# AECIZATION OF MEDICAL DEVICES STERILIZED TO ETHYLENE OXIDE: CONSIDERATIONS ABOUT BRAZILIAN REGULATION

## *Aeração de dispositivos médicos esterilizados a óxido de etileno: considerações acerca da regulação brasileira*

## *Aireación de dispositivos médicos esterilizados con óxido de etileno: consideraciones sobre la regulación brasileña*

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**ABSTRACT: Objectives:** To describe acceptable residual levels of ethylene oxide in medical devices, analyze recommended aesther processes and compare them with the Brazilian regulation. **Method:** Integrative literature review, with specific descriptors, without year of publication restriction. Data search between October and November 2019, which resulted in 34 studies included in the study. **Results:** Current Brazilian regulation is outdated in relation to product classification, the determination of waste values ethylene oxide toxic in medical devices and the recommended processes for the aecization of these products, and may contribute to risks of adverse events for patients users of inappropriately aenated devices, and consequently urge their update. **Conclusion:** The shortcomings of this regulatory framework indirectly benefit companies that outsource ethylene oxide sterilization by omitting essential controls for safety of the patient exposed to possible toxic residues of ethylene oxide, unsafe practices of sterilization of health products, in addition to hindering the control of health service by the country's health surveillance.
**Keywords:** Equipment and supplies. Sterilization. Ethylene oxide; Toxic waste.

**RESUMO: Objetivos:** Descrever níveis residuais aceitáveis de óxido de etileno em dispositivos médicos, analisar processos de aeração recomendados e compará-los com a regulação brasileira. **Método:** Revisão integrativa da literatura, com descritores específicos, sem restrição de ano de publicação. Busca dos dados entre outubro e novembro de 2019, que resultou em 34 estudos incluídos no estudo. **Resultados:** A regulação brasileira vigente está desatualizada em relação à classificação de produtos, à determinação de valores de resíduos tóxicos de óxido de etileno em dispositivos médicos e aos processos recomendados para a aeração desses produtos, podendo contribuir para riscos de eventos adversos para pacientes usuários de dispositivos inadequadamente aerados, e, consequentemente, urge sua atualização. **Conclusão:** As lacunas desse marco regulatório beneficiam indiretamente as empresas que terceirizam a esterilização a óxido de etileno ao omitir controles essenciais para a segurança do paciente exposto a possíveis resíduos tóxicos de óxido de etileno, favorecer práticas inseguras de esterilização de produtos para saúde, além de dificultar o controle de serviço de saúde pelas vigilâncias sanitárias do país.
**Palavras-chave:** Equipamentos e provisões. Esterilização. Óxido de etileno. Resíduos tóxicos.

**RESUMEN: Objetivos:** Describir los niveles residuales aceptables de óxido de etileno (OE) en dispositivos médicos, analizar los procesos de aireación recomendados y compararlos con la normativa brasileña. **Método:** revisión integrativa de la literatura, con descriptores específicos, sin restricción de año de publicación. Búsqueda de datos entre octubre y noviembre de 2019, que resultó en 34 estudios incluidos en el estudio. **Resultados:** La normativa brasileña actual está desactualizada en cuanto a la clasificación de productos, determinación y valores de residuos tóxicos de OE en dispositivos médicos y procesos recomendados para la aireación de estos productos, lo que puede contribuir al riesgo de eventos adversos para los pacientes que utilizan una aireación inadecuada de dispositivos y, en consecuencia, se necesita urgentemente una actualización. **Conclusión:** Las brechas en este marco regulatorio benefician indirectamente a las empresas que externalizan la esterilización a OE, al omitir controles esenciales para la seguridad de los pacientes expuestos a posibles residuos tóxicos de OE, favoreciendo prácticas inseguras de esterilización de productos sanitarios, además de dificultar el control de servicio de salud por la Vigilancia Sanitaria del país.
**Palabras clave:** Equipos y suministros. Esterilización. Óxido de etileno; Residuos tóxicos.

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## INTRODUCTION

The reuse of medical devices classified as "reusable" or "multiple-use" requires reprocessing, a method that consists of converting a contaminated product into a ready-to-use instrument. It includes not only cleaning, disinfecting, or sterilizing the product but also ensuring its technical-functional safety through integrity and functionality testing[1-4].

The literature agrees that the reprocessing of health products (HP) is a complex issue, given the risks related to the potential transmission of pathogens and the integrity and performance problems of reused products[5-7].

The risk of pathogen transmission through the use of medical products depends on the presence of microorganisms, the type of procedure to be performed, and the body site where the product will be used[5]. Among the risks associated with HP reprocessing and reuse, the literature mentions: infection, presence of endotoxins, biofilms, loss of material integrity, bioincompatibility, and others[1-7].

Medical devices considered critical (inserted into sterile body parts) and thermosensitive (those that do not resist high-temperature sterilization methods) require low-temperature sterilization methods to be reused, including ethylene oxide (EO), hydrogen peroxide plasma, formaldehyde vapor, and ozone sterilization[8,9]. Among these methods, EO sterilization is the oldest and regarded as the gold standard due to the high diffusibility and power of the sterilizing gas; however, it is also the most toxic[8-19].

EO-sterilized products may present toxic residues (ethylene chlorohydrin [ECH] and ethylene glycol), which, if not removed, can harm patients users of these products, professionals who manipulate them, and the environment. Therefore, it is imperative that these HP be submitted to a process called "aeration" to remove toxic waste[8-20].

In Brazil, the standard regulating the EO sterilization of medical devices — Interministerial Decree No. 482[21] — dates back to the 1990s.

In this scenario, this study prioritizes the risk of toxic EO residues in products sterilized by this agent and seeks to answer the following central question: what are the acceptable levels of EO residues in sterile medical devices, and which parameters guide their aeration?

## OBJECTIVES

The present study aims to describe acceptable residual levels of EO in medical devices, analyze aeration processes recommended in the literature, and compare them to the current Brazilian regulation in order to prevent risks for patients who use these devices.

## METHOD

This is an integrative literature review, a method that allows analyzing studies with different methodologies on a particular theme, potentially producing new knowledge[22].

The present investigation followed these steps: identification of the study object and elaboration of the guiding question; data search and definition of inclusion and exclusion criteria for the sample; determination of the information to be extracted from the selected studies; assessment of the studies included in the review; presentation of the review; summary of the results.

The studies were obtained from searches in the Virtual Health Library portal, CAPES journals, and Web of Science. The set of health descriptors used in the search for publications was: *ethylene oxide gas sterilization* AND *time aeration of sterilized materials*; *ethylene oxide gas sterilization* AND *absorption sterilized materials*.

The inclusion criteria adopted in the study were: articles published in English, Spanish, and Portuguese, in any year, in the databases consulted, and with access to the full text. Articles on EO that did not address product aeration, published in other languages, and with paid access were excluded.

Data were searched online in October and November 2019, yielding 1,189 articles. After reading the titles and abstracts, 827 articles were excluded, 27 were selected, and 7 were incorporated from the references of the selected studies, totaling 34 articles in this review (references 8–21 and 23–42).

After selection, the full articles available and the abstracts of unavailable articles were read. Next, the studies were critically analyzed by exploring the material, treating the results obtained, interpreting the findings, and identifying explanations for different or conflicting results in order to make recommendations for the practice. The study was systematized using a data collection instrument that included: article title, objectives, method, results, and conclusion.

This review adopts the term "medical device" as a synonym for material, medical product, and HP, in accordance with the Brazilian Health Regulatory Agency (*Agência Nacional de Vigilância Sanitária* — ANVISA). The terms reprocessing and product processing are also used as synonyms, despite considerations about the differences between them.

## RESULTS

Out of the 34 articles analyzed, 13 (38.2%) were literature reviews, 11 (32.3%) were experimental studies, 8 (23.5%) were recommendations from official agencies, and 2 (5.8%) were studies with varying methodologies. Regarding origin, 16 studies (47.0%) were carried out in the United States, 11 (32.3%) in Brazil, and 7 (20.5%) in other countries.

The articles from this integrative review are presented below.

### Presentation of selected studies on ethylene oxide sterilization and aeration of medical devices

EO sterilization is the oldest low-temperature method, used since 1950. It is extremely effective for its high penetration power, high diffusibility, and permeability, favoring the sterilization of products within sealed packages and access to long and narrow lumens composed of any raw material[8-17,19,23-35].

This gas agent is explosive, colorless at atmospheric temperature and pressure, has an unpleasant smell, is soluble in water at 10°C, reacts in acid pH forming ethylene glycol, and reacts with chlorine forming ECH, both toxic. Its excellent bactericidal, virucidal, fungicidal, and sporicidal activity is attributed to the alkylation of proteins and nucleic acids of microorganisms; however, it does not inactivate prions[8-17,23-25,27-31,35].

It is considered a mutagenic, carcinogenic, teratogenic, and neurotoxic agent. Exposure to this gas may cause eye and respiratory tract irritation, headache, nausea, vomiting, contact dermatitis, burns through direct contact, and high exposures can lead to chromosomal aberrations in the short term. When inhaled, it has carcinogenic effects, resulting in several types of neoplasms, such as leukemia, brain cancer, and breast tumor[8-17,25,27-29,33,35-38].

The maximum level of EO vapors in the air in working environments is 1 ppm for an average of 8 hours of exposure and 5 ppm for maximum exposure of 15 minutes[8,9,14-17,20,23,24,27,28,33].

In 2010, the US Environmental Protection issued a regulation to reduce EO levels in workplaces and prevent the occupational carcinogenic potential related to this agent. It demanded that hospitals and health services use a single chamber, combining sterilization and aeration[34,39].

EO sterilization requires special inter-related controls that vary according to the type of sterilizer, but the general characteristics are: gas concentration from 450 to 1,200 mg/L; temperature between 37 and 63°C; relative humidity from 40 to 80%; exposure time from 4 to 6 hours. Surveillance should be performed by mechanical monitors (temperature, gas concentration, pressure, exposure time) at each sterilization load, chemical monitors (each package), and biological monitors (*Bacillus atrophaeus sp.*) at each cycle. The basic cycle consists of five stages: preconditioning or humidification, gas introduction, exposure, evacuation, and air washes and irrigation[8,9,14-17,19,20,29,33,35-37].

Excessive levels of residual EO or its by-products, such as ethylene glycol and ECH, in medical products are potentially toxic and should be removed from materials after the sterilization cycle to prevent harming patients who use these products[8,9,14-20,26,29-36,40].

Aeration é o método através do qual o óxido de etileno can be performed by the sterilizing chamber itself (mechanical aeration) or in exclusive rooms (ambient aeration). Mechanical aeration is considered the most efficient and safe method of EO waste removal[16,17,19,20,34,35,39-41].

Ambient aeration should be performed in exclusive and restricted rooms, under negative pressure, with control of air temperature and flow (minimum of 25 air changes/hour)[21,25,31,33], and exhaust to the outside environment. This aeration process is not only lengthy but exposes workers to toxic vapors during the transfer of sterile loads to the aeration room, may not be effective depending on air temperature and flow conditions, and is contraindicated by international regulatory bodies[20,27,34,35,39].

The aeration duration relies on some variables, such as: features of the medical device (composition, shape, density, weight, and packaging used), type of packaging, type of sterilizer, temperature of the aeration chamber, number of air filter changes per hour, and characteristics of the air flow, as well as the purpose of the product (external or internal use)[8-11,16,17,20,26,30,35,40].

Mechanical aeration parameters also influence the length of time required to remove EO from products. Temperature and the number of chamber air changes have a significant impact on the aeration process. The higher the temperature, the shorter the time required for product aeration[16,17,20,30,35,40].

Some authors report that aeration time can range from six hours to seven days depending on the composition, device size, aeration system, and type of sterilizer[26,29]. Another author[33] recommends a minimum aeration time of 12 hours when not specified by the product manufacturer.

A Cuban study reveals that total disposal or reduction of EO residues to permissible limits requires a detoxification process that can last from 48 hours to more than 10 days,

according to the number of sterilizations performed in the same device[36].

Before the regulation prohibiting ambient aeration in health services in the United States[39], the Centers for Disease Control and Prevention (CDC) recommended mechanical aeration from 8 to 12 hours at a temperature of 50 to 60°C or ambient aeration in exclusive rooms for 7 days at 20°C[8,9,27].

In Cuba, the aeration of EO-sterilized products follows a strict pattern: 24 hours of aeration inside the chamber after the end of sterilization, 8 hours of detoxification at 60°C, and ambient aeration from 7 to 10 days in a ventilated room[15].

A Brazilian study aimed to identify EO residues in polyethylene enteral feeding containers sterilized by this agent. After the standard sterilization cycle (430 mg/L EO for 6 hours, at 55°C, and relative humidity >35%), the samples were mechanically aerated with 14 pulses in air and vacuum and placed in an ambient aeration room at a temperature of 55°C with 27 air changes/hour. The samples were removed at 0, 4, 12, 24, and 48 hours, and their residual concentration for the limit of 10 µg/mL EO showed significant waste reduction ($p<0.05$) after 6 hours of aeration[31].

Another study that determined the aeration time of EO-sterilized products packaged in rigid containers revealed they needed 17 hours of aeration to be free from residues of this agent[32].

Research that evaluated the aeration time of EO-sterilized products in Southeastern Brazil identified that 100% of EO-sterilizing companies have aeration rooms, as recommended by the Brazilian standard, but present heterogeneous parameters regarding ambient aeration[14].

The American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardi (American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization [20]ANSI/AAMI/ISO) international standard 10993-7 updated the acceptable residual EO and ECH levels for medical devices in 2012. This regulation adopts the criterion time of patient contact with the product, classifying it as "limited exposure" (time <24 hours), "prolonged exposure" (>24 hours and up to 30 days), and "permanent exposure" (>30 days). The residual EO and ECH daily dose should not exceed 20 mg and 12 mg, respectively, while for prolonged and permanent exposure products, it should not exceed the limit of 60 mg, as shown in Tables 1 and 2.

Recommendations of the Interministerial Decree No. 482/1999[21] differ from international standards and studies in various aspects, specifically concerning acceptable levels of EO residues, as well as procedures for HP aeration.

The Brazilian regulation classifies implantable products by weight (10 to 100 g) and contact of the device with the patient's mucosa, blood, and skin, recommending the control of EO residues in ready-to-use and single-use products, such as surgical sponges, intrauterine devices, and intraocular lenses.

In Decree No. 482/1999, residual EO and ECH levels range from 25 ppm (blood-contact products) to 250 ppm (mucosal-contact products); such limits were determined by the Food and Drug Administration (FDA) in 1978[42] and disagree with current levels for this toxic waste, as described in Table 3.

As for product aeration processes, the current Brazilian standard only recommends an aeration room for services that adopt this sterilization method, without mentioning mechanical aeration or defining the exposure time for ambient aeration.

**Table 1.** Maximum acceptable limits of ethylene oxide and ethylene chlorohydrin residues in health products, according to contact time.

| Contact time | Ethylene oxide | Ethylene chlorohydrin |
|---|---|---|
| Medical product with prolonged contact | Maximum of 4 mg in the first 24 hours.<br>Maximum of 60 mg in the first 30 days. | Maximum of 9 mg in the first 24 hours.<br>Maximum of 60 mg in the first 30 days. |
| Medical product with permanent contact | Maximum of 4 mg in the first 24 hours.<br>Maximum of 60 mg in the first 30 days. | Maximum of 9 mg in the first 24 hours.<br>Maximum of 60 mg in the first 30 days. |

Source: ANSI/AAMI/ISO 10993-7:2008 (R) 2012.

## Summary of the results

The results of this review point to EO as an ideal sterilizing agent for critical and heat-sensitive devices, despite its toxicity and the need for controls related to sterilizers, workers, medical devices, and the environment.

As explained above, the Brazilian regulatory framework is outdated as to the determination of toxic EO residues in medical products, contributing to the health risk related to this sterilization method.

First, the classification of products based on "contact with the patient's mucosa, blood, and skin" adopted in this legislation differs from the current international standard[20], which specifies maximum limits according to the toxicological risk of these residues for the patient, considering the length of time the patient is exposed to the EO-sterilized device.

Residual levels defined in Decree No. 482 are higher than those recommended by the international standard, increasing the potential risk of adverse events for patients who use EO-reprocessed products.

The Brazilian standard recommends ambient aeration for the desorption of EO-sterilized products, which may not be effective, as it depends on many variables. Moreover, this process is contraindicated, as it has órgãos reguladores internacionais e been proscribed in the United States since 2010[20,27,34,35,39] In this scenario, mechanical aeration, not mentioned by this standard, is the gold standard for aeration of EO-sterilized products; nonetheless, this process also requires temperature and air flow control within the chamber[16,17,20,30,35,40].

Authors have reached a consensus that the duration of aeration relies on factors already described in this review. Among products made of polyvinyl chloride (PVC), polystyrene and rubbers are the ones that most absorb EO. Therefore, there is no recommended standard aeration time for all devices sterilized by this agent[8-11,16-18,20,23,26,30,35,40].

Os tempos de aeração descritos nesse estudo variam de seis horas a sete dias[26,29], 12 horas[33], 48 horas a dez dias[36], aeração mecânica a 50°C por 12 horas ou a 60°C por oito horas[27,35].

In order to overcome difficulties related to the duration of HP aeration, a study recommends that, if the medical device has an unknown composition, aeration should be performed with the most challenging parameters (as if the product was made of PVC), using mechanical aeration at 50°C for 12 hours or at 60°C for 8 hours. The American Hospital Association recommends these parameters as the minimum for any type of medical device[35].

**Table 3.** Maximum limits of ethylene oxide residues in related products (ppm).

| Related Product | EO | ECH | EG |
|---|---|---|---|
| Implants | | | |
| Small (10 g) | 250 | 250 | 5,000 |
| Intermediate (>10 – <100 g) | 100 | 100 | 2,000 |
| Large (>100 g) | 25 | 25 | 500 |
| Intrauterine devices | 5 | 10 | 10 |
| Intraocular lenses | 25 | 25 | 500 |
| Mucosal-contact products | 250 | 250 | 5,000 |
| Blood-contact products | 25 | 25 | 250 |
| Skin-contact products | 250 | 250 | 5,000 |
| Surgical sponges | 25 | 250 | 500 |

EO: ethylene oxide; ECH: ethylene chlorohydrin; EG: ethylene glycol.

Source: Brazil. Interministerial Decree No. 482/1999.

**Table 2.** Summary of permitted limits of ethylene oxide and ethylene chlorohydrin (per product).

| Health product category | Ethylene oxide | Ethylene chlorohydrin |
|---|---|---|
| Product with limited contact (<24 hours) | 4 mg | 9 mg |
| Product with prolonged contact (>24 h <30 days) | 60 mg/30 days | 60 mg/30 days |
| Product with permanent contact (>30 days) | 2.5 g/for life | 10 g/for life |
| Tolerable contact limit | 10 µg/cm² | 5 mg/cm² |
| Intraocular lenses | 0.5 µg/lens/day 1.25 µg/lens | 4 x the suggested EO limit |
| Blood cell separators (apheresis) | 10 mg | 22 mg |
| Blood oxygenators | 60 mg | 45 mg |
| Cardiopulmonary bypass products | 20 mg | 9 mg |
| Blood purification products=-0987654321+ (hemodialyzers) | 4.6 mg | 4.6 mg |
| Dressings in contact with intact skin | 10 µg/cm² | 5 mg/cm² |

Source: ANSI/AAMI/ISO 10993-7:2008 (R) 2012.

Since most products sent for EO-sterilization are thermosensitive and made of plastic polymers, particularly PVC, the possibility of absorption of high volumes of toxic residues increases as they undergo repeated sterilizations[35], a common situation in the routine of sterile processing departments (SPDs), requiring at least knowledge of residual EO and ECH levels of reprocessed products.

The issue is that the Brazilian standard does not regulate the periodicity of EO residue controls in sterile products by companies that outsource the EO sterilization process. Consequently, the implementation and delivery of these controls to contracting health services depend on the availability, initiative, and interest of these companies, with health services becoming prisoners in this context.

The basic cycle of EO sterilization including aeration may last from 14 to 30 hours. This interval restricts the availability of medical product rotation and can cause significant problems to health services[35]. In this regard, SPD nursing managers can contribute to unsafe practices regarding EO-sterilized products by receiving instruments returned from outsourced sterilization companies in times incompatible with the performance of aeration.

Given the considerations described above and the problems involving the aeration of EO-sterilized products, this study ratifies some questions raised by an author[35] back in the 1990s, while including other issues that also seem relevant and current: What are the criteria used by SPD nursing managers to indicate EO sterilization for certain products? Is the routine of sending and receiving EO-sterilized products compatible with their aeration process? What is the frequency of reports about residual EO levels in products sterilized by this agent? Taking into account that the volume of EO absorption also depends on the number of sterilizations, how often are these products used? Are health care leaders aware of the implications of EO sterilization?

## CONCLUSION

This review has achieved its objectives by describing the residual EO levels in products sterilized by this agent and the methods of aeration for these products, as well as by comparing the current Brazilian standard with international studies on this theme.

Possible limitations of this study include using review articles and recommendations from official bodies as theoretical support, with a small number of experimental studies, which could report the risks related to EO toxicity and contextualize more concrete situations.

This review also showed that Decree No. 482 is outdated in crucial points related to the control and safety of EO sterilization of medical devices, such as the obsolescence of acceptable residual levels of this agent, product classification, and aeration methods, contributing to the risk of adverse events for patients, workers, and the environment. Thus, updating the current regulation is urgent.

Furthermore, the shortcomings of this regulatory framework indirectly benefit companies that outsource EO sterilization by omitting essential controls for the safety of patients who use products sterilized by this extremely toxic agent, favoring the unsafe sterilization of medical products, in addition to hindering the supervision of health services by the country's health surveillance.

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