AGA Linde Healthcare

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane
Room 1061
(HFA-305)
Rockville, MD 20852

01 JUN 25 P1:50

Docket No. OID-0193

June 11, 2001

Dear Sir/Madam:

As instructed in the referenced docket, here are my comments and suggestions.

COMMENT 1:

-section I part C definitions (Page 3)

A definition for **diffusion challenge** should be added not only to the definitions section, but this concept should pervade all thinking in regard to sterilization. There is little value to a sterilization process which can not successfully penetrate to the places in the load where the microorganisms exist. Likewise any biological indicator which fails to address the concept of diffusion challenge, also most likely fails to provide adequate sterility assurance. The degree of sterility assurance possible from biological indication is only as good as the diffusion challenge's ability to simulate the most difficult to reach microorganisms.

SUGGESTION 1:

The definition proposed for addition:

"Diffusion Challenge: Means to present a purposefully difficult penetration path for the sterilant to contact the BI spores. This concept includes; placing the BI inside a syringe or other restricted entry orifice device; sealing the BI and syringe in a pouch or bag of identical materials, construction and sealing method as those bags or pouches used for items in the load; and BI placement deep within the load. Practiced in order to simulate the difficulties sterilants may have in penetrating the various items and packagings to reach microorganisms deep within the load."

COMMENT 2:

-section III part H Efficacy Data

I strongly agree with this comment, and add the observation that viable spore populations in the BI are critical. I further submit the attached publications as background for the criticality of this parameter validation in consideration of 510(k) clearance, as some of the authors have apparently researched this very issue and have made some interesting observations if not outright conclusions.

I am further curious as to what subsequent actions or inquiries FDA has made regarding the questions posed in these publications for the BI involved with the hydrogen peroxide plasma method. I am unaware whether the manufacturer may have made modifications to their BI or sterilization process or equipment subsequent to these publications, and would appreciate any information you can furnish.

OID-0193

C1

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COMMENT 3:

-Section III part J 2 Test Packs and section III part J3 Throughput Process Indicators

I strongly agree with the positions articulated in these sections and in the Appendix I checklist. Previously, certain manufacturers may have overlooked these issues. In particular, there seemed at one point to be little similarity of BI diffusion challenge or spore resistance for their new process BI as compared to those for ethylene oxide. Additionally, there were chemical indicators in use, which exhibited color change after exposure to fluorescent light in the absence of the sterilant.

The attached publications detail these concerns as expressed by the various authors.

Respectfully Submitted,

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Attachments:

1. Koller W, Lessky E: Microbiological Test Results and Observations with a Hydrogen Peroxide Plasma Sterilizer. *Zentral Sterilisation.* 1996: 4(2): 79-87.
2. Kramer A: News Update. *Hyg Med.* 1995: 20: 52-53 (in German)
3. Mecke P, et al: On the Efficacy and Validation of H_2O_2 Sterilizers. *Zentral Sterilisation.* 1993; 1(6): (in German)
4. MacNeal J, Glaser Z: Comparison of Health Care-Based Sterilization Technologies: Safety, Efficacy and Economics. *Journal of Healthcare Safety, Compliance & Infection Control.* 1997: 1(2): 91-107.

W. Koller* und E. Lessky

Mikrobiologische Ergebnisse und Beobachtungen mit einem H_2O_2-Plasmasterilisator[1]

Das untersuchte Wasserstoffperoxid-Plasmaverfahren konnte auf Mattglas die Sporen von Bacillus subtilis, Bacillus stearothermophilus und Aspergillus niger in allen untersuchten Proben um mindestens 6,0 log-Stufen reduzieren. Bei Verwendung von Kunststoff-Keimträgern mit flachen Vertiefungen (Näpfchen) wurde dagegen dieses Ziel bei mehr als einem Viertel der Proben verfehlt.
Die Keimtötung in langen, dünnen Lumina wurde hier nicht untersucht.
Die von uns gemessenen Prozeßtemperaturen waren deutlich höher als die vom Hersteller angegebenen.
Das untersuchte Gerät konnte mit gebrauchten, leeren Wasserstoffperoxid-Kassetten wie mit intakten betrieben werden.

Offene Fragen ergaben sich insbesondere hinsichtlich folgender Anliegen:
- Zuverlässigkeit der Verfahrenskontrolle (automatische Erkennung von Wirkstoffmangel)
- validierte Vorreinigung der zu sterilisierenden Güter
- zuverlässige biologische Prozeßkontrolle (das vom Hersteller angebotene Modell ist Gegenstand von Kritik)
- Definition von Materialien, die das Wirkprinzip zu stark belasten (nicht nur Papier und andere Zelluloseprodukte, sondern z. B. auch Latexgummi) oder die beschädigt werden (materialtechnische Analysen; Temperatursprünge an Kontaktstellen zwischen Metall und Kunststoff)

Es ist zu hoffen, daß diese Fragen im Zusammenwirken von Verfahrenstechnikern, Werkstoffspezialisten, Instrumentenherstellern und Hygienikern geklärt werden können. Dies ist die Voraussetzung dafür, daß ein Verfahrenstyp für die Wasserstoffperoxid-Plasmasterilisation definiert werden kann, der den heutigen Anforderungen an ein Sterilisationsverfahren standhält und daher für den praktischen Einsatz empfohlen werden kann.

1 Einleitung

Die wachsende Häufigkeit und Vielfalt von Instrumenten in der Medizin, die ganz oder teilweise aus hitze-, druck- und feuchtigkeitsempfindlichen Materialien her-

Prof. Dr. Walter Koller, Dr. E. Lessky, Hygieneinstitut der Universität Wien, Währinger Gürtel 18–20, A-1090 Wien

[1] Teile dieser Arbeit wurden am 13. Dosch-Symposium im Mai 1985 in Wien vorgetragen.

W. Koller* and E. Lessky

Microbiological Test Results and Observations with an H_2O_2 Plasma Sterilizer[1]

The tested hydrogen peroxide plasma sterilization procedure reduced spores of Bacillus subtilis, Bacillus stearothermophilus and Aspergillus niger on frosted glass slides by at least 6.0 log units in all samples tested. By contrast, when plastic carriers with shallow wells (cups) were used, reduction by at least 6 log units was not achieved in more than a quarter of the samples.
Reduction in long, narrow lumina was not investigated.
The operating temperatures recorded by us were considerably higher than those indicated by the manufacturer.
The test apparatus ran on empty hydrogen peroxide cartridges exactly as it did on intact cartridges.

Important points to be clarified are as follows:
- Reliability of process control (automatic recognition of empty cartridges)
- Validated precleaning of the items to be sterilized
- Reliable biological process control (the set provided by the manufacturer is open to criticism)
- Definition of materials that the active principle cannot cope with (not only paper and other cellulose products, but also latex rubber etc.), or that are damaged by the system (materials analyses; temperature differences at the contact points between metal and plastics)

It is to be hoped that these points can be clarified with the aid of process engineers, materials specialists, instrument manufacturers and infection control experts. This is the prerequisite for defining a procedure for hydrogen peroxide plasma sterilization which meets modern sterilization standards and can therefore be recommended for practical use.

1 Introduction

The increasing use and diversity of medical instruments made entirely or partly of materials resistant to heat, pressure and moisture brings with it a correspon-

[1] Parts of this paper were presented at the 13th Dosch Symposium, 18–19 May 1985, Vienna.

gestellt sind, erhöht den Bedarf an hierfür geeigneten Verfahren zur Desinfektion und Sterilisation. Die Entwicklung von Untersuchungs- und Behandlungsinstrumenten geht rascher vor sich als die Entwicklung zugehöriger Hilfsverfahren, z. B. solcher zur Sterilisation. Fortschritte der Medizin durch neue instrumentelle Verfahren werden von der Ärzteschaft oft schon als neuer Standard angenommen, wenn die Aufbereitungsverfahren noch keinen adäquaten Standard erreicht haben (1, 2, 3). Nicht selten bleiben solche Unvollkommenheiten wegen noch fehlender begleitender Qualitätssicherung zunächst unerkannt (5). Damit bleibt aber auch der tatsächliche Nutzen eines neuen instrumentellen Verfahrens unter dem angegebenen Wert. Als Beispiel sei die Entwicklung der Endoskopie und der Aufbereitungsverfahren für flexible Endoskope angeführt: Erst nach Vorliegen erdrückender Belege für die Auslösung von Infektionen durch eine Endoskopie (zitiert in 5, 6, 7, 8) war man bereit, auch entsprechende Summen in die Entwicklung adäquater Aufbereitungsverfahren zu investieren; dabei hatten Hygieniker von Anfang an betont, daß die von Herstellerseite ursprünglich als einzig vertretbar bezeichneten Aufbereitungsmethoden nicht dem Stand des Wissens entsprechen und ungenügend sind.

Keimtötungsverfahren mit Wasserstoffperoxid-Plasma sind als „neue Generation" von Sterilisationsverfahren für thermolabile Güter in der Diskussion. Niedrige Arbeitstemperatur, geringes Schädigungspotential für das Behandlungsgut, einfache Installation (nur Stromanschluß und Wasserstoffperoxid-Spender), geringer Energieverbrauch und das Fehlen schädlicher Abfallprodukte (11) sind Vorzüge dieser Technologie, die sie zu einem vielversprechenden Kandidaten machen. Wir hatten für eine limitierte Untersuchungsserie ein nach diesem Prinzip arbeitendes Verfahren zur Verfügung. Hier sollen unsere Befunde und Erfahrungen berichtet werden.

2 Material und Methoden

2.1 Untersuchtes Verfahren

Wir verwendeten einen Sterrad-100-Plasmasterilisator (Johnson & Johnson). Bei diesem Verfahren wird das Sterilisiergut in einer Faradayschen Kammer im Hochvakuum einer durch Hochfrequenz angeregten Wasserstoffperoxidgas-Atmosphäre (Wasserstoffperoxid-Plasma) ausgesetzt.

Die Betriebsmittel sind elektrischer Strom und H_2O_2. Dieses wird in Einzel-Ampullen in einer Kassette bereitgestellt; mit einer Kassette können 10 Sterilisierzyklen gespeist werden. Für die Behandlung von Instrumenten mit langen dünnen Lumina werden überdies sogenannte Diffusionsverstärker bereitgestellt: Dies sind H_2O_2-gefüllte Brechampullen mit Schaumstoff-Ansatz zum Aufstecken auf die Eingänge besagter Lumina. Derartige Adapter standen für unsere Untersuchungen nicht zur Verfügung.

ding need for procedures suitable for the sterilization and disinfection of such instruments. Instruments for diagnosis and treatment are being developed more rapidly than the corresponding accessories, such as sterilization systems. Advances in medicine made possible by new instrumental techniques are often adopted by physicians as a standard before the technologies to sterilize and disinfect these instruments have been properly developed (1, 2, 3). Not uncommonly, such inadequacies are not immediately recognized because of insufficient attention to quality assurance (5). The result is that the potential benefits of a given new instrumental procedure are not realized to the extent commonly declared. The development of endoscopy and processing technologies for flexible endoscopes are a case in point. A willingness to invest suitable sums of money in the development of adequate hygienic procedures did not become apparent until evidence of infection associated with endoscopy had amassed (cited in 5, 6, 7, 8) – despite the fact that hygiene experts had insisted from the beginning that the sterilization techniques advocated by the manufacturers were insufficient and did not correspond to the state of the art.

Microbicidal procedures using hydrogen peroxide plasma are being proposed as a 'new generation' of procedures for the sterilization of thermolabile materials. Low working temperatures, low risk of damaging the items to be sterilized, simple installation (all that is required is a power point and hydrogen peroxide supply), low energy consumption, and lack of harmful waste (11) are advantages of the technology that make it a promising candidate. We used a procedure based on this principle for a limited series of tests. Our results and observations are reported in this paper.

2 Materials and Methods

2.1 Test procedure

We used the Sterrad 100 plasma sterilizer by Johnson & Johnson. In this sterilization procedures the items to be sterilized are placed in a Faraday chamber with a high vacuum and are exposed to a high-frequency hydrogen peroxide environment (hydrogen peroxide plasma).

The system runs on electricity and H_2O_2. The latter is supplied in single ampoules in a cartridge. One cartridge is sufficient for 10 sterilization cycles. Diffusion adapters are supplied for the processing of instruments with long, narrow lumina. These are ampoules filled with H_2O_2 with a foam rubber attachment for placing in the openings of the lumina. Such adapters were not available for our tests.

Operating cycle:

1. Vacuum phase (high vacuum)
2. Injection phase (the ampoule is perforated, H_2O_2

Programmablauf:

Vakuumphase (Hochvakuum)
Injektionsphase (Ampulle wird perforiert. H_2O_2 verdampft in den Nutzraum)
Diffusionsphase (H_2O_2 verteilt sich im Nutzraum und diffundiert in Hohlräume)
4. Plasmaphase (H_2O_2-Dampf wird durch Hochfrequenz zu Plasma angeregt)
5. Belüftungsphase (Energiezufuhr und Vakuum werden abgebrochen, Luft strömt ein).

Die Gesamtdauer eines Sterilisierzyklus beträgt ca. 70 min.

Die Schritte des Programmablaufes sind im Gerät fest einprogrammiert und können vom Bediener nicht verändert werden. Auch wir konnten für den Zweck unserer Untersuchungen keine Variation einzelner Parameter erreichen.

2.2 Verpackungsmaterial für Sterilisiergut

Wir verwendeten papierfreie PE-Verbundfolie (luftdurchlässige Polyester-Folie).

2.3 Mikrobiologische Testmethoden

2.3.1 Testsporen

Testkeime dienten Sporen von:
Bacillus subtilis var. niger (ATCC 9372)
Bacillus subtilis (Stammsammlung des Hygiene-Instituts)
- *Bacillus stearothermophilus* (ATCC 7953)
- *Aspergillus niger* (Stammsammlung des Hygiene-Instituts)

Die Bacillus-Sporen wurden in sterilem 70%igem Ethanol, die Pilz-Sporen in sterilem destilliertem Wasser suspendiert.

2.3.2 Sporenpräparation

Die Präparation der Bacillus-Sporen erfolgte gemäß DIN 58948.

Die Pilz-Sporen wurden durch Abschwemmen einer Pilzkultur auf Sabouraud-Agar (SA) mit sterilem destilliertem Wasser gewonnen und durch sterilen Baumwollbatist filtriert.

2.3.3 Keimträger

Es wurde mit drei Arten von Keimträgern gearbeitet:
- Polyestergewebe 30 × 10 mm (Verpackungsfolie)
  Polystyrol-Platte mit 4 × 6 eingetieften Näpfchen (Ø 15 mm), dazu Deckel mit Belüftungsstegen
- Mattglasscheiben 40 × 40 mm

2.4 Präparation und Konditionierung der Keimträger

- Beladung mit je 0.1 ml Sporensuspension, bei Mattglasscheiben mit sterilem Glashaken auf einer Kreisfläche von ca. 25 mm verteilt

evaporates into the usable space)
3. Diffusion phase (H_2O_2 is distributed in the usable space and diffuses into hollow spaces)
4. Plasma phase (by applying high-frequency plasma is generated from H_2O_2 vapor)
5. Aeration phase (power supply and vacuum are turned off, air enters the system)

Each sterilization cycle lasts about 70 minutes.

The sequence of this cycle is programmed into the sterilizer and cannot be adjusted by the operator. Neither was it possible for us to adjust individual parameters for the purpose of our investigations.

2.2 Packaging of the items to be sterilized

We used paperless polyester (PE) wrap (air-permeable polyester).

2.3 Microbiological test methods

2.3.1 Test spores

The test organisms were spores from
- *Bacillus subtilis var. niger* (ATCC 9372)
- *Bacillus subtilis* (stock samples of the Hygiene Institute)
- *Bacillus stearothermophilus* (ATCC 7953)
- *Aspergillus niger* (stock samples of the Hygiene Institute)

The bacillus spores were suspended in sterile 70% ethanol. The fungal spores were suspended in sterile distilled water.

2.3.2 Spore preparation

The bacillus spores were prepared according to DIN 58948.

The fungal spores were obtained by elutriation of a fungal culture on Sabouraud agar (SA) using sterile distilled water and filtering through sterile cotton gauze.

2.3.3 Carriers

Three different kinds of carriers were used:
- Polyester fabric strip 30 × 10 mm (wrapper)
- Polystyrene plate with 4 × 6 shallow cup-shaped wells (Ø 15 mm) and lid with air inlets
- Frosted glass slides 40 × 40 mm

2.3.4 Preparation and conditioning of the carriers

- Loading with 0.1 ml of spore suspension. For the frosted glass, the suspension was spread onto the slides in a circular area of approximately 25 mm in diameter.
- Drying overnight in an incubator at a temperature of 52 °C.
- Wrapping in PE.

- Trocknen über Nacht bei 52 °C im Brutschrank
- Verpacken in PE-Verbundfolie

2.3.5 Sporen-Rückgewinnung nach Exposition der Keimträger im untersuchten Gerät

Die im folgenden beschriebenen Schritte wurden in einer reinen Werkbank durchgeführt.

PE-Gewebestreifen: Die Gewebestreifen wurden nach aseptischem Öffnen der Verpackung mit sterilem Werkzeug entnommen, in Röhrchen mit je 5 ml steriler Casein-Soya-Bouillon (CSB) übertragen und anschließend mit Hilfe eines Vortex-Rotationsschüttlers 10 s bei maximaler Umdrehungszahl geschüttelt. Anschließend wurde 1 ml Flüssigkeit zur quantitativen Kultur direkt plattiert. Für die Bacillussporen-Rückkultur wurde Casein-Soya-Agar (CSA) und für die Pilzsporen-Rückkultur Sabouraud-Agar (SA) verwendet. Die restlichen 4 ml wurden als Anreicherungskultur 7 Tage bei 35 °C *(B. subtilis* und *A. niger)* oder bei 56 °C *(B. stearothermophilus)* bebrütet.

Polystyrol-Näpfchen: Die Näpfchen wurden mit 2 ml CSB befüllt, und durch Rühren mit einem sterilen Glashaken wurde der Inhalt resuspendiert. 1 ml wurde zur Direktkultur ausplattiert (s. o.), 1 ml wurde in 4 ml CSB oder Sabouraud-Bouillon übertragen und als Anreicherungskultur 7 Tage bei 35 °C *(B. subtilis* und *A. niger)* oder bei 56 °C *(B. stearothermophilus)* bebrütet.

Mattglas: Die Mattglas-Keimträger wurden in eine sterile Petrischale gelegt, mit 2 ml CSB überschichtet und der Rückstand mit einem sterilen Glashaken resuspendiert. Die Kultivierung erfolgte wie oben angegeben.

2.4 Temperaturmessung

Zur Messung der Temperaturen wurden zwei verschiedene Verfahren gewählt:

a) Mit geeichten Maximalthermometern, die zum Schutz vor elektromagnetischen Wellen in dünnwandigen Metallbehältern untergebracht waren, wurden die Maximaltemperaturen an verschiedenen Positionen in der Kammer registriert. Dabei wurden die Meßwerte bei drei verschiedenen Beladungszuständen erhoben: Kammer leer, Kammer mit 1 kg

Tabelle 1 Maximaltemperaturen (° C) bei unterschiedlicher Beladung

Meßposition	Beladungszustand		
	leer	1 kg	3 kg
nahe Hinterwand li	63	61	55
nahe Hinterwand re	62	62	55
nahe Vorderwand li	63	61	58
nahe Vorderwand re	65	63	56
Zentrum	62	60	54
Kontakt zur Kammerwand	75	69	67

2.3.5 Spore recovery after exposure of the carriers in the test apparatus

The steps described below were performed on a ste work bench.

PE strips: The fabric strips were unpacked aseptica removed with sterile instruments, transferred to tul containing 5 ml of sterile tryptic soy broth (TSB) ea and then vortexed for 10 s at maximum speed. 1 ml liquid was then spread immediately onto plates quantitative culture. Tryptic soy agar (TSA) was us for bacillus spore recovery and Sabouraud agar (S for fungal spore recovery. The remaining 4 ml were cubated as an enrichment culture for 7 days at 35 °C *subtilis and A. niger)* or 56 °C *(B. stearothermophilus)*

Polystyrene plate: Each cup-shaped well was filled w 2 ml of TSB. The contents was resuspended by stirri with a sterile pipette. 1 ml was removed for immedia culturing (see above), 1 ml was transferred to 4 ml TSB or Sabouraud broth and incubated as an enric ment culture for 7 days at 35 °C (*B. subtilis* and *A. nig* or 56 °C (*B. stearothermophilus*).

Frosted glass slides: The frosted glass carriers we placed in a sterile Petri dish and coated with 2 ml TSB. The residue was resuspended with a sterile gla rod. Culturing was as described above.

2.4 Temperature measurement

Two different procedures were used to measure t temperatures:

a) Calibrated maximum thermometers, which we kept in thin-walled metal containers to protect the from electromagnetic waves, were used to record t maximum temperatures at various positions in t chamber. Readings were taken in three loading st tes: chamber empty, chamber containing 1 kg of p lyethylene items, and chamber containing 3 kg of p lyethylene items (stoppers of identical make). Th objects were placed in thin-walled aluminium tube
b) Recording of temperature profile with EBI da loggers and EBI-PC software (Ebro Elektronik). Th data loggers are hermetically sealed in disk-shape stainless steel capsules.

Table 1 Maximum temperatures (° C) with different loads

Measurement site	Loading status		
	Empty	1 kg	3 kg
Near posterior wall (left)	63	61	55
Near posterior wall (right)	62	62	55
Near anterior wall (left)	63	61	58
Near anterior wall (right)	65	63	56
Center	62	60	54
In contact with chamber wall	75	69	67

und Kammer mit 3 kg Polyäthylengegenständen (Stöpseln einer Bauart) befüllt. Das Beladungsmaterial war in dünnwandigen Aluminiumwannen untergebracht.

b) Registrierung des Temperaturverlaufes mit EBI-Datenloggern und dem Programm EBI-PC (Ebro Elektronik). Die genannten Datenlogger sind in diskusförmigen Edelstahlkapseln hermetisch eingeschlossen.

2.5 Versuchsablauf

Nach Prüfläufen zur Temperaturmessung wurden etwa 20 Durchgänge mit Keimträgern gefahren und mikrobiologisch evaluiert. Dabei wurde das Gerät auch mit gebrauchten Wasserstoffperoxid-Kassetten befüllt und in Betrieb genommen.

3 Ergebnisse

3.1 Temperaturmessungen

Die Ergebnisse der Maximaltemperaturmessungen sind in Tabelle 1 dargestellt: Bei leerer, mit 1 kg und mit 3 kg beladener Kammer wurden Temperaturen zwischen 62 und 75 °C, 60 und 69 °C bzw. 54 und 67 °C registriert. Die jeweils niedrigsten Werte wurden im Zentrum der Kammer, die höchsten bei Kontakt mit der Kammerwand gemessen. Letztgenannte lagen 7.6 bis 11.8 °C über dem Durchschnittswert der anderen Positionen.

Die mit Datenloggern registrierten Temperaturen erreichten und überschritten jeweils die 50-°C-Marke. Typischerweise wurden in der Hochfrequenzphase im Zentrum der Kammer 50 °C für etwa 5 min überschritten und als Gipfelwert 52 °C erreicht, an der hinteren Kammerwand hingegen lag der Gipfelwert für etwa 10 min Dauer bei 59 °C; hier war die 50-°C-Marke für die Dauer von etwa 20 min überschritten.

3.2 Mikrobiologische Befunde

In den Tabellen 2 bis 5 sind die Befunde aus zahlreichen Einzelexperimenten zusammengefaßt. Tabelle 2 gibt die den dargestellten Ergebnissen zugrundeliegenden Sporenbelastungen wieder. In den Tabellen 3 bis 5 ist

Tabelle 2 Sporenbelastung der Keimträger (log_{10} KBE/Keimträger)

Table 2 Spore contamination of the carriers (log_{10} cfu/carrier)

Keimträger *Carriers*	Testkeime/*Test organisms* B. subtilis v. n.	B. subtilis	B. stearoth.	A. niger
Kunststoff-Näpfchen *Plastic wells*	8.0	6.0–9.0	6.5	6.8–8.8
PE-Gewebe *PE fabric*	6.0–7.6	6.7	6.5	nicht untersucht *not tested*
Mattglas *Frosted glass*	8.2–8.9	9.0	6.5–7.7	7.7–8.3

2.5 Test design

After preliminary runs to record the temperature, approximately 20 cycles were run with different carriers and microbiologically evaluated. For experimental purposes, the sterilizer was also loaded and operated with empty hydrogen peroxide cartridges.

3 Results

3.1 Temperature recordings

The results of maximum temperature recordings are presented in Table 1. Temperatures ranging from 62 to 75 °C, 60 to 69 °C and 54 to 67 °C were recorded with the chamber empty, with a 1 kg load, and with a 3 kg load, respectively. The lowest readings were obtained from the center of the chamber and the highest at points of contact with the walls of the chamber. The latter temperatures were 7.6 to 11.8 °C above the mean values for the other positions.

The temperatures recorded by the data loggers reached and exceeded the 50 °C mark. In most cases, temperatures rose above 50 °C during the high-frequency phase in the center of the chamber and remained at this level for about 5 min: a temperature peak of 52 °C was recorded here. At the back wall of the chamber, a peak level of 59 °C was maintained for around 10 min, and the 50 °C mark was exceeded for about 20 min.

Tabelle 3 Ergebnisse der Sporen-Abtötungsversuche mit Polystyrol-Näpfchen

Table 3 Results of the spore inactivation tests with polystyrol wells

Testkeim *Test organism*	beobachtete Reduktionen (log_{10}-Stufen) *Reductions observed (log_{10} units)* 3	4	5	6	7	8	9	n Keimträger *n carriers*
B. subtilis (Hyg. Inst.)	–	–	–	3 ×	3 ×	3 ×	12 ×	21
B. subtilis var. nig.	–	–	12 ×	–	–	–	–	12
B. stearothermophilus	3 ×	–	2 ×	6 ×	–	–	–	11
A. niger				4 –	16 –	–	–	20

Tabelle 4 Ergebnisse der Sporen-Abtötungsversuche mit PE-Gewebestreifen

Table 4 Results of the spore inactivation tests with PE fabric strips

Testkeim *Test organism*	beobachtete Reduktionen (log_{10}-Stufen) *Reductions observed (log_{10} units)*							n Keimträger *n carriers*
	3	4	5	6	7	8	9	
B. subtilis (Hyg. Inst.)	–	–	1 ×	8 ×	–	–	–	9
B. subtilis var. nig.	–	–	–	12 ×	8 ×	–	–	20
B. stearothermophilus	–	–	–	8 ×	–	–	–	8

angegeben, wie oft bei welchem Testkeim und bei welcher Keimträgerart welche Höhe der Keimreduktion beobachtet wurde. Tabelle 3 zeigt die Ergebnisse mit Kunststoff-Näpfchen, Tabelle 4 die mit PE-Gewebestreifen und Tabelle 5 die mit Mattglasscheibchen als Keimträgern. Bei 17 von 64 (26,5%) Kunststoff-Näpfchen, bei einem von 37 (2,7%) und bei keinem von 20 Mattglas-Keimträgern wurden Keimreduktionen < 6.0 log-Stufen beobachtet.

3.3 Probezyklen mit gebrauchten Wasserstoffperoxid-Kassetten

Es gelang mehrmals, Sterilisationszyklen mit leeren Wasserstoffperoxid-Kassetten zu fahren, ohne daß diese Fehlfunktion von der Steuerung des Gerätes erkannt und ein Fehler am Ausdruck des Schreibers dargestellt wurde.

4 Diskussion

Die hier dargestellten mikrobiologischen Befunde konnten nur ein unvollständiges Bild über die Leistungsfähigkeit des geprüften Verfahrens geben. Insbesondere war es nicht möglich, in die Programmsteuerung einzugreifen und die Parameter des Verfahrens zu variieren. Außerdem existieren für dieses Verfahren noch keine allgemein akzeptierten Vereinbarungen über Auswahl, Vorbereitung und Applikation der Testkeime. Eines unserer Anliegen war daher, unterschiedliche Testsporen auf unterschiedlichen Keimträgern im Parallelansatz zu prüfen.

Die Muster der Empfindlichkeiten der einzelnen Sporenarten waren bei Kunststoff-Näpfchen und Mattglas ähnlich (Tabellen 3 und 5), wenngleich sie bei Mattglas

3.2 Microbiological results

The results of numerous individual experiments ar collated in Tables 2 to 5. Table 2 gives the spore cor tamination for the respective results. Tables 3 to show the levels of reduction for each test organism an carrier type. The results for the plastic wells are give in Table 3, for the PE strips in Table 4, and for th frosted glass slides in Table 5. Reductions of the micro bial count by < 6.0 log units were seen in 17 of 6 (26.5%) plastic wells, one of 37 (2.7%) PE strips, an zero out of 20 frosted glass slides.

3.3 Trial runs with empty, used hydrogen peroxide cartridges

In several of the sterilization cycles run with empty hy drogen peroxide cartridges, the controls of the appar atus did not recognize the malfunction and the re corder did not indicate that anything was amiss.

4 Discussion

The data reported here do not provide a complete pic ture of the performance of the tested procedure. In par ticular, it was not possible to change the programming of the apparatus and modify selected parameters. Moreover, there are no generally accepted guidelines for the selection, preparation and application of test or ganisms. One of our aims was, therefore, to test differ ent test spores on different carriers in a parallel ap proach.

The sensitivity profile of the individual spore species was similar when exposed in plastic wells and in frosted glass (Tables 3 and 5), although slightly higher

Tabelle 5 Ergebnisse der Sporen-Abtötungsversuche mit Mattglas

Table 5 Results of the spore inactivation tests with frosted glass

Testkeim *Test organism*	beobachtete Reduktionen (log_{10}-Stufen) *Reductions observed (log_{10} units)*							n Keimträger *n carriers*
	3	4	5	6	7	8	9	
B. subtilis (Hyg. Inst.)	–	–	–	–	–	–	5 ×	5
B. subtilis var. nig.	–	–	–	–	–	5 ×	–	5
B. stearothermophilus	–	–	–	1 ×	4 ×	–	–	5
A. niger	–	–	–	–	1 ×	4 ×	–	5

in Richtung höherer Keimzahl-Reduktionen verschoben waren. Auf PE-Gewebe (Tabelle 4) waren dagegen die Unterschiede zwischen den untersuchten Sporenarten nicht sehr groß.

Sporen von *B. stearothermophilus* erwiesen sich als die resistentesten der geprüften Sporenpräparationen, und Sporen von *A. niger* erwiesen sich als ähnlich resistent gegenüber dem Verfahren wie die von *B. subtilis*. Ähnliche Befunde berichteten auch Peters und Borchers (10). Es muß daher gefragt werden, warum in dem vom Hersteller des Verfahrens angebotenen Bioindikator-Set (BI Test Pack) *B. subtilis* als Testkeim verwendet wird. Auch die Konfektionierung dieses Sets ist zu kritisieren: Der Hersteller argumentiert, daß durch die gewählte Konfiguration und die Zwischenschaltung eines Latexgummistückes (Latexgummi inaktiviert Peroxidplasma offenbar deutlich!) einem langen Endoskop-Kanal vergleichbare, schwierige Bedingungen gegeben sind. Diese Sichtweise wird von uns und von anderen Untersuchern (3, 10, 12) nicht geteilt.

In Kunststoffnäpfchen angeboten waren die Sporen deutlich schwerer abzutöten als auf Mangtas ausgebreitet (26,5% vs. 0% Reduktionen < 6,0 log-Stufen). Offenbar wird die Zuverlässigkeitsgrenze des Verfahrens überschritten, wenn die Testkeime nicht mehr in einer dünnen, einschichtigen Lage vorliegen, sondern auf der Oberfläche und in ihren Vertiefungen aggregiert sind. Zu beachten ist, daß bei unseren Versuchen keinerlei Belastungen der Sporensuspensionen mit Blut oder Serum verwendet wurden, wie dies von anderen Untersuchern vorgeschlagen wird (9, 10). Offenbar genügt bereits die durch die Testsporen bereitgestellte Biomasse, um in solchen Situationen das Überleben einzelner Individuen zu ermöglichen. Wir erklären diese Beobachtungen mit der geringen Belastbarkeit des Wirkprinzips (Wasserstoffperoxid und seine Radikale werden durch organische Begleitstoffe stark gezehrt) und durch die geringe Wirkstoffreserve bei diesem Verfahren (im Hochvakuum ist nur ein sehr geringer Wirkstoffpool verfügbar; 9). Sehr gute mechanische Entfernung von Verschmutzungen ist daher eine unverzichtbare Voraussetzung für den Einsatz dieses Verfahrens (9). Für Verfahren, die ähnlich wie dieses nur nach optimaler Reinigung akzeptable Sicherheit der Sterilisationswirkung bieten, wird die Vorreinigung mit einem validierten Reinigungsverfahren vorausgesetzt (4).

Die von uns gemessenen Temperaturen lagen deutlich über den vom Hersteller angegebenen Prozeßtemperaturen. Bei unseren Messungen waren Metallteile anwesend, die durch die Hochfrequenz erwärmt werden. Wir haben diese Anordnung bewußt aus folgenden Gründen in Kauf genommen: Das Verfahren wird für hitzelabiles Instrumentarium und insbesondere für flexible Endoskope empfohlen. Insbesondere letztgenannte sind komplex aufgebaut und enthalten unverzichtbare

reductions in microbial counts were seen for frosted glass. By contrast, for the PE fabric strips, the results with respect to the various spore species did not differ greatly (see Table 4).

B. stearothermophilus spores were shown to be the most resistant of the spore preparations tested. *A. niger* spores were similar to *B. subtilis* in terms of resistance to the procedure. Similar findings are reported by Peters and Borchers (10). Thus the question arises why the bioindicator set supplied by the manufacturer (BI Test Pack) uses *B. subtilis* as a test organism. The composition of the set has to be criticized also. The manufacturer argues that the chosen configuration and the use of latex rubber in between (latex rubber apparently inactivates peroxide plasma to a great degree!) mimics the difficult conditions applicable to sterilization of a long endoscope lumen. This is an opinion that we and other investigators do not share (3, 10, 12).

When plastic wells were used as carriers, the spores were much harder to eliminate than when spread on frosted glass (26.5% vs. 0% reductions < 6.0 log-units). This procedure appears to be no longer reliable if the test organisms are not presented in a thin, single layer but are clumped together on the surface or at some depth. It is important to note that the spore suspensions used by us were not loaded with blood or serum, as recommended by other authors (9, 10). The biomass of test spores alone is apparently sufficient to ensure the survival of individual organisms. Our explanation for this is the lack of robustness of the active principle (hydrogen peroxide and its radicals react strongly with organic substances), and the low active substance reserves in this technology (the active substance pool is very small indeed in a high vacuum; 9). Therefore, optimal mechanical removal of contaminated matter is an absolute prerequisite to the use of this procedure (9). Procedures such as this that offer an acceptable standard of microbiological safety only after optimum cleaning of the contaminated items require a validated cleaning procedure (4).

The temperatures recorded by us were far above those indicated by the manufacturer. Our experiments included metal parts that are heated by applying high frequency waves. We chose this set-up for carefully thought-out reasons: the procedure is recommended for thermolabile instruments, flexible endoscopes in particular. The latter are of complex composition and always contain certain metal parts. Our readings are therefore probably much more realistic than those obtained using the metal-free temperature sensors which are recommended by the manufacturer and which were unavailable to us. Another matter that requires investigation is the effect of different levels of warming on the points of contact between metal and plastic. These points are unavoidable in such instruments and are

lität nähekommen als solche, bei denen das vom Hersteller empfohlene und für uns nicht greifbare Verfahren mit metallfreien Temperatursensoren eingesetzt wird. Es muß überdies gefragt werden, wie sich die differente Erwärmung auf die Kontaktstellen zwischen Metall und Kunststoff auswirkt, die in solchen Instrumenten unvermeidlich sind und für die Funktion des Instruments kritische Stellen betreffen.

Daß das untersuchte Gerät mit gebrauchten, leeren Wasserstoffperoxid-Kassetten wie auch mit intakten betrieben werden konnte, ist als fataler Mangel einzustufen. Auf eine automatische Erkennung von Wirkstoffmangel und eine sofortige Reaktion der Gerätesteuerung kann unter keinen Umständen verzichtet werden.

Nachdem vom Hersteller Latexgummi als „Erschwernis" im Bioindikatorsystem eingesetzt wird, muß gefragt werden, wie die Sterilisation von anderen Weichgummiteilen (z. B. flexible Ummantelungen der Spitzen flexibler Endoskope) zu sehen ist.

Aufgrund unserer Beobachtungen (mehrere exponierte Polyamid-Kabelbinder waren nach 20 Sterilisationszyklen so brüchig, daß sie spontan zerbrachen) sollten mit allen für dieses Sterilisationsverfahren vorgesehenen medizinischen Geräten umfangreiche und kunststofftechnisch orientierte Materialtests durchgeführt werden, um unliebsamen Überraschungen vorzubeugen.

Das uns zur Verfügung stehende Benutzerhandbuch enthielt kaum Angaben über Auswahl des Sterilisiergutes und empfohlene Chargengrößen, über die Verpackung des Sterilisiergutes und über die richtige Beschickung des Gerätes. Um im praktischen Betrieb Mißverständnisse auszuschalten, erscheinen genauere Definitionen der genannten Parameter unter Berücksichtigung aller im praktischen Betrieb auftretenden Probleme erforderlich (1, 2, 3, 4).

5 Schlußfolgerungen

Aufgrund unserer Auseinandersetzung mit diesem neuen Verfahren und aufgrund unserer Experimente ergaben sich einige grundlegende Fragen, die der Klärung bedürfen. Es ist zu hoffen, daß diese Fragen im Zusammenwirken von Verfahrenstechnikern, Werkstoffspezialisten, Instrumentenherstellern und Hygienikern geklärt werden können. Dies ist die Voraussetzung dafür, daß ein Verfahrenstyp für die Wasserstoffperoxid-Plasmasterilisation definiert werden kann, der den heutigen Anforderungen an ein Sterilisationsverfahren standhält und daher für den praktischen Einsatz empfohlen werden kann.

Aus human- und ökotoxikologischer Sicht wäre dieser Verfahrenstyp eine begrüßenswerte Alternative zu der-

The fact that the test apparatus ran on empty hydroge peroxide cartridges exactly as it did on intact ones is fatal deficiency. Automatic recognition of the lack o sufficient quantities of the active substance and an im mediate failsafe shutdown are absolutely indispen sable.

The fact that the manufacturer uses latex rubber as hindrance in the bioindicator system makes co wonder how the system can be expected to cope wit the sterilization of other soft rubber parts (eg flexibl coating on the tips of flexible endoscopes).

Our observations (a number of exposed polyamid cable connectors were so worn out after 20 sterilizatio cycles that they simply fell apart) suggest that an medical devices and instruments planned for sterili ation with this process should be first subjected t comprehensive materials stress testing, focusing o plastics compatibility, in order to avoid unpleasant sur prises.

The operating manual supplied lacked adequate in formation on the selection of suitable objects for ste rilization and recommended batch sizes, packaging o the items to be sterilized, and how to load the appe ratus. In order to eliminate misunderstandings in day to-day use of the system, there is a need for more pre cise definitions of the stated parameters and more at tention to problems likely to occur in practice.

5 Conclusions

Our investigations into this new sterilizing procedur and the results of our experiments with Sterrad reveal led a number of points which need clarification. It is t be hoped that, once these points have been clarifie with the aid of process engineers, materials specialists instrument manufacturers and infection control ex perts, a technology for hydrogen peroxide plasma ste rilization can be defined that meets modern sterilizat tion standards and can be recommended for practica use.

From the point of view of human and environmental to xicology, a technology that meets these requirement would be a very welcome alternative to current proce dures. However – going by the current state of know ledge – hydrogen peroxide plasma sterilization wi only add to but not replace conventional gas sterilizat tion techniques (ethylene oxide and formaldehyde lov pressure steam sterilization).

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On the Efficacy and Validation of H_2O_2 Plasma Sterilisers[1]

M. Borneff, U. Färber, H. Getreuer, P. Heeg, U. Junghannß, R. Machmerth, P. Mecke, J. Peters
(Guests: Christiane Höller, Heike Martiny)

Hydrogen peroxide plasma sterilisers are increasingly being employed for the sterilisation of thermo-labile medical instruments.

In this process, hydrogen peroxide 58% is evaporated at a negative pressure of 0.4 mbar and room temperature. After a considerably long diffusion phase of 50 min (pressure range 8 to 18.7 mbar) and another lowering of the pressure to 0.7 mbar, a plasma is formed by means of high frequency in the mega hertz range. The radicals of the hydrogen peroxide plasma are supposed to form bonds with the functional building blocks of microbial cells, exerting a fatal effect on these microorganisms.

With this process, the cycle time is 75 min at a operating temperature below 50 °C. Based on current knowledge, there is no likelihood of hazardous residues remaining on the sterile supplies or in the air of the work area.

In the absence of an appropriate test standard, no type test, as stipulated by the Medical Standardisation Committee for conventional medical sterilisers, has been conducted so far.

In situ efficacy testing is generally performed with biological indicators *supplied by the manufacturer* of the sterilisation system. Initially they contained spores of *B. pumilus*, and, of late, those of *B. subtilis*. *American and German studies have revealed that certain Aspergillus and mycobacterial species are considerably more resistant.* The test spores mentioned above therefore do not seem to be representative for all human pathogens.

In 1992, this critical situation gave rise to the formation of the working group "Gas Plasma Sterilisation" within the framework of the sterilisation section of the German Society for Hospital Hygiene (DGKH). Its goal was to evaluate the sterilisation performance of this process on the basis of the existing documentary sources, while taking due account of any test results obtained by the group itself, and in the event of recognition of its suitability, to elaborate recommendations for the biological efficacy testing.

As a general basis for the efficacy of medical sterilisation processes, the working group refers to the sterilisation safety of 10^{-6}, which is being aspired to as a European standard, and to the fact that delicate instruments, even when meticulously cleaned, can still contain approx. 10^2 microbial pathogens.

Therefore, a medical sterilisation process, irrespective of its microbicidal principle, must be able to reduce the number of the most resistant human pathogens by at least 8 log levels. This also applies when they lodge in long and narrow lumen medical instruments, enclosed in protective soil residues, which as is well known cannot be ruled out under everyday use conditions. Moreover, its microbicidal principle should be defined by corresponding physical and chemical parameters. New processes should exhibit at least the same microbicidal efficacy as conventional sterilisers.

Based on existing documentation, the stipulated sterilisation safety of 10^6 appears to be assured by the process referred to, *if the test organisms are to be found on smooth surfaces of easy access.* Our tests have demonstrated that the process is not sufficiently efficacious in the presence of blood and crystallized minerals, or when using narrow lumen instruments with a dead end.

Neither does the active principle produce a sufficient deep action when using patent narrow lumen instruments. The channels of these instruments must be sterilised with so-called diffusion accelerators. These are small elastic plastic tubes, containing a breakable glass ampoule with 50% hydrogen peroxide.

They must be inserted in a gas-tight manner via a connector into the respective channel entrances and the glass ampoule must be broken immediately before starting the steriliser.

If the gas-tight connection is successful, additional hydrogen peroxide vapor from 0.17 ml highly concentrated hydrogen peroxide will form during the vacuum phase, being forced to fill up the respective channel systems. However, then the area where the connector adheres gas-tight to the channel wall cannot be reached by the active principle of the process. If the connection between diffusion accelerator (connector) and entry into the hollow instrument is not gas-tight (for example due to loosening when packing and transporting the instruments), the hydrogen peroxide vapor additionally formed does not, as intended, only fill up the respective channel systems, but will also spread to the evacuated sterilisation chamber, thus rendering basically no effect.

The working group is unanimously of the opinion that this diffusion accelerator cannot be accepted, because even when handled most carefully it still entails a considerable safety risk for sterilisation.

With the exception of hollow instruments with a dead end, the manufacturer of the currently marketed hydrogen peroxide plasma steriliser recommends its use for all

[1] First statement of the working group "Gas Plasma Sterilisation" (chaired by P. Mecke, Lübeck) of the section "Sterilisation" of the German Society for Hospital Hygiene (DGKH) on the occasion of the 2nd Congress of the DGKH, November 18-20, 1993 in Erfurt

items which can be also sterilised with ethylene oxide or formaldehyde. This is contradictory to the biological test procedure for efficacy testing provided by the manufacturer. This test pack consists of a chemical and a biological indicator enclosed in a large lumen plastic wrapping with a remarkably large inlet port (5 x 8 mm) for the active principle. *The working group cannot accept this "biological test system" for the following reasons:*

1. *The chemical process indicator changes colour already on exposure to daylight*, thus, does not react specifically to hydrogen peroxide or its plasma.
2. *The diffusion resistance of the large lumen test object is not representative* for long and narrow lumen hollow instruments used in daily medical practice.
3. The biological indicators used do not contain specifications as to whether they exhibit sufficient resistance to the active principle when taking into due account all human pathogens. The resistance required for biological indicators for sterilisation processes is to be expressed by the D-value. No proof exists for the currently operated hydrogen peroxide plasma sterilisers as to *which is the actual active principle:* hydrogen peroxide vapor or its plasma. Consequently, determination of the D-value should be problematic.

The working group in its present composition is unanimous that hydrogen plasma sterilisers are principally interesting and worthy of development.

However, these sterilisers can be recommended for employment in medical practice only after the drawbacks outlined here have been eliminated, and when its efficacy has been proven under field conditions, when an acceptable biological test standard is available and when the manufacturer compiles a catalogue of those items for which the proof that they can be reliably sterilised according to the process referred to has been furnished on the basis of sufficient validations. ■

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On the Validation of the Sterrad® Plasma Sterilisation Process

Notification of the Board of Directors of the German Society for Hospital Hygiene (DGKH) on the Current State of Knowledge about the Validation of the Sterrad® Plasma Sterilisation Process with the Resultant Conclusions for Practical Application[1]

Due to the statement recently published in "Management & Krankenhaus" (1994; 6), the survey by Geiss et al. in the journal "Zentralsterilisation – Central Service" (1994; 4: 263–269) as well as to the expert report by G. Salrein and M. Scherer, Freiburg, on the economical and practical investigations of the Sterrad® plasma sterilisation, several queries on the practical applicability of the sterilisation system were addressed to the board of directors of the German Society for Hospital Hygiene (DGKH). In October 1993, the Federal Ministry for Health, Sports and Consumer Protection informed the state health management authorities in Austria about problems with the sterilisation system and advised against the installation of plasma sterilisers pending clarification of all questions. We therefore deem it necessary to give a review of the current situation and of the attempts being made for validating the Sterrad® process.

Following the two statements by the DGKH board of directors published in "Hygiene und Medizin" (cf. 1992; 17: 452 and 1993; 18: 184, and Zentr Steril 1993; 1: 6 and 1: 90, respectively), the publication by P. Mecke on the findings on the performance limitations of the mentioned process (Hyg Med 1992; 17: 537–543) and an empirical report by H. Rudolph et al. (Zentr Steril 1993; 1: 179–192), the DGKH board of directors convened a meeting on September 9, 1993 in Hannover on the subject "Efficacy and Tolerance of the Hydrogen Peroxide Plasma Sterilisation Process".

Apart from the members of the board of directors of the DGKH and representatives from Johnson & Johnson in Germany as well as from the research centre in Arlington/Texas, this meeting was attended by H. Rudolph in his capacity of chairman of the German-speaking working group for hospital hygiene as well as by other expert representatives from Germany, Austria and Switzerland. Without focusing on the details of the discussion, the conclusion drawn was that "plasma sterilisation" cannot be viewed at present as an alternative to ethylene oxide (EO) and formaldehyde (FA) sterilisation, particularly because of the restrictive design features of certain products to be sterilised und the still unclarified issues of validation, challenge, test indicators and test pieces. The sterilisation system must not be employed in the hospital setting before adequate validation. A further conclusion drawn unanimously was that after testing the performance capabilities of the system while sterilising different products, a detailed positive and negative list of the articles and materials lending themselves or not lending themselves to this process would have to be compiled.

Already back in 1992, the working group "Gas Plasma Sterilisation" was founded within the sterilisation section of the DGKH in order to clarify the further validation measures needed before introducing the process for practical use. This working group published an assessment of the procedure in Hygiene und Medizin (1993; 18: 557–558), focusing on the following points:

- The general basis for evaluating the efficacy of a new sterilisation process, will be the sterilisation safety of at least 10^{-6}, which is being aspired to as a European standard.
- Based on the investigation findings presented so far, the stipulated sterilisation safety of 10^{-6} appears to be assured by the process, if the test organisms are to be found on smooth surfaces that can be easily accessed by the active principle. In the presence of blood and crystallised minerals or when using narrow non-patent lumen instruments, the process is not sufficiently efficacious.
- Neither does the active principle generate a sufficiently deep action when using patent narrow lumen instruments. Therefore the manufacturer recommends employing the so-called "diffusion accelerator". The working group members unanimously agreed that this diffusion accelerator cannot be accepted, because even when handled with utmost care it still entails a considerable safety risk for sterilisation, e.g. safety with regard to emptying, efficacy of plasma on the contact surfaces of diffusion accelerator and products to be sterilised.
- The biological test system currently made available by Johnson & Johnson is not acceptable, neither with respect to the indicators (chemical, biological) nor to the absence of simulation of the actual conditions prevailing in long narrow lumen instruments.

The conclusion drawn was that the process was interesting and worthy of development. However, medical application of the process can only be contemplated after its efficacy has been demonstrated under field conditions, after an acceptable biological test standard has been formulated and the manufacturer has compiled a catalogue of those items for which the proof that they can be reliably sterilised according to the process referred to has been furnished on the basis of sufficient validation.

In an investigative report on "Economical and Practical Investigations of the Sterrad® Plasma Sterilisation", published on November 11, 1993, by the authors G. Salrein, infection control nurse, and M. Scherrer, hospital ecologist, from the Department for Environmental Medicine and Hospital Hygiene of Freiburg University, Prof. F. D. Daschner attests in the summary that this process "is ideal for use in hospitals for sterilisation of heat-sensitive materials. Even angiographic and heart catheters can be reprocessed easily and reliably with the process". For the reasons given below, these far-reaching observations cannot, however, be inferred from the findings presented, in view of current knowledge for assessing the sterilisation safety of a new process:

1. Based on the findings of investigations conducted by Johnson & Johnson, of the spores tested so far *Bacillus stearothermophilus* manifests the greatest resistance, therefore the employment of *Bacillus pumilus* as indicator pathogen cannot be justified.
2. Quite apart from the fact that it is unusual to have the test carriers for validation of a new process prepared by the manufacturer of the process, the microbial count on the test carriers used in these investigations was on 26 March 1993: $2.8 \cdot 10^2 - 6.0 \cdot 10^2$ cfu

on 16 April 1993:
$3.0 \cdot 10^3 - 5.0 \cdot 10^4$ cfu
on 6 May 1993:
apparently on four occasions 0 cfu
once $1.0 \cdot 10^2$ cfu
on 27 May 1993:
once 0 cfu
otherwise
50 cfu to $6.0 \cdot 10^4$

per contaminated thread or catheter/thread and was thus far below the value of 10^6 cfu per test carrier which has been advocated as proof of sterilisation. No quantitative definition is available for the tests performed on December 11, 1992 and on February 11, 1993. The findings have no relevancy due to the severe methodical drawbacks. This does not impinge on the reality that proof was obtained twice of the presence of indicator pathogens in two catheters subjected to the process.

3. To prove the suitability of a gas sterilisation process (formaldehyde) in Germany, it is stipulated that, in compliance with DIN 58948, Part 13, the test pathogens be inactivated in a receptacle at the end of a 1.5 meter long tube with a 2 mm inner diameter. Proof has been obtained that these stipulations are fulfilled by certain formaldehyde and ethylene oxide sterilisation processes. To preclude any penetration in these processes, this efficacy was also substantiated in Germany for ethylene oxide and formaldehyde using similar models, however, made of metal. If, despite the grievous methodical drawbacks outlined above, a process is hailed in the cited expert report as a "new, revolutionary sterilisation process", which is "ideal for use in hospitals for sterilisation of heat-sensitive materials", this claim cannot be corroborated.

At the request of Johnson & Johnson Inc., the board of directors' members Prof. Kramer and Prof. Werner as well as Prof. Mecke as head of the working group "Gas Plasma Sterilisation" of the section "Sterilisation" of the DGKH participated in a detailed problem discussion in the ASP sterilisation centre of Johnson & Johnson in Irvine (USA), focusing on the performance capabilities and the current performance limitations of the Sterrad' process.

They also addressed the topic of which investigations are deemed indispensable for introduction of the process for practical application as well as the pertinent methodical fundamentals.

Johnson & Johnson made the following important declarations, characterising the imperatives targeted by the process development:

- Sterilisation at low temperatures,
- No adverse environmental impact due to the process,
- No residue problems owing to toxic residues of the sterilant in the item sterilised,
- With respect to the implications for ethylene oxide (EO), Johnson & Johnson stated "Not necessary to replace EO. Only necessary to solve problems which alternatives did not address (Implies displacement of EO in some applications)". Formaldehyde was not discussed in this context, as it is not common in the USA.

The ensuing discussion dealt in depth with the findings of the microbiological investigations presented by Johnson & Johnson. The most important issues still unresolved can be summarised as follows:

- The comparative investigations conducted on the assessment of resistance development of various pathogen species have limited relevancy, owing to the methodical differences of various tests.
- The greater resistance of the spores *Bacillus stearothermophilus* compared to *Bacillus subtilis* mandates that *Bacillus stearothermophilus* preparations be employed for process validation. At the same time, the other camp has presented different or insufficient findings for the microbial resistance evinced in this process, espedally for spores of diverse Bacillus strains, mycobacteria and Aspergillus types.
- In further investigations, the influence of water of standard hardness and of various challenges such as dried native human blood in different layer thickness should be analysed concurrently, since this would permit one to ascertain the safety of the process also when facing these challenges. If such findings are not presented, a standardised and validated cleaning process with process documentation would have to be employed.
- The process or the process steps should be validated quantitatively.
- The principal efficacy in this model, even when challenged by blood and serum, is derived from the investigation findings presented by Johnson & Johnson on the inactivation of *B. subtilis* or *B. pumilus* spores in narrow lumen tubes as a model for endoscopy, while using extensions. By virtue of the constructional features of endoscopes, it is recommended that future test series should use dummies with similar tube pieces and connections, in order to simulate the conditions actually prevailing in endoscopes. Only then can further conclusions be drawn for practical applicability. In no way can the commercially available blister test pack (with *B. subtilis* spores) be used to make a statement, irrespective of its formulation, on the efficacy in tubular systems or narrow lumen instruments as a basis for validation.
- Johnson & Johnson has realised that the test stipulations of DIN 58948, Part 13, for a gas sterilisation process cannot be fulfilled with the Sterrad® plasma sterilisation process due to system drawbacks. Also for this reason, the system cannot be declared an alternative to ethylene oxide and formaldehyde processes. At the same time, the application limitations must be defined, i.e. – as already noted during the round-table discussion in Hannover – a detailed positive and a negative list of instruments that can or cannot be sterilised by the Sterrad® process is needed.

Johnson & Johnson agreed to continue systematically working on the existing drawbacks, so as to be able in this manner to define the application possibilities and performance limitations as a prerequisite for employing the process in the medical setting.

Based on current knowledge, the board of directors of the DGKH cannot endorse the claim alleging that "plasma sterilisation is an alternative to other sterilisation processes", thus implying that the latter can be replaced in a general manner. On the contrary, only a specific, detailed description of the respective instruments can enable one to decide with which sterilisation process they can be sterilised, Therefore, a detailed positive and a negative list must be compiled, a task for which the manufacturer is responsible. ■

(Prof. Dr. med. habil.
A. Kramer,
First Chairman of the DGKH)

[1] German text originally published in Hyg Med 1995; 20: 52–53.

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Comparison of health care-based sterilization technologies: Safety, efficacy, and economics

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Comparison of health care-based sterilization technologies: Safety, efficacy, and economics

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Abstract

The authors examined recent scientific and technical data pertaining to the efficacy and effectiveness of a variety of sterilizing technologies presently available within health care facilities. They discuss safety, toxicology, and hazardous materials—aspects of each of the technologies. Also discussed is the critical importance of sterilization cycle development, sterility assurance, process validation, and the feasibility of their development within the health care setting by health care staff. Economic aspects (i.e., operating costs and capital investment) and benefits are evaluated in a novel way that emphasizes objectivity by demonstrating ways to minimize bias in the analysis and in reviewing the effectiveness and economic data that exist for each technology. Lastly, the authors combine the various facets of safety, efficacy and economics to assist in the selection of sterilizing technology that provides the highest equal standard of care for all patients, at the optimal cost. Throughout this paper, several common sterilizing technology misconceptions are identified and addressed.

Introduction

In order to evaluate and compare sterilizing technologies objectively, one must first acknowledge the actual condition of medical devices, equipment, instruments, supplies, and other related items as they are received within the health care facility for reprocessing following use by, on, or in a patient. Such items are "dirty," often contaminated with potentially infectious organisms and often wet or moist. The items to be sterilized may have contacted proteins and other organic matter, such as pus and/or fecal matter; may be coated with lubricant or encrusted with inorganic material, minerals and salt, or dried blood; and may be protected against sterilant contact, depending in large part on the penetration capability of the chemical sterilant.

Recent studies[1] conducted in health care facilities in Iowa, Massachusetts and Colorado, which used a flexible fiberoptic (FFO) micro-endoscope to examine the interior (i.e., the "operative/ working channels") of other FFO endoscopes, yielded interesting and startling information.

Data from Dr. Jack McCracken[1] of the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA), show that 47 percent of the facilities studied had at least one patient-ready endoscope whose suction and/or biopsy channels were "visibly encrusted with debris." It also was noted that many of the processed endoscopes and accessories were stored while still wet, often in dark cabinets, at room temperature.

More than 10 percent of the examined FFO endoscopes were found to have scratched operative channels/lumens, providing the possibility of pockets for debris. Only 5.4 percent of the facilities that attempted to dry the endoscopes between procedures were successful. A moist, dark channel maintained at room temperature—or slightly higher—generally presents an excellent opportunity for any microorganisms present in the debris to multiply and grow rapidly.

The McCracken study generally confirms the findings of Alvarado and Maki[2] regarding the extreme difficulty in adequately cleaning the "crud" from within the long, narrow lumen of FFO endoscopes. The study demonstrates that conditions are ripe for the transfer of microbiological contamination—possibly containing infectious/pathogenic organisms—from one patient to another. Such transfer can be prevented if sterilizing technology penetrates such debris successfully, aggressively and reproducibly to inactivate all of the microorganisms and their spores. The FDA became interested in this crucial issue and performed the study because of several outbreaks of illnesses linked to inadequate reprocessing of endoscopes and related devices and instruments. [1]

The organisms responsible for tuberculosis (TB), human immunodeficiency virus (HIV), hepatitis B virus (HBV), and the organisms *E. faecalis*, *E. coli*, *Pseudomonas aeruginosa*, *Clostridium* species, and a host of others are present in a wide variety of instruments, items and devices that are presented routinely for reprocessing within health care facilities. Many other reusable devices, such as instruments and their accessories, are reprocessed by washing, inspecting, wrapping, labeling, sterilizing, storing, and distributing within pertinent departments within health care facilities. This

reprocessing may involve the use of various chemicals to facilitate removal and/or to inactivate some of the bioburden, thus producing some decontamination or disinfection. Similar reprocessing operations also are performed in many stand-alone ambulatory and oral surgery centers, practitioners' offices, etc.

Evaluation of available sterilization technology efficacy/effectiveness

The Canadian federal government recently published the results of a scientific evaluation of the effectiveness of various sterilizing technologies against deliberately contaminated items. The study, conducted by Dr. Michelle Alfa and co-workers,[3] evaluated the various technologies' ability to sterilize surfaces and the narrow lumen of penicylinders—which approximate the conditions of some representative devices—in the presence of a challenge barrier. The barrier consisted of tissue culture medium containing 10 percent blood serum and 0.65 percent salt that had been "inoculated" with *E. faecalis, B. sterothermophilus, B. subtilus, E. coli, P. aeruoginosa, M. cheloni* and *B. circulans*. This mixture was a simulation (i.e., surrogate) of the typical microbiological contamination on an uncleaned or inadequately cleaned instrument.

The sterilization technologies initially evaluated in the Canadian study included 12 percent ethylene oxide (ETO)/88 percent chlorofluorocarbon (CFC)-12 (i.e., the well-known "12/88 mixture"); 100 percent ETO (from two different manufacturers); hydrogen peroxide (H_2O_2) plasma; peracetic acid ($C_2H_4O_3$)/H_2O_2 plasma; and vapor phase H_2O_2. The study concluded that surface sterilization by all but the 12/88 ETO mixture was hampered severely in the presence of the serum and salt. We have seen earlier and confirmed in the McCracken study that, in the real world, instruments presented for reprocessing are frequently dirty and microbiologically contaminated, and can pose a significant penetration challenge to the sterilant.

Figure 1. Sterilization technology efficacy

Sterilant	12% ETO/88 % CFC (12/88)	100% ETO (A)	100% ETO (B)	Peracetic acid/ hydrogen peroxide plasma	Hydrogen peroxide plasma	Vapor phase hydrogen peroxide
Surface	97%	78%	49%	32%	37%	35%
Lumen	44%	33%	29%	6%	35%	N/A

Figure 1. Sterilization technologies evaluated and their relative efficacies against an inoculated challenge barrier on surfaces and lumens. Data of Dr. M. Alfa, Winnipeg, for the Canadian Federal Government.

While all the processes experienced difficulty inactivating the bioburden hidden in the lumen/channel of the devices, the study concluded that "the margin of safety for the non-CFC-based sterilizers is less than that of the 12/88 ETO sterilizers." The 12/88 ETO technology was demonstrated to be the technology that was best able to inactivate the challenge organisms in the face of the significant penetration obstacles established in the test.

In a recent publication, Alfa[4] provided additional details of the methodology used in her study. Alfa utilized a six- to eight-hour cycle at 55° C for the peracetic acid/H_2O_2 plasma procedures. She also utilized the so-called diffusion accelerator (lumen adapter, available in Canada, but not cleared by the FDA for use in the United States) and used the fixed cycle setting of 75 to 85 minutes at 40° C in the H_2O_2 plasma procedures.

We assume that Alfa selected the optimal parameters of concentration, contact time, and temperature for the peracetic acid/hydrogen peroxide plasma equipment. She utilized the only cycle time and temperature settings available with the hydrogen peroxide plasma, but took the extra measure of utilizing the diffusion accelerator (lumen adapter) to optimize hydrogen peroxide entry into the lumen.

Based on Alfa's study, the 12/88 ETO sterilant mixture was demonstrated to be the broadest spectrum and most potent sterilant of all the available technologies tested. Alfa has recently extended her studies to include the ETO/HCFC sterilant mixture and has established that it is equal in sterilization efficacy to the older 12/88 ETO/CFC sterilizing mixture. Alfa's new research data has just been published.[5]

We believe that one of the reasons the 12/88 ETO sterilant mixture and the ETO/HCFC sterilant mixture penetrated better than the other sterilants is because it is the only technology tested that operates at a positive pressure. Additionally, both plasma technologies lack substantive humidity control. Uncontrolled moisture is a detriment in the H_2O_2 plasma process, constituting a poten-

Figure 2. Operating pressures of Alfa's evaluated sterilizing technologies

Technology	Operating pressure
ETO/HCFC	10-12 psig
100% ETO	subatmospheric
Hydrogen peroxide plasma	subatmospheric
Peracetic acid/ Hydrogen peroxide plasma	subatmospheric

tial contributing factor to cycle aborts. All the other technologies operate under conditions of partial vacuum and also lack the "driving power" and the physical penetration ability of the 12/88 ETO/CFC and ETO/HCFC sterilizing mixtures.

Other researchers have found similar evidence of the apparent lack of penetrating power by subatmospheric pressure technology. In regard to the H_2O_2 plasma technology, Drs. Walter Koller and E. Lessky[6] recently published the following:

> The procedure appears to be no longer reliable if the test organisms are presented not in a thin, single layer but are clumped together on the surface or at some depth. It is important to note that the spore suspensions used by us were not loaded with blood or serum, as recommended by other authors. The biomass of test spores alone is apparently sufficient to ensure the survival of individual organisms. Our explanation for this is the lack of robustness of the active principle (hydrogen peroxide and its radicals react strongly with organic substances) and the low active substance reserves in this technology (the active substance pool is very small in a high vacuum).

Note that the plasmas tend to have what Koller and Lessky termed "low active substance reserves." Sterilizers using either the ETO/CFC mixture (12/88) or the ETO/HCFC mixture maintain very high active substance reserves, in that the ETO will not be "depleted" during the cycle by chemical reaction with bioburden, biomass, or other materials. The 12/88 and ETO/HCFC sterilizers automatically maintain a constant pressure (and therefore a constant ETO concentration) in the chamber, establishing a readily available reserve of the sterilizing agent. This automatic function has been termed sterilant "make-up" by the industry.

It is interesting to note further that Koller and Lessky (in the same publication) pointed out that the H_2O_2 plasma system had a "fatal deficiency," in that "the apparatus ran on empty H_2O_2 cartridges exactly as it did on intact ones." Apparently, the unit gave no "fault or problem" warning to signal this significant operational failure, *i.e.*, that no sterilant was present. We understand that newer H_2O_2 plasma units may have been modified recently in this respect but do not know whether any previously manufactured units have been upgraded in the field.

Commenting on the Alfa study, Drs. William Rutala and David Weber,[7] in an editorial in the same issue of *Infection Control and Hospital Epidemiology*, provided some interesting insights regarding the protective effects of the combination of salt and serum.

The importance of Alfa's studies cannot be understated. As published in the *Canada Communicable Disease Report*,[8] the journal editor commented "...there is little objective information in the literature to evaluate the efficacy of the [non-CFC] sterilants and their associated technologies. Alfa's study of the comparative efficacy of some of the available replacements to the 12/88 sterilizer is most welcome."

In the US, new sterilizing technology is reviewed by the CDRH of the FDA, in procedures known as the "510(k) review," or the "PMA (premarket approval) process." The FDA does not generally perform tests to confirm the data submitted to the FDA by the manufacturer, developer, or importer of the device, equipment, or process. The acceptance of the application by the FDA is based primarily upon a review of the data submitted by the applicant.

ETO, CFC, and HCFC environmental regulation

The microbiocidal effectiveness of ETO has long been recognized. It has been stated frequently that the entire disposable medical device manufacturing industry was initially based on ETO sterilization.[9,10] Proper aeration of items following ETO sterilization assures removal of so-called "residues"[11,12] following treatment with ETO. ETO has been rendered nonflammable and nonexplosive by blending it with CFC-12. The 12/88 ETO/CFC sterilant technology has been a proven, reliable workhorse technology for decades. CFCs, as a class of chemicals, have been phased out (due to concerns for their possible role in stratospheric ozone depletion) under the same regulations that

specifically authorize the environmentally acceptable replacement, hydrochlorofluorocarbons (HCFCs), for use in the US through the year 2030. The Montreal Protocol and US Clean Air Act specifically authorize the HCFC flammability/explosion-suppressant for continued use with the sterilant ETO. In fact, Penngas 2, an HCFC-based ETO sterilant mixture was awarded the "Stratospheric Ozone Protection Award" in 1991 by the US Environmental Protection Agency (EPA).

It has been demonstrated by extensive testing that the ETO/HCFC mixtures perform quite similarly to the 12/88 ETO mixture, due to the virtually identical physical and chemical properties of CFC-12 and the new HCFC blends. It must be noted that commercial ETO/HCFC mixtures do not consist of a single HCFC, but rather utilize two different HCFC compounds blended together. This permits a virtually identical match with the properties of the 12/88 ETO/CFC mixture and does not result in the considerable increase in consumption (compared to 12/88) that was encountered with ETO and a single HCFC.

William Dennis of the Duke University Medical Center, an advisor to the US working team of the Montreal Protocol assembly, participated in the Significant New Alternative Products (SNAP) program of the EPA to evaluate CFC alternatives. Dennis believes there are no further EPA regulatory actions coming that relate to ETO or to the specific HCFCs in commercial ETO/HCFC mixtures. There are no chemical or product bans coming. There are no HCFC taxes being contemplated. HCFC-containing products are not in regulatory, tax, or supply jeopardy.

While it is true that some states have enacted ETO abatement regulations, previous abatement technology, such as catalytic conversion, has been improved upon dramatically by utilizing "scrubbing" technology, and the capital and operating costs associated with abatement have been reduced significantly compared to only a few years ago. Simple scrubbing technology has been demonstrated to abate ETO adequately and ensure regulatory compliance. (Scrubbing technology is covered in more detail in the "Conclusions" section of this article.)

It is the authors' sincere hope that the information just presented has helped to clear up regulatory and/or environmental misconceptions about ETO and HCFC that may have existed. Unfortunately, we continue to hear these troubling misconceptions from time to time. It is clear in this regard that all statements, information and data, whatever the source, should be verified carefully and thoroughly.

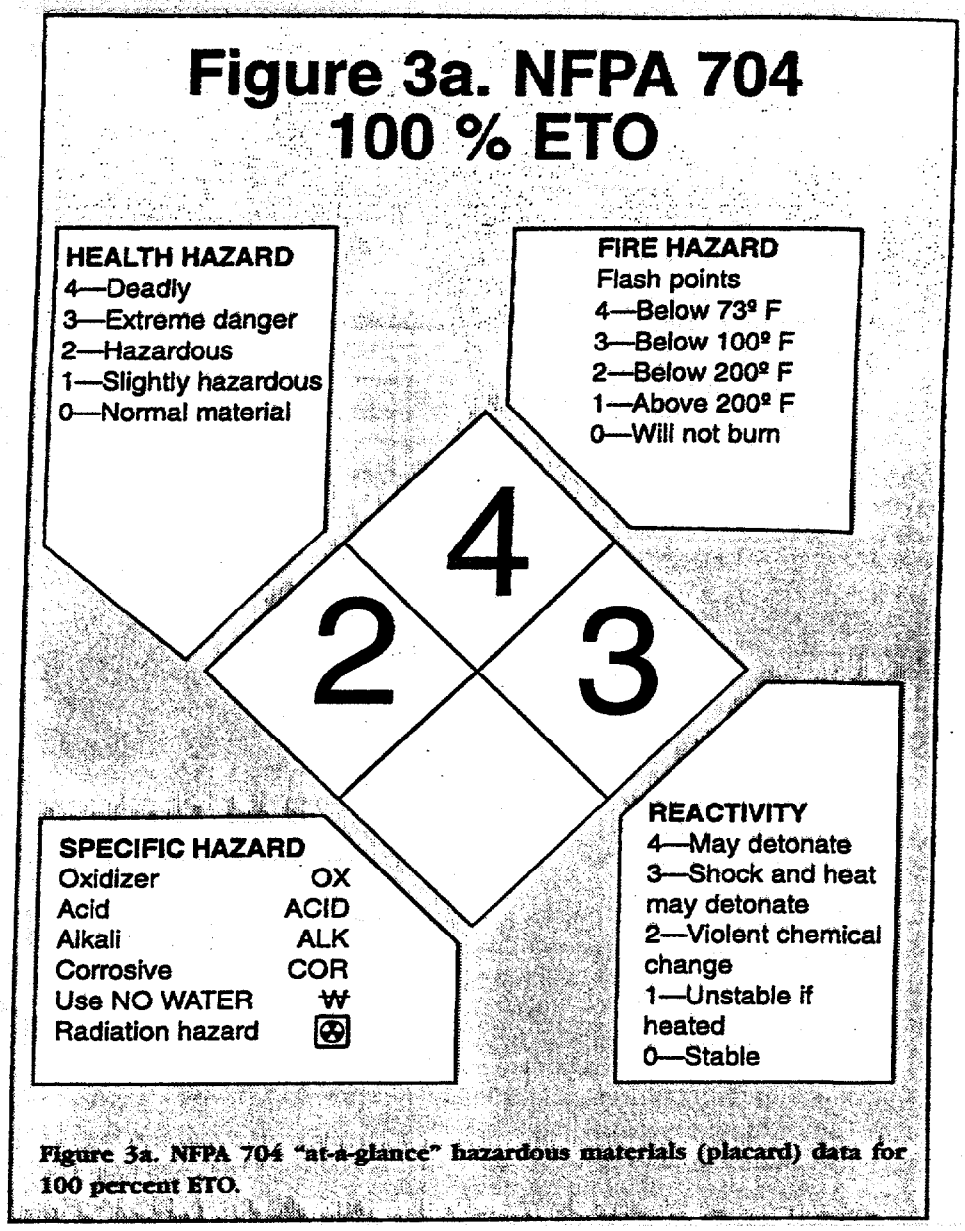

Figure 3a. NFPA 704 "at-a-glance" hazardous materials (placard) data for 100 percent ETO.

Use of hazardous and/or toxic sterilants

Another common misconception about sterilizing technology is the myth of the nontoxic, nonhazardous sterilant. All chemical and/or physical sterilizing processes involve the use of hazardous and/or toxic materials.

The purpose of the sterilizing chemical or physical process is to inactivate and/or kill all microbiological organisms on or in a device, including spores. ETO is clearly a hazardous and toxic chemical. However, even pressurized steam can be extremely hazardous when misused, producing burns, explosions, etc.

ETO requires well-known significant measures to minimize its flammability and explosion hazards, such as mixing it with a flammability and explosion suppressant to enable its use in nonintrinsically safe environments that may be capable of providing a spark or an ignition source. Occupational Safety and Health Administration (OSHA) regulations, National Institute for Occupational Safety and Health (NIOSH) recommendations, and Association for the Advancement of Medical Instrumentation (AAMI) guidelines must be followed carefully to ensure health care employee/worker safety when using ETO in any form.

Many facilities have undergone the experience of implementing required workplace safety measures associated with ETO use. Working safely, as well as effectively, with ETO has become routine. It also should be noted that HCFC-124, the principle flammability and explosion suppressant in commercial ETO/HCFC mixtures demonstrates very low toxicity and must not be confused with other HCFC chemicals such as HCFC-123, which does have moderate toxicity.

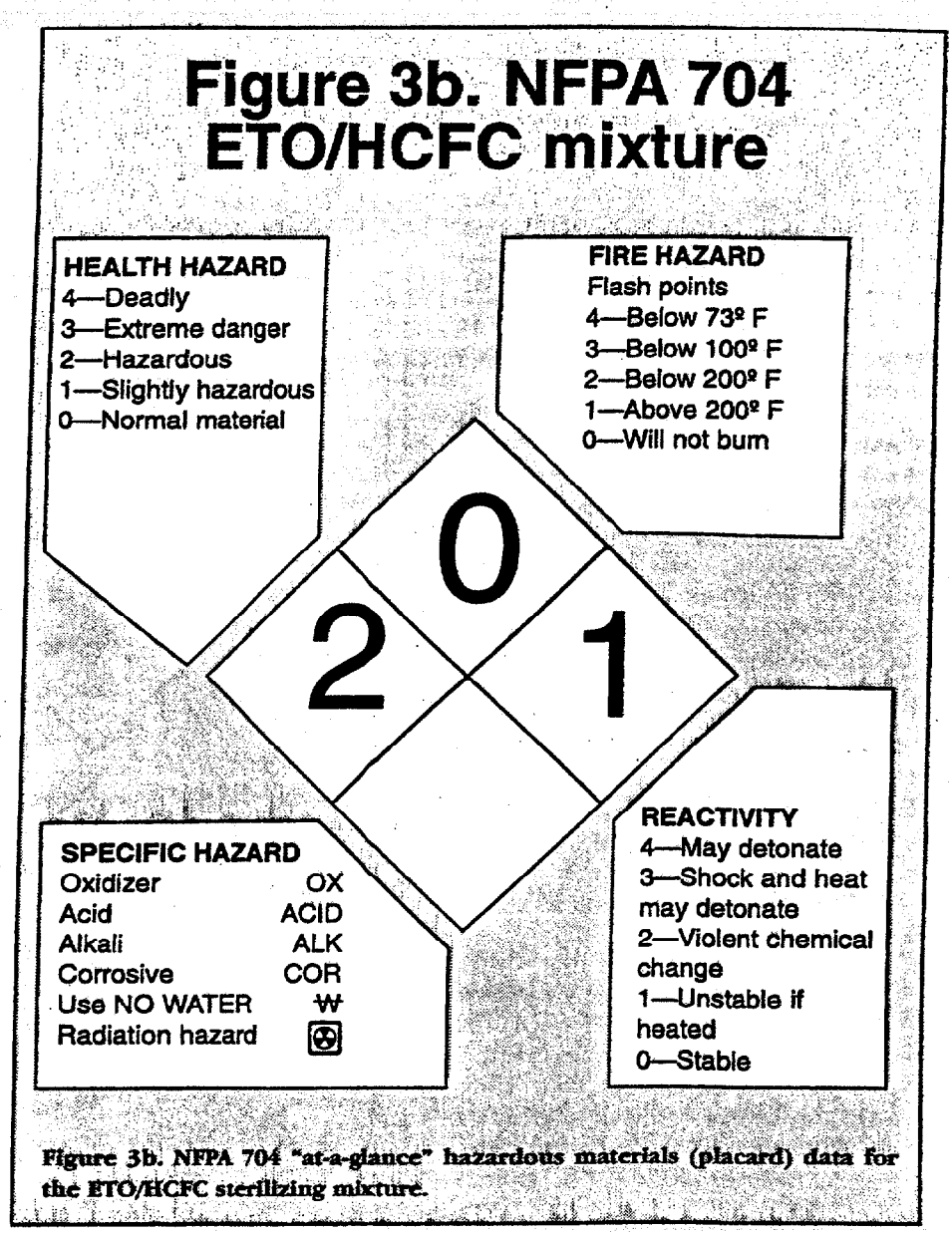

Figure 3b. NFPA 704 "at-a-glance" hazardous materials (placard) data for the ETO/HCFC sterilizing mixture.

The National Fire Protection Association (NFPA) has developed a nationally recognized and accepted consensus system for the visual recognition of the relative health, flammability, reactivity, and special hazards and risks associated with various substances. This system, using placards, provides "at-a-glance" information on the hazards of a particular substance. The system, designated as NFPA 704, uses numerical values on a scale of 0 to 4 to indicate increasing severity of risk in each of the categories mentioned earlier. The diamond-shaped symbols use different colors to designate these categories; blue for health risk, red for flammability risk, yellow for reactivity (or stability) risk, and white for any special risks (such as "oxidizer," "radioactive," or "dangerous when wet").

The NFPA 704 symbol shown in Figure 3a represents the "at-a-glance" hazard information for 100 percent ETO, indicating the highest possible flammability hazard rating for unsuppressed ETO. By contrast, commercial ETO/HCFC mixtures that utilize HCFCs as the flammability and explosion suppressant have an NFPA rating of "0" for flammability and a rating of "1" for stability (Figure 3b), indicating NFPA's assignment of nonflammability and significantly improved stability for these new ETO/HCFC blends.

However, unsuppressed ETO is explosively flammable in concentrations from 3 percent to 100 percent per volume. It does not require air to burn. The ignition energy is so low that a static spark, not even strong enough to be perceived by the human skin, is sufficient to cause

ignition. The US military made use of the potent energy release potential of ETO by using ETO as an explosive in rockets and bombs during the Vietnam hostilities. There can be no question that risk management concerns are significantly greater when 100 percent ETO—not suppressed—is used.

Testing conducted at the Illinois Fire Service Institute demonstrated the flammable and explosive nature of 100 percent ETO as compared to the flammable gas butane, which is used in most disposable cigarette lighters. There is a great difference in energy release from similar quantities of the gases when they escape from their containers in the presence of an ignition source.

The standard means of "supply" for the sterilant gas used in the 100 percent ETO sterilizer, located in the health care facility up to this point in time, has been to utilize a relatively small, disposable cartridge or canister containing 100 gm of 100 percent ETO. However, one sterilizer manufacturer has begun to promote the use of a relatively large cylinder containing 20 lbs of 100 percent ETO for supply of sterilant to their sterilizer. The use of cylinders containing 20 lbs of 100 percent ETO should be very carefully evaluated in the context of practices that may be regulated by local building and fire codes and by state and federal OSHA.

NFPA and OSHA categorize 100 percent ETO as a Class I, Group B flammable liquid, which, according to NFPA 30 (Flammable and Combustible Liquids Code), is prohibited in any quantity from the basement of buildings, whether a fire-suppressing water sprinkler system is installed or not. Depending on the quantities involved, various elements of NFPA 70 (National Electric Code) also must be observed when considering electrical service in areas where 100 percent ETO is used or stored. This is prompted by the concept of "hazard zone," which identifies a hazardous location where a flammable or explosive vapor may be present in concentrations sufficiently high enough to result in a fire or explosion in the presence of a source of ignition.

If one considers the required volume of air in a room at standard temperature and pressure with which a given quantity of 100 percent ETO must be thoroughly mixed and diluted so as to become assuredly nonflammable, the size of the "danger zone" produced by the complete discharge of the contents of a container of 100 percent ETO can be calculated and visualized. The necessity for application of special NFPA 70-mandated electrical installations then becomes clear.

A 100 gm canister of 100 percent ETO requires almost 127 cu ft of air dilution to reduce the ETO concentration below 1.5 percent, which is 50 percent of the lowest concentration at which ETO will burn or explode. This value is calculated by taking the weight of 100 percent ETO liquid in the particular container, multiplied by the specific volume of 100 percent ETO, to obtain the volume occupied by the 100 percent ETO when vaporized. This vapor volume is then divided by 0.015 (or 1.5 percent) to determine the volume of air required to dilute the ETO to below 50 percent of its lower explosive limit (LEL). (For an example of these computations, see Figure 4 on this page.)

Figure 4

100 gm (of 100 percent ETO) ÷ 454 gm/lb =
0.22 lbs (of 100 percent ETO)

0.22 lbs (of 100 percent ETO) x 8.43 cu ft/lb (of 100 percent ETO) =
1.9 cu ft of ETO vapor from the 100 gm canister of 100 percent ETO

1.9 cu ft of vapor ÷ 0.015 = 126.6 cu ft of dilution air

This volume in Figure 4 represents a space roughly 5 ft wide, by 5 ft long, and 5 ft high. The hazard zone for a carton containing 10 canisters of 100 percent ETO, each canister containing 100 gm of 100 percent ETO, is 1266 cu ft, or a space roughly 12 ft wide, 13 ft long, and 8 ft high. Note that a 20 lb cylinder of 100 percent ETO has a danger zone of approximately 11,240 cu ft, or a space roughly 37 ft wide, 38 ft long, and 8 ft high. For a 10 gm ampoule of 100 percent ETO, by similar calculation, the hazard zone is roughly 12.7 cu ft, or a space which measures 3 x 2 x 2 ft.

According to NFPA 99, relating to health care facilities, careful note should be made that cylinders of 100 percent ETO may not be stored in the same room as oxygen or nitrous oxide. This necessitates an alternative storage arrangement from the old "cylinder room" that is common in most health care facilities.

These Fire Code and OSHA regulations, requirements and aspects should not be overlooked but should be evaluated rigorously by a professional engineer or other certified individual who is experienced in interpreting these safety codes and regulations. Failure to observe strict safety practices with significant quantities of 100 percent ETO can have devastating consequences. Even the use of appropriate safety equipment and procedures is not an absolute guarantee of safety, as is evidenced by the recent explosion and subsequent destruction of a facility of one of the manufacturers of 100 gm 100 percent ETO canisters. Unfortunately, loss of life accompanied this explosion.

It was precisely this explosive nature that prompted the US Army's military medical research command to develop the use of CFC-12 as a flammability and explosion suppressant in mixture with ETO.[13,14] Thus was born

the 12/88 sterilizing mixture, produced in 1958 for US military *medical* applications by the Pennsylvania Engineering Company.[14,15]

Note that carbon dioxide (CO_2) mixtures with ETO do not completely eliminate flammability concerns because the two materials do not remain uniformly mixed and are usually not discharged uniformly. This is evidenced by the fact that "empty" cylinders of ETO/CO_2 sterilant mixture, as determined by weight, still contain slightly less than half of the original content by weight, having discharged most of the original quantity of ETO in ever-changing proportion to the CO_2. These factors prompted at least one major sterilizer manufacturer, AMSCO, to issue the following cautionary statement to their customers in August 1994: "CO_2 blends must not be used as a 12/88 alternative in [sterilizing] equipment due to stratification in the gas cylinder, which can cause an inconsistent concentration of ETO to be supplied to the sterilizer, resulting in possible biological failures and/or explosion hazards."

It must be stated clearly and emphasized that the ETO/HCFC mixtures do not have the flammability/explosion concerns that are associated with the 100 percent ETO and ETO/CO_2 mixture.

Sterilizer chamber concentrations of ETO are lower with ETO/CO_2 mixtures than are specified in the AAMI/ANSI[16,17] and the International Organization for Standardization (ISO) recommendation of 600 mg of ETO per liter of chamber volume. Generally, with ETO/CO_2 mixtures, the ETO concentration approximates 400 mg/l. ETO concentration in the sterilizing chamber is lower with ETO/CO_2, as compared to ETO/HCFC, due to two factors. First, the maximum concentration of ETO in the ETO/CO_2 supply cylinder cannot exceed 9 percent (actual ETO concentration is 8.5 percent, by weight). Otherwise, the ETO/CO_2 cylinder could not be labeled and shipped as a nonflammable gas but instead would be classified by the US Department of Transportation as a flammable gas. The ETO concentration in ETO/HCFC is 10 percent, by weight.

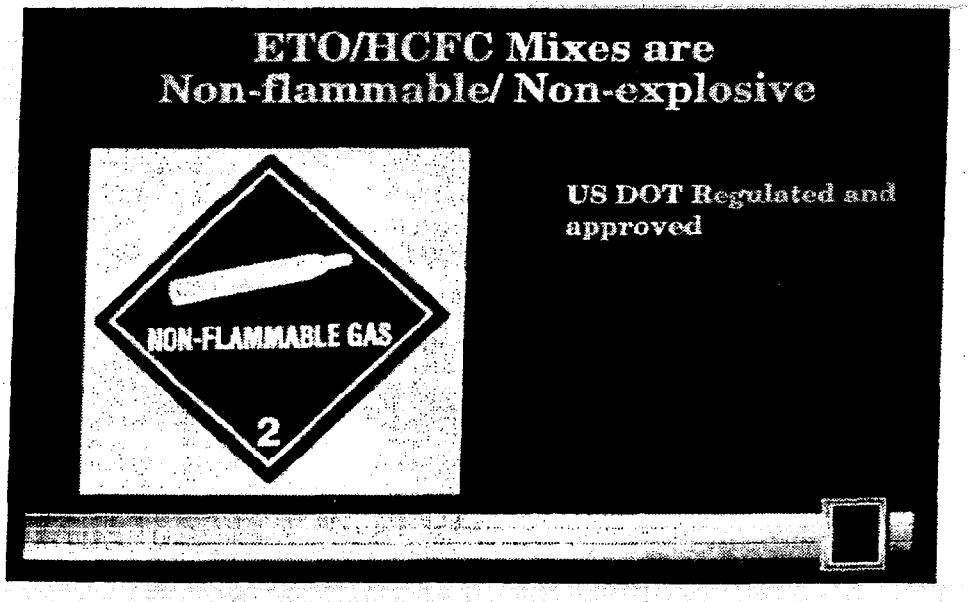

Figure 5. US Department of Transportation (DOT) Hazard Class label for ETO/HCFC mixture.

Second, the ETO concentration in the sterilizer chamber is limited by the maximum design pressure of the chamber. Despite pressurizing the chamber to the maximum allowable pressure, the combination of pressure limitations in the chamber *and* concentration of ETO in the supply cylinder result in a considerably lower chamber concentration of ETO with ETO/CO_2, as compared to ETO/HCFC—400 mg/l vs. 600 mg/l, respectively.

Normal pressure in the ETO/CO_2 supply cylinder is about 750 pounds per square inch gauge (psig). For this reason, operating pressures in the sterilizer piping system are increased to about 750 psig, as compared to the pressure when ETO/HCFC mixture is used (60 psig). ETO/CO_2 sterilizer chamber pressure is also significantly higher. When contemplating the use of ETO/CO_2 mixtures, it is imperative to ascertain that the sterilizer chamber is rated for the significantly higher operating pressures required to establish the concentration of ETO necessary for microbiocidal activity.

As a consequence of the reduced ETO concentration, ETO/CO_2 mixtures actually require cycle times that are from one to 2½ hours longer than the normal ETO/CFC or ETO/HCFC cycle times, depending on cycle temperature.

Among current sterilizing technology options, ETO does not stand alone as a uniquely hazardous or toxic substance. If we search the chemical health, safety, and toxicological literature, we discover very quickly that H_2O_2—used in the plasma system—and peracetic acid also are extremely toxic materials. ETO and hydrogen peroxide share the same Threshold Limit Value (TLV) of one part of the chemical per million parts of air (1 ppm), suggesting comparable toxicity. (The TLV is a trademark of the American Conference of Governmental Industrial Hygienists [ACGIH] and is established by its Chemical Agents Committee.) We can assume that because the peracetic acid/H_2O_2 mixture used in one plasma system also consists chiefly of hydrogen peroxide, this mixture also

Figure 6. Comparative toxicities

Sterilant	TLV (OSHA)	IDLH (NIOSH)	RQ (EPA)	Health (NFPA)	Tumorigen mutagen
ETO	1 ppm	800 ppm	10 lb	2	Yes
Hydrogen peroxide	1 ppm	75 ppm	1 lb	3	Yes
Hydrogen peroxide/ Peracetic acid mix	1 ppm	75 ppm	1 lb	3	Yes

Figure 6. Comparative toxicity: consisting of the threshold limit value (TLV), the concentration thought to be an "immediate danger to life and health" (IDLH), EPA Reportable Quantity (RQ), and NFPA 704 Health Hazard assignment for 100 percent ETO, Hydrogen Peroxide, and Peracetic Acid/ Hydrogen Peroxide mixture (extrapolated).

would have a TLV of about 1 ppm. It is appropriate to note that peracetic acid decomposes to acetic acid, for which the TLV is 10 ppm, and H_2O_2.

Another significant toxicological exposure limit, used by the NIOSH to indicate the potential for a substance to present an "immediate danger to life and health" (IDLH), has a value of 800 ppm for ETO but only 75 ppm for H_2O_2 and 50 ppm for acetic acid. That means that NIOSH and others believe that it will require a significantly lower exposure and/or dose of H_2O_2 and/or acetic acid to present an immediate danger to the health of an employee, as compared to the dose of ETO.

The EPA has named ETO, H_2O_2 and peracetic acid to its list of Extremely Hazardous Substances. Acetic acid also appears in the Toxic Substances Control Act (TSCA) inventory list. However, ETO spills have an EPA reportable quantity (RQ) of 10 lbs, while H_2O_2, and peracetic acid have reportable quantities of only 1 lb. The RQ is the quantity of an Extremely Hazardous Substance, spilled or released, that triggers mandatory notification of the local fire department, the Local Emergency Planning Committee (LEPC), the State Emergency Response Commission (SERC), and the National Response Center (NRC). Notification is required within 30 minutes of the spill or release. The RQ is a relative measure of the individual hazardous materials spill consequences.

NFPA, under the previously discussed "704" system, has assigned a health risk of "2" to ETO, a "3" to H_2O_2, and a "3" to peracetic acid, thus attributing greater health risk to the latter chemical sterilants. All three materials are mutagenic and tumorigenic, according to a host of published toxicological and industrial hygiene literature. Both ETO and H_2O_2 are capable of producing cancer in experimental animals, with ACGIH classifying hydrogen peroxide as an animal carcinogen.[18]

Thus, as compared to ETO, the IDLH and RQ limits are 10 times less for H_2O_2 and for the peracetic acid/H_2O_2 mixture, the NFPA Health Risk rating is greater, and the TLVs are equal. Does this mean that H_2O_2 and its mixtures with peracetic acid are more dangerous and/or more toxic than ETO? That may be so, but at least a rough equality is established among the three materials in terms of toxicity and their hazardous nature. In addition, ETO and hydrogen peroxide both generate concerns about carcinogenicity and reproductive effects.

Regarding the liquid phase of these sterilants, ETO, due to its very high vapor pressure and volatility, evaporates extremely rapidly and produces frost bite on exposed skin. On the other hand, H_2O_2, due to its very low vapor pressure, tends to remain liquid and forms droplets and aerosols. Hydrogen peroxide presents a very severe corrosive hazard to skin and other tissue (including the eye and lungs), producing blistering, ulceration, and discoloration upon contact.

We need to understand fully that there is no escape from the significant problems associated with working with extremely hazardous materials by simply abandoning nonflammable ETO sterilizing technology. The toxicity issues and related risks are every bit as important with all forms of current sterilizing technology, including the H_2O_2 plasma process and the peracetic acid/H_2O_2 plasma process. Eliminating or at least minimizing exposure of personnel to the sterilant is an essential and mandatory concern for all practitioners of sterilization, regardless of the technology utilized.

Recent independent studies[19,20] of health care facility sterilizer operating personnel utilizing H_2O_2 plasma revealed surprising results. H_2O_2 vapor had been detected upon the opening of the sterilizer door at the conclusion of the cycle in the operator's Breathing Zone (BZ). The results from a number of measurements demonstrate that the short-term, localized, H_2O_2 concentration

Figure 7. Operator removing processed packages from a hydrogen peroxide plasma sterilizer.

exceeded 3 ppm after the plasma sterilizer door was opened. Some of the personnel performing the sterilizing operations reported episodes of eye and mucous membrane irritation. Packages removed from the sterilizer after one hour continued to emit residual H_2O_2 gas at short-term or instantaneous concentrations of up to 2.5 ppm, for up to 1.3 hours following their removal from the sterilizer.

In addition, Easterling,[21] among others,[22] observed and measured similar concentrations of H_2O_2 and peracetic acid during operation of the mixed component plasma system.

Monitoring data obtained by MacNeal and Glaser[22] suggest that there is similarity in the timing and location of peak peroxide levels with both the H_2O_2 plasma and the peracetic acid/H_2O_2 plasma systems. Observation and measurement suggests that the peak peroxide concentrations may be significantly higher with the peracetic acid/H_2O_2 plasma system, despite that system's series of "air washes." This would seem to suggest that a separate aeration cycle might be required to remove residual peroxides from certain items processed by either of the plasma units. Certain types of packaging and packaging materials appear to retain greater amounts of the residual chemicals for extended periods of time—many hours to days—upon removal from the sterilizer.

In addition to measurable concentrations of H_2O_2 vapor in the operator's BZ, we have identified at least one documented case of dermal exposure to liquid hydrogen peroxide by an operator of a H_2O_2 plasma system. The operator was splashed on the face by a droplet of H_2O_2, which rapidly produced severe blistering and caused a pronounced discoloration of the skin. At the time the injury took place, the operator was removing items from the sterilizer.

The toxicology literature[23] notes that sensitive individuals can experience upper respiratory tract irritation from hydrogen peroxide exposure at sub-ppm (less than 1 ppm) concentrations. It has been reported that residual H_2O_2 on disinfected endoscopes has been, on occasion, responsible for a form of chemically-induced colitis. Thus it is interesting to note that H_2O_2 is not "non-toxic," apparently does not decompose immediately and completely to "non-toxic products" by the end of the cycle, and can remain as a toxic residue on or in some processed packages for an extended period of time. Much the same can be said for the peracetic acid/H_2O_2 plasma process.

Given the similar toxicities of H_2O_2 and peracetic acid, as compared to ETO, one cannot help but wonder how long it will be before H_2O_2 and peracetic acid are each subjected to workplace regulatory health and safety controls similar to those of ETO established by OSHA and state regulatory agencies.

There already exist applicable OSHA regulations that require written hazard communication plans, emergency spill cleanup procedures, possible medical monitoring, and, of course, training of and for employees who work with hazardous chemicals, as well as documentation and record keeping requirements. Even in the absence of such regulation, we now know enough to warrant virtually identical practices for worker protection while using any of these potent chemicals. No one would consider knowingly exposing workers to ETO. With the newly documented operator exposure data, how then can exposures to H_2O_2 and/or peracetic acid, which are equally insidious, be permitted?

Considerations for sterility assurance and biological indicators

In an ongoing series of reports by Peter Mecke *et al* published in the German journals *Zentral Sterilisation* and *Hygiene-Medizin*, the German Society for Hospital Hygiene made a number of significant criticisms relating to the biological and chemical indicators used with the H_2O_2 plasma technology.[24,25]

Specifically, the reports include the following comments:

- The microorganism utilized, *B. subtilis*, is considerably less resistant to the H_2O_2 plasma sterilization process than is *B.*

sterothermophilus. Therefore, the study questions whether the organism chosen for the biological indicator (BI) is the appropriate one.

- The BI test pack container has a remarkably large entrance port (5 mm x 8 mm), providing little diffusion challenge in comparison to the challenge experienced by ETO.

- The chemical indicator, which is supposed to indicate the presence of H_2O_2 inside sealed packages by color change, apparently is affected by exposure to light and was found to change color in the absence of hydrogen peroxide.

In addition, it has been noted that the BI is not buried in the load but is placed in the open on the lower rack of the H_2O_2 plasma sterilizer. Also, physical "shadows" and void spaces—such as valve interiors and tightly mating parts—may prevent the plasma from effectively reaching all surfaces. Taken collectively, there is little similarity to the degree of challenge that is traditionally placed upon the ETO BI and the challenge placed upon hydrogen peroxide plasma BIs. Therefore, the German studies suggest that confidence that sterilization has, in fact, been consistently accomplished (especially on "interior" surfaces) with the H_2O_2 plasma method may be reduced.

Subsequent to the appearance of Mecke's reports, Koller and Lessky,[6] in an article entitled "Microbiological Test Results and Observations with a Hydrogen Peroxide Plasma Sterilizer," question the appropriateness of the indicator organism chosen for the BI and criticize the configuration of the BI test pack.

In a follow-up letter[26] commenting on the earlier article in *Zentral Sterilisation*, Koller also points out that the H_2O_2 plasma chemical indicator does not discriminate between liquid or vapor phase H_2O_2, thus demonstrating the apparent inability to establish that the plasma phase was present in the sterilizer.

Independently, other questions have been raised regarding:

- the adequacy of the recommended frequency of biological monitoring within the chamber (i.e., one or more BIs/load vs. one or more BIs/day);

- the need to quarantine items processed in the sterilizer;

- the implications of obtaining a "positive BI," and its impact on prior "unmonitored" loads (loads run without BIs);

- the need for specific materials for packaging and/or wrapping of items to be sterilized, and to provide maintenance of the sterility of the processed items;

- recordkeeping requirements, as well as a number of other questions.

Because of the complexity of the process compared to steam, and the variability (especially of bioburden levels) of the loads to be sterilized, we maintain that a BI should be used for every load processed in any chemical sterilizer, especially one in which there are many variables. This will ensure that every load has appropriate sterility assurance. Otherwise, up to several loads per day can be distributed for patient use with little or no ability to ascertain that all facets of the technology were operated properly and inactivated all microbiological entities. This is especially important to users of the H_2O_2 plasma system, since at least some of the units may provide no warning if an empty cassette has been used inadvertently.

According to FDA Medical Device Reports (MDRs), recent incidents of infection and a death have occurred in an institution utilizing the H_2O_2 plasma technology—a strong indicator that every load should be biologically monitored. These instances were apparently accompanied by positive BIs, seemingly indicating that for some reason(s) sterilization had not occurred in some items in those individual loads.

These events also provide a compelling reason to quarantine processed loads until the BIs have been conclusively evaluated, to assure that sterilization has occurred.

It should be noted that adequate quarantine practice can yield sterility-assured items in about one day with ETO/HCFC technology, as opposed to at least several days for the plasma processes, due to the respective incubation and "grow-out" times for the biological indicators. ETO/HCFC technology, when compared under conditions of proper quarantine procedure, is therefore considerably shorter in total cycle time than either of the plasma technologies.

Materials compatibility considerations

Most materials from which medical, dental, and veterinary devices are manufactured are compatible with ETO. Indeed, it has been stated frequently that the entire disposable medical device industry was based initially upon the use of ETO as a sterilant. The compatibility consideration is also true for the materials from which most reusable items are manufactured.

Certain products and materials cannot be processed in some of the H_2O_2 plasma and other non-ETO sterilization equipment, due to composition of the product (cellulosics), reactivity with the materials, and construction of the device or product. Examples are closed cell foams and the fact that they give off gases as the chamber pressure is reduced in the sterilizer. The presence of these gases and vapors from certain materials, such as polyurethane foams and moisture, can interfere with the plas-

ma generation, causing the H_2O_2 plasma cycle to abort. This complicates the processing of certain devices and items such as trays for nursing services, because the trays often contain gauze, bandages, and/or moist or other cellulosic items, along with other incompatible devices. In addition, changes in surface—including those associated with certain anodized coatings, discoloration, paint, ink color and marking changes—and/or reduced readability or legibility have been reported.

Latex rubber and certain other polymers also are incompatible with or inactivate the H_2O_2 plasma process. Koller and Lessky noted that certain nylon (polyamide) electrical cable connectors disintegrated following 20 cycles in the H_2O_2 plasma unit due to accelerated aging and chemical attack. In addition, damage to certain other materials sterilized in the chamber was observed. Koller also has measured the temperatures in the H_2O_2 plasma chamber. Chamber temperature was found to range between 54 and 75°C. The measured chamber temperature variations suggest an uneven pattern of temperature establishment and/or maintenance within the H_2O_2 plasma chamber that may contribute to the localized material damage.

Koller and Lessky[6] suggest that a thorough evaluation of all materials be performed prior to exposure to the H_2O_2 plasma, including evaluation of potential instability of each material at elevated temperatures.

Cycle development, process validation, and sterility assurance

Sterilization cycle validation must be accomplished for every device, instrument and item that is processed in any sterilizer, regardless of the sterilization technology utilized. Generally, the responsibility for validation of a device rests with the device manufacturer, while validation of a sterilizing process rests with the sterilizer manufacturer. The steps involved in sterilizer process and cycle validations are extremely complex. In fact, validation is often so complex and time consuming that many manufacturers contract with recognized and experienced testing laboratories to perform sterilization cycle development and validation studies for their new or modified products.

Very few health care facilities, including hospitals, have the experience, personnel, equipment, time and money to conduct the validation studies and to perform the required microbiological laboratory measurements properly (*i.e.*, rigorously, statistically, and using scientifically designed protocols).

This is further complicated by the knowledge that medical device, instrument, and equipment manufacturers generally sterilize new (clean) devices. Health care facilities, on the other hand, must deal with the reality of sterilizing used (dirty) items, which may pose a significant challenge to sterilant penetration.[27] Clearly, such challenges further complicate validation studies and make it even more difficult for health care facilities to appropriately establish their own cycle validation.

It has recently come to our attention that at least two sterilizer manufacturers, as well as some device manufacturers, are suggesting that the health care facility is at least partially responsible for the validation of the cycle for various items to be reprocessed using a particular sterilization technology. In other words, this critical information is either not available from or not provided by the device, instrument, equipment, or sterilizer manufacturer. This is a disturbing situation.

The issue of who validates the sterilization cycle is made even more interesting by a recently published survey[28] of Central Service (CS) professionals who are using "alternative" technologies to sterilize instruments. The survey revealed that 76 percent of the alternative sterilization technology users believe that the sterilizer manufacturer has performed the cycle/process validation testing. The survey also revealed that 7 percent of the end-users of alternative sterilization technologies know that their sterilization process has not been validated.

Thus, we may well be in a situation where 83 percent of the sterilization performed by end-users of alternative technology has not been validated at all. This is an even more disturbing situation.

We maintain, as does the FDA, that process validation is the responsibility of the sterilizer manufacturer and that cycle development and validation is the responsibility of both the sterilizer and device manufacturers, not the end user. Full validation information—such as the demonstrated appropriateness of the technology; cycle parameters; material compatibilities; biocompatibility; absence of physical, chemical, and mechanical changes; necessary sterilant concentration and contact time; and statistically valid scientific data proving the process and cycle for the individual item(s) in question—should be provided by the respective manufacturers. End-users are cautioned against blindly "throwing everything into the sterilizer," unless they have the above mentioned critical validation data in hand. To do otherwise may jeopardize confidence in the sterility assurance of certain reprocessed critical items.

This point is indeed a major issue. Both commercial H_2O_2/peracetic acid and H_2O_2 plasma sterilizers have FDA 510(k)s that limit the types and kinds of medical devices that can be sterilized. Almost all other medical devices are to be qualified by the medical and/or health care facility—not by either of the sterilizer manufacturers or by the device manufacturers. This situation is addressed by both FDA and AAMI, who, while recommending that the health care facility request reprocessing information from manufacturers, also point out that the responsibility

for implementing the recommendations rests with the health care facility.

Utilization of other sterilization technology in health care facilities cannot convey the capability to replace or displace general purpose sterilization using other validated and FDA-cleared sterilizing technologies. This is, in part, due to the lack of FDA clearance for use of the plasma technologies as a complete general purpose sterilizer. Such utilization of dual technologies also may introduce a very serious potential compromise of sterility assurance by introducing the potential error of mistakenly processing an item in a sterilizer that is not appropriate for that item. Maintaining multiple sterilization technologies also represents a duplication of investment and costs.

Yet one more misconception needs to be addressed at this point, validation of ETO/ HCFC sterilizing processes. We continue to hear disturbing comments suggesting that ETO/HCFC sterilizing technology has "never been validated" and "could never pass the FDA requirements." The sterilizing community needs to be fully aware and informed that two separate manufacturers of ETO/HCFC sterilizers performed extensive validation studies of ETO/HCFC technology. The process validations are documented fully, as are the associated materials compatibility studies. Also, suppliers of ETO/HCFC sterilants have submitted technical information to the EPA and the FDA for their sterilant mixtures. In addition, a significant number of device manufacturers, as well as other users, have validated ETO/HCFC sterilization for their devices and have submitted that data to the FDA when filing device 510(k) notification, modification, or seeking device premarket clearance.

Current Good Manufacturing Practices (cGMPs)

Lack of requisite validation data may undermine a health care facility's capability to conduct processing to render used devices sterile. This data is necessary to fulfill the mandates of the FDA current Good Manufacturing Practices (cGMPs)/ Quality System Regulation, and Good Laboratory Practices (GLPs). cGMPs may become one of the major regulatory concerns of the near future for health care facilities, as the FDA contemplates possible expansion of its regulatory influence into health care facilities.

The FDA has discussed the possibility of considering the reprocessing/ resterilizing of used medical devices within health care facilities to be a form of "device manufacturing or re-manufacturing." As such, the health care facility could be subject to cGMP regulation, like the original manufacturers of the devices. To the manufacturer, cGMPs entail rigid procedural and administrative activities such as recordkeeping requirements; documentation of training; knowledge and documentation of all materials, ingredients, and components; audit "trails"; statistical process and quality control; measuring, monitoring, and documenting of equipment processing parameters and calibrations; and formal compliance with published directives and protocols. This could establish the FDA's ability to declare items, deemed to be improperly processed, to be adulterated or misbranded. In that event, depending on the severity of the violation, the FDA could issue a warning letter, fine the health care facility, seize the product, and/or shut down the operation. Incidentally, CDRH/FDA has already been petitioned (9/97) by the Health Industry Manufacturers Association (HIMA) to regulate the commercial reprocessors of "single use" medical devices.

Health care facilities that perform sterilization for other health care facilities or organizations are technically engaged in the "manufacture" of medical devices, according to the FDA, and need to be extremely diligent to establish and follow full cGMP procedures and comply with other sections of the FDA requirements. It appears to be a less risky and less complex situation (from the perspective of compliance with FDA regulations) for health care facilities not to engage in the act of sterilization of instruments, devices, and equipment that they do not own.

Economic comparisons

There are two phases of economics that must be explored fully to evaluate the financial impact of a given technology—operating cost and investment analysis.

Operating cost is relatively straightforward but must be examined in detail to be certain that supplier bias and evaluation errors are eliminated. To examine the operating cost of competing technology, one must first determine the daily or weekly volume, in cubic feet, of products/items/devices that must be sterilized.

Next, one must determine by physical measurement the actual *usable* chamber volume for the given technology. Note also how densely the items to be sterilized can be packed into the chamber; whether items can be placed on top of other items in the chamber; whether items can be placed out to the walls of the chamber; and whether items must remain a certain distance from the walls. Realize that a chamber with curved walls and with nonadjustable shelves limits the size, shape, and volume of items that can be sterilized.

Also, supplies, such as BIs, consumed per cycle and the number of cycles run per day or per week to meet the sterilizing demand must be determined. Beware of biased cost entries for such items as training, regulatory compliance, hazard insurance, and/or liability provisions. All of the current technologies are roughly equivalent in the moral and ethical, if not regulatory, need for training, employee and environmental monitoring and protection, as well as risk management and control. The need for adequate hazard insurance coverage exists with all the sterilization methods, along with the need to protect one's staff and facili-

ty from liability and lawsuits. There is no clear advantage or economy to any of the current sterilizing technologies in these areas.

Investment analysis deals with balancing the projected cost savings, if any, against the investment required. Although very sophisticated methods exist to measure the economic desirability of purchasing a specific instrument, device, or equipment, a rather simple method—*payback*—generally suffices.

Payback is defined as the period (number of months or years) that pass before the operating cost savings realized from the expenditure of funds equals the investment made. Essentially, this analyzes how long it takes to pay back an interest-free loan from operating savings. Most health care institutions will not invest money in a project unless the payback period is less than 18 months.

The following economic comparison uses operating cost data for each sterilizing technology and applies that data to an ETO/HCFC sterilizer with a chamber volume of 8.8 cu ft This permits an objective comparison of each technology to see which is lowest in operating cost. The economic summary presented in Figure 8 is based on the comprehensive economic analysis presented as Appendix A and uses cost data generally available from the manufacturers of each technology. The comparison demonstrates that the HCFC-based sterilizers are the lowest-cost sterilization method, both in terms of operating cost and capital investment

Appendix A is a comprehensive economic analysis for a typical 8.8 cu ft sterilizer, which has internal dimensions of 20 x 20 x 38 in, using ETO/HCFC mixture. Costs for other technologies, including 100 percent ETO, ETO/CO_2, H_2O_2 plasma, and peracetic acid/H_2O_2 plasma for equivalent daily processed volumes are shown for comparison. The cost data relating to the non-ETO/HCFC technologies used for the economic analyses is publicly available in promotional literature and advertisements from the manufacturers.

Figure 8. Economic comparison of sterilizing methods considered

(8.8cf ETO/HCFC sterilizer as baseline)

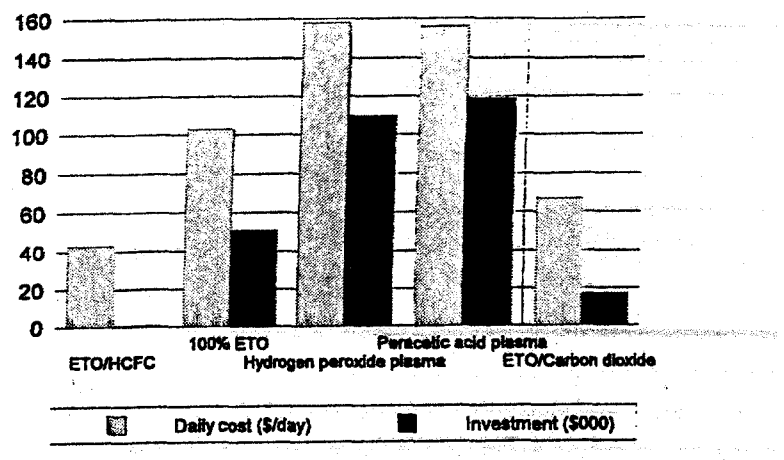

Figure 8. Chart illustrating comparison of daily cost and investment, to the baseline of an 8.8 cubic foot (cf) sterilizer equipment for units using ETO/HCFC, 100 percent ETO, ETO/CO_2, hydrogen peroxide plasma, and peracetic acid/hydrogen peroxide plasma. Cost basis for comparable daily volumes processed have been calculated using cost data provided or published by manufacturers of each technology. (See Appendix A).

Interestingly, whether one invests approximately $115,000 in new sterilization technology or a comparable amount in additional instruments, devices and/or equipment, the financial impact is the same. However, some of these instruments, devices and/or equipment cannot be sterilized by the new plasma technology, essentially negating any cycle time advantage or instrument/device inventory reduction. This also strongly indicates that ETO sterilization will need to remain in place, even if the new plasma sterilization technology is utilized.

If the choice is between investing in new technology that cannot terminally sterilize all types of instruments and investing in additional instruments to ensure that a sufficient number of sterile instruments are available while the "used" instruments are being processed, we recommend investment in additional instruments. This course of action will ensure to all patients equal treatment *and* the highest "standard of care" by ensuring the provision of terminally sterilized (not merely disinfected) endoscopic and related instruments and their accessories.

A US Department of Defense (DOD) health care-related technical library information bulletin,[29] issued in March 1995, dealing with the topic of Ozone Depleting Substances (ODS), specifically concluded that converting existing sterilizers from ETO/CFC mixture to ETO/HCFC mixture, as opposed to purchasing new sterilizers, showed significant economic advantage. The conversion offers an environmentally acceptable alternative and retains the sterilization efficacy required by military medical standards.

Suggested evaluation criteria and interpretation

In order to effectively choose a "winner" among the competing sterilization technologies being consid-

ered, one must consider the following issues:

- efficacy/effectiveness, especially in the microbiocidal sense;
- safety to staff, environment, reprocessed devices and instruments;
- absence of toxic residue or byproduct on or in the sterilized item;
- amount of disruption of the Standard Operating Procedures (SOPs) from the sterilization process/practice/technology;
- number of repetitive cycles needed to be run in order to meet the sterilizing demand and to accommodate the volume/number of each item required;
- total cycle time, including BI grow-out time required for sterility assurance;
- ability to sterilize the wide variety of devices, instruments, and equipment used within the health care facility;
- 510(k) clearance or PMA approval (for the list of FDA-approved items that may be sterilized as of the current date);
- materials compatibility;
- process and cycle validations;
- operating costs;
- investment payback;
- investment duplication and cost because not all items needing sterilization can be processed in plasma sterilizers.

It has been shown in every category, that the ETO/HCFC-based sterilizers are the best performers. ETO/HCFC cycle time may become even more rapid. Several new ETO sterilizers that use the nonflammable mixture are being tested currently with strong evidence of cycle times (for certain loads) as short as 1½ to six hours, plus BI incubation time. These shortened cycle times may reduce the need to acquire additional instruments, devices and supplies.

Among those sterilizing technologies and processes presently available, the ETO/HCFC mixtures are the broadest spectrum, most reliable, effective and rapid (considering BI "grow-out" time) sterilizing technology currently available for use within health care facilities. In addition, in well-maintained sterilizers, the ETO/HCFC sterilizing mixtures offer superior safety and economic performance. Consequently, new ETO/HCFC sterilizers or reconditioned 12/88 ETO/CFC sterilizers represent the most useful, reliable, safe and cost-effective devices.

Conclusion

Nonflammable ETO/HCFC mixtures provide an excellent technological foundation for general purpose terminal sterilization of items that cannot be steam or dry heat sterilized. Much attention has been focused on ETO toxicity, on the misconception of comparatively lengthy cycle times for this technology, and on ETO abatement requirements. However, the scientific and ethical issues necessitate quarantining all sterilized items, regardless of what sterilizing method is used, until the results of the BI have been received and demonstrate that sterilization has occurred.

These authors believe that it is in the best interest of the health care-based sterilizer-using community for the major manufacturers of sterilizing equipment that use the ETO/HCFC mixture to commit their resources to achieving further reductions in total cycle times. As noted earlier, shorter cycle times for the ETO/HCFC sterilant mixtures already have been demonstrated successfully (in the 1.5- to six-hour range, plus BI incubation time) and may soon become commercially available.

When proper quarantine procedures are followed and the BI is allowed adequate time to grow out/incubate properly, complete cycle times for ETO technology are shorter than either of the so-called "rapid" plasma technologies.

The toxic nature of ETO, H_2O_2, and peracetic acid has been discussed here and elsewhere.[30] It is clear that each of these chemicals is roughly equivalent in terms of health risks, and that virtually identical employee, practitioner, and patient exposure prevention practices, procedures, and equipment are needed when using any of these toxic materials.

Compliance with the OSHA ETO Regulations has taught the sterilizing community to work safely with ETO. This is evidenced by the documented steady decline in employee exposures to ETO in US health care facilities.

We have reported and discussed data regarding employee exposures to hydrogen peroxide and peracetic acid associated with the use of the respective plasma sterilizers in health care facilities. Glaser[31] provided similar data for ETO in 1977 that was instrumental in the development and promulgation of the OSHA ETO regulations. We believe that similar regulation of H_2O_2 and peracetic acid in health care facilities is required based on documented worker exposures to these materials.

Terminal sterilization cannot be sacrificed for perceived cycle time reduction, particularly where laproscopes, flexible endoscopes and similar instruments and devices are concerned. As we discussed previously, we generally favor investment in additional diagnostic, therapeutic and related surgical instruments, as opposed to unnecessary duplication of sterilization system investment.

In ETO abatement, the previously utilized catalytic combusters have a fairly high capital cost (approximate-

ly $80,000) and require extensive space and installation requirements. Catalytic combustion abatement ("disposers") utilize relatively high temperatures to react ETO with oxygen, yielding nontoxic products. However, this oxidation reaction is actually a combustion or burning operation. This may be of great concern when used with 100 percent ETO. A series of explosions have occurred—unfortunately, involving loss of life—where 100 percent ETO was involved; these incidents may be related to the use of catalytic combustion for ETO abatement. The EPA has advised a halt to the use of catalytic combusters with 100 percent ETO while it continues its investigation into the actual cause(s) of the explosions.[32]

Currently, the newer, yet field-proven, low temperature scrubber technology has reduced the cost and complexity of ETO abatement drastically. Scrubbing technology providers have reduced ETO abatement capital costs by over 50 percent and have virtually eliminated system maintenance and operating costs, while satisfying regulatory requirements for ETO abatement. One such commercial technology is utilized in our sample economic analyses for its technical relevancy and cost effectiveness.

It must be made clear to the sterilizing community that old ETO sterilizers utilizing the 12/88 ETO/CFC sterilizing mixture remain a valuable asset that can be reconditioned readily, easily, and economically. In reality, the most expensive portion of an ETO mixture-using sterilizer is the pressurizable chamber, which is permanently certified to the specifications of the ASME (American Society of Mechanical Engineers) and rarely wears out. Like steam sterilizers, ETO sterilizers that use the nonflammable ETO/HCFC or ETO/CFC mixture, are completely reconditionable because only the controls, plumbing/piping, and seals need to be replaced. A growing number of health care facilities are discovering the surprisingly attractive economics of ETO mixture-using sterilizer reconditioning. It is also relatively simple to upgrade the sterilizer's controls during reconditioning. Reconditioned sterilizers are becoming more available for outright purchase, in which case a simple drop-in installation is possible. When a drop-in installation is utilized, the existing sterilizer may have some trade-in value. As long as the sterilizer is reconditioned without disrupting the already validated operating parameters (such as cycle time, operating pressure, etc.), FDA notification/clearance does not have to be reobtained. Even the addition of the capital cost for the reconditioning of an existing sterilizer does not substantially change the operating costs, nor the fact that ETO/HCFC is still the most economical method to utilize. Service organizations are available to provide installation, routine maintenance, and repairs. This is also an attractive, effective, and economical option if no existing ETO mixture-using sterilizer is available onsite.

Thus, taken as a total systems concept, we recommend:

- Purchasing sufficient numbers of instruments and devices, so that the required "turn-around" time necessary for reprocessing doesn't impact the surgical schedule adversely or sacrifice sterility for speed.

- Adequate reprocessing between patient procedures, consisting of efficacious microbiocidal treatment, following thorough cleaning.

- Utilization of general purpose terminal sterilization using the ETO/HCFC mixture, rather than high level disinfection.

- Scrupulous, scientific and ethical consideration of load quarantine until sterility assurance can be established. This involves the biological monitoring of each load reprocessed.

- Reconditioning of existing ETO mixture-using sterilizers, as opposed to investment in new sterilizing technology.

- Where required, use of ETO scrubbing technology to assure safe environmental compliance, minimize capital investment, and avoid multi-sterilizer sequencing delays (up to several hours) encountered with catalytic combusters/disposers.

- Appropriate training of all involved staff members—including maintenance staff and support personnel—in the proper procedures so as to assure compliance with applicable state and OSHA regulations, and AAMI, AORN, and related recommendations.

- These recommendations go hand-in-hand with realizing the final objective, i.e., the highest equal standard of care for all patients; minimal risk to patients, health care workers, the community, and the environment; and the best cost-to-benefit ratio.

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Appendix A					
Technology	10% EO/HCFC PENNGAS2	3M/AMSCO 100% ETO	J&J Peroxide	AbTOX Peracetic	Castle ETO/CO_2
Nameplate volume (cubic feet)	8.8	4.8	5.0	5.0	8.8
Useable volume (cubic feet)	6.0	2.9	2.9	4.3	6.0
Utilization factor	0.75	0.75	0.60	0.60	0.75
Daily cycles	1.0	2.8	3.4	2.3	1.0
Sterilant used per actual cycle	2.9 pounds	1.0 cartridge	0.1 cassette	0.4 bottle	3.4 pounds
Sterilant unit cost	$6.25/pound	$6.00/cartridge	$80.00/cassette	$18.75/bottle	$6.21/pound
Plasma gas	$0	$0	$0	$600/cylinder	$0
Sterilant cost per actual cycle	$18.15	$6.00	$8.00	$11.16	$21.21
Sterilant cost per day	$18.15	$16.55	$27.59	$25.95	$21.21
Biological indicator unit cost	$4.00	$4.00	$4.00	$2.25	$4.00
Biological indicator cost per day	$4.00	$11.03	$13.79	$5.23	$4.00
Chemical indicator unit cost per day	$0.80	$0.80	$0.05	$0.10	$0.80
Chemical indicator cost per day	$0.80	$2.21	$1.72	$2.33	$0.80
Utilities per actual cycle	$9.00	$2.00	$0.24	$0.24	$9.00
Utilities per day	$9.00	$5.52	$0.83	$0.56	$9.00
Cylinder rent per day	$0.20	$0.00	$0.00	$0.20	$0.60
Retraining rewrite procedures cost per day	$0.03	$0.13	$0.13	$0.13	$0.04
Monitors/protective equipment per day	$2.88	$2.88	$2.88	$2.88	$2.88
Maintenance daily	$16.03	$25.64	$22.44	$22.44	$16.03
Subtotal daily cost	$51.09	$63.96	$69.38	$59.72	$54.56
Financial costs (* new sterilizer)	$0.00	$40.87*	$86.54*	$93.97*	$12.82
Total cost per day	$51.09	$104.83	$155.92	$153.69	$67.38
Investment analysis					
Technology	10% EO/HCFC PENNGAS2	3M/AMSCO 100% ETO	J&J Peroxide	AbTOX Peracetic	Castle ETO/CO_2
New sterilizer	$0	$33,000	$106,000	$115,000	$0
Conversion of existing sterilizer	$0	$0	$0	$0	$16,000
Aerator	$0	$14,000	$0	$0	$0
Additional equipment	$0	$4,000	$2,000	$2,275	$0
Total investment	$0	$51,000	$108,000	$117,275	$16,000
Cost of capital@10% (Annual) (Per day)	$0 $0.00	$2,550 $8.17	$5,400 $17.31	$5,864 $18.78	$800 $2.56
Amortization (Annual) (Per day)	$0 $0	$10,200 $32.69	$21,600 $69.23	$23,455 $75.18	$3,200 $10.26
Total financial costs (Annual) (Per day)	$0 $0	$12,750 $40.87	$27,000 $88.54	$29,319 $93.97	$4,000 $12.82

Update
April, 1998

"Comparison of health care-based sterilization technologies: Safety, efficacy, and economic"
Journal of Healthcare Safety, Compliance & Infection Control
Volume 1, Number 2, December, 1997

The United States Environmental Protection Agency has recently changed the reportable quantities for hydrogen peroxide and peracetic acid. The new reportable quantities and 1000 pounds for each material. There has been no change for ethylene oxide. The NFPA 704 health ratings for sterilants may differ, depending upon which manufacturer' material safety data sheets (MSDS) are consulted. Ethylene oxide, hydrogen peroxide and peracetic acid continue to exhibit approximately similar toxicities, making worker protection a continued potential concern for health care sterilization operations.

Please make a note of these changes as you evaluate this journal article.

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