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The Myths of Sterilant Gas Safety Exposed

Sterilization is of vital importance in healthcare and while steam and heat provide reliable service for the majority of medical supplies, chemical sterilants and especially gas sterilants are the main methods used for those medical devices and supplies which are heat- and moisture-sensitive.

The gold standard in sterilant gases is ethylene oxide (EtO) which is a very efficient sterilizing agent and has excellent penetrating powers enabling it to penetrate fine lumens, and diffuse into packages. Ethylene oxide is compatible with most materials used in medical devices and so has widespread applicability. Ethylene oxide however, has three principle downsides:

1. EtO is flammable from the lower explosive limit of 3 percent all the way up to 100 percent toxic.
2. EtO is hazardous, both toxic and a known human carcinogen (IARC class I)[2]
3. EtO requires long aeration times until the off gassed EtO is at safe levels, which limits the throughput of the sterilizer.

Several new gas sterilization technologies have been developed that promise greater throughput and greater safety. The most popular alternative is Advanced Sterilization Products' Sterrad®[3] line of hydrogen peroxide gas plasma sterilizers. These sterilizers offer a cycle time of about an hour and the most recent Sterrad® NX has a total cycle time of only 28 minutes[4] compared with a typical 12 to 14 hours for EtO sterilization. TSO3, a Québec-based company, has recently received FDA approval for an ozone-based sterilizer, the 125L, which has a cycle time of 4.5 hours. These newer technologies compete against EtO on the basis of increased throughput and greater safety. Several myths have arisen regarding the use of these alternatives to EtO and this report will attempt to answer them.

Myth 1: *Hydrogen peroxide and ozone are much safer than EtO.*

Sterilant chemicals are designed to kill all life, whether within or without the sterilizer and therefore chemicals that are used in a sterilizer will cause harm to humans who are exposed to them. The current sterilant gases fall into two main modes of action, alkylation or oxidation. EtO is a alkylating agent that reacts with nucleic acids which prevents normal cellular metabolism and thus destroys the microbe. Many alkylating agents are known to be mutagenic and carcinogenic. Hydrogen peroxide and ozone are strong oxidizing agents as is shown in Table 1 and they destroy the microbe through oxidation.

Table 1. Electrode Potentials of Oxidizing Sterilant Gases[5]

Sterilant Gas	Redox Couple	E vs. SHE
Hydrogen Peroxide	$H_2O_2 + 2H^+ + 2e \Leftrightarrow 2H_2O$	1.776
Ozone	$O_3 + 2H^+ + 2e \Leftrightarrow O_2 + H_2O$	2.076 V
Chlorine	$Cl_2 + 2e \Leftrightarrow 2Cl^-$	1.358

Organizations such as the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH) have spent considerable effort in assessing the hazards of various gases and have developed exposure limits based on the determined health risks. The toxicity of the sterilant gases can be compared to other common toxic gases by their OSHA-permissible exposure limits (PELS) and NIOSH-issued Immediately Dangerous to Life and Health levels (IDLH).

Table 2. Hazards of Gaseous Sterilants

Chemical Name	Chemical Formula	OSHA PEL (ppm)[6]	NIOSH IDLH (ppm)[7]
Ozone	**O_3**	**0.1**	**5**
Phosgene	$Cl_2C{=}O$	0.1	2
Chlorine	Cl_2	1(Ceiling)	10
Formaldehyde	$H_2C{=}O$	0.75	20
Hydrogen Peroxide	**HOOH**	**1.0**	**75**
Ethylene oxide	**CH_2OCH_2**	**1.0**	**800**
Hydrogen cyanide	HCN	10	50
Carbon monoxide	CO	50	1,200

Hazards from toxic gases can be considered as acute (short-term effect upon exposure to a large concentration) and chronic (impact of a long-term exposure). The NIOSH IDLH represents a measure of the acute hazard. The IDLH is defined by OSHA as an atmospheric concentration of any toxic, corrosive or asphyxiant substance that poses an immediate threat to life or would cause irreversible or delayed adverse health effects or would interfere with an individual's ability to escape from a dangerous atmosphere.[8]

From Table 1, it can be seen that whereas the IDLH of ethylene oxide is 800 ppm, the IDLH of hydrogen peroxide and ozone are 75 ppm and 5 ppm respectively. If there were a mechanical failure in a sterilizer and there were a leak that released 100 ppm of gas into the air, and if the gas were ethylene oxide, anyone present may not even notice it immediately since the odor threshold is around 500 ppm.[9] If the gas were hydrogen peroxide or ozone, then people in that immediate area would have severely stinging eyes, respiratory and other immediate problems and at that concentration, an individual's ability to escape may be impaired.

The original OSHA PELs were taken from the Threshold Limit Values (TLVs) developed by the ACGIH. This organization defines the TLV as a time-weighted average; the concentration of a substance to which most workers can be exposed without adverse effects. The TLV (and OSHA PEL) for EtO used to be 50 ppm, but as more information became available about its carcinogenicity the level was reduced in 1984 to the current 1 ppm.[10] The OSHA PEL for hydrogen peroxide has always been 1 ppm since OSHA adopted the ACGIG TLVs. Thus the overall magnitude of harm from chronic exposure to ethylene oxide is now believed to be similar to hydrogen peroxide.

This equality does not mean that a hydrogen peroxide burn is the same as a cancer tumor, but rather the equality should be understood in terms of the risk of harm. For EtO, the potential harm is severe (i.e. cancer) but the probability of developing that harm upon exposure is small. For hydrogen peroxide, the harm is much less but the probability of harm occurring upon exposure to a strong oxidant is much higher. For ozone, the OSHA PEL is only 0.1 ppm, thus the risk of harm is one-tenth that of exposure to either EtO or hydrogen peroxide.

Therefore, it can be seen that the overall risk of exposure to hydrogen peroxide and ozone is not less than the risk of exposure for EtO for either acute exposure or for chronic exposure. For acute exposure, the concentration at which either ozone or hydrogen peroxide become hazardous is much less than for EtO. For chronic exposure, the concentration at which hydrogen peroxide is considered hazardous is similar to that of EtO, but the concentration for ozone is one-tenth that of EtO.

Myth 2: *There are no OSHA regulations for hydrogen peroxide or ozone.*

Many people believe incorrectly that there are no regulations for hydrogen peroxide or ozone. It is perhaps worth taking a moment to review the regulatory structure in the United States. In 1970 Congress passed the Occupational Health and Safety Act which, among other things, created OSHA, authorized it to promulgate workplace safety regulations, and imposed a legal duty on employers to provide a safe workplace.

SEC. 5. Duties

(a) Each employer —
  (1) shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees;
  (2) shall comply with occupational safety and health standards promulgated under this Act.

(b) Each employee shall comply with occupational safety and health standards and all rules, regulations, and orders issued pursuant to this Act which are applicable to his own actions and conduct.

Employers are required to identify risks and mitigate the risks so as to create a safe work environment and employees are required to follow the safety rules and regulations. Some sterilants such as peracetic acid are not currently regulated by OSHA, but the employer has an affirmative duty to identify the risks and ensure that there is a safe work environment. Thus an employer using peracetic acid must identify the risks of peracetic acid and ensure through various means that the employees are not exposed to unsafe concentrations of peracetic acid. For many common gases and vapors OSHA has issued regulations to limit their exposure. As discussed above, OSHA adopted the ACGIH TLV values for its permissible exposure levels for many chemicals. OSHA regulation 29 CFR 1910.1000 states that:

> 1910.1000(a)(2)
> Other substances — 8-hour Time Weighted Averages. An employee's exposure to any substance in Table Z-1, the exposure limit of which is not preceded by a "C", shall not exceed the 8-hour Time Weighted Average given for that substance any 8-hour work shift of a 40-hour work week.

The appendix to this section Z-1 lists individual gases and their permissible exposure limits including hydrogen peroxide and ozone.

TABLE Z-1. - LIMITS FOR AIR CONTAMINANTS[11]

Substance	CAS No.	ppm	mg/m3
Hydrogen peroxide	7722-84-1	1.0	1.4
Ozone	10028-15-6	0.1	0.2

Thus there are OSHA regulations for both hydrogen peroxide and ozone. Some gases, notably commonly-used carcinogens such as formaldehyde and ethylene oxide, have more extensive regulations. EtO and formaldehyde are in sections 1910.1047 and 1910.1048 respectively. OSHA does not require continuous gas monitoring for any of the sterilant gases because the agency has a policy of setting the goal but not defining the means to the goal. The reason for this policy is to avoid regulations becoming obsolete as technology marches forward and to ensure that the regulations apply across all applicable workplaces. For example, the same regulations apply to a hospital using hydrogen peroxide for sterilization and a titanium mill using hydrogen peroxide as a component in its pickling tanks to remove mill scale from 20-ton ingots. The regulatory requirement is that an employee's exposure must not exceed the PEL and the legal burden is on the employer to ensure the regulation is met, by appropriate means. These means may include use of substitute chemicals, changes in work practices, engineering controls and continuous monitoring etc. The means employers must demonstrate that the workers' exposure is below the PEL and the burden is on the employer.

Therefore, while EtO has its own section along with other commonly used carcinogenic compounds, hydrogen peroxide and ozone are also directly regulated by OSHA in section 1910.1000. Even those compounds not listed are indirectly regulated because the general duty clause in the OSHA Act imposes a burden on employers to provide a safe workplace and OSHA can and has prosecuted employers under this general duty clause.

Myth 3: *Sterilizers never leak.*

While everyone may wish this myth were true, unfortunately the evidence suggests it is not. Again, the simplest approach is to consider the overall risk as comprising the harm caused by failure and the risk of the failure. For a sterilizer, the harm caused by failure from a workplace safety standpoint is exposure of workers to toxic gas or vapors and this has already been discussed above. The next step is to review the risk of the toxic vapors being released. The risk of leakage from a sterilizer depends in part on the concentration of sterilant gas in it during the sterilization cycle. 3M's XL 5 EtO sterilizer is a good example of an EtO sterilizer. It uses 96 g of EtO, filling a chamber size of 160 l, at an operating temperature of 37 degrees C[12] which at atmospheric pressure corresponds to an EtO concentration of about 9 percent.

The ASP Sterrad 100S injects 1.8 ml of 59 percent hydrogen peroxide into a chamber volume of 170 l, which is estimated to be equivalent to a 10 percent hydrogen peroxide vapor at atmospheric pressure and similarly the TSO3 125L sterilizer employs ozone concentration of 60 to 85 mg/l[13] which is equivalent to nearly 4 percent ozone at atmospheric pressure. It should be noted that the Sterrad and 125L sterilizers are designed to operate at reduced pressure which improves their safety since any leaks will tend to be in rather than out.

For all of these sterilant gases, the concentration in the sterilizer is in the low percent concentration range and 1 percent by volume corresponds to 10,000 ppm. It would not take much of a gas leak to produce an outside concentration around 1 ppm. The next question is whether there have been any leaks of sterilant gas from sterilizers. There have been several studies of leakage from EtO sterilizers. One study in Massachusetts documented that two-thirds of the responding hospitals (58 of 90) had reported evacuations of the sterilization department or area in response to a real or suspected EtO leak or an EtO alarm at some time during 1985 to 1993. Fifty percent of EtO-using Massachusetts hospitals (46 of 92) reported accidental releases during this period and 33 percent (32 of 90) reported accidental releases during the period of 1990 to 1992. A related survey of medical surveillance providers conducted as part of the Massachusetts Hospital EtO Health and Safety Study produced data suggesting that one or more workers at 19 percent of EtO-using Massachusetts hospitals had experienced EtO-related health effects during the time period covered by the survey.[14] From the data available, EtO sterilizers can and sometimes do leak, posing a risk for personnel nearby.

This result is supported by data from OSHA's IMIS database which contains 25 records of incidents occurring between 1990 and 1996 that involved accidental exposure to EtO used in sterilization operations. Three of these accidents resulted from the use of incorrect work practices, nine occurred during sterilant gas tank changing, and 13 were the result of

sterilizing equipment failures. These 25 incidents involved a total of 73 workers.[15] There is much less data available for hydrogen peroxide and ozone sterilizers and to our knowledge, there have been no systematic studies of these sterilization technologies. While the ozone sterilizer is still a recent addition to the sterilization business, the Sterrad line of sterilizers has seen over a decade of service. In that time it has acquired a very good safety record, with no serious injuries reported. There have however been many minor injuries, most due to burns on the hand caused by residual hydrogen peroxide and several cases of exposure to hydrogen peroxide vapors and/or oil mists resulting in stinging eyes and respiratory tract etc.[16] The Sterrad sterilizers include a catalyst to break down any residual hydrogen peroxide in the exhaust to oxygen and water. However, if oil from the catalyst gets contaminated with oil mist from the vacuum pump then the catalyst will not function correctly. We are aware of at least case, where this failure mode resulted in release of hydrogen peroxide vapor. It is not difficult to see how oil vapor could lead to emission of the sterilant gas. In both the Sterrad and TSO3 sterilizers a catalyst breaks down any residual hydrogen peroxide or ozone respectively in the exhaust gases. Advanced Sterilization Products report that the exhaust gases from a fully functioning Sterrad will contain less than 0.1 ppm of hydrogen peroxide and TSO3 report that the 125L will emit less than 0.02 ppm ozone in its exhaust.[17] The efficiency of these catalysts is very impressive, using the 125L as an example, the catalyst efficiency is very high, around 99.99995 percent.[18] However, it would only take a very small decrease in the catalyst efficiency (~ 0.01 percent) to have an ozone output equal to the PEL. As a general rule catalyst systems lose activity with time, due to contamination to deactivation of the catalytic sites; thus showing the importance of regular maintenance to keep the sterilizer operating safely.

As of the time of writing, there are more than 50 ChemDAQ Inc. hydrogen peroxide monitors providing protection from leaks from hydrogen peroxide gas plasma sterilizers and customers often report significant hydrogen peroxide concentrations near their sterilizers, especially when the door is opened. The customer usually corrects these problems by having the sterilizer serviced. While this evidence is anecdotal, it does show that hydrogen peroxide gas plasma sterilizers, as with any other piece of complex equipment, needs to be maintained properly if it is to perform to its specification.

In conclusion, sterilizers can and sometimes do leak. Studies have shown significant incidences of leakage with EtO sterilizers and there are documented cases of hydrogen peroxide vapor being emitted from Sterrads. So far, the author is not aware of any reports of leakage from ozone sterilizers, but ozone sterilizers are still a very new technology and there are only a handful of sterilizers in service in hospitals. There is no reason to believe that the ozone sterilizers while made to the same high standards employed by the manufacturers of other gaseous sterilizers, will not be subject to the same susceptibility to wear and tear, aging and user error as occurs with the other sterilizers.

Myth 4: *Hydrogen peroxide is as safe as mouthwash.*

Many people have small brown bottles of 3 percent hydrogen peroxide in their bathrooms and some brave souls even use it for mouthwash. While the hydrogen peroxide in the brown bottles is chemically the same as is used in sterilization, the key difference is concentration. Concentration is the most critical factor in toxicology. Many things are harmless or useful at low concentration, only to become dangerous at high concentration (e.g., glass of red wine versus alcohol poisoning). Another good example is chlorine (Cl2) usually used as sodium or calcium hypochlorite (NaOCl). The addition of small amounts of chlorine to disinfect drinking water has probably had a greater impact of human health than any other innovation. However, drinking concentrated sodium hypochlorite solution (aka bleach) would be very unpleasant and potentially fatal. Hydrogen peroxide is a strong oxidant and at low concentrations (3 percent) it has disinfectant properties and is generally considered harmless with normal use; though the Agency for Toxic Substances and Disease Registry states that "inhalation of household-strength hydrogen peroxide (3 percent) can cause respiratory irritation.

Exposure to household strength hydrogen peroxide can cause mild ocular irritation. Inhalation of vapors from concentrated (higher than 10 percent) solutions may result in severe pulmonary irritation… eye exposure to 3 percent hydrogen peroxide may result in pain and irritation, but severe injury is rare. More concentrated solution may result in ulceration or perforation of the cornea. Skin contact can cause irritation and temporary bleaching of the skin and hair. Contact with concentrated solutions may cause severe skin burns with blisters.[19] For comparison, the stock solutions for the Sterrad hydrogen peroxide gas plasma 100S sterilizers is nominally 59 percent and the Sterrad NX internally concentrates the solution to around 90 percent to increase its sterilization efficacy. The Sterrads use high concentrations of hydrogen peroxide in order to effectively sterilize the load. If three percent hydrogen peroxide were used instead, it would not be effective. The hydrogen peroxide used in a medical sterilizer is not mouthwash.

Myth 5: *If a sterilant is good for the environment, it must be safe for me.*

Frequently people relate environmental pollutants to human health hazards, and this correlation is often true, for example lead, chromium, PCBs, etc., are all environmental pollutants that can cause severe health effects in exposed people. The principle feature about these compounds though is their long residence time in the environment. Lead and chromium for example are elements and so cannot be destroyed, PCBs are very stable chemicals and so persist in the environment for a long time (years). Ozone and hydrogen peroxide are very reactive substances, otherwise they would not be much good as sterilants and if released into the environment, they rapidly either react with something in the environment or decompose to harmless biproducts.

Ozone decomposes to produce oxygen:

$$2O3 \Rightarrow 3O2$$

Hydrogen peroxide decompose to product oxygen and water:

$$2H_2O_2 \Rightarrow 2H_2O + O_2$$

This high reactivity means that hydrogen peroxide and ozone do not last long in the environment and so they are generally not considered to be environmentally harmful. Therefore the aggressiveness of ozone and hydrogen peroxide make them efficient sterilants, and severe irritants to anyone exposed, but they are both very environmentally friendly materials. Environmental safety is not the same as personal safety.

Myth 6: *Small ozone leaks are OK because ozone freshens the air.*

Many ozone generators are marketed to consumers touting the benefits of ozone including reducing odors, freshening the air and promoting health. Ozone is as strong oxidant and will destroy many odor causing chemicals and serves as a commercial disinfectant in for example water supplies, but these applications only use ozone under conditions where personal exposure is avoided. The same strongly oxidizing properties of ozone that make it useful as a bleaching agent and sterilant, make ozone hazardous to human health, as was discussed above. Several federal agencies have set exposure limits for ozone, including OSHA (0.1 ppm 8 Hr PEL), NIOSH (recommended exposure limit is a ceiling of 0.1 ppm), EPA ambient air (0.75 ppm, National Ambient Air Quality Standards for Ground-level Ozone, eight-hour time weighted average). The Environmental Protection Agency has studied the use of ozone generators for consumer-level odor control and came to two main conclusions.[20] The first is that many ozone generators targeted at consumers were producing ozone levels that exceeded safe levels and therefore posed a health risk to users. The second conclusion is that ozone at concentrations low enough to be safe is ineffective at reducing odor.

The Food and Drug Administration (FDA) has reviewed ozone and came to the following conclusion: (a) Ozone is a toxic gas with no known useful medical application in specific, adjunctive, or preventive therapy. In order for ozone to be effective as a germicide, it must be present in a concentration far greater than that which can be safely tolerated by man and animals. [21 CFR801.415].

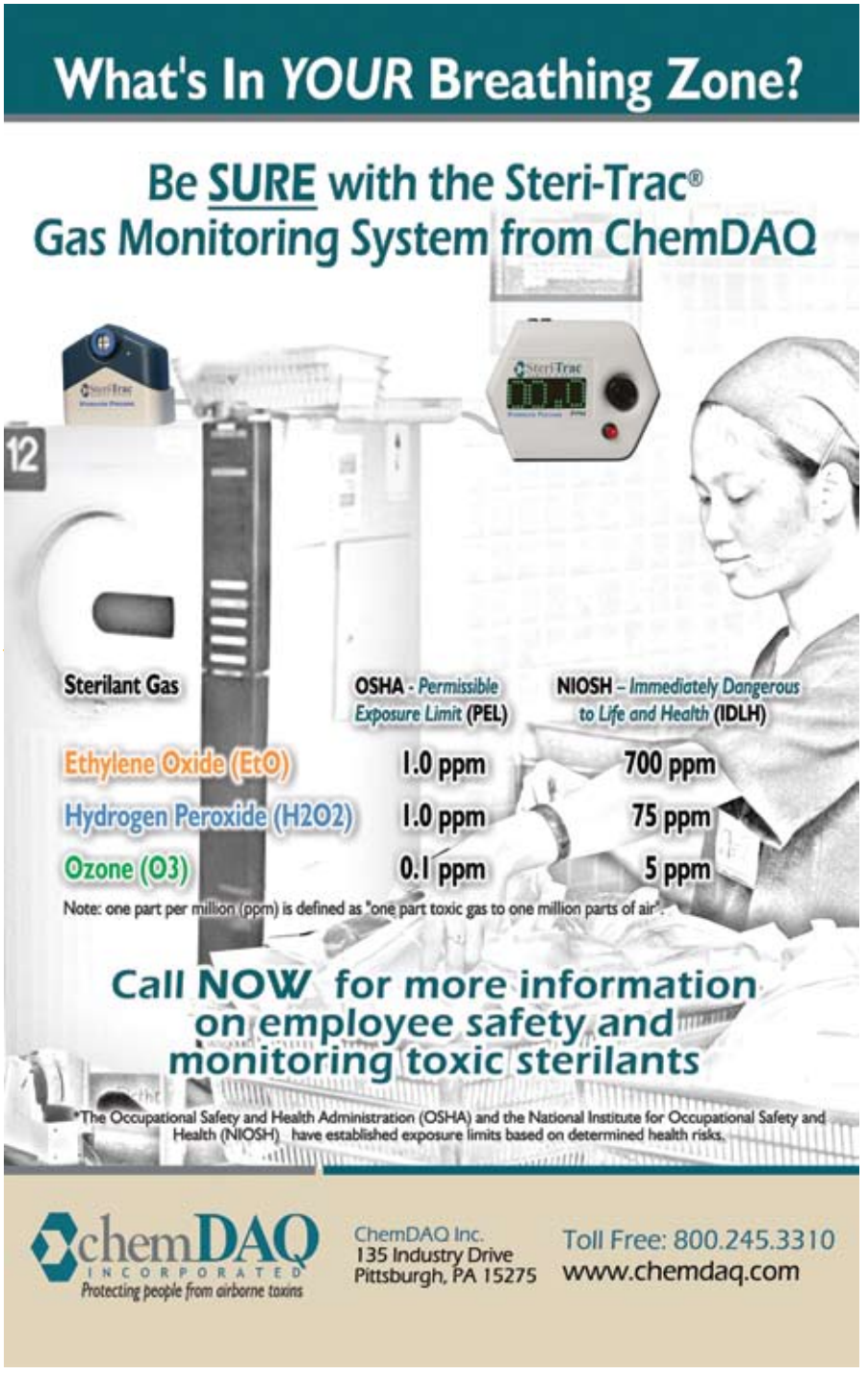
In 1995 the FTC took action against the manufacturers of some ozone generators because their claims were unsubstantiated.[21] Therefore, these devices offer no benefit and the American Lung Association and many local health departments recommended not using them.[22,23] The overwhelming conclusion of these various government agencies is that ozone is a toxic gas, with no health benefits in the atmosphere near ground level. Small emissions of ozone that approach the OSHA PEL should be detected and corrected.

Myth 7: *I don't need a sterilant gas monitor because I will smell the gas if it leaks.*

For ethylene oxide, the odor threshold is around 500 ppm[24] and thus EtO is not even perceptible until it is 500 times the OSHA eight-hour PEL. Therefore odor cannot be used to detect the presence of ethylene oxide leaks unless they far exceed the OSHA PEL. For hydrogen peroxide, there is no published odor threshold, and even 100 percent hydrogen peroxide is reported to have almost no odor.[25] The odor threshold is thus well over times the OSHA PEL of 1 ppm and over the IDLH of 75 ppm. The Agency for Toxic Substances and Disease Registry states that "Inhalation of vapors, mists, or aerosols from concentrated solutions of hydrogen peroxide can cause significant morbidity. Because it is nearly odorless and nonirritating except at high concentrations, persons may not be aware of its presence. No odor threshold was located for hydrogen peroxide (the OSHA PEL is 1 ppm). Detection of odor does not provide adequate warning of hazardous concentrations."[26]

Therefore as for ETO, odor does not provide a means to detect hydrogen peroxide leaks unless the concentration greatly exceeds OSHA PEL. Ozone in contrast, has a distinct odor which can be detected at low concentrations 0.01 to 0.05 ppm[27] which is below the eight-hour OSHA PEL of 0.1 ppm.[28] However, odor is not a reliable indicator of ozone concentration or warning that potentially hazardous concentrations of ozone are present since there are wide variations in the lower concentration detection limit between individuals and additionally olfactory fatigue occurs (i.e. the ability to smell ozone is lost quickly as exposure continues).[29] Thus if the ozone concentration slowly increases as may occur for a leak, it may not be possible to detect the ozone until the concentration exceeds safe levels. Hence, perceived odor is not a reliable indicator of ozone's presence.[30]

For all three sterilant gases, the odor threshold is either far above the OSHA PEL or the odor is an unreliable method for detecting the presence of the gas because the gas numbs the olfactory senses. The only reliable method to detect the unexpected presence of these sterilant gases in time to prevent exposure exceeding the OSHA PELs is some form of continuous monitor. Continuous monitors are available for all three sterilant gases from several manufacturers.



Conclusion

While EtO remains the gold standard of sterilization, the newer technologies, especially hydrogen peroxide gas plasma, and more recently ozone, offer significant improvements in throughput time. Though these two sterilant chemicals are not known human carcinogens like EtO, they are both strong oxidants and severe irritants resulting in regulated exposure levels the same or less than EtO respectively. While there is no reason to doubt that the manufacturers of the sterilizers use the highest engineering standards, any complex equipment is subject to the effects of wear and tear, aging or misuse and leaks can and for EtO and hydrogen peroxide are known to have occurred. Since none of the three sterilant gases can be reliably detected by odor at safe levels, some form of continuous monitoring is required to ensure that users are not exposed to potentially hazardous levels of these three sterilant gases. Suitable continuous monitors for sterilant gases are available from several manufacturers. ICT

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