



The Ethylene Oxide Sterilization Association, Inc.

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November 11, 2014

Via E-Mail

Mr. Aaron Yeow
Designated Federal Officer (DFO)
Science Advisory Board Staff Office
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460-4164

Re: Ethylene Oxide Sterilization Association, Inc. Comments to the Chemical Assessment Advisory Committee for the Integrated Risk Information System Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft -- August 2014)

Dear Mr. Yeow:

The Ethylene Oxide Sterilization Association, Inc. (EOSA) appreciates the opportunity to submit these comments to the Science Advisory Board (SAB) Chemical Assessment Advisory Committee (CAAC) for consideration in responding to the draft charge questions for the revised draft Integrated Risk Information System (IRIS) assessment for ethylene oxide (EO). EOSA is a non-profit organization whose members include medical device manufacturers, sterilization consultants, laboratories, contract sterilizers, raw materials suppliers, and equipment manufacturers with a common interest in promoting the safe use of EO.

As users of EO, the accuracy and completeness of the scientific basis for the draft IRIS assessment is extremely important to EOSA members. EOSA has significant concerns regarding the U.S. Environmental Protection Agency's (EPA) cancer risk estimates for EO and the revised draft IRIS assessment as a whole. In addition to our specific comments provided below, we fully support all comments submitted by the American Chemistry Council's (ACC) EO Panel. We believe that the current assessment results in the risk of EO being inappropriately magnified by more than 1,500-fold. The risk estimates are significantly stricter than natural background levels of EO in the atmosphere and endogenous levels in humans. Based on the draft inhalation unit risk values, EO would be identified as one of the most potent chemicals within the IRIS database. This exaggerated risk will not only severely and adversely impact the EO sterilization industry, but it will also result in significant adverse public health impacts. The CAAC must consider the benefits of EO sterilization in contrast to the adverse impacts on public health that would result from the lowered risk estimates and exposure levels presented in the draft IRIS assessment.

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Benefits and Use of EO Sterilization

Since its discovery as an effective sterilant, EO has played a critical role in antimicrobial sterilization to protect public health and is essential to a functioning U.S. healthcare system. Decades later, it is now used to sterilize more than 20 billion medical devices each year in the U.S. alone. This represents more than 50 percent of all medical devices that are sterilized. The use of EO sterilization provides unparalleled benefits to society by its use throughout the medical community. Numerous medical, hospital, and laboratory processes rely on EO to sterilize devices and equipment to protect millions of patients from the real risks of infectious diseases caused by bacteria, viruses, and fungi. Hepatitis, Severe Acute Respiratory Syndrome (SARS), and Tuberculosis are just some of the many notable diseases that are effectively controlled by the use of EO for sterilization purposes. EO sterilization is critical in the safe delivery of sterile devices and medical care.

The relatively low temperatures at which the EO sterilization occurs give great flexibility to the devices and products that it can sterilize. Many critical healthcare products are complex and sophisticated devices or equipment. For the majority of these healthcare products, EO sterilization is not just the most effective and efficient sterilization technology; it is the only acceptable method. The gentle nature of EO sterilization allows for the sterilization of healthcare products and devices that would otherwise be destroyed and rendered unusable by radiation, moist heat, dry heat, harsh chemicals, and/or other properties of alternative sterilization methods.

The EO sterilization industry continues to pay particular attention to worker and environmental safety. Workplace safety and efficacy continue to improve as EO sterilization equipment and processes have advanced with the introduction of technology. Sterilization processes are designed to minimize potential exposure of workers and work practices are modified to ensure workplace safety. Environmental exposures have also been significantly reduced through the development of more efficient sterilization processes and emissions control technology.

Adverse Impacts on Public Health

EOSA believes the current draft IRIS assessment will have significant adverse impacts on those who use EO to sterilize healthcare products, and the medical community at large. By inappropriately magnifying the risk associated with the use of EO, users could be forced to switch to less effective, impractical, or unavailable alternatives with significant adverse public health consequences. A change in sterilization technology could introduce the real risks of medical device integrity and biocompatibility issues that would likely exceed the currently known risks of EO sterilization. For some medical devices and pharmaceutical products, proper sterility assurance levels might not be achieved with any change in this sterilization technology.

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For other products, no other method of sterilization exists and the product would become unavailable, likely resulting in a public health crisis.

Frequently, medical devices and healthcare products are designed with a specific sterilization method in mind. The de-selection that would result from the current draft IRIS assessment would make it impossible to sterilize many of these items. In many cases, any change to the sterilization method would require a complete redesign of the product to be sterilized. Even a redesign may not allow the product to be sterilized adequately without the use of EO. Furthermore, it is not feasible for medical device manufacturers to change to alternative sterilization methods within a realistic timeframe. Switching to any alternative sterilization technology for many products would simply exchange one risk for another. This would result in delays, inadequate sterilization, increased risks to public health, the inability to perform certain medical procedures, increased morbidity and mortality, and increased healthcare costs. In addition to overcoming technological difficulties, a tremendous amount of work goes into gaining approvals from the U.S. Food and Drug Administration (FDA). This would result in further delays, increased costs, and additional public health consequences due to inadequate sterilization.

In its current form, the revised draft IRIS assessment would result in more than 50 percent of all medical products that are used in pre-sterilized kits becoming unavailable. These kits include devices such as syringes, endotracheal tubes, catheters, vascular stents, and many other components. These types of single-use devices are critical items in hospitals, doctor's offices, and healthcare clinics across the U.S. Many reusable devices are currently only qualified for EO sterilization. A reduction in the limits as proposed would result in these products no longer being able to be sterilized adequately. A number of life-saving medical devices with difficult to reach enclosed areas, such as IV tubes, kidney dialysis machines, and endoscopes, can only be sterilized by EO. Products such as pacemakers and implantable defibrillators contain sensitive electronic components that cannot withstand the heat and harshness of alternative methods. The inability to sterilize these products and equipment with EO would significantly increase the risk of infection. These risks are far greater than those suggested by the draft assessment.

The critical importance of and need for EO sterilization to ensure the proper and effective sterilization of millions of healthcare devices in products that save lives on a daily basis is unquestionable. The conclusions reached in the current draft IRIS assessment would cause extreme public health consequences by terminating the availability of these life-saving devices, products, and procedures.

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Comments on Specific Charge Questions

Charge Question #1 -- Exposure Lagging: *Exposure-response modeling was conducted separately for lymphohematopoietic cancer mortality, with attention to lymphoid cancer, and breast cancer incidence and mortality. In the Cox proportional hazards models, a lag period was used to represent an interval before cancer death (or diagnosis, in the case of breast cancer incidence), or the end of follow-up, during which any exposure was disregarded because it was not considered relevant for the development of the cancer outcome observed. The lag period for each of the different cancer types was selected empirically based on statistical fit. These exposure lag periods were included in EPA's exposure-response analyses using other model forms for the derivation of cancer risk estimates.*

EOSA agrees with and supports comments made by Dr. Chris Kirman that “[p]recedents represented in the IRIS assessments of other chemicals do not support the selection of a single 15-year lag period. A no lag period should be presented or a range of lag periods including a no lag alternative should be considered in this assessment.” The IRIS assessment for EO will have significant impacts on public health. Such a significant assessment should be consistent with the majority of assessments in the IRIS database.

Charge Question #2 -- Breast Cancer Incidence -- Model Selection: *As discussed in the Background section, a number of different statistical models were examined and a number of considerations were used in the selection of the preferred model (the two-piece linear spline model), which was selected for the derivation both of estimates of risk in the range of the occupational exposures of concern and of estimates of risk as exposures well below the occupational range of concern.*

The CAAC is asked to comment on whether the considerations used by EPA for model selection and their application in the selection of preferred exposure-response models for breast cancer incidence to estimate low-exposure cancer risks and occupational exposure cancer risks are clearly and transparently described and scientifically appropriate. EOSA continues to be concerned that the National Institute for Occupational Safety and Health (NIOSH) breast cancer incidence data are not publicly available. This concern has also been identified by other public comments. Without the ability to review the data, EPA's analysis of the endpoint cannot be verified.

In 2007, the SAB recommended that EPA focus on individual data. In this assessment, EPA continues to evaluate exposure-response models based on a summary of available data rather than individual data points. EPA has dismissed more appropriate models, and the analysis in the revised draft assessment continues to be based on a non-peer-reviewed two-piece spline model for breast cancer incidence.

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Charge Question #4 -- Uncertainty in the Cancer Risk Estimates: *Please comment on whether the qualitative discussions of uncertainty (Sections 4.1.4, 4.5, 4.7, and Chapter 1) are clear, objective, and scientifically appropriate.*

EPA has dismissed the Union Carbide Corporation (UCC) exposure assessment study for dose-response assessment due to specific uncertainties and therefore relies on the NIOSH exposure assessment. While the UCC study includes uncertainties as noted by EPA, the NIOSH exposure assessment is not without its faults. For example, the NIOSH study does not include exposure data prior to 1975 and includes only limited data between 1976 and 1978. The latter period is when most of the worker exposure occurred in the study.

The NIOSH study included workers who began working in the EO industry as early as 1943. During this time, the workplace exposure limit for EO was as high as 100 parts per million (ppm) until 1957 when the American Conference of Governmental Industrial Hygienists (ACGIH) set the Threshold Limit Value (TLV) Time-Weighted Average (TWA) to 50 ppm. This level was reduced to ten ppm in 1981 and then reduced further to one ppm in 1984. The U.S. Occupational Safety and Health Administration (OSHA) followed a similar pattern reducing the workplace exposure limit from 50 ppm in 1971 to one ppm in 1984. The limitations contained within the NIOSH study largely invalidate the decision to solely rely on it and EPA has failed to justify the exclusion of the UCC study. As the IRIS assessment can lead to the further regulation of EO exposure, the CAAC should recommend that, at a minimum, the results from both the UCC and NIOSH studies should be presented and considered to improve the credibility of the assessment.

Furthermore, EO sterilization today is conducted in a vacuum sealed chamber only. The exposure levels that would result from this draft assessment would be significantly lower than the current OSHA eight-hour TWA of one ppm and could not be attained in a commercial or hospital setting.

Charge Question #5: *Please comment on the accuracy, objectivity, and transparency of the revised draft assessment, with particular emphasis on the following sections, which are either new or substantially revised since the 2007 external peer review:*

- *Section 3.3.3 and Appendix C (genotoxicity); and*
- *Appendix H (EPA's responses to the 2007 external review comments), in particular the responses to the comments on endogenous EtO (p. H-4), a nonlinear approach (p. H-13 to H-17), and the cancer hazard characterization.*



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The SAB in 2007 made recommendations to EPA that it utilize both linear and nonlinear calculations in a revised assessment. In Appendix H, EPA states that it “the inclusion of a nonlinear approach is not warranted.” According to the EPA Cancer Guidelines, “a *nonlinear approach* should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses.” Under these guidelines, the assessment should at least consider both linear and nonlinear modes-of-action. If EO is considered a weak mutagenic substance, the inclusion of both linear and nonlinear modes-of-action is further warranted.

EOSA appreciates the opportunity to submit these comments. We urge the CAAC to review this information, and the comments submitted by the ACC EO Panel, as it develops draft responses to the charge questions. We look forward to engaging the CAAC in discussions during the **November 18-20, 2014**, meeting. If you have any questions, or would like to request additional information, please do not hesitate to contact me at 410-255-2773 or jvandevort@bc-cm.com.

Sincerely,

Jake Vandevort
Manager
The Ethylene Oxide Sterilization Association, Inc.