

Low-temperature sterilization alternatives in the 1990s

Philip M. Schneider

ABSTRACT: Vapor phase hydrogen peroxide, gas plasma, ozone, and peracetic acids have been commercialized as alternative technologies for low-temperature sterilization. None are viewed as a total replacement for ethylene oxide for on-site sterilization of reusable, heat-sensitive medical materials in healthcare facilities.

KEYWORDS: Disposables, low temperature, medical surgical supplies, sterilization, substitutes.

Ethylene oxide (EO) has been widely used as a low-temperature sterilant and fumigant since the 1950s. Radiation sterilization was also developed during this period but was not a widely available alternative to EO until the late 1970s. In 1977, the National Institute for Occupational Safety and Health (NIOSH) reported that animal studies indicated EO was a possible carcinogen. One year later the Environmental Protection Agency (EPA) determined EO to be a mutagen and announced that its use would be restricted. These actions led to the rapid development of cobalt-60 (Co^{60}) sterilization and the growth of electron beam sterilization.

Ionizing radiation has provided manufacturers of single-use medical devices with an alternative for low-

temperature sterilization. However, EO remains as the only proven method for low-temperature sterilization within healthcare institutions. Numerous technologies were researched and developed during the mid-1980s as possible alternatives for EO in this setting. Among these were vapor phase hydrogen peroxide (VPHP), chlorine dioxide, ozone, gas plasmas (primary and secondary), peracetic acid, ultraviolet (UV) radiation, and low-temperature steam formaldehyde (1). Of these, VPHP, gas plasma, ozone, and peracetic acid systems have been or are in the process of being commercialized. These and other low-temperature sterilization methods are discussed in this article and contrasted in **Table I**.

Technical considerations

The technical considerations faced by the developers of these new technologies may best be described by defining the attributes of the ideal low-temperature ($<60^\circ\text{C}$) sterilant for use in healthcare. These attributes are:

- High efficacy—be bactericidal, sporicidal, tuberculocidal, fungicidal, and virucidal
- Rapid activity—achieve sterilization as quickly as possible
- Strong penetrability—penetrate common medical device packaging materials and penetrate into the interior of device lumens
- Materials compatibility—produce negligible changes in either the appearance or function of processed items and packaging materials even after repeated cycling
- Nontoxic—present no health risk to the operator or to the patient and pose no potential hazard to the environment
- Organic material resistance—withstand reasonable organic material challenge without loss of efficacy
- Adaptability—suitable for large or small (point of use) installations
- Monitoring capability—monitored easily and accurately with both chemical and biological process monitors
- Cost effectiveness—reasonable cost for installation and for routine operation.

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Simply stated, the ideal sterilant does not exist. Current low-temperature sterilization methods and the emerging technologies all have some degree of limitations. These methods are examined with special emphasis on packaging material compatibility.

Regulatory considerations

In addition to being proven technically, any new sterilization method is subject to regulatory approval before marketing. New (or existing) sterilants used in the processing of medical devices are regulated in the United States by both the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) through its 510K Approval System. While the primary focus of EPA on chemical sterilants is safety and efficacy, the FDA is concerned more with the overall performance of the sterilant or sterilization system. Also, the FDA review process may be very lengthy; it may take years before approval is granted.

Emerging low-temperature sterilization technologies

Vapor phase hydrogen peroxide (H_2O_2)

Hydrogen peroxide (H_2O_2) solutions have been used for many years to kill microorganisms. Its bactericidal and sporicidal properties are well documented. Commercially available solutions containing 3% hydrogen peroxide are commonly used as antiseptics and for the disinfection of inert surfaces. In recent years, the food industry has employed vapor phase hydrogen peroxide (VPHP) for the sterilization of packaging materials in conjunction with aseptic packaging (2). However, VPHP was not developed for the sterilization of medical equipment until the mid-1980s when the American Sterilizer Co. (AMSCO), Erie, PA, acquired patent rights for VPHP technology and received EPA-approved registration for a hydrogen peroxide sterilization system. One of the most appealing aspects of this system is the breakdown

I. Phases, temperature ranges, and modes of action of low-temperature sterilization processes

Agent	Phase	Temp. range/CM °C	Mechanism
Vapor phase Hydrogen peroxide	Vapor	4-80	Oxidation
Hydrogen peroxide Plasma	Vapor	37-44	Oxidation/ activated species?
Gas plasma/peracetic acid vapor	Vapor	37-57	Activated species?/ oxidation
Ozone	Vapor or liquid	20-30	Oxidation
Peracetic acid	Liquid or vapor (liquid)	50-55	Oxidation
Ionizing radiation	Energy	20-25	Ionization
Glutaraldehyde	Liquid	20-25 (Some 60)	Condensation/ ring closure
Ethylene oxide	Vapor	37-55	Alkylation

of hydrogen peroxide into water and oxygen following sterilization.

Two different approaches have been developed for delivering VPHP to its reaction site (3). One approach uses a deep vacuum to pull liquid hydrogen peroxide (30% concentration) from a disposable cartridge through a heated vaporizer and then, following vaporization, into the sterilization chamber. The vacuum level is approximately the same as that used in a 100% EO system or in a prevacuum steam sterilizer. The initial system using this approach operated at 55°C and was shown to sterilize intravenous administration sets packaged in Tyvek peel pouches with a 4.5-h cycle. This technology has since been adapted to other uses such as decontamination of laboratory and biomedical equipment and has been shown to be effective at temperatures as low as 4°C (4).

The second method of VPHP delivery is the "flow-thru" approach in which the vaporized hydrogen peroxide is carried into the sterilization chamber, or any enclosed space, by a carrier gas such as air. This method uses either a slight negative pressure (vacuum) or a

slight positive pressure and operates effectively in the range of 23-37°C. Applications of this technology include a dental sterilizer, an endoscope sterilizer, and a portable VPHP generator (VHP™ 1000) for decontamination of both large and small enclosed areas. The VHP™ 1000 is commercially available and the endoscope sterilizer is awaiting regulatory approval to market.

This technology has several appealing aspects, but it has limitations. Porous cellulosic materials, e.g., paper, are not recommended for use with the VPHP process. Nylon and some natural rubbers are not considered compatible with VPHP. Additionally, some materials such as polypropylene/polyester packaging have been shown to have hydrogen peroxide residual levels that require a post-treatment aeration period. While hydrogen peroxide is considered relatively nontoxic, the Permissible Exposure Limit of hydrogen peroxide gas, as established by the Occupational Safety and Health Administration (OSHA), is 1 ppm as an 8-h time-weighted average. Adequate ventilation of the sterilization

work area would be required as with an EO process. Probably the most limiting aspect of this technology is the fact that VPHP does not have the penetration capabilities of EO and consequently does not have the same broad potential for sterilization of medical materials as does EO.

Gas plasma

A gas plasma is a highly ionized body of gas that has unique properties different from the gas itself. Gas plasmas have been referred to as the fourth state of matter (liquids, solids, gases, and gas plasmas). In commercial applications, gas plasmas are generally formed in an enclosed chamber under very deep vacuum using radio frequency (RF) or microwave energy to excite the gas molecules and produce ions, electrons, and neutral species (5). The type of seed gas used and the depth of the vacuum are two important variables that can determine the effectiveness of this process. Neon lights represent a practical application of this technology. A naturally occurring plasma is the aurora borealis or so-called Northern lights.

Gas plasmas have been used to etch circuit boards in the manufacture of semiconductor devices since the early 1970s. Not until the mid-1980s, however, did Surgikos Advanced Sterilization Products, Arlington, TX, begin field testing the STERRAD® hydrogen peroxide gas plasma system for the sterilization of medical devices. In this process, the sterilization chamber is evacuated and hydrogen peroxide is injected into the chamber where it vaporizes. After a period in which the hydrogen peroxide diffuses throughout the chamber, RF energy is applied to the chamber to create a gas plasma. This process operates in the range of 37–44°C and has a total cycle time of 1 h, 15 min (6).

Because product items in this process are directly exposed to the highly reactive (primary) gas plasma, there is a concern for materials damage. Penetration and inability to use highly absorptive materials or paper (as with

VPHP) are also concerns. Penetration of the hydrogen peroxide vapor into narrow lumens has been addressed by the use of a "diffusion intensifier." This is a small ampoule of highly concentrated hydrogen peroxide with an elastic connector that is inserted into the device lumen and crushed immediately before sterilization (7). This system has recently received FDA 510K approval to market with limited application for the sterilization of medical devices.

AbTox, Inc., Mundelein, IL, is also currently field testing a gas plasma sterilizer. The AbTox PLAZLYTE sterilization system differs from the STERRAD unit in two distinct ways. First, product items in the PLAZLYTE sterilizer are exposed only to a secondary or downstream gas plasma which has been characterized as less damaging to materials than a primary plasma. This is accomplished by creating the gas plasma from hydrogen and oxygen gases outside of the sterilization chamber and then flowing it into the chamber. Second, the PLAZLYTE system uses a nonplasma, peracetic acid vapor phase that is alternated with the plasma treatment (8).

The AbTox PLAZLYTE gas plasma sterilization system is claimed to be "safe, effective, and compatible with many of the materials commonly used in medical devices." Additionally, "it functions through Tyvek and paper packaging materials, penetrates lumens, and deposits no toxic residues on the sterilized devices" (9). While the AbTox system seems to have overcome some of the historical limitations of gas plasma sterilization, supporting data from field evaluations are not publicly available at this time.

This gas plasma sterilization system has not received 510K approval to market as of this point in time.

Ozone (O₃)

Atmospheric ozone protects us from the harmful effects of the sun's ultraviolet rays. Ozone has been used for many years as a drinking water disinfectant and more recently as an empty-

container sterilant in the food industry. Chemically, ozone (O₃) is made up of three oxygen atoms rather than the two atoms comprising an oxygen molecule (O₂). This additional oxygen atom is what makes ozone so reactive and feasible as a gas sterilant. In commercial applications, ozone is generally formed by an ozone generator using an electrical discharge in the presence of oxygen or air. The fresh-air smell following an electrical storm is an example of ozone occurring naturally. Ozone's highly unstable nature gives it the unique property of self-destruction; it converts back to oxygen shortly after its formation.

In February 1989, Life Support, Inc., Erie, PA, obtained FDA approval to market an ozone sterilizer for healthcare applications. The system uses hospital oxygen to produce ozone which is then combined with high humidity and dispersed into the sterilization chamber. The ozone gas is produced continually and flows through the chamber during the entire cycle. When the sterilization exposure time has been completed, the ozone generator is shut off and the chamber is purged by the continuous oxygen flow. Residual ozone is catalytically converted back to oxygen (10). This system operates at ambient temperature and pressure but can be modified to operate under vacuum conditions. Typical cycles would run 30 min to 2 h and require little or no post-sterilization aeration.

CyclO₃ss Medical Systems, Salt Lake City, UT, has developed an ozone system for sterilization of rigid endoscopes and many endoscope accessories. The SterO₃-Zone 100 uses a modular container/chamber system in which a rigid aluminum sterilization container serves as the primary sterilization chamber. The rigid container is placed inside a stationary master chamber and connected to feed gas lines with special fittings. Following a 40–60-min sterilization cycle at ambient temperature, the ozone is catalytically converted to oxygen and the container can be removed for transport or stor-

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age of the sterile instruments. The Ster-0₃-Zone 100 requires no cooldown or degassing of the instruments before handling or use and is supplied with multiple sterilization containers. This system is currently awaiting FDA 510K approval to market (11).

Materials compatibility is the major concern with using ozone as a sterilant. The highly reactive nature of ozone gas will cause irreversible damage to many plastics and rubber materials such as polypropylene and latex. Paper and Tyvek packaging materials are also subject to degradation in longer exposure cycles. With stainless steel instruments and rigid metal containers however, materials corrosion is not an issue. Penetrability and the requirement for high chamber humidity (75–95% RH) are additional limitations of ozone sterilization. Despite the fact that ozone occurs naturally and is self-destructing, there are OSHA requirements for both the Permissible Exposure Limit (0.1 ppm per 8-h time weighted average) and Short Term Exposure Limit (0.3 ppm).

Peracetic acid

Peracetic acid (or peroxyacetic acid) in both aqueous and aerosol forms has been widely used in the food industry as a disinfectant. It has been applied as a hard-surface sanitizer in the dairy and beverage industries and as a spray to control mold growth on fruits and vegetables. Peracetic acid has also been used for kidney machine sterilization and dialyzer reprocessing in several European countries for more than 20 years. Minntech Corp., Minneapolis, MN, currently markets a peracetic acid-based product for dialyzer reprocessing. Peracetic acid is currently listed by the Centers for Disease Control and Prevention (CDC) as both a high-level disinfectant and as a chemical sterilant.

Chemically, peracetic acid is the equilibrium mixture of hydrogen peroxide, peracetic acid, and acetic acid. In concentrated form (>30% solution), peracetic acid is corrosive with a characteristic pungent odor but is essen-

tially odorless when diluted to actual use concentration (0.2%). The concentrates of peracetic acid contain stabilizers that allow for safe transport and storage, but diluted solutions have limited storage stability. Although concentrated peracetic acid is irritating to the skin and mucous membranes, the compatibility limit on human skin is 0.4%, which is generally higher than use concentrations. Peracetic acid is biodegradable and decomposes into oxygen, water, and acetic acid (12).

Interest in the use of peracetic acid for healthcare applications was broadened in 1988 with the introduction of a sterilizer developed by the Steris Corp., Painesville, OH. The Steris tabletop unit is designed for sterile processing of immersible diagnostic and surgical instruments. The peracetic acid sterilant is supplied in concentrated form in sealed, single-use containers that also accommodate powdered corrosion-inhibiting and buffering chemicals. The use concentration of peracetic acid in the system is 0.2%. Following exposure to the 0.2% aqueous peracetic acid solution, the processed items are rinsed with filter sterilized water and then flushed with sterile air. The unit operates at 50–55°C and has a total cycle time of less than 30 min. Removable processing containers are also available which facilitate the transport of processed items (13).

Although several patents have been filed in recent years describing the use of peracetic acid vapor for sterilization of medical devices, the peracetic acid vapor phase described in the AbTox process is the only known application of this technology used in the medical field.

The limitations of peracetic acid in solution are those inherent with any aqueous system: restriction to immersible items and maintenance of the sterile condition. At present, there is no biological indicator available that has been designed for the monitoring of liquid sterilization systems. Materials corrosion is also a concern. Vapor phase peracetic acid may have the po-

tential to circumvent these limitations but very little information is available pertaining to actual use of peracetic acid vapor as a sterilant for medical devices.

Existing low-temperature sterilization technologies

Ionizing radiation

Ionizing radiation consists of high-frequency bundles of energy. These forms of high energy are capable of modifying the ionic balance in the microbial cell and consequently destroying its viability without an appreciable rise in temperature. Sterilization of medical devices with ionizing radiation provides a wide choice of product and packaging materials. The gas permeability concerns with EO and other gases for packaging are negligible and the low processing temperatures allow most heat-sensitive materials to be used.

Gamma and electron beam ionizing radiations systems are the two types commercially available. Both of these processes are limited to industrial installation only due to the high capital equipment costs, installation space requirements, and government regulations required for these systems. Gamma irradiation uses Co⁶⁰ or cesium¹³⁷ as the radioactive source. Since these materials are in a constant state of decay they must be periodically replaced, which creates supply and disposal concerns. Electron beam radiation, on the other hand, is produced by either dc accelerators or microwave linear accelerators; consequently the radioactive source can be shut off when not in use. In 1991, there were an estimated 170 industrial gamma irradiators in 45 countries (14). While electron beam sterilization has cost and materials compatibility advantages over gamma irradiation, there are only about 30 electron beam sterilization facilities in operation in 10 countries (15). Overall, an estimated 50% of single-use medical devices are sterilized with ionizing radiation.

Ethylene oxide (EO)

Despite negative publicity in recent times, EO will continue for many years to be the method most often selected by healthcare institutions for sterilization of temperature-sensitive medical devices (16). The long-awaited results of the study conducted by NIOSH did not show an increase in any of the diseases monitored as a result of exposure to EO (17). These findings, however, do not minimize the need to control EO exposure and emissions. This awareness has led to many advances in both EO sterilization equipment and worker training to make EO sterilization an ever safer and more reliable process.

EO emission control devices are now available for virtually every type of EO sterilizer. These devices convert EO into carbon dioxide and water or ethylene glycol, depending on the system used. Ethylene oxide recovery systems are also available and may be economically feasible for large-volume EO users. Systems have been developed that claim more efficient removal of EO from the chamber following sterilization, thereby minimizing the potential for worker exposure and shortening aeration times (18). Portable or fixed EO monitoring devices can be used to provide a continuous real-time monitoring of the work area, thus assuring adequate ventilation. Personal EO monitoring devices, or badges, can be used to monitor actual work shifts and individual practices.

A separate but related EO emissions issue is that of chlorofluorocarbons (CFCs), which cause destruction of the earth's stratospheric ozone layer. Although CFCs are not an integral component of the EO sterilization process, they are used as a flame retardant in 88-12 (88% CFC 12% EO) sterilizers. Drop-in CFC replacements (HCFCs) are expected to be available in 1994, but these new substitutes are considered only an interim solution to the CFC problem and will also be expensive (19). Mixtures of EO and carbon dioxide are being developed and should be ready for use in 1994. One

hundred percent EO systems using a single-dose cartridge have been available for many years and represent a safe, reliable alternative to EO gas mixtures.

Glutaraldehyde

Glutaraldehyde solutions have been used in healthcare for more than 20 years. Glutaraldehyde is considered a chemical sterilant, but its primary use has been as a high-level disinfectant for soaking trays or in automated washer/disinfectors. It is a severe eye irritant and a moderate skin irritant and so must be used with caution and proper ventilation. Other limitations of glutaraldehyde include its restriction to immersible items, the need for adequate rinsing, and the issue of transfer and storage of processed item.

Conclusions

Although all of the new technologies offer intriguing possibilities for future low-temperature sterilization needs, none of them are predicted to have the same broad application as EO. Most likely the new technologies will occupy niche areas of use in healthcare institutions such as endoscopy or dental practice where quick turnaround of instruments is essential but broad application is not required. It is unlikely that any of the new technologies described will find broad use in industrial sterilization, although there will be niche applications in industry as well. As developmental activities continue, improvements in many of the low-temperature sterilization technologies are likely. Today, EO remains as the only proven method for sterilization of temperature-sensitive devices within healthcare institutions. ■

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Received for review June 8, 1993.

Accepted July 19, 1993.

Presented at the 1993 TAPPI Polymers, Laminations and Coatings Conference.