

February 18, 2020

U.S. Environmental Protection Agency
EPA Docket Center
Docket ID No. EPA-HQ-OAR-2018-0746
Mail Code 28221T
1200 Pennsylvania Avenue, NW
Washington, DC 20460

*Re: Docket No. EPA-HQ-OAR-2018-0746 National Emission Standards for
Hazardous Air Pollutants: Miscellaneous Organic Chemical Manufacturing
Residual Risk and Technology Review*

Dear Sir/Madam:

The Advanced Medical Technology Association (AdvaMed) provides these comments in response to a request in Federal Register Volume 84, Number 242 (Tuesday, December 17, 2019), in which the U.S. Environmental Protection Agency (EPA) published the proposed rulemaking concerning the residual risk and technology review (RTR) for the National Emission Standards for Hazardous Air Pollutants (NESHAP) for the Miscellaneous Organic Chemical Manufacturing source category.

The Advanced Medical Technology Association (AdvaMed) is the world's largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed has more than 400 member companies, ranging from the largest to the smallest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement, and access to international markets.

Although AdvaMed member companies are not regulated by the NESHAP for the Miscellaneous Organic Chemical Manufacturing entities, AdvaMed provides these comments demonstrating that, 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. The 2016 IRIS assessment of ethylene oxide (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.¹ 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.”² 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.³ EPA's Risk Assessment Principles & Practices documentation asserts that risk assessment involves using the weight of evidence provided by all available scientific data.⁴

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

¹ National Research Council/National Academy of Sciences (NAS). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011)

² National Research Council/National Academy of Sciences (NAS). Review of the Environmental Protection Agency's Integrated Risk Information System (IRIS) Process (2014)

³ 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

⁴ 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.”⁵

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.⁶ Sources of ethylene and ethylene oxide include metabolism by gut microflora, lipid peroxidation, and oxidation of hemoglobin and methionine.⁷ 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.⁸ 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/m³ (0.15 ppb).⁹ The State of Georgia’s Environmental Protection Division has reported average ethylene oxide concentrations in Georgia ranging from 0.2 µg/m³ (0.1 ppb) in more rural areas to 0.4 µg/m³ (0.2

⁵ USEPA (2005) Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. EPA/630/P-03/001F

⁶ 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

⁷ 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

⁸ 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

⁹ *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.¹⁰ 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.¹¹ 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.¹²

- 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.

¹⁰ <https://epd.georgia.gov/ethylene-oxide-information>

¹¹ 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

¹² <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.¹³ Curtailing one very small hypothetical or theoretical air toxics risk might subject the public to a much larger risk.¹⁴

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:

¹³ 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”)

¹⁴ See generally Graham JD & Wiener JB, eds. Risk vs. Risk: Tradeoffs in Protecting Health and the Environment (1997)

- 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.
- 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."¹⁵ 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,

¹⁵ *About BEST*, National Academy of Sciences Board on Environmental Studies & Toxicology (2018), <http://dels.nas.edu/global/best/About-Us>

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 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.

In addition to our position on the use of IRIS, AdvaMed is expressing views on one other provision of the NESHAP.

Equipment Leaks (FR Page 69215 (right column) also page 69251)

EPA has requested comment on two options for controlling risks from equipment leaks. Option 1 and 2 are provided on Table 6 on page 69216. Option 1 is the traditional NESHAP method of a nation-wide requirement. Option 2 allows for the same nation-wide requirements, but also specifically calls out enhanced requirements for two facilities based on the surrounding cancer risk ≥ 100 -in-1 million. AdvaMed members support Option 1, maintaining a nation-wide requirement for leak detection and repair.

By using Option 2, EPA proposes to use the IRIS risk value to drive varying degrees of fugitive emissions controls based on the surrounding risk for a facility (defined by the National Air Toxics Assessment (NATA)), rather than nation-wide fugitive emissions control practices. For the reasons outlined above, the scientific validity of the IRIS risk value is highly questionable and any reliance on that method to implement stricter leak detection and repair programs under Option 2 would be inappropriate.

AdvaMed appreciates the opportunity to provide this information and 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