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Comparison of Alternative Sterilization Chemicals to Ethylene Oxide (EtO)

AST STAFF

EtO has long been an essential chemical used by manufacturing and the healthcare industry. EtO was discovered by the French chemist Charles-Adolphe Wurtz in 1859.[1] In 1914, the German chemical manufacturing business Badische Anilin- und Sodafabrik (BASF – Baden Aniline and Soda Factory), built the first EtO plant.[1]

During the 1930s and '40s, it was used to fumigate hospital ward rooms and by the 1950s was commonly used to sterilize surgical instruments.[2] Other landmark dates include the following.[2]

- 1928 – Scientists reported that EtO is a strong insecticide.
- 1940 – Two executives at Griffith Laboratories, now called Griffith Foods located in Chicago, patented a method that pumped EtO into a vacuum chamber to sterilize spices. The U.S. Army later used EtO to fumigate troop rations during World War II.
- 1948 – A study establishes that EtO is a mutagen.
- 1987 – California declares EtO is a human carcinogen.
- 1990s - Other sterilizers to possibly replace EtO are developed including hydrogen peroxide and peracetic acid.

EtO continues to be produced in large quantities by companies because of its use as an important source in the manufacturing of common items. In 2018, the U.S. produced 2.92 metric tons of EtO

LEARNING OBJECTIVES

- Compare and contrast alternative sterilization chemicals to ethylene oxide
- Discuss the advantages of alternative sterilization chemicals
- List the disadvantages between EtO and CD, ND, VHP
- Debate whether one of the chemicals has more perceived sustainability than the others
- Explain the reasons why healthcare facilities might use one of the chemicals over the others

worth $3.49 billion.[3] More than 97% of the amount produced is used to make other chemicals that are used to manufacture a range of products, including adhesives, antifreeze (ethylene glycol or propylene glycol), detergents, plastics, and textiles.[3] Less than 1% of manufactured EtO is used as a fumigant, to sterilize food (spices) and cosmetics.[3] Yet, EtO is the most used sterilization method for medical devices in the U.S, with more than 20 billion devices sold in the U.S. annually that are sterilized with EtO, equal to approximately 50% of devices that require sterilization.[4] However, because of health concerns, the controversy of using EtO in healthcare facilities increased over time prompting the EPA to tighten regulations to decrease the potential risk of exposure from EtO sterilization processes. On March 14, 2024, the EPA announced their most recent ruling regarding commercial EtO sterilizers to reduce exposure to the colorless gas.[5]

This has also led to the research and development of alternative sterilization chemicals as a possible replacement for EtO in healthcare facilities. The remainder of this article will discuss the alternative sterilization chemicals chlorine dioxide (ClO_2 – referred to as CD), nitrogen dioxide (NO_2 – referred to as ND), and vaporized hydrogen peroxide (VH_2O_2 - referred to as VHP).

Alternative sterilization chemicals have been in existence for several decades. For example, the vapor form of hydrogen peroxide was first identified as a sterilant in the late 1970s.[6] In the late 1980s, the first hydrogen peroxide gas plasma system for sterilization of medical and surgical devices was field-tested, and later in the 1990s, the use of vaporized hydrogen peroxide slightly increased. However, alternative sterilization chemicals are still not in wide use and primarily used by commercial sterilization businesses and healthcare manufacturers.

CHLORINE DIOXIDE

CD is one of the newer sterilization agents that provide manufacturers with an environmentally alternative to sterilization of medical devices that avoids carcinogenic emissions. It was registered as an EPA sterilant in 1988. In early 2021, the US Food and Drug Administration (FDA) approved CD for contract sterilization of medical devices and subsequently, ClorDiSys Solutions, located in New Jersey, became an FDA-registered contract sterilization facility.[7]

CD is produced by a chemical reaction by mixing sodium chlorite ($NaClO_2$) with an acidic solution, typically hydrochloric acid (HCl), which then fills the sterilization chamber. It is a greenish yellow or reddish yellow colored gas that smells like chlorine at an ambient temperature. It is effective as a biocide against bacteria, fungi, spores, and viruses.[8] It kills microbes by disrupting the cell membrane and cellular proteins through the process of oxidation.[8]

CD has multiple advantages over EtO.

- CD is a true gas sterilant and operates at ambient temperature.[9]
- Facilities using EtO can convert the chamber into a CD sterilization chamber.[9]
- An important advantage because CD is not explosive, devices embedded with batteries, such as pacemakers, can be sterilized using the agent.[8]
- Shorter sterilization cycle time and aeration than EtO providing a faster turnover time of medical devices and instrumentation. Aeration typically is under 60 minutes.[9]
- CD has not been linked to birth defects or cancer. However, because there have been no cancer studies completed on human exposure to CD, the EPA cannot assign a carcinogenicity classification.[8]
- CD is used to sterilize a variety of items including artificial joints, electronic devices, endoscopes, implantable contact lenses, prefilled syringes, surgical kits, suture products, and vial stoppers.
- At normal sterilizing condition of 4% concentration CD is not explosive or flammable. However, over 10% concentration it is explosive and therefore, prohibited from transport by the US Department of Transportation unless shipped frozen.[8]
- It does not pose a risk to patients because it does not leave a residue on medical devices making it a surface sterilant that can be used to sterilize pre-filled syringes without effecting the integrity of the drug. It also has the capability to sterilize medical devices with narrow lumens and complex geometries.[8] Additionally, because of no residue, its by-products can be exhausted to the environment. The by-products are chlorate, chloride, and chlorite that are non-carcinogenic, non-cytotoxic, and non-teratogenic.

There are drawbacks to the use of CD. The agent is not manufactured in large enough quantities as compared to EtO. At the commercial sterilization level, the chambers are not as large as the big EtO chambers, thus reducing the amount of product that can be sterilized simultaneously.[8]

NITROGEN DIOXIDE

ND is the most recent addition of the three alternative sterilization methods discussed. There isn't a documented date for the discovery of ND as a sterilant. The FDA categorizes sterilization processes as either "established" (Category A), which includes current methods such as dry heat, electron beam, EtO, and gamma radiation, or "novel" (Category B), which includes technologies that do not have an established history for sterilizing medical devices that includes ND.[10] However, in June 2016, Noxilizer, Inc. received FDA 510(k)[a] clearance for a medical device terminally sterilized using its ND sterilization process.[11] Additionally, in June 2019, the FDA announced their *Innovation Challenge 1: Identify New Sterilization Methods and Technologies* and subsequently, in November 2019, Noxilizer, Inc. was chosen to work with the FDA in further developing ND sterilization.[12]

Liquid nitrogen that is stored in a container is vaporized to create the true gas that is injected into the sterilization chamber. It is non-carcinogenic and non-flammable. It kills microorganisms by damaging their DNA referred to as "DNA degradation."[13] Because of its low boiling point, 21˚ C, ND sterilizes at an ultra-low temperature of 10˚ - 30˚ C making it ideal for heat-sensitive items.[13] Cycle times are shorter than EtO and humidity added to the sterilizing chamber assists in speeding up the sterilization process. The low boiling point coupled with a low sterilant concentration, allows rapid aeration by the introduction of air into the sterilization chamber making it possible to immediately handle sterilized packages.[13,14] The low boiling point also allows the gas to be introduced into the sterilization chamber with minimal to no vacuum.[14]

ND gas does not condense on devices because of the low sterilant concentration. Therefore, it is a surface sterilant providing the advantage that it can be used to sterilize pre-filled syringes without compromising the drug and reach complex geometries of medical devices.[13] ND is compatible with aluminum, glass, gold plating, polycarbonate, polyethylene, polypropylene, PVC, silicone, and stainless steel.[13] Therefore, ND can be used with non-woven polypropylene packaging, Tyvek® pouches, and Tyvek® - Mylar® pouches, and silicone rubber.

A disadvantage is that porous packaging is required, so medical grade paper cannot be used because cellulosic materials are not compatible with the ND sterilization process.[13] Another disadvantage ND is toxic gas and proper safety precautions must be followed during handling.

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VAPORIZED HYDROGEN PEROXIDE

VPH will be discussed in greater detail because of its rise in popularity with healthcare facilities, which can be attributable to the ANSI/AAMI ST 91 standard that advocates for flexible endoscope reprocessing to be consistently changed from high-level disinfection to sterilization.[15] There are different types according to the additive such as ozone or plasma, but the sterilizing agent is the VHP. To fully understand VHP plasma also needs to be understood. Plasma is the fourth state of matter with gas, liquid, and solid being the other three. Plasma is created when a gas is heated adequately or exposed to a strong electromagnetic field. When the gas becomes plasma, it has undergone a chemical reaction causing it to become an ionized gas.[16]

Examples of manmade plasmas include fluorescent light bulbs, neon signs, nuclear fusion, and plasma displays used for computer monitors and televisions. Naturally occurring examples are the well-known Northern Lights, tales of comets, fire, lightening, sun and stars.

The sterilization cycle occurs in three phases: conditioning, sterilization, and venting. Conditioning begins with air removal from the chamber to facilitate the penetration of VHP and to remove traces of moisture remaining on the load.[17] Sterilization starts with heating the liquid hydrogen peroxide to convert to a gas. The

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gas is heated to a higher temperature to convert to plasma that is injected into the chamber.[16] VHP condenses inside the chamber and forms a microlayer of condensate on the enclosed items.[17] The sterilization phase is repeated one or more times. During the venting phase, the plasma is transferred to a catalytic convertor to convert the plasma to oxygen and water that is safely evaporated into the atmosphere.[17] Because VHP is an oxidizing agent it kills microorganisms by destroying the microbes DNA, enzymes, and proteins.

An important detail to emphasize is ensuring that items to be sterilized are completely dried following the manufacturer's instructions. As with any sterilization process, instruments are cleaned and disinfected according to the manufacturer's instructions. However, failure to thoroughly dry the instruments can cause complications such as impeding the ability of the VHP to properly contact the surface of the instruments causing items to be non-sterile as well as the moisture can act as a protective shield for microorganisms. Additionally, residual hydrogen peroxide can remain on the surface of the load at the end of the cycle causing risks to health care personnel and patients.[17] As mentioned, a low amount of residual moisture will evaporate during the conditioning phase. However, a high amount of moisture continues evaporating during the vacuum, that impedes pressure reduction and can cause the cycle to abort. Secondly, the evaporated moisture reduces the temperature of the heat from the evaporation of remaining liquid causing it to form ice.[18] The ice could prevent the VHP to contact the surface of the items in the load as well as block narrow lumens.[18] Therefore, it is essential to ensure that moisture on items to be sterilized is at a minimum or non-existent.

On July 24, 2023, the FDA's Center for Devices and Radiological Health (CDRH) announced that it updated the *Recognized Consensus Standards* database to include complete recognition of the ISO[b] 22441:2022 *Sterilization of health care products – Low temperature vaporized hydrogen peroxide – Requirements the development, validation, and routine control of sterilization process for medical devices*.[19] Because of this recognition, the FDA switched VHP from a novel sterilization technique (Category B) to established (Category A) on January 8, 2024. The FDA commented "that it considers vaporized hydrogen peroxide (VHP) to be an established method of sterilization for medical devices, recognizing VHP's long history of safety and effectiveness. [T]he FDA is adding VHP to Established Category A, which the agency expects will strengthen industry's capacity to adopt alternative sterilization processes that pose less potential risk to the environment and communities in which they operate."[4]

Medical devices that healthcare facilities commonly sterilize using VHP include the following.

- Non-hollow devices: defibrillator pads, dopplers, electrocautery instruments, laser probes, ophthalmic lenses
- Hollow devices: fiber optic light cables, laryngoscopes, surgical power equipment (drills, saws)
- Endoscopes: flexible and rigid
- Advantages of VHP include the following.
- VHP operates at lower temperatures that reduce energy utilization making it an energy-efficient system.[17]
- The sterilization process is less than one hour, with the average cycle running 35-45 minutes contributing to a faster turnover of sterilized items.[17]
- It is environmentally friendly and safe. Because VHP does not produce toxic fumes or residue, a long aeration cycle is not required, and the sterilized items can be immediately handled by health care personnel.

There are two main disadvantages. Only Tyvek® packaging materials can be used and because VHP does not penetrate as well as EtO, medical devices with lumens are challenging to sterilize.

The use of CD and ND, primarily by manufacturers, and VHP by healthcare facilities and manufacturers represent an advancement in the field of sterilization, material compatibility, environmental safety and health care personnel and patient safety. The three alternative sterilization methods provide a future for sustainable practices

that are cost effective and poised to play a continuing role in advancing medical device safety.

510(k) is a premarket submission made to the FDA to demonstrate that a device to be marketed is safe and effective and substantially equivalent to a legally marketed device. The applicant must compare their device to one or more similar legally marketed devices and support their equivalence claims. (U.S. FDA, Premarket Notification 510(k), August 22, 2024, https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k.

ISO, International Organization for Standardization, is an independent, international standard development organization whose membership consists of other national standards organizations of member countries. It has published over 25,000 international standards addressing multiple areas of technology and manufacturing, including healthcare. (ISO, https://www.iso.org/home.html)

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Comparison of Alternative Sterilization Chemicals to Ethylene Oxide (EtO)

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1. What percentage of medical devices are sterilized with EtO?
A. 20%
B. 30%
C. 40%
D. 50%

2. Which of the following packaging material is not compatible with nitrogen dioxide?
A. Tyvek
B. Cellulose
C. Polypropylene
D. Silicone rubber

3. How does chlorine dioxide kill microorganisms?
A. DNA degradation
B. Disrupts cellular metabolism
C. Oxidation
D. Causes lysis of cellular wall

4. What federal organization changed vaporized hydrogen peroxide from a novel sterilization technique to established?
A. EPA
B. AAMI
C. FDA
D. ISO

5. Which of the following is an advantage of chlorine dioxide?
A. Devices with batteries can be sterilized
B. Aeration is not required.
C. High concentrations can be transported
D. Sterilizing chambers are larger than EtO chambers

6. What is added to the nitrogen dioxide sterilizing chamber to speed up the sterilization cycle?
A. Oxygen
B. High heat
C. Humidity
D. Electromagnetic field

7. What EPA carcinogenic classification has been assigned to chlorine dioxide?
A. B
B. C
C. D
D. No category

8. How does nitrogen dioxide kill microorganisms?
A. Denature enzymes
B. DNA degradation
C. Cause leakage of protoplasm
D. Alkylation of cellular proteins

9. During the venting phase, vaporized hydrogen peroxide is converted to:
A. Oxygen and water
B. Residue
C. Oxygen only
D. Gas

10. What substance can form within the vaporized hydrogen peroxide chamber if there is too much evaporated moisture?
A. Hydrogen peroxide residue
B. Oxygen
C. Plasma
D. Ice

COMPARISON OF ALTERNATIVE STERILIZATION CHEMICALS TO ETHYLENE OXIDE (ETO)
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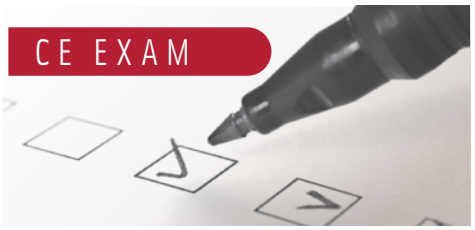

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