Review of the Controversy Surrounding the Use of Ethylene Oxide in Medical Device Sterilization

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Introduction

Since the inception of its use as an insecticide 160 years ago, Ethylene Oxide (EO) has been used within industry across a spectrum of applications, ranging from the manufacture of anti-freeze to the sterilization of medical devices. While medical devices can be sterilized through several methods utilizing steam, dry heat, radiation and certain gases that have been vaporized, EO has been found to be an excellent alternative for devices made out of materials or components that are easily damaged by other sterilization methods. Additionally, EO is effective at penetrating multiple layers of packaging to facilitate sterilization within the final packaging, therefore it is attractive to manufacturers as this aids in preventing contamination of a sterile product after it undergoes sterilization. Furthermore, EO is able to reach areas that are difficult to sterilize, such as the lumens of catheters or the individual components of complex medical devices.[1] These distinguishing qualities have allowed EO to capture approximately 50% of the medical device sterilization market, ranging from those used in general healthcare (e.g. sutures) to more specialized devices (e.g. stents and complex medical devices).[2] Despite this well-established track record of use within the medical community and other industries, safety concerns have arisen over its use, igniting controversy that has the potential to threaten the medical device supply chain.

The controversial effects of EO on surrounding communities

This controversy is rooted in the discovery in 1948 that EO is a mutagen, but regardless of this discovery, its use in the sterilization of medical devices began in the 1950s. Following a chemical disaster in India in 1986 that resulted in thousands of fatalities, Congress approved the Emergency Planning and Community Right-to-Know Act. This act was established to require the EPA to annually publish a Toxics Release Inventory,[3] to provide the public with information regarding the pollution being released by individual factories and refineries. The following year, California announced their determination that EO is a human carcinogen and despite the availability of safer alternative sterilization methods such as irradiation and gaseous hydrogen peroxide, EO continued to grow in popularity. Adding to this controversy, in 1994, the EPA aligned itself with regulations for EO emissions established for commercial sterilization facilities.[4] Following this controversial move, the EPA further participated in another questionable move in 2001 by allowing companies to disconnect pollution-control equipment from the exhaust vents after several facilities experienced explosions. It was later determined that operator error was at fault for the explosions, thus nullifying the justification for disconnecting the pollution control equipment. A couple of years after these incidents, the National Institute of Occupational Safety and Health (NIOSH) reported that they had determined that EO causes breast cancer and lymphomas. Even with this evidence, the administration under George W. Bush refused in early 2006 to update the regulations governing EO use until a new scientific review was conducted. Roughly four months later, the EPA released a scientific report, exposing their findings regarding the hazards of EO use and their conclusion that it is a human carcinogen, however this report was opposed by the American Chemistry Council and Sterigenics (Willowbrook, IL) as they feared this could force facilities to discontinue their use of this sterilization method. The following year, an independent panel of scientists agreed with the EPA's conclusion that EO is in fact a human carcinogen, yet they advised the EPA to undertake the task of improving their risk assessment, a task that took an additional nine years to complete. During these nine years, California took the initiative to add EO to its list of toxic

substances that could lead to developmental complications in juveniles. In addition to this, they modified their 1987 determination that EO leads to reproductive issues in women, to also include infertility issues in men.

After nine years of re-evaluating their assessment, and meeting with a second independent panel of scientific reviewers, the EPA published their conclusions of the risk that EO posed to the public. This report did not differ significantly from their 2006 draft, and the EPA stood resolute in their decision that EO is in fact a human carcinogen.

Recent events at the Sterigenics Willowbrook facility in Illinois have further spurred along this controversy. Late in 2018, after the publication of the National Air Toxics Assessment, which is in line with the Toxics Release Inventory, it was observed that 109 of the nation's 73,057 census tracts exceeded the EPA's guidelines on emissions relating to cancer risk.[5] One of the areas impacted by this increased risk of cancer was the area around Sterigenics in Willowbrook, Illinois. This revelation prompted Sterigenics to implement more stringent pollution controls, however, two months after the publication of the Assessment, the Illinois Attorney General sued Sterigenics in state court. Surprisingly, four months after the installation of the new pollution controls, the levels of EO in the air surrounding Sterigenics were found to be markedly elevated. Following these findings, Illinois Governor J.B. Pritzker directed the Illinois EPA to ban the use of EO by Sterigenics at their Willowbrook location on February 15, 2019. This decision was further supported by the disclosure of the U.S. EPA about a week after this decision that the levels of EO in the area surrounding the Willowbrook Sterigenics location were at their highest levels since they started being monitored in May of 2018.[6] Two months after closure of the Willowbrook Sterigenics facility, it was determined that the levels of EO that had been detected in Willowbrook and surrounding communities had greatly decreased and had remained relatively low during the closure. Along with this finding, came the publication of an Illinois Department of Public Health study that examined data collected from women and girls who lived near the Willowbrook facility from 1995 to 2015, showing that certain cancers associated with long-term exposure to EO occurred at higher than expected rates in this population.[7] Further supporting these concerns, top officials within the EPA declared in May 2019 that they had confirmed that despite the installation of additional pollution-control equipment at the Willowbrook Sterigenics location, the EO pollution was responsible for long-term cancer risks that were up to ten times higher than what was considered to be acceptable. About a month after the release of this report, Governor Pritzker signed legislation which would require sterilization facilities to implement protocols that will prevent the emissions of EO into the surrounding communities. In accordance with this new legislation, Sterigenics filed a proposal to reduce emissions of EO from their facility as part of their bid to reopen their facility in Willowbrook. Approximately three weeks after submitting this proposal, Sterigenics and the state reached a legal settlement which would allow the facility to resume activities at their Willowbrook locations once they had completed the tasks outlined in the protocol. This legal settlement was approved by the DuPage County judge approximately 2 weeks after that. Despite these efforts though, the residents in the communities surrounding the Willowbrook facility had lost faith that they would be protected against EO exposure by Sterigenics and their state regulators. Subsequent to this expression of distrust within the communities, Sterigenics released a statement at the end of September 2019, announcing that due to failing to broker a deal on their new lease, they would be redirecting their Willowbrook business to other facilities, citing an "unstable legislative and regulatory landscape" that "created an environment in which it is not prudent to maintain these critical sterilization operations in Willowbrook."[8]

Characteristics of Ethylene Oxide and its Mechanism of Action

EO, a colorless but combustible gas, was developed at a time when there were few alternatives to sterilization methods that were compatible with materials and devices sensitive to conditions imposed upon them by standard sterilization methods. Certain devices constructed with materials such as some polymers (plastic or resin), metals, or glass, have the propensity to be damaged by high temperatures, moisture, irradiation, or other chemical compounds.[9] For these specified devices, EO alone, has the ability to effectively sterilize them without negatively impacting the integrity of the device and its components.

EO's sterilization capabilities are accomplished through the alkylating of the proteins, DNA, and RNA of the targeted microorganisms. This prevents the normal functioning of the cell's metabolism and replication pathways, through the placement of an alkyl group where a hydrogen atom should be present. This singular change impacts proteins specifically by leading to a conformational change to the protein, thus, rendering them ineffective. At the same time, alkylation of a DNA or RNA strand will lead to mutations, thus, preventing the synthesis of the intended protein, or leading to an alteration in that protein.

The alkylation process imposed by EO is influenced by four essential parameters: gas concentration (see Figure 1), temperature, relative humidity (see Figure 2), and exposure time. While an increase in concentration and temperature may shorten the sterilization time, there are certain limitations that must be adhered to as many devices sterilized with this method are temperature sensitive.

Figure 1: Ethylene oxide gas concentration vs sterilization efficiency[10]

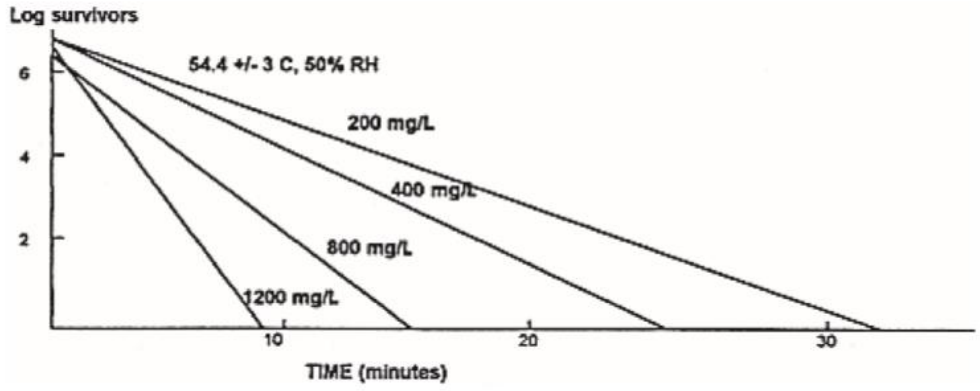
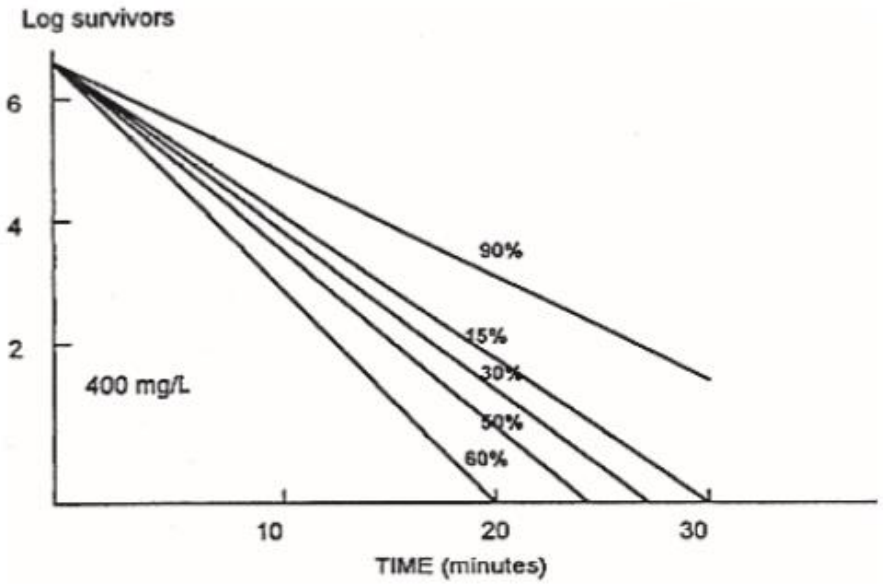


Figure 2: Humidity vs sterility efficiency[11]

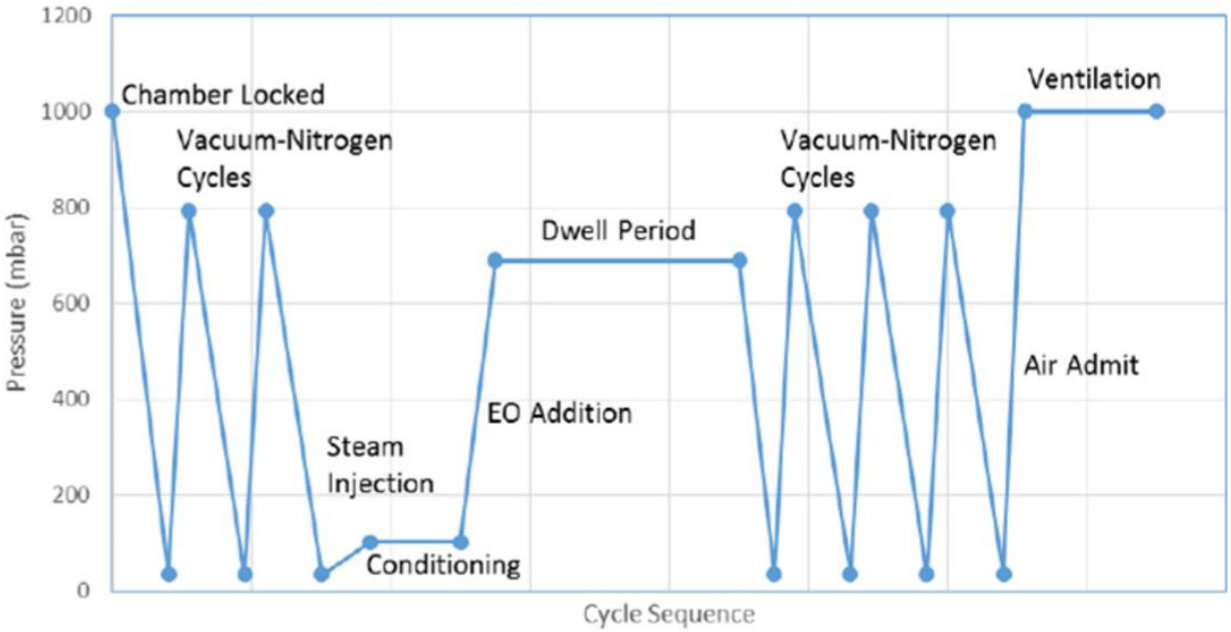


Despite its benefits, there are significant disadvantages in its use, most notably the hazards it poses to patients and staff, but also in the time involved and the cost of the process. Acute exposure to EO can result in irritation to the surfaces it contacts such as skin and the respiratory tract but can also result in the depression of the central nervous system. However chronic exposure, such as seen in healthcare settings or environmental exposure, can lead to more concerning health concerns such as spontaneous abortions, various cancers, hematologic changes, genetic damage, and nerve damage. Additionally, patients can be inadvertently exposed to EO if residue is present, such as on the surface of an implant, or capillary flow dialysis membrane.[12]

Sterilization process

The sterilization process consists of 5 stages which include: preconditioning and humidification; gas introduction; exposure; evacuation; air washes; and aeration (see Figure 3).

Figure 3: Sterilization cycles and sequencing[13]



The preconditioning stage takes place outside of the sterilization chamber and is responsible for allowing the sterilization process to be reproducible, regardless of external influences such as varying climatic conditions. This process involves heating and humidifying the devices to a stable internal temperature of 118^{o} and a moisture content of 65 percent prior to entering the vacuum chamber.[14] This stage can take anywhere from 12 to 72 hours to complete.

Once the preconditioning stage is complete and prior to initiation of the humidification stage, 97 percent of the air within the vacuum-tight chamber must be removed through one of two processes (1) pulling a deep vacuum, or (2) performing a series of partial vacuums followed by a series of nitrogen injections.[15] The removal of the air and re-introduction of the nitrogen facilitates a safe environment for the EO to be introduced.

This evacuation of air can remove a significant amount of moisture that was previously introduced during the preconditioning stage, thus requiring a later humidification stage using steam injections. Humidification must be completed prior to introduction of EO as successful product sterilization is dependent upon the predetermined criteria for heat, relative humidity, gas concentration, and time being met.[16]

The gas introduction stage is initiated after the appropriate amount of time for humidification has passed in order to restore the missing moisture to the devices. During this phase, EO is injected into the chamber in its gaseous form until the minimum gas concentration is reached. Upon introduction of the EO gas into the chamber, the exposure stage is begun, and the devices are exposed for a predetermined length of time.

In order to prevent EO residues from being present, the EO gas must be removed by completing a series of washes involving post-vacuums followed by nitrogen backfills. This process is completed until the amount of EO present in the chamber is below the flammable limit, 3 percent or 30,000 ppm. To further reduce the residues of EO present on the surface of the medical devices, the devices are placed in a heated room that facilitates the removal of the EO gaseous residues through the outgassing process. This stage of the sterilization process can take anywhere from eight to twelve hours to complete when the room's temperature is set to 50 to 60^{o}C, however this process can take up to seven days to complete if the room is set to 20^{o}C demonstrating the variation that can occur dependent on device needs.

Potential solutions under development

Currently, the use of EO is regulated by the EPA and the Clean Air Act as well as through two voluntary consensus standards, ANSI AAMI ISO 11135:2014 and ANSI AAMI ISO 10993-7:2008(R)2012.[17] These standards not only set the expectations for sterilization processes as they are developed and validated, but they also describe the mechanisms that should be followed to establish a robust sterilization process. In addition to providing guidance on the development of the sterilization process, these standards also outline what levels of EO residues are acceptable and provide additional insight into mechanisms that will provide sufficient control over the sterilization process. Despite these standards being in place, there is an ongoing push for improvement.

Recognizing the need for alternative sterilization methods, strategies, and technologies, the EPA partnered with device manufacturers, governmental agencies and sterilization experts to work to find processes and methods to reduce levels of EO associated with its use. In cooperation with these efforts, the FDA made an announcement on July 15, 2019 regarding two challenges being initiated. These two challenges were initiated with the hopes of accelerating the development of a solution to this controversy.

Challenge 1 focused on identifying alternative sterilization methods that meet the following criteria:[18]

- Compatibility with large cross-section of materials used to manufacture or fabricate medical devices as well as packaging materials or sterile barriers.
- Scalability and High Throughput: have the potential to be scalable and allow for the effective sterilization of large volumes of devices.

Table 1: The five submissions selected for Challenge 1:[19]

Company	Reduction Technology/Strategy Category
NovaSterilis	Supercritical Carbon Dioxide Sterilization
Noxilizer, Inc.	Nitrogen Dioxide Sterilization
STERIS	Accelerator-Based Radiation Sterilization
STERIS	Vaporized Hydrogen Peroxide Sterilization
TS03, now a part of Stryker	Vaporized Hydrogen Peroxide-Ozone Sterilization

Challenge 2 involved the development of strategies or technologies to reduce EO emissions from the sterilization process to as close to zero as possible.

Table 2: The eight submissions selected for Challenge 2:[20]

Company	Alternative Technology Category
Abbot	Enhanced EO Cycle Design and Processes
Andersen Scientific, Inc.	Use of EO-Flexible Chamber Technology
Becton, Dickinson and Company (BD)	Enhanced EO Cycle Design and Processes
DMB Apparatebau GmbH	Reduced Sterilant Concentration
Medtronic plc	Enhanced EO Cycle Design and Processes
Sterigenics U.S., LLC	Enhanced EO Cycle Design and Processes
STERIS	Enhanced EO Cycle Design and Processes
Taiwan Advanced Sterilization Technologies Inc.	Abatement Strategy

Following selection, these twelve participants selected for the two challenges will continue to work directly with the FDA to further develop these strategies and technologies, striving to provide these as reliable and effective alternatives to the EO sterilization process.

Despite their selection for the challenges, "review of these challenge submissions does not constitute regulatory acceptance or endorsement of a process associated with a premarket submission. These methods or technologies would still have to be reviewed through the relevant premarket pathway."[21] This means that sufficient data must be generated, showing the processes' efficacy and compatibility with its intended market.

<u>Alternative viewpoints to this controversy</u>

An alternative viewpoint regarding this controversy is the concern that with the removal of EO as a potential sterilization method, there could be shortages of medical devices requiring EO sterilization. According to Karl Hemmerich, the chairman of a 40-member working group for the Association for the Advancement of Medical Instrumentation, stated, "in some limited number of cases, it's going to be difficult to switch."[22] Despite Hemmerich estimating that only a small portion, approximately 20 percent, of the medical device market will be impacted by the removal of EO as an approved sterilization method, this impact will be mostly felt by companies marketing electronic medical devices as EO is the only sterilization method that is compatible with their devices.

In addition to this concern is the fact that switching the sterilization process of an approved/cleared device is incredibly expensive, one such expense that companies may choose to not undertake. Not only does switching sterilization techniques cost an exorbitant amount, it can also take years to validate the process, thus putting the market availability of the device in jeopardy. These two factors combined could lead to companies removing their products from the market rather than making the necessary sterilization changes, thus leading to a reduction of medical device options as well as limiting development.

Discussion

Undoubtably changes must be made to the EO sterilization process and the regulations that govern it to protect the public's health. However, one should not be of the opinion that this issue will be resolved through an uncomplicated nor expeditious process, but rather it will require years of collaboration and partnerships to provide medical device manufacturers with an alternative sterilization process that fulfills their needs while protecting the general public. During this discovery and development phase, medical device manufacturers should look to explore limiting their use of EO as their sterilization for devices that are under development and should look to develop devices that are compatible with other sterilization methods such as gamma irradiation or gaseous-phase hydrogen peroxide. Similarly, EO sterilization plants should look to modify their systems to aide in limiting the amount of EO that is released into the surrounding communities. This could be accomplished through the installation of additional filtering systems and implementation of a quality plan that outlines a regular inspection schedule that will limit potential leaks within the facility. While it would be preferable to resolve this sterilization controversy within a matter of a year, we must accept that this will be a prolonged process that will require us to form a collaboration between industry and regulators that will work towards the common goal of finding a solution.

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