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U.S. Environmental Protection Agency
EPA Docket Center
Docket ID No. EPA-HQ-OAR-2019-0178
Mail Code 28221T
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

Re: Docket No. EPA-HQ-OAR-2019-0178 National Emission Standards for Hazardous Air Pollutants: Ethylene Oxide Commercial Sterilization and Fumigation Operations

Dear Sir/Madam:

The Advanced Medical Technology Association (AdvaMed) provides these comments in response to a request in an advance notice of proposed rulemaking (ANPRM) (Federal Register Volume 84, Number 239 (Thursday, December 12, 2019), in which the U.S. Environmental Protection Agency (EPA) solicited information that will aid in potential future revisions to the Ethylene Oxide Emission Standards for Sterilization Facilities.

AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. Our members range from the largest to the smallest medical technology innovators and companies.

For many medical devices, due to their material composition, size, shape or complexity, ethylene oxide (EtO) is the only effective method for sterilization currently recognized by FDA. The compatibility and effectiveness of EtO with the plastics and polymers commonly used in medical products allow for the sterilization of many medical devices that would otherwise be rendered ineffective or unsafe if sterilized by radiation, moist heat, dry heat, or other alternative methods. Viable sterilization methods not only need to ensure the safety of devices but also provide the ongoing capacity and scale required to process the billions of medical devices required by today's modern health care systems in delivering care to patients including the volume of devices needed for millions of surgical procedures each year. Heart valves, pacemakers, implantable cardioverter/defibrillators, drug-eluting stents, feeding tubes and breathing tubes, surgical drapes and kits, and syringes are just a few of the many products critical to modern patient care that can only be sterilized using EtO.

For decades, AdvaMed members have invested hundreds of millions of dollars to ensure workplace safety and environmental protection. There has been a continual advancement in the deployment of pollution control technologies to improve emission controls,

allowing for the continued use of EtO within stringent federal, state, and local regulations. The effectiveness of our emission control technology is not only based on scientific design principles but is also validated through actual testing. Our members have continued to lower employee exposures in accordance with OSHA regulations and have significantly reduced emissions. Our members have also invested in talent with subject matter expertise in multiple disciplines related to sterilization operations (process safety management, environmental engineering, industrial hygiene and sterility assurance), to ensure the right capabilities to safely use EtO.

It should also be noted that AdvaMed member companies are committed to actively exploring methods and processes that reduce the amount of EtO used for a sterilization cycle, thus further reducing EtO emissions from the process. AdvaMed continues to work collaboratively with FDA, EPA, and other governmental agencies to further innovate current sterilization practices and cycle designs to optimize our use of EtO and reduce emissions.

Further, AdvaMed members are committed to investigating alternative sterilization methods that will provide the same sterility assurance and result in the same device performance as EtO, at the scale required by today's modern healthcare systems. But it must be recognized that this is a long-term process. At a November 2019 meeting of FDA's General Hospital and Personal Use Panel of the Medical Devices Advisory Committee, experts noted that development of an effective alternative to EtO would likely take more than a decade. Until there is a safe and effective replacement for EtO, we will continue to pursue our goal to reduce the amount of EtO used and minimize emissions from the process. Optimizing EtO sterilization cycles, innovating new medical device packaging configurations, and evaluating new approaches to validation are examples of possible ways to minimize the amount of EtO sterilant necessary to sterilize devices.

In the meantime, the continued safe use of EtO is vital to ensure that patients and physicians continue to have access to critical medical devices. Therefore, it is crucial that any regulation which could cause a significant adverse impact on the continued supply of EtO, or the ability to use EtO for sterilization at the scale required, be based on the most rigorous scientific methods and evidence.

In the ANPRM, EPA has requested comment on the use of an emissions factor of 0.5% of EtO usage for the calculation of fugitive emissions from the EtO sterilization source category (Comment C-2a). In the Notice, EPA recognizes that the magnitude of fugitive emissions across all commercial sterilization facilities would be very difficult to characterize due to a number of factors, including differences among building and sterilization equipment designs, air handling systems, and the capacity of air pollution control systems. Nevertheless, the EPA has requested comment on the feasibility of using an emissions factor of 0.5% of EtO usage based on data obtained near a single commercial sterilization facility.

AdvaMed believes that the use of a uniform emissions factor to calculate fugitive emissions across the entire commercial EtO sterilization source category is not appropriate and should not be adopted by the EPA. Further, if EPA were to adopt such an emissions factor, it should not do so based on analysis conducted at one location.

AdvaMed believes that the likelihood of fugitive emissions and quantification varies significantly facility-to-facility among the commercial EtO sterilization source category. Applying a uniform percentage calculation for fugitive emissions would be problematic due to a multitude of variables that will differ facility-to-facility, including:

- Facility size;
- Sterilization chamber and/or aeration room size;
- Cycle design;
- Duration of aeration;
- Building ventilation and air pollution control device ("APCD") equipment;
- Types of medical devices undergoing sterilization;
- Sterilization load configuration;
- Materials of construction for medical devices undergoing sterilization;
- Materials used and instructions for product packaging; and
- Sterilization cycle parameters such as quantity of EtO used for sterilization, number of purges, and number of inert washes.

Further, fugitive emissions data would vary seasonally and would be impacted by whether fugitives occur post-building ventilation and air pollution controls. Accordingly, AdvaMed believes that calculating a uniform emissions factor for fugitive emissions is not practicable and should not be adopted by EPA.

EPA has also requested comments on the availability of data that can be used to help quantify facility-wide and area/room-specific fugitive emissions from commercial EtO sterilization facilities (Comment C-2b). For large sterilization chambers, continuous monitoring occurs in sterilization chambers and aeration rooms, continuous monitoring can be utilized in the rooms where the sterilization chamber is located or where aeration occurs. Smaller sterilization chambers are self-contained and EtO monitoring is not conducted continuously. Periodic monitoring of ambient air where EtO sterilized products are stored is conducted based on Occupational Safety and Health Administration ("OSHA") Occupational Exposure Limit ("OEL") monitoring.[1]

AdvaMed would also like to provide additional comments on the EPA's updated Integrated Risk Information System (IRIS) value for ethylene oxide. For the scientific and policy reasons indicated below, AdvaMed believes the 2016 IRIS value should NOT be used for regulatory purposes. Rather EPA should use an updated cancer risk value based on current science and common-sense considerations of ambient and endogenously formed ethylene oxide concentrations.

[1] 29 C.F.R. § 1910.1047.

1. **The 2016 IRIS assessment of EtO should NOT be used for regulatory purposes because it is inconsistent with a variety of recommendations made by the National Academy of Sciences and by EPA's own risk assessment guidance.**

The National Academy of Sciences (NAS) has encouraged EPA to move away from its old paradigm of selecting a single "best" model and "best" toxicity value, and instead to develop approaches for integrating multiple studies and toxicity values.[2] The NAS also "strongly suggests that EPA consider approaches to integration of as much of the evidence as possible rather than selecting a limited segment of the evidence in deriving an organ-specific, system-specific, or an overall toxicity value."[3] In other words, the NAS has repeatedly admonished IRIS to avoid biases toward inclusion of certain outcomes, such as only positive outcomes, as was done for ethylene oxide. The goal should be to interpret possible reasons for disagreement among studies, not to select the "best" ethylene oxide study and rely on it even if it is contradicted by other study results. Omitting studies that do not show a dose-response relationship in the direction IRIS favors discounts valuable information, particularly information that could inform mode of action as well as dose-response.

Despite the NAS' admonishment to do otherwise, the IRIS assessment of ethylene oxide relies on a single epidemiologic study as the basis for its cancer potency estimate, although a much larger body of data is available. Failing to use the larger body of epidemiologic data available for risk quantification of ethylene oxide is inconsistent with using the weight of scientific evidence, contradicting the direction to do so provided repeatedly by various NAS committees and by EPA's own risk assessment guidance documents. For example, EPA's Information Quality Guidelines state that when EPA develops "influential" scientific risk assessments, it intends to use all relevant information and reach a position based on careful consideration of all such information, a process typically referred to as the "weight-of-evidence" approach.[4] EPA's Risk Assessment Principles & Practices documentation asserts that risk assessment involves using the weight of evidence provided by all available scientific data.[5]

Other inconsistencies with EPA's own guidance are IRIS' underestimation of exposure and inappropriate choice of dose-response relationship (the supralinear dose-response model). Those choices lead to a substantial over-estimation of ethylene oxide risk. EPA's Guidelines for

[2] National Research Council/National Academy of Sciences (NAS). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011)

[3] National Research Council/National Academy of Sciences (NAS). Review of the Environmental Protection Agency's Integrated Risk Information System (IRIS) Process (2014)

[4] USEPA (2002) Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency. Office of Environmental Information. EPA/260R-02-008,

[5] USEPA (2004) Risk Assessment Principles and Practices. Office of the Science Advisor. EPA/100/B-04/001

Carcinogen Risk Assessment specifically warn against using a supralinear dose-response model because "a steep slope [i.e., supralinear] also indicates that errors in an exposure assessment can lead to large errors in estimating risk."[6]

2. The 2016 IRIS assessment of EtO should NOT be used for regulatory purposes because it defies science and common sense in the context of everyday human exposures, both endogenous and exogenous.

EtO is made normally in the human body as a natural product of metabolism. It is also generated endogenously from ethylene, another normal body constituent.[7] Sources of ethylene and ethylene oxide include metabolism by gut microflora, lipid peroxidation, and oxidation of hemoglobin and methionine.[8] Using hemoglobin adduct concentrations measured in non-workplace-exposed populations compared with exposed workers, a mean endogenous concentration of 1.9 ppb (range, 0.13–6.9 ppb) has been calculated.[9] Thus IRIS' revised cancer potency estimate results in a one-in-a-million lifetime excess cancer risk estimate for exogenous exposure that is approximately 20,000 times lower than mean endogenous exposure. **The incremental exposure to ethylene oxide that would occur at IRIS' 10^{-6} concentration (or 10^{-5}, 10^{-4}, or 10^{-3} concentrations) would be both negligible and undetectable against the background of endogenously formed ethylene oxide.**

As a product of combustion and various natural processes, EtO is also a normal component of ambient air. Recent air monitoring studies conducted by the EPA as part of its National Air Toxics program found a national average ethylene oxide concentration of 0.3 μg/m^3 (0.15 ppb).[10] The State of Georgia's Environmental Protection Division has reported average ethylene oxide concentrations in Georgia ranging from 0.2 μg/m^3 (0.1 ppb) in more rural areas to 0.4 μg/m^3 (0.2

[6] USEPA (2005) Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. EPA/630/P-03/001F

[7] Filser et al., *Pharmacokinetics of ethylene in man; body burden with ethylene oxide and hydroxyethylation of hemoglobin due to endogenous and environmental ethylene* (1992) Arch Toxicol 66:157; Törnqvist et al., *Ethylene oxide doses in ethene-exposed fruit store workers* (1989) Scand J Work Environ Health 15:436

[8] Clemens et al., *Volatile hydrocarbons from hydrogen peroxide-induced lipid peroxidation of erythrocytes and their cell components* (1983) Biochem Pharmacol 32:3877; Lieberman et al., *Genesis and Biogenesis of Ethylene* (1964) Nature 204:343; Törnqvist et al., *Ethylene oxide doses in ethene-exposed fruit store workers* (1989) Scand J Work Environ Health 15:436; Sagai et al., *Age-related changes in lipid peroxidation as measured by ethane, ethylene, butane and pentane in respired gases of rats* (1980) Life Sci 27:731

[9] Kirman & Hays, *Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide* (2017) Regul Toxicol Pharmacol 91:165

[10] *Ethylene Oxide Ambient Concentrations at National Air Toxics Trends Stations and Urban Air Toxics Monitoring Program stations October 1, 2018 – March 31, 2019.* https://www.epa.gov/sites/production/files/2019-11/documents/data_summary_stations.pdf

ppb) in suburban areas.[11] IRIS' revised cancer unit risk estimate results in a one-in-a-million lifetime excess cancer risk estimate for ambient exposure that is thousands of times lower than mean ambient exposure concentrations. **The incremental exposure to ethylene oxide that would occur at IRIS' 10^{-6} concentration (or 10^{-5}, 10^{-4}, or 10^{-3} concentrations) would be both negligible and undetectable against the background of ambient ethylene oxide concentrations.**

IRIS' cancer potency estimate was derived based on epidemiologic data from workers exposed to ethylene oxide occupationally. Much of that exposure occurred before occupational safety limits were in place. Workers were exposed to extraordinarily high concentrations of ethylene oxide at parts-per-million levels, with concentrations averaging approximately one to two million times higher than ambient concentrations and daily job exposures ranging from about 15,000 to 32,000,000 times higher than ambient concentrations. No increase in cancer incidence was seen except among those exposed to the very highest concentrations for the very longest periods of time in one study.[12] In other words, thousands of workers were exposed daily for decades to ethylene oxide concentrations millions of times higher than normal, non-occupational exposure levels and did not experience increased risks of cancer; only those exposed to the most extreme levels for the longest periods of time saw an increased risk (in one study). Again, deriving a cancer potency estimate that predicts a 10^{-6} excess lifetime cancer risk at exposures tens of millions of times lower than the occupational exposures upon which it was based defies biological plausibility. Worldwide, current occupational exposures to ethylene oxide are limited to levels that are 6 million to 50 million times higher than the IRIS 10^{-6} concentration.[13]

3. **For regulatory purposes, EPA should use a recalculated ethylene oxide potency estimate that fully considers the weight of the scientific evidence to identify an exposure level that increases the concentration of ethylene oxide already present in the human body as a result of endogenous production, and that therefore might plausibly be associated with an increase in cancer risk.**

Regulating exogenous exposure to substances that have substantial endogenous production requires special consideration. Humans have evolved generating many chemicals endogenously, so clearly have adapted to those exposures with conserved protection mechanisms. Against the background of endogenous exposures, low-dose exogenous exposures might make such a small contribution that they are trivial, lost in the signal-to-noise ratio and not biologically meaningful.

[11] https://epd.georgia.gov/ethylene-oxide-information

[12] Based on 20 peer-reviewed studies cited by Steenland K, Stayner L, Deddens J (2004) *Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998*. Occup Environ Med 61:2–7

[13] https://www.regulations.gov/document?D=EPA-HQ-OAR-2018-0417-0127

Risk management of such substances should use a pragmatic, data-driven approach to identifying exogenous exposures that significantly increase steady-state levels of biomarkers of exposure reflecting endogenous formation, like DNA adducts, hemoglobin adducts, or mutation frequency. A parallel situation might be drawn from risk management of substances that occur at high background levels in soil, like arsenic and manganese. In the case of arsenic, a carcinogen, risk-based cleanup levels can be orders of magnitude lower than background soil levels. Some states have approached this problem by assuming that small increases in arsenic compared to its background level in soil would likely not increase risk to an extent that justifies cleanup.

4. **The 2016 IRIS assessment of EtO toxicity should NOT be used for regulatory purposes because of the unacceptable public health risk-risk tradeoffs involved.**

As part of its decision whether to use the IRIS number for regulation, EPA should first consider the risk-risk tradeoffs between adopting a more stringent air toxics standard on the one hand and triggering detrimental public health consequences on the other. As explained in the introduction, ethylene oxide plays a critical role in the sterilization of medical equipment, including medical instruments and devices that cannot be sterilized using alternative methods. Because ethylene oxide is frequently the only method of ensuring the sterility of such equipment, imposing use restrictions in response to the 2016 IRIS assessment could have devastating effects on public health.

The Clean Air Act explicitly provides that EPA may consider risk-risk tradeoffs before promulgating emission standards [CAA 112(f)(2)]. The public health consequences of eliminating a vital method of medical sterilization certainly qualify as "safety, and other relevant factors" that EPA may consider under that section. EPA has made it clear that "other relevant factors" is a broad, circumstance-specific category.[14] Curtailing one very small hypothetical or theoretical air toxics risk might subject the public to a much larger risk.[15]

5. **EPA should request that the National Academy of Sciences review the 2016 IRIS ethylene oxide assessment.**

EPA should request a National Academy of Sciences (NAS) review of the 2016 ethylene oxide assessment because:

- The arguments supporting the alleged scientific basis of the outcome are inconsistent with the many recommendations that NAS has made to IRIS over the years.

[14] *See* National Emission Standards for Hazardous Air Pollutants; Benzene Emissions From Maleic Anhydride Plants, Ethylbenzene/Styrene Plants, Benzene Storage Vessels, Benzene Equipment Leaks, and Coke By-Product Recovery Plants, 54 Fed.Reg. 38,044, 38,045 (Sept. 14, 1989) (the "Benzene rulemaking")

[15] *See generally* Graham JD & Wiener JB, eds. Risk vs. Risk: Tradeoffs in Protecting Health and the Environment (1997)

- The outcome has needlessly provoked fear and anger among people who believe their health is in imminent danger from ethylene oxide.
- There is no effective substitute for use in sterilizing many medical instruments and medical devices, so needlessly limiting its use would create a public health threat due to their subsequent unavailability.
- Serious yet needless economic damages will continue to result from plant closings, product shortages, and job loss.

An NAS committee would:

- Review the approach IRIS used to characterize the alleged dangers of ethylene oxide and make recommendations for improvements.
- Use the best science and independent scientific experts to draw evidence-based conclusions about the nature and extent of ethylene oxide's potential risks to human health.
- Evaluate potential public health risk-risk tradeoffs.
- Provide the objective scientific peer review necessary to establish consistency with Executive Order 12866 and other peer review standards.

The NAS is in a unique position to perform this review because it is the nation's pre-eminent source of high-quality, objective advice on science. Each year thousands of the world's foremost scientists volunteer their time to address some of society's toughest challenges by serving on the hundreds of study committees that are convened to answer specific sets of questions. The Academy's peer-reviewed reports present the evidence-based consensus of these committees of experts. In particular, the specific mission of the Board on Environmental Studies and Toxicology is "[t]o provide our nation with independent, objective advice and dialog on matters related to the impacts of human activities and environmental exposures on environmental quality and human health."[16] Thus, the NAS is in the best position to convene the most qualified experts in the world to review the ethylene oxide assessment and provide authoritative, independent findings and recommendations.

While a draft of ethylene oxide's IRIS assessment was reviewed by EPA's Science Advisory Board (SAB), the final draft was never reviewed subsequently and deviated from the SAB's recommendations and guidance. Furthermore, SAB review is not equivalent to review by the NAS. Unlike NAS review, the SAB review process is neither independent nor free from financial conflict. EPA staff oversees the formation and conduct of advisory panels by selecting reviewers, formulating charge questions, and providing staff support for the review process. In contrast, the NAS process for selecting scientific panel members and conducting reviews assures independence

[16] *About BEST*, National Academy of Sciences Board on Environmental Studies & Toxicology (2018), http://dels.nas.edu/global/best/About-Us

and objectivity. The substantial differences historically between many, but not all, IRIS assessments and NAS reviews of IRIS assessments clearly illustrate the continuing need for NAS review.

AdvaMed appreciates the EPA notice of proposed rulemaking to solicit information to inform the EPA as you consider future rulemaking to further address emissions of EtO from commercial sterilizers. AdvaMed welcomes the opportunity to provide the requested information.

AdvaMed looks forward to working with EPA to continue the safe use of EtO for the essential use as a sterilant for certain medical devices. Please contact me (Ruey Dempsey rdempsey@advamed.org) with questions related to this submission.

Sincerely,

/s/

Ruey C. Dempsey
Vice President
Technology and Regulatory Affairs