk among the highest ever estimated by EPA.

During the period of the study follow-up, there were 2,852 deaths observed from all causes among the 18,235 workers. The authors compared these values to life table data of the general population and found that the 2,852 deaths were about 90% of what would have been expected based on the general population. There were 860 cancer mortalities and that was only 98% of the expected number from comparison with the life tables. For all haematopoietic cancers and non-Hodgkin lymphoma (NHL) (the largest cancer type in EPA's analysis of lymphoid tumors), there was 79 and 31 mortalities, respectively, which were exactly the number expected based on comparison to the general population. For breast cancer, there were 103 mortalities, which was 99% of the expected number from comparing with the general population.

Epidemiologists typically consider risks as relative to a background risk, such as the natural rate of a given cancer type absent exposure. However, the risks estimated by EPA are not relative to a background. The 1 in 10 risk estimate associated with 0.2 ppm over a working lifetime is the risk associated with ethylene oxide exposure for sterilizer workers. It does not mean that there is a 10% excess risk above background risk. It means that 10% of the worker population exposed to current levels in sterilizer facilities would eventually develop a cancer associated with ethylene oxide.

In comparing the 1 in 10 risk with the NIOSH mortality study results for lymphoid tumors, it is important to consider that the IRIS potency estimates the risk for cancer incidence and NIOSH measures mortality risk. EPA makes the tenuous assumption that the exposure-response for incidence is the same as mortality (Valdez-Flores and Sielken, 2013). This analysis focuses on lymphoid cancer mortality which has a much greater contribution to the IRIS unit risk estimate compared to breast cancer incidence (Table 4-26 of EPA IRIS, 2016a). The breast cancer incidence data is unavailable due to privacy concerns.

The exposures in the NIOSH study were much greater than in the current environment in sterilizer facilities for which EPA is estimating cancer risk over a working lifetime (35 years). Based on industrial hygiene data provided by EOTF, EPA estimated a mean exposure in present day sterilizer facilities of 0.23 ppm (U.S. EPA, 2023). Assuming a 35-year career at 240 days per year, the estimated cumulative exposure is 1,932 ppm-days. However, the NIOSH study includes workers dating back to the 1940s, where industrial hygiene controls were far less effective. Some workers in the NIOSH study were exposed much more than 13,500 ppm-days. The average exposure in the cohort was about 9,855 ppm-days⁹ with exposures ranging up to

⁹ The average cumulative exposure was 27 ppm-year and was normalized to 365 days. Thus, the average cumulative exposure in ppm-days is 9,855.

150,000 ppm-days. Thus, the workers in the NIOSH study were exposed to about 5-fold higher levels of cumulative exposure (average NIOSH cohort exposure of 9,855 ppm-days compared to EPA estimate for sterilizer workers of 1,932 ppm-days). If the IRIS value were accurate, one would expect a far higher than 1 in 10 risk among the NIOSH study subjects.

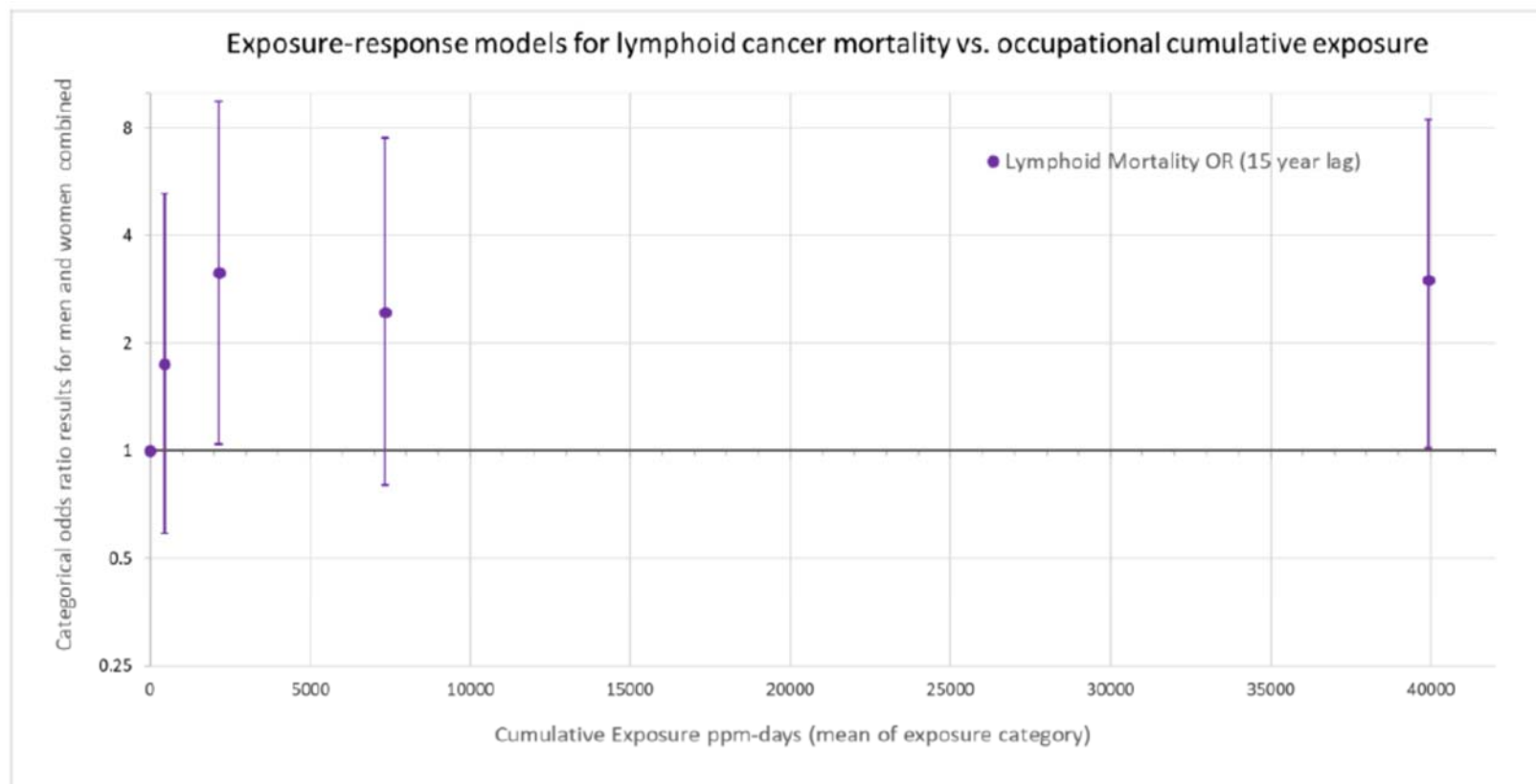
Nonetheless, through the follow-up in the study, the authors found 860 cancer mortalities (about 5% of the cohort) which was comparable to the expected cancer mortality in the cohort. Given that exposures in the NIOSH study were even higher than for current sterilizer workers, where EPA's 1 in 10 risk is calculated, it is impossible to see how there would not be a clearer signal in the cancer mortalities in the NIOSH study if the IRIS value is correct. The following sections will provide a firm quantitative basis to demonstrate that the IRIS potency value vastly overestimates the cancer mortality associated with EO exposure.

Exposure-Response from NIOSH Study is Highly Uncertain

While there is little evidence for an overall excess cancer risk in the NIOSH study, NIOSH and EPA found limited evidence for a exposure-response when it compared workers with differing cumulative exposures. However, the evidence for an exposure-response is weak and uncertainty bounds on the group risk estimates are wide.

In the original NIOSH mortality study, the subjects were divided into four exposure groups: >0-1199 ppm-days, 1200-3679 ppm-day, 3680-13,499 ppm-days, and 13,500+ ppm-days. Males and females were analyzed separately, and the authors concluded that there was only an effect in males. The group odds ratios (ORs) for the cumulative exposure analysis for male lymphoid cancers were with a 15 yr. lag: 1.00, 0.90 (0.16-5.24), 2.89 (0.65-12.86), 2.74 (0.65-11.55), and 3.76 (1.03-13.64). Only the (OR) for the top exposure group (13,500+ ppm-days) was statistically significant, and only barely with a lower confidence limit of 1.03. No steep increase among males was seen at the low exposure (OR=0.90). The confidence intervals on the ORs were large as they were based on small numbers of cases and again hardly consistent with a clear effect. EPA IRIS compared models of individual data to these ORs without consideration of these wide uncertainty bounds and, as discussed in detail in the attached ACC comments to OEHHA, incorrectly along the y-axis.

Figure 1. Confidence intervals for lymphoid exposure-response for males and females combined



The EPA IRIS (2016a) assessment combined the males and females together. Figure 1 shows the odd ratios for EPA's internal analysis with the associated confidence intervals that EPA relied upon for visual comparisons of models. The confidence intervals are very wide and the evidence for a particular exposure-response shape is limited to the appearance of a few ORs which are not representative of the actual individual data modeled. EPA's IRIS exposure-response model is not even statistically significant ($p=0.07$, as reported by EPA) and $p=0.14$ after properly correcting for the loss of a degree of freedom for estimation of the knot (see below).

EPA IRIS (2016a) applied an unprecedented number of statistical models (and variations on each model) to the NIOSH data and reported statistically significant p-values for the continuous model with the logarithm of cumulative exposure and two-piece linear spline model. These statistical modeling results together with the shape of the internal categorical estimates (Figure 1) led EPA to select the two-piece spline model with the knot at 1600 ppm-years. Yet, there are several inconsistencies and flaws with EPA's approach.

- First, EPA (IRIS, p. H-26, H-34) rejects the log cumulative exposure models because these models are “excessively sensitive to changes in exposure level in the low-dose region, and thus, were not biologically realistic”. Thus, it is contradictory for EPA to use a model that EPA rejected because it is not biologically plausible to justify the selection of a spline model.
- Second, EPA's *a priori* criteria for selecting the two-piece spline model was to systematically evaluate different knots in increments of 100 ppm- days and selecting with the knot that resulted in the best (largest) model likelihood. EPA states that this model “yielded a very steep slope in the exposure range below the knot of 100 ppm-days, and there was low confidence in the slope, given the limited data in the low exposure region.” Instead a knot of 1600 ppm-days was used, but no clear statistical or biological basis for selecting this knot compared to other knots. As shown in detail in the present comments as well as those by ACC (2023), TCEQ has shown the 2-piece spline model is also unrealistic in that it significantly over-predicts the number of observed cancer deaths in the NIOSH study.
- Third, the statistical basis for selection of the spline model is flawed because the knot was clearly a parameter in the model since there was a systematic search for the knot with the largest model likelihood. As discussed in detail in ACC (2023), the corrected p-values indicate that there is no statistical basis to select the spline model over the CPH model. For lymphoid mortality, the p-values are 0.14 (corrected from 0.07) and 0.22 for the spline and CPH models, respectively. For breast cancer incidence, the p values are 0.04 (corrected from 0.01) and 0.02 for the spline and CPH model.
- Fourth, the categorical data for males and females combined were used for visual comparisons for the different models that IRIS applied without any consideration of the

confidence intervals as shown in Figure 1 or the original authors' conclusions that males have a different pattern than females.

- Fifth, the selection of models did not consider the putative genotoxic mode of action, pharmacokinetic data and other animal data in any integrated manner to inform the selection of the dose-response model. The final section of these comments explain in detail why the CPH model has greater biological plausibility than the spline model.

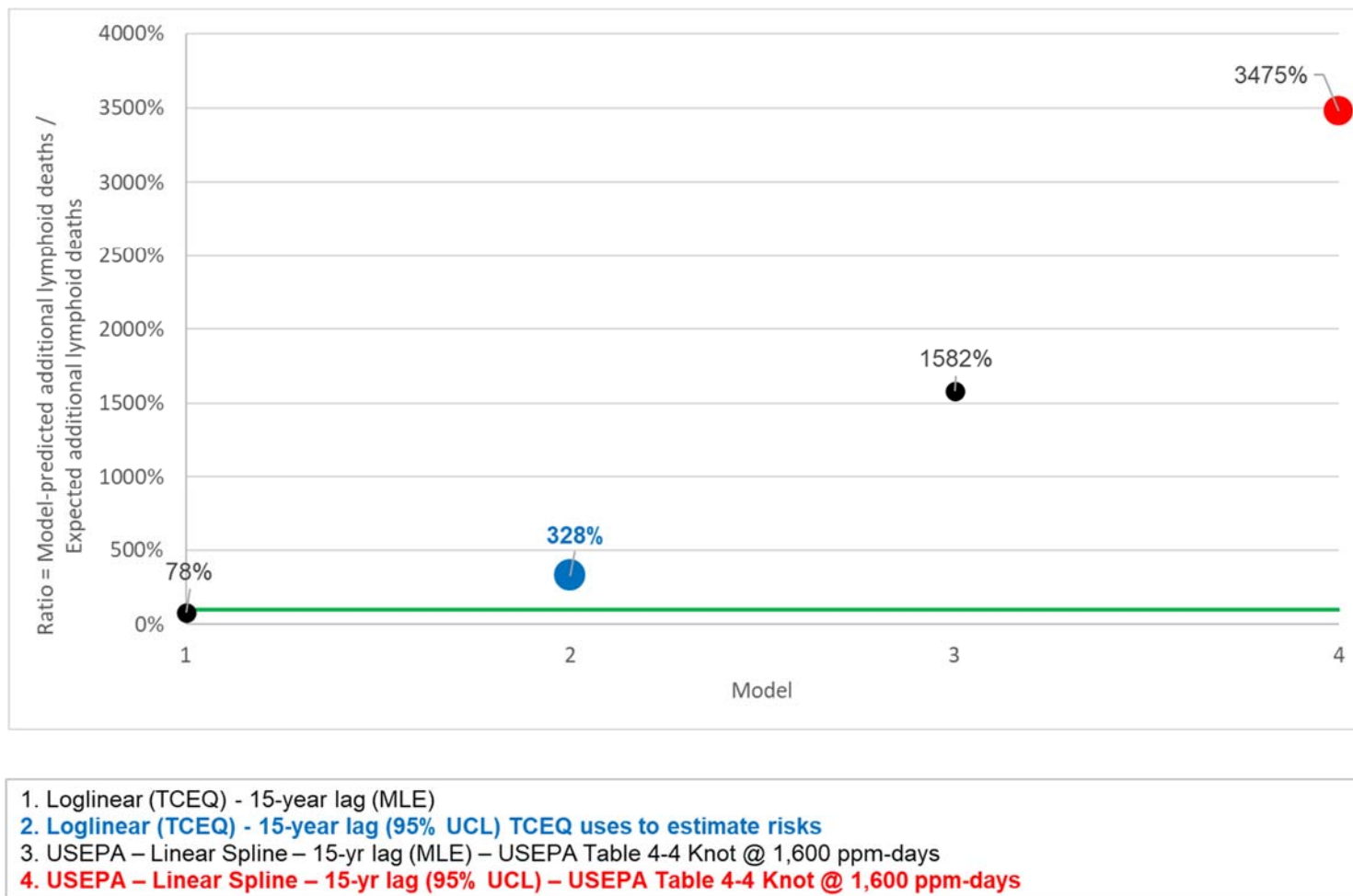
IRIS Potency Value Vastly Overestimates Expected Cancer Mortalities

The Texas Commission on Environmental Quality (TCEQ) has shown that the EPA model significantly overestimates the expected cancer cases in the NIOSH cohort (TCEQ, 2020a). The standard log-linear Cox Proportional Hazards (CPH) model used by TCEQ estimated 52.4 lymphoid mortalities compared to 53 observed mortalities. By contrast, the EPA's 2-piece linear spline model with a knot estimates 91.7 mortalities.

ACC's (2023) recent comments on the draft OEHHA IUR include additional analyses for both the overall and the first exposure category below the knot (Quintile 2) that provide additional support for TCEQ's prediction analyses by addressing EPA's (2022) response to public comments. These analyses indicate that the TCEQ standard CPH model accurately predicts the number of lymphoid deaths observed in the NIOSH study, while EPA's two-piece linear spline model statistically significantly (at the 2.5% significance level) overpredicts the total number of lymphoid deaths observed in the NIOSH study as well as the number of lymphoid deaths observed in Quintile 2. This is true with and without consideration of a reasonably high HWE of 15% to account for any differences that might exist between the general US population and the NIOSH worker cohort given the absence of a HWE in the NIOSH cohort (Steenland et al. 2004) and for longer follow-up cancer studies (Monson, 1986; Fox and Collier, 1976).

While TCEQ's and ACC's analyses are very useful in showing that the EPA model overpredicts cancer cases in the NIOSH cohort, it does not tell the whole picture given that the vast majority of the cases are background cases, so only comparing total cases obscures the true difference in cases associated with ethylene oxide. Therefore, an analysis is presented below for only excess cases associated with EO exposure. Figure 2 shows the observed cases associated with EO exposure based on a comparison with population background levels from life tables and the estimated cases using the IRIS potency value. The graphic shows estimates using the TCEQ exposure-response model, EPA's exposure-response model, and EPA's exposure-response model with no increase in risks after the knot (one ultimately used for the IRIS value). The central tendency and upper-bound estimates are shown for each model. The IRIS value is ultimately based on the upper-bound of the model with no increasing risks after the knot.

Figure 2. Estimation of overprediction of EPA IRIS potency value for lymphoid cancers associated with ethylene oxide

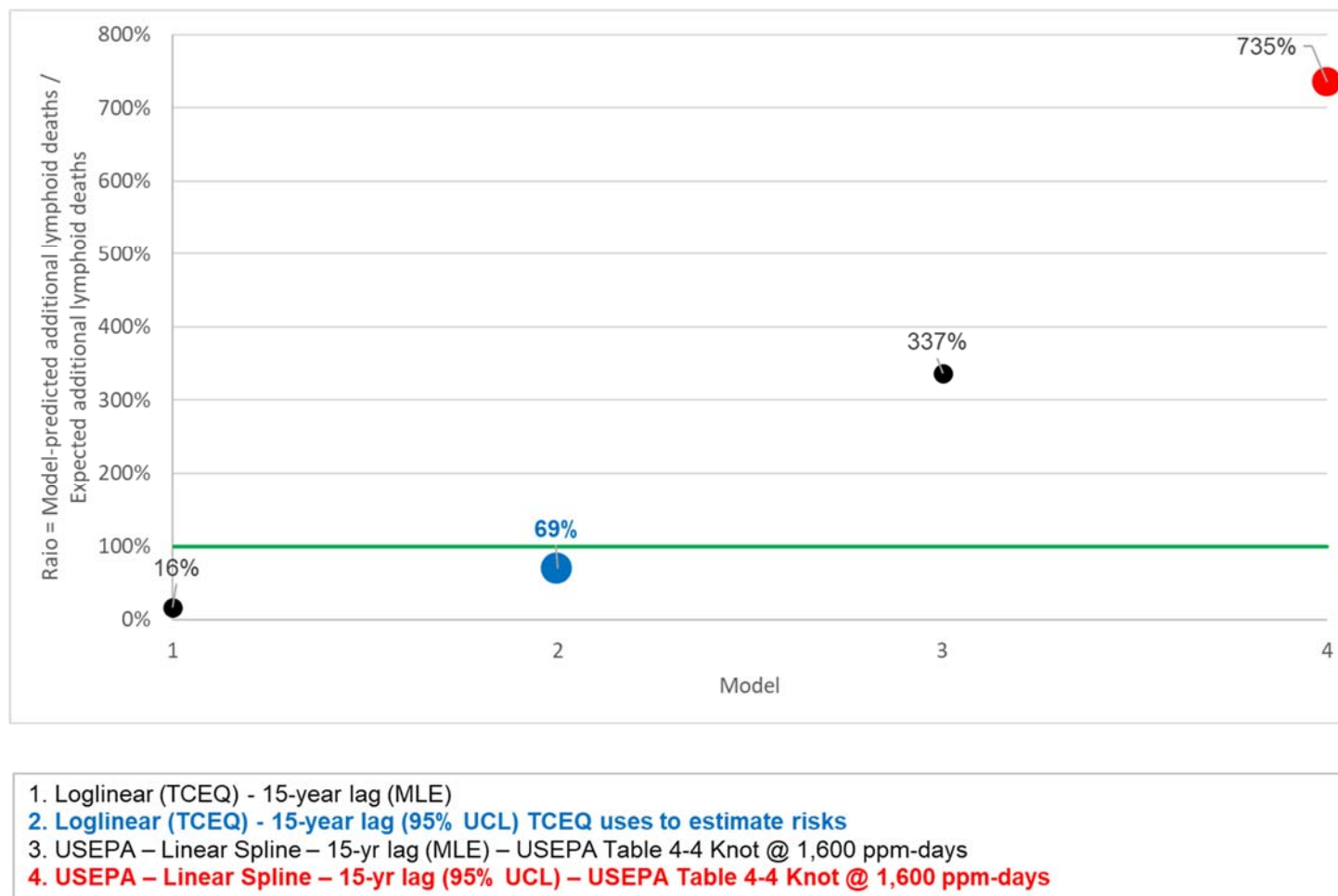


There were 53 lymphoid cases in the NIOSH cohort. Based on life table data, the predicted cancer cases would be 50.4, leaving 2.6 excess cases. However, the EPA model, that the IRIS value is based on, predicts 41.3 and 90.7 excess cases, respectively, for the central tendency and upper-bound. Even the central tendency of the EPA model vastly overpredicts the excess cases and the upper-bound overpredicts the excess cases by 3500%. By contrast, the TCEQ central tendency estimate accurately predicts the excess cases. It predicts 2.03 excess cases compared to 2.61 excess cases based on the life tables, so the estimate is 78% of the actual value. The TCEQ upper-bound value predicts 8.6 excess cases, or 330% of the actual value based on the life tables, leaving ample margin of safety. One possible reason that EPA has offered to explain its higher predictions of excess cases compared to the life table analysis is that there is a HWE in the cohort; and, therefore, the expected cases without ethylene oxide exposure are fewer than would be predicted by the life tables. With lower expected cases from background, a greater portion of the observed cases are assumed to be due to EO exposure.

However, as noted above, the NIOSH study provides little evidence for a HWE. There were nearly exactly the number of cancer cases in the cohort as expected by the life tables. There is modest evidence for a HWE for all cause mortality where the observed deaths of 2852 were 90% of the values expected from the life tables. These results are consistent with the generally understood concept that a HWE exists primarily for non-cancer causes. Because both the NIOSH and UCC studies have extensive follow up, HWE would not be a plausible explanation for the absence of increases with general population comparisons, as Steenland et al. note in their publication. IARC's textbook *Cancer Epidemiology: Principles and Methods* (IARC, 1999) states that the HWE "is known to vary with type of disease, being smaller for cancer than for other major diseases, and it tends to disappear with time since recruitment into the workforce." Thus, the observed data are not consistent with a HWE for cancer, which is consistent with generally accepted epidemiologic principles.

Nonetheless, to evaluate the impact of a possible HWE, the excess cases were compared by TCEQ to values for the expected cases assuming a 15% HWE for males and a 16% HWE for females (TCEQ, 2020a). It is highly unlikely that the true HWE is this high given the lack of any evidence for a HWE for cancer or any cancer subtypes in the NIOSH study, and the general lack of applicability of a HWE for cancer. Nonetheless, a HWE was assumed to illustrate the EPA model still overestimates the excess cases even when assuming a HWE as a surrogate for potential differences between the general population and the NIOSH worker cohort. The results are shown in Figure 3. In this case, the observed excess cancer mortalities are 10.4. The EPA model predicts 35.0 and 76.4 excess cancer mortalities, respectively, for the central tendency and upper-bound. These values are 340% and 740% above the observed excess cases, respectively. Thus, the EPA model still substantially overpredicts the excess cancers even assuming a HWE. In this case, the TCEQ model underpredicts the excess cases, though not unexpectedly given the lack of evidence for a HWE in the cohort.

Figure 3. Estimation of overprediction of EPA IRIS potency value for lymphoid cancers associated with ethylene oxide assuming a HWE (15% for males and 16% for females)



NIOSH Study Relies on Highly Uncertain Exposure Estimates

The EPA IRIS assessment describes the NIOSH exposure assessment as “high quality” (EPA, 2016a, p. 1-2), but this conclusion is not supported. There are substantial data and analyses showing that the NIOSH exposure model is flawed. One of the fundamental flaws of the NIOSH model is that there were no industrial hygiene data before 1978 and most of cohort worked prior to 1978 with an average year of hire of 1970. The NIOSH exposure model concludes that concentrations increased from the 1930s to the 1970s, contrary to the generally expected trend of improved industrial hygiene and stricter regulations over this period. The limitations of the NIOSH multiple regression exposure model predictions for early sterilization workers have the potential to overestimate risk.

There are several reasons to question the reliability of NIOSH model predictions of early sterilizer worker exposure estimates:

- First, the NIOSH multiple regression exposure model validation (Hornung et al., 1994) was based using a portion of the 1978-1986 industrial hygiene data to develop the model and another portion of the data to test the model. Therefore, the model was validated for the years with data but not for the early years for which no concentration measurements were available. Hornung et al. (1994) provided no other data, information or analyses for sterilizer workers or processes in this earlier time period to check the applicability to this NIOSH exposure model to sterilization workers in the cohort who worked from the 1940s to later 1970s, which encompasses the vast majority of all cohort worker and fraction with most reported cancers. These facts regarding the NIOSH model validation should have raised concern about model predictions for early sterilization workers.
- Second, Hornung et al. (1994) selected Calendar year, a surrogate for improvement in work practices, as the key variable to apply the NIOSH exposure model to the pre-1978 cohort workers. This variable was applied conditionally on the max year 1978 forcing the inverse parabolic fit for years before 1978. This application of calendar year inferred that there were no major changes in work practices in sterilization operations between the late 1930s and late 1970s that would have affected worker exposures, i. e., the effect of calendar year was held constant.

Contrary to this inference, substantial published information and data on early work practices and changes in work practices were found in technical literature, industry documents, and from early workers and industry experts (Bogen et al., 2019). In other words, Bogen et al. (2019) brought far more information and data to inform the validity of the NIOSH model prior to 1978, when NIOSH had insufficient (1976-1978) or no (<1976) data. For example, the numbers of repeated cycles of in chamber, post-

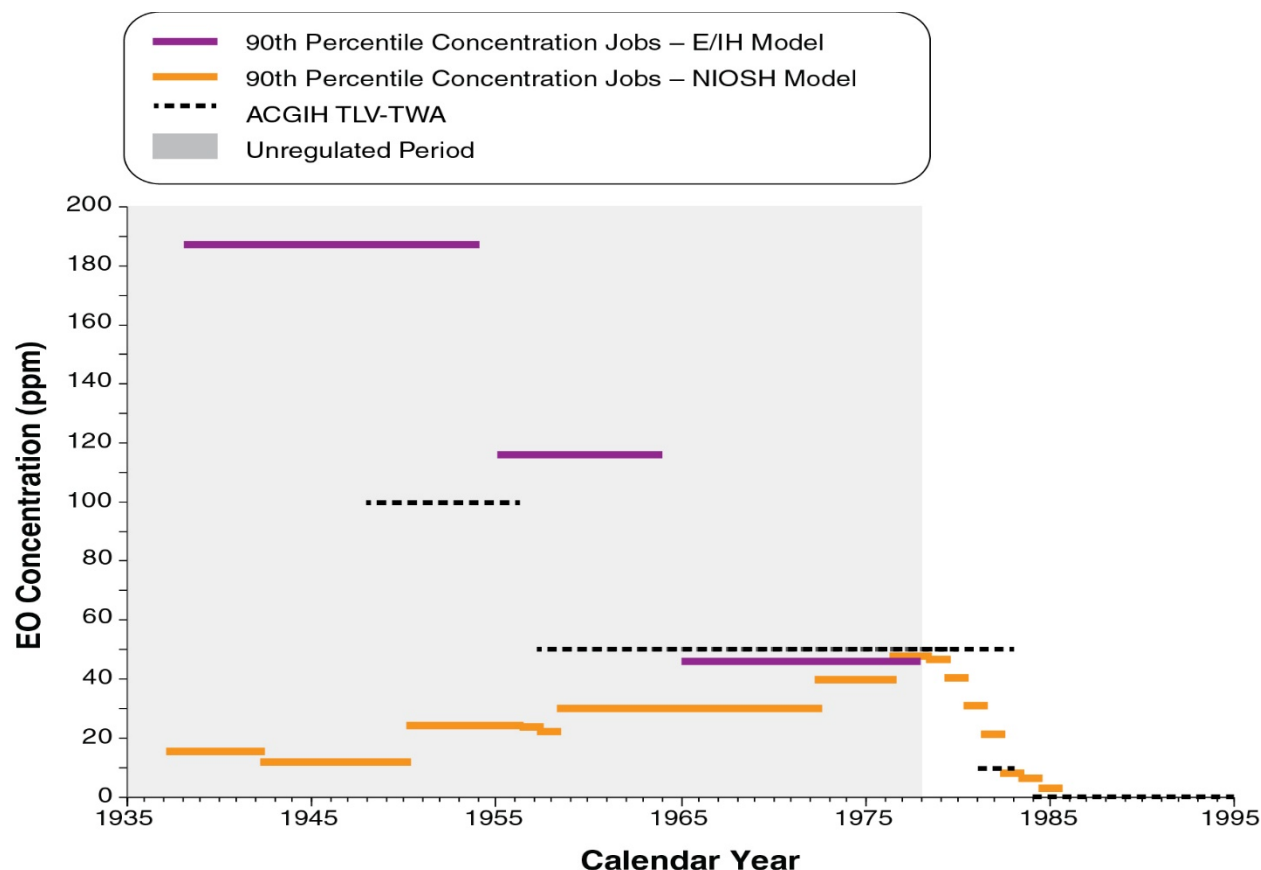
exposure vacuum air- or nitrogen washes have increased from two or fewer from early operation up to ten or more for operations in the 1980s leaving high levels of EO residues to off gas from sterilized materials and packaging from early operations and lower levels in later operations (Goldgraben and Zank, 1981; Buonicore et al., 1984).

Consistent with few wash cycles, there are several published studies of rates of EO off gassing from sterilized materials representing conditions in the 1950s through 1980s (Bruch, 1961; 1972; Buonicore et al., 1984; FDA, 1978; Stetson et al., 1976; White, 1977). As importantly, early operations stored sterilized materials in the same room as ongoing sterilizer operations where both operational emissions and sterilized material off gassing contributed to worker exposure while later operations moved sterilized material to a separate warehouse room, reducing the exposure of highly exposed sterilizer operators (Bogen et al., 2019). Clearly there were important work practice changes over time that need be considered in assessing the exposure of cohort workers.

- Third, the NIOSH exposure model based on the conditioning of calendar year predicted early sterilization workers were exposed to EO concentration substantially lower than workers in 1978 when exposure concentration predictions were based on measurements (see Figure 4 below from Bogen et al., 2019). One would not expect low exposure concentrations when equipment and processes were relatively crude and little known about EO toxicity and when there were no worker protection regulations. The NIOSH model is inconsistent with industrial hygiene data collected in other industries showing higher concentrations in the early era (e.g., Von Grote et al., 2003, 2006) and inconsistent with historic worker exposure guidance (ACGIH 1948, 1957) for EO exposure concentrations in the workplace. ACGIH provided an exposure limit for EO of 100 ppm in 1948 and 50 ppm in 1957 to encourage reductions in workplace exposure. As a reality check, no ACGIH guidance would have been needed had EO concentration been as low as predicted by the NIOSH exposure model.

Figure 4 compares alternative estimates developed by Bogen et al. (2019) (E/IH model with purple lines) versus the NIOSH estimates (orange lines). The Bogen et al. (2019) estimates, based on historical data on work practices and interviews with early workers and industry experts, are considerably higher in the early era where many of the workers that developed cancer worked. The Bogen et al. (2019) shows the potentially very substantial exposure misclassification in the NIOSH cohort, which would have unpredictable results.

Figure 4. Comparison of historical trends for Bogen et al. (2019) engineering/industrial hygiene (E/IH purple lines) and NIOSH statistical regression (NIOSH orange lines) exposure model estimates of occupational respiratory exposures to EO in facilities that sterilized medical/health products



Note: Comparison of Bogen et al. engineering/industrial-hygiene (E/IH purple lines) and NIOSH statistical regression (NSR orange lines) exposure model estimates of occupational respiratory exposures to EO in facilities that sterilized medical/health products and prevailing ACGIH TLV limits for EO (dashed lines). Shaded area represents the period during which very limited or (pre-1976) no contemporaneous measurements were available to validate NSR model predictions and during which no EO-specific regulations were in place to limit occupational EO exposures. Adapted from Figure 5 of Bogen et al. (2019). Due to limitations in data prior to 1978, Bogen et al. emphasizes that the primary objective of this modeling study was to examine whether any historical **trend** (increasing, decreasing, or constant) is exhibited in the EO exposure levels prior to 1978.

This understanding of exposure limitations of the NIOSH study indicates that a more balanced consideration of the negative UCC study should be considered in selecting the exposure-response model. The UCC exposure estimates are superior in quality to the NIOSH exposure estimates because exposure data for the most recent periods, 1957-1973 and 1974-1988, were available for more than 75% of the cohort based on routine monitoring, personal sampling and a

plant wide survey in another UCC plant using the same process (Greenberg et al., 1990; Teta et al., 1993; Swaen et al., 2009). Accordingly, the new cited data and modeling estimate for the historical exposure trend from the Bogen et al. paper indicates that the EPA IRIS (2016a) assessment should downgrade the NIOSH study quality with respect to the earlier (pre-1978) exposure periods and the UCC study needs to be more fully integrated. The evidence from both of these studies, individually and combined, do not support selection of a 2- slope exposure-response model with a very steep initial slope. The log-linear exposure-response model is far more consistent with the weight of evidence from the NIOSH and UCC studies as described in greater detail in the ACC OEHHA IUR comments (ACC, 2023)

EPA justifies the fit of its exposure-response model using a misleading figure

The EPA (2016a) IRIS figures showing the fit of the exposure-response model (IRIS Figures 4-3 to 4-9) are misleading because EPA uses a small number of categorical modeled data points (odds ratios) to visually evaluate the fit of their favored model and various continuous models, as if these cruder categorical data represent the true underlying shape of the exposure response curve. EPA's major reliance on visual fit using the categorical data essentially ignores EPA's Science Advisory Board (SAB) warning in an early draft of the EO IRIS assessment that categorical modeling should not be the primary data for modeling an exposure-response relationship (SAB, 2007). EPA (2022) states that the categorical model is a well-accepted method to represent the data. This true statement is irrelevant to whether "eyeballing" visual fit comparisons is an acceptable method for determining goodness of fit of the model to the underlying individual data. By putting all of the models on the same graphic, EPA has produced a misleading model comparison. EPA acknowledges this in a footnote to the figures, but reviewers might easily miss this. As a prominent example, in its recent review, California EPA's OEHHA missed the footnote and used the graphic to justify the fit of EPA's model with other competing models (OEHHA, 2023).

As described in greater detail in ACC (2023)'s response to OEHHA, graphical display of data is subject to manipulations including the choice of how data are expressed on the y-axis and resolution of categorical models to represent the underlying individual data that were modeled. While TCEQ (2020a) provides graphics that provide a fairer model comparison, TCEQ only discusses visual fit (and only in an Appendix) because of EPA's reliance on it. TCEQ's graphics shows that the TCEQ model fits the individual data as well as the EPA model on a visual basis. Importantly, TCEQ (2020 a, b) emphasizes that they do not rely on visual model fit as a primary consideration for model choice, but rather principally relies on mode of action and more objective statistical diagnostics of model fit (i.e. corrected AIC and p-values) combined with accurate model predictions in a sensitivity and validation analyses.

EPA applies improper statistics to justify the fit of its exposure-response model

Statistical significance of the model applied to the NIOSH data was an important consideration in model selection by EPA IRIS. EPA IRIS reported the p-value for the IRIS model as 0.07, and for the TCEQ model the p-value is 0.22. This would suggest that the EPA model is closer to statistical significance ($p < 0.05$) than the TCEQ model. Though, it must be stressed, neither model was statistically significant.

However, EPA IRIS made an error in the calculation of the p-value of the IRIS model by not accounting for all parameters estimated in the model. EPA's reported p-value calculation is incorrect because EPA IRIS (EPA, 2016a, p. 4-67) did not include the knot as an estimated parameter in the model. Contrary to EPA's claim that they fixed the knot *a priori*, EPA searched for the knot that maximized the likelihood (fit).¹⁰ In other words, the knot is an estimated parameter in the model even if done in a two-step process.

When corrected, the p-value for the IRIS model is 0.14, indicating comparable statistical significance for both the IRIS and TCEQ models (TCEQ, 2020a). Neither model is statistically significant, but the TCEQ model at least has the advantage of parsimony (simpler model) and biological plausibility as discussed in greater detail in later sections.

Two TCEQ peer reviewers with statistical backgrounds agreed that EPA IRIS statistical calculations are incorrect because the knot parameter in the spline model was not included as an estimated parameters (TCEQ, 2020b).

Expert 5: "I do believe that TCEQ has identified a real problem with the USEPA AIC and p-value calculations. The explanation of the issue and the resolution supplied in DSD seems appropriate. That is, I agree with TCEQ that the knot parameter in the spline models should be considered in the count of the parameters, that the AICs reported by USEPA for those models are too low by a value of 2, and that the p-values should be computed using an approximation to a chi-square with 3 degrees of freedom."

Expert 6: "I consider that the location of the spline should be considered a parameter when evaluating fits of spline models, as long as the data were used in determining the knot, as it apparently was in EPA's model. I believe also that the lag should also be considered a parameter when the data are used to determine its value. But, in general, I consider the AIC in such complex models to be essentially only a rough guide to evaluating fit. Therefore, I think TCEQ's conclusion that the "lower AIC means that TCEQ's selected model is a statistically superior model fit than USEPA's selected model when taking into account model complexity" is an overstatement. Comparing a model with an AIC = 464.5 to one with an AIC = 264.4[sic¹¹], you can only conclude with confidence that the *two models fit about equally well [emphasis added]*. Additionally, the overall fit is not of major importance – the fit at small doses is much more important when the object of the fitting is to estimate the risk at very small doses."

¹⁰ EPA IRIS (EPA, 2016a) p. 4-67 and Appendix D Figure D-14 indicates that the knot was selected based on consideration of the maximum likelihood (lowest AIC).

¹¹ Expert really meant 464.4

In summary, when the EPA IRIS statistical analysis is corrected, both the TCEQ and IRIS models fit the data “equally well” based on the p-values and AIC criteria. Importantly, there are no recognized exceptions to the penalty component of the balance incorporated into the AIC metric when applied in a valid procedure for model-selection (Burnham et al., 2002). This general principle is well recognized also to apply specifically to including the estimated “knot” or inflection point from 2-piece linear spline models by experts publishing research using spline models (Berman et al., 1996; Li et al., 2011; Fearnhead et al., 2019; Gkioulekas et al., 2018; Rodríguez-Domínguez et al., 2018; Molinari et al., 2001).

In fact, in the EPA IRIS (EPA, 2016b) assessment Appendix D (at p. D-13), Dr. Steenland recalculated the p-value with the knot as an estimated parameter to conclude that there was no substantial effect on the p-value in the breast cancer analysis. Unfortunately, this analysis is buried in the appendices, and IRIS (U.S. EPA 2016a; b) does not include a similar analysis for lymphoid, which results in substantive change from $p=0.07$ to a clearly non-significant $p=0.14$.

IRIS (EPA, 2016a) also identifies parsimony as another chief criteria for selecting the final exposure-response model yet fails to acknowledge that the standard log-linear Cox Proportional Hazards (CPH) model (same model used by TCEQ, 2020a) is more parsimonious than the IRIS (EPA, 2016a) model. This is consistent with National Research Council guidance on “Models in Environmental regulatory Decision Making”, which states that the strategy to pick the “best model” for regulatory decision making should be “subject to a penalty function reflecting the number of model parameters, thus effectively forcing a trade-off between improving model fit by adding addition[al estimated] model parameters versus having a parsimonious description” (NRC, 2007, pp. 174). However, EPA IRIS and subsequent EPA’s response to public comments fail to point out that the one slope standard CPH model is more parsimonious than the 2-slope spline model selected by EPA IRIS.

Instead, EPA IRIS and subsequent ORD responses to public comments claim that EPA IRIS approach to statistics was reviewed and approved by EPA SAB (EPA, 2022). IRIS (EPA, 2016b, Appendix D.3.2. at p D-38) quoted the EPA SAB in justifying the statistical treatment in relation to the knot: “The knot is preselected and is not considered a parameter in these analyses, consistent with SAB’s concept of parsimony [footnote 14: “in some setting 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” [page 12 of SAB (2015)]]”. However, prior to fitting its two-piece spline model, EPA did not simply “fix” or “select” the position of the knot in that model “rather than estimating” its position, as specified by the SAB. Instead, IRIS tested 20 alternative knots for breast cancer and 70 knots for lymphoid mortality, and then among these, selected knot values that maximized the

likelihood of data fit to a corresponding 2-piece spline model. This is not what EPA SAB intended when they suggested that the knot could be “pre-selected” prior to spline-model fitting. More importantly, EPA ORD is inconsistently relying on the EPA SAB report when ORD (a) did not follow EPA SAB exact advice, (b) never mentions in any response to public comments the fact that TCEQ peer reviewers with statistical expertise conclude EPA IRIS statistical analysis is incorrect, and (c) overwhelming new evidence provided by EOTF in earlier comments that have been ignored by EPA ORD in response to comments.

As will be discussed in greater detail below, TCEQ utilized a superior objective statistical method to demonstrate that the fit at lower cumulative exposures is as good if not superior to that of EPA’s model. The method TCEQ utilized is very similar to the method EPA IRIS and EPA OPP relies on for estimating extra risk.

EPA’s inclusion of breast cancer incidence in the IRIS exposure-response model is inappropriate due to clear evidence of under-ascertainment in the NIOSH study

Breast cancer, like other types of cancers considered by EPA IRIS (2016a) from both animal and human studies, is a cancer endpoint that deserves consideration in the weight of evidence for cancer classification. However, the NIOSH breast cancer incidence data should not be used for quantitative risk assessment based on substantial under-ascertainment of incident cases reported by Steenland et al (2003) and subsequent risk deficits in the lower exposures.

There are two major reasons why breast cancer should not be included in EO quantitative exposure response analysis: 1) the evidence related to causation is weak and 2) under-ascertainment of incident cases due to non-participation in the interview study raises a serious potential selection bias.

Neither the NIOSH breast cancer incidence study (Steenland et al., 2003) nor the NIOSH mortality study (Steenland et al., 2004) report an overall excess of breast cancer. The positive NIOSH findings are not robust in that they are seen with a certain lag and exposure metric that are not evident with numerous other exposure metrics, models, or lags. The breast cancer incidence findings are at most suggestive, not only due to inconsistencies in the exposure-response, but also due to incomplete cancer ascertainment and the subsequent potential for bias. This disease endpoint is only weakly supported by other epidemiology studies and is inconsistent with others.

The IRIS breast cancer incidence analysis relied on data from the subpopulation of the NIOSH cohort that was interviewed, which required both locating subjects and identifying those

diagnosed with breast cancer. Of the 7,576 women in the NIOSH cohort, only 5,139 (68%) were included in the interview portion of the study. The percent non-response was of concern, according to the authors. The majority of these, 22%, could not be located and therefore any breast cancer diagnosis would have been missed. Steenland et al. (2003) indicated that cases lost are more likely to be shorter term (i.e., lower cumulative exposure) employees. Those who work longer (i.e., higher cumulative exposures) stay in the area longer and are more likely to get picked up in the state tumor registries and be found for interview. Shorter duration workers with lower cumulative exposures are more likely to leave the area and not be captured in the overall analyses and less likely to be interviewed. If more cases were missed among those with lower cumulative exposures (shorter term employees), then the data would be biased toward seeing a positive slope and/or elevated risk in the higher exposure groups, as reported by Steenland et al (2003).

Steenland et al. (2003) considered the subcohort of women who were interviewed to be “complete.” In other words, all the women who were interviewed were identified as having breast cancer or not. This, however, does not account for the missing cases among non-participants in the interview study or for cases never identified in the overall target population. Importantly, there is no way of knowing that the distribution of cases by level of exposure in the subcohort of interviewed breast cancer cases is comparable to the distribution in the fully ascertained total cohort. Due to the greater difficulty of locating women with short term employment, there is a high potential for bias in missing cases at lower cumulative exposure. Steenland et al. (2003) correctly indicates “there are possible biases due to patterns of non-response and cancer ascertainment which introduce additional uncertainties in the findings,” and concluded that the epidemiological evidence was only suggestive for breast cancer.

Steenland et al. (2003) made an attempt to investigate possible selection bias but noted he didn’t have adequate data to address this concern: “A second possible bias was the preferential ascertainment of breast cancer among women with stable residence in states with cancer registries; women with stable residency might be expected to have longer duration of employment in companies under study, and hence greater cumulative exposure. Unfortunately, we didn’t have residential history, limiting our ability to explore this possibility (Steenland et al., 2003).” Without the incidence data, selection bias cannot be properly tested. However, several issues support this explanation: 1) the overall population long-term (higher exposed) women would be easier to identify as having breast cancer as they remain for longer periods in states of employment that have tumor registries, 2) similarly, longer employed and higher cumulative exposure women would be easier to locate and thus interviewed, and 3) duration of employment in Steenland et al. (2003) showed a stronger relationship with breast cancer than did actual cumulative exposure.

Steenland et al. (2003) recognized this limitation as one reason he was tempered in his causation conclusions: “Our data suggest that ETO is associated with breast cancer, but a causal interpretation is weakened due to some inconsistencies in exposure-response trends and possible biases due to non-response and incomplete cancer ascertainment.”

In contrast, breast cancer mortality in the Steenland et al. (2004) study was fully ascertained, i.e. complete because of complete coverage of deaths in the U.S., as opposed to only partial coverage of cancer diagnosis. The study reported 103 cancer deaths and 103 expected, based on general population rates. Using CPH regression analyses, a positive trend was reported only with log cumulative exposure and a 20-year lag. Applying CPH in a categorical analysis with cumulative exposure and a 20 year lag resulted in a statistically significant excess only in the highest exposure group.

EOTF emphasizes that if human data are used, lymphoid mortality is the most appropriate endpoint for quantitative risk assessment because the weight-of-evidence for breast cancer is weak (discussed in detail in previous EOTF, 2021a, b comments). However, if EPA feels compelled to include breast cancer in the quantitative risk estimate, then breast cancer **mortality** is more appropriate for quantitative risk assessment purposes because breast cancer mortality is fully ascertained (e.g., no missing data) and is publicly accessible. As part of the IRIS analysis, EPA also used the breast cancer mortality data to estimate a cancer slope factor. For purposes of sensitivity analysis, EPA (2019) appropriately compared models without including the EPA’s age-dependent adjustment factor (ADAF). EPA IRIS (2016a, Table 4-11) reported the central and lower-bound unit risk estimates for the cancer slope factor to be 0.019¹² and 0.035¹³ per ppm, respectively, using a POD of 1/100¹⁴ extra risk (no ADAF factor added). This is in contrast to the application of the 2-piece spline model for the under-ascertained breast cancer incidence of 0.72¹⁵ and 1.5¹⁶ per ppm for the central estimate and upper bound (see also EPA IRIS 2016a, Table 4-15, not including ADAF). Further analysis will be needed to add the ADAF and to select the appropriate POD so that it is in the lower range of the experimental data before these cancer slope estimates can be applied for quantitative risk assessment purposes.

In summary, the weak association of EO with breast cancer and the exposure-response uncertainty due to the sizeable number of missing breast cancer cases precludes use of the NIOSH interview data in derivation of IURs. This, together with the unavailability of the breast

¹² EPA IRIS (2016a) Table 4-11 EC01(ppm) = 0.5305, not including ADAF

¹³ EPA IRIS (2016a) Table 4-11 LEC01 (ppm) = 0.285, not including ADAF

¹⁴ Note: EPA IRIS provided no justification for applying the POD of 1/100 extra risk. An appropriate POD should be selected to ensure it is appropriately in the lower range of the experimental data. TCEQ (2020a) demonstrated that the IRIS CPH POD of 1/100 extra risk is at the higher range of experimental data.

¹⁵ EPA IRIS (2016a) Table 4-15 EC01(ppm) = 0.0138, not including ADAF

¹⁶ EPA IRIS (2016a) Table 4-15 LEC01(ppm) = 0.00675, not including ADAF

cancer incidence data to other researchers to independently examine these issues raises quality issues that indicate the data are inappropriate for exposure-response modeling for regulatory cancer risk assessment purposes.

Consistency of EPA's IRIS URE With Other Evidence

Smokers are exposed to high levels of ethylene oxide but smoking is not associated with NHL

Cigarette smokers are exposed to high levels of EO (Kirman et al., 2021), yet smoking is not associated with NHL.

Tobacco smoking is a well-established carcinogenic factor in humans and has been strongly linked to many cancers, including cancers of the lung, larynx, mouth, esophagus, throat, bladder, kidney, liver, stomach, pancreas, colon and rectum, and cervix, as well as acute myeloid leukemia¹ by the International Agency for Research on Cancer (IARC, 2004), and part of the World Health Organization. However, studies evaluating the association between smoking and non-Hodgkin's lymphoma (NHL) have reported inconsistent results beginning in the 1970's and 80's, a trend that has continued during subsequent and more current studies (Sergentanis et al., 2013; Castillo and Dalia, 2012; Milani et al., 2008; Schöllkopf et al., 2005; Troy et al., 2010).

Smoking as a potential carcinogen for NHL has been evaluated by IARC during two monographs, in 2004 and again in 2012, with the most recent monograph evaluating the evidence of five additional studies that had been published since the 2004 monograph (IARC, 2004; 2012). However, the 2012 IARC committee came to the same conclusion that the data from these studies generally “fail to support an effect of smoking on the incidence of non-Hodgkin lymphoma” (IARC, 2004; 2012). They additionally observed that there may be a weak but positive association between smoking and follicular lymphoma, but importantly, no other histological types (IARC, 2004; 2012). In the United States, the lack of evidence is reflected by the National Cancer Institute at the National Institutes of Health, which fails to provide a statement supporting any association between smoking and risk of NHL, though tobacco is listed as a general risk factor for cancers previously identified by IARC monographs.

To our knowledge, there have been five peer-reviewed reviews, pooled analyses, and meta-analyses that have been conducted since the early 2000's on this topic (see Table 1). The results from the reviews that were identified have generally reported inconsistent results on the association between cigarette smoking and NHL, as results tend to vary by sex, definition of smoking, NHL subtype, and study type between studies (Sergentanis et al., 2013; Castillo and Dalia, 2012; Milani et al., 2008; Peach and Barnett, 2001; Morton et al., 2005). Two of these studies (Peach and Barnett, 2001; Morton et al., 2005) were previously reviewed by IARC monographs, described above (IARC, 2004; 2012). A 2001 review by Peach and Barnett evaluated seven cohort studies, nine population-based base-control studies, and five hospital-

Table 1. Summary of reviews considered describing the association between cigarette smoking and non-Hodgkin lymphoma

Publication (Author, Year)	Type of Publication	Total Studies Included	Cohort	Case-control	Pooled-Analysis	Review
Peach and Barnett, 2001	Review	19	5	14	0	0
Morton et al., 2005	Pooled-analysis	9	0	9	0	0
Milani et al., 2008	Meta-analysis	18	0	18	0	0
IARC, 2004	Review	8	6	1	0	1 ^b
IARC, 2012	Review	12	6	4	1 ^c	1 ^b
Castillo and Dalia, 2012	Meta-analysis	24	7	17	0	0
Sergentanis et al., 2013	Meta-analysis	39	9 ^d	30 ^e	0	0

^a Study inclusion periods for reviews presented here were cut-off prior to 2012.

^b Peach and Barnett, 2001

^c Morton et al., 2005

^d 1 of these cohort studies did not distinguish between non-Hodgkin lymphoma and Hodgkin lymphoma

^e 2 of these case-control studies did not distinguish between non-Hodgkin lymphoma and Hodgkin lymphoma

based case-control studies (Peach and Barnett, 2001). The majority of these studies found no association between either current or past smoking and risk of NHL, the exception being a reported association between current smoking and follicular lymphoma only, with no evidence of an exposure-response trend (Peach and Barnett, 2001). Less than half of the case-control studies reviewed by Peach and Barnett reported positive associations, though multiple limitations were noted, including lack of adjustment for multiple comparisons, loss of statistical significance after eliminating potential bias, not exploring features of causality, and only reporting a significant association among particular participant subgroups (heavy smokers, participants younger than 45 (Peach and Barnett, 2001). In 2005, the International Lymphoma Epidemiology Consortium (InterLymph) published a pooled analysis to clarify the relationship between cigarette smoking and NHL with the statistical power to consider NHL subtypes, by combining original patient data from nine case-control studies of NHL from the United States (n=5), Europe (n=3), and Australia (n=1) for a total study population of 15,486 participants (6,594 cases and 8,892 controls) (Morton et al., 2005). In this analysis, using joint fixed effects logistic regression models adjusted for study center, age, sex, and race, Morton et al. (2005) reported that ever smokers had a slightly elevated risk for NHL compared to non-smokers (odds ratio (OR) 1.07, 95% confidence interval (CI) 1.00-1.15). However, no similar significant associations were seen among current smokers or former smokers compared to non-smokers (Morton et al., 2005). In stratified analyses by disease subtype, the only subtype with consistently increased risk was follicular lymphoma. The study authors concluded that results only supported an association specific to follicular lymphoma (Morton et al., 2005).

Other meta-analyses have been conducted more recently examining the association between cigarette smoking and NHL (Sergentanis et al., 2013; Castillo and Dalia, 2012; Milani et al., 2008). A meta-analysis of 18 case-control studies was conducted in 2008, which found no increased risk for NHL among former smokers compared to never smokers (OR 1.02, 95% CI 0.92-1.12), though the degree of heterogeneity between studies may have influenced this finding ($p < 0.001$, $I^2 = 75.3\%$) (Milani et al., 2008). A small association, similar to what was observed by Morton et al. (2005) was observed for current smokers compared to never smokers (OR 1.06, 95% CI 1.00-1.14), though again, some degree of heterogeneity was observed ($p = 0.04$, $I^2 = 41.1\%$). A large 2013 meta-analysis of 50 observational studies (41 case-control and 9 cohort studies) reported a similarly small pooled effect estimate of risk of NHL among ever smokers compared to never smokers (1.05, 95% CI 1.00-1.09) (Sergentanis et al., 2013). However, the study authors noted that the associations between current smoking (pooled-effect estimate 1.03, 95% CI 0.6-1.11) and former smoking (pooled-effect estimate 1.01, 95% CI 0.97-1.05) and NHL risk were not statistically significant, and that significant publication bias ($p = 0.029$, Egger's test) likely influenced their results (Sergentanis et al., 2013). In contrast, a 2012 meta-analysis of 24 observational studies observed a higher risk of NHL among female current smokers (OR 1.40, 95% CI 1.14-1.73), however, this association was only seen among case-control studies and no increased risk of NHL was observed among men (Castillo and Dalia,

2012). There was no association observed between smoking and the most common NHL subtypes, including follicular lymphoma, with the exception of a statistical trend toward a higher incidence of T-cell lymphoma (Castillo and Dalia, 2012).

In conclusion, guidance published within the past approximately 20 years has been unable to publish a definitive statement supporting a link between cigarette smoking and an increased risk of NHL (IARC, 2004; 2012). A main contributor to this has been a lack of consistent evidence supporting a strong, causal relationship between cigarette smoking and NHL, as results from studies reviewed in meta-analyses, pooled analyses, and reviews have varied by sex, definition of smoking, NHL subtype, and study type. Given the current epidemiologic evidence and the observations by Morton et al (2005). of an increase in NHL incidence worldwide without a corresponding increase in cigarette smoking in developed countries, it seems unlikely that smoking has contributed substantially to any long-term increase in risk of NHL even though smokers have high EO exposure.

TCEQ considered this issue and conducted a plausibility analysis as a reality check. Assuming the IRIS URE, TCEQ estimated that the background incidence of lymphoid cancer for non-smokers would be 1.35% based on an estimate of endogenous exposures, which is about half of the background rate of 3% for lymphoid cancers. This would mean that, if the IRIS URE were accurate, about half of lymphoid cancers in non-smokers would be caused by EO, and more than 1% of the non-smoker population would, in their lifetime, get a lymphoid cancer from endogenous EO exposure. This is highly implausible. It is acknowledged that EPA is estimating extra risk from the epidemiologic data and that this technically applies to exposure beyond the endogenous range. However, it would be expected that the exposure-response in the endogenous range would be similar to exposures right above the endogenous range.

TCEQ estimated that, based on the IRIS URE, smokers would have a lymphoid cancer incidence of 13.3% based on HEV adduct data. EPA quibbles with this estimate in the response to the MON because it assumes a smoker that smokes throughout their adult lifetime (EPA, 2022). However, many smokers do smoke for their adult life. Villeneuve and Mao (1994) estimate a lifetime lung cancer risk for current smokers of 17% for males and 12% for females. It is highly unlikely that the EO risks for lymphoid cancers would rival that for lung cancer.

If only a 30-year smoker was assumed, the risk can be estimated based on a $39 \mu\text{g}/\text{m}^3$ equivalent air concentration for smoker (Kirman et al., 2021) and URE of 1.1×10^{-3} per $\mu\text{g}/\text{m}^3$ (excludes the early life susceptibility adjustment), which yields a lifetime risk of 1.6%. This value is significant compared to the lymphoid background rate of 3%. Given the large number of epidemiologic studies that have evaluated lymphoid cancers and smoking, it would be expected that there would be a signal for smokers if the IRIS URE were valid, but no such signal is seen. In contrast, the published literature does show an increased risk of acute myelogenous leukemia

(AML) among smokers (IARC 2012b). The average smoker is exposed to 1.8 mg/day of benzene, which is ten times that of non-smokers and benzene is a known cause of AML (ATSDR 2007).

Another large epidemiologic study finds no cancer risk associated with ethylene oxide and EPA inappropriately dismisses the study findings

EPA gives little credence of the Union Carbide Corporation (UCC) cohort of EO manufacturing workers with generally higher exposures than in the NIOSH study. The UCC study is very important to consider in the weight of evidence because it included long-term follow-up of workers from the 1940s, the infancy in EO production (Greenberg et al., 1990; Teta et al., 1993; Swaen et al., 2009). The absence of findings in the UCC cohort for male LH is not consistent with a steep slope at low concentrations and does not support the IRIS derivation of one of the highest inhalation unit risk levels ever developed by EPA. The UCC cohort of 2,174 workers was a subset of another NIOSH study of or more than 29,000 UCC chemical workers in the Kanawha Valley of West Virginia (Rinsky et al., 1988).

Compared to the NIOSH sterilizer worker mortality study, the UCC study has a smaller cohort sample size compared to the NIOSH sterilizer worker mortality study, but it has comparable numbers of lymphohematopoietic (LH) and lymphoid cancers as those reported in the male component of the NIOSH cohort (only males had elevated LH and lymphoid cancers).

Furthermore, the UCC study exposure assessment provides an improvement in quality to the NIOSH study because it employed individual exposure estimates for a substantial period between 1925-1988, utilizing the Greenberg et al. (1990) categorization of EO producing and using departments by level of exposure and quantitative estimates of average intensity by these categories developed by Teta et al. (1993). There were no potential confounders to other chemical exposures because such workers were removed from analysis by Teta et al. (1993), Swaen et al. (2009) and Valdez-Flores et al. (2010). Exposure data were available for study subjects at the West Virginia (WV) locations starting in 1974. Exposure data were also available from Union Carbide's Texas City plant that operated identically to the WV location from the early 1960s. Estimates from EO operations in the literature were used for the earliest time periods. As discussed in detail above, this represents an important advantage of the UCC study over the NIOSH study, which had no exposure data prior to 1978 (Bogen et al., 2019).

There were 12 NHL cases compared to 11.5 expected based on life tables giving an SMR of 104.7 that was not close to statistical significance.

The absence of elevated LH and lymphoid cancers in the UCC study (in both external and/or internal comparisons) calls into question the biological plausibility of the very high IRIS inhalation unit risk for LH cancers. It also calls into question EPA's risk estimates as high as 1 in 10 for sterilizer workers in current working conditions given there was no evidence of elevated cancer in a population of workers exposed to far greater levels.

Ethylene oxide is formed endogenously at substantial levels, and EPA's IRIS model implausibly predicts high risks even associated with natural endogenous levels

Endogenous production of EO results from the oxidation of ethylene resulting from (1) production of ethylene by bacteria normally present in the gastrointestinal tract, which is then absorbed into the body; and (2) systemic production of ethylene by specific precursors and by oxidative stress. These pathways are operable in all mammalian species, with measured EO biomarker levels (2-hydroxyethyl valine or HEV) generally being higher in laboratory rats and mice than in humans.

Endogenous exposures to EO are variable. These exposures vary from person to person (interindividual variation) and from day to day (temporal variation), and can be modulated by diet (e.g., fatty acid composition; diet content of precursors that are metabolized to ethylene), medications (e.g., antibiotics), and underlying conditions (e.g., oxidative stress).

Recently, OEHHA draft cancer inhalation unit for ethylene oxide (OEHHA, 2023) and EPA (2022) response to public comments on the MON raised questions about the reliability of the Kirman et al. (2021) method of estimating endogenous levels. These comments favored speculative uncertainty and tangential information over the toxicokinetic and converging evidence from animals and humans that was presented in detail by Kirman et al. (2021) and by data in Filser and Klein (2019). As discussed in detail by ACC's response to the draft OEHHA IUR, endogenous levels can greatly exceed the levels to which residents near sterilization facilities may be exposed (ACC, 2023). While EPA's potency estimate technically only applies to exposures above endogenous levels, it is questionable that a chemical would be a potent carcinogen at levels that the body produces through natural processes.

In addition to ACC's detailed comments to OEHHA, EOTF includes the following specific responses to the EPA (2022) response to public comments (EPA comments are in italics):

p. 63: "...*The unit risk estimates the EPA developed are for extra risk (i.e., above background); background and endogenous levels of EtO, which would be relevant to (the true) background risk, are not integral to the development of the estimates of extra risk.*"

p. 64: *“IRIS risk estimate for EtO represents the increased cancer risk due to exposure to EtO emissions – above any potential existing risks from endogenous or ambient background levels of EtO exposure”*

- While this statement is technically true, it is misleading. In the interest of sound science, EPA has an obligation to assess and communicate total exposure and risk from EO (including endogenous and background sources), as noted in CERCLA policy (EPA, 2002):

“In some cases, the same hazardous substance, pollutant, and contaminant associated with a release is also a background constituent. These constituents should be included in the risk assessment, particularly when their concentrations exceed risk-based concentrations. In cases where background levels are high or present health risks, this information may be important to the public. Background information is important to risk managers because the CERCLA program, generally, does not clean up to concentrations below natural or anthropogenic background levels.”

Furthermore, this statement applies to both the TCEQ and EPA models because both estimate extra risk, but the TCEQ model is more reasonably conservative.

Page 64: *“however, all study participants were also exposed to ambient background levels of EtO in the air, meaning the “endogenous equivalent” value is an approximation of exposure to endogenous plus ambient background levels of EtO.*

- This criticism of Kirman and Hays (2017) is outdated and misleading. Adjustments for ambient exposures has been addressed in Kirman et al. (2021) in which the exogenous pathway for EO in air was explicitly included in the estimates of endogenous exposures to EO.

Page 64: *“The occupational exposures in the NIOSH study represent workplace EtO levels these workers experienced – and are in addition to any endogenous or broad population background exposures to which the workers may also have been exposed. Similarly, the relative risk estimates for workers are made in comparison to risks to individuals in the absence of occupational exposure – but these reference individuals would also have exposure to population background and endogenous EtO. Thus, methodologically, the levels of endogenous exposures (and baseline population level risks that may result from these exposures) have been accounted for in the EtO IRIS dose-response assessment.”*

- This statement is incomplete. While it may be reasonable to assume that endogenous exposures to EO and ambient EO exposures to workers in the NIOSH cohort are

approximately the same as experienced by the current US population, this is not true for EO exposures from smoking which are expected to be an important contributor to background EO exposure. Specifically: 1) Smoking is an important source of EO exposure (Kirman and Hays, 2017; NHANES data); 2) Smoking and associated EO exposures were larger in the past (peaking in the 1950s-60s) than they are today; and 3) Smoking habits can differ between salaried and non-salaried workers (Hsu et al., 2019). For these reasons, smoking by NIOSH workers has the potential to confound EO exposure estimates (rather than confounders on health response measurements). This effect is not accounted for in the analysis of the NIOSH cohort data and the application of potency estimates to the current US population.

Page 64-67: *“Additionally, the analysis was based on measurements of an exposure biomarker but did not include any direct measurements of endogenous EtO levels.”*

“ACC does not reference any direct measurements of endogenous EtO levels”

“NHANES does not provide direct data on exposures to EtO.”

- These statements are misleading. HEV measurements, as collected by NHANES, are well accepted as an appropriate and specific biomarker of EO exposure (e.g., CDC refers HEV as “Ethylene Oxide Hemoglobin Adducts”. As noted in EPA’s IRIS document *“Formation of hemoglobin adducts has been used as a measure of exposure to EtO... Hemoglobin adducts are good general indicators of exposure because they are stable...”*. HEV measurements, which are stable and reflect cumulative exposures to EO, are a much better biomarker of EO exposure than any direct measurements of EO in blood. As such, “direct data” are not required to conclude with high confidence that exposure to EO has occurred.
- EPA’s ambient air monitoring data for EO do provide “direct data” on exogenous exposures to EO, and NHANES provides definitive data on total exposure to HEV.
- Indirect estimation of endogenous levels by subtracting exogenous contributions from total HEV burden (as performed in Kirman et al., 2021) is a scientifically sound approach.

Page 66: *“However, Kirman et al. (2021),⁷² which was funded by the ACC, as well as related publications by Lewis et al. (2022)⁷³ and Sheehan et al. (2021),⁷⁴ do not provide new information to substantiate the validity of proposed calculations of “endogenous equivalent air concentrations”.*

- This statement is factually incorrect. New data in Kirman et al. (2021), which significantly improve the assessment for calculating endogenous equivalents include the following:
 - NHANES HEV measurements made in >4,500 individuals (Table 1 of Kirman et al., 2021) are new data were not available in 2017. These new data replace pooled HEV data from control groups, and show that we underestimated total EO exposures to the U.S. population in Kirman and Hays (2017)
 - EPA’s measurements for EO in ambient air (Table 6 of Kirman et al., 2021) are new data that were not available in 2017. These new data replace an assumption that the exogenous pathway is negligible, and show that contributions to HEV are small (but not negligible), and for this reason we underestimated contributions from this pathway in Kirman and Hays (2017).
 - Kirman et al. (2021) indicated that “*datasets are also available for characterizing the relationship between occupational exposures to ethylene oxide in air and HEV level (Boogaard, Rocchi, and van Sittert 1999; Brugnone et al. 1986; Duus et al. 1989; Hagmar et al. 1991; Norpoth and Bolt 1995; Törnqvist et al. 1986a), and are generally consistent with the correlation defined in Equation (1), within a factor of approximately 2.*” Although these data are not new, their use to justify the linear relation between EO exposure and HEV is a new application. Use of the Filser and Klein’s (2018; Figure 5 below) along with the NHANES data as a function of cigarettes per day (see Figure 6 below) provide independent validation of the linear relationship used, and as such EPA should considered this relationship to be factually substantiated.
 - In light of EPA’s skeptical response on the endogenous pathway as characterized in Kirman and Hays (2017), we conducted an extensive review of the literature to characterize the underlying biochemical basis for HEV formation in preparing our follow-up paper (Kirman et al., 2021). These data help explain why HEV is readily detected in nearly all people and improves the biological plausibility of our assessment.

Figure 5. Hemoglobin adducts (HEV, nmol/g Hb) in workers exposed to EtO in air (from Filser and Klein, 2018).

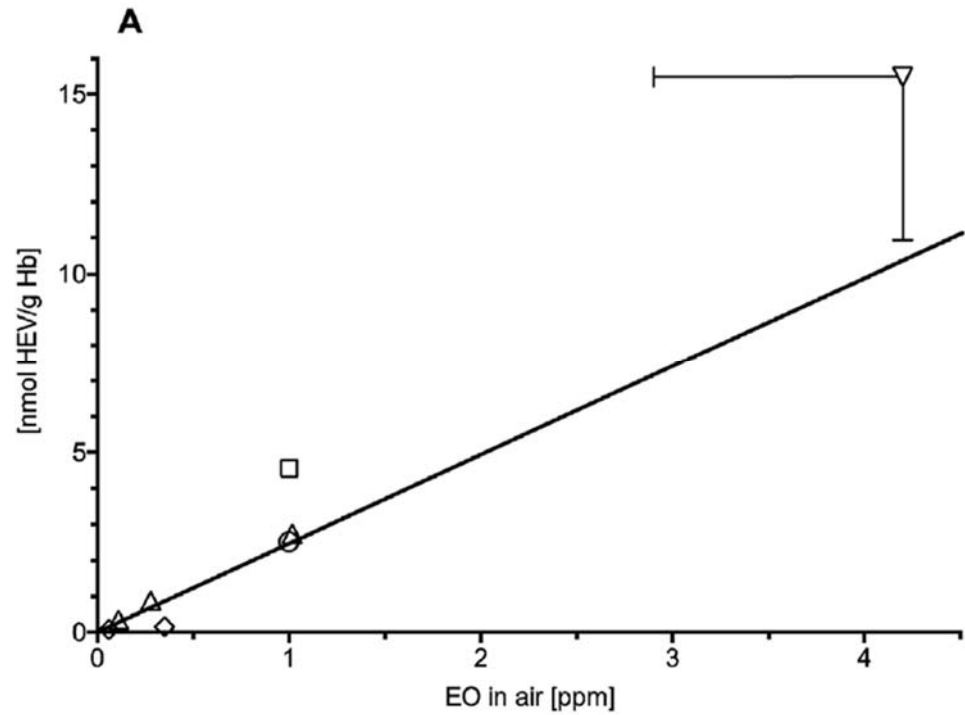
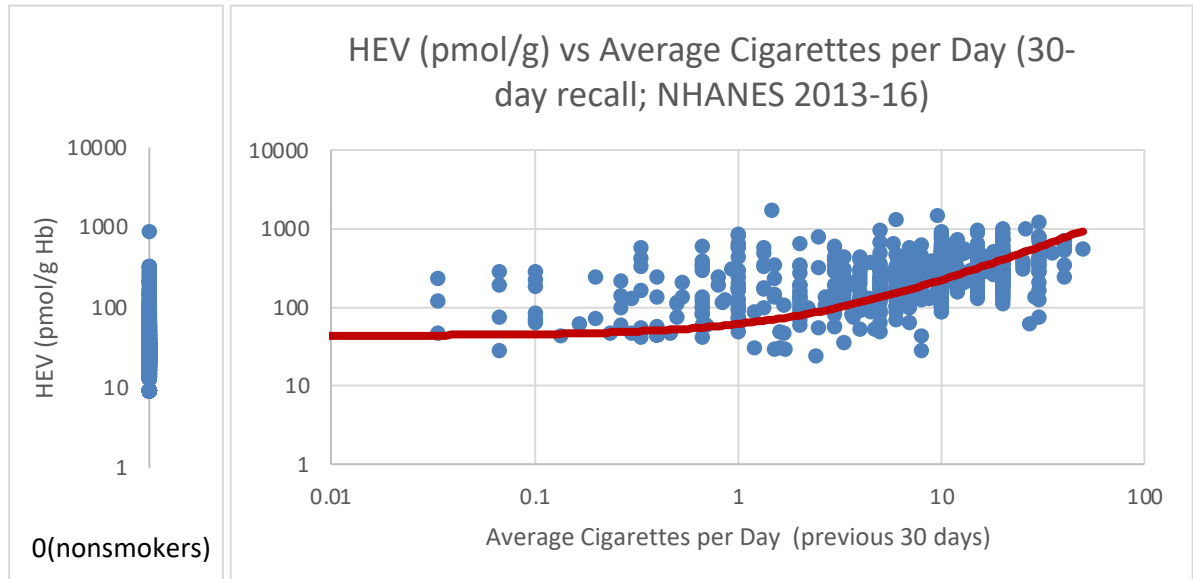


Figure 6. Hemoglobin adducts (HEV, pmol/g Hb) in U.S. smokers exposed to EtO in cigarette smoke (NHANES, 2013-16).



p. 66: *“However, Kirman et al. (2021) utilizes this result to infer that a specific amount of human endogenous EtO can be attributed to production by gut bacteria. EPA considers this inference that EPA considers to be highly speculative”*

- The biochemical pathways described in Kirman et al. (2021) for endogenous production are expected to be operational in ALL mammalian species.
- HEV levels are detectable in mice, rat, and humans at levels that cannot be explained by exogenous exposures, which only account for a small fraction of the measured adduct burden. Therefore, endogenous exposures to EO can be concluded with a high degree of confidence.
- Inferences from rodent studies are often made in human health risk assessment (e.g., absorption estimates based on rodent toxicokinetic studies; rodent tumors used to derive cancer potency estimates). There may be some uncertainty and variation with respect to the source of endogenous (GI lumen production vs systemic production), but this does not detract from the conclusions that both pathways are expected to be operable, and that endogenous production occurs in humans.

p. 66 *“a second investigation from the same laboratory using different dietary lipids (Kautiainen et al., 1991) provided little quantitative support for the hypothesis”*

- This statement is misleading. This study assessed a different oil (soya) compared to coconut oil, and did report a significant effect on HEV (when data were pooled together due to small sample sizes), albeit by a smaller amount than would be expected based on percent unsaturated fatty acid content of soya oil. This results of this study support the conclusion that dietary lipids can alter HEV burden.

p. 66: *“A more recent study (Paaradekooper et al, 2017) observed traces of ethylene exhaled by human volunteers administered an agent to induce an inflammatory response, which the authors attributed to peroxidation processes. However, in this experiment, both the baseline exhalation of ethylene and the increase attributed to the inflammatory agent were modest (roughly 0.5 ppb at baseline and a 0.5 ppb increase after treatment) - a finding that does not suggest a large source of endogenous exposure.”*

- This statement is misleading and incomplete. The low levels of endogenous ethylene production reported in this study are inconsistent with NHANES data, which should carry greater weight. In addition, there are other publications that address this topic that appear to report higher levels of ethylene in exhaled breath (e.g, Bratu, 2019; Cristescu et al. 2014; Popa et al., 2015). A more thorough review of available data on ethylene levels in exhaled breath is needed.

p.65-67: “...this calculation amounts to a major and unvalidated change in the interpretation of the industrial hygiene relationship which specifically correlated increases in adduct levels above background with substantial occupational exposures to EtO.”

”however the applicability of the assumed relationship for "equivalent" air concentrations from Kirman and Hayes (2017) is simply assumed to apply to the NHANES adduct data.”

“Kirman et al (2021) also apply their hypothesized relationship between adduct levels and equivalent air concentrations”

“However, EPA concludes that these calculations represent a hypothesis as applied to population background adduct levels. As explained above, EPA does not believe that these assumptions have been factually substantiated.”

- EPA’s repeated use of qualifiers “unvalidated”, “assumed”, and “hypothesized” is a misleading characterization of the weight of evidence that supports our assessment. EPA appears to question two aspects of this assessment: (1) the applicability of biomarker data from occupational exposures (generally collected at high EO concentrations) to the general population (considerably lower concentrations of EO), and (2) the linear relationship observed between measured HEV and EO in air. Use of occupational exposure data to make inferences for the general population is a common extrapolation (and ironically one that EPA has adopted to estimating cancer risk from EO in the general population using data from occupationally exposed workers). In Kirman and Hays (2017), we adopted the relationship as characterized by Germany’s DFG, which we considered a trusted, unbiased source to support our assessment.
- The linear correlation between HEV and EO in air relied upon in Kirman and Hays (2017) and Kirman et al. (2021) is scientifically sound based upon multiple, independent sources of validation:
 - Physiologically based pharmacokinetic (PBPK) models are widely considered to be the “gold standard” for extrapolating from high doses to low doses in human health risk assessment. The best available PBPK model for EO (Filser and Klein, 2018) predicts a linear relationship between EO exposures in air and HEV burden (solid black line shown in Figure 5 above).
 - From an empirical standpoint, the HEV data from exposed workers, as summarized by Filser and Klein (2018; individual markers in Figure 5 above) and cited in Kirman et al. (2021), are also consistent with a linear relationship. The available worker data depicted in this figure indicate that a linear relationship between HEV adducts and EO in air is at least maintained across a broad range of concentrations (~0.1 ppm to ~4 ppm).

- o For exposure levels below the range of worker exposures, the NHANES biomonitoring data in smokers and in non-smokers are also consistent with a linear relationship (Figure 6 above) depicted by redline; note - log-log scale which permits inspection of the data, but also distorts the shape of a linear relationship at low exposures) between EO exposure (using cigarettes per day as a metric) and HEV adduct formation:
- o These data, as shown in Figure 6, indicate that the linear relationship between EO exposure is maintained from background exposure levels up to 30x background levels. The linear relationship in this figure is also consistent with a linear relationship (e.g., assessed by multilinear regression analyses) for another EO biomarker (urinary 2-hydroxyethyl mercapturic acid) as reported by CDC scientists (Kenwood et al., 2021). Together, these data provide strong and convincing evidence to support a linear relationship between HEV and EO exposure as used in Kirman and Hays (2017) and Kirman et al. (2021).
- o Because the exogenous exposures to ET and EO can be characterized with a high degree of confidence based upon available air monitoring data, and because there is high confidence in the NHANES biomonitoring data for HEV as a measure of total exposure to EO, estimates of endogenous exposure to EO from these data can also be inferred with a high degree of confidence. There are no other known sources of EO exposure that could contribute to the HEV levels measured by CDC.

p. 68-9: *“As cigarette smoke contains many carcinogens, there is not a reason to expect, in advance, that EtO exposures to smokers would contribute a large part of total cancer risks due to cigarette smoking.”*

- This statement is incorrect. EPA’s large unit risk value for derived for EO serves as the reason for expecting EO contributes a large part of total leukemia risk due to smoking. EPA’s unit risk value for EO (3×10^{-3} per $\mu\text{g}/\text{m}^3$) is **two to three orders of magnitude higher** than the unit risk values derived by EPA for any other leukemogen present in tobacco smoke (e.g., benzene, 1,3-butadiene, formaldehyde).

p. 70: *“We have found that canister age, materials used to line the inside of the canisters, and how the canisters are cleaned before they are put into service, can cause results to be biased high.”*

- This statement serves to increase the importance of endogenous exposure to EO, for which EPA appears dismissive in other parts of the document. To the extent that EPA’s air sampling data is biased high, our estimates of endogenous exposures (as presented Kirman et al., 2021), which utilize EPA’s data to adjust for exogenous exposure contributions to HEV, would be underestimated. That is to say, endogenous production estimates may be

biased low as a result of relying upon EPA's air sampling, thereby increasing the relative importance of the endogenous pathway to total EO exposure.

p. 79: *"In the figures below, EPA provides graphs of observed dose-response shapes seen in animal inhalation cancer bioassays and in animal inhalation studies of mutagenesis and genotoxicity. For the cancer bioassay data, the graphs include a curve connecting responses for the lowest and highest dose response points. When intermediate data points line above this line it suggests a plateauing response. While when intermediate points fall below the line the graph suggests a upward curving response. If intermediate points fall on the line, the response is essentially linear. (Due to the property that these "quantile" tumor response data cannot exceed a probability of one, the basic "one-stage" linear hazard model is shown rather than a straight line.) The graphs for the mutation and genotoxicity studies can be similarly interpreted. (For these studies, a simple straight line is shown as do not have probabilities of effect approaching 1.) For both cancer bioassays and genotoxicity studies, these graphs include examples with concave-down (plateauing) shapes, examples with generally linear shapes, and examples showing upward curving patterns. The number of examples showing concave-down, plateauing, response shapes indicates that collectively these experimental cancer and mechanistic data are not consistent with claims from some commenters that such dose-response shapes are biologically implausible for EtO."*

- This statement is misleading. EPA is conflating dose-response plateaus at high concentrations in rodents with proposed plateaus at range of low concentrations (*e.g.*, a knot at 100 ppm-days can result from 100 days exposure to 1 ppm or from 10,000 days exposure to 0.01 ppm) that correspond to the knots assumed for cumulative exposure in their spline analysis. This conflation is not transparent due to different units used in rodents (ppm) and epidemiology (ppm-days) data sets. There is no evidence of low-concentration plateaus in the animal data sets.

Biological Plausibility of IRIS Value

As described in great detail in our previous comments, the epidemiological evidence and biological evidence is more consistent with the TCEQ model than the IRIS model. These comments build on earlier comments and more directly address recent EPA (2022) responses to public comments on the MON. Our earlier comments indicate that the EPA IRIS emphasis on statistical and visual fit is flawed and cannot be used as a basis for selecting between the TCEQ and IRIS model. Thus, biological plausibility is of paramount importance.

While the IRIS assessment includes summaries of the genotoxicity, toxicology, epidemiology and toxicokinetics, there is virtually no integration of these important lines of evidence into the final quantitative risk assessment process. On one hand, EPA states that their evidence integration to inform MOA for hazard assessment was adequate and appropriate. On the other hand, the agency argues that “not enough is known about the MOA to use evidence integration to inform the shape of a dose-response model representing cumulative lifetime human exposure..”. These contradictory positions precluded the integration of valuable information on biological plausibility into risk assessment. Instead, the IRIS exposure-response assessment is driven by exhaustive statistical modeling. The EPA (2005) carcinogen risk assessment guidelines captures the general issue of applying multiple curve-fitting models based on statistical modeling approaches that applies to the EPA IRIS (2016a) assessment for EO:

“Another problem occurs when a multitude of alternatives are presented without sufficient context to make a reasoned judgment about the alternatives. This form of model uncertainty reflects primarily the availability of different computer models and not biological information about the agent being assessed or about carcinogenesis in general. In cases where curve-fitting models are used because the data are not adequate to support a toxicodynamic model, there generally would be no biological basis to choose among alternative curve-fitting models. However, in situations where there are alternative models with significant biological support, the decisionmaker can be informed by the presentation of these alternatives along with their strengths and uncertainties.”

Similarly, the EPA SAB (2015) emphasized that “any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data.” Thus, the epidemiological weight of evidence should play a very important role in the consideration of the model selection. The absence of findings in the UCC study at any exposure, and absence of statistically significant findings at lower exposures

in males in the NIOSH study are more consistent with a standard CPH model than an extremely steep initial exposure-response slope.

In the most recent EPA (2022) response to public comments regarding this lack of consideration of the biological evidence in the dose-response assessment, EPA conducts a highly subjective visual inspection of genotoxicity and cancer bioassay data to support their claim that the biological evidence cannot be used to inform biological plausibility. The EPA (2022) evaluation involved (a) plotting the data as point estimates without error bars, (b) drawing a straight line between the response levels for the lowest and highest dose levels, and (c) declaring the dose-response to be supralinear or sublinear depending on whether the responses for the mid-dose levels visually appeared to be above or below the line. This visual inspection did not involve any consideration of statistical significance or evaluation of which data set and dose regimen is most relevant and useful to inform epidemiology data based on cumulative exposures. In their response to public comments, EPA opined that the dose-response information obtained from animal genotoxicity and carcinogenicity studies would not allow selection of dose response models for human risk assessment for EO. This position seems to be at odds with the agency's 2005 carcinogen risk assessment guidelines stating that "[i]f dose-response analysis of nontumor key events is more informative about the carcinogenic process for an agent, it can be used in lieu of, or in conjunction with, tumor incidence analysis for the overall dose-response assessment." Except for studies investigating sister chromatid exchanges (SCE), which are no longer considered as reflective of investigating genetic damage (Wilson and Thompson, 2007), the dose response information for other genotoxicity endpoints from animal studies should be considered in the selection of the model for EO risk assessment.

The putative genotoxic mode of action and toxicokinetic data should be a major consideration when selecting a model for risk assessment

While there is clear evidence that EO is genotoxic and carcinogenic, this does not necessarily mean that EO is acting through a genotoxic MoA for its carcinogenicity. Currently, this MoA should be considered as a default assumption in the absence of a convincing alternate MoA that does not involve genotoxicity as the initial key event. The dose-response and temporality of EO induced genotoxicity in the etiology of either animal or human tumors has not been fully vetted through a formal process such as the one recommended by International Program on Chemical Safety (Boobis et al., 2006).

For a direct acting alkylating agent such as EO, the default dose-response for the induction of mutations is linear. This is the worst-case scenario since at low doses closer to the origin, one should expect cellular protective mechanisms (e.g., detoxification and DNA repair) to offer protection, resulting in a shallower slope in this region when compared to higher doses. Based

on a presumed genotoxic MoA, both TCEQ and EPA/OEEHA estimate cancer risk based on a linear extrapolation from the POD to the origin but apply very different statistical models to the same epidemiological study to derive the POD, i.e., Cox proportional hazards (CPH) model by TCEQ vs. the two-piece spline model by the EPA/OEEHA. In the 2-two-piece spline model, the initial slope rises rapidly at lower exposure levels and then rises more gradually for higher exposures. This type of dose-response is not consistent with the biology of how EO works as a direct acting genotoxicant as evidenced from studies conducted in rodents. In their response to public comments, the EPA (2022) states that “EPA does not agree that observed dose response pattern at high dose in rodent genotoxicity or carcinogenicity studies will generally be predictive of dose-response patterns in humans.” While it is true that the dose-response observed at high doses in rodent studies often overestimate the hazard potential at low, environmentally relevant exposures, they seldom underestimate the hazard at the lower exposure levels for a vast majority of chemicals and most certainly for direct acting (i.e., those that do not require metabolic activation) DNA-reactive agents. Secondly, even in those so-called high dose studies, there are often lower dose levels with no detectable effects supporting the argument that the slope at the lower end of the dose-response cannot be steeper than at the higher doses.

The dose-response curves for EO-induced gene mutations in the bone marrow (Recio et al., 2004, Figure 7) and lung (Manjanatha et al., 2017, Figure 8) tissues of transgenic Big Blue mice illustrate the above point. These two tissues are selected to illustrate the dose-response since they represent targets for EO-induced tumors. In both cases, there is no evidence for a steeper initial slope at the low end. In fact, the mutant frequency at 25 and 50 ppm EO was not statistically different from the concurrent negative control group in Recio et al. study whereas only the 200 ppm, but not 100 ppm, was significantly elevated from the control in the Manjanatha et al. study. and the dose-response pattern is more consistent with the CPH model than the 2-piece spline.

Figure 7. Dose-Response for EO-Induced *lacI* mutations in Mouse Bone Marrow (6 h/day; 5days/week; 48 weeks from Recio et al., 2004)

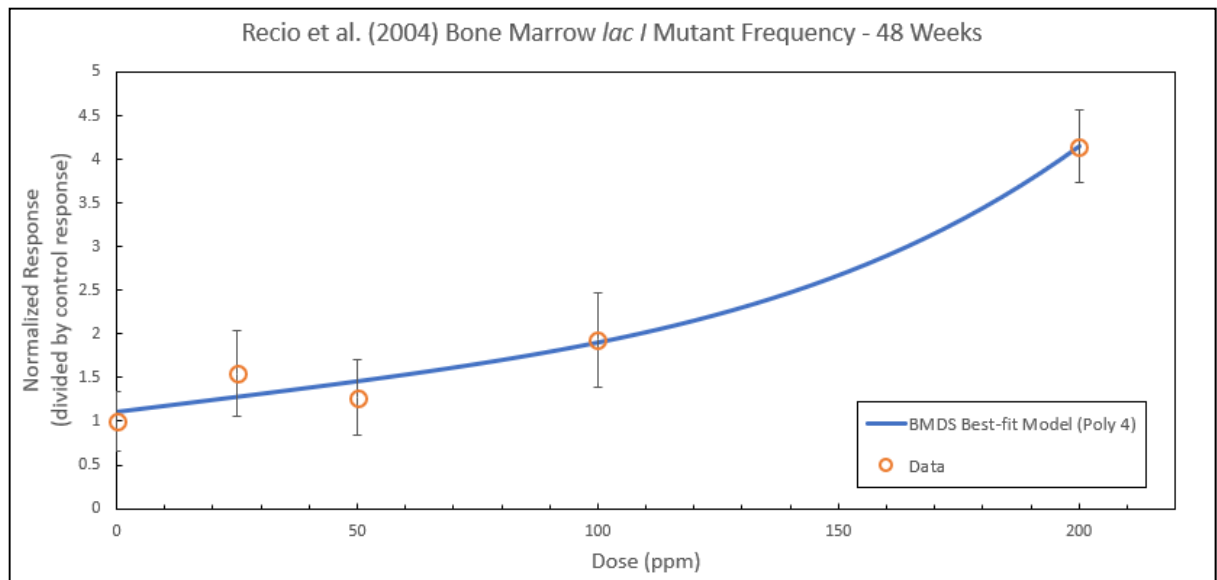
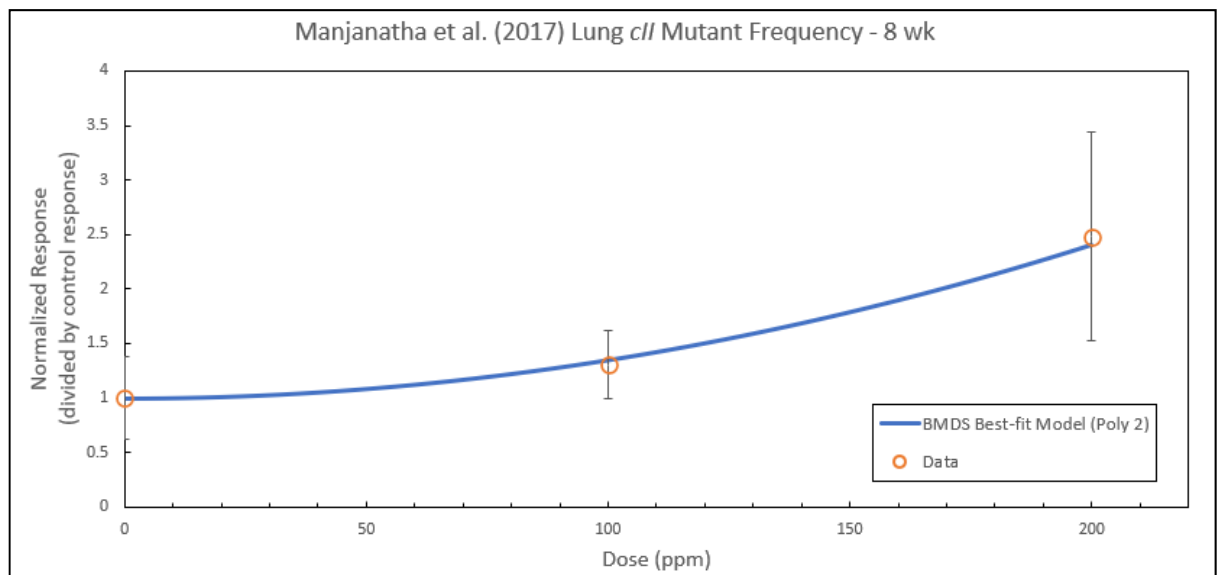
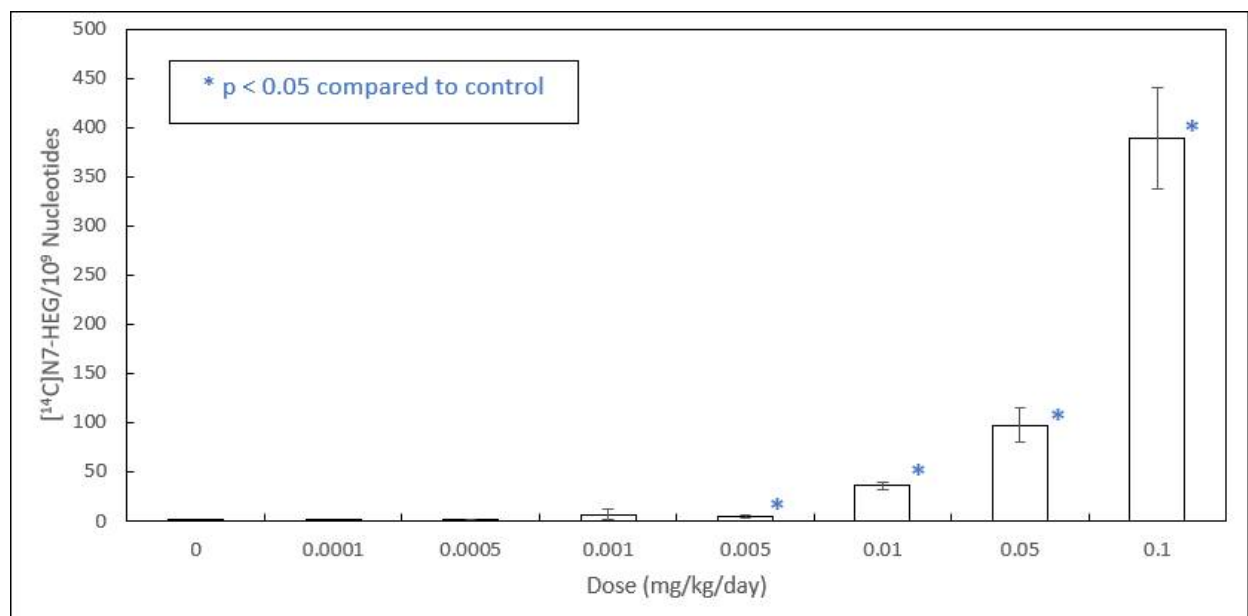


Figure 8. Dose-response for the Induction of *cII* mutations in the lung tissue of Big Blue B6C3F1 transgenic mice at 8 weeks of inhalation exposure to EO (Manjanatha et al., 2017).



The above dose-response patterns are fully consistent with the molecular initiating event(s) leading to EO-induced mutagenicity, i.e., the formation for DNA adducts (Marsden et al., 2009). Marsden et al. have shown that significant increases in N7-(2-hydroxyethyl)guanine (N7-HEG) adducts in the livers of rats treated i.p. with EtO were observed at the four higher i.p. doses, but not at the three lower doses (Fig. 9). This study using a wide range of dose levels provides no evidence for a steeper dose response at the lower dose levels. The likelihood of such a steeper response at dose levels below the range investigated is virtually zero.

Figure 9. Dose-response for exogenously derived DNA adducts in liver of [¹⁴C]EO-treated rats measured by LC-MS/MS (Marsden et al., 2009).



EPA (2022) makes the following three statements in their response to public comments with regards to DNA adduct studies:

1. “...much of the DNA adduct measurement studies evaluated by EPA were based on intermediate exposure durations (e.g., ≤ 4 weeks), which may not be informative of cumulative lifetime human exposures...”
2. “... Marsden et al. (2009) did not evaluate the effect of EtO exposure on DNA repair pathway activity, meaning the hypothesized repair at lower doses that is overwhelmed at higher doses was not confirmed...”
3. “...DNA adducts may not be the sole source of EtO-induced carcinogenesis...”

EPA's concern that adducts data derived from studies with ≤ 4 weeks of EO exposure duration might not be informative of cumulative lifetime human exposure seems to be speculative since no literature citation(s) were provided to substantiate their concern. Generally, the adducts are expected to reach a steady state, the duration of which is dependent upon the adduct type and the tissue in question. For example, the N7-HEG adduct has been shown to reach a steady state in 7-10 days whereas other adducts take a longer exposure duration (Pottenger et al., 2019).

With regards to the second statement, it is not clear why not having DNA repair data would change the fact that there was no significant increase in DNA adducts at lower doses in Marsden et al. study. Although DNA repair is one plausible explanation, other cellular protective mechanisms such as protein binding, GSH conjugation etc. also play a role in protecting DNA from EO-induced adducts. The most important take away from Marsden et al study is that the adducts levels induced at lower exposures of EO are negligible and not what would have been predicted by the 2-piece spline model. Although the N7-HEG adducts measured by Marsden et al. are not considered mutagenic, they are the most abundant DNA adducts formed following EO exposure (Walker et al., 1992). Thus, the shape of the dose-response curve for the N7-HEG adduct can be considered as the worst-case scenario for EO-induced adducts, including the most mutagenic O⁶-HEG adduct whose abundance is approximately 300 times lower than that of the N7-HEG adduct (Walker et al., 1992). In reality, the slope for the mutagenic O⁶-HEG adducts is expected to be much shallower than that for N7-HEG because of the kinetics of their formation and repair (Swenberg et al., 2008).

EPA's statement that the adducts not being the sole source of EO-induced carcinogenesis is accurate only in so far as the complex carcinogenic process is concerned. DNA adducts are biomarkers of exposure of the critical target and are not biomarkers of effect. However, for a direct acting alkylating agent such as EO that is considered to act through a mutagenic MoA for its carcinogenic property, DNA adduction represents the molecular initiating event whose dose response is informative of the subsequent events that follow depending upon the nature of the adduct, e.g., mutagenicity and carcinogenicity.

In conclusion, EO is a weak genotoxic chemical and requires relatively high and prolonged exposures to induce mutagenicity. The experimentally observed dose-response patterns for mutagenicity/carcinogenicity show that the CPH model is biologically more plausible than the IRIS (EPA, 2016a) 2-slope model. On the contrary, there is little support for a steeper initial slope in EO dose-response for the key events (DNA adduction and genotoxicity) in the cancer MOA. Accordingly, the CPH model should be the model of choice for risk assessment purposes especially if an alternate model is not a better fit to the observed data.

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Attachment 3

American Chemistry Council's Comments to OEHHA on the Draft Cancer Inhalation Unit Risk Factor (IUR) for Ethylene Oxide



June 14, 2023

Submitted via Email: Kannan.krishnan@oehha.ca.gov

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1001 I Street, 12th Floor
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Re: ACC Comments on Draft Cancer Inhalation Unit Risk Factor (IUR) for Ethylene Oxide

Dear Dr. Krishnan,

The Ethylene Oxide Panel (EO Panel) of the American Chemistry Council appreciates the opportunity to provide comments on the OEHHA's proposed Cancer Inhalation Unit Risk Factor for ethylene oxide (EtO) and its accompanying Draft Technical Support Document (Draft IUR). The EO Panel includes the major producers and users of EO in North America.

The Draft OEHHA IUR adopts the US EPA IUR and rejects the TCEQ IUR. We urge OEHHA to reconsider this decision and, at a minimum, to revise the Draft IUR Technical Support Document to address errors and other issues impacting the dose-response assessment of the NIOSH lymphoid mortality and breast cancer incidence data.

EPA's selection of the final IRIS model was based on a questionable statistical analysis and assessment of visual fit in relation to the categorical (grouped) model estimates. Unfortunately, the Draft IUR's acceptance of EPA's EtO IRIS 2016 methodology and assumptions results in the same errors and flaws leading to an implausible IUR and Residual Risk Specific Concentration (RSC). While OEHHA admirably attempts to conduct an "independent" evaluation of bias in EPA's model and the NIOSH epidemiological data, their efforts are based on assumptions in the absence of access to the actual data being considered and repeats EPA's faulty reasoning.

As OEHHA correctly points out, the IRIS IUR is based on both lymphoid mortality and breast cancer incidence from the study by the National Institute of Occupational Safety and Health (NIOSH), whereas the TCEQ IUR is based on lymphoid mortality alone. As discussed in our

detailed comments, the unavailability and incomplete ascertainment of the breast cancer data precludes the use of the NIOSH breast cancer data for quantitative risk assessment purposes. The weaker evidence of causation for breast cancer in the epidemiology studies further supports focus on lymphoid cancers from the NIOSH study. However, the major reasons for the large difference in magnitude between the two IURs are (a) the type of exposure-response model used to fit the epidemiologic data and (b) the interpretation and value of information in related epidemiological and biological evidence to inform the selection of the model.

The Description of the NIOSH and Union Carbide Corporation (UCC) cohort studies need to be corrected

The epidemiological evidence indicates that the NIOSH and Union Carbide Corporation (UCC) EtO Cohort studies are comparable in terms of the number of lymphoid cases (an important factor to consider in the power of the study) and the exposure assessment. While we do not dispute the use of just the NIOSH study to derive the IUR for EtO, the Draft IUR description of the strength and weaknesses of these two studies should be corrected so that both of the studies can inform the selection of the exposure-response model.

Specifically, the Draft IUR should be corrected to limit the description of the NIOSH study exposure assessment as “high quality” and “validated” to apply only to the narrow exposure period after 1978 when data were available to validate the exposure regression model. Prior to 1978, there was very limited or no exposure data available. Furthermore, the model validated after 1978 was altered for years prior to 1978 by holding a key variable “calendar year” fixed at the predicted level in 1978. This calendar year variable is described by the authors of the NIOSH exposure model to be a “surrogate for improvement in work practices.” By holding the variable calendar year fixed prior to 1978, the NIOSH exposure model estimates lower exposure in earlier years compared to 1978. No effort was made by the NIOSH authors to independently validate this substantial adjustment to the model prior to 1978.

Bogen et al (2019) addressed this limitation by finding many sources of new information including but not limited to interviews with sterilizer operators and managers. Independent of any modeling effort, Bogen et al (2019) cited several references from the 1950’s -70’s which provided clear evidence that there were changes in work practices prior to 1978 that did not support holding the variable calendar year fixed prior to 1978. Ironically, the draft IUR dismisses the Bogen et al (2019) model showing the opposite but more plausible trend for historical exposures (e.g., higher exposures in earlier years) because “*the authors were unable to validate their pre-1978 predictions since no actual worker measurement were available from that time*”, and thus, “*the accuracy of the Bogen et al. (2019) assessment is unknown to OEHHA.*”

By the same reasoning, OEHHA should also conclude that the accuracy of the NIOSH model prior to 1978 is unknown, and OEHHA should indicate that the data NIOSH used to develop the model are no longer available (lost) (EPA IRIS, 2016, Appendix H, p H-28).

In contrast, the UCC exposure estimates are superior in quality to the NIOSH exposure estimates because exposure data for the most recent periods, 1957-1973 and 1974-1988, were available for more than 75% of the cohort based on routine monitoring, personal sampling and a plant wide survey in another UCC plant using the same process (Greenberg et al., 1990; Teta et al., 1993; Swaen et al., 2009). Accordingly, at a minimum the NIOSH study needs to be downgraded with respect to these earlier exposure periods and the UCC study needs to be more fully integrated.

These corrections are necessary for a more balanced consideration by OEHHHA of both the NIOSH and UCC studies in selecting the most appropriate exposure-response model. The evidence from both of these studies, individually and combined, do not support selection of a 2-slope exposure-response model with a very steep initial slope. The log-linear exposure-response model is far more consistent with the weight of evidence from the NIOSH and UCC studies as described in greater detail in this submission.

Biological and epidemiological evidence should play a primary role in selecting the exposure-response model

The dose-response model used by IRIS (2016) for both breast cancer and lymphoid is a “supralinear”¹ two-slope linear spline model (2-slope model), suggesting that risk increases sharply at low exposures and less steeply at higher cumulative exposures above 1600 ppm-days for lymphoid cancer and 5750 ppm-days for breast cancer incidence. In contrast, the dose-response model used by TCEQ (2020a) is the standard² log-linear Cox Proportional Hazards (CPH) model, which is virtually linear at relevant exposure concentrations for estimating cancer risk for the general population³.

The steep initial slope of the USEPA IRIS (2016) supralinear two-slope spline model, which gives rise to one of the highest inhalation cancer potency estimates derived by IRIS, is not justified based on the relatively weak epidemiological findings reported in the original NIOSH peer-reviewed publications, the weight of evidence in the epidemiological literature including the UCC cohort, and the biological evidence in cancer bioassays and analysis of genotoxicity data.

Our comments provide evidence that the TCEQ model is more consistent with epidemiological evidence and has greater biological plausibility than the IRIS model. While the IRIS assessment includes summaries of genotoxicity, toxicology, epidemiology and toxicokinetics, there is no integration of these important lines of evidence into the final quantitative risk assessment process. Instead, the IRIS dose response assessment is driven by exhaustive statistical modeling analyses divorced from consideration of dose-response concordance with genotoxicity,

¹ EPA IRIS uses the term “supralinear” to describe the exposure-response relationship. Ironically, EPA (2022) attributes “supralinear” to ACC as if this is not an appropriate description.

² EPA (2022) attributes the term “standard” to ACC to describe the CPH model TCEQ uses, yet this is the correct term EPA IRIS (2016) uses to describe the log-linear CPH model

³ EPA (2022) correctly acknowledges on p.57 that “the log linear Cox model is essentially linear in the low dose range”.

toxicology and epidemiological weight-of-evidence. Similarly, OEHHA makes no attempt to integrate the different lines of evidence to inform selection of the dose-response.

The EPA (2005) carcinogen risk assessment guidelines states:

“Another problem occurs when a multitude of alternatives are presented without sufficient context to make a reasoned judgment about the alternatives. This form of model uncertainty reflects primarily the availability of different computer models and not biological information about the agent being assessed or about carcinogenesis in general. In cases where curve-fitting models are used because the data are not adequate to support a toxicodynamic model, there generally would be no biological basis to choose among alternative curve-fitting models. However, in situations where there are alternative models with significant biological support, the decisionmaker can be informed by the presentation of these alternatives along with their strengths and uncertainties.”

Similarly, the EPA SAB (2015) emphasized that “any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data.” Thus, the epidemiological weight of evidence should play a very important role in the consideration of the model selection. The absence of findings in the UCC study at any exposure, and absence of statistically significant findings at lower exposures in males in the NIOSH study are more consistent with a standard CPH model than an extremely steep initial exposure-response slope.

In the most recent EPA (2022) response to public comments regarding this lack of consideration of the biological evidence in the dose-response assessment, EPA conducts a highly subjective visual inspection of genotoxicity and cancer bioassay data to support its claim that the biological evidence cannot be used to inform biological plausibility. The EPA (2022) evaluation involved (a) plotting the data as point estimates without error bars, (b) drawing a straight line between the response levels for the lowest and highest dose levels and (c) declaring the dose-response to be supralinear or sublinear depending on whether the responses for the mid-dose levels visually appeared to be above or below the line. This visual inspection did not involve any consideration of statistical significance or evaluation of which data set and dose regimen is most relevant and useful to inform epidemiology data based on cumulative exposures. Our comments explain why a single slope CPH model linear at lower exposures that gradually increases at higher exposure is more consistent with the epidemiological, toxicological, and genotoxicity evidence compared to a 2-slope model with a very steep initial slope leading to derivation of one of the highest EPA IRIS IURs.

The Proposed NSRL model selection criteria is based on flawed statistics and visual fit analysis

The Draft IUR reiterates the EPA IRIS (2016) rationale for selecting the 2-slope model based on statistical and visual fit, without considering important new information that was available in the final TCEQ (2020a) DSD and in TCEQ (2020b) response to comments. For example, ***OEHHA reports a p-value of 0.01 for EPA’s 2-slope model for breast cancer, suggesting that OEHHA is unaware that statistics literature as well as independent peer reviewers of the TCEQ Development Support Document (DSD) with strong statistical backgrounds agreed with TCEQ that the p-values for the 2-piece spline models were incorrectly calculated.*** The corrected p-values are summarized in Table 1 and indicate that there is no statistical basis to select the 2-slope model over the CPH model. Our comments provide ample evidence for why OEHHA’s Draft TSD should report corrected p-values for lymphoid mortality and breast cancer incidence. Table 1. Corrected p-values for IRIS 2-slope linear spline and IRIS standard CPH model

	EPA IRIS (corrected) 2-slope linear spline	EPA IRIS Standard CPH Model
Lymphoid Mortality	P=0.14 corrected from 0.07	P=0.22
Breast Cancer Incidence	P=0.04 corrected from 0.01	P=0.02

Source: Corrected and IRIS reported p-values are based on IRIS (2016; Tables 4-2, 4-4, 4-6, 4-12, 4-13, Appendix D) and Final TCEQ DSD (2020a).

The draft OEHHA IUR includes mistakes with visual fit comparisons made in the IRIS (2016) assessment by stating the following:

“Other models, including the log-linear models (e.g., Cox regression) and the models using categorical data or exposure transformation, generally resulted in slopes that appear to dramatically over- or under-predict the actual study results, especially in the lower-exposure ranges.”

OEHHA makes two errors in this statement:

First, OEHHA incorrectly equates the “actual study results” for lymphoid cancers with the 5 categorical modeled estimates which appear as filled purple dots in IRIS Figure 4-3 and the draft OEHHA IUR Figure 6 with the first “dot” at the origin representing the lagged-out group considered to have zero exposures. Categorical rate ratios (RR) are calculated with respect to a baseline background hazard rate that is also estimated non-parametrically (i.e. not estimated by the CPH procedure). For the continuous models, the actual data modeled are the individual hazard rates not represented graphically in EPA IRIS figures. For example, for lymphoid cancers, there are 53 individual hazard rates-

each reflecting comparisons between one lymphoid mortality case against a risk set of “control” workers defined as those who survived to at least the age of the index case⁴.

The risk set of “control” workers includes both exposed and unexposed workers and is different for each of the 53 lymphoid mortality cases. These “control” risk sets are different from the underlying background hazard rate implied by the nonparametric relative rate (or rate ratios; RR) represented by EPA IRIS as the first categorical purple “dot” at the origin. The true (or implicit) y-intercept (or baseline hazard rate at cumulative exposures) for each continuous model applied to the 53 individual hazard rates will be normalized to 1 at zero lagged exposure⁵. The higher the implicitly modeled y-intercept, the lower the graph will appear on a graph of RR.

Second, OEHHA makes the mistake of assessing whether various models underestimate or overestimate the “actual study results” by making subjective comparisons along the y-axis in direct contradiction to the warning note EPA IRIS and OEHHA included in the figure legends: *“Note that, with the exception of the categorical results, the various 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).”*⁶ In other words, it is impossible to make conclusions about over- or under- predicting the actual study results even if one were to incorrectly define the “actual data” as the 5 categorical RR estimates. As explained above, this is because the baseline background hazard rates implied by the nonparametric (categorical) RRs and the underlying background hazard rates implied by the parametric models are generally different, but when graphed as RR values are all normalized to 1 making it impossible to make any conclusions about under- or over-estimations.

Valdez-Flores and Sielken (2013) and TCEQ (2020a) explain in greater detail why OEHHA’s and EPA IRIS’s visual fit approaches are inappropriate because it cannot be assumed that summary RRs describe the true underlying exposure–response relationship for the continuous models. The SAB 2007 implied the same recommendation against visual fit when it instructed EPA to use the individual data to fit the dose-response models. The SAB 2007 concluded “The Panel was unanimous in its recommendation that the EPA develop its risk models based on direct analysis of the individual exposure and cancer outcome data for the NIOSH cohort **rather than the approach based on grouped data** that is presently used.”[emphasis added].

⁴ See IRIS (2016) Appendix D p. D-3, D-69. Note that EPA relied on Steenland et al. 2004 assumption that 100 randomly picked “controls” from the risk set is representative of the full risk set. In contrast, TCEQ (2020a, p. 51) more accurately utilized the full risk set each possibly having more than 17,000 individuals in the risk set for each case.

⁵ Allison (2010), a practical guide to survival analysis using SAS, explains that the intercept is part of the arbitrary function of time, which drops out of the estimating equations”.

⁶ IRIS (2016) Figures 4-2, 4-3, 4-4, 4-5, 4-6, 4-7, 4-9 for lymphoid and breast cancers

The OEHHA Proposed NSRL should reconsider TCEQ’s objective method for assessing model fit based on theoretical concerns that were addressed, instead of relying on incorrect statistical and visual fit methods

Compared to the IRIS and OEHHA visual “eyeballing” comparisons using graphs that are not fit for this purpose, TCEQ (2020a) provided a more objective method to check how well each of the two models (i.e., the standard CPH model⁷ and the 2-piece spline model⁸) applied to general population background cancer rates predicted the number of lymphoid cancer deaths (the key cancer endpoint) that were actually observed in the NIOSH cohort. Table 2 compares the number of lymphoid cancer deaths that were observed in the NIOSH cohort versus the predictions by the IRIS and TCEQ models. In this model ground-truthing exercise, the TCEQ model was not only able to better predict the actual total number of lymphoid cancers in the NIOSH cohort but also the number of cancers in Quintile 2,⁹ demonstrating superior global and local fit below the knot. This approach used to predict cancer deaths from the model is essentially the same well-accepted approach IRIS (2016, Section 4.7) used to estimate extra risk for various occupational exposure levels by applying the IRIS model to the general population background cancer rates in the life-table program.

Table 2. Comparison of observed versus predicted number of lymphoid cancer deaths in NIOSH study using IRIS and TCEQ models

	Observed	Predicted (95% CI)	
		2-piece linear spline model with knot	Standard log-linear CPH model (linear at POD of 1/100 and below)
Total number of cancer deaths	53	91.69 (70.1, 122.4)	52.42 (40.1, 70.0)
Quintile 2 ⁸ cancer deaths	11	20.9 (11.7, 42.0)	14.4 (8.1, 28.9)

Source: TCEQ (2020a) Appendix 3 Table 29 and 30

OEHHA dismissed TCEQ’s prediction method based on an unsupported vague claim that the analysis is flawed because it does not account for differences that might exist between the general US population and the NIOSH worker cohort. Epidemiologic literature has shown that a healthy worker effect (HWE) is predominantly related to workers with shorter follow-up and non-cancer causes (Monson, 1986; Fox and Collier, 1976). Most importantly, the NIOSH study authors themselves concluded that there was unlikely to be a cancer HWE in this longer follow-

⁷ TCEQ’s model using 15-yr lag and the full risk set

⁸ EPA IRIS model using 15-yr lag and 100 workers randomly selected individuals from each case’s risk set

⁹ TCEQ (2020a) defined Quintile 1 as the 9 lagged-out cases (no exposures). The remaining 44 cases were equally divided into 4 groups designated by TCEQ as Quintiles 2-5. EPA IRIS (2016, p. 4-15) reported 13 exposed cases below the knot of 1600 ppm-days. Thus, prediction of Quintile 2 comprised of 11 cases with the lowest exposures best reflects “local” fit below the knot.

up study (Steenland et al., 2004¹⁰). Their conclusions are consistent with that of the International Agency for Research on Cancer textbook on Cancer Epidemiology: Principles and Methods (IARC, 1999), which specifically notes that HWE “is known to vary with type of disease, being smaller for cancer than for other major diseases, and it tends to disappear with time since recruitment into the workforce.” Thus, it is unlikely that there is a HWE in the NIOSH cohort.

OEHHA did not appear to be aware of the TCEQ DSD¹¹ sensitivity analysis to demonstrate that the TCEQ model still better predicts the overall actual cancers after applying a high HWE of 15-16% for lymphoid cancers. Although one can quibble with the TCEQ’s selection of 15-16% based on overall¹² cancer SMRs from a Norwegian worker study with relatively short average follow-up of 11.5 yrs. (Kirkeleit et al., 2013), the larger point is that 15% HWE is a reasonable estimate for differences between the general population and the NIOSH worker cohort given the unlikelihood of a cancer HWE in the NIOSH study (Steenland et al., 2004). Figures 1 and 2 show the TCEQ model better predicts the observed lymphoid deaths than the IRIS model overall, and locally at Quintile 2. **Taken together, the OEHHA IUR should be corrected to indicate that the TCEQ model has excellent overall and local fit based on the TCEQ’s prediction analysis, which considers a possible HWE effect as a reasonable surrogate for differences that might exist between the general US population and the NIOSH worker cohort.**

¹⁰ “The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons.” (Steenland et al. 2004)

¹¹ TCEQ Section A3.3.2

¹² Kirkeleit et al, (2013) did not find a HWE for lymphoid (SMR of 0.97 for males, 1.07 for females) or breast cancer (SMR of 1.02), but TCEQ conservatively used the overall cancer SMR of 0.85 and 0.84 for male and females workers. It is unknown if the Norwegian workers are representative of the NIOSH sterilizer workers.

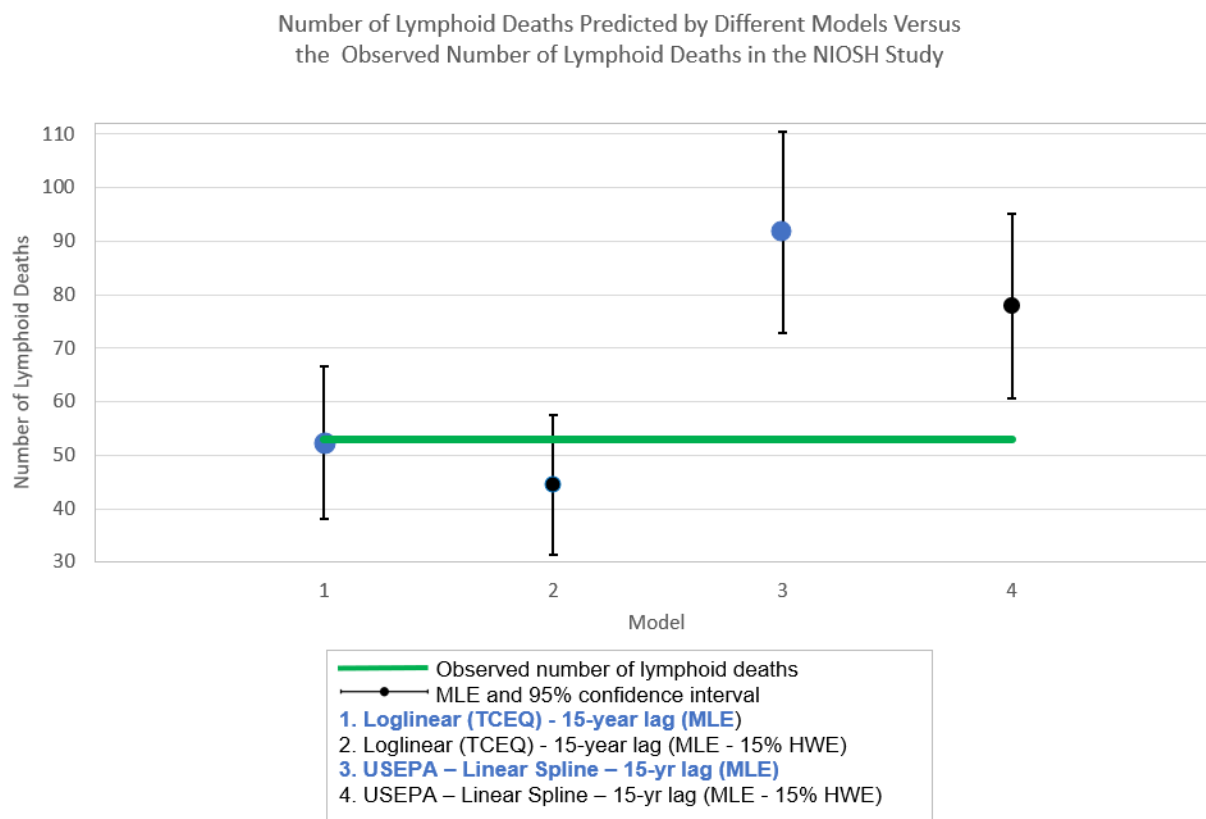


Figure 1. Comparison of Overall Fit of TCEQ and IRIS Models To the NIOSH Study

Note: Confidence intervals (CI's) shown are based on Poisson distribution and are very similar to those calculated by TCEQ (2020a) as described in our detailed comments. These similar results provide additional support for TCEQ's conclusions that the TCEQ model has greater overall fit to the data. (See TCEQ, 2020a)

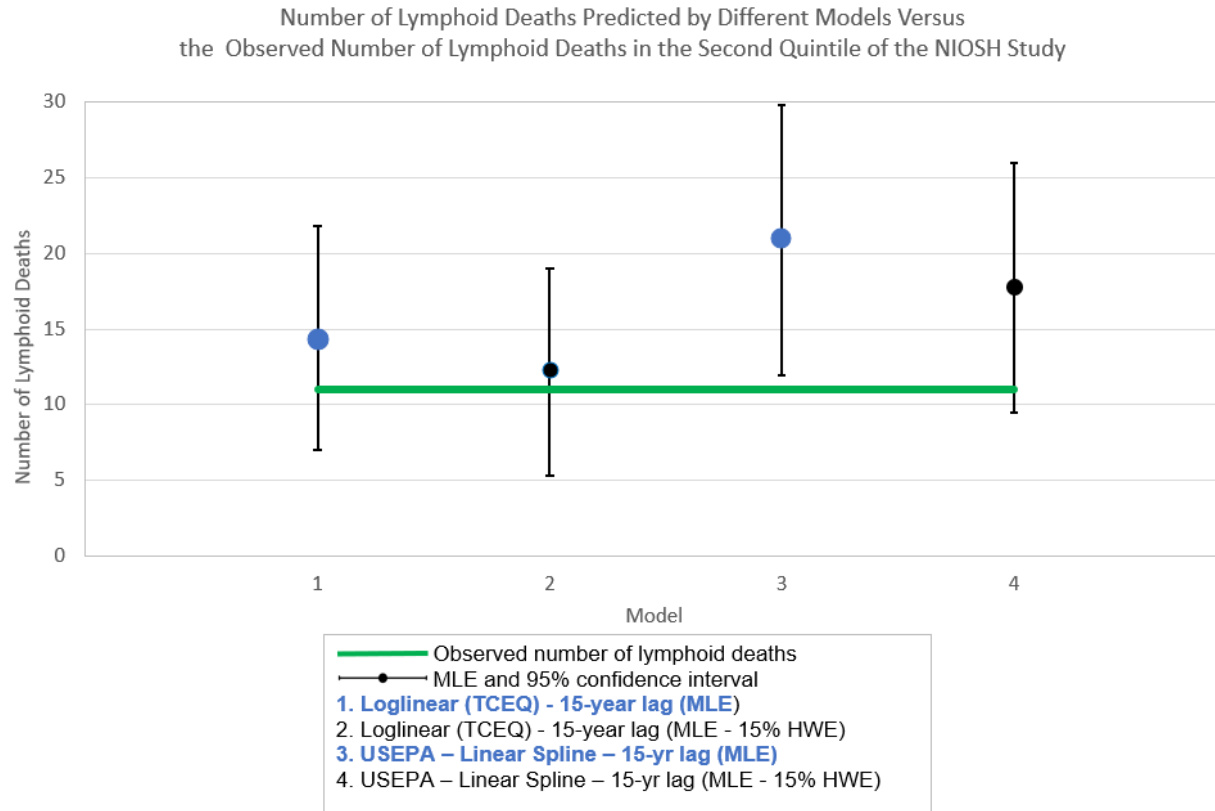


Figure 2. Comparison of Local Fit of TCEQ and IRIS Models To Quintile 2 of the NIOSH study

Note: CI's shown are based on Poisson distribution and are very similar to those calculated by TCEQ (2020a) as described in our comments. These similar results provide additional support for TCEQ's conclusions that the TCEQ model has greater *local* fit below the knot.

OEHHA makes an incorrect and unsubstantiated claim that the CPH model is sublinear at the point of departure (POD) and is therefore less accurate than a linear model (e.g., first initial linear model before the knot). The standard CPH model is essentially linear over the range of exposures for the NIOSH study, and the POD of 1/100,000 was selected by TCEQ to be within the experimental dose-range. Although EPA also prefers a POD of 1/100, EPA (2022, p. 57) agrees that the CPH model is linear at and below the POD of 1/100: "Given that the log linear Cox model is essentially linear in the low dose range, this choice of the POD would likely not have major effect on bottom line estimates, but the use of such a low POD is not a sound risk assessment practice."

Neither OEHHA nor EPA may have considered that TCEQ's (2020a, Appendix 4) selection of the POD is based on USEPA cancer guidelines (2005 page 1-13) and that the POD should be in the range of the observed data "near the lower end of the observed range, without significant extrapolation to lower doses." The exposure concentration (EC) for an extra risk of 1 in 100 (354,399 ppm-days) using TCEQ's model is outside (above) the range of cumulative exposures

for the male lymphoid mortalities in the NIOSH study. In contrast, the EC for an extra risk of 1 in 100,000 is near the lower end of the observed range of cumulative exposures to EtO, and is consistent with TCEQ and USEPA guidelines (TCEQ 2015, USEPA 2005a) on the selection of a POD at the low-end of the observable range of exposures

Background endogenous and ambient levels of EtO provide important reality checks for model selection. The key assumptions in extrapolating the exposure-response relationships at lower exposures are scientifically valid and are now corroborated by independent data sets.

Background endogenous and ambient levels of ethylene oxide are an important reality check for the TCEQ and IRIS model. **While OEHHA is correct that the potency estimates technically only apply to exposures above endogenous levels, it is implausible that a chemical would be a potent carcinogen at fraction of levels that the body produces through natural processes and also be well within the population variability.** We applaud OEHHA for including a section on endogenous levels. However, we disagree with OEHHA's claim in the toxicokinetic section that the data presented by Kirman et al. (2021) is inadequate to estimate ambient equivalent EtO levels at exposures below occupational.

The linear relationship between HEV adducts and EtO exposures is well-supported by data across a broad range of exposure levels (i.e., ranging from background levels to ~4 ppm in workers). As explained in the comments below, this well-supported linear relationship is also supported by a "forward" analysis suggested by EPA (2022) based on measured EtO concentrations in mainstream cigarette smoke that corroborates the Kirman et al. (2021) linear relationship.

In summary, we urge OEHHA to adopt the TCEQ model for lymphoid cancers or use CPH model estimates from the IRIS assessment and revise the draft IUR proposal and background Appendix to better reflect the following:

- 1. The original NIOSH study upon which OEHHA's IUR is based found no indication of increased risk of lymphoid cancers in males at lower categories of exposures and concluded there were no exposure-related effects in females. The TCEQ dose response model is more consistent with the original findings of the NIOSH mortality study.**
- 2. Breast cancer, like other types of cancers OEHHA considered from both animal and human studies, is a cancer endpoint that deserves consideration in the weight of evidence for cancer classification. However, the NIOSH breast cancer incidence data should not be used for quantitative risk assessment based on substantial under-ascertainment of incident cases reported by Steenland et al (2003) and subsequent risk deficits in the lower exposures.**

3. **OEHHA's rationale for supporting EPA IRIS model selection is based on uncritical acceptance of EPA's statistical analysis that did not account for a systematic statistical search for the knot as an estimated statistical parameter. Independent peer reviewers for TCEQ agreed with TCEQ's corrections of the statistics, which puts the TCEQ model on par with the IRIS model based on statistical significance alone.**
4. **The TCEQ dose-response model is more plausible based on the biological and toxicological evidence, and the mode of action.**
5. **OEHHA repeats IRIS's visual fit comparisons by comparing ("eyeballing") whether graphs of different models are above or below the categorical (grouped) estimates to incorrectly conclude that the models over- or underestimate "the data." EPA IRIS footnotes (repeated in OEHHA's figure legends) clearly indicate that such comparisons along the y-axis should not be made. OEHHA appears to equate the 5 categorical rate ratios with the 53 rate ratios, and/or assumes that the shape of the exposure-response curve for the actual data can be based on grouping the actual data into 5 categorical rate ratios.**
6. **OEHHA dismisses TCEQ's prediction analysis which is a more objective method than visual fit to check how well each of the two models (i.e., TCEQ's vs EPA's) applied to general population background lymphoid cancer rates can predict the number of lymphoid cancer deaths (the key cancer endpoint) that were observed in the NIOSH cohort. In this model ground-truthing exercise, the TCEQ model was not only able to better predict the actual total number of lymphoid cancers in the NIOSH cohort but also the number of cancers in every quintile and specifically in the lowest Quintile 2¹³ demonstrating superior global and local fit.**
7. **OEHHA's reliance on internal analyses and OEHHA's exclusion of external analysis is based on a scientifically oversimplified main conclusion that all external analysis should be ignored because it is confounded by HWE. This is contradicted by the NIOSH study authors' own published conclusions that "the healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons." Furthermore, OEHHA's acceptance of conclusions of a more recent paper by Park (2020) that there is a Healthy Worker Survival Effect (HWSE) led OEHHA to support EPA IRIS model. However, the conclusions are not supported by the actual results in the paper.**
8. **Based on uncritical acceptance of the IRIS evaluation, OEHHA inaccurately exaggerates the reliability of the NIOSH worker exposure estimates prior to 1978.**

¹³ TCEQ (2020a) defined Quintile 1 as the 9 lagged-out cases (no exposures). The remaining 44 cases were equally divided into 4 groups designated by TCEQ as Quintiles 2-5. EPA IRIS (2016, p. 4-15) reported 13 exposed cases below the knot of 1600 ppm-days. Thus, prediction of Quintile 2 comprised of 11 cases with the lowest exposures best reflects "local" fit below the knot.

9. The Union Carbide Corp. (UCC) cohort should play a prominent role in considering the strength and consistency of the epidemiology data in supporting the IRIS vs. TCEQ IUR. Table 7 and OEHHA's description of this cohort in the text is missing the internal analysis by Valdez-Flores et al. (2010) which included exploration of different exposure metrics and lag times. The absence of findings in the UCC cohort for male LH is not consistent with a steep slope at low concentrations.
10. The OEHHA Draft IUR questions the reliability of the Kirman et al. (2021) method of estimating endogenous levels of EtO by favoring speculative uncertainty and tangential information on DNA adducts over the well-documented toxicokinetic and converging evidence from animals and humans as presented by Kirman et al. and independently confirmed by data in Filser and Klein (2018). Endogenous levels greatly exceed the levels to which residents near sterilization facilities may be exposed. While EPA's potency estimate technically only applies to exposures above endogenous levels, it is implausible that a chemical would be a potent carcinogen at levels that the body produces through natural processes.
11. OEHHA cites two studies reporting an association between smoking and lymphohematopoietic (LH) cancers published in 2012 (Diver et al., 2012 and Kroll et al., 2012) to discount Kirman et al. (2021) reality checks. These two studies are inconsistent with the lymphoid cancer (NHL, lymphocytic leukemia, multiple myeloma) findings from the NIOSH mortality study (Steenland et al., 2004), upon which IRIS 2016 developed their low exposure high risk model and do not constitute a weight-of-evidence evaluation akin to the Surgeon General report, *The Health Consequences of Smoking —50 Years of Progress* (US DHHS 2014). In addition, OEHHA cites an IARC review associating a positive relationship between tobacco smoking and breast cancer, though not for lymphoid cancer.
12. OEHHA's estimated EtO 10^{-5} Risk Specific Concentration provide little utility in managing general population risk if background exogenous exposure isn't considered as an initial reality check. There has been an extensive ambient air measurement campaign over the last several years, including measurements near many sterilizer facilities and at background locations. In many cases, the levels of ethylene oxide far away from sterilizer facilities are similar to the levels near sterilizer facilities. Although the sources of this exogenous background ethylene oxide is currently not fully characterized, what is clear is that, in many cases, residents living near sterilizer facilities are not exposed to higher ethylene oxide than people living far away.

DETAILED COMMENTS

1. The original NIOSH study upon which OEHHHA's IUR is based found no indication of increased risk of lymphoid cancers in males at lower categories of exposures and concluded there were no exposure-related effects in females. The TCEQ dose response model is more consistent with the original findings of the NIOSH mortality study.

Pertaining to IUR p. 12-18, 34-43

The extremely steep dose response model selected by EPA IRIS (2016) and adopted by OEHHHA for lymphoid cancer mortality has led to the derivation of an IUR that is among the highest EPA IRIS inhalation IURs for known or likely carcinogens. This is inconsistent with the following original conclusions by the NIOSH study authors regarding both internal and external comparisons (Steenland et al., 2004):

- “There was little evidence of any excess cancer mortality for the cohort as a whole”
- “The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons”
- “Positive exposure-response trends for lymphoid tumors were found for males only (15-year lag)”
- “It is not known why we find an association for males and not females for haematopoietic cancer. . .there was sufficient variation in the exposure of women to have observed an exposure-response if one existed.

A large number of models were considered by IRIS, including those using log transformation of cumulative exposure, which IRIS (2016) correctly excluded as biologically implausible. Of the models using cumulative exposures, the strongest trend was seen in male lymphoid mortality. As described in detail in the next section, breast cancer incidence is not an appropriate endpoint based on the weight-of-evidence and quality issues. Therefore, of the critical endpoints selected by IRIS, male lymphoid mortality is the most appropriate endpoint for risk assessment, protective of effects in females who showed no sensitivity.

In the internal categorical analysis for male lymphoid tumors, the only statistically significant increase in male lymphoid odds ratio (OR) is only at the highest cumulative exposure level. Were EtO a potent carcinogen as IRIS suggests, one would expect to see a statistically significant increase at these lower cumulative exposures.

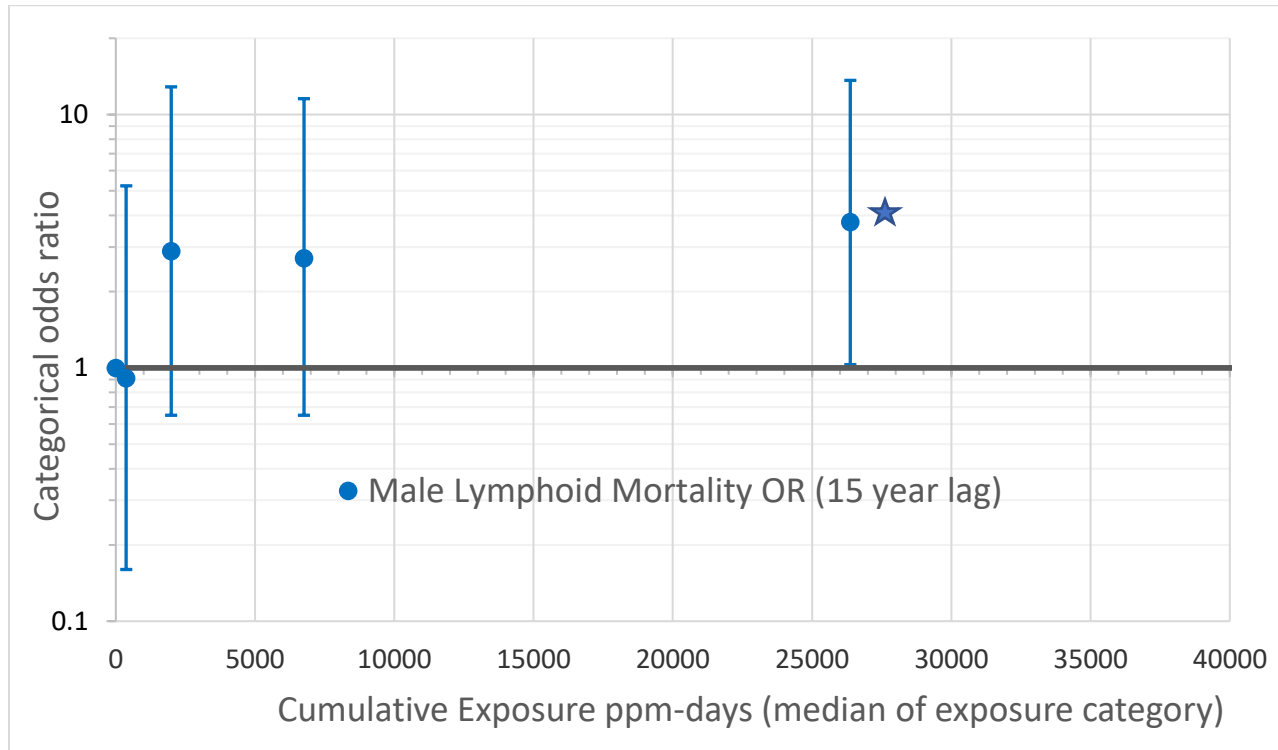


Figure 3. Categorical Odds ratios (OR) for males (95% Confidence Intervals):

Note: Male ORs for exposure categories 0 (lagged out), >0-1200 ppm-days, 1201-3680 ppm-days, 3681-13,500 ppm-days, >13,400 ppm-days are, respectively, 1, 0.91 (0.16-5.23), 2.89 (0.65-12.86), 2.71 (0.65-11.55), **3.76 (1.03-13.64)** (EPA IRIS, 2016, Table D-28)

Statistical modeling can take on a life of its own if not checked against epidemiological data which do not indicate an extremely steep low-dose dose response and/or a major discontinuity in the dose response. It is important to keep into perspective that the relevant epidemiology, including a large number of human studies published over a forty-year period, indicates that there is inconclusive evidence of carcinogenicity (IARC 2012a). For example, the UCC study of EtO chemical workers with comparable numbers of lymphoid cancers and substantial exposures to EtO show no increased risk of male lymphoid cancers. The findings from EtO epidemiology conflict with the IRIS risk values which imply EtO is a highly potent carcinogen at lower cumulative exposures. Were EtO a highly potent carcinogen, one would have expected to see a strong signal rather than many studies being inconclusive.

2. Breast cancer, like other types of cancers OEHHHA considered from both animal and human studies, is a cancer endpoint that deserves consideration in the weight of evidence for cancer classification. However, the NIOSH breast cancer incidence data should not be used for quantitative risk assessment based on substantial under-ascertainment of incident cases reported by Steenland et al (2003) and subsequent risk deficits in the lower exposures.

Pertaining to IUR p. 20, 35, 39, 45

The primary reason breast cancer should not be included in EtO quantitative exposure response analysis is that there is substantial under-ascertainment of incident cases due to non-participation in the interview study. This raises a serious issue- potential selection bias. The evidence related to causation is weak for breast cancer, supporting the focus on lymphoid cancers for quantitative risk assessment based on the epidemiological data.

Neither the NIOSH breast cancer incidence study (Steenland et al., 2003) nor the NIOSH mortality study (Steenland et al., 2004) report an overall excess of breast cancer. The positive NIOSH findings are not robust in that they are seen with a certain lag and exposure metric that are not evident with numerous other exposure metrics, models, or lags. The breast cancer incidence findings are at most suggestive, not only due to inconsistencies in the exposure-response, but also due to incomplete cancer ascertainment and the subsequent potential for bias. This disease endpoint is only weakly supported by other epidemiology studies and is inconsistent with others.

The IRIS breast cancer incidence analysis relied on data from the subpopulation of the NIOSH cohort that was interviewed, which required both locating subjects and identifying those diagnosed with breast cancer. Of the 7,576 women in the NIOSH cohort, only 5,139 (68%) were included in the interview portion of the study. The percent non-response was of concern, according to the authors. The majority of these, 22%, could not be located and therefore any breast cancer diagnosis would have been missed. Steenland et al. (2003) indicated that cases lost are more likely to be shorter term (i.e., lower cumulative exposure) employees.

Those who work longer (i.e., higher cumulative exposures) stay in the area longer and are more likely to get picked up in the state tumor registries and be found for interview. Shorter duration workers with lower cumulative exposures are more likely to leave the area and not be captured in the overall analyses and less likely to be interviewed. If more cases were missed among those with lower cumulative exposures (shorter term employees), then the data would be biased toward seeing a positive slope and/or elevated risk in the higher exposure groups, as reported by Steenland et al. (2003).

Steenland et al. (2003) stated that “breast cancer ascertainment in the sub-cohort with interviews was considered complete.” In other words, all the women who were interviewed were identified as having breast cancer or not. This, however, does not account for the missing cases among

non-participants in the interview study or for cases never identified in the overall target population. Importantly, there is no way of knowing that the distribution of cases by level of exposure in the subcohort of interviewed breast cancer cases is comparable to the distribution in the fully ascertained total cohort. Due to the greater difficulty of locating women with short term employment, there is a high potential for bias in missing cases at lower cumulative exposure. The rate ratios for breast cancer incidence in the lowest exposed groups in the entire cohort were 0.88 (15 yr. lagged out group) and 0.74 (<647 ppm-days, no lag), the latter of which was a statistically significant deficit (Steenland et al., 2003, Table 3). These deficits contributed to suggested positive trends.

Steenland et al. (2003) made an attempt to investigate possible selection bias but noted he didn't have adequate data to address this concern:

“A second possible bias was the preferential ascertainment of breast cancer among women with stable residence in states with cancer registries; women with stable residency might be expected to have longer duration of employment in companies under study, and hence greater cumulative exposure. Unfortunately, we didn't have residential history, limiting our ability to explore this possibility. (Steenland et al. 2003)”

Without the incidence data, selection bias cannot be properly tested. However, several issues support this explanation: 1) the overall population long-term (higher exposed) women would be easier to identify as having breast cancer as they remain for longer periods in states of employment that have tumor registries, 2) similarly, longer employed and higher cumulative exposure women would be easier to locate and thus interviewed, and 3) duration of employment in Steenland et al. (2003) showed a stronger relationship with breast cancer than did actual cumulative exposure.

Steenland et al. (2003) recognized this limitation as one reason he was tempered in his causation conclusions:

“Our data suggest that ETO is associated with breast cancer, but a causal interpretation is weakened due to some inconsistencies in exposure-response trends and possible biases due to non-response and incomplete cancer ascertainment.”

In summary, the weak association of EtO with breast cancer and the exposure-response uncertainty due to the sizeable number of missing breast cancer cases precludes use of the NIOSH interview data in derivation of IURs. This, together with the unavailability of the breast cancer incidence data to other researchers to independently examine these issues raises quality issues that indicate the data are inappropriate for exposure-response modeling for regulatory cancer risk assessment purposes.

3. OEHHA’s rationale for supporting EPA IRIS model selection is based on uncritical acceptance of EPA’s statistical analysis that did not account for EPA’s systematic statistical search for the knot as an estimated parameter. Independent peer reviewers for TCEQ agreed with TCEQ’s corrections of the statistics, which puts the TCEQ model on par with the IRIS model based on statistical significance alone.

Pertaining to IUR 34, 47

OEHHA accepts EPA IRIS (2016) conclusions on model fit that are based on incorrect statistical analysis and inappropriate visual fit comparisons (described below). TCEQ (2020a) provided corrected AIC and p-values for the spline models that OEHHA could have easily verified were correct. The peer review of TCEQ’s dose-response assessment included two independent reviewers who had strong statistical modeling expertise. Both peer reviewers agreed that EPA incorrectly calculated p-values because they did NOT correct for including the knot as an estimated parameter in the model, a basic violation of statistical principles:

Expert 5: “I do believe that TCEQ has identified a real problem with the USEPA AIC and p-value calculations. The explanation of the issue and the resolution supplied in DSD seems appropriate. That is, I agree with TCEQ that the knot parameter in the spline models should be considered in the count of the parameters, that the AICs reported by USEPA for those models are too low by a value of 2, and that the p-values should be computed using an approximation to a chi-square with 3 degrees of freedom.” (TCEQ 2020b, p. 45)

Expert 6: “I consider that the location of the spline should be considered a parameter when evaluating fits of spline models, as long as the data were used in determining the knot, as it apparently was in EPA’s model. I believe also that the lag should also be considered a parameter when the data are used to determine its value. But, in general, I consider the AIC in such complex models to be essentially only a rough guide to evaluating fit. Therefore, I think TCEQ’s conclusion that the ‘lower AIC means that TCEQ’s selected model is a statistically superior model fit than USEPA’s selected model when taking into account model complexity’ is an overstatement. Comparing a model with an AIC = 464.5 to one with an AIC = 264.4[sic¹⁴], you can only conclude with confidence that the two models fit about equally well. Additionally, the overall fit is not of major importance – the fit at small doses is much more important when the object of the fitting is to estimate the risk at very small doses.” (TCEQ 2020b, p. 50)

The basic principle of accounting for all modeled parameter is clearly articulated in the National Research Council report entitled “Models in Environmental Regulatory Decision Making”, which states that the strategy to pick the “best model” for regulatory decision making should be “subject to a penalty function reflecting the number of model parameters, thus effectively forcing a trade-off between improving model fit by adding addition[al estimated] model parameters

¹⁴ Expert really meant 464.4

versus having a parsimonious description” (NRC, 2007, pp. 174). Importantly, there are no recognized exceptions to the penalty component of the balance incorporated into the AIC metric when applied in a valid procedure for model-selection (Burnham et al., 2002). This general principle is well recognized in the peer reviewed literature to apply specifically to including the estimated “knot” or inflection point from reporting the use of 2-piece linear spline models (Berman et al., 1996, Li et al., 2011; Gkioulekas et al. 2018, Molinari et al., 2001).

EPA ORD incorrectly claims that they fixed the knot and then conducted a sensitivity analysis. However, EPA ORD did not simply “fix” or “select” the position of the knot in that model. Instead, IRIS systematically tested 20 alternative knots for breast cancer and 70 knots for lymphoid mortality, and then among these, selected knot values that maximized the likelihood of data fit to a corresponding 2-piece spline model.

In the EPA IRIS (2016 Appendix D at p. D-13), Dr. Steenland provided statistical analysis considering the knot as a parameter for breast cancer to show this had no substantial effect in that analysis, but a similar examination was not presented in the case of lymphoid cancer. In other words, there was clear acknowledgement and recognition expressed in the IRIS (2016) assessment that each knot value that was used to obtain a final spline-model fit is appropriately interpreted as an estimated parameter. Thus, IRIS should have reported the p-values considering the knot as an estimated parameter for breast and lymphoid cancers in the summary tables of the main report for greater transparency.

OEHHA should revise their discussion of fit of the data to reflect the corrected p-values reported by TCEQ (2020a) for the IRIS selected 2-piece spline provided in Table 1 of our comments above. Based on corrected statistical analysis alone, neither EPA IRIS ($p=0.14$) nor the TCEQ ($p=0.22$) dose-response models for lymphoid cancers provide strong evidence that the exposure-response slope differs from zero. Based on statistics alone, the CPH model fits the data similarly to the supralinear 2-piece spline slope but has the advantage of parsimony (simpler model) and biological plausibility (described below). Also described in greater detail below, the CPH model more accurately predicts the observed lymphoid mortalities overall and at lower exposures in the NIOSH study compared to the IRIS (2016) selected 2-piece spline model.

In addition to Table 1, we suggest OEHHA include Table 3 in their detailed analyses, which provides a more complete and direct comparison between the statistics and IUR derivation for the 2-piece spline model and the CPH model. Table 3 will provide users of OEHHA’s assessment an understanding of the range of values that can be estimated for risk assessment based on the IRIS (2016) preferred methods and assumptions.

Table 3. Comparison of IRIS (2016) derived models (IURs not including the ADAF)

	2-piece linear spline Linear at EPA POD 1/100	Standard CPH Linear at EPA POD 1/100
Model of individual data?	Yes	Yes
IRIS full model name	Linear spline model with knot at 1,600 ppm x days	Log-linear model (standard Cox regression model)
<u>LYMPHOID INCIDENCE (Males and Females)</u>		
IRIS p-value	0.14 corrected from 0.07	0.22
Central estimate IUR (per ppm)	1.34	0.0095
Upper bound IUR (per ppm)	5.26	0.020
<u>BREAST CANCER INCIDENCE (Females)</u>		
IRIS p-value	0.04 corrected from 0.01	0.02
Central estimate IUR (per ppm)	0.71	0.08
Upper bound IUR (per ppm)	1.48	0.14
<i>These data are not appropriate for quantitative risk assessment purposes because authors report substantial number of missing cases with higher potential for those with shorter employment missing (Steenland et al. 2003). These data have not been available for independent evaluation by EPA or the public, and, thus, lack transparency, verification, and independent analysis.</i>		
<u>LYMPHOID & BREAST CANCER INCIDENCE (Males and Females)</u>		
Central estimate IUR (per ppm)	2.1	0.1
Upper bound IUR (per ppm)	6.1	0.15
<i>These data are not appropriate for risk assessment because the breast cancer incidence data are included. EPA provided no justification for the POD of 1/100. TCEQ (2020a) analysis shows that the POD 1/100 for the standard CPH model extrapolates above or in the high range of the experimental data!</i>		

4. The TCEQ dose-response model is more plausible based on the biological and toxicological evidence, and the mode of action.
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Pertaining to IUR p 15-18, 20-23

A biological mode of action should be a major consideration when selecting a model for risk assessment.

Currently, genotoxic MoA is considered as a default assumption in the absence of a convincing alternate MoA that does not involve genotoxicity as the initial key event. The dose-response and temporality of EtO induced genotoxicity in the etiology of either animal or human tumors has not been fully vetted through a formal process such as the one recommended by International Program on Chemical Safety (Boobis et al., 2006).

For a direct acting alkylating agent such as EtO, the default dose-response for the induction of mutations is linear. This is the worst-case scenario since at low doses closer to the origin, one should expect cellular protective mechanisms (e.g., detoxification and DNA repair) to offer protection, resulting in a shallower slope in this region when compared to higher doses. Based on a presumed genotoxic MoA, both TCEQ and EPA/OEEHA estimate cancer risk based on a linear extrapolation from the POD to the origin but apply very different statistical models to the same epidemiological study to derive the POD, i.e., Cox proportional hazards (CPH) model by TCEQ vs. the two-piece spline model by the EPA/OEEHA.

In the 2-two-piece spline model, the initial slope rises rapidly at lower exposure levels and then rises more gradually for higher exposures. This type of dose-response is not consistent with the biology of how EtO works as a direct acting genotoxicant. The dose-response curve for EtO-induced gene mutations in the bone marrow (Recio et al., 2004, Figure 4) and lung (Manjanatha et al., 2017, Figure 5) tissues of transgenic Big Blue mice is especially informative since these tissues represent targets for EtO-induced tumors. In both cases, there is no evidence for a steeper initial slope and the dose-response pattern is more consistent with the CPH model than the 2-piece spline.

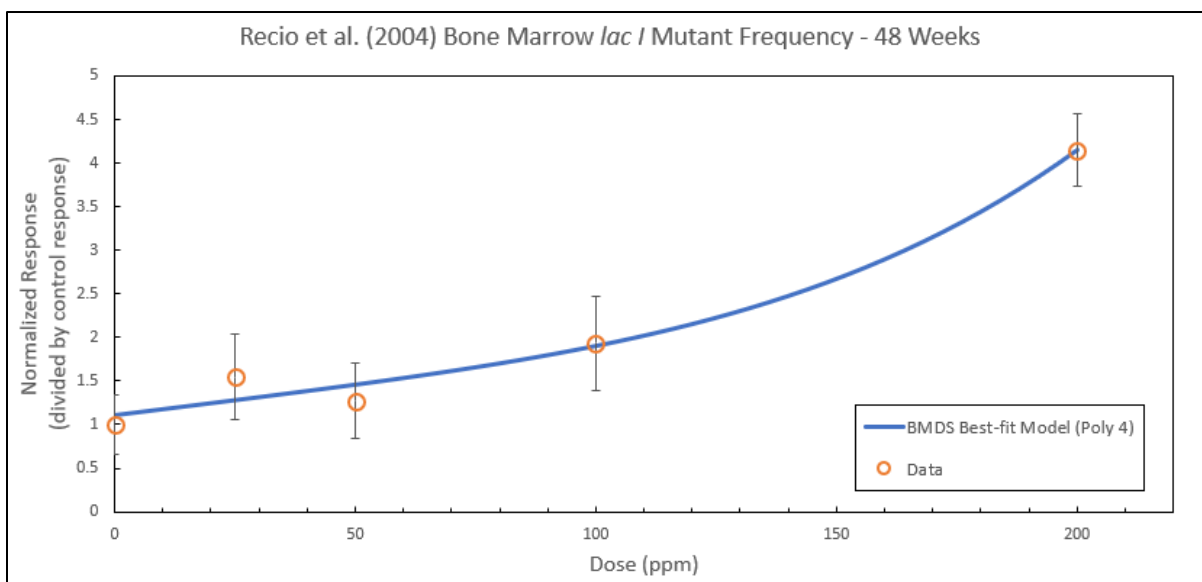


Figure 4. Dose-Response for EtO-Induced *lacI* mutations in Mouse Bone Marrow (6 h/day; 5 days/week; 48 weeks from Recio et al., (2004)

Recio et al. (2004) observed increases in *lacI* mutant frequency in the bone marrow of transgenic Big Blue B6C3F1 mice at EtO exposure concentrations of 100 and 200 ppm (but not at 25 or 50 ppm) after 48 weeks of exposure. No increases were observed following 12 and 24 weeks of exposure.

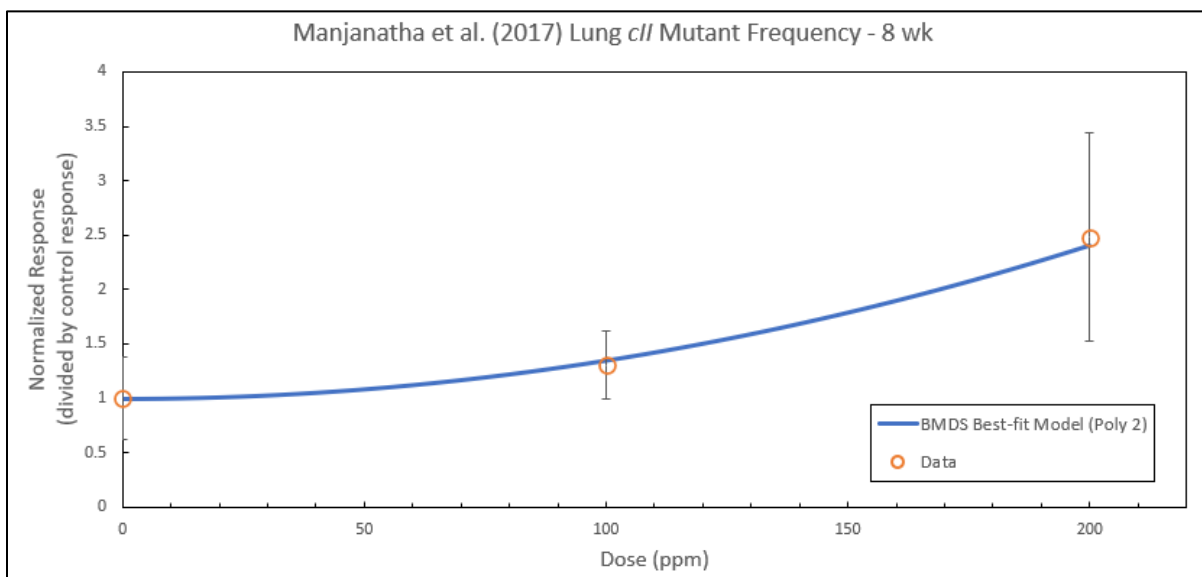
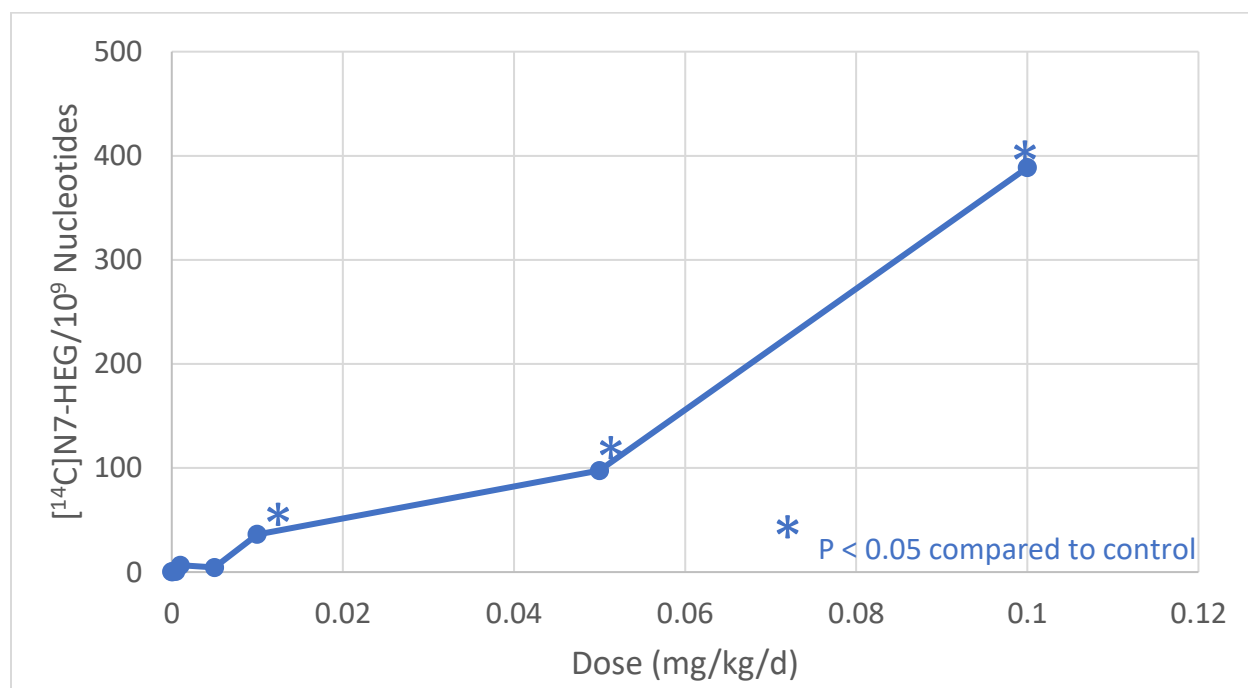


Figure 5. Dose-response for the Induction of *cII* mutations in the lung tissue of Big Blue B6C3F1 transgenic mice at 8 weeks of inhalation exposure to EtO (Manjanatha et al., 2017).

Similarly, Manjanatha et al. (2017) investigated exposure-response and temporality for EtO-induced mutations at the *cII* locus in the lung tissue of transgenic Big Blue male B6C3F1 mice exposed to 0, 10, 50, 100, or 200 ppm EtO for 6 hr/day, 5 days/week over 4 weeks (in all exposure groups) or for 8 or 12 weeks (in only the two highest exposure groups). A significant increase was observed only following 8 or 12 weeks of exposure and only at the highest concentration studied (200 ppm), which was twice the tumorigenic concentration used in the NTP (1987) bioassay in the same strain of animal. Contrary to expectations consistent with a mutagenic MOA, no statistically significant increase in mutant frequency or mutational spectrum were observed following 4 weeks of EtO exposure (which is considered to be adequate exposure duration for detecting chemically-induced mutations as per OECD test guideline 488). These results are inconsistent with modified Hill criteria for exposure-response and temporality assuming a mutagenic MOA when considering the NTP (1987) studies in male and female B6C3F1 mice exposed to 0, 50, 100 ppm, 6 hrs/day, 5 days/wk for 102 weeks that were described in the draft IUR (p.7)

The above dose-response patterns are fully consistent with the molecular initiating event(s) leading to EtO-induced mutagenicity, i.e., the formation for DNA adducts. Marsden et al. (2009) using a highly sensitive liquid chromatography-tandem mass spectrometry and high-performance liquid chromatography-accelerator mass spectrometry analysis have shown that the dose-response for the induction of N7-(2-hydroxyethyl)guanine (N7-HEG) adducts in the livers of rats treated with EtO is at best described as linear, with significant increases over the background being observed only at the three higher tested doses.



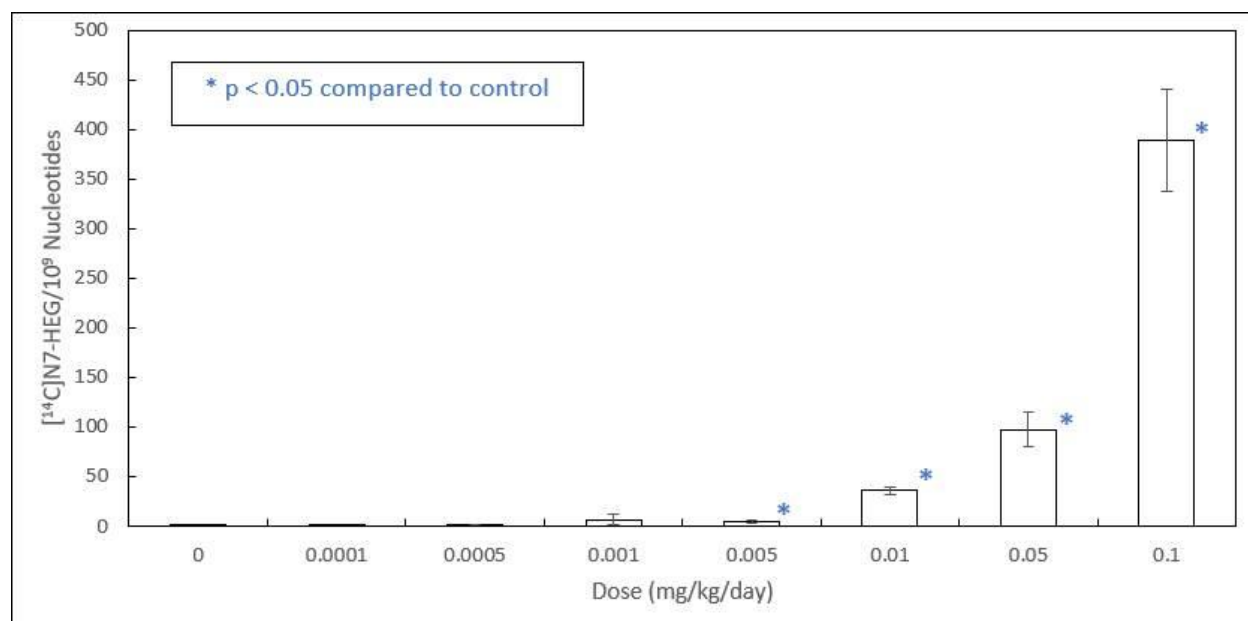


Figure 6. Dose-response for exogenously derived DNA adducts in liver of [¹⁴C]EtO-treated rats measured by LC-MS/MS (Marsden et al., 2009).

Although the N7-HEG adducts are not considered mutagenic, they are the most abundant DNA adducts formed following EtO exposure (Walker et al., 1992). Thus, the shape of the dose-response curve for the N7-HEG adduct can be considered as the worst-case scenario for EtO-induced adducts, including the most mutagenic O⁶-HEG adduct whose abundance is approximately 300 times lower than that of the N7-HEG adduct (Walker et al., 1992). In reality, the slope for the mutagenic O⁶-HEG adducts is expected to be much shallower than that for N7-HEG because of the kinetics of their formation and repair (Swenberg et al., 2008). Accordingly, the dose-response pattern for the molecular initiating event leading to EtO-induced mutagenicity is expected to be non-linear or at best linear at the low end of the dose-response curve and the efficiency of adduct formation increasing at higher exposure levels due to saturation of the DNA-repair processes.

Further evidence for the implausibility of a steeper initial slope in the EO dose-response comes from genotoxicity and carcinogenicity studies conducted with ethylene. Since ethylene is metabolized in vivo to EtO, it forms the same type of protein and DNA adducts as EtO. Based upon a physiologically based toxicokinetic model, Filser and Klein (2018) predicted that exposures to 10000 ppm ethylene induces adduct levels equivalent to EO exposures of 3.95 (mice), 5.67 (rats), or 0.313 ppm (humans). Ethylene is not an in vivo genotoxicant in the rat or the mouse (Vergens and Pritts, 1994; Walker et al., 2000).

In a chronic bioassay, ethylene was not carcinogenic in male and female Fischer 344 rats following exposed 6 hr/day, 5 days/week, for up to 24 months to concentrations of 300, 1000, or 3000 ppm (Hamm et al., 1984). DNA adducts resulting from 300, 1000 or 3000 ppm ethylene are shown to be quantitatively to 2.4, 5.3 and 5.5 ppm EtO, respectively (Filser and Klein, 2018).

Lack of ethylene carcinogenicity in the rat, in spite of increased DNA adducts equivalent to low ppm-level EtO exposure, informs that the potency of EtO's carcinogen is not higher at the lower exposures, an observation contrary to the prediction based on the IRIS (2016) 2-slope dose response model. On the other hand, the dose-response for EtO carcinogenicity is conservatively consistent with a default linear risk model with a single slope.

Fennell and Brown (2001) showed that blood concentrations of EtO in mice, rats, and humans increased linearly with exposures between 50 and 200 ppm (see figure below). Dose-disproportionate increases in blood EtO occurred only in mice at exposures exceeding 200 ppm and were attributed to substantial depletion of GSH, which limits the overall GSH conjugation capacity. It needs to be emphasized that the dose-disproportionate response in mice involved an increased (not decreased) rate of blood EtO concentration at exposures >200 ppm EtO. These observations do not support the plausibility for a steeper slope at lower exposures either for genotoxicity or carcinogenicity.

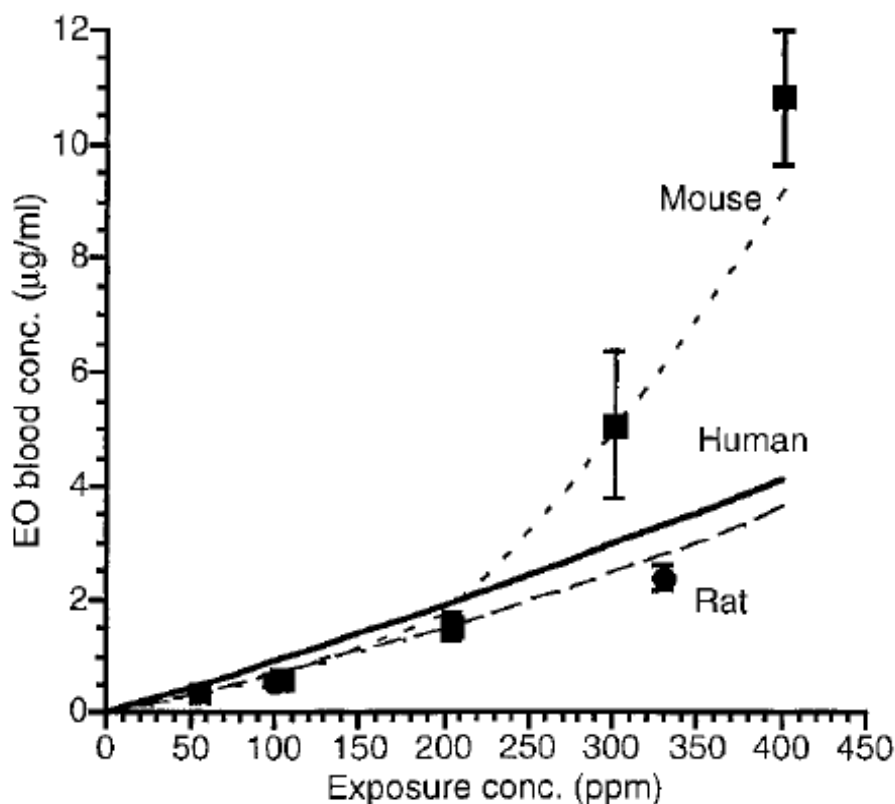


Figure 7. Toxicokinetics of EtO from Fennell and Brown (2001).

In conclusion, EtO is a relatively weak genotoxicant and requires relatively high and prolonged exposures to induce mutagenicity. The experimentally observed dose-response patterns for mutagenicity/carcinogenicity show that the CPH model is biologically more plausible than the IRIS (2016) 2-slope model. Accordingly, the CPH model should be the model of choice for risk assessment purposes especially if an alternate model is not a better fit to the observed data.

Qualitative and quantitative analysis of genotoxicity data by Gollapudi et al. (2021) provide independent converging evidence supporting TCEQ's quantitative risk assessment.

The recent literature search conducted by OEEHA missed the publication by Gollapudi et al. (2021). These authors analyzed the dose-response data to identify a point-of-departure for EtO-induced in vivo genotoxicity from an exhaustive list of published studies that employed various endpoints, tissues, and species and derived 238 ppt as the lowest permitted daily exposure (PDE) from this analysis. The PDE of 238 ppt proposed in this publication is more than three orders of magnitude higher than the 0.1 ppt established by the U.S. EPA (2016) and similar to the 240 ppt estimated from TCEQ (2020a) risk values for 1-in-10⁶ (1/M) extra risk. Thus, if EtO were operating through a genotoxic mode of action (MoA) for its carcinogenicity, then the risk assessment model used by the TCEQ, rather than the one used by the EPA, is consistent with the biology based on the analysis by Gollapudi et al., (2020).

Regarding Carlsson et al. (2017) and Zeljezic et al. (2016) genotoxicity study in workers

The results from the studies by Carlsson et al. (2017) and Zeljezic et al. (2016) identified in the recent literature search by OEEHA should be interpreted with caution since the subjects in this study were exposed to multiple carcinogenic/genotoxic chemicals including EtO and hence it is difficult to attribute the effects observed to any single chemical. Accordingly, the statement by OEEHA that the results “..... are consistent with the overall evidence for the genotoxicity of ethylene oxide” is an overstatement.

- 5. OEHHA repeats IRIS’s visual fit comparisons by comparing (“eyeballing”) whether graphs of different models are above or below the categorical (grouped) estimates to conclude that the models over- or underestimate “the data.” EPA IRIS footnotes (repeated in OEHHA’s figure legends) clearly indicate that such comparisons along the y-axis should not be made. OEHHA appears to equate the 5 categorical rate ratios with the actual 53 hazard rates, and/or assumes that the shape of the exposure-response curve for the actual data can be based on grouping the actual data into 5 categorical rate ratios.**

Pertaining to IUR p. 36, 37, 40

OEHHA relies on IRIS’s visual fit comparisons using figures that compare continuous models with categorical models, as if the categorical model with only five points were the gold standard for understanding the shape of the exposure-response curve. While categorical models with a small number of odds ratios can be useful for identifying possible associations, they do not identify the shape of the dose-response curve based on continuous data modeling as shown in detail by Valdez-Flores and Sielken (2013). Based on these visual fit comparisons, OEHHA concludes that models either over or underpredict the categorical model, which are not the data modeled.

TCEQ provided new information that OEHHA may not have been aware of. Graphical display of data is subject to manipulations including the choice of how data are expressed on the y-axis and resolution of categorical models to represent the underlying individual data that were modeled. TCEQ’s purpose is best expressed in response to peer review comments (TCEQ 2020b, p.49. 51):

“The TCEQ only discusses visual fit (and only in an Appendix) because of USEPA’s reliance on it. By contrast, the TCEQ does not rely on visual model fit as a primary consideration for model choice, but rather principally relies on MOAs and various statistical diagnostics of model fit (i.e. AIC and p-values, statistical analyses of model accuracy), consistent with the comment.”

TCEQ’s explains in text and illustrates in figures that EPA’s graphs are misleading because EPA uses the categorical modeling results (which are not the primary data being modeled) to visually evaluate the fit of models as though these cruder categorical estimates represent the true underlying dose response. EPA correctly points out that each of these individual case categories will have very wide confidence intervals (CI) but fails to address TCEQ’s major point which is that the categorical estimates graphed as point estimates without the CI are not representative of the underlying 53 hazard rates modeled. EPA IRIS did not exhibit the wide confidence intervals associated with the EPA’s categorical model in the graphs used to illustrate visual fit. Thus, TCEQ produced similar figures without the CI’s to better illustrate the underlying individual hazard rates that are being modeled. TCEQ explains why comparison of the dose-response model results to the categorical model results is inappropriate on p. 52 of TCEQ’s (2020b) response to the peer review.

“This is because while assessing model fit by visual inspection to the underlying modeled datapoints is a commonly used technique. . . , the dose-response models being judged by visual fit to the categorical results were fit to different data, the more refined individual data. The USEPA should not have used the categorical modeling results (which are not the primary data) to visually evaluate the fit of models to other data (the individual data) as though the cruder categorical data represent the true underlying dose-response.”

EPA counters TCEQ stating that the categorical model is a well-accepted method to represent the data. This true statement is irrelevant to addressing TCEQ’s main point- visual fit based on categorical models are not appropriate for the purpose of determining goodness of fit of the model to the underlying data, because the categorical model is NOT the underlying individual data. TCEQ cites Valdez-Flores and Sielken (2013) which is a peer-reviewed paper that demonstrates how the shape of categorical results can change with different numbers of categories.

TCEQ is not advocating the use of these graphs to assess visual fit as a method to select the models, but instead is informing that these graphs should not be used for visual fit. Instead, TCEQ relies on a more objective statistical modeling approaches to evaluate goodness of fit, rather than “eyeballing” comparisons using figures that are not fit for this purpose and distort the true comparisons of models against the underlying individual data that were modeled.

OEHHA should correct their discussion of visual fit so that all OEHHA’s claims of over or underprediction are omitted, as they violate EPA IRIS’ warning that such comparisons along the y-axis are incorrect comparisons of over or under prediction.

6. OEHHA dismisses TCEQ’s prediction analysis which is a more objective method than visual fit to check how well each of the two models (i.e., TCEQ’s vs EPA’s) can predict the number of lymphoid cancer deaths (the key cancer endpoint). In this model ground-truthing exercise, the TCEQ model was not only able to better predict the actual total number of lymphoid cancers in the NIOSH cohort (with and without an HWE) but also the number of cancers in Quintile 2¹⁵ demonstrating superior global and local fit.

Pertaining to IUR p. 47-48

As described above in our general comments, OEHHA dismissed TCEQ’s “reality check” (Table 4) based on a prediction analysis because the models are applied to general population background cancer rates, which OEHHA considered to be a flawed analysis because the NIOSH study is based on a specific cohort of occupational workers. Yet, this approach is essentially the same approach used by IRIS (2016, Section 4.7) to estimate extra risk for various occupational exposure levels by applying the model to the general population background cancer rates in the life-table program.

Table 4: Total NIOSH Cohort Lymphoid Cancer Mortalities Predicted by TCEQ (2020a) and EPA IRIS (2016) Models

Model (15-yr lag, MLE)	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × Ratio: Predicted / Observed	100% × SMR: Observed / Predicted	95% Poisson CI if the Model were True
TCEQ (CPH)	2.81E-06	52.42	98.9%	(40.1, 70.0)	(38.2, 66.6)
IRIS 2-slope spline 15-yr lag (MLE)	7.58E-04	91.69	173.0%	(70.1, 122.4)	(72.9, 110.4)

Note: There are 53 actual lymphoid mortalities. 53 is within the CI’s for the TCEQ model but not within the CI’s for the IRIS model. Thus, the TCEQ model accurately predicts the actual cancers. In contrast, the IRIS model statistically significantly (bold font) over-predicts the actual number of cancers. TCEQ used the inverse of the confidence intervals of the SMRs. We calculated the confidence intervals based on the Poisson distributions. TCEQ (2020a, Table 6).

¹⁵ TCEQ (2020a) defined Quintile 1 as the 9 lagged-out cases (no exposures). The remaining 44 cases were equally divided into 4 groups designated by TCEQ as Quintiles 2-5. EPA IRIS (2016, p. 4-15) reported 13 exposed cases below the knot of 1600 ppm-days. Thus, prediction of Quintile 2 comprised of 11 cases with the lowest exposures best reflects “local” fit below the knot.

EPA (2022) also raised a question about TCEQ’s calculation of the confidence interval (CI) based on the inverse of the SMR CI as described in detail by TCEQ (2020a). Thus, it is useful to show that another well-accepted approach for estimating the 95% CI results in the exact same conclusion that the TCEQ model accurately predicts the actual 53 cases, whilst the IRIS model over-predicts the number of cases (Table 4)

OEHHA claims that TCEQ calculations did not accurately account for any differences that might exist between the general US population and the NIOSH cohort. It is unclear if OEHHA is aware that the TCEQ (2020a) DSD¹⁶ includes a sensitivity analysis to demonstrate that the TCEQ model better predicts the overall actual cancers even after applying a high HWE of 15-16% for lymphoid cancers as a sensitivity analysis (Table 5).

Table 5: Total NIOSH Cohort Lymphoid Cancer Mortalities Predicted by TCEQ (2020a) and EPA IRIS (2016) Models with 15% HWE as a Sensitivity Analysis

Model (15-yr lag, MLE)	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × Ratio: Predicted / Observed	95% Poisson CI if the Model were True
TCEQ (CPH)	2.81E-06	44.56	84.1%	(31.4, 57.6)
IRIS 2-slope spline 15-yr lag (MLE)	7.58E-04	77.94	147.1%	(60.6, 95.2)

Note: The TCEQ model still accurately predicts the actual cancers after accounting for a theoretical HWE. In contrast, the IRIS model statistically significantly (bold font) over-predicts the actual number of cancers after including a theoretical HWE¹⁷. TCEQ used the inverse of the confidence intervals of the SMRs. We calculated the confidence intervals based on the Poisson distributions.

Although one can quibble with the TCEQ’s selection of 15-16% based on a Norwegian worker study with relatively short average follow-up of 11.5 yrs (Kirkeleit et al. 2013)¹⁸, the larger point is that a 15% HWE is a very reasonable high estimate for any differences that might exist between the general US population and the NIOSH worker. The NIOSH study authors themselves concluded that there was unlikely to be a cancer HWE in this longer follow-up study (Steenland et al. 2004¹⁹) cohort. This conclusion of the NIOSH study authors is very consistent with the general experience in cancer epidemiology that HWE is known to vary with type of

¹⁶ TCEQ Section A3.3.2

¹⁷ Predicted is based on multiplying predicted values in Table 4 by 0.85 for HWE of 15%, and CI’s calculated using Poisson distribution. Compare with TCEQ (2020a, p. 102, Section A3.3.2) estimates of 44.3 (95% CI: 33.9, 59.2) and 77.5 (95% CI: 59.3, 103.6) based on 15 and 16% HWE for males and females, respectively.

¹⁸ Kirkeleit et al (2013) did not find a HWE for lymphoid or breast cancer. It is unknown if the Norwegian cohort is representative of the NIOSH sterilizer workers.

¹⁹ “The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons.” (Steenland et al. 2004)

disease, being smaller for cancer than for other major diseases, and it tends to disappear with time since recruitment into the workforce (IARC, 1991). In addition, the epidemiologic literature has shown that a HWE is predominantly related to populations with shorter follow-up and non-cancer causes (Monson, 1986; Fox and Collier, 1976).

Using a 15% HWE, the CPH model statistically estimates the observed number (53) of lymphoid deaths in the NIOSH study (Table 5). In contrast, the linear 2-piece spline model statistically significantly overestimates the number of observed lymphoid deaths in the NIOSH study (Table 5). In addition, a quintile analysis was also performed by TCEQ (2020a) to address EPA IRIS (2016) emphasis on the local fit of the models below the knot. EPA IRIS (2016, p. 4-15) reported 13 exposed cases below the knot of 1600 ppm-days. Thus, prediction of Quintile 2 comprised of 11 cases best reflects “local” fit below the knot. Table 6 summarizes TCEQ CPH and EPA 2-piece spline model predictions of the number of lymphoid deaths at each quintile. Table 6 shows that for each quintile, the CPH model has superior local fit. These results indicate that the CPH model not only has better local fit below the knot, but also at the highest quintile.

Table 6: Quintile-Specific NIOSH Cohort Lymphoid Cancer Mortalities Predicted by Cox and Linear Two-Piece Spline Models

Model	Quintile 2	Quintile 3	Quintile 4	Quintile 5
<i>Lymphoid Cancer Deaths Observed in NIOSH Cohort</i>	<i>11</i>	<i>11</i>	<i>11</i>	<i>11</i>
Standard Cox model – 15-yr lag (MLE)	14.4 (8.1, 28.9) ²⁰ (7, 21.8) ²¹	8.0 (4.5, 16.1) (2.4, 13.5)	9.4 (5.2, 18.8) (3.3, 15.4)	9.1 (5.1, 18.3) (3.2, 15.0)
Linear two-piece spline with knot @ 1,600 ppm-days – 15-yr lag (MLE)	20.9 (11.7, 42.0) ²⁰ (11.9, 29.8) ²¹	17.6 (9.8, 35.2) (9.3, 25.8)	20.8 (11.6, 41.7) (11.8, 29.7)	20.9 (11.7, 41.9) (11.9, 29.8)

Note: The TCEQ model accurately predicts the actual cancers for the lowest exposure quintile 2. In contrast, the IRIS model statistically significantly (bold font) over-predicts the actual number of cancers. See TCEQ (2020a, Table 6).

In conclusion, the TCEQ standard CPH model accurately predicts the number of lymphoid deaths observed in the NIOSH study while EPA’s two-piece linear spline model statistically significantly (at the 2.5% significance level) overpredicts the number of lymphoid deaths observed in the NIOSH study. This is true with and without consideration of a reasonably high

²⁰ TCEQ (2020a) used the inverse of the confidence intervals of the SMRs

²¹, for comparison we calculated the CI based on Poisson distribution

HWE of 15% which reasonably accounts for any differences that might exist between the general US population and the NIOSH worker cohort given the absence of a HWE in the NIOSH cohort. This TCEQ “reality check” is a well-accepted approach that is essentially the same approach used by IRIS (2016, Section 4.7) to estimate extra risk for various occupational exposure levels by applying the model to the general population background cancer rates.

7. OEHHA’s reliance on internal analyses and OEHHA’s exclusion of external analysis is based on an oversimplified main conclusion that all external analysis should be ignored because it is confounded by HWE. This is contradicted by the NIOSH study authors’ own published conclusions that “the healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons.” Furthermore, OEHHA’s uncritical acceptance of conclusions of a more recent paper by Park (2020) that there is a Healthy Worker Survival Effect (HWSE) led OEHHA to support EPA IRIS model. However, the conclusions are not supported by the actual results in the paper. Improvements in these and other descriptions of the human epidemiological studies are needed to accurately assess the epidemiological weight-of-evidence.

Pertaining to IUR p. 44

External (comparisons to the general population) and internal analyses (worker to worker comparisons) in occupational epidemiology studies are complementary approaches to the examination of potential exposure-response associations. When they agree, confidence in the presence or absence of risk is enhanced. When they disagree, it is incumbent upon the researchers to explore explanations. In some cases, and more often in the early years of occupational epidemiology, the identification of the potential for the HWE led to a general preference in favor of internal analyses. The HWE, particularly for cancer outcomes, is of much lesser concern in external analyses of cohort studies that have been updated with longer observation periods. The UCC study has had two published updates since the original Greenberg et al. 1990 publication (Teta et al. 1993, Swaen et al., 2009), such that the average follow-up of study subjects has gone from 20 to 37 years. This is what Steenland et al. 2004 was referring to below when he noted the change observed from the original study published in 1991.

“The healthy worker effect has diminished (all-cause mortality was up to an 0.90 from the prior SMR of 0.81) as would be expected with increased follow up.”

ACC’s analysis and explanation of the HWE is also supported by IARC (1999) in its textbook on Cancer Epidemiology: Principles and Methods, which specifically notes that HWE “is known to vary with type of disease, being smaller for cancer than for other major diseases, and it tends to disappear with time since recruitment into the workforce.”

Furthermore, comparisons to worker populations can have their own limitations, such as small sample sizes, baseline risks that suggest they are non-representative of the true low or non-exposed population (e.g., Mikoczy et al., 2011).

OEHHA's complete reliance on internal analyses leads them to consider well-conducted meta-analyses as "flawed" and ignore their conclusions. In general, meta-analysis is a well-accepted method for summarization of results from multiple studies, despite being generally limited to pooled overall risk estimates, as many studies do not provide data by levels of exposure. Furthermore, OEHHA is incorrect in saying that Marsh et al. (2019) did not consider the results of NIOSH internal analyses. In fact, these authors, state:

"However, similar to the LHC results, the NIOSH findings, which revealed no overall excess for breast cancer, were limited to the exposure-response analyses using the log-transformed EtO exposure metric and were questioned by the authors due to their inconsistency across the other EtO metrics considered and potential case over-ascertainment in the higher exposure categories. As discussed above, due to the questionable validity of the positive EtO exposure-response of Mikoczy et al. (2011), these findings add little weight to the overall evidence for EtO exposure and breast cancer."

It is, therefore, scientifically unjustified to ignore the absence of any overall excess of breast cancer in the NIOSH 2004 mortality study and the relevant meta-analyses (Marsh et al. 2019; Vincent et al., 2019).

OEHHA's incomplete evaluations and acceptance of Park, 2020 led them to unequivocally support the EPA model.

Pertaining to IUR p. 43-44

OEHHA states they conducted several qualitative and quantitative assessments of potential bias and errors in the NIOSH study and its use by EPA.

1. Their discussion of exposure assessment is limited to the successful validation NIOSH performed of the post 1978 estimates from their regression model. OEHHA does not consider the NIOSH limitations related to exposure estimates for the pre-1978 period that had no validation, as ACC has previously discussed in detail. Instead, they criticize Bogen et al. (2019) for not validating their estimates. OEHHA cannot simultaneously criticize Bogden, which has contemporaneous material underlying it with respect to pre-1978 exposures and find NIOSH to be of high quality when the author of that study acknowledges that his model incorporates an unsubstantiated assumption that there were no changes in practices that would have reduced worker exposure. As described below, that assumption is manifestly inconsistent with cited literature

2. While OEHHA raises the issues of the HWE and the healthy worker survivor effect (HWSE), they conclude that the internal analyses by NIOSH removed the HWE issue and there is no more than a minor downward OR bias (10% or less), due to the HWSE. They cite Park 2020 to support the existence of a HWSE in the NIOSH data. We agree with OEHHA that neither of these types of biases are relevant. However, any HWE in the NIOSH study has diminished due to extensive follow up, as noted by Steenland, which adds to the relevance of the external analyses of these data. The absence of findings in external analyses of the NIOSH (and UCC data) adds to the uncertainty of the EPA model suggesting a highly potent carcinogen.
3. We also disagree with citing Park (2020) in support of the existence of a HWSE in the NIOSH study, such that control for employment duration leads to a stronger association between cumulative exposure and breast and hematopoietic cancers. In Section 3.2 of Park (2020), the author discusses the findings reported in Table 2. The models include both cumulative exposure to EtO and duration of employment – variables that are very likely highly correlated. For example, if there are two workers doing the same job, one for five years and another for 10, the exposure of the second worker would be double that of the first (absent some significant change in practices).

Park reports “statistically significant negative effect of duration (diminishing rate of leaving with increasing time on job) and positive effects of EtO cumulative exposure that are highly significant for all but the smaller work group of black women (Table 2).” These two variables are in the model used to fit the data with a similar multiplicative role. Given the high correlation between cumulative exposure and duration of employment, a negative coefficient for duration of employment would have to be compensated by a positive coefficient for cumulative exposure. Thus, it is not surprising that a negative coefficient for one variable results in a negative coefficient for the other variable. In fact, in three of the analyses reported in Table 2, the more negative of the coefficient for duration resulted in more positive coefficients for cumulative exposure.

Park (2020) Table 5 shows the results of Park’s models for female breast cancer. There, Park does not find any statistically significant relationship between breast cancer and EtO exposures or employment duration. Park states “For the 102 deaths from female breast cancer, there was no statistically significant difference in mortality on cumulative EtO exposure with a 10-year lag.” Park goes on to indicate that “with 20-year lag, the contribution of cumulative EtO was significant.” It is interesting that although the model is significant, the 95% confidence intervals indicate that the coefficients for cumulative exposures to EtO are not statistically significantly different from zero. That is, the 95% confidence intervals indicate that breast cancer in female workers is not related to cumulative exposure to EtO lagged 20 or 10 years.

Park (2020) Table 6 shows the results for lymphopoietic cancer deaths in the male and female workers. There, Park showed the results for male black workers only because “The 73 lymphopoietic cancer deaths did not represent an overall excess (SMR = 0.96; 95% CI, 0.76-

1.20), based on U.S. rates, particularly for white men (SMR = 0.92), and white women (SMR = 0.85), but among black workers, there was a statistically significant increase in SMR with cumulative EtO exposure (lagged 2.5 years; LRT: $P = .011$) (Table 6; model 1).” Similar to the results in Table 5 for breast cancer, in Table 6 the models statistically significantly improved the model fit to the lymphohematopoietic deaths in black workers but the coefficients for the cumulative exposure to EtO were not significantly different from zero; that is, there is no statistically significant increasing relationship between lymphopoietic cancer and cumulative exposure to EtO lagged 10 years even in the most sensitive subgroup of workers in the NIOSH study.

The above data are inconsistent with Park’s description of his results in his abstract that were accepted by OEHHHA.

4. OEHHHA attempted to address the possibility that high intensity- short exposures might explain the NIOSH findings and therefore not be generalizable to the general population, not subject to such types of exposures. Without actual NIOSH data and with incorporation of several questionable assumptions, OEHHHA concludes that excluding workers with these exposures from the NIOSH study would have little impact on the EPA exposure-response slope. They assumed that workers with this type of exposure would most likely be in the middle categories of cumulative exposure.

OEHHHA then estimated case and control counts in each exposure category, recalculated ORs and exposure-response slopes after excluding various percentages of participants (e.g., 10–30% high intensity-short duration exposed workers) in the middle exposure categories, using guestimates since the actual data were not available. “Exclusions were done at the case/control ratio equal to or slightly lower than that reported in the highest exposure category (where almost all workers probably had at least some high intensity exposure). Overall, these exclusions (with and without replacing the excluded participants into the highest category) had little impact on exposure-response slopes (e.g., 10% or less). This suggests that this issue did not have a major effect on the unit risk calculations or the generalizability of the NIOSH findings.” This conclusion is hardly justified using this obscure analysis and exclusion assumptions, in the absence of actual NIOSH data.

We agree with OEHHHA’s summary of the limitations of community-based studies, which makes them inappropriate for exposure-response but disagree that they are useful for hazard assessment.

Pertaining to IUR p. 13, 46

On p.13 OEHHHA states, “Four epidemiological studies not included in the US EPA’s IRIS assessment were identified by OEHHHA (Garcia et al., 2015; Bulka et al., 2016; Hart et al., 2018; and Jones et al., 2023). These studies investigated associations between residential proximity to EtO-emitting facilities and increased cancer risk. Emissions data were obtained at the community

level from US EPA's TRI (Bulka et al., 2016; Jones et al., 2023; US EPA, 2023a) and National Air Toxics Assessment (Garcia et al., 2015; Hart et al., 2018; US EPA, 2018) databases. While these community-based air pollutant studies can be useful for hazard identification, they were judged by OEHHA to be less useful for dose-response assessment of EtO compared to the occupational studies (Steenland et al., 2003 and 2004; Swaen et al., 2009; and Mikoczy et al., 2011) due to greater uncertainty in estimating individual exposures. This can result in non-differential exposure misclassification, and bias in risk estimates towards the null (Shy et al., 1978). Furthermore, there were lower exposure levels, fewer exposed cases, and potentially less exposure contrast in these community-based studies of EtO, decreasing the sensitivity of the studies to detect an effect."

We agree with the limitations noted by EPA but disagree that community-based studies are useful for hazard identification of EtO, precisely because of limitations noted in EPA's final sentence. But in addition to concerns about sensitivity (study power), there are serious concerns in such studies related to confounding risks that may be related to potential errors in exposure assessment due to confounding by other sources of EtO exposure, such as smoking and highways. Bias can, therefore, be in either the positive (specificity) or negative direction (sensitivity), making such designs uninformative.

OEHHA fails to discuss the most important limitation of the Mikoczy et al. 2011 study – the questionable comparison group in the internal analyses

Pertaining to IUR p. 16

OEHHA has but one criticism of Mikoczy et al (2011): "Exposures were much lower than in the NIOSH and Union Carbide cohorts, which decreases the ability to detect an effect." This is apparently OEHHA's explanation for the failure in this study to detect any increase in LH cancers.

While not noted by OEHHA, Mikoczy et al. (2011) has been incorrectly cited in IRIS as supportive of a supralinear association with breast cancer, despite an overall deficit of breast cancer (SIR= 0.81), with or without consideration of a latency period. However, the two higher cumulative exposure groups had statistically significant elevated rates of breast cancer, due to a substantial and statistically significant deficit of breast cancer in the low dose reference group. This deficit is not explained by the HWE, which is primarily related to non-cancer causes and declines with length of follow up. As discussed above, there are clearly advantages to comparing workers to workers in epidemiology studies to overcome possible biases in external comparisons to the general population. However, there may also be disadvantages to using an internal comparison group that may not be recognized. One danger is selecting a referent group that has an unusual deficit of the disease of interest that creates an artifact of an excess as is illustrated in this study, whose referent group breast cancer rates are 50% of general population baseline. This serious limitation was also illuminated in Marsh et al. (2019):

“The validity of the Mikoczy et al. (2011) finding and conclusion can be challenged, however, on the basis of several methodological issues. First, the greater than 2-fold relative excesses in breast cancer incidence risk in the two highest cumulative EO exposure categories were ensured by an inordinately large, statistically significant 48% deficit in breast cancer incidence in the baseline category. The inordinately low baseline SIR for breast cancer is puzzling given that regional rates were used in the external comparisons and that there was no apparent problem with under-ascertainment of breast cancer cases. The healthy worker effect is also not a reasonable explanation for the low baseline breast cancer rate (Gridley et al. 1999). It appears that for unknown reasons, the baseline group used by Mikoczy et al. (2011) differs from the highest two cumulative EO exposure groups on factors other than EO exposure that may be related to breast cancer.”

The IRIS report quantitatively demonstrated the inconsistency of the excesses reported at very low exposures in this population with excesses at only higher exposures in the NIOSH study.

“Thus, crude comparison analyses were done to evaluate whether or not the exposure-response models of the NIOSH study that were used to derive unit risk estimates in this assessment gave predictions consistent with the Mikoczy et al. (2011) internal incidence ratios (IIRs) for the two highest exposure quartiles (see Section J.2.2 of Appendix J). The predicted values for lymphoid cancer were within the 95% CIs for the IIRs for lymphohematopoietic cancer reported by Mikoczy et al. (2011). The predicted values for breast cancer incidence, however, were below the lower limit of the 95% CIs for the IIRs for breast cancer, suggesting that the Mikoczy et al. (2011) results are consistent with a higher unit risk estimate for breast cancer incidence than the one derived in this assessment. The reasons for the discrepancies are unknown... “(IRIS 2016, p.60-61)

Marsh et al. (2019) also addressed this exposure inconsistency:

“Second, cumulative EO exposure levels in the Mikoczy et al. (2011) study were very low relative to both the UCC cohort (Swaen et al. 2009) and NIOSH breast cancer cohort incidence study (Steenland et al. 2003).”

EPA more recently argues that there were substantial exposures in the Mikoczy et al. cohort, making it more comparable to the exposures in the NIOSH cohort, backtracking from the IRIS report. OEHHA reports the breast cancer findings from the internal analysis and ignores the potential bias associated with a non-representative worker comparison group.

8. Based on its acceptance of the IRIS evaluation, OEHHA inaccurately exaggerates the reliability of the NIOSH worker exposure estimates prior to 1978

Pertaining to IUR p. 18, 45

OEHHA could improve the weight of evidence of the epidemiological data by more accurately describing the substantial limitations of the NIOSH worker exposure estimates prior to 1978. Furthermore, NIOSH has lost the electronic files needed to independently assess the NIOSH estimates of exposure prior to 1978 for which NIOSH had no direct measurements²². These data quality issues make open access and independent assessment of the IRIS IUR difficult for lymphoid cancers and impossible for breast cancers.

OEHHA makes the same definitive statement regarding the NIOSH cohort exposure assessment, *“Each participant’s EtO exposure was estimated using a validated multiple regression exposure model that incorporated information on workplace air measurements, sterilization unit size, engineering controls, timing of sterilization, product type, calendar year, and historical process changes.”* (IUR p. 18)

OEHHA also states,

“The NIOSH study was judged by US EPA to be of “high quality” based on the availability of quantitative exposure estimates for individual workers, high-quality exposure assessment, longitudinal study design, large sample size, inclusion of males and females, adequate follow-up, absence of known confounding exposures, multiple study locations, and use of internal comparison groups. The NIOSH study was also reviewed by OEHHA, using the Bradford-Hill guidelines for causal inference and NTP’s risk of bias tool (Hill, 1965; NTP, 2019), and determined to be of high quality and unlikely to be affected by important bias or confounding.” (IUR p. 18)

OEHHA dismisses a robust analysis of the trend of the NIOSH exposure data by Bogen et al. (2019):

“Bogen et al. (2019) have suggested that exposures occurring prior to 1978, the first year that EtO sampling data were available for the NIOSH cohort, may have been dramatically under-predicted by the NIOSH exposure model. However, as noted by these authors, several assumptions were used in their assessment, and the information used to support these assumptions, “were limited in scope and quantitative detail.” In addition, the authors were unable to validate their pre-1978 predictions since no actual worker measurements were available from that time. Overall, because of these and other weaknesses, the accuracy of the Bogen et al. (2019) assessment is unknown to OEHHA.” (IUR, p.44)

²² In response to the panel’s suggestion that the Hornung analysis represents an “invaluable opportunity” for further analysis of the impact of possible errors in exposure estimation, the EPA investigated the possible use of the “errors in variables” approach (page 27 of the panel report). . . Unfortunately, the electronic data files used in the exposure analysis were no longer available, so that analysis based on the errors-in-variables approach was not possible.

These OEHHA statements show, at a minimum, a lack of rigor in evaluating the NIOSH exposure model (Hornung et al. 1994) and its “validation”, and a biased evaluation of the Bogen et al. (2019) paper as discussed in our general comments above.

A more correct statement describing the NIOSH multiple regression exposure model is that the model was only validated for the period 1979-1985 (very few samples were collected from 1976-1978) during which EtO concentration measurements were collected from six facilities, but not for the earlier period of sterilizer facility operations (pre-1978; from late 1930’s to late 1970’s) when a majority of cohort workers were occupationally exposed to EtO and no exposure measurements were collected. An incorrect assumption by Hornung et al. in applying the NIOSH model to the Pre1978 sterilizer operations regarding a key variable “calendar year”, a surrogate for improvement in work practices, inferred no changes in the pre-1978 period and raises serious question about reliability of the NIOSH model in predicting early worker exposures and the dose-response relationship based on the exposures of these early workers in this cohort.

There are several reasons to question the reliability of NIOSH model predictions of early sterilizer worker exposure estimates:

- First, the NIOSH multiple regression exposure model validation (Hornung et al., 1994) was based using a portion of the 1978-1986 to develop the model and another portion of the data to test the model. Therefore, the model was validated for the years with data but not for the early years for which no concentration measurements were available. Hornung et al. provided no other data, information or analyses for sterilizer workers or processes in this earlier time period to check the applicability to this NIOSH exposure model to sterilization workers in the cohort who worked from the late 1930’s to later 1970’s. These facts regarding the NIOSH model validation should have raised concern about model predictions for early sterilization workers.
- Second, Hornung et al. selected Calendar year, a surrogate for improvement in work practices, as the key variable in the NIOSH exposure model to pre-1978 cohort workers. This variable was applied conditionally on the max year 1978 forcing the inverse parabolic fit for years before 1978. This application of calendar year inferred that there were no major changes in work practices in sterilization operations between the late 1930’s and late 1970’s that would have affected worker exposures.

Contrary to this inference, substantial published information and data on early work practices and changes in work practices were found in technical literature, industry documents, and from early workers and industry experts (Bogen et al., 2019). In other words, Bogen et al. (2019) brought far more information and data to inform the validity of the NIOSH model prior to 1978, when NIOSH had insufficient (1976-1978) or no (<1976) data. For example, the numbers of repeated cycles of in chamber, post-exposure vacuum air- or nitrogen washes have increased from two or fewer from early operation up to ten or more for operations in the 1980’s leaving high levels of EtO residues to off

gas in from sterilized materials and packaging from early operations and lower levels in later operations (Goldgraben and Zank 1981; Buonicore et al., 1984).

Consistent with few wash cycles, there are several published studies of rates of EtO off gassing from sterilized materials representing conditions in the 1950's through 1980's (Bruch 1961, 1972; Buonicore et al., 1984; FDA 1978; Stetson et al., 1976; White, 1977). As importantly, early operations stored sterilized materials in the same room as ongoing sterilizer operations where both operational emissions and sterilized material off gassing contributed to worker exposure while later operations moved sterilized material to a separate warehouse room reducing the exposure of highly exposed sterilizer operators (Bogen et al., 2019). Clearly there were important work practice changes over time that need be considered in assessing the exposure of cohort workers.

- Third, the NIOSH exposure model based on the conditioning of calendar year predicted early sterilization workers were exposed to EtO concentration substantially lower than workers in 1978 when exposure concentration predictions were based on measurements (see Figure 8 below from Bogen et al., 2019). One would not expect low exposure concentration when equipment and processes were crude, and little was known about EtO toxicity and no worker protection regulations. The NIOSH model predicted early worker increasing exposure pattern is inconsistent with industrial hygiene data collected in other industries (e.g., on Grote et al., 2003, 2006) and inconsistent with historic worker exposure guidance (ACGIH 1948, 1957) for EtO exposure concentrations in the workplace. ACGIH provided an exposure limit for EtO of 100 ppm in 1948 and 50 ppm in 1957 to encourage reductions in workplace exposure. As a reality check, no ACGIH guidance would have been needed had EtO concentration been as low as predicted by the NIOSH exposure model.
- Fourth, Bogen et al. (2019) performed an engineering/industrial hygiene evaluation of early sterilization worker EtO exposure to assess the reliability of NIOSH exposure model predictions of an increasing exposure trend. Bogen et al. concluded that from the late 1930's to 1978 there was a decreasing exposure trend for sterilizer workers rather than increasing trend from very low exposures to high exposures predicted by the NIOSH exposure model (Figure 8 from Bogen et al., 2019, Figure 5).

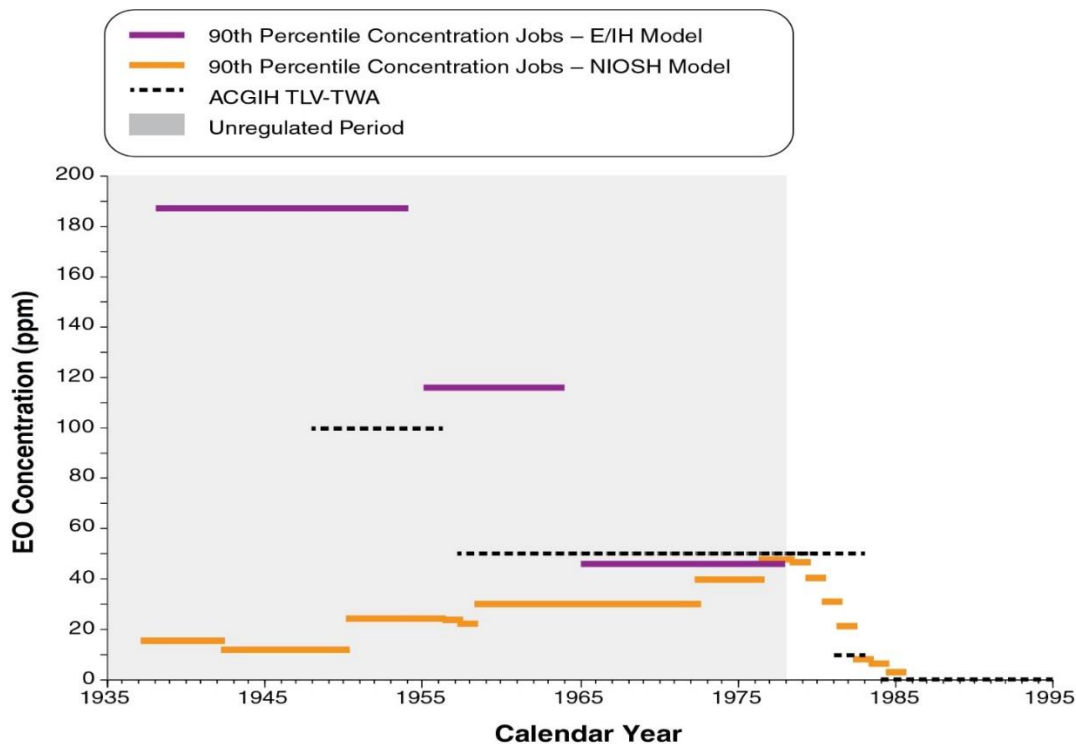


Figure 8. Comparison of E/IH (purple lines) and NSR (orange lines) exposure model estimates of occupational respiratory exposures to EtO in facilities that sterilized medical/health products and prevailing ACGIH TLV limits for EtO (dashed lines). Shaded area represents the period during which very limited or (pre-1976) no contemporaneous measurements were available to validate NSR model predictions and during which no EtO-specific regulations were in place to limit occupational EtO exposures. Adapted from Figure 5 of Bogen et al. (2019)

There are no data or analyses available to support OEHHA’s agreement with EPA that the NIOSH model produced a “high-quality exposure assessment.” To the contrary, Bogen et al. (2019) published substantial data and analyses showing that the NIOSH model is flawed and, there was a decreasing rather than increasing EtO exposure trend for pre-1978 sterilizer operators contributing uncertainty to the EPA and OEHHA EtO risk assessments. OEHHA should recognize the limitations of the NIOSH multiple regression exposure model predictions for early sterilizer operators and the potential adverse effects it has on estimation of risk.

Assigning cases with underestimated exposures means that the lymphoid cancer is associated with lower EtO levels than the workers with lymphoid cancers had been exposed to. Underestimating exposures associated with cancers will lead to an overestimation of potency. As there are data on worker exposures to EtO pre-1978 for production workers, it is suggested that OEHHA review production worker cohort monitoring data to ascertain a more reliable picture of early worker exposure patterns. After doing so, OEHHA can further evaluate how to view the NIOSH study in its weight of evidence analysis.

9. The Union Carbide Corp. (UCC) cohort should play a prominent role in considering the strength and consistency of the epidemiology data in supporting the IRIS vs. TCEQ IUR. OEHHA's description of this cohort in the text and Table 7 is missing the internal analysis by Valdez-Flores et al. (2010) which included exploration of different exposure metrics and lag times. The absence of findings in the UCC cohort for male LH is not consistent with a steep slope at low concentrations.

Pertaining to IUR p. 12-13, 16

This UCC study is very important to consider in the weight of evidence because it included long-term follow-up of workers from the 1940s, the infancy in EtO production. The absence of findings in the UCC cohort for male LH is not consistent with a steep slope at low concentrations and does not support the IRIS (2016) derivation of one of the highest IURs. This cohort of 2,174 workers was a subset of another NIOSH study of or more than 29,000 UCC chemical workers in the Kanawha Valley (KV) of WV (Rimsky et al., 1988).

Compared to the NIOSH sterilizer worker mortality study, the UCC study has a smaller cohort sample size but has comparable numbers of LH and lymphoid cancers as those reported in the male component of the NIOSH cohort. The UCC study is, therefore, informative, with respect to males, and the increases in LH and lymphoid cancers reported in the NIOSH study were limited to males (Steenland et al., 2004). Moreover, it is of similar quality to the NIOSH study, especially considering the problems with the NIOSH study noted above.

Furthermore, the quality of the UCC study exposure assessment is comparable to that of the NIOSH study. It employed individual exposure estimates for a substantial period between 1925-1988, utilizing the Greenberg et al. (1990) validated categorization of EtO producing and using departments by level of exposure and quantitative estimates of average intensity by these categories developed by Teta et al. (1993). There were no potential confounders to other chemical exposures because such workers were removed from analysis by Teta et al. (1993), Swaen et al. (2009) and Valdez-Flores et al. (2010).

Exposure data were available for study subjects at the West Virginia (WV) locations starting in 1974. They were available from Union Carbide's Texas City plant that operated identically to the WV location from the early 1960s. This represents an important advantage of the UCC study over the NIOSH study, which had no exposure data prior to 1978 (Bogen et al., 2019; see previous section for detailed discussion). Estimates from EtO operations in the literature were used for the 1940-1956 exposure period, although only a small percentage of the cohort were employed during that period.

Contrary to Table 7 of OEHHA's Draft IUR, there was exploration of log cumulative exposures and multiple lag times. Valdez Flores et al. (2010) reports that Table S11 in Supplemental materials indicates that the fit (maximum likelihood) varies depending upon the exposure scale used in the log cumulative exposure model (i.e., ppm-days, ppm-years, ppb-days, and ppb-

years). Table S11 also illustrates that the Cox proportional hazard model with the slope parameter multiplying cumulative EO exposure fits the data better than any of these four alternative log cumulative exposure models in more than 55% of the combinations of 12 endpoints. None of the other lag periods resulted in a change in statistical significance, therefore no lag was included in the Valdez-Flores et al. (2010) publication. Nevertheless, to be consistent with NIOSH, a lag period of 15 years was applied to the lymphoid analysis by TCEQ (2020a).

In summary, the absence of increases in LH and lymphoid cancers in the UCC study (in both external and/or internal comparisons), as well as the statistically significant increases in the NIOSH study limited to male highest exposure groups in internal comparisons conducted by Steenland et al. (2004), call into question the biological plausibility of the very high IRIS IUR for LH cancers. Overall, the epidemiological evidence does not support EtO as a potent carcinogen with a steep exposure-response pattern at low exposures. The standard CPH model used to derive the TCEQ IUR is a model well-accepted by epidemiologists in cancer exposure-response analysis, is linear at exposure levels of interest, and consistent with an assumption of no-threshold that reflects the epidemiological weight of evidence.

10. The draft IUR document questions the reliability of the Kirman et al. (2021) method of estimating endogenous levels by favoring speculative uncertainty and tangential information on DNA adducts over the toxicokinetic and converging evidence from animals and humans that was presented by Kirman et al. and by data in Filser and Klein (2018). Endogenous levels can greatly exceed the levels to which residents near sterilization facilities may be exposed. While EPA’s potency estimate technically only applies to exposures above endogenous levels, it is questionable that a chemical would be a potent carcinogen at levels that the body produces through natural processes.

Pertaining to IUR p. 29, 30

OEHHA’s Draft IUR indicates that cancer risks account for endogenous levels.

“The EtO exposures from ambient and endogenous sources contribute to HEV levels, other adduct levels, and cumulative cancer risks (i.e., including from other chemicals and conditions). Thus, EtO and ethylene exposures are part of the risk factors accounting for the background cancer risk in the general population, including lymphoid and breast cancers (US EPA, 2016a; 2016b).” (IUR p. 29)

This is a true statement for both the TCEQ and IRIS cancer risk calculation and should not be used as a basis to ignore consideration of endogenous levels as part of an important reality check for derivation of cancer risk specific concentrations. It does not make sense for risk specific concentrations to be orders of magnitude below human endogenous levels, or to be a fraction of the population variability of human endogenous levels.

Most general population background exposure will be endogenous.

Pertaining to IUR p. 29

We applaud OEHHA for including a section on endogenous exposure to EtO. As illustrated by our comments above, this topic is important to future risk assessment and risk management decisions made for EtO.

We recommend to expand this section to include the following:

The biochemical pathways that contribute to endogenous exposures, include: (1) production of ethylene by bacteria normally present in the gastrointestinal tract, which is then absorbed into the body; and (2) systemic production of ethylene by specific precursors and by oxidative stress. Endogenous production of EtO results from the oxidation of ethylene resulting from both sources. These pathways are operable in all mammalian species, with measured EtO biomarker levels (2-hydroxyethyl valine or HEV) generally being higher in laboratory rats and mice than in humans.

Endogenous exposures to EtO are variable. These exposures vary from person to person (interindividual variation) and from day to day (temporal variation), and can be modulated by diet (e.g., fatty acid composition; diet content of precursors that are metabolized to ethylene), medications (e.g., antibiotics), and underlying conditions (e.g., oxidative stress).

Kirman et al. (2021) estimated endogenously produced EtO is the largest contributor to EtO-biomarker levels in general population nonsmokers. The estimated average HEV burden of 29.2 pmol/g Hb resulting from endogenous exposure corresponds to an equivalent median inhalation exposure to 2.3 ppb EtO in air. In this context, EtO RSC exposure (0.0016 ppb) is more than 1000-fold lower than the endogenous exposure and would generally be considered negligible.

Background exogenous exposure is generally a small fraction of total background exposure

Pertaining to IUR p. 29

Most of the general population background exposure arises from endogenous production (~95%), whereas exogenous exposure via inhalation of EtO in ambient air generally constitutes a small fraction (~5%) of total exposure (Kirman et al., 2021). EtO in ambient air has been sampled since 2018 at background monitoring locations across the U.S. under the EPA NATTS and UAT hazardous substances monitoring programs. Samples also have been collected by state agencies and others at local/regional background locations as part of monitoring programs for EtO emitting facilities. Therefore, substantial data exists to characterize general population background exogenous exposures.

Total background exposure from endogenous and exogenous pathways has been characterized from CDC NHANES biomarker data and Kirman et al. (2021) equivalent concentrations

Pertaining to IUR p. 29; NISRL p 18

Our knowledge of EtO background exposure is informed by CDC internal dose data in the form of a representative exposure biomarker, N-(2-hydroxyethyl)-valine (HEV) adduct levels, measured in erythrocytes for nonsmokers and smokers in the U.S. population (CDC 2019; Kirman et al., 2021). HEV adduct levels represent an individual's total background EtO exposure from endogenous and exogenous sources. Kirman et al. 2021 developed a relationship between biomarker (HEV) concentration and total and endogenous equivalent concentrations (equivalent continuous exposure concentrations in ppb) for smokers and nonsmokers in the U.S. population. Endogenous and total equivalent levels reflect air concentrations of EtO that are equivalent to the levels that are produced endogenously, and endogenously and exogenously, respectively. Filser and Klein (2018; Figure 12A) provides an independent PBPK model-based validation of the linear equivalent relationship adopted by Kirman et al. (2021).

OEHHA mischaracterizes the relevance and importance of background endogenous and endogenous equivalent exposure

“While the hemoglobin adducts such as the HEV resulting from endogenous and exogenous EtO may serve as sensitive markers of EtO exposure, the paucity of data on their relationship with the relevant DNA adducts makes it a limiting factor for use in risk assessment (Rietjens et al., 2021[sic]²³).” (IUR p. 30)

- EtO hemoglobin adducts (HEV) are useful biomarkers of exposure, a point also noted in this publication, “...Hb alkylation may serve as a particularly sensitive marker of exposure...” They are used as a cumulative measure of the internal doses of EtO present in blood for several months prior to measurement.
- Kirman’s analysis utilizes HEV to apportion total exposures to EtO from different pathways.
- There are several technical issues associated with measuring EtO based on the best quantifiable DNA adduct (N7-HEG), including high variation across analytical methods, difficulties in sample preparation, uncertainties in repair half-life/depuration rates, and limited data availability, which limit the utility of N7-HEG as a biomarker of exposure.
- Limitations in the understanding in the relationship between HEV and DNA biomarkers does not detract from the utility of HEV biomarkers or from the application in the analysis of Kirman et al. (2021). The “paucity” of data referred to in this comment applies equally to the relationship between external dose measures (e.g., air concentrations) and N7-HEG.

“Alternatively, using the HEV levels to back-calculate endogenous-equivalent air concentrations of EtO is untenable at present as there are no relevant toxicokinetic models or data to support it.” (IUR p. 30)

- Steady state blood levels of EtO (area under the curve or AUC) can be estimated from measured HEV levels with a high degree of confidence since the values for the reaction rate constants for EtO binding to hemoglobin and erythrocyte lifespans are known, as described in Motwani and Tornqvist (2014; see equations 2-3b).
- Although a toxicokinetic model that fully encodes the endogenous formation pathways (Kirman et al. 2021, Figure 4) are not yet available, the model of Filser and Klein (2018) and data cited therein (Figure 12A of Filser and Klein, 2018) are fully consistent with the use of a linear correlation between EtO in air and HEV measurements in humans, as adopted in Kirman et al. (2021) :

²³ OEHA typo. It should be 2022.

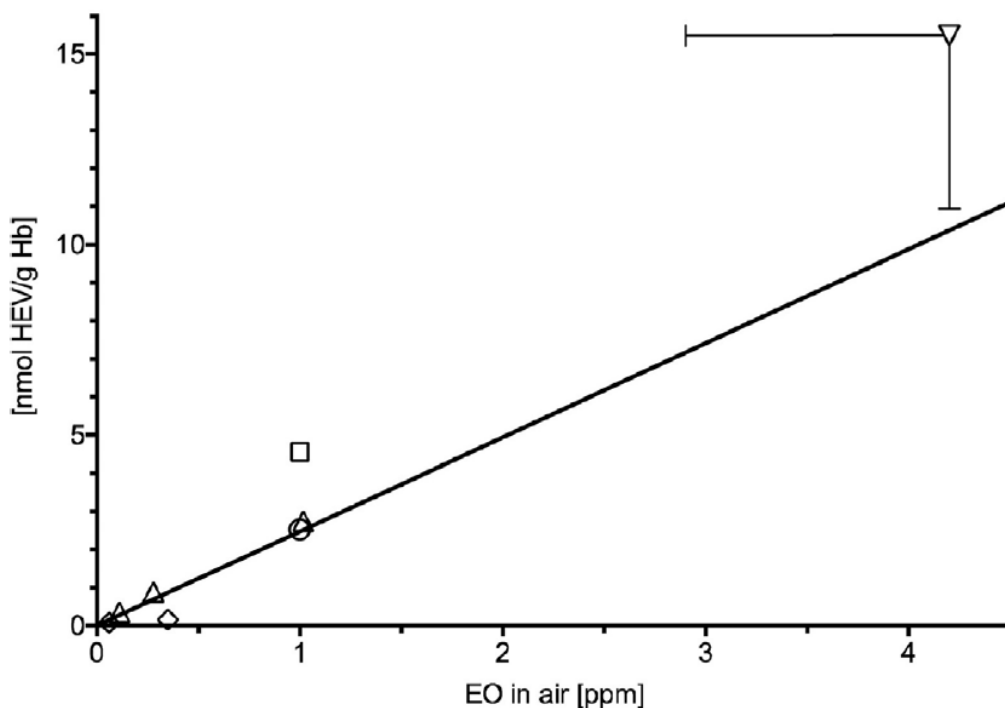


Figure 9. Hemoglobin adducts (HEV, nmol/g Hb) in workers exposed to EtO in air (from Filser and Klein, 2018).

- The available worker data depicted in this figure indicate that a linear relationship between HEV adducts and EtO in air is across a broad range of concentrations (~ 0.1 ppm to ~ 4 ppm). Furthermore, the PBPK model of Filser and Klein (2018) predict a linear relationship across this range of exposures, as well as for exposures extrapolated below this concentration range (solid black line). Lastly, for exposure levels below the range of worker exposures, the NHANES biomonitoring data in smokers and in non-smokers are also consistent with a linear relationship (depicted by redline; note - log-linear scale) between EtO exposure (using cigarettes per day as a metric) and HEV adduct formation:

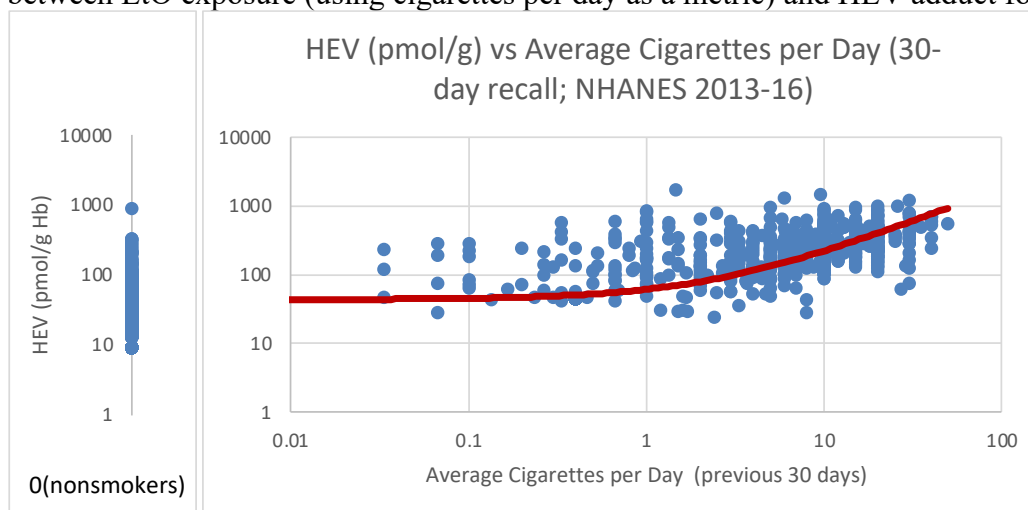


Figure 10. Hemoglobin adducts (HEV, pmol/g Hb) in U.S. smokers exposed to EtO in cigarette smoke (NHANES, 2013-16)

- These data indicate that the linear relationship between EtO exposure is maintained from background exposure levels up to 30x background levels. The linear relationship between cigarettes per day and HEV in this figure is consistent with a linear relationship (e.g., assessed by multilinear regression analyses) for another EO biomarker (urinary 2-hydroxyethyl mercapturic acid) as reported by CDC scientist (Kenwood et al., 2021). Together, these data provide evidence to support a linear relationship between HEV and EO exposure as used in Kirman and Hays (2017) and Kirman et al. (2021).

“In this regard, ATSDR (2022) concluded that data are not available to demonstrate that background levels in non-smokers are direct indicators of internal, endogenous EtO exposures.” (IUR p. 30)

- “Direct” measurements of endogenous exposure in isolation are not possible. However, as noted above, indirect estimates of endogenous exposure can be inferred from available data sets (EtO and ET air monitoring; NHANES biomonitoring data).

“The dose-response relationship for endogenous EtO exposures might be different from the dose-responses seen with ambient exposures, possibly sublinear but ultimately unknown (US EPA, 2016a).” (IUR p. 30)

- Measured HEV levels in human populations are dependent upon three parameters: (1) circulating levels of EtO in blood; (2) hemoglobin binding rates; and (3) erythrocyte lifespan. Although there are some possible sources of high-dose nonlinearity (e.g., induction of endogenous production of ethylene by EtO at high doses; theoretical exposure-related effects on erythrocyte turnover due to cytotoxicity) there are no documented sources of low-dose nonlinearity for EtO exposure and HEV formation. Any such nonlinearity would only be relevant at exposures above the range of observation (~0.1 to ~4 ppm) defined by Figure 12A above from Filser and Klein (2018). As noted above, there is no evidence of nonlinearity in the NHANES HEV biomonitoring data as a function of EO exposure (using cigarettes per day).

We believe that there are reliable data for characterizing background endogenous and endogenous equivalent EtO exposure and provide a preface for using background exposure as context for managing and communicating EtO risk.

Kirman et al. (2021) model of external EtO exposures and internal EtO HEV hemoglobin adducts (EtOHEV) is validated in a “forward” analysis as suggested by EPA (2022)

The relationship between NHANES HEV biomonitoring data as a function of EO exposure (using cigarettes per day) established by Kirman and Hays (2017) and Kirman et al. (2021) is validated with a “forward” analysis, as suggested by EPA (2022), based on measured EtO concentrations in mainstream cigarette smoke. Using the linear relationship between external EtO exposures and internal EtO HEV hemoglobin adducts (EtOHEV), Kirman et al. (2021) calculated that an approximate 10-fold increase in general population EtOHEV adducts in smokers compared to non-smokers (CDC NHANES, 2019) was equivalent to a continuous EtO

air exposure of 21.7 ± 20.2 ppb (mean $\pm$ SD). EPA (2022) suggested that the Kirman exposure model could be validated if “forwards determinations of smokers total exposures to EtO” compared reasonably to “backward” estimated EtO exposures derived from the Kirman EOHEV adduct/exposure relationship:

p.69: “EPA also notes that the assumed relationship between HEV adduct measurements and EtO exposures in smokers (Kirman et al. 2017 and 2021) also needs validation. Cigarette smoke contains EtO and ethylene which may be metabolized to EtO. Smokers also experience physiological and biochemical changes that could affect their EtO exposures and/or formation of protein adducts. For validation of the HEV based projections, “forwards” determinations of smokers total exposures to EtO (e.g., as might be assessed using exhaled breath measurements) could be compared with “backwards” calculations of projected EtO exposure levels hypothesized from HEV from adduct level. Paired measurements of breath levels of EtO and ethylene and HEV adduct levels could provide useful bottom-line data to test the HEV/equivalent inhaled concentration hypothesis.”

Importantly, and directly responsive to the EPA-recommended validation exercise, multiple datasets have been published that describe reliable analytically-determined concentrations of EtO in individual cigarettes that can then be converted to total daily EtO smoker exposures dependent on the intensity of smoking behavior (Table 1; Liu et al., 2014; Forster et al., 2018; Jaccard et al., 2019).

Liu et al. (2014) reported for Kentucky Reference 3R4F cigarettes mean concentrations of $8.37 \mu\text{g EtO/cig}$ under the International Organization for Standardization (ISO) smoking regimen and $26.03 \mu\text{g EtO/cig}$ under the “Health Canada intensive” (HCI) smoking regimen. Forster et al. (2018) reported for the updated Kentucky Reference 1R6F cigarettes mean concentrations of $17.2 \mu\text{g EtO/cig}$ (HCI) and $19.3 \mu\text{g EtO/cig}$ (HCI) for Kentucky Reference 3R4F cigarettes. Jaccard et al. (2019) reported for Kentucky Reference 1R6F cigarettes mean concentrations of $5.92 \mu\text{g EtO/cig}$ (ISO) and $17.3 \mu\text{g EtO/cig}$ (HCI). Jaccard et al. (2019) also reported for Kentucky Reference 3R4F cigarettes which yielded mean concentrations of $6.78 \mu\text{g EtO/cig}$ (ISO) and $19.2 \mu\text{g EtO/cig}$ (HCI).

Daily EtO exposure concentrations (EC) can be estimated as $C \times \text{CpD} / \text{IR}$, where C is the reported EtO concentration per cigarette ($\mu\text{g/cig}$), CpD is the number of cigarettes smoked per day (cig/day), and IR is the daily inhalation rate (m^3/day). CpD conservatively assumed to be 17 cig/day based on the average number of cigarette smoked by daily smokers in 2005 as reported by CDC (2018), and IR is assumed to be $16 \text{ m}^3/\text{day}$ based mean inhalation rates for adults aged > 16 yr (EPA 2011). The estimated ECs, shown in Table 7 below, ranged from 3.5 to 15 ppb. These estimates are generally consistent with Kirman et al. (2021) estimates of 21.7 ppb for smokers, 1.9 ppb for non-smokers, which results in 19.8 ppb from smoking contribution, and confirms that HEV adducts can provide reliable estimates of EO exposure.

Table 7. Estimated daily ethylene oxide exposure concentrations based on measured ethylene oxide concentrations in mainstream smoke

Source of EtO Mainstream Smoke Concentration Data	Reference Cigarette	Regimen	Estimated Daily Exposure Concentration (ppb)
Liu et al. 2014	3R4F	ISO	4.98
	3R4F	HCI	15.49
Forster et al. 2018	1R6F	HCI	10.23
	3R4F	HCI	11.48
Jaccard et al. 2019	1R6F	ISO	3.52
	1R6F	HCI	10.29
	3R4F	ISO	4.03
	3R4F	HCI	11.42

The data in Table 7 indicate that the “forward” analytical measurements of EtO in cigarette smoke, when converted to total daily EtO ppm exposures, are in excellent agreement with the “backwards” estimates of the mean and SD measurements of EtO ppm exposure calculated from the high-quality CDC smoker EtOHEV data using the Kirman EtO-EOHEV endogenous-equivalent model approach.

A preliminary analysis of the NHANES HEV data for smokers as a function CpD (see previous figure), demonstrates a linear relationship. The linear slope in this figure (18 pmol/g per average CpD) would correspond exactly with the slope of 10.9 pmol/g per ppb (continuous) if the conversion factor for ppb to CpD is approximately 0.6 ppb per CpD. Using the mean estimated daily concentration from Table 7 (8.9 ± 4.3 ppb) along with the value of 17 CpD, results in an independently derived conversion factor of 0.53 ± 0.25 ppb per CpD. Together these data indicate that the linear correlation between HEV in smoker exposures to EtO is excellent agreement with the linear correlation between HEV and occupational exposures to EtO (i.e., the slope of 10.9 pmol/g per ppb).

The consistency between the “forward” and “backward” smoking-derived EtO exposures can also be used to explore the plausibility of the IRIS IUR as a reasonable predictor of cancer risks associated with low EO exposures. If the IUR is assumed as correct, a 10 ppb (10,000 ppt, as a representative midpoint from Table 7) external EO exposure contributed by smoking is predicted to produce an upper-bound estimate on the order of 1×10^{-2} to 10^{-1} risk of cancers (i.e., the 0.1 ppt 10^{-6} risk projected by IUR), 5 orders of magnitude less than the approximate 10,000 ppt smoking exposures estimated by Kirman et al. (2021) and validated by direct measurement of EtO in cigarettes. This suggests smoking should result in a readily demonstrable cancer signal, but the overall epidemiological data are weak or equivocal for this endpoint. Thus, the smoking data and associated EtO exposure analyses are an important and reliable “reality check” that the IRIS IUR substantially overestimates the low-exposure cancer risks of EtO.

11. OEHHA cites two studies reporting an association between smoking and lymphohematopoietic (LH) cancers published in 2012 (Diver et al. 2012 and Kroll et al., 2012) to discount Kirman et al., (2021) reality checks. These two studies are inconsistent with the lymphoid cancer (NHL, lymphocytic leukemia, multiple myeloma) findings from the NIOSH mortality study (Steenland et al., 2004), upon which IRIS 2016 developed their low exposure high risk model and do not constitute a weight-of-evidence evaluation akin to the Surgeon General report, *The Health Consequences of Smoking —50 Years of Progress*. In addition, OEHHA cites IARC review associating a positive association between tobacco smoking and breast cancer, though not for lymphoid cancer.

Pertaining to IUR p. 29

OEHHA has responded to Kirman et al.'s plausibility argument that, if EtO caused lymphoid tumors, it would be seen in smoker studies, and such an association has not been reported. The draft OEHHA IUR (p. 29) cites two smoker studies, however, published in 2012 (Diver et al. and Kroll et al.) in an attempt to provide biological plausibility for the IRIS cancer risk for lymphoid cancers:

“Since the IARC review, new results from two large prospective cohort studies have found significant associations with lymphoid cancer. The American Cancer Society Cancer Prevention Study II identified 1926 non-Hodgkin lymphoma cases in a cohort of 152,958 men and women (Diver et al., 2012). The study found an association between current smoking and non-Hodgkin lymphoma in women (RR = 1.37, 95% CI = 1.04–1.81), with a positive trend for years smoked ($p < 0.01$). The UK Million Women Study identified 7047 lymphoid cancers in a cohort of 1.3 million women (Kroll et al., 2012). This study found associations between tobacco smoking and Hodgkin lymphoma (1.45 per 10 cigarettes/day, 95% CI = 1.22–1.72) and mature T-cell malignancies (1.38 per 10 cigarettes/day, 95% CI = 1.10–1.73). These large-cohort findings support the plausibility of increased cancer risks from low concentrations of EtO.”

These two studies do not support this statement. They are inconsistent with the lymphoid cancer (NHL, lymphocytic leukemia, multiple myeloma) findings from the NIOSH mortality study (Steenland et al., 2004), upon which IRIS 2016 developed their low exposure high risk model.

Diver et al. is a large cohort study of the relationship between smoking among men and women and the risk for non-Hodgkin lymphoid neoplasms (NHL), a cancer endpoint in IRIS 2016, based on the NIOSH findings for this group of cancers. Diver et al. examined smoking history in detail including status, intensity, duration, cigarettes /day. OEHHA cites Diver et al.'s statistically significant RR for currently smoking women (1.37) but fails to note the deficit in currently smoking males (0.88), the positive trend with cigarettes per day and years smoked for females, no trends for males. This lack of positive association in smoking males occurred despite the fact that males smoked more than females. Furthermore, they fail to note these gender increases are in the opposite direction of the NIOSH gender results associated with EtO exposure, SMRs=1.29

for males and 0.73 for females and the positive slope for males and the negative slope for females in internal analyses.

Given the large number of cases in this study, they were able to demonstrate gender differences statistically. Despite gender differences, they also presented data for males and females combined. A statistically significant trend for NHL was seen for women but no trend for both genders combined. The results for other subtypes of the NIOSH lymphoid category either are positive for females only (lymphocytic leukemia) or non-positive for both genders (multiple myeloma). Diver et al conclude, “In the present study, current smoking was associated with an increased risk of NHL in women but not in men.”

The Kroll et al. (2012) large cohort study was limited to females and examined the relationship between smoking and hematological cancers (both lymphoid and myeloid). OEHHHA cites the increased risk observed in this study for **Hodgkin** lymphoma, which is not included in the NIOSH lymphoid category, which includes **non-Hodgkin** lymphoma. So OEHHHA cites positive results but for a different disease. The authors do provide RRs for lymphoid cancers in their low exposure smokers (<15 cigarettes per day). No statistically significant increases were seen; no evidence of steep increases at low concentrations.

Both papers summarize the existing literature related to smoking and hematologic cancers as “inconclusive” or “inconsistent”, indicating a need for their research. Based upon their findings, Diver et al., (2012) conclude, “this large cohort study supports an association with cigarette smoking and increased risk of follicular lymphoma in women”, while Kroll et al. (2012) conclude, “Cigarette smoking was associated with increased risk of Hodgkin lymphoma, consistent with previous reports.” The weight of evidence related to smoking and lymphoid tumors (as defined by NIOSH) overall and at low exposure concentrations remain inconsistent and inconclusive.

EPA has also addressed this issue by raising the bar beyond a reality check of the existing literature requiring detailed quantitative analyses with adjustment for confounding and error bounds to rule out an association, ignoring theoretically easy detection of their putative IRIS conclusion of high risk at low exposures.

“As cigarette smoke contains many carcinogens, there is not a reason to expect, that EtO exposures to smokers would contribute a large part of total cancer risks due to cigarette smoking. A quantitative statistical analysis, which has not been reported, would be needed to place bounds on the potential levels of risk from lymphoid and breast cancers in smokers to support comparisons EtO cancer risks. Results from such analyses, appropriately controlled for other risk factors, might support reasonable comparisons of lymphoid and breast cancer rates in smokers and levels of risk of these tumors that would be predicted by EtO exposures from smoking. However, such analyses, to EPA's knowledge, do not appear to have been undertaken” (EPA, 2022, p. 68).

The Agency concedes smokers have elevated EtO exposures “EPA notes that as smokers do have elevated exposures to EtO, further work to define and validate EtO exposure estimates and to

determine statistical bounds on risks for EtO associated cancers in the smokers could in the future contribute important information for EtO risk assessment” (EPA 2022, p. 69).

Neither OEHHA nor EPA considered the published literature showing increased risk of acute myelogenous leukemia (AML) among smokers (IARC, 2012b). The average smoker is exposed to 1.8 mg/day of benzene, which is ten times that of non-smokers (ATSDR, 2007). These findings are plausible and a reasonable reality check, given that benzene is a known cause of AML. Extensive quantitative analyses as described above by EPA is not needed for this purpose, nor would it be needed to question the plausibility of an EtO/lymphoid tumor relationship based on highly exposed smokers.

The citation of these two studies reporting an association between smoking and LH cancers (Diver et al., 2012; Kroll et al., 2012) does not constitute a weight-of-evidence evaluation akin to the Surgeon General report, *The Health Consequences of Smoking —50 Years of Progress* (US DHHS, 2014). More importantly, it does not address the point that an extraordinarily large potency estimate derived by USEPA for EtO is inconsistent with isolated or weak associations. HEV levels in smokers (236 pmol/g Hb; per NHANES) are equivalent to daily exposures to 780 ug/day, which is more than 4 orders of magnitude higher than the NSRL value, which would place predicted cancer risks above 1×10^{-1} . Because smoking prevalence and intensity was much higher in the past, HEV burdens (and predicted risks from EtO exposures) would also be much higher than measured by NHANES. If the unit risk for EtO were truly predictive of its potency, the reported associations between smoking and lymphoid cancers would be larger and more consistently reported across epidemiological studies of smokers.

12. OEHHA’s estimated EtO 10^{-5} Risk Specific Concentration (RSC) provide little utility in managing general population risk if background exogenous exposure isn’t considered as an initial reality check. There has been an extensive ambient air measurement campaign over the last several years, including measurements near many EO facilities and at background locations. In many cases, the levels of ethylene oxide far away from facilities are similar to the levels near the facilities.

Pertaining to IUR p. 41; NSRL p. 49, 51

EtO is unique among managed hazardous substances

- Ethylene is emitted to air from natural sources including plants where it functions as a hormone, microbial activity in soils, sediment and plant litter, as well as plants in aquatic systems (reviewed by Sawada and Totsuka 1986; Morgott 2015; Health Canada, 2016). A vast majority of ethylene emissions are from natural sources (Health Canada 2016). Ethylene also is emitted from anthropogenic sources such as biomass burning, including forest fires, and from exhaust emissions from gasoline and diesel vehicles (Swada and Totsuka, 1986; Margott, 2015; Health Canada, 2016). Early reviews also suggested EtO is emitted from vehicle exhaust (EPA 1985) although there is little current published supporting data. As both ethylene and EtO are constituents of tobacco smoke, combustion of tobacco (see Kirman et al., 2021), it seems reasonable that both ethylene and EtO may be emitted by biomass combustion and combustion exhaust from vehicles. As early as the 1970’s, ethylene from natural and unregulated sources was being measured at relatively high levels in urban air (39-700 ppb; Ables and Heggstad, 1973). More recently, EtO has also been measured in ambient air at multiple locations across the U.S. away from known industrial sources to characterize this background exogenous source (median levels 0.03-0.33 ppb; ATSDR 2022; Sheehan et al. 2021; Lewis et al., 2022; Georgia EPD 2022).

Based on the limitations of its risk assessment, OEHHA should consider including discussion of EtO general population background exposure to provide context for risk management and risk communication

OEHHA makes the following statements regarding background exposure,

“Measurements of specific hemoglobin adduct levels, such as N-2-hydroxyethylvaline (HEV), in humans or other species, reflect the integrated exposure to ethylene (endogenous + exogenous) and EtO (endogenous + exogenous). Kirman et al. (2021) showed background exposures to EtO and ethylene in ambient air alone are insufficient to account for HEV levels seen in non-smokers, and endogenous EtO production contributes more to non-smoker HEV levels than ambient EtO and ethylene exposures do. The EtO exposures from ambient and endogenous sources contribute to HEV levels, other adduct levels, and cumulative cancer risks (i.e., including

from other chemicals and conditions). Thus, EtO and ethylene exposures are part of the risk factors accounting for the background cancer risk in the general population, including lymphoid and breast cancers (US EPA, 2016a; 2016b)."

EtO background exposure contributes more to understanding risk than just accounting for background cancer risk; it provides a reality check on managing EtO general population risk when there are unaddressed questions about the representativeness of the risk model. It is likely reasonable to assume that these exposures do not impact the conversions between relative risk and extra risk measures in the dose-response assessment. However, this assumption is not valid for exposures to EtO from smoking, which has changed significantly over time (Kirman et al., 2021) and can vary between worker sub-populations (e.g., salaried vs. hourly workers; Hsu et al., 2019). As such, smoking is a potential confounder for EtO exposures (vs. a confounder to observed cancer response) in the NIOSH cohort. In addition, there is a clear need to include discussion of background exposures for the purposes of risk management and risk communication of total EtO exposures and potential risks. Based on the limitations in the OEHHHA EtO risk assessment described above and the unique characteristics of EtO background exposure, a risk management check based on general population background exposure is warranted as a reality check of the utility of OEHHHA's assessment RSCs in managing general population EtO risk.

The draft OEHHHA assessment estimated EtO RSC provides little utility in managing general population risk if background exogenous exposure isn't considered as an initial reality check

Based on reported monitoring around emitting facilities, the OEHHHA 10^{-5} RSC for EtO would be a small fraction of substantially higher ambient background concentrations from natural and unregulated anthropogenic EtO sources otherwise associated with industrial emissions. The EtO IUR document reported ambient background EtO concentrations for the Los Angeles area ranging from 0.02-0.17 ppb. Based on data from the EPA NATTS and UAT monitoring programs for the October 2018 to September 2019 period, ATSDR estimated a national mean background EtO concentration of 0.13 ppb (ATSDR, 2022). Similarly, the same monitoring data for years 2018-2021 showed median (50th percentile) background EtO concentrations ranged from 0.03-0.33 ppb nationally (summarized in Lewis et al., 2022). Local/regional location background EtO concentration for eight sterilization facilities evaluated over an extended period again showed median and 90th percentile background concentrations ranging from 0.07 and 0.26 to 0.13 and 0.56 ppb, respectively (Sheehan et al., 2021).

These data show that background concentrations are variable but more importantly, that everyone nationally (including Californians) is exposed exogenously to mean/median background concentrations of EtO substantially greater (~50-fold) than the EtO RSC. Although it has been suggested that true background concentration based on a refined sampling method (TO 15A) may be lower than measurements based on EPA Method (TO 15), calculations from

recent Georgia EPD background samples by both methods show refined background levels are still substantially greater than the OEHHA RSC.

The OEHHA updated EtO RSC provides little utility in assessing general population risk unless total background exposure from combined exogenous and endogenous contributions are considered as an ultimate reality check

At some monitoring locations, there may be EtO concentrations significantly greater than background concentrations, or modeling may predict risk above RSCs. The total exposure concentration compared to total equivalent background exposure concentration distributions for nonsmokers provides a final reality check of the utility of OEHHA RSC estimates. There are published examples of where total equivalent concentration comparisons have been useful in informing whether further risk mitigation beyond recent emission controls was warranted.

For example, Sheehan et al. (2021) compared 50th and 90th percentile ambient exogenous concentrations from monitoring around eight facilities plus 50th percentile endogenous equivalent concentration (total exposure concentrations) with 50th and 95th percentile total equivalent background concentrations for nonsmokers in the U.S. population and concluded that facility concentrations are contributing negligibly to near residential population total exposure. Similarly, Lewis et al. (2022) compared 5-year average EtO modeled concentrations at near facility residences in Georgia plus background and endogenous concentrations (total exposure) with the 50th 60th and 95th total equivalent concentrations for the nonsmoking U.S. population and again concluded that facility contributions to residential exposure are negligible (see Figure 4 below from Lewis et al. 2022). These total exposure comparisons provide an additional reality check on the health significance of the facility emission contributions to near facility residential EtO exposure.

We suggest that for populations in California living close to emitting facilities, OEHHA consider total equivalent exposure concentrations or the TCEQ RSCs as a final check in managing risk as the proposed OEHHA RSCs have no practical risk management utility.

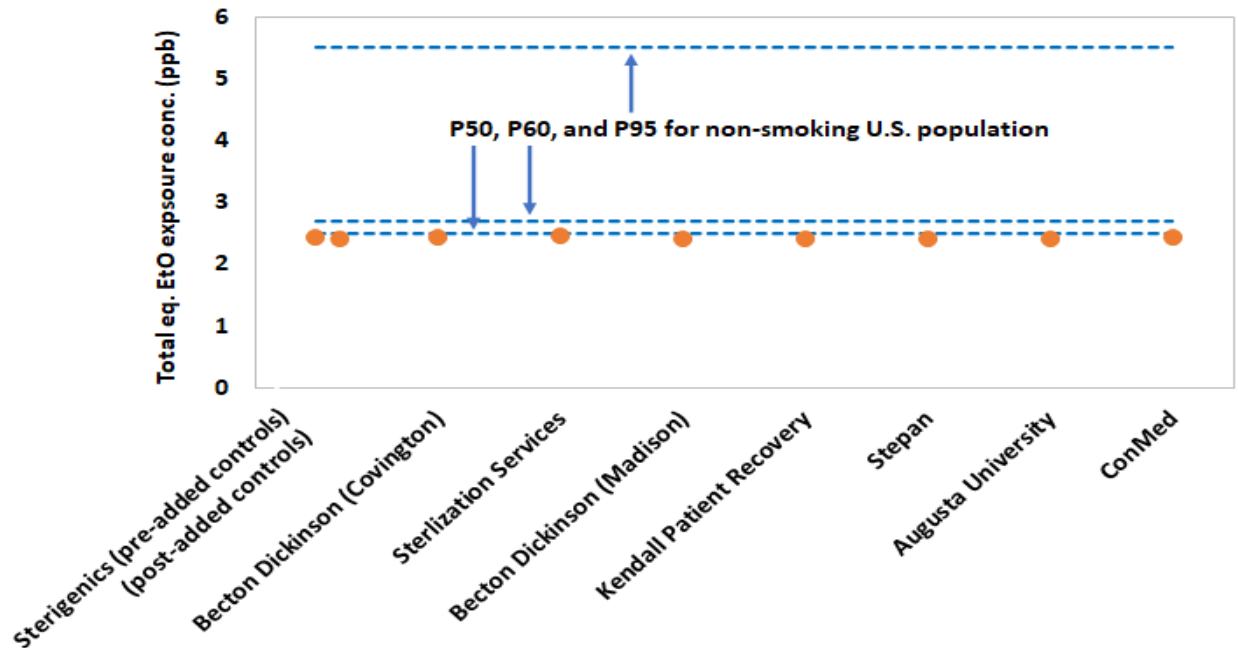


Figure 11. Estimated total equivalent exposure for the highest 5-year average modeled EtO concentration for all residential receptors by facility ((50th percentile endogenous equivalent for the non-smoking U.S. population, or 2.3 ppb) + (50th percentile background EtO concentration for Georgia, or 0.12 ppb) + (highest 5-year average modeled EtO concentration for all residential receptors by facility)) relative to that of the 50th, 60th, and 95th percentiles of the non-smoking U.S. population (2.5, 2.7, and 5.5 ppb, respectively).

We urge OEHHHA to consider these comments and adopt an alternative such as the TCEQ approach. Thank you.

Sincerely,

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Attachment 4

American Chemistry Council's Comments to OEHHA on the Draft No Significant Risk Level (NSRL) for Ethylene Oxide



June 14, 2023

Submitted via OEHHA Website: <https://oehha.ca.gov/comments>

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Re: ACC Comments on Draft No Significant Risk Level (NSRL) for Ethylene Oxide

The Ethylene Oxide Panel of the American Chemistry Council appreciates the opportunity to provide comments on the OEHHA's proposed update to Proposition 65 No Significant Risk Level (NSRL) for ethylene oxide (EtO) and its accompanying Initial Statement of Reasons supporting the update (Proposed NSRL). The Proposed NSRL for EtO is derived by adopting the U.S. Environmental Protection Agency (EPA) Inhalation Cancer Unit Risk (UR) and rejecting the UR derived by the Texas Commission on Environmental Quality (TCEQ). We strongly urge OEHHA to reconsider this decision and to correct the Proposed NSRL Initial Statement of Reasons of errors impacting exposure-response assessment of the NIOSH lymphoid mortality and breast cancer incidence data.

Revision of the NSRL from 2 µg/day to 0.058 µg/day could have a substantial impact on users of EtO. The IUR from which the NSRL is derived is equivalent to 1 drop of water in a volume of 20 Olympic-sized swimming pools. Potentially impacted uses include ethylene that is metabolized to EtO. Potentially impacted downstream users include: treatment of fruits and vegetables, cosmetics and personal care products, paints and coatings, medical products sterilized with EtO, and numerous other uses. Labeling products that may contain such a minute concentration of EtO will only unnecessarily scare consumers and may result in decreased use of very beneficial products. It is important to note that exogenous and endogenous values of EtO also exceed the NSRL.

EPA's selection of the final Integrated Risk Information System (IRIS) exposure-response model was based on a fundamentally flawed statistical analysis and incorrect assessment of visual fit of categorical (grouped) model estimates. Unfortunately, the OEHHA's uncritical acceptance of

EPA's EtO IRIS 2016 methodology and assumptions results in the same errors and flaws leading to an implausible cancer unit risk (UR) of 6.1 per ppm (3.3×10^{-3} per $\mu\text{g}/\text{m}^3$) and cancer slope factor (CSF) of 12 per mg/kg-day, from which the Proposed NSRL of 0.058 $\mu\text{g}/\text{day}$ was derived. While OEHHA admirably attempts to conduct an "independent" evaluation of bias in EPA's model and the National Institute of Occupational Safety and Health (NIOSH) epidemiological data, their efforts are based on questionable assumptions in the absence of access to the actual data being considered and mimicking EPA's faulty reasoning.

As OEHHA correctly points out, the IRIS UR is based on both lymphoid mortality and breast cancer incidence from the NIOSH study (Steenland et al., 2003, 2004) whereas the TCEQ UR is based on lymphoid mortality alone. As discussed in our detailed comments, the unavailability and incomplete ascertainment of the breast cancer data precludes the use of the NIOSH breast cancer incidence data for quantitative risk assessment purposes. The weaker evidence of causation for breast cancer in the epidemiology studies further supports focus on lymphoid cancer incidence data from the NIOSH study. However, the major reasons for the large difference in magnitude between the two URs are (a) the type of exposure-response model used to fit the epidemiologic data and (b) the interpretation and value of information in related epidemiological and biological evidence to inform selection of the model.

The Description of the NIOSH and Union Carbide Corporation (UCC) cohort studies need to be corrected in the Proposed NSRL Initial Statement of Reasons.

The NIOSH and Union Carbide Corporation (UCC) EtO cohort studies are comparable in terms of the number of lymphoid cancer mortalities (an important factor to consider in the power of the study) and the exposure assessment. While we do not dispute the use of just the NIOSH study to derive the UR/CSF for EtO, the Proposed NSRL description of the strength and weaknesses of these two studies should be corrected so that both the NIOSH and UCC studies can inform selection of the exposure-response model.

Specifically, the Proposed NSRL should limit the description of the NIOSH study exposure assessment as "high quality" and "validated" to apply only to the narrow exposure period after 1978 when data were available to validate the exposure regression model. Prior to 1978 this model is unvalidated because there was very limited or no exposure data available. Furthermore, the model validated after 1978 was altered for years prior to 1978 by holding a key variable "calendar year" fixed at the predicted level in 1978. The calendar year variable is described by the authors of the NIOSH exposure model to be a "surrogate for improvement in work practices." By holding the variable calendar year fixed prior to 1978, the NIOSH exposure model estimates lower exposure estimates in earlier years compared to 1978. No effort was made by the NIOSH authors to independently validate this substantial adjustment to the model prior to 1978.

Bogen et al. (2019) addressed this limitation by finding multiple sources of new information and data indicating changing work practices in earlier years. Ironically, the Proposed NSRL dismisses the Bogen et al. (2019) model showing the opposite but more plausible trend for historical exposures (e.g., higher exposures in earlier years) because *“the authors were unable to validate their pre-1978 predictions since no actual worker measurement were available from that time,”* and thus, *“the accuracy of the Bogen et al. (2019) assessment is unknown to OEHHA.”* By the same reasoning, OEHHA must also conclude that the accuracy of the NIOSH model prior to 1978 is unknown, and OEHHA should indicate that the data NIOSH used to develop the model are no longer available (lost) (EPA IRIS, 2016b, Appendix H, p H-28).

Compared to the NIOSH exposure data before 1978, the UCC exposure estimates are superior in quality to the NIOSH exposure estimates because exposure data for the most recent periods, 1957-1973 and 1974-1988, were available for more than 75% of the cohort based on routine monitoring, personal sampling, medical records on severe acute toxicity (e.g. respiratory irritation, nausea and vomiting), and a plant wide survey in another UCC plant using the same process (Greenberg et al., 1990; Teta et al., 1993; Swaen et al., 2009). The UCC cohort experienced more than twice the average estimated cumulative exposure (67 ppm-years) compared with the larger and younger NIOSH cohort (27 ppm-years) (Valdez-Flores et al., 2010). The OEHHA Proposed NSRL Table 1 should be corrected to add the Valdez-Flores et al. (2010) paper and indicate in the third column that 6 different lag years and different exposure scales and models (including log cumulative exposures and cumulative exposures) were analyzed.

These corrections are necessary for a more balanced consideration by OEHHA of both the NIOSH and UCC studies in selecting the most appropriate exposure-response model. The evidence from both of these studies, individually and combined, do not support selection of a 2-slope exposure-response model with a very steep initial slope. The log-linear exposure-response model is far more consistent with the weight of evidence from the NIOSH and UCC studies as described in greater detail in our detailed comments (see Detailed Comments).

Biological and epidemiological evidence should play a primary role in selecting exposure-response model

The exposure-response model used by IRIS (EPA, 2016a) for both breast cancer and lymphoid is a “supralinear”¹ two-slope linear spline model (2-slope model), suggesting that risk increases sharply at low exposures and less steeply at higher cumulative exposures above 1,600 ppm-days for lymphoid cancer and 5,750 ppm-days for breast cancer incidence. In contrast, the

¹ EPA IRIS uses the term “supralinear” to describe the exposure-response relationship. Ironically, EPA (2022) attributes “supralinear” to ACC as if this is not an appropriate description.

dose-response model used by TCEQ (2020a) is the standard² log-linear Cox Proportional Hazards (CPH) model, which is virtually linear at relevant exposure concentrations for estimating cancer risk for the general population.³

The steep initial slope of the EPA IRIS (2016a) supralinear two-slope spline model, which gives rise to one of the highest inhalation cancer potency estimates derived by IRIS, is not justified based on the relatively weak epidemiological findings reported in the original NIOSH peer-reviewed publications, the weight of evidence in the epidemiological literature including the UCC cohort, and the biological evidence in cancer bioassays and analysis of genotoxicity data.

Our detailed comments explain why the epidemiological evidence and biological evidence is more consistent with the TCEQ model than the IRIS model. While the IRIS assessment includes summaries of the genotoxicity, toxicology, epidemiology and toxicokinetics, there is virtually no integration of these important lines of evidence into the final quantitative risk assessment process. Instead, the IRIS exposure-response assessment is driven by exhaustive statistical modeling analyses divorced from consideration of exposure-response concordance with genotoxicity, toxicology and epidemiological weight-of-evidence. Similarly, OEHHHA makes no attempt to integrate the different lines of evidence to inform selection of the exposure-response model. This EPA (2005) carcinogen risk assessment guidelines captures this issue well:

“Another problem occurs when a multitude of alternatives are presented without sufficient context to make a reasoned judgment about the alternatives. This form of model uncertainty reflects primarily the availability of different computer models and not biological information about the agent being assessed or about carcinogenesis in general. In cases where curve-fitting models are used because the data are not adequate to support a toxicodynamic model, there generally would be no biological basis to choose among alternative curve-fitting models. However, in situations where there are alternative models with significant biological support, the decisionmaker can be informed by the presentation of these alternatives along with their strengths and uncertainties.”

Similarly, the EPA SAB (2015) emphasized that “any model that is to be considered reasonable for risk assessment must have a dose-response form that is both biologically plausible and consistent with the observed data.” Thus, the epidemiological weight of evidence should play a very important role in the consideration of the model selection. The absence of findings in the UCC study at any exposure, and absence of statistically significant findings at lower exposures in

² EPA (2022) attributes the term “standard” to ACC to describe the CPH model TCEQ uses, yet this is the correct term EPA IRIS (2016) uses to describe the log-linear CPH model

³ EPA (2022) correctly acknowledges on p.57 that “the log linear Cox model is essentially linear in the low dose range”.

males in the NIOSH study are more consistent with a standard CPH model than an extremely steep initial exposure-response slope.

In the most recent EPA (2022) response to public comments regarding this lack of consideration of the biological evidence in the dose-response assessment, EPA conducts a highly subjective visual inspection of genotoxicity and cancer bioassay data to support their claim that the biological evidence cannot be used to inform biological plausibility. The EPA (2022) evaluation involved (a) plotting the data as point estimates without error bars, (b) drawing a straight line between the response levels for the lowest and highest dose levels, and (c) declaring the dose-response to be supralinear or sublinear depending on whether the responses for the mid-dose levels visually appeared to be above or below the line. This visual inspection did not involve any consideration of statistical significance or evaluation of which data set and dose regimen is most relevant and useful to inform epidemiology data based on cumulative exposures. Our detailed comments explain why a single slope CPH model linear at lower exposures that gradually increases at higher exposure is much more consistent with the epidemiological, toxicological and genotoxicity evidence compared to a 2-slope model with a very steep initial slope leading to derivation of one of the highest EPA IRIS UR.

The Proposed NSRL model selection criteria is based on flawed statistics and visual fit analysis

The Proposed NSRL reiterates the EPA IRIS (2016a) rationale for selecting the 2-slope model based on statistical and visual fit of different models, without meaningful consideration of important new information that was available in the final TCEQ (2020a) Development Support Document (DSD) and in TCEQ (2020b) response to comments. For example, ***OEHHA reports a p-value of 0.01 for EPA's 2-slope model for breast cancer, suggesting that OEHHA is unaware that independent peer reviewers of the TCEQ DSD who provided in-depth statistics comments agreed with TCEQ that the p-values for the 2-piece spline models were incorrectly calculated.*** The corrected p-values are summarized in Table 1 and indicate that there is no statistical basis to select the 2-slope model over the CPH model. Our detailed comments provide ample evidence for why OEHHA's Proposed NSRL should report the corrected p-values for lymphoid mortality and breast cancer incidence.

Table 1. Corrected p-values for IRIS 2-slope linear spline and IRIS standard CPH model

	EPA IRIS (corrected) 2-slope linear spline	EPA IRIS Standard CPH Model
Lymphoid Mortality	P=0.14 corrected from 0.07	P=0.22
Breast Cancer Incidence	P=0.04 corrected from 0.01	P=0.02

Source: Corrected and IRIS reported p-values are based on IRIS (EPA, 2016a, Tables 4-2, 4-4, 4-6, 4-12, 4-13; EPA, 2016b, Appendix D) and final TCEQ DSD (2020a).

The OEHHA Proposed NSRL perpetuates mistakes with visual fit comparisons made in the IRIS (EPA, 2016a) assessment by stating the following:

“Other models, including the log-linear models (e.g., Cox regression) and the models using categorical data or exposure transformation, generally resulted in slopes that appear to dramatically over- or under-predict the actual study results, especially in the lower-exposure ranges.”

OEHHA makes two errors in this statement:

First, OEHHA incorrectly equates the “actual study results” for lymphoid cancers with the 5 categorical modeled estimates which appear as filled purple dots in IRIS Figure 4-3 with the first “dot” at the origin representing the lagged-out group considered to have zero exposures. Categorical rate ratios (RR) are calculated with respect to a baseline background hazard rate that is also estimated non-parametrically (i.e., not estimated by the CPH procedure). For the continuous models, the actual data modeled are the individual hazard rates not represented graphically in EPA IRIS figures⁴. The true (or implicit) y-intercept (or baseline hazard rate at cumulative exposures) for each continuous model applied to the 53 individual hazard rates will be normalized to 1 at zero lagged exposure.⁵ The higher the implicitly modeled y-intercept, the lower the graph will appear on a graph of RR.

Second, the OEHHA Proposed NSRL is making the mistake of assessing whether various models underestimate or overestimate the “actual study results” based on the IRIS (EPA, 2016a) subjective visual comparisons along the y-axis. This type of visual comparison is incorrect as clearly indicated in the EPA IRIS (2016a) figure legends: *“Note that, with the exception of the categorical results, the various 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).”*⁶ In other words, it is impossible to make conclusions about over- or under- predicting the actual study results even if one were to

⁴ For lymphoid cancers there are 53 individual hazard rates each reflecting comparisons between one lymphoid mortality case against a risk set of “control” workers defined as those who survived to at least the age of the index case. The risk set of “control” workers includes both exposed and unexposed workers and is distinctly different from the underlying background hazard rate implied by the nonparametric relative rate (or rate ratios; RR) represented by EPA IRIS as the first categorical purple “dot” at the origin.

⁵ Allison (2010), a practical guide to survival analysis using SAS, explains that the intercept is part of the arbitrary function of time, which drops out of the estimating equations”.

⁶ IRIS (EPA, 2016a) Figures 4-2, 4-3, 4-4, 4-5, 4-6, 4-7, 4-9 for lymphoid and breast cancers.

incorrectly define the “actual data” as the 5 categorical RR estimates. As explained above, this is because the baseline background hazard rates implied by the nonparametric (categorical) RRs and the underlying background hazard rates implied by the parametric models are generally different, but when graphed as RR values are all normalized to 1 making it impossible to make any conclusions about under- or over-estimations.

Valdez-Flores and Sielken (2013) and TCEQ (2020a) explain in greater detail why these types of visual comparisons based on IRIS (EPA, 2016a) figures are inappropriate because it cannot be assumed that summary RRs describe the true underlying exposure–response relationship for the continuous models. The SAB (2007) implied the same recommendation against visual fit when they instructed EPA to use the individual data to fit the dose-response models. The SAB (2007) concluded “The Panel was unanimous in its recommendation that the EPA develop its risk models based on direct analysis of the individual exposure and cancer outcome data for the NIOSH cohort rather than the approach based on grouped data that is presently used.”

OEHHA Proposed NSRL should reconsider TCEQ’s objective method for assessing model fit based on theoretical concerns that were addressed, instead of relying on incorrect statistical and visual fit methods

Compared to the IRIS and OEHHA visual “eyeballing” comparisons using graphs that are not fit for this purpose, TCEQ (2020a) provides a far more objective method to check how well each of the two models (i.e., the standard CPH model⁷ and the 2-piece spline model⁸) applied to general population background cancer rates can predict the number of lymphoid cancer deaths (the key cancer endpoint) that were actually observed in the NIOSH cohort. This approach used to predict cancer deaths from the model is essentially the same well-accepted approach IRIS (2016a, Section 4.7) used to estimate extra risk for various occupational exposure levels by applying the IRIS model to the general population background cancer rates in the life-table program.

Table 2 compares the number of lymphoid cancer deaths that were observed in the NIOSH cohort versus the predictions by the IRIS and TCEQ models. In this model ground-truthing exercise, the TCEQ model was not only able to better predict the actual total number of lymphoid cancers in the NIOSH cohort but also the number of cancers in Quintile 2⁹ demonstrating superior global and local fit below the knot.

⁷ TCEQ’s model using 15-yr lag and the full risk set.

⁸ EPA IRIS model using 15-yr lag and 100 workers randomly selected individuals from each case’s risk set.

⁹ TCEQ (2020a) defined Quintile 1 as the 9 lagged-out cases (no exposures). The remaining 44 cases were equally divided into 4 groups designated by TCEQ as Quintiles 2-5. EPA IRIS (2016a, p. 4-15) reported 13 exposed cases below the knot of 1,600 ppm-days. Thus, prediction of Quintile 2 comprised of 11 cases with the lowest exposures best reflects “local” fit below the knot.

Table 2. Comparison of observed versus predicted number of lymphoid cancer deaths in NIOSH study using IRIS and TCEQ models

	Observed	Predicted (95% CI)	
		2-piece linear spline model with knot	Standard log-linear CPH model (linear at POD of 1/100 and below)
Total number of cancer deaths	53	91.69 (70.1, 122.4)	52.42 (40.1, 70.0)
Quintile 2 ⁸ cancer deaths	11	20.9 (11.7, 42.0)	14.4 (8.1, 28.9)

Source: TCEQ (2020a) Appendix 3 Table 29 and 30.

OEHHA’s dismissed TCEQ’s “Reality Check” using a prediction method based on an unsupported vague claim that the analysis is flawed because “TCEQ’s calculations did not accurately account for any differences that might exist between the general US population and the NIOSH worker cohort.” The epidemiologic literature has shown that a healthy worker effect (HWE) is predominately related to workers with shorter follow-up and non-cancer causes (Monson, 1986; Fox and Collier, 1976). Most importantly, the NIOSH study authors themselves concluded that there was unlikely to be a cancer HWE in this longer follow-up study (Steenland et al., 2004¹⁰). Their conclusions are consistent with that of the International Agency for Research on Cancer (IARC) textbook, *Cancer Epidemiology: Principles and Methods* (IARC, 1999), which specifically notes that HWE “is known to vary with type of disease, being smaller for cancer than for other major diseases, and it tends to disappear with time since recruitment into the workforce.” Thus, it is unlikely that there is a HWE for the cancers of interest in the NIOSH cohort.

OEHHA did not appear to be aware of the TCEQ DSD¹¹ sensitivity analysis to demonstrate that the TCEQ model still better predicts the overall actual cancers after applying a high HWE of 15-16% for lymphoid cancers. Although one can quibble with the TCEQ’s selection of 15-16% based on overall¹² cancer SMRs from a Norwegian worker study with relatively short average follow-up of 11.5 yrs (Kirkeleit et al., 2013), the larger point is that 15% HWE is a reasonable estimate for differences between the general population and the NIOSH worker cohort given the

¹⁰ “The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons.” (Steenland et al., 2004)

¹¹ TCEQ (2020a) Section A3.3.2.

¹² Kirkeleit et al. (2013) did not find a HWE for lymphoid (SMR of 0.97 for males, 1.07 for females) or breast cancer (SMR of 1.02), but TCEQ conservatively used the overall cancer SMR of 0.85 and 0.84 for male and female workers. It is also unknown whether the Norwegian workers are representative of the NIOSH sterilizer workers.

unlikelihood of a cancer HWE in the NIOSH study (Steenland et al., 2004). Figures 1 and 2 show the TCEQ model better predicts the observed lymphoid deaths than the IRIS model overall, and locally at Quintile 2. **Taken together, OEHHHA's Proposed NSRL should be corrected to indicate that the TCEQ model has excellent overall and local fit based on the TCEQ's prediction analysis, which considers a possible HWE effect as a reasonable surrogate for differences that might exist between the general US population and the NIOSH worker cohort.**

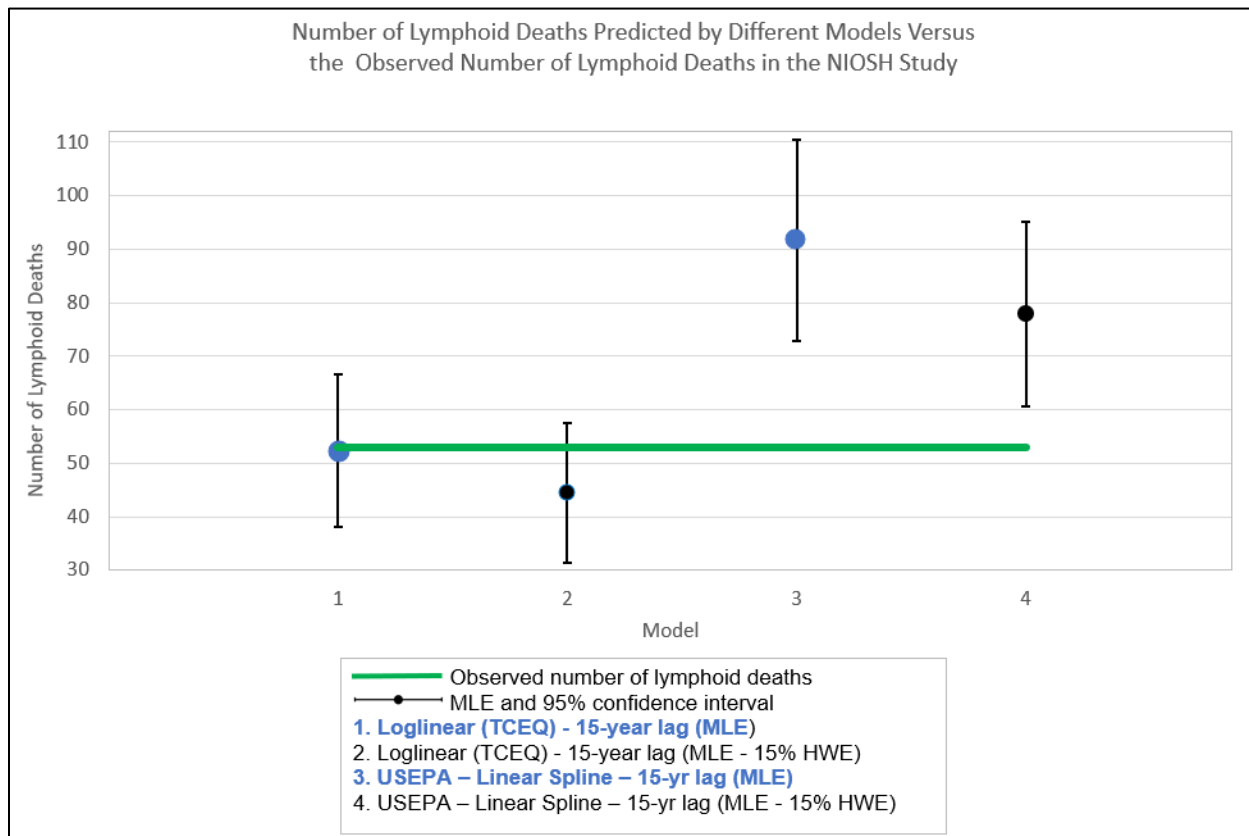


Figure 1. Comparison of overall fit of TCEQ and IRIS models to the NIOSH study

Note: Confidence intervals (CI's) shown are based on Poisson distribution and are very similar to those calculated by TCEQ (2020a) as described in our detailed comments. These similar results provide additional support for TCEQ's conclusions that the TCEQ model has greater overall fit to the data. (See TCEQ, 2020a)

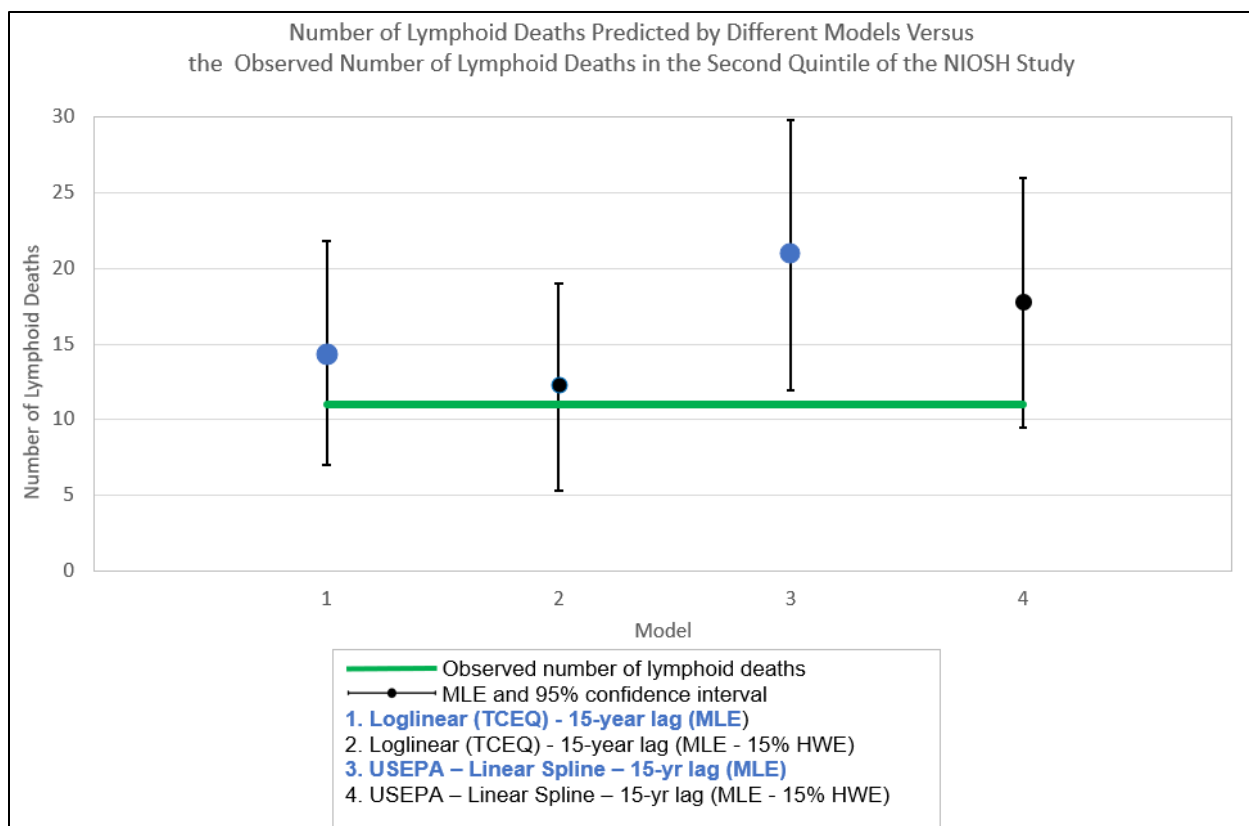


Figure 2. Comparison of local fit of TCEQ and IRIS models to Quintile 2 of the NIOSH study

Note: CI's shown are based on Poisson distribution and are very similar to those calculated by TCEQ (2020a) as described in our detailed comments. These similar results provide additional support for TCEQ's conclusions that the TCEQ model has superior *local* fit below the knot.

Background endogenous and ambient levels of EtO provide important reality checks for model selection. The key assumptions in extrapolating the exposure-response relationships at lower exposures are scientifically valid and are now corroborated by independent data sets.

Background endogenous and ambient levels of EtO are an important reality check for the TCEQ and IRIS model. While OEHHA is correct that the potency estimates technically only apply to exposures above endogenous levels, it is implausible that a chemical would be a potent carcinogen at levels that the body produces through natural processes and also well within the population variability.

We applaud OEHHA for including a section on endogenous levels. However, we disagree with OEHHA's conclusion that the exposure-response relationship for endogenous ethylene oxide exposures is unknown, and therefore cannot be estimated using the Kirman et al. (2021) method. The linear relationship between hemoglobin N-2-hydroxyethylvaline (HEV) adducts

and EtO exposures is well-supported by data across a broad range of exposure levels (i.e., ranging from background levels to ~4 ppm in workers). As explained in detailed comments below, this well-supported linear relationship is also supported by a “forward” analysis suggested by EPA (2022) based on measured EtO concentrations in mainstream cigarette smoke that corroborates the Kirman et al. (2021) linear relationship.

In summary, we urge OEHHA to adopt the TCEQ model for lymphoid cancers or use CPH model estimates from the IRIS assessment and revise the Proposed NSRL to better reflect the following:

- 1. The original NIOSH study upon which OEHHA’s Proposed NSRL is based found no indication of increased risk of lymphoid cancers in males at lower categories of exposures and concluded there were no exposure-related effects in females. The TCEQ dose response model is more consistent with the original findings of the NIOSH mortality study.**
- 2. Breast cancer, like other types of cancers OEHHA considered from both animal and human studies, is a cancer endpoint that deserves consideration in the weight of evidence for cancer classification. However, the NIOSH breast cancer incidence data should not be used for quantitative risk assessment based on substantial under-ascertainment of incident cases reported by Steenland et al. (2003) and subsequent risk deficits in the lower exposures.**
- 3. OEHHA’s rationale for supporting EPA IRIS model selection is based on uncritical acceptance of EPA’s incorrect statistical analysis that did not account for EPA’s systematic statistical search for the knot as an estimated statistical parameter. Independent peer reviewers for TCEQ agreed with TCEQ’s corrections of the statistics, which puts the TCEQ model on par with the IRIS model based on statistical significance alone.**
- 4. The TCEQ exposure-response model is much more plausible based on the biological and toxicological evidence, and the mode of action.**
- 5. OEHHA appears to equate the 5 categorical rate ratios with the 53 rate ratios, and/or assumes that comparisons of the exposure-response curve can be compared visually with the EPA IRIS (2016a) graphical representation 5 categorical rate ratios.**
- 6. OEHHA dismisses TCEQ’s prediction analysis which is a much more objective method than visual fit to check how well each of the two models (i.e., TCEQ’s vs EPA’s) can predict the observed number of lymphoid cancer deaths (the key cancer endpoint). In this model ground-truthing exercise, the TCEQ model better predicted not only the overall number**

of lymphoid cancers in the NIOSH cohort but also the observed cancers below the knot in the lowest exposure quintile.¹³

7. OEHHA's sole reliance on internal analyses and OEHHA's extreme and complete exclusion of external analysis is based on a main conclusion that all external analysis should be ignored because it is confounded by HWE. This is contradicted by NIOSH study authors' own published conclusions that "the healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons." Furthermore, OEHHA's uncritical acceptance of conclusions of a more recent paper by Park (2020) that there is a Healthy Worker Survival Effect (HWSE) led OEHHA to support EPA IRIS model. However, the conclusions are not supported by the actual results in the paper. Improvements in these and other descriptions of the epidemiological evidence are needed to accurately assess the epidemiological weight-of-evidence.
8. Based on uncritical acceptance of the IRIS evaluation, OEHHA inaccurately exaggerates the reliability of the NIOSH worker exposure estimates prior to 1978.
9. The Union Carbide Corporation (UCC) cohort should play a prominent role in considering the strength and consistency of the epidemiology data in supporting the IRIS vs. TCEQ UR. OEHHA's description of this cohort incorrectly omits the internal analysis by Valdez-Flores et al. (2010) which included exploration of different exposure metrics and lag times. The absence of findings in the UCC cohort for male lymphoid cancer mortality is not consistent with a steep slope at low concentrations.
10. While EPA's potency estimate technically only applies to exposures above endogenous levels, it is implausible that a chemical would be a potent carcinogen at levels that the body produces through natural processes. The key assumptions in extrapolating the dose-response relationships at lower exposures are scientifically valid and are now corroborated by independent data sets on smoking.
11. OEHHA cites two studies reporting an association between smoking and lymphohematopoietic (LH) cancers published in 2012 (Diver et al. 2012 and Kroll et al. 2012) to discount Kirman et al. (2021) reality checks. These two studies are inconsistent with the lymphoid cancer (NHL, lymphocytic leukemia, multiple myeloma) findings from the NIOSH mortality study (Steenland et al., 2004), upon which IRIS 2016 developed their

¹³ TCEQ (2020a) defined Quintile 1 as the 9 lagged-out cases (no exposures). The remaining 44 cases were equally divided into 4 groups designated by TCEQ as Quintiles 2-5. EPA IRIS (2016, p. 4-15) reported 13 exposed cases below the knot of 1600 ppm-days. Thus, prediction of Quintile 2 comprised of 11 cases with the lowest exposures best reflects "local" fit below the knot.

low exposure high risk model and do not constitute a weight-of-evidence evaluation akin to the Surgeon General report, *The Health Consequences of Smoking —50 Years of Progress* (US DHHS 2014). In addition, OEHHA cites IARC review indicating a positive association between tobacco smoking and breast cancer, though not for lymphoid cancer.

12. OEHHA's Proposed NSRL is an estimated EtO 10^{-5} risk specific intake level. This risk-specific intake level provides little utility in managing general population risk if background exogenous exposure isn't considered as an initial reality check. There has been an extensive ambient air measurement campaign over the last several years, including measurements near many sterilizer facilities and at background locations. In many cases, the levels of ethylene oxide far away from sterilizer facilities are similar to the levels near sterilizer facilities. Although the sources makeup of this exogenous background ethylene oxide is currently not fully characterized, what is clear is that, in many cases, residents living near sterilizer facilities are not exposed to higher ethylene oxide than people living far away.

DETAILED COMMENTS

- 1. The original NIOSH study upon which OEHHHA's Proposed NSRL is based found no indication of increased risk of lymphoid cancers in males at lower categories of exposures and concluded there were no exposure-related effects in females. The TCEQ dose response model is more consistent with the original findings of the NIOSH mortality study.**

**** Pertaining to NSRL p. 23-38 ****

The extremely steep dose response model selected by EPA IRIS (2016a) and adopted by OEHHHA for lymphoid cancer mortality is based on an UR that is among the highest EPA IRIS inhalation URs for known or likely carcinogens. This is inconsistent with the following original conclusions by the NIOSH study authors regarding both internal and external comparisons (Steenland et al., 2004):

- “There was little evidence of any excess cancer mortality for the cohort as a whole”
- “The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons”
- “Positive exposure-response trends for lymphoid tumors were found for males only (15-year lag)”
- “It is not known why we find an association for males and not females for haematopoietic cancer. . .there was sufficient variation in the exposure of women to have observed an exposure-response if one existed.

A large number of models were considered by IRIS, including those using log transformation of cumulative exposure, which IRIS (EPA, 2016a) correctly excluded as “biologically implausible.” Of the models using cumulative exposures, the strongest trend was seen in male lymphoid mortality. As described in detail in the next section, breast cancer incidence is not an appropriate endpoint based on the weight-of-evidence and quality issues. Therefore, of the critical endpoints selected by IRIS, male lymphoid mortality is the most appropriate endpoint for risk assessment, protective of effects in females who showed no sensitivity.

In the internal categorical analysis for male lymphoid tumors, the only statistically significant increase in male lymphoid odds ratio (OR) is only at the highest cumulative exposure level. Steenland et al. (2004) concluded that there was no association of EtO with lymphoid cancers in females. These peer-reviewed conclusions of the original authors are far more consistent with the shallower linear slope of the TCEQ's log-linear exposure response model as compared to a steep initial exposure response of the EPA's 2-slope model.

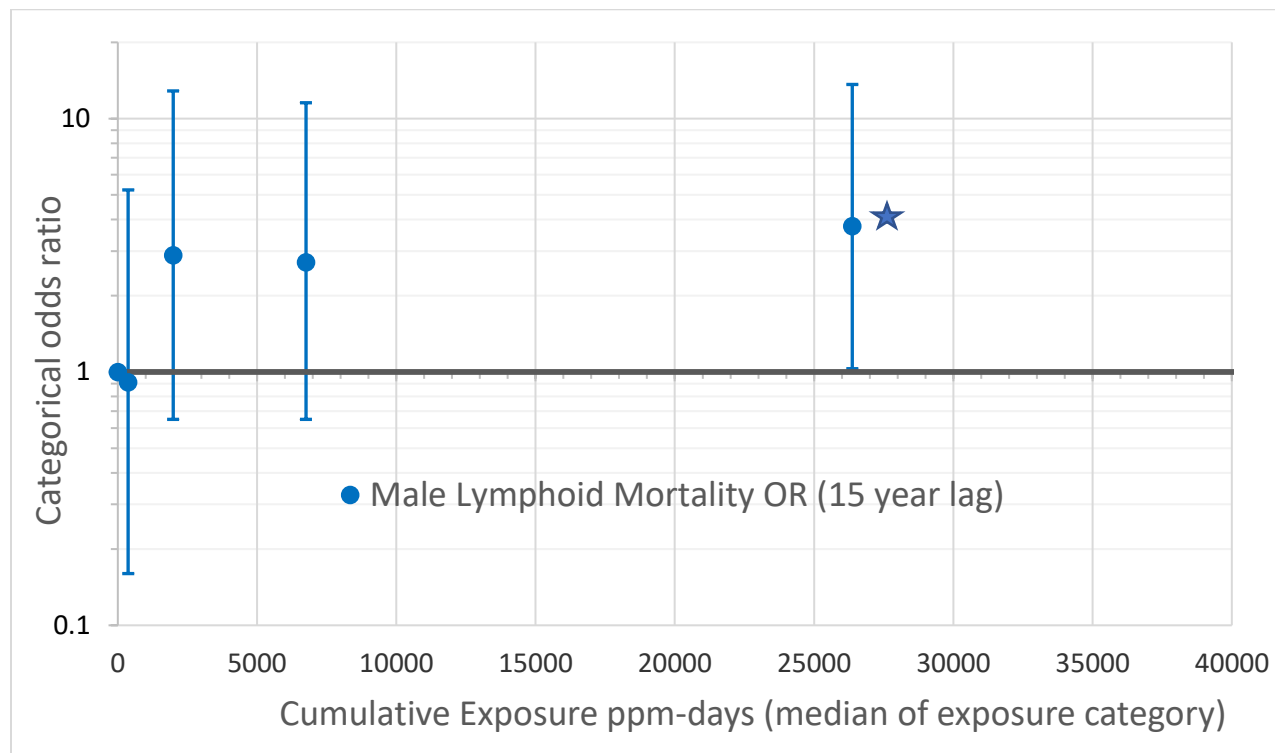


Figure 3. Categorical Odds ratios (OR) for males (95% Confidence Intervals):

Note: Male ORs for exposure categories 0 (lagged out), >0-1,200 ppm-days, 1,201-3,680 ppm-days, 3,681-13,500 ppm-days, >13,400 ppm-days are, respectively, 1, 0.91 (0.16-5.23), 2.89 (0.65-12.86), 2.71 (0.65-11.55), **3.76 (1.03-13.64)** (EPA IRIS, 2016b, Table D-28)

Statistical modeling can take on a life of its own if not checked against the epidemiological data which do not indicate an extremely steep low-dose dose response and/or a major discontinuity in the dose response. The UCC study of EtO chemical workers with comparable numbers of lymphoid cancers and substantial exposures to EtO show no increased risk of male lymphoid cancers. It is important to keep into perspective that the relevant epidemiology, including a large number of human studies published over a forty-year period, indicates that there is inconclusive evidence of carcinogenicity (IARC 2012a). Taken together, the findings from EO epidemiology conflict with the IRIS risk values which imply EtO is a highly potent carcinogen at lower cumulative exposures.

2. Breast cancer, like other types of cancers OEHHA considered from both animal and human studies, is a cancer endpoint that deserves consideration in the weight of evidence for cancer classification. However, the NIOSH breast cancer incidence data should not be used for quantitative risk assessment based on substantial under-ascertainment of incident cases reported by Steenland et al. (2003) and subsequent risk deficits in the lower exposures.

**** Pertaining to NSRL p. 29, 35 ****

The primary reason breast cancer should not be included in EtO quantitative exposure response analysis is that there is a substantial under-ascertainment of incident cases due to non-participation in the interview study that raises a serious potential selection bias. In addition, the evidence related to causation is weak for breast cancer, supporting the focus on lymphoid cancers for quantitative risk assessment based on the epidemiological data.

Neither the NIOSH breast cancer incidence study (Steenland et al., 2003) nor the NIOSH mortality study (Steenland et al., 2004) report an overall excess of breast cancer. The positive NIOSH findings based on internal analyses are not robust in that they are seen with a certain lag and exposure metric that are not evident with numerous other exposure metrics, models, or lags. The breast cancer incidence findings are at most suggestive, not only due to inconsistencies in the exposure-response, but also due to incomplete cancer ascertainment and the subsequent potential for bias. This disease endpoint is only weakly supported by other epidemiology studies and is inconsistent with others. Thus, the NIOSH study breast cancer incidence findings are not consistent with the selection of a 2-slope model with a steep initial slope.

The IRIS breast cancer incidence analysis relied on data from the subpopulation of the NIOSH cohort that was interviewed, which required both locating subjects and identifying those diagnosed with breast cancer. Of the 7,576 women in the NIOSH cohort, only 5,139 (68%) were included in the interview portion of the study. The percent non-response was of concern, according to the authors. The majority of these, 22%, could not be located and therefore any breast cancer diagnosis would have been missed. Steenland et al. (2003) indicated that cases lost are more likely to be shorter term (i.e., lower cumulative exposure) employees. Those who work longer (i.e., higher cumulative exposures) stay in the area longer and are more likely to get picked up in the state tumor registries and be found for interview. Shorter duration workers with lower cumulative exposures are more likely to leave the area and not be captured in the overall analyses and less likely to be interviewed. If more cases were missed among those with lower cumulative exposures (shorter term employees), then the data would be biased toward seeing a positive slope and/or elevated risk in the higher exposure groups, as reported by Steenland et al (2003).

Steenland et al. (2003) stated that “breast cancer ascertainment in the sub-cohort with interviews was considered complete.” In other words, all the women who were interviewed were identified as having breast cancer or not. This, however, does not account for the missing cases among non-participants in the interview study or for cases never identified in the overall target population. Importantly, there is no way of knowing that the distribution of cases by level of exposure in the subcohort of interviewed breast cancer cases is comparable to the distribution in the fully ascertained total cohort. Due to the greater difficulty of locating women with short term employment, there is a high potential for bias in missing cases at lower cumulative exposure. The rate ratios for breast cancer incidence in the lowest exposed groups in the entire cohort were 0.88 (15 yr. lagged out group) and 0.74 (<647 ppm-days, no lag), the latter of which was a statistically significant deficit (Steenland et al., 2003, Table 3). These deficits contributed to suggested positive trends.

Steenland et al. (2003) made an attempt to investigate possible selection bias but noted he didn’t have adequate data to address this concern:

“A second possible bias was the preferential ascertainment of breast cancer among women with stable residence in states with cancer registries; women with stable residency might be expected to have longer duration of employment in companies under study, and hence greater cumulative exposure. Unfortunately, we didn’t have residential history, limiting our ability to explore this possibility.” (Steenland et al., 2003)

Without the incidence data, selection bias cannot be properly tested. However, several issues support this explanation: 1) the overall population long-term (higher exposed) women would be easier to identify as having breast cancer as they remain for longer periods in states of employment that have tumor registries; 2) similarly, longer employed and higher cumulative exposure women would be easier to locate and thus interviewed; and 3) duration of employment in Steenland et al. 2003 showed a stronger relationship with breast cancer than did actual cumulative exposure.

Steenland et al. (2003) recognized this limitation as one reason the authors were tempered in their causation conclusions:

“Our data suggest that ETO is associated with breast cancer, but a causal interpretation is weakened due to some inconsistencies in exposure-response trends and possible biases due to non-response and incomplete cancer ascertainment.”

In summary, the weak association of EtO with breast cancer and the exposure-response uncertainty due to the sizeable number of missing breast cancer cases precludes use of the NIOSH interview data in derivation of UR or CSF, and the subsequent NSRL. This, together with

the unavailability of the breast cancer incidence data to other researchers to independently examine these issues raises quality issues that indicate the data are inappropriate for exposure-response modeling for regulatory cancer risk assessment purposes.

3. OEHHHA's rationale for supporting EPA IRIS model selection is based on uncritical acceptance of EPA's incorrect statistical analysis that did not account for EPA's systematic statistical search for the knot as an estimated parameter. Independent peer reviewers for TCEQ agreed with TCEQ's corrections of the statistics, which puts the TCEQ model on par with the IRIS model based on statistical significance alone.

**** Pertaining to NSRL p. 26, 37 ****

OEHHHA uncritically accepts EPA IRIS (2016a) conclusions on model fit that are based on incorrect statistical analysis and inappropriate visual fit comparisons (described below). TCEQ (2020a) provided corrected Akaike information criterion (AIC) and p-values for the spline models that OEHHHA could have easily verified were correct. The peer review of TCEQ dose-response assessment included two independent reviewers who provided in-depth statistical review. Both peer reviewers agreed that EPA incorrectly calculated p-values because they did NOT correct for including the knot as an estimated parameter in the model, a basic violation of statistical principles:

Expert 5: "I do believe that TCEQ has identified a real problem with the USEPA AIC and p-value calculations. The explanation of the issue and the resolution supplied in DSD seems appropriate. That is, I agree with TCEQ that the knot parameter in the spline models should be considered in the count of the parameters, that the AICs reported by USEPA for those models are too low by a value of 2, and that the p-values should be computed using an approximation to a chi-square with 3 degrees of freedom." (TCEQ 2020b, p. 45)

Expert 6: "I consider that the location of the spline should be considered a parameter when evaluating fits of spline models, as long as the data were used in determining the knot, as it apparently was in EPA's model. I believe also that the lag should also be considered a parameter when the data are used to determine its value. But, in general, I consider the AIC in such complex models to be essentially only a rough guide to evaluating fit. Therefore, I think TCEQ's conclusion that the 'lower AIC means that TCEQ's selected model is a statistically superior model fit than USEPA's selected model when taking into account model complexity' is an overstatement. Comparing a model with an AIC = 464.5 to one with an AIC = 264.4[sic¹⁴], you can only conclude with confidence that the two models fit about equally well. Additionally, the overall fit is not of major importance – the fit at small doses is much more important when the object of the fitting is to estimate the risk at very small doses." (TCEQ 2020b, p. 50)

¹⁴ Expert really meant 464.4

The basic principle of accounting for all modeled parameter is clearly articulated in the National Research Council report entitled “Models in Environmental Regulatory Decision Making”, which states that the strategy to pick the “best model” for regulatory decision making should be “subject to a penalty function reflecting the number of model parameters, thus effectively forcing a trade-off between improving model fit by adding addition[al estimated] model parameters versus having a parsimonious description” (NRC, 2007, pp. 174). Importantly, there are no recognized exceptions to the penalty component of the balance incorporated into the AIC metric when applied in a valid procedure for model-selection (Burnham et al., 2002). This general principle is well recognized in the peer reviewed literature to apply specifically to including the estimated “knot” or inflection point from reporting the use of 2-piece linear spline models (Berman et al., 1996; Li et al., 2011; Gkioulekas et al., 2018; Molinari et al., 2001).

EPA Office of Research and Development (ORD) incorrectly claims that they fixed the knot and then conducted a sensitivity analysis. However, EPA ORD did not simply “fix” or “select” the position of the knot in that model. Instead, IRIS systematically tested 20 alternative knots for breast cancer and 70 knots for lymphoid mortality, and then among these, selected knot values that maximized the likelihood of data fit to a corresponding 2-piece spline model.

In the EPA IRIS (2016b, Appendix D at p. D-13), Dr. Steenland provided statistical analysis considering the knot as a parameter for breast cancer to show this had no substantial effect in that analysis, but a similar examination was not presented in the case of lymphoid cancer. In other words, there was clear acknowledgement and recognition expressed in the IRIS (EPA, 2016b) assessment that each knot value that was used to obtain a final spline-model fit is appropriately interpreted as an estimated parameter. Thus, IRIS should have reported the p-values considering the knot as an estimated parameter for breast and lymphoid cancers in the summary tables of the main report for greater transparency.

OEHHA should revise their discussion of fit of the data to reflect the corrected p-values reported by TCEQ (2020a) for the IRIS selected 2-piece spline provided in Table 1 of our comments above. Based on corrected statistical analysis alone, neither EPA IRIS ($p=0.14$) nor the TCEQ ($p=0.22$) exposure-response models for lymphoid cancers provide strong evidence that the exposure-response slope differs from zero. Based on statistics alone, the CPH model fits the data similarly to the supralinear 2-piece spline slope but has the advantage of parsimony (simpler model) and biological plausibility (described below). Also described in greater detail below, the CPH model more accurately predicts the observed lymphoid mortalities overall and at lower exposures in the NIOSH study compared to the IRIS (EPA, 2016a) selected 2-piece spline model.

In addition to Table 1, we suggest OEHHA include Table 3, below, in its detailed analyses, which provides more complete and direct comparison between the statistics and UR derivation for the 2-piece spline model and the CPH model. Table 3 will provide users of OEHHA’s assessment an

understanding of the range of values that can be estimated for risk assessment based on the IRIS (EPA, 2016a) preferred methods and assumptions.

Table 3. Comparison of IRIS (EPA, 2016a) derived models (URs not including the ADAF)

	2-piece linear spline Linear at EPA POD 1/100	Standard CPH Linear at EPA POD 1/100
Model of individual data?	Yes	Yes
IRIS full model name	Linear spline model with knot at 1,600 ppm x days	Log-linear model (standard Cox regression model)
<u>LYMPHOID INCIDENCE (Males and Females)</u>		
IRIS p-value	0.14 corrected from 0.07	0.22
Central estimate UR (per ppm)	1.34	0.0095
Upper bound UR (per ppm)	5.26	0.020
<i>Note: IRIS (EPA, 2016a) derived UR for lymphoid incidence data based on slope in the fitted mortality model together with background incidence rates in a life-table calculation. It is incorrect to assume that a cancer slope based on mortality can be applied to incidence data (see Sielken and Valdez-Flores, 2009 for detailed explanation)</i>		
<u>BREAST CANCER INCIDENCE (Females)</u>		
IRIS p-value	0.04 corrected from 0.01	0.02
Central estimate UR (per ppm)	0.71	0.08
Upper bound UR (per ppm)	1.48	0.14
<i>These data are not appropriate for quantitative risk assessment purposes because authors report substantial number of missing cases with higher potential for those with shorter employment missing (Steenland et al., 2003). These data have not been available for independent evaluation by EPA or the public, and, thus, lack transparency, verification, and independent analysis.</i>		
<u>LYMPHOID & BREAST CANCER INCIDENCE (Males and Females)</u>		
Central estimate UR (per ppm)	2.1	0.1
Upper bound UR (per ppm)	6.1	0.15
<i>These data are not appropriate for risk assessment because the breast cancer incidence data are included. EPA provided no justification for the POD of 1/100. TCEQ (2020a) analysis shows that the POD 1/100 for the standard CPH model extrapolates above or in the high range of the experimental data!</i>		

4. The TCEQ exposure-response model is much more plausible based on the biological and toxicological evidence, and the mode of action.

**** Pertaining to NSRL p. 15-18, 20-38****

A biological mode of action should be a major consideration when selecting a model for risk assessment.

While there is clear evidence that EtO is genotoxic and carcinogenic, this does not necessarily mean that EtO is acting through a genotoxic MoA for its carcinogenicity. Currently, this MoA should be considered as a default assumption in the absence of a convincing alternate MoA that does not involve genotoxicity as the initial key event. The dose-response and temporality of EtO induced genotoxicity in the etiology of either animal or human tumors has not been fully vetted through a formal process such as the one recommended by International Program on Chemical Safety (Boobis et al., 2006).

For a direct acting alkylating agent such as EtO, the default dose-response for the induction of mutations is linear. This is the worst-case scenario since at low doses closer to the origin, one should expect cellular protective mechanisms (e.g., detoxification and DNA repair) to offer protection, resulting in a shallower slope in this region when compared to higher doses. Based on a presumed genotoxic MoA, both TCEQ and EPA/OEEHA estimate cancer risk based on a linear extrapolation from the POD to the origin but apply very different statistical models to the same epidemiological study to derive the POD, i.e., Cox proportional hazards (CPH) model by TCEQ vs. the two-piece spline model by the EPA/OEEHA. In the 2-two-piece spline model, the initial slope rises rapidly at lower exposure levels and then rises more gradually for higher exposures. This type of dose-response is not consistent with the biology of how EtO works as a direct acting genotoxicant. The dose-response curve for EtO-induced gene mutations in the bone marrow (Recio et al., 2004, Figure 4) and lung (Manjanatha et al., 2017, Figure 5) tissues of transgenic Big Blue mice is especially informative since these tissues represent targets for EtO-induced tumors. In both cases, there is no evidence for a steeper initial slope and the dose-response pattern is more consistent with the CPH model than the 2-piece spline.

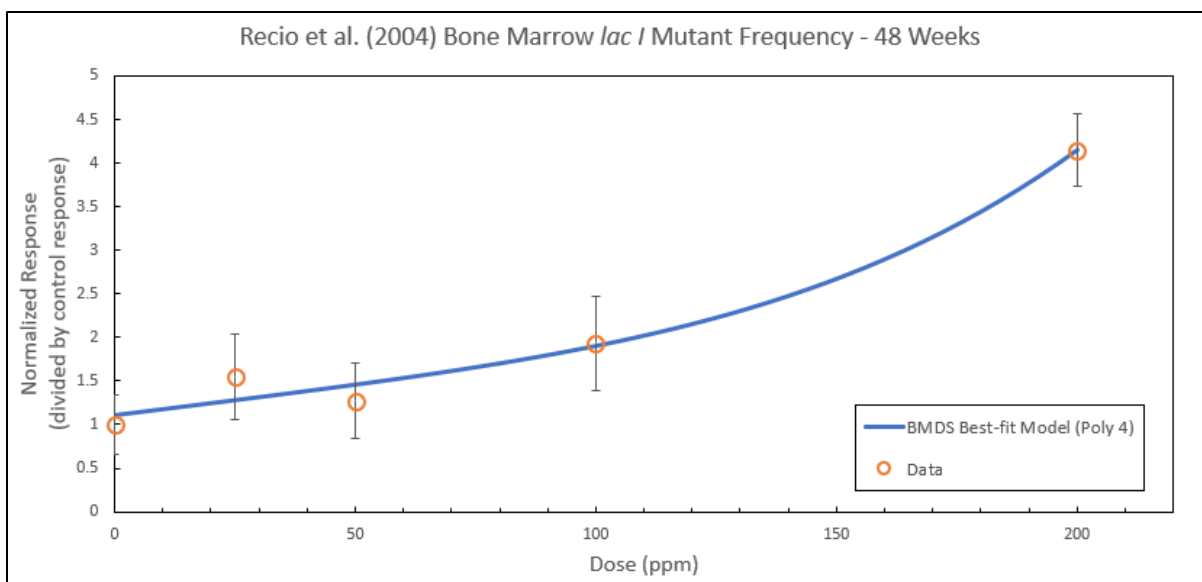


Figure 4. Dose-Response for EtO-Induced *lacI* mutations in Mouse Bone Marrow (6 h/day; 5 days/week; 48 weeks from Recio et al., (2004)

Recio et al. (2004) observed increases in *lacI* mutant frequency in the bone marrow of transgenic Big Blue B6C3F1 mice at EtO exposure concentrations of 100 and 200 ppm (but not at 25 or 50 ppm) after 48 weeks of exposure. No increases were observed following 12 and 24 weeks of exposure.

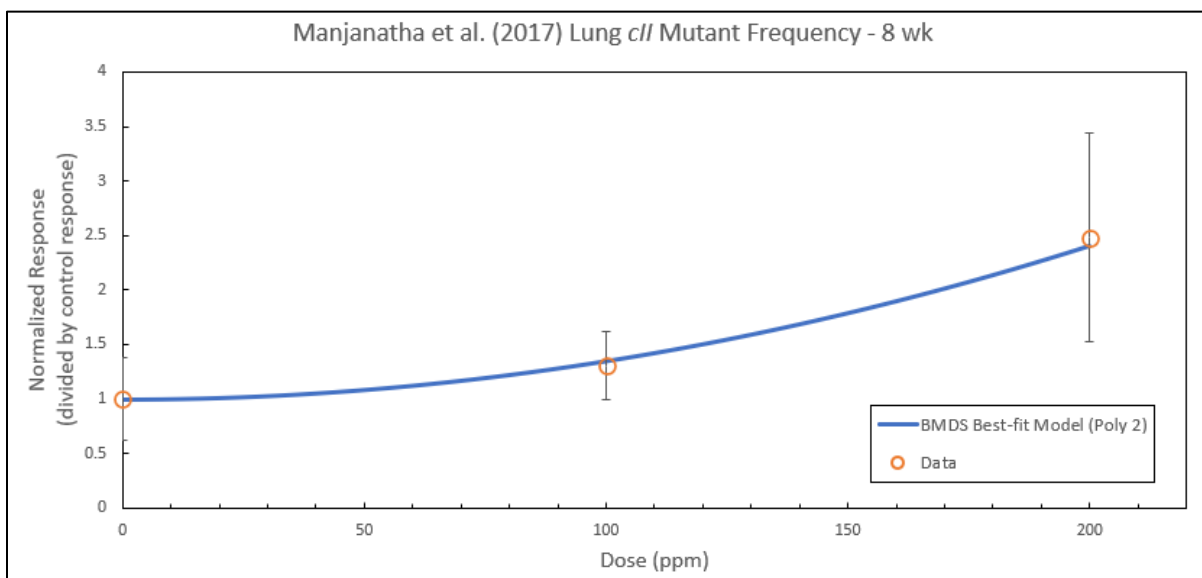


Figure 5. Dose-response for the Induction of *cII* mutations in the lung tissue of Big Blue B6C3F1 transgenic mice at 8 weeks of inhalation exposure to EtO (Manjanatha et al., 2017).

Similarly, Manjanatha et al. 22 (2017) investigated exposure-response and temporality for EtO-induced mutations at the *cII* locus in the lung tissue of transgenic Big Blue male B6C3F1 mice exposed to 0, 10, 50, 100, or 200 ppm EtO for 6 hr/day, 5 days/week over 4 weeks (in all

exposure groups) or for 8 or 12 weeks (in only the two highest exposure groups). A significant increase was observed only following 8 or 12 weeks of exposure and only at the highest concentration studied (200 ppm), which was twice the tumorigenic concentration used in the NTP (1987) bioassay in the same strain of animal. Contrary to expectations consistent with a mutagenic mode-of-action (MOA), no statistically significant increase in mutant frequency or mutational spectrum were observed following 4 weeks of EtO exposure (which is considered to be adequate exposure duration for detecting chemically-induced mutations as per OECD test guideline 488). These results are inconsistent with modified Hill criteria for exposure-response and temporality assuming a mutagenic MOA when considering the NTP (1987) studies in male and female B6C3F1 mice exposed to 0, 50, 100 ppm, 6 hrs/day, 5 days/wk for 102 weeks.

The above dose-response patterns are fully consistent with the molecular initiating event(s) leading to EtO-induced mutagenicity, i.e., the formation for DNA adducts. Marsden et al. (2009) using a highly sensitive liquid chromatography-tandem mass spectrometry and high-performance liquid chromatography-accelerator mass spectrometry analysis have shown that the dose-response for the induction of N7-(2-hydroxyethyl)guanine (N7-HEG) adducts in the livers of rats treated i.p. with EtO is at best described as linear, with significant increases over the background being observed at the four higher i.p. doses.

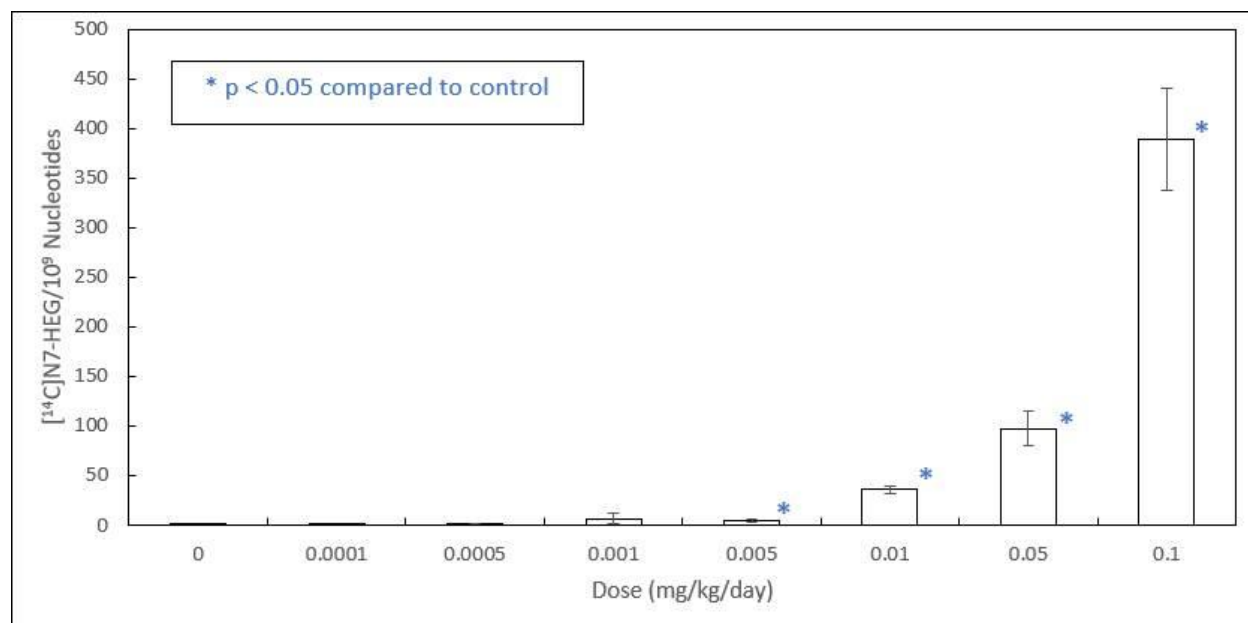


Figure 6. Dose-response for exogenously derived DNA adducts in liver of [¹⁴C]EtO-treated rats measured by LC-MS/MS (Marsden et al., 2009).

Although the N7-HEG adducts are not considered mutagenic, they are the most abundant DNA adducts formed following EtO exposure (Walker et al., 1992). Thus, the shape of the dose-response curve for the N7-HEG adduct can be considered as the worst-case scenario for EtO-

induced adducts, including the most mutagenic O⁶-HEG adduct whose abundance is approximately 300 times lower than that of the N⁷-HEG adduct (Walker et al., 1992). In reality, the slope for the mutagenic O⁶-HEG adducts is expected to be much shallower than that for N⁷-HEG because of the kinetics of their formation and repair (Swenberg et al., 2008). Accordingly, the dose-response pattern for the molecular initiating event leading to EtO-induced mutagenicity is expected to be non-linear or at best linear at the low end of the dose-response curve and the efficiency of adduct formation increasing at higher exposure levels due to saturation of DNA-repair processes.

Further evidence for the implausibility of a steeper slope initial slope in EtO dose-response comes from genotoxicity and carcinogenicity studies conducted with ethylene. Since ethylene is metabolized in vivo to EtO, it forms the same type of protein and DNA adducts as EtO. Based upon a physiologically based toxicokinetic model, Filser and Klein (2018) predicted that exposures to 10,000 ppm ethylene induces adduct levels equivalent to EtO exposures to 3.95 (mice), 5.67 (rats), or 0.313 ppm (humans). Ethylene is not an in vivo genotoxicant in the rat or the mouse (Vergens and Pritts, 1994; Walker et al., 2000). In a chronic bioassay, ethylene was not carcinogenic in male and female Fischer 344 rats following exposed 6 hr/day, 5 days/week, for up to 24 months to concentrations of 300, 1000, or 3,000 ppm (Hamm et al., 1984). DNA adducts resulting from 300, 1000 or 3000 ppm ethylene are shown to be quantitatively to 2.4, 5.3 and 5.5 ppm EtO, respectively (Filser and Klein, 2018). Lack of ethylene carcinogenicity in the rat, in spite of increased DNA adducts equivalent to low ppm-level EtO exposure, informs that the potency of EtO's carcinogen is not higher at the lower exposures, an observation contrary to the prediction based on the IRIS (EPA, 2016a) 2-slope exposure-response model. On the other hand, the dose-response for EtO carcinogenicity is conservatively consistent with a default linear risk model with a single slope.

Fennell and Brown (2001) showed that blood concentrations of EtO in mice, rats, and humans increased linearly with exposures between 50 and 200 ppm (see figure below). Dose-disproportionate increases in blood EtO occurred only in mice at exposures exceeding 200 ppm and were attributed to substantial depletion of GSH, which limits the overall GSH conjugation capacity. It needs to be emphasized that the dose-disproportionate response in mice involved an increased (not decreased) rate of blood EtO concentration at exposures >200 ppm EtO. These observations do not support the plausibility for a steeper slope at lower exposures either for genotoxicity or carcinogenicity.

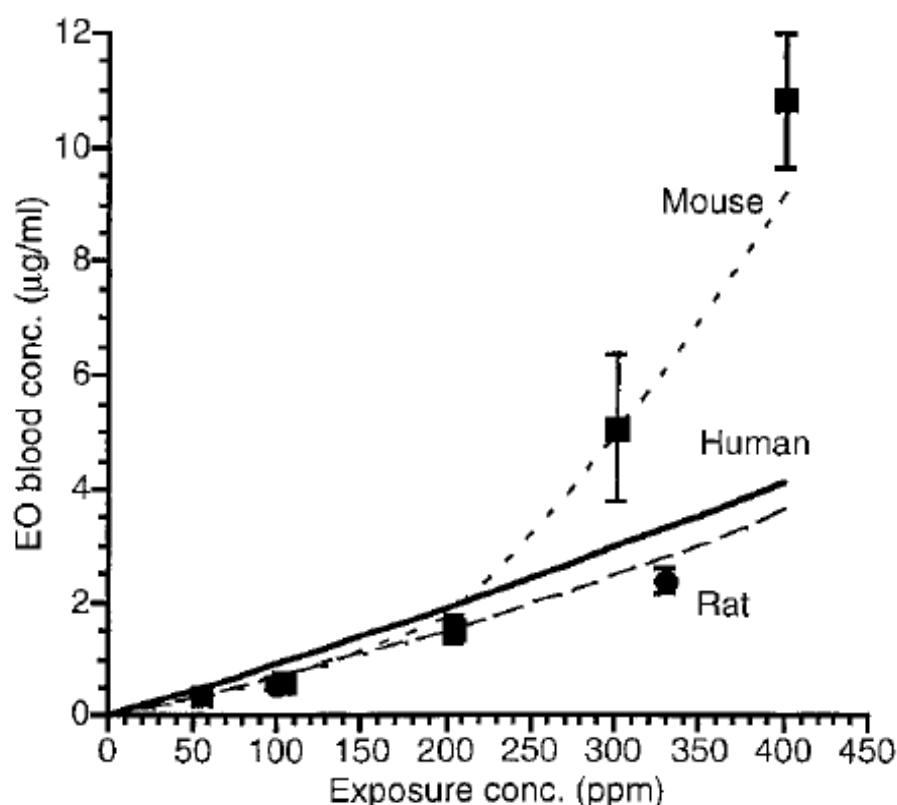


Figure 7. Toxicokinetics of EtO from Fennell and Brown (2001).

In conclusion, EtO is a relatively weak genotoxicant and requires relatively high and prolonged exposures to induce mutagenicity. The experimentally observed dose-response patterns for mutagenicity/carcinogenicity show that the CPH model is biologically more plausible than the IRIS (EPA, 2016a) 2-slope model. Accordingly, the CPH model should be the model of choice for risk assessment purposes especially if an alternate model is not a better fit to the observed data.

Qualitative and quantitative analysis of genotoxicity data by Gollapudi et al. (2021) provide independent converging evidence supporting TCEQ's quantitative risk assessment.

The recent literature search conducted by OEEHA missed the publication by Gollapudi et al. (2021). These authors analyzed the dose-response data to identify a point-of-departure for EtO-induced in vivo genotoxicity from an exhaustive list of published studies that employed various endpoints, tissues, and species and derived 238 ppt as the lowest permitted daily exposure (PDE) from this analysis. The PDE of 238 ppt proposed in this publication is more than three orders of magnitude higher than the 0.1 ppt established by the EPA (2016a) and similar to the 240 ppt estimated from TCEQ (2020a) UR values for 1-in-10⁶ (1/M) extra risk. Thus, if EtO were operating through a genotoxic MoA for its carcinogenicity, then the exposure-response model

used by the TCEQ, rather than the one used by the EPA, is consistent with the biology based on the analysis by Gollapudi et al.

Regarding Carlsson et al. (2017) and Zeljezic et al. (2016) genotoxicity studies

The results from the studies by Carlsson et al. (2017) and Zeljezic et al. (2016) identified in the recent literature search by OEEHA should be interpreted with caution since the subjects in this study were exposed to multiple carcinogenic/genotoxic chemicals including EtO and hence it is difficult to attribute the effects observed to any single chemical. Accordingly, the statement by OEEHA that the results “..... are consistent with the overall evidence for the genotoxicity of ethylene oxide” is an overstatement.

5. OEHHA appears to equate the 5 categorical rate ratios with the 53 rate ratios, and/or assumes that comparisons of the exposure-response curve can be compared visually with the EPA IRIS (2016a) graphical representation 5 categorical rate ratios.

**** Pertaining to NSRL p. 26 ****

OEHHA relies on IRIS's visual fit comparisons using figures that compare continuous models with categorical models, as if the categorical model with only 5 data points were the gold standard for understanding the shape of the exposure-response curve. While categorical models with a small number of odds ratios can be useful for identifying possible associations, they do not identify the shape of the dose-response curve based on continuous data modeling as shown in detail by Valdez-Flores and Sielken (2013). Based on these visual fit comparisons, OEHHA concludes that models either over or underpredict the categorical model, which are not the data modeled.

TCEQ provided new information that OEHHA may not have been aware of. Graphical display of data is subject to manipulations including choice of how data are expressed on the y-axis and resolution of categorical models to represent the underlying individual data that were modeled. TCEQ's purpose is best expressed in TCEQ's response to peer review comments (TCEQ 2020b, p.49. 51):

"The TCEQ only discusses visual fit (and only in an Appendix) because of USEPA's reliance on it. By contrast, the TCEQ does not rely on visual model fit as a primary consideration for model choice, but rather principally relies on MOAs and various statistical diagnostics of model fit (i.e. AIC and p-values, statistical analyses of model accuracy), consistent with the comment."

TCEQ's explains in text and illustrates in figures that EPA's graphs are misleading because EPA uses the categorical modeling results (which are not the primary data being modeled) to visually evaluate the fit of models as though these cruder categorical estimates represent the true underlying dose response. EPA correctly points out that each of these individual case categories will have very wide confidence interval (CI) but fails to address TCEQ's major point which is that the categorical estimates graphed as point estimates without the CI are not representative of the underlying 53 hazard rates modeled. EPA IRIS did not exhibit the wide confidence intervals associated with the EPA's categorical model in the graphs used to illustrate visual fit. Thus, TCEQ produced similar figures without the CI's to better illustrate the underlying individual hazard rates that are being modeled. TCEQ explains why comparison of the exposure-response model results to the categorical model results is inappropriate on p. 52 of TCEQ (2020b) response to peer review.

"This is because while assessing model fit by visual inspection to the underlying modeled datapoints is a commonly used technique. . . , the dose-response models being judged by visual fit to the categorical results were fit to different data, the more refined

individual data. The USEPA should not have used the categorical modeling results (which are not the primary data) to visually evaluate the fit of models to other data (the individual data) as though the cruder categorical data represent the true underlying dose-response.”

EPA counters TCEQ that the categorical model is a well-accepted method to represent the data. This true statement is irrelevant to addressing TCEQ’s main point that visual fit based on categorical models are not appropriate for the purpose of determining goodness of fit of the model to the underlying data, because the categorical model is NOT modeling the underlying individual data. In addition, TCEQ cites Valdez-Flores and Sielken (2013) which is a peer-reviewed paper that demonstrates how the shape of categorical results can change with different number of categories. TCEQ is not advocating the use of these graphs to assess visual fit as a method to select the models, but instead is informing that these graphs should not be used for visual fit comparison. Instead, TCEQ relies on a more objective statistical modeling approaches to evaluate goodness of fit, rather than “eyeballing” comparisons using figures that are not fit for this purpose and distort the true comparisons of models against the underlying individual data that were modeled.

OEHHA should correct their discussion of visual fit so that all of OEHHA’s claims of over or underprediction are omitted because they violate EPA IRIS’ warning that such comparisons along the y-axis are incorrect comparisons of over- or under-prediction.

6. OEHHA dismisses TCEQ’s prediction analysis which is a much more objective method than visual fit to check how well each of the two models (i.e., TCEQ’s vs EPA’s) can predict the observed number of lymphoid cancer deaths (the key cancer endpoint). In this model ground-truthing exercise, the TCEQ model better predicted not only the overall number of lymphoid cancers in the NIOSH cohort but also the observed cancers below the knot in Quintile 2.¹⁵

**** Pertaining to NSRL p. 38-39 ****

As described above in our general comments, OEHHA dismissed TCEQ’s “reality check” (Table 4) based on a prediction analysis because the models are applied to general population background cancer rates, which OEHHA considered to be a flawed analysis because the NIOSH study is based on a specific cohort of occupational workers. Yet, this approach is essentially the same approach used by IRIS (EPA, 2016a, Section 4.7) to estimate extra risk for various occupational exposure levels by applying the model to the general population background cancer rates in the life-table program.

Table 4: Total NIOSH cohort lymphoid cancer mortalities predicted by TCEQ (2020a) and EPA IRIS (EPA, 2016a) models

Model (15-yr lag, MLE)	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × Ratio: Predicted / Observed	100% × SMR: Observed / Predicted	95% Poisson CI if the Model were True
TCEQ (CPH)	2.81E-06	52.42	98.9%	(40.1, 70.0)	(38.2, 66.6)
IRIS 2-slope spline 15-yr lag (MLE)	7.58E-04	91.69	173.0%	(70.1, 122.4)	(72.9, 110.4)

Note: There are 53 actual lymphoid mortalities. 53 is within the CIs for the TCEQ model but not within the CIs for the IRIS model. Thus, the TCEQ model accurately predicts the actual cancers. In contrast, the IRIS model statistically significantly (bold font) over-predicts the actual number of cancers. TCEQ used the inverse of the confidence intervals of the SMRs. We calculated the confidence intervals based on the Poisson distributions. See TCEQ (2020a, Table 6).

¹⁵ TCEQ (2020a) defined Quintile 1 as the 9 lagged-out cases (no exposures). The remaining 44 cases were equally divided into 4 groups designated by TCEQ as Quintiles 2-5. EPA IRIS (2016a, p. 4-15) reported 13 exposed cases below the knot of 1600 ppm-days. Thus, prediction of Quintile 2 comprised of 11 cases with the lowest exposures best reflects “local” fit below the knot.

EPA (2022) also raised a question about TCEQ’s calculation of the confidence interval (CI) based on the inverse of the SMR CI as described in detail by TCEQ (2020a). Thus, it is useful to show that another well-accepted approach for estimating the 95% CI results in the exact same conclusion that the TCEQ model accurately predicts the actual 53 cases, whilst the IRIS model over-predicts the number of cases (Table 4)

OEHHA claims that TCEQ calculations did not accurately account for any differences that might exist between the general US population and the NIOSH cohort. It is unclear if OEHHA is aware that the TCEQ (2020a) DSD¹⁶ includes a sensitivity analysis to demonstrate that the TCEQ model better predicts the overall actual cancers even after applying a high HWE of 15-16% for lymphoid cancers as a sensitivity analysis (Table 5).

Table 5: Total NIOSH cohort lymphoid cancer mortalities predicted by TCEQ (2020a) and EPA IRIS (EPA, 2016a) models with 15% HWE as a sensitivity analysis

Model (15-yr lag, MLE)	Slope Parameter (per ppm-day)	Predicted if the Model were True	100% × Ratio: Predicted / Observed	95% Poisson CI if the Model were True
TCEQ (CPH)	2.81E-06	44.56	84.1%	(31.4, 57.6)
IRIS 2-slope spline 15-yr lag (MLE)	7.58E-04	77.94	147.1%	(60.6, 95.2)

Note: The TCEQ model still accurately predicts the actual cancers after accounting for a theoretical HWE. In contrast, the IRIS model statistically significantly (bold font) over-predicts the actual number of cancers after including a theoretical HWE¹⁷. TCEQ used the inverse of the confidence intervals of the SMRs. We calculated the confidence intervals based on the Poisson distributions.

Although one can quibble with the TCEQ’s selection of 15-16% based on a Norwegian worker study with relatively short average follow-up of 11.5 yrs (Kirkeleit et al. 2013),¹⁸ the larger point is that a 15% HWE is a very reasonable high estimate for any differences that might exist between the general US population and the NIOSH worker. The NIOSH study authors themselves concluded that there was unlikely to be a cancer HWE in this longer follow-up study (Steenland et al., 2004¹⁹) cohort. This conclusion of the NIOSH study authors is very consistent with the general experience in cancer epidemiology that HWE is known to vary with type of

¹⁶ TCEQ Section A3.3.2

¹⁷ Predicted is based on multiplying predicted values in Table 4 by 0.85 for HWE of 15%, and CI’s calculated using Poisson distribution. Compare with TCEQ (2020a, p. 102, Section A3.3.2) estimates of 44.3 (95% CI: 33.9, 59.2) and 77.5 (95% CI: 59.3, 103.6) based on 15 and 16% HWE for males and females, respectively.

¹⁸ Kirkeleit et al (2013) did not find a HWE for lymphoid or breast cancer. It is unknown if the Norwegian cohort is representative of the NIOSH sterilizer workers.

¹⁹ “The healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons.” (Steenland et al., 2004)

disease, being smaller for cancer than for other major diseases, and it tends to disappear with time since recruitment into the workforce (IARC, 1999). In addition, the epidemiologic literature has shown that a HWE is predominantly related to populations with shorter follow-up and non-cancer causes (Monson, 1986; Fox and Collier, 1976).

Using a 15% HWE, the CPH model accurately estimates the observed number (53) of lymphoid deaths in the NIOSH study (Table 5). In contrast, the linear 2-piece spline model statistically significantly overestimates the number of observed lymphoid deaths in the NIOSH study (Table 5). In addition, a quintile analysis was also performed by TCEQ (2020a) to address EPA IRIS (2016a) emphasis on the local fit of the models below the knot. EPA IRIS (2016a, p. 4-15) reported 13 exposed cases below the knot of 1600 ppm-days. Thus, prediction of Quintile 2 comprised of 11 cases best reflects “local” fit below the knot. Table 6 summarizes TCEQ CPH and EPA 2-piece spline model predictions of the number of lymphoid deaths at each quintile. Table 6 shows that, for each quintile, the CPH model has superior local fit. These results indicate that the CPH model not only has better local fit below the knot, but also at the highest quintile.

Table 6: Quintile-specific NIOSH cohort lymphoid cancer mortalities predicted by Cox and linear two-piece spline models

Model	Quintile 2	Quintile 3	Quintile 4	Quintile 5
<i>Lymphoid Cancer Deaths Observed in NIOSH Cohort</i>	11	11	11	11
Standard Cox model – 15-yr lag (MLE)	14.4 (8.1, 28.9) ²⁰ (7, 21.8) ²¹	8.0 (4.5, 16.1) (2.4, 13.5)	9.4 (5.2, 18.8) (3.3, 15.4)	9.1 (5.1, 18.3) (3.2, 15.0)
Linear two-piece spline with knot @ 1,600 ppm-days – 15-yr lag (MLE)	20.9 (11.7, 42.0)²⁰ (11.9, 29.8)²¹	17.6 (9.8, 35.2) (9.3, 25.8)	20.8 (11.6, 41.7) (11.8, 29.7)	20.9 (11.7, 41.9) (11.9, 29.8)

Note: The TCEQ model accurately predicts the actual cancers for the lowest exposure quintile 2. In contrast, the IRIS model statistically significantly (bold font) over-predicts the actual number of cancers. TCEQ used the inverse of the confidence intervals of the SMRs. We calculated the confidence intervals based on the Poisson distributions. See TCEQ (2020a, Table 6).

In conclusion, the TCEQ standard CPH model accurately predicts the number of lymphoid deaths observed in the NIOSH study while EPA’s two-piece linear spline model statistically

²⁰ TCEQ (2020a) method was used for CI, for comparison we calculated the CI based on Poisson distribution.

²¹ CI calculation based on normal distribution for all Quintiles.

significantly (at the 2.5% significance level) overpredicts the number of lymphoid deaths observed in the NIOSH study. This is true with and without consideration of a reasonably high HWE of 15% which reasonably accounts for any differences that might exist between the general US population and the NIOSH worker cohort given the absence of a HWE in the NIOSH cohort. This TCEQ “reality check” is a well-accepted approach that is essentially the same approach used by IRIS (EPA, 2016a, Section 4.7) to estimate extra risk for various occupational exposure levels by applying the model to the general population background cancer rates.

7. OEHHHA’s sole reliance on internal analyses and OEHHHA’s extreme and complete exclusion of external analysis is based on a main conclusion that all external analysis should be ignored because it is confounded by the HWE. This is contradicted by NIOSH study authors’ own published conclusions that “the healthy worker effect would seem an unlikely explanation for the lack of cancer excesses in the exposed versus non-exposed comparisons.” Furthermore, OEHHHA’s uncritical acceptance of conclusions of a more recent paper by Park (2020) that there is a Healthy Worker Survival Effect (HWSE) led OEHHHA to support the EPA IRIS model. However, the conclusions are not supported by the actual results in the paper. Improvements in these and other descriptions of the human epidemiological studies are needed to accurately assess the epidemiological weight-of-evidence.

**** Pertaining to NSRL p. 30 ****

External (comparisons to the general population) and internal analyses (worker to worker comparisons) in occupational epidemiology studies are complementary approaches to the examination of potential exposure-response associations. When they agree, confidence in the presence or absence of risk is enhanced. When they disagree, it is incumbent upon the researchers to explore explanations. In some cases, and more often in the early years of occupational epidemiology, the identification of the potential for the HWE led to a general preference in favor of internal analyses. The HWE, particularly for cancer outcomes, is of much lesser concern if the external analyses of cohort studies have been updated with longer observation period. We have commented on this being the case for the NIOSH and UCC studies. The UCC study has had two published updates since the original Greenberg et al. (1990) publication (Teta et al. 1993, Swaen et al. 2009), such that the average follow-up of study subjects has gone from 20 to 37 years. This is what Steenland et al. 2004 was referring to below when he noted the change observed from the original study published in 1991.

“The healthy worker effect has diminished (all-cause mortality was up to an 0.90 from the prior SMR of 0.81) as would be expected with increased follow up.”

ACC’s analysis and explanation of the HWE is also supported by IARC (1999) in its textbook on Cancer Epidemiology: Principles and Methods, which specifically notes that HWE “is known to

vary with type of disease, being smaller for cancer than for other major diseases, and it tends to disappear with time since recruitment into the workforce.”

Furthermore, comparisons to worker populations can have their own limitations, such as small sample sizes, baseline risks that suggest they are non-representative of the true low or non-exposed population (e.g., Mikoczy et al., 2011).

OEHHA’s complete reliance on internal analyses leads them to consider well-conducted meta-analyses as “flawed” and ignore their conclusions. In general, meta-analysis is a well-accepted method for summarization of results from multiple studies, despite being generally limited to pooled overall risk estimates, as many studies do not provide data by levels of exposure. Furthermore, OEHHA is incorrect in saying that Marsh et al. (2019) did not consider the results of NIOSH internal analyses. In fact, these authors, state:

“However, similar to the LHC results, the NIOSH findings, which revealed no overall excess for breast cancer, were limited to the exposure–response analyses using the log-transformed EtO exposure metric and were questioned by the authors due to their inconsistency across the other EtO metrics considered and potential case over-ascertainment in the higher exposure categories. As discussed above, due to the questionable validity of the positive EtO exposure–response of Mikoczy et al. (2011), these findings add little weight to the overall evidence for EtO exposure and breast cancer.”

It is, therefore, scientifically unjustified to ignore the absence of any overall excess of breast cancer in the NIOSH 2004 mortality study and the relevant meta-analyses (Marsh et al. 2019; Vincent et al. 2019).

OEHHA’s crude and incomplete evaluations and uncritical acceptance of Park, 2020 led them to unequivocally support the EPA model.

**** Pertaining to NSRL p. 33-34****

OEHHA states that they conducted several qualitative and quantitative assessments of potential bias and errors in the NIOSH study and its use by EPA.

1. Their discussion of exposure assessment is limited to the successful validation NIOSH performed of the post 1978 estimates from their regression model. OEHHA does not consider the NIOSH limitations related to exposure estimates for the pre-1978 period that had no validation, as ACC has previously discussed in detail. Instead, they criticize Bogen et al. (2019) for not validating their estimates.

2. While OEHHHA raises the issues of the healthy worker effect (HWE) and the healthy worker survivor effect (HWSE), they conclude that the internal analyses by NIOSH remove the HWE issue and there is no more than a minor downward OR bias (10% or less), due to the HWSE. They cite Park 2020 to support the existence of a HWSE in the NIOSH data. We agree with OEHHHA that neither of these types of biases are relevant. However, there is no HWE in the NIOSH study due to extensive follow up, as noted by Steenland, which adds to the relevance of the external analyses of these data. The absence of findings in external analyses of the NIOSH (and UCC data) adds to the uncertainty of the EPA model suggesting a highly potent carcinogen.
3. We also disagree with citing Park 2020 in support of the existence of a HWSE in the NIOSH study, such that control for employment duration leads to a stronger association between cumulative exposure and breast and hematopoietic cancers. In Section 3.2 of Park 2020, the author discusses the findings reported in Table 2. The models include both cumulative exposure to EtO and duration of employment – variables that are very likely highly correlated. Park reports “statistically significant negative effect of duration (diminishing rate of leaving with increasing time on job) and positive effects of EtO cumulative exposure that are highly significant for all but the smaller work group of black women (Table 2).” These two variables are in the model used to fit the data with a similar multiplicative role. Given the high correlation between cumulative exposure and duration of employment, a negative coefficient for duration of employment would have to be compensated by a positive coefficient for cumulative exposure. Thus, it is not surprising that a negative coefficient for one variable results in a negative coefficient for the other variable. In fact, in three of the analyses reported in Table 2, the more negative of the coefficient for duration resulted in more positive coefficients for cumulative exposure.

Park (2020) Table 5 shows the results of Park’s models for female breast cancer. There, Park does not find any statistically significant relationship between breast cancer and EtO exposures or employment duration. Park states “For the 102 deaths from female breast cancer, there was no statistically significant difference in mortality on cumulative EtO exposure with a 10-year lag.” Park goes on to indicate that “with 20-year lag, the contribution of cumulative EtO was significant.” It is interesting that although the model is significant, the 95% confidence intervals indicate that the coefficients for cumulative exposures to EtO are not statistically significantly different from zero. That is, the 95% confidence intervals indicate that breast cancer in female workers is not related to cumulative exposure to EtO lagged 20 or 10 years.

Park (2020) Table 6 shows the results for lymphopoietic cancer deaths in the male and female workers. There, Park showed the results for male black workers only because “The 73 lymphopoietic cancer deaths did not represent an overall excess (SMR = 0.96; 95% CI, 0.76-1.20), based on U.S. rates, particularly for white men (SMR = 0.92), and white women

(SMR = 0.85), but among black workers, there was a statistically significant increase in SMR with cumulative EtO exposure (lagged 2.5 years; LRT: $P = .011$) (Table 6; model 1).” Similar to the results in Table 5 for breast cancer, in Table 6 the models statistically significantly improved the model fit to the lymphohematopoietic deaths in black workers but the coefficients for the cumulative exposure to EtO were not significantly different from zero; that is, there is no statistically significant increasing relationship between lymphopoietic cancer and cumulative exposure to EtO lagged 10 years even in the most sensitive subgroup of workers in the NIOSH study.

The above data are inconsistent with Park’s description of his results in his abstract that were uncritically accepted by OEHHA.

4. OEHHA attempted to address the possibility that high intensity- short exposures might explain the NIOSH findings and therefore not be generalizable to the general population, not subject to such types of exposures. Without actual NIOSH data and with incorporation of several questionable assumptions, OEHHA concludes that excluding workers with these exposures from the NIOSH study would have little impact on the EPA exposure-response slope. Firstly, they assumed that workers with this type of exposure would most likely be in the middle categories of cumulative exposure. Then OEHHA estimated case and control counts in each exposure category, recalculated ORs and exposure-response slopes after excluding various percentages of participants (e.g., 10–30% high intensity-short duration exposed workers) in the middle exposure categories, using guestimates since the actual data were not available. “Exclusions were done at the case:control ratio equal to or slightly lower than that reported in the highest exposure category (where almost all workers probably had at least some high intensity exposure). Overall, these exclusions (with and without replacing the excluded participants into the highest category) had little impact on exposure-response slopes (e.g., 10% or less). This suggests that this issue did not have a major effect on the unit risk calculations or the generalizability of the NIOSH findings.” This conclusion is hardly justified using this obscure analysis and exclusion assumptions, in the absence of actual NIOSH data.

We agree with OEHHA’s summary of the limitations of community-based studies, which makes them inappropriate for exposure-response but disagree that they are useful for hazard assessment.

**** Pertaining to NSRL p. 9, 37 ****

The proposed NSRL (p. 9) states:

In addition to the three human epidemiological studies in Table 1, OEHHA identified four epidemiological studies that investigated associations between residential proximity to

ethylene oxide emitting facilities and increased cancer risk (Garcia et al., 2015; Bulka et al., 2016; Hart et al., 2018; and Jones et al., 2023). Emissions data were obtained at the community level from US EPA databases: the Toxics Release Inventory (TRI) (Bulka et al., 2016; Jones et al., 2023; US EPA, 2023a) and the National Air Toxics Assessment (NATA) (Garcia et al., 2015; Hart et al., 2018; US EPA, 2018). While these community-based air pollutant studies can be useful for hazard identification, OEHHA judged them to be less useful for dose-response assessment of ethylene oxide compared to the occupational studies (Steenland et al., 2003 and 2004; Swaen et al., 2009; and Mikoczy et al., 2011) due to greater uncertainty in estimating individual exposures. This can result in non-differential exposure misclassification and bias risk estimates towards the null (Shy et al., 1978). Furthermore, there were fewer exposed cases, and there may be less exposure contrast in these community-based studies of ethylene oxide, decreasing the sensitivity of the studies to detect an effect.”

We agree with the limitations noted by EPA but disagree that community-based studies are useful for hazard identification of EtO, precisely because of limitations noted in EPA's final sentence. But in addition to concerns about sensitivity (study power), there are serious concerns in such studies related to confounding risks that may be related to potential errors in exposure assessment due to confounding by other sources of EtO exposure, such as smoking and highways. Bias can, therefore, be in either the positive (specificity) or negative direction (sensitivity), making such designs uninformative.

OEHHA fails to discuss the most important limitation of the Mikoczy et al., 2011 study – the questionable comparison group in the internal analyses

** Pertaining to NSRL p. 12 **

OEHHA has but one criticism of Mikoczy et al (2011): “Exposures were much lower than in the NIOSH and Union Carbide cohorts, which decreases the ability to detect an effect.” This is apparently OEHHA's explanation for the failure in this study to detect any increase in LH cancers.

While not noted by OEHHA, Mikoczy et al. (2011) has been incorrectly cited in IRIS as supportive of a supralinear association with breast cancer, despite an overall deficit of breast cancer (SIR= 0.81), with or without consideration of a latency period. However, the two higher cumulative exposure groups had statistically significant elevated rates of breast cancer, due to a substantial and statistically significant deficit of breast cancer in the low dose reference group. This deficit is not explained by the HWE, which is primarily related to non-cancer causes and declines with length of follow up. As discussed above, there are clearly advantages to comparing workers to workers in epidemiology studies to overcome possible biases in external

comparisons to the general population. However, there may also be disadvantages to using an internal comparison group that may not be recognized. One danger is selecting a referent group that has an unusual deficit of the disease of interest that creates an artifact of an excess as is illustrated in this study, whose referent group breast cancer rates are 50% of general population baseline. This serious limitation was also illuminated in Marsh et al. 2019:

“The validity of the Mikoczy et al. (2011) finding and conclusion can be challenged, however, on the basis of several methodological issues. First, the greater than 2-fold relative excesses in breast cancer incidence risk in the two highest cumulative EO exposure categories were ensured by an inordinately large, statistically significant 48% deficit in breast cancer incidence in the baseline category. The inordinately low baseline SIR for breast cancer is puzzling given that regional rates were used in the external comparisons and that there was no apparent problem with under-ascertainment of breast cancer cases. The healthy worker effect is also not a reasonable explanation for the low baseline breast cancer rate (Gridley et al. 1999). It appears that for unknown reasons, the baseline group used by Mikoczy et al. (2011) differs from the highest two cumulative EO exposure groups on factors other than EO exposure that may be related to breast cancer.”

The EPA (2016a) IRIS report quantitatively demonstrated the inconsistency of the excesses reported at very low exposures in this population with excesses at only higher exposures in the NIOSH study.

“Thus, crude comparison analyses were done to evaluate whether or not the exposure-response models of the NIOSH study that were used to derive unit risk estimates in this assessment gave predictions consistent with the Mikoczy et al. (2011) internal incidence ratios (IIRs) for the two highest exposure quartiles (see Section J.2.2 of Appendix J). The predicted values for lymphoid cancer were within the 95% CIs for the IIRs for lymphohematopoietic cancer reported by Mikoczy et al. (2011). The predicted values for breast cancer incidence, however, were below the lower limit of the 95% CIs for the IIRs for breast cancer, suggesting that the Mikoczy et al. (2011) results are consistent with a higher unit risk estimate for breast cancer incidence than the one derived in this assessment. The reasons for the discrepancies are unknown... “(EPA 2016a, p.60-61)

Marsh et al. 2019 also addressed this exposure inconsistency:

“Second, cumulative EO exposure levels in the Mikoczy et al. (2011) study were very low relative to both the UCC cohort (Swaen et al. 2009) and NIOSH breast cancer cohort incidence study (Steenland et al. 2003).”

EPA more recently argues that there were some substantial exposures in the Mikoczy et al. cohort, making it more comparable to the exposures in the NIOSH cohort, backtracking from the IRIS report. OEHHA reports the breast cancer findings from the internal analysis and ignores the potential bias associated with a non-representative worker comparison group.

8. Based on uncritical acceptance of the IRIS evaluation, OEHHA inaccurately exaggerates the reliability of the NIOSH worker exposure estimates prior to 1978.

**** Pertaining to NSRL p. 23, 24, 34 ****

OEHHA can improve the weight of evidence of the epidemiological data by more accurately describing the substantial limitations of the NIOSH worker exposure estimates prior to 1978. Furthermore, NIOSH has lost the electronic files needed to independently assess the NIOSH estimates of exposure prior to 1978 for which NIOSH had no direct measurements²². These data quality issues make open access and independent assessment of the IRIS cancer slope factor difficult for lymphoid cancers and impossible for breast cancers.

OEHHA makes the following statement regarding the NIOSH cohort exposure assessment, *“Each participant’s EtO exposure was estimated using a validated multiple regression exposure model that incorporated information on workplace air measurements, sterilization unit size, engineering controls, timing of sterilization, product type, calendar year, and historical process changes.”* (Proposed NSRL p. 23)

OEHHA also states, *“US EPA judged the NIOSH study to be of “high quality” based on the availability of quantitative exposure estimates for individual workers, high-quality exposure assessment, longitudinal study design, large sample size, inclusion of males and females, adequate follow-up, absence of known confounding exposures, multiple study locations, and the use of internal comparison groups. OEHHA reviewed the NIOSH study using the Hill guidelines for causal inference and the National Toxicology Program (NTP)’s risk of bias tool, and also concluded that this study is of high quality, and unlikely to be affected by important bias or confounding.”* (Proposed NSRL p. 24)

OEHHA dismisses a robust analysis of the trend of the NIOSH exposure data by Bogen et al. (2019):

“Bogen et al. (2019) have suggested that exposures occurring prior to 1978, the first year that EtO sampling data were available for the NIOSH cohort, may have been dramatically under-predicted by the NIOSH exposure model. However, as noted by these authors, several assumptions were used in their assessment, and the information used to support these assumptions, “were limited in scope and quantitative detail.” In addition,

²² In response to the panel’s suggestion that the Hornung analysis represents an “invaluable opportunity” for further analysis of the impact of possible errors in exposure estimation, the EPA investigated the possible use of the “errors in variables” approach (page 27 of the panel report). . . Unfortunately, the electronic data files used in the exposure analysis were no longer available, so that analysis based on the errors-in-variables approach was not possible.

the authors were unable to validate their pre-1978 predictions since no actual worker measurements were available from that time. Overall, because of these and other weaknesses, the accuracy of the Bogen et al. (2019) assessment is unknown.” (Proposed NSRL p. 34)

These OEHHA statements show, at a minimum, a lack of rigor in evaluating the NIOSH exposure model (Hornung et al. 1994) and its “validation”, and a biased evaluation of the Bogen et al. (2019) paper as discussed in our general comments above.

A more correct statement describing the NIOSH multiple regression exposure model is that the model was only validated for the period 1979-1985 (very few samples were collected from 1976-1978) during which EtO concentration measurements were collected from six facilities, but not for the earlier period of sterilizer facility operations (Pre 1978; from late 1930's to late 1970's) when a majority of cohort workers were occupationally exposed to EtO and no exposure measurements were collected. An incorrect assumption by Hornung et al. in applying the NIOSH model to the Pre1978 sterilizer operations regarding a key variable “calendar year”, a surrogate for improvement in work practices, inferred no changes in the Pre1978 period and raises serious question about reliability of the NIOSH model in prediction early worker exposures and the dose-response relationship based on the exposures of these early workers in this cohort.

There are several reasons to question the reliability of NIOSH model predictions of early sterilizer worker exposure estimates:

- First, the NIOSH multiple regression exposure model validation (Hornung et al. 1994) was based using a portion of the 1978-1986 to develop the model and another portion of the data to test the model. Therefore, the model was validated for the years with data but not for the early years for which no concentration measurements were available. Hornung et al. provided no other data, information or analyses for sterilizer workers or processes in this earlier time period to check the applicability to this NIOSH exposure model to sterilization workers in the cohort who worked from the late 1930's to later 1970's. During this time period the vast majority of cohort worker and fraction with most reported cancers. These facts regarding the NIOSH model validation should have raised concern about model predictions for early sterilization workers.
- Second, Hornung et al. selected Calendar year, a surrogate for improvement in work practices, as the key variable in the NIOSH exposure model to Pre1978 cohort workers. This variable was applied conditionally on the max year 1978 forcing the inverse parabolic fit for years before 1978. This application of calendar year inferred that there were no major changes in work practices in sterilization operations between the late 1930's and late 1970's that would have affected worker exposures. Contrary to this

inference, substantial published information and data on early work practices and changes in work practices were found in technical literature, industry documents, and from early workers and industry experts (Bogen et al. 2019). In other words, Bogen et al. (2019) brought far more information and data to inform the validity of the NIOSH model prior to 1978, when NIOSH had insufficient (1976-1978) or no (<1976) data. For example, the numbers of repeated cycles of in chamber, post-exposure vacuum air- or nitrogen washes have increased from two or fewer from early operation up to ten or more for operations in the 1980's leaving high levels of EtO residues to off gas in from sterilized materials and packaging from early operations and lower levels in later operations (Goldgraben and Zank 1981; Buonicore et al. 1984). Consistent with few wash cycles, there are several published studies of rates of EtO off gassing from sterilized materials representing conditions in the 1950's through 1980's (Bruch 1961, 1972; Buonicore et al. 1984; FDA 1978; Stetson et al. 1976; White 1977). As importantly, early operation stored sterilized materials in the same room as ongoing sterilizer operations where both operational emissions and sterilized material off gassing contributed to worker exposure while later operations moved sterilized material to a separate warehouse room reducing the exposure of highly exposed sterilizer operators (Bogen et al. 2019). Clearly there were important work practice changes over time that need be considered in assessing the exposure of cohort workers.

- Third, the NIOSH exposure model based on the conditioning of calendar year predicted early sterilization workers were exposed to EtO concentration substantially lower than workers in 1978 when exposure concentration predictions were based on measurements (see Figure 8 below from Bogen et al. 2019). One would not expect low exposure concentration when equipment and process were crude, and little was known about EtO toxicity and no worker protection regulations. The NIOSH model predicted early worker increasing exposure pattern is inconsistent with industrial hygiene data collected in other industries (e.g., on Grote et al. 2003, 2006) and inconsistent with historic worker exposure guidance (ACGIH 1948, 1957) for EtO exposure concentrations in the workplace. ACGIH provided an exposure limit for EtO of 100 ppm in 1948 and 50 ppm in 1957 to encourage reductions in workplace exposure. As a reality check, no ACGIH guidance would have been needed had EtO concentration been as low as predicted by the NIOSH exposure model.
- Fourth, Bogen et al. (2019) performed an engineering/industrial hygiene evaluation of early sterilization worker EtO exposure to assess the reliability of NIOSH exposure model predictions of an increasing exposure trend. Bogen et al. concluded that from the late 1930's to 1978 there was a decreasing exposure trend for sterilizer workers rather than increasing trend from very low exposures to high exposures predicted by the NIOSH exposure model (Figure 8 from Bogen et al. 2019, Figure 5).

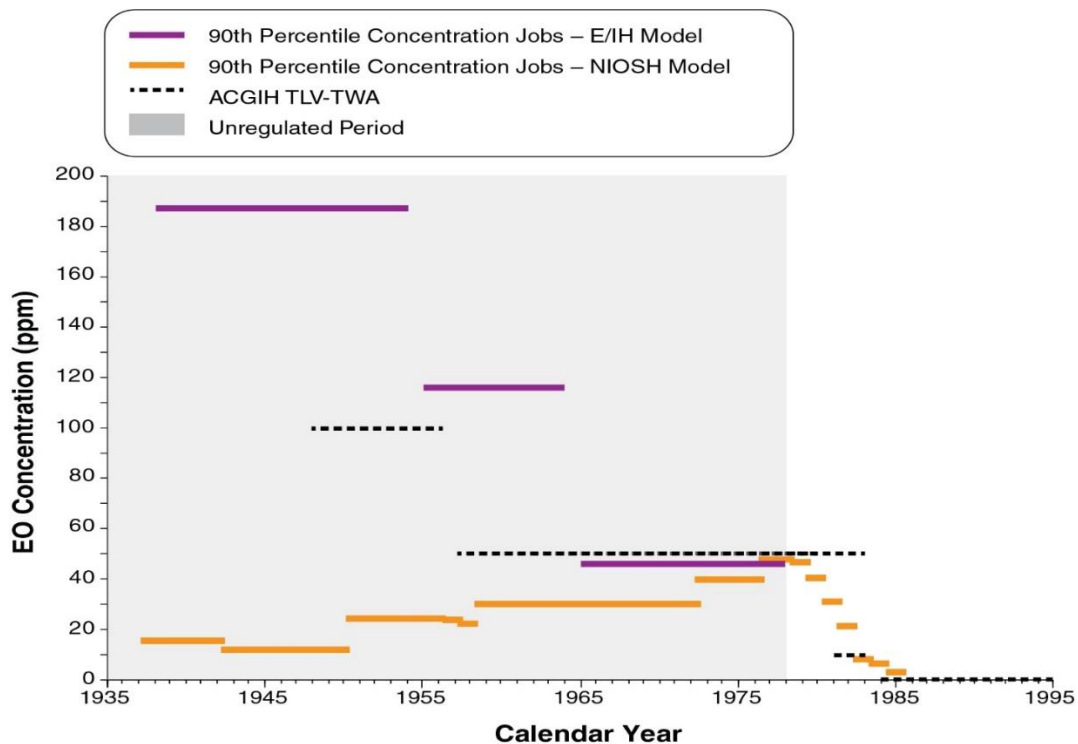


Figure 8. Comparison of E/IH (purple lines) and NSR (orange lines) exposure model estimates of occupational respiratory exposures to EtO in facilities that sterilized medical/health products and prevailing ACGIH TLV limits for EtO (dashed lines). Shaded area represents the period during which very limited or (pre-1976) no contemporaneous measurements were available to validate NSR model predictions and during which no EtO-specific regulations were in place to limit occupational EtO exposures. Adapted from Figure 5 of Bogen et al. (2019)

There are no data or analyses available to support OEHHA's agreement with EPA that the NIOSH model produced a "high-quality" exposure assessment. To the contrary, Bogen et al. (2019) published substantial data and analyses showing that the NIOSH model is flawed and there was a decreasing rather than increasing EtO exposure trend for pre1978 sterilizer operators contributing uncertainty to the EPA and OEHHA EtO risk assessments. OEHHA should recognize the limitations of the NIOSH multiple regression exposure model predictions for early sterilizer operators and the potential adverse effects it has on estimation of risk. Assigning cases with underestimated exposures means that the lymphoid cancer is associated with lower EtO levels than the workers with lymphoid cancers had been exposed to. In general, underestimating exposures associated with cancers will lead to an overestimation of potency. In addition, as there are data on worker exposures to EtO pre-1978 for production workers, it is suggested that OEHHA review production worker cohort monitoring data to ascertain a more reliable picture of early worker exposure patterns.

9. The Union Carbide Corporation (UCC) cohort should play a prominent role in considering the strength and consistency of the epidemiology data in supporting the IRIS vs. TCEQ UR. OEHHHA's description of this cohort incorrectly omits the internal analysis by Valdez-Flores et al. (2010) which included exploration of different exposure metrics and lag times. The absence of findings in the UCC cohort for male lymphoid cancer is not consistent with a steep slope at low concentrations.

**** Pertaining to NSRL p. 9, 11 ****

This UCC study is very important to consider in the weight of evidence because it included long-term follow-up of workers from the 1940s, the infancy in EtO production. The absence of findings in the UCC cohort for male LH is not consistent with a steep slope at low concentrations and does not support the IRIS (EPA, 2016a) derivation of one of the highest IURs. This cohort of 2,174 workers was a subset of another NIOSH study of or more than 29,000 UCC chemical workers in the Kanawha Valley (KV) of WV (Rimsky et al., 1988).

Compared to the NIOSH sterilizer worker mortality study, the UCC study has a smaller cohort sample size but has comparable numbers of LH and lymphoid cancers as those reported in the male component of the NIOSH cohort. The UCC study is, therefore, informative, with respect to males, and the increases in LH and lymphoid cancers reported in the NIOSH study were limited to males (Steenland et al., 2004).

Furthermore, the quality of the UCC study exposure assessment is comparable to that of the NIOSH study. It employed individual exposure estimates for a substantial period between 1925-1988, utilizing the Greenberg et al. (1990) validated categorization of EtO producing and using departments by level of exposure and quantitative estimates of average intensity by these categories developed by Teta et al. (1993). There were no potential confounders to other chemical exposures because such workers were removed from analysis by Teta et al. (1993), Swaen et al. (and Valdez-Flores et al. (2010). Exposure data were available for study subjects at the West Virginia (WV) locations starting in 1974. They were available from Union Carbide's Texas City plant that operated identically to the WV location from the early 1960s. This represents an important advantage of the UCC study over the NIOSH study, which had no exposure data prior to 1978 (Bogen et al., 2019; see previous section for detailed discussion). Estimates from EtO operations in the literature were used for the 1940-1956 exposure period, although only a small percentage of the cohort were employed during that period.

Contrary to Table 7 of OEHHHA's Proposed NSRL, there was exploration of log cumulative exposures and multiple lag times in the UCC study. Valdez Flores et al. (2010) reports that Table S11 in Supplemental materials indicates that the fit (maximum likelihood) varies depending upon the exposure scale used in the log cumulative exposure model (i.e., ppm-days,

ppm-years, ppb-days, and ppb-years). Table S11 also illustrates that the Cox proportional hazard model with the slope parameter multiplying cumulative EO exposure fits the data better than any of these four alternative log cumulative exposure models in more than 55% of the combinations of 12 endpoints. None of the other lag periods resulted in a change in statistical significance, therefore no lag was included in the Valdez-Flores et al. (2010) publication. Nevertheless, to be consistent with NIOSH, a lag period of 15 years was applied to the lymphoid analysis by TCEQ (2020a).

In summary, the absence of increases in LH and lymphoid cancers in the UCC study (in both external and/or internal comparisons), as well as the statistically significant increases in the NIOSH study limited to male highest exposure groups in internal comparisons conducted by Steenland et al. 2004, call into question the biological plausibility of the very high IRIS IUR for LH cancers. Overall, the epidemiological evidence does not support EtO as a potent carcinogen with a steep exposure-response pattern at low exposures. The standard CPH model used to derive the TCEQ IUR is a model well-accepted by epidemiologists in cancer exposure-response analysis, is linear at exposure levels of interest, and consistent with an assumption of no-threshold that reflects the epidemiological weight-of-evidence.

10. We applaud the proposed NSRL for including a section on endogenous exposure to EtO and have recommendations for improvement. While EPA's potency estimate technically only applies to exposures above endogenous levels, it is implausible that a chemical would be a potent carcinogen at levels that the body produces through natural processes. The key assumptions in extrapolating the dose-response relationships at lower exposures are scientifically valid and are now corroborated by independent data sets on smoking.

**** Pertaining to NSRL p. 18, 19 ****

We applaud the OEHHA NSRL and IUR supporting technical documents for including a section on endogenous exposure to EtO in their documents. This topic area is important to future risk assessment and risk management decisions made for this unique chemical. We recommend making the following improvements to this section:

The biochemical pathways that contribute to endogenous exposures, include: (1) production of ethylene by bacteria normally present in the gastrointestinal tract, which is then absorbed into the body; and (2) systemic production of ethylene by specific precursors and by oxidative stress. Endogenous production of EtO results from the oxidation of ethylene resulting from both sources. These pathways are operable in all mammalian species, with measured EtO biomarker levels (2-hydroxyethyl valine or HEV) generally being higher in laboratory rats and mice than in humans.

Endogenous exposures to EtO are variable. These exposures vary from person to person (interindividual variation) and from day to day (temporal variation), and can be modulated by diet (e.g., fatty acid composition; diet content of precursors that are metabolized to ethylene), medications (e.g., antibiotics), and underlying conditions (e.g., oxidative stress).

Kirman et al. (2021) estimated endogenously produced EtO is the largest contributor to EtO-biomarker levels in general population nonsmokers. The estimated average HEV burden of 29.2 pmol/g Hb resulting from endogenous exposure corresponds to an equivalent median inhalation exposure to 2.3 ppb EtO in air. In this context, EtO RSC exposure (0.0016 ppb) is more than 1000-fold lower than the endogenous exposure and would generally be considered negligible.

The Proposed NSRL can clarify that background exogenous exposure is generally a small fraction of total background exposure

**** Pertaining to NSRL p. 18 ****

As most of general population background exposure arises from endogenous production (~95%), whereas exogenous exposure via inhalation of EtO in ambient air generally constitutes a small fraction (~5%) of total exposure (Kirman et al. 2021). EtO in ambient air has been sampled since 2018 at background monitoring locations across the U.S. under the EPA NATTS and UAT hazardous substances monitoring programs. Samples also have been collected at local/regional background locations as part of monitoring programs for EtO emitting facilities. Therefore, there are substantial data characterizing general population background exogenous exposure.

The Proposed NSRL can add that total background exposure from endogenous and exogenous pathways has been characterized from CDC NHANES biomarker data and Kirman et al. equivalent concentrations

**** Pertaining to NSRL p 18-19 ****

Our knowledge of EtO background exposure is informed by CDC internal dose data in the form of a representative exposure biomarker, N-(2-hydroxyethyl)-valine (HEV) adduct levels, measured in erythrocytes for nonsmokers and smokers in the U.S. population (CDC 2019; Kirman et al. 2021). HEV adduct levels represent an individual's total background EtO exposure from endogenous and exogenous sources. Kirman et al. 2021 developed a relationship between biomarker (HEV) concentration and total and endogenous equivalent concentrations (equivalent continuous exposure concentrations in ppb) for smokers and nonsmokers in the U.S. population. Endogenous and total equivalent levels reflect air concentration of EtO that are equivalent to the levels that are produced endogenously, and endogenously and exogenously, respectively. Filser and Klein (2018; Figure 12A) study provides an independent PBPK model-based validation of the linear equivalent relationship adopted by Kirman et al. (2021).

Although OEHHA's Proposed NSRL (p. 19) is correct that cancer risks account for endogenous levels, OEHHA can more clearly indicate that they can be used as an important reality check for selection of exposure-response models:

"The ethylene oxide cancer potency estimate derived from the NIOSH epidemiological study (see Section "Estimation of Cancer Potency" of this document) is based on excess risk. In other words, the human CSF expresses risk over and above the background risk. The background risk includes cancer risk due to endogenous exposures to ethylene oxide. Thus, in the case of ethylene oxide, the CSF is meant for use in computing risk levels associated with non-zero exogenous exposures (i.e., ambient air concentrations > 0 ppm).

This is a true statement for both the TCEQ and IRIS cancer risk calculation. This statement should not be used as a basis to ignore considering endogenous levels as part of an important reality check for derivation of cancer risk specific concentrations. It does not make sense for risk specific concentrations to be orders of magnitude below human endogenous levels, or to be a fraction of the population variability of human endogenous levels.

OEHHA's Proposed NSRL (p. 20) appears to incorrectly suggest that the dose-response relationship for endogenous ethylene oxide exposures is unknown at lower exposures:

"The dose-response relationship for endogenous ethylene oxide exposures within the homeostatic range might be different from the dose-responses seen with ambient exposures, possibly sublinear but ultimately unknown."

- We maintain that EtO hemoglobin adducts (HEV) are useful biomarkers of exposure, a point also noted in this publication, "...Hb alkylation may serve as a particularly sensitive marker of exposure...". It serves as an excellent cumulative measure of the internal doses of EtO present in blood for several months prior to measurement.
- Kirman analysis utilizes HEV to apportion total exposures to EtO from different pathways, which is a valid use of a biomarker of exposure.
- A toxicokinetic model is not required to utilize HEV data. Steady state blood levels of EtO (area under the curve or AUC) can be estimated from measured HEV levels with a high degree of confidence since the values for the reaction rate constants for EtO binding to hemoglobin and erythrocyte lifespans are known, as described in Motwani and Tornqvist (2014; see equations 2-3b).
- Although a toxicokinetic model that fully encodes the endogenous formation pathways (Kirman et al. 2021, Figure 4) are not yet available, the model of Filser and Klein (2018) and data cited therein (Figure 12A of Filser and Klein, 2018) are fully consistent with the use of a linear correlation between EtO in air and HEV measurements in humans, as adopted in Kirman et al. (2021) :

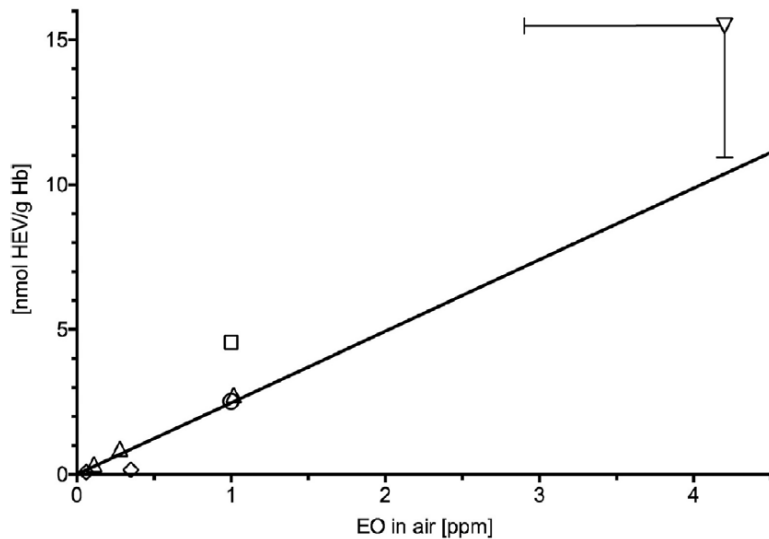


Figure 9. Hemoglobin adducts (HEV, nmol/g Hb) in workers exposed to EtO in air (from Filser and Klein, 2018).

- The available worker data depicted in this figure indicate that a linear relationship between HEV adducts and EtO in air is maintained across a broad range of concentrations (~0.1 ppm to ~4 ppm). Furthermore, the PBPK model of Filser and Klein (2018) predicts a linear relationship across this range of exposures, as well as for exposures extrapolated below this concentration range (solid black line). Lastly, for exposure levels below the range of worker exposures, the NHANES biomonitoring data in smokers and in non-smokers are also consistent with a linear relationship (depicted by red line; note - log-linear scale) between EtO exposure (using cigarettes per day as a metric) and HEV adduct formation:

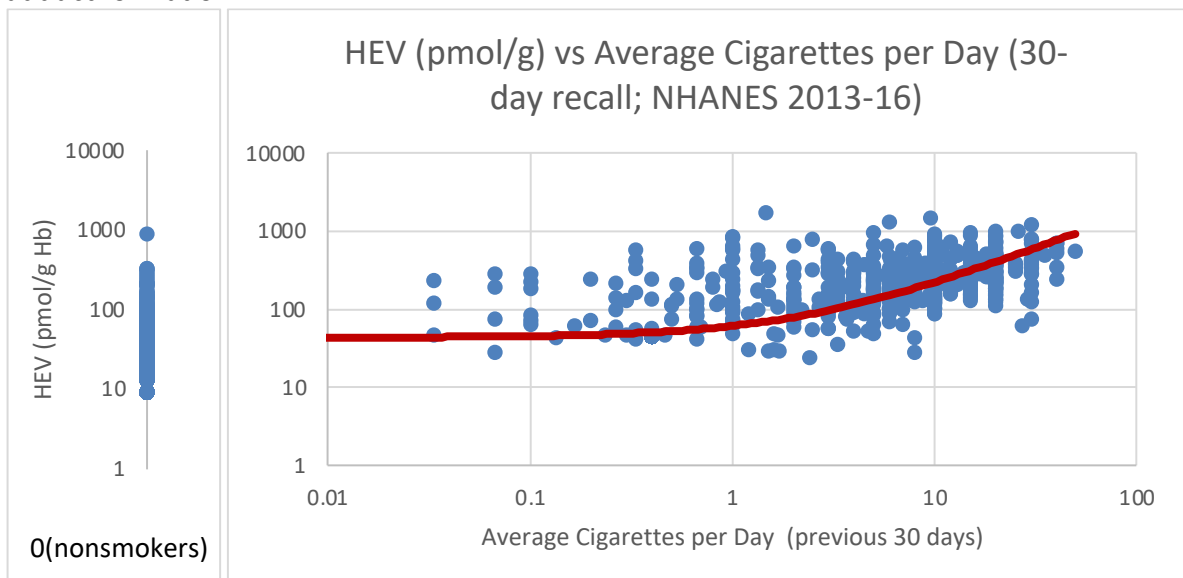


Figure 10. Hemoglobin adducts (HEV, pmol/g Hb) in U.S. smokers exposed to EtO in cigarette smoke (NHANES, 2013-16)

- These data indicate that the linear relationship between EtO exposure is maintained from background exposure levels up to 30x background levels. The linear relationship between cigarettes per day and HEV in this figure is consistent with a linear relationship (e.g., assessed by multilinear regression analyses) for another EO biomarker (urinary 2-hydroxyethyl mercapturic acid) as reported by CDC scientist (Kenwood et al. 2021). Together, these data provide strong and convincing evidence to support a linear relationship between HEV and EO exposure as used in Kirman and Hays (2017) and Kirman et al. (2021).
- Because the exogenous exposures to ET and EtO can be characterized with a high degree of confidence based upon available air monitoring data, and because there is high confidence in the NHANES biomonitoring data for HEV as a measure of total exposure to EO, estimates of endogenous exposure to EtO from these data can also be inferred with a high degree of confidence. There are no other known sources of EtO exposure that could contribute to the HEV levels measured by CDC.
- Measured HEV levels in human populations are dependent upon three parameters: (1) circulating levels of EtO in blood; (2) hemoglobin binding rates; and (3) erythrocyte lifespan. Although there are some possible sources of high-dose nonlinearity (e.g., induction of endogenous production of ethylene by EtO at high doses; theoretical exposure-related effects on erythrocyte turnover due to cytotoxicity) there are no documented sources of low-dose nonlinearity for EtO exposure and HEV formation. Any such nonlinearity would only be relevant at exposures above the range of observation (~0.1 to ~4 ppm) defined by Figure 12A above from Filser and Klein (2018). As noted above, there is no evidence of nonlinearity in the NHANES HEV biomonitoring data as a function of EO exposure (using cigarettes per day). As such this comment is inconsistent with available data sets, and inconsistent with default assumptions for chemical toxicokinetics.

The above comments show that there are reliable data for characterizing background endogenous and endogenous equivalent EtO exposure and provide a preface for using background exposure as context for managing and communicating EtO risk.

Kirman et al. (2021) model of external EtO exposures and internal EtO HEV hemoglobin adducts (EtOHEV) is validated in a “forward” analysis as suggested by EPA (2022)

The relationship between NHANES HEV biomonitoring data as a function of EO exposure (using cigarettes per day) established by Kirman and Hays (2017) and Kirman et al. (2021) is validated with a “forward” analysis, as suggested by EPA (2022), based measured EtO concentrations in mainstream cigarette smoke. Using the linear relationship between external EtO exposures and internal EtO HEV hemoglobin adducts (EtOHEV), Kirman et al. (2021) calculated that an approximate 10-fold increase in general population EtOHEV adducts in smokers compared to non-smokers (CDC NHANES, 2019) was equivalent to a continuous EtO air exposure of 21.7 ± 20.2 ppb (mean $\pm$ SD). EPA (2022) suggested that the Kirman exposure model could be validated if “forwards determinations of smokers total exposures to EtO” compared reasonably

to “backward” estimated EtO exposures derived from the Kirman EOHEV adduct/exposure relationship:

p.69: “EPA also notes that the assumed relationship between HEV adduct measurements and EtO exposures in smokers (Kirman et al. 2017 and 2021) also needs validation. Cigarette smoke contains EtO and ethylene which may be metabolized to EtO. Smokers also experience physiological and biochemical changes that could affect their EtO exposures and/or formation of protein adducts. For validation of the HEV based projections, “forwards” determinations of smokers total exposures to EtO (e.g., as might be assessed using exhaled breath measurements) could be compared with “backwards” calculations of projected EtO exposure levels hypothesized from HEV from adduct level. Paired measurements of breath levels of EtO and ethylene and HEV adduct levels could provide useful bottom-line data to test the HEV/equivalent inhaled concentration hypothesis.”

Importantly, and directly responsive to the EPA-recommended validation exercise, multiple datasets have been published that describe reliable analytically-determined concentrations of EtO in individual cigarettes that can then be converted to total daily EtO smoker exposures dependent on the intensity of smoking behavior (Table 1; Liu et al, 2014; Forster et al., 2018; Jaccard et al., 2019).

Liu et al. (2014) reported for Kentucky Reference 3R4F cigarettes mean concentrations of 8.37 µg EtO/cig under the International Organization for Standardization (ISO) smoking regimen and 26.03 µg EtO/cig under the “Health Canada intensive” (HCI) smoking regimen. Forster et al. (2018) reported for the updated Kentucky Reference 1R6F cigarettes mean concentrations of 17.2 µg EtO/cig (HCI) and 19.3 µg EtO/cig (HCI) for Kentucky Reference 3R4F cigarettes. Jaccard et al. (2019) reported for Kentucky Reference 1R6F cigarettes mean concentrations of 5.92 µg EtO/cig (ISO) and 17.3 µg EtO/cig (HCI). Jaccard et al. (2019) also reported for Kentucky Reference 3R4F cigarettes which yielded mean concentrations of 6.78 µg EtO/cig (ISO) and 19.2 µg EtO/cig (HCI).

Daily EtO exposure concentrations (EC) can be estimated as $C \times \text{CpD} / \text{IR}$, where C is the reported EtO concentration per cigarette (µg/cig), CpD is the number of cigarettes smoked per day (cig/day), and IR is the daily inhalation rate (m³/day). CpD conservatively assumed to be 17 cig/day based on the average number of cigarette smoked by daily smokers in 2005 as reported by CDC (2018), and IR is assumed to be 16 m³/day based mean inhalation rates for adults aged > 16 yr (EPA 2011). The estimated ECs, shown in Table 1 below, ranged from 3.5 to 15 ppb. These estimates are generally consistent with Kirman et al. (2021) estimates of 21.7ppb for smokers, 1.9 ppb for non-smokers, which results in 19.8 ppb from smoking contribution, and confirms that HEV adducts can provide reliable estimates of EO exposure.

Table 7. Estimated daily ethylene oxide exposure concentrations based on measured ethylene oxide concentrations in mainstream smoke

Source of EtO Mainstream Smoke Concentration Data	Reference Cigarette	Regimen	Estimated Daily Exposure Concentration (ppb)
Liu et al. 2014	3R4F	ISO	4.98
	3R4F	HCI	15.49
Forster et al. 2018	1R6F	HCI	10.23
	3R4F	HCI	11.48
Jaccard et al. 2019	1R6F	ISO	3.52
	1R6F	HCI	10.29
	3R4F	ISO	4.03
	3R4F	HCI	11.42

The data in Table 7 indicate that the “forward” analytical measurements of EtO in cigarette smoke, when converted to total daily EtO ppm exposures, are in excellent agreement with the “backwards” estimates of the mean and SD measurements of EtO ppm exposure calculated from the high-quality CDC smoker EtOHEV data using the Kirman EtO-EOHEV endogenous-equivalent model approach.

In addition, a preliminary analysis of the NHANES HEV data for smokers as a function CpD (see previous figure), demonstrates a linear relationship. The linear slope in this figure (18 pmol/g per average CpD) would correspond exactly with the slope of 10.9 pmol/g per ppb (continuous) if the conversion factor for ppb to CpD is approximately 0.6 ppb per CpD. Using the mean estimated daily concentration from Table 7 (8.9 ± 4.3 ppb) along with the value of 17 CpD, results in an independently derived conversion factor of 0.53 ± 0.25 ppb per CpD. Together these data indicate that the linear correlation between HEV in smoker exposures to EtO is excellent agreement with the linear correlation between HEV and occupational exposures to EtO (i.e., the slope of 10.9 pmol/g per ppb).

The consistency between the “forward” and “backward” smoking-derived EtO exposures can also be used to explore the plausibility of the IRIS IUR as a reasonable predictor of cancer risks associated with low EO exposures. If the IUR is assumed as correct, a 10 ppb (10,000 ppt, as a representative midpoint from Table 7) external EO exposure contributed by smoking is predicted to produce an upper-bound estimate on the order of 1×10^{-2} to 10^{-1} risk of cancers (i.e., the 0.1 ppt 10^{-6} risk projected by IUR) is 5 orders of magnitude less than approximate 10,000 ppt smoking exposures estimated by Kirman et al (2021) and validated by direct measurement of EtO in cigarettes). Such a conclusion suggests smoking should result in a readily demonstrable cancer signal in smokers where in fact the overall epidemiological data are weak or equivocal for this endpoint at best. Thus, the smoking data and associated EtO

exposure analyses are an important and reliable “reality check” that the IRIS IUR substantially overestimates the low-exposure cancer risks of EtO.

11. OEHHA cites two studies reporting an association between smoking and lymphohematopoietic (LH) cancers published in 2012 (Diver et al. 2012 and Kroll et al. 2012) to discount Kirman et al. (2021) reality checks. These two studies are inconsistent with the lymphoid cancer (NHL, lymphocytic leukemia, multiple myeloma) findings from the NIOSH mortality study (Steenland et al., 2004), upon which IRIS 2016 developed their low exposure high risk model and do not constitute a weight-of-evidence evaluation akin to the Surgeon General report, *The Health Consequences of Smoking —50 Years of Progress* (US DHHS 2014). In addition, OEHHA cites IARC review indicating a positive association between tobacco smoking and breast cancer, though not for lymphoid cancer.

**** Pertaining to NSRL p. 19 ****

OEHHA has responded to Kirman et al.'s plausibility argument that, if EtO caused lymphoid tumors, it would be seen in smoker studies, and such an association has not been reported. The Proposed NSRL (p. 19) cites two smoker studies published in 2012 (Diver et al. and Kroll et al.) in an attempt to provide biological plausibility for the IRIS cancer risk for lymphoid cancers:

"Since the IARC review, new results from two large prospective cohort studies have found significant associations with lymphoid cancer. The American Cancer Society Cancer Prevention Study II identified 1926 non-Hodgkin lymphoma cases in a cohort of 152,958 men and women (Diver et al., 2012). The study found an association between current smoking and non-Hodgkin lymphoma in women (RR = 1.37, 95% CI = 1.04–1.81), with a positive trend for years smoked ($p < 0.01$). The UK Million Women Study identified 7047 lymphoid cancers in a cohort of 1.3 million women (Kroll et al., 2012). This study found associations between tobacco smoking and Hodgkin lymphoma (1.45 per 10 cigarettes/day, 95% CI = 1.22–1.72) and mature T-cell malignancies (1.38 per 10 cigarettes/day, 95% CI = 1.10–1.73). These large-cohort findings support the plausibility of increased cancer risks from low concentrations of EtO."

These two studies do not support this statement. More importantly, they are inconsistent with the lymphoid cancer (NHL, lymphocytic leukemia, multiple myeloma) findings from the NIOSH mortality study (Steenland et al., 2004), upon which IRIS 2016 developed their low exposure high risk model.

Diver et al. is a large cohort study of the relationship between smoking among men and women and the risk for non-Hodgkin lymphoid neoplasms (NHL), a cancer endpoint in IRIS 2016, based on the NIOSH findings for this group of cancers. Diver et al. examined smoking history in detail including status, intensity, duration, cigarettes /day. OEHHA cites Diver et al.'s statistically significant RR for currently smoking women (1.37) but fails to note the deficit in currently smoking males (0.88), the positive trend with cigarettes per day and years smoked for females,

no trends for males. This lack of positive association in smoking males occurred despite the fact that males smoked more than females. Furthermore, they fail to note these gender increases are in the opposite direction of the NIOSH gender results associated with EtO exposure, SMRs=1.29 for males and 0.73 for females and the positive slope for males and the negative slope for females in internal analyses. Given the large number of cases in this study, they were able to demonstrate gender differences statistically. Despite gender differences, they also presented data for males and females combined. A statistically significant trend for NHL was seen for women but no trend for both genders combined. The results for other subtypes of the NIOSH lymphoid category either are positive for females only (lymphocytic leukemia) or non-positive for both genders (multiple myeloma). Diver et al conclude, “In the present study, current smoking was associated with an increased risk of NHL in women but not in men.”

The Kroll et al. large cohort study was limited to females and examined the relationship between smoking and hematological cancers (both lymphoid and myeloid). OEHA cites the increased risk observed in this study for **Hodgkin** lymphoma, which is not included in the NIOSH lymphoid category, which includes **non-Hodgkin** lymphoma. So OEHA cites positive results but for a different disease. The authors do provide RRs for lymphoid cancers in their low exposure smokers (<15 cigarettes per day). No statistically significant increases were seen, and there was no evidence of steep increases at low concentrations.

Both papers summarize the existing literature related to smoking and hematologic cancers as “inconclusive” or “inconsistent”, indicating a need for their research. Based upon their findings, Diver et al., conclude, “this large cohort study supports an association with cigarette smoking and increased risk of follicular lymphoma in women”, while Kroll et al. conclude, “Cigarette smoking was associated with increased risk of Hodgkin lymphoma, consistent with previous reports.” The weight of evidence related to smoking and lymphoid tumors (as defined by NIOSH) overall and at low exposure concentrations remain inconsistent and inconclusive.

EPA has also addressed this issue by raising the bar beyond a reality check of the existing literature requiring detailed quantitative analyses with adjustment for confounding and error bounds to rule out an association, ignoring theoretically easy detection of their putative IRIS conclusion of high risk at low exposures.

“As cigarette smoke contains many carcinogens, there is not a reason to expect, that EtO exposures to smokers would contribute a large part of total cancer risks due to cigarette smoking. A quantitative statistical analysis, which has not been reported, would be needed to place bounds on the potential levels of risk from lymphoid and breast cancers in smokers to support comparisons EtO cancer risks. Results from such analyses, appropriately controlled for other risk factors, might support reasonable comparisons of lymphoid and breast cancer rates in smokers and levels of risk of these tumors that would be predicted by EtO exposures from smoking. However, such analyses, to EPA's knowledge, do not appear to have been undertaken” (EPA 2022, p. 68).

The Agency concedes smokers have elevated EtO exposures “EPA notes that as smokers do have elevated exposures to EtO, further work to define and validate EtO exposure estimates and to determine statistical bounds on risks for EtO associated cancers in the smokers could in the future contribute important information for EtO risk assessment” (EPA 2022, p. 69).

Neither OEHHA nor EPA considered the published literature showing increased risk of acute myelogenous leukemia (AML) among smokers (IARC 2012b). The average smoker is exposed to 1.8 mg/day of benzene, which is ten times that of non-smokers (ATSDR 2007). These findings are plausible and a reasonable reality check, given that benzene is a known cause of AML. Extensive quantitative analyses as described above by EPA is not needed for this purpose, nor would it be needed to question the plausibility of an EtO/lymphoid tumor relationship based on highly exposed smokers.

The citation of these two studies reporting an association between smoking and LH cancers (Diver et al. 2012; Kroll et al. 2012) does not constitute a weight-of-evidence evaluation akin to the Surgeon General report, *The Health Consequences of Smoking —50 Years of Progress* (US DHHS 2014). More importantly, it does not address the point that an extraordinarily large potency estimate derived by USEPA for EtO is inconsistent with isolated or weak associations. HEV levels in smokers (236 pmol/g Hb; per NHANES) are equivalent to daily exposures to 780 ug/day, which is more than 4 orders of magnitude higher than the NSRL value, which would place predicted cancer risks above 1×10^{-1} . Because smoking prevalence and intensity was much higher in the past, HEV burdens (and predicted risks from EtO exposures) would also be much higher than measured by NHANES. If the unit risk for EtO were truly predictive of its potency, the reported associations between smoking and lymphoid cancers would be larger and more consistently reported across epidemiological studies of smokers.

12. OEHHA's Proposed NSRL is an estimated EtO 10^{-5} risk-specific intake level. This intake level provides little utility in managing general population risk if background exogenous exposure isn't considered as an initial reality check. There has been an extensive ambient air measurement campaign over the last several years, including measurements near many sterilizer facilities and at background locations. In many cases, the levels of ethylene oxide far away from sterilizer facilities are similar to the levels near sterilizer facilities. Although the source makeup of this exogenous background ethylene oxide is currently not fully characterized, what is clear is that, in many cases, residents living near sterilizer facilities are not exposed to higher ethylene oxide than people living far away.

**** Pertaining NSRL p. 49, 51 ****

OEHHA's RSCs provide little utility in managing EtO risk

- OEHHA's proposed NSRL is based on the cancer unit risk of 3.3×10^{-3} per microgram per cubic meter ($\mu\text{g}/\text{m}^3$)⁻¹ from the EPA IRIS (2016a) assessment. Thus, based on the updated UR, an equivalent risk-specific concentration (RSC) for 10^{-5} cancer risk is 0.003 $\mu\text{g}/\text{m}^3$ or 0.002 ppb. This RSC is so low relative to background that it provides little utility in managing EtO risk.

EtO is quite unique among the managed hazardous substances

- Everyone in the U.S. is exposed to EtO regardless of where they live or work. Ethylene, the primary precursor of EtO, is released from natural and unregulated anthropogenic sources, abundant in ambient air, also produced metabolically and contributes substantially to background EtO exposure. EtO also is emitted from natural and likely unregulated anthropogenic sources and measurable in ambient air. The measurement of hemoglobin adduct 2-hydroxyethylvaline (HEV) has provided a biomarker of total background exposure to EtO, (exogenous EtO, exogenous ethylene and endogenous EtO). Background HEV levels have been measured in U.S. smokers and nonsmokers (CDC NHANES, 2019). The primary source of EtO background exposure in nonsmokers has been estimated to be endogenous production (reviewed by Kirman et al. 2021). These factors make EtO unique among most hazardous substances and indicate risk management challenges unless background exposure is considered.
- Ethylene is emitted to air from natural sources including plants where it functions as a hormone, microbial activity in soils, sediment and plant litter, as well as plants in aquatic systems (reviewed by Sawada and Totsuka, 1986; Morgott 2015; Health Canada 2016). A vast majority of ethylene emissions are from natural sources (Health Canada, 2016). Ethylene also is emitted from anthropogenic sources such as biomass burning, including

forest fires, and from exhaust emissions from gasoline and diesel vehicles (Swada and Totsuka, 1986; Margott, 2015; Health Canada, 2016). Early reviews also suggested EtO is emitted from vehicle exhaust (EPA 1985) although there is little current published supporting data. As both ethylene and EtO are constituents of tobacco smoke, combustion of tobacco (see Kirman et al., 2021), it seems reasonable to hypothesize that both ethylene and EtO may be emitted by biomass combustion and combustion exhaust from vehicles. As early as the 1970's, ethylene from natural and unregulated sources was being measured at relatively high levels in urban air (39-700 ppb; Ables and Heggstad, 1973). More recently, EtO has also been measured in ambient air at multiple locations across the U.S. away from known industrial sources to characterize this background exogenous source (median levels 0.03-0.33 ppb; ATSDR 2022; Sheehan et al. 2021; Lewis et al., 2022; Georgia EPD 2022).

- Because EtO is unique with ethylene as a precursor and its primary metabolic contribution to background exposure as well as EtO natural sources and likely unregulated anthropogenic source contributions to exposure, it is unlike nearly all other regulated hazardous substances and as such, presents unprecedented risk management and risk communication challenges. Considering that EtO management in California will be driven by the OEHHA risk assessment with its identified limitations, a reality check of OEHHA's proposed NSRL considering general population background exposure is warranted to better inform risk management of industrial emissions.

Based on the limitations of its risk assessment, OEHHA should consider including discussion of EtO general population background exposure to provide context for risk management and risk communication

OEHHA makes the following statements regarding background exposure,

“Measurements of specific hemoglobin adduct levels, such as N-2-hydroxyethylvaline (HEV), in humans or other species, reflect the integrated exposure to ethylene (endogenous + exogenous) and EtO (endogenous + exogenous). Kirman et al. (2021) showed background exposures to EtO and ethylene in ambient air alone are insufficient to account for HEV levels seen in non-smokers, and endogenous EtO production contributes more to non-smoker HEV levels than ambient EtO and ethylene exposures do. The EtO exposures from ambient and endogenous sources contribute to HEV levels, other adduct levels, and cumulative cancer risks (i.e., including from other chemicals and conditions). Thus, EtO and ethylene exposures are part of the risk factors accounting for the background cancer risk in the general population, including lymphoid and breast cancers (US EPA, 2016a; 2016b).”

EtO background exposure contributes more to understanding risk than just accounting for background cancer risk; it provides a reality check on managing EtO general population risk when there are unaddressed questions about the representativeness of risk model. It is likely reasonable to assume that ambient exogenous and endogenous exposures have remained relatively constant over time, and therefore these exposures do not impact the conversions between relative risk and extra risk measures in the dose-response assessment. However, this assumption is not valid for exposures to EtO from smoking, which has changed significantly over time (Kirman et al., 2021) and can vary between worker sub-populations (e.g., salaried vs. hourly workers; Hsu et al., 2019). As such, smoking is a potential confounder for EtO exposures (vs. a confounder to observed cancer response) in the NIOSH cohort. In addition, there is a clear need to include discussion of background exposures for the purposes of risk management and risk communication of total EtO exposures and potential risks. Based on the limitations in the OEHA EtO risk assessment described above and the unique characteristics of EtO background exposure, a risk management check based on general population background exposure is warranted as a reality check of the utility of OEHA's assessment RSCs in managing general population EtO risk.

The draft OEHA proposed NSRL provides little utility in managing general population risk if background exogenous exposure isn't considered as an initial reality check

The proposed OEHA NSRL of 0.058 µg/day is equivalent to an inhalation 10^{-5} RSC of 0.003 µg/day or 0.002 ppb. For comparison purposes, the RSC inhalation exposure units are used. The RSC is a small fraction of substantially higher ambient background concentrations from natural and unregulated anthropogenic EtO sources otherwise associated with industrial emissions. The EtO technical support document reported ambient background EtO concentrations for the Los Angeles area ranging from 0.02-0.17 ppb. Based on data from the EPA national air toxics trends and urban air toxics monitoring programs for the October 2018 to September 2019 period, ATSDR estimated a national mean background EtO concentration of 0.13 ppb (ATSDR 2022).

Similarly, the same monitoring data for years 2018-2021 showed median (50th percentile) background EtO concentrations ranged from 0.03-0.33 ppb nationally (summarized in Lewis et al. 2022). Local/regional location background EtO concentration for eight sterilization facilities evaluated over an extended period again showed median and 90th percentile background concentrations ranging from 0.07 and 0.26 to 0.13 and 0.56 ppb, respectively (Sheehan et al. 2021). These data show that background concentrations are variable but more importantly, that everyone nationally (including Californians) is exposed exogenously to mean/median background concentrations of EtO substantially greater (~50-fold) than the proposed EtO RSC of 0.002 ppb.

Although it has been suggested that true background concentration based on a refined sampling method (TO 15A) may be lower than measurements based on EPA Method (TO 15), calculations from recent Georgia EPD background samples by both methods show refined background levels are still substantially greater than the OEHHA RSC.

An unwillingness of regulators to consider background exogenous exposure concentrations relative to RSCs as an initial reality check, particularly if concentrations at near facility locations are indistinguishable from concentrations at background locations, will face a serious risk management and communication problems (i.e., everyone in California is exposed to background EtO in ambient air from non-industrial background sources well above the RSC). As background EtO source emissions are not affected by managing industrial EtO emissions, managing risk under the proposed OEHHA risk assessment is untenable without considering ambient background levels.

The OEHHA updated EtO NSRL provides little utility in assessing general population risk unless total background exposure from combined exogenous and endogenous contributions are considered as an ultimate reality check

At some monitoring locations, there may be EtO concentrations significantly greater than background concentrations, or modeling may predict risk above the RSCs. The total exposure concentration compared to total equivalent background exposure concentration distributions for nonsmokers provides a final reality check of the utility of the OEHHA RSC and related NSRL estimates. There are published examples of where total equivalent concentration comparisons have been useful in informing whether further risk mitigation beyond recent emission controls was warranted.

For example, Sheehan et al. (2021) compared 50th and 90th percentile ambient exogenous concentrations from monitoring around eight facilities plus 50th percentile endogenous equivalent concentration (total exposure concentrations) with 50th and 95th percentile total equivalent background concentrations for nonsmokers in the U.S. population and concluded that facility concentrations are contributing negligibly to near residential population total exposure. Similarly, Lewis et al. (2022) compared 5-year average EtO modeled concentrations at near facility residences in Georgia plus background and endogenous concentrations (total exposure) with the 50th 60th and 95th total equivalent concentrations for the nonsmoking U.S. population and again concluded that facility contributions to residential exposure are negligible (see Figure 4 below from Lewis et al. 2022). These total exposure comparisons provide an additional reality check on the health significance of the facility emission contributions to near facility residential EtO exposure.

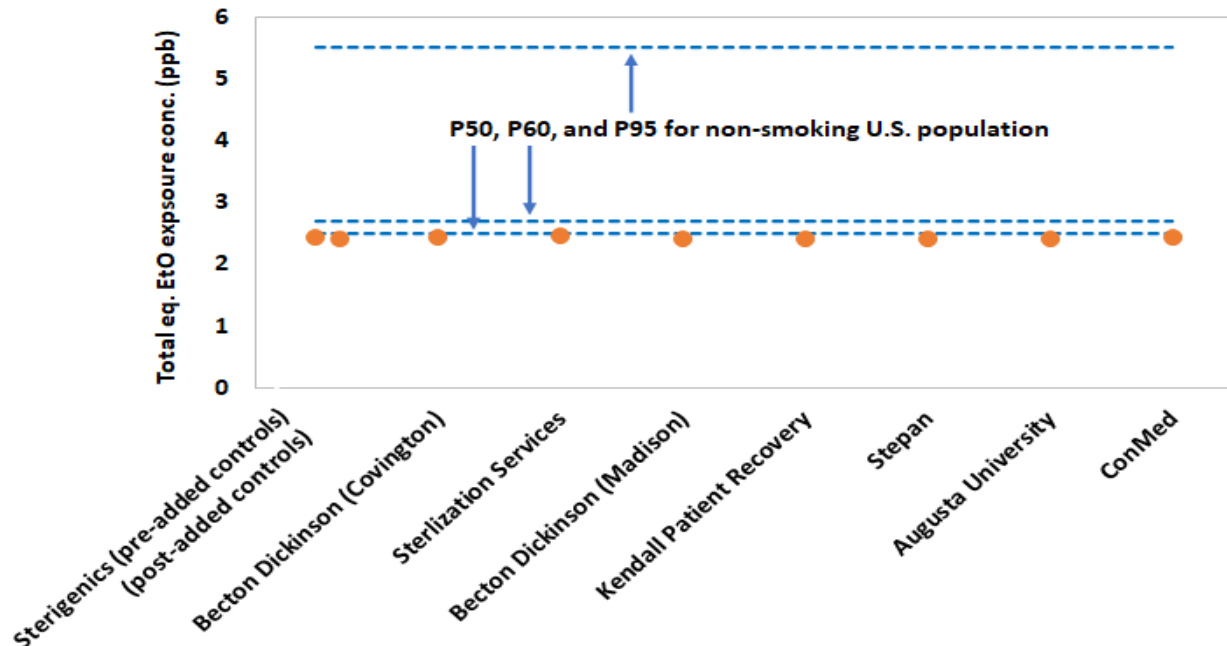


Figure 11. Estimated total equivalent exposure for the highest 5-year average modeled EtO concentration for all residential receptors by facility ((50th percentile endogenous equivalent for the non-smoking U.S. population, or 2.3 ppb) + (50th percentile background EtO concentration for Georgia, or 0.12 ppb) + (highest 5-year average modeled EtO concentration for all residential receptors by facility)) relative to that of the 50th, 60th, and 95th percentiles of the non-smoking U.S. population (2.5, 2.7, and 5.5 ppb, respectively).

We suggest that for populations in California living close to emitting facilities, OEHHA consider total equivalent exposure concentrations or the TCEQ RSCs as a final check in managing risk as the proposed OEHHA RSCs have no practical risk management utility.

We urge OEHHA to consider these comments and adopt an alternative such as the TCEQ risk value to derive the NSRL. Thank you.

Sincerely,

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