INTERNATIONAL STANDARD

ISO 10993-7

Second edition
2008-10-15

Biological evaluation of medical devices —

Part 7: Ethylene oxide sterilization residuals

Évaluation biologique des dispositifs médicaux —

Partie 7: Résidus de stérilisation à l'oxyde d'éthylène

Reference number
ISO 10993-7:2008(E)

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Published in Switzerland

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 10993-7 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO 10993-7:1995) which has been technically revised.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Evaluation and testing within a risk management system*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for in vitro cytotoxicity*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Framework for identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and skin sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials* [Technical Specification]

— *Part 20: Principles and methods for immunotoxicology testing of medical devices* [Technical Specification]

Introduction

Requirements for the development, validation and routine control of an ethylene oxide sterilization process for medical devices are given in International Standards developed by ISO/TC 198. Certain requirements relating to medical devices for biological testing, selection of tests, and the allocation of devices to categories are dealt with in a variety of International Standards developed by ISO/TC 194. The specific requirement for ethylene oxide and other sterilization process residuals was referred to ISO/TC 194. Other International Standards delineate particular requirements for biological testing for specific products.

As noted in the introduction to ISO 11135-1:2007, when determining the suitability of ethylene oxide (EO) for sterilization of medical devices, it is important to ensure that the levels of residual EO, ethylene chlorohydrin (ECH) and ethylene glycol (EG) pose a minimal risk to the patient in normal product use. Therefore, it is important that the use of alternative materials and sterilization processes be considered during product design and development. EO is known to exhibit a number of biological effects. In the development of this part of ISO 10993, consideration was given to these effects, which include irritation, organ damage, mutagenicity and carcinogenicity in humans and animals, and reproductive effects in animals. Similar consideration was given to the harmful effects of ECH and EG. In practice, for most devices, exposure to EO and ECH is considerably lower than the maximum values specified in this part of ISO 10993.

Moreover, when the choice for EO sterilization has been made, irrespective of the provisions of this part of ISO 10993, exposure to EO residues should be minimized. Requirements herein are in addition to the biological evaluation and testing requirements for each individually designed medical device as indicated in ISO 10993-1. The biological evaluation and testing requirements, combined with the EO-sterilization process residue limits, form the justification that an EO-sterilized device is acceptable for use. Maximum allowable residues for ethylene chlorohydrin (ECH), when ECH has been found to be present in medical devices sterilized with EO, are also specified. Local effects (e.g., irritation) have been considered and are incorporated in the tolerable contact limit (TCL) as given in 4.3.5.2 and Annex G for EO, and in 4.3.5.3 and Annex H for ECH.

Biological evaluation of medical devices —

Part 7:
Ethylene oxide sterilization residuals

1 Scope

This part of ISO 10993 specifies allowable limits for residual ethylene oxide (EO) and ethylene chlorohydrin (ECH) in individual EO-sterilized medical devices, procedures for the measurement of EO and ECH, and methods for determining compliance so that devices may be released. Additional background, including guidance and a flowchart showing how this document is applied, are also included in the informative annexes.

EO-sterilized devices that have no patient contact (e.g., *in vitro* diagnostic devices) are not covered by this part of ISO 10993.

NOTE This part of ISO 10993 does not specify limits for ethylene glycol (EG).

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1:—[1)], *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-3, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

ISO 10993-10, *Biological evaluation of medical devices — Part 10: Tests for irritation and delayed-type hypersensitivity*

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-17:2002, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1, ISO 10993-17 and the following apply.

3.1
simulated-use extraction
extraction to demonstrate compliance with the requirements of this part of ISO 10993, by evaluating residue levels available to the patient or user from devices during the routine use of a device with water extraction to simulate product use

1) To be published. (Revision of ISO 10993-1:2003)

3.2
exhaustive extraction
extraction until the amount of EO or ECH in a subsequent extraction is less than 10 % of that detected in the first extraction, or until there is no analytically significant increase in the cumulative residue levels detected

NOTE As it is not possible to demonstrate the exhaustive nature of residual recovery, the definition of exhaustive extraction adopted is as above.

4 Requirements

4.1 General

NOTE Information on the derivation of the limits in this part of ISO 10993 as well as other important background information and guidance relevant to the use of this document is contained in the informative annexes.

This clause specifies maximum allowable residues for ethylene oxide (EO) for each individual medical device sterilized with EO. As noted in the introduction to ISO 11135-1:2007, when determining the suitability of EO for sterilization of medical devices, it is important to ensure that the levels of residual EO, ethylene chlorohydrin (ECH) and ethylene glycol (EG) pose a minimal risk to the patient in normal product use. Moreover, when the choice for EO sterilization has been made, irrespective of the provisions of this standard, exposure to EO residues should be minimized. Maximum allowable residues for ECH, when ECH has been found to be present in medical devices sterilized with EO, are also specified. Local effects (e.g., irritation) have been considered and are incorporated in the tolerable contact limit (TCL) as discussed in 4.3.5.2 and Annex G for EO, and 4.3.5.3 and Annex H for ECH. No device limits are specified for EG because a risk assessment (Annex I) indicates that calculated allowable levels are higher than those likely to occur in a medical device. However, the potential exists for acute haemodynamic and haemolytic effects to occur following rapid intravenous administration of hyperosmolar compounds like EG. Ethylene oxide sterilization of medical devices would not be expected to produce hyperosmolar solutions. Methods for the determination of EO and ECH are given in 4.4.

The requirements in this part of ISO 10993 are in addition to the biological testing requirements set out in ISO 10993-1. For devices sterilized using ethylene oxide, attention shall be paid in particular to ISO 10993-3 and ISO 10993-10. All applicable requirements of ISO 10993-1 shall take into account the EO residual level at the time of release for each individually designed medical device.

Results of the biological assessment of the device may dictate more stringent limits than those specified in 4.3, which are designed to protect against systemic effects.

4.2 Categorization of devices

In establishing the maximum daily doses of EO and ECH that a medical device is allowed to deliver to patients, devices shall be categorized according to the duration of contact.

Devices shall be placed into one of three exposure categories in accordance with ISO 10993-1:—, 5.3:

a) limited exposure (A) – devices whose cumulative single, multiple or repeated use or contact is up to 24 h;

b) prolonged exposure (B) – devices whose cumulative single, multiple, or repeated long-term use or contact is likely to exceed 24 h but not 30 d;

c) permanent contact (C) – devices whose cumulative single, multiple or repeated long-term use or contact exceeds 30 d.

If a material or device can be placed in more than one duration category, the more rigorous testing and/or evaluation considerations should apply. With multiple exposures, the decision into which category a device is placed should take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

NOTE As it is applied in this part of ISO 10993, “multiple use” is defined to mean repeated use of the same device type, e.g. dialyser cartridges.

4.3 Allowable limits

4.3.1 General

For each medical device, the maximum allowable doses of EO and ECH delivered to patients shall not exceed the values given below for the exposure category that the device has been placed into in accordance with 4.2.

The limits for permanent contact and prolonged exposure devices are expressed as maximum average daily doses. These limits carry additional constraints for the first 24 h of the exposure period and, in the case of the permanent contact devices, for the first 30 days. These constraints place limitations on the amount of EO and ECH that can be delivered to the patient during these early time periods. If data are available, consideration should be given for proportioning the limits downward if multiple devices with the residue of concern are used at one time, or proportioning the limits upward when device use is only for a part of the exposure period of concern. These concomitant exposure factors (CEF) and proportional exposure factors (PEF) are given in ISO 10993-17. The procedure that was used to establish the allowable limits is described in Annex G for EO, in Annex H for ECH, and the rationale for considering the establishment of allowable limits for EG is described in Annex I.

4.3.2 Permanent contact devices

The average daily dose of EO to patient shall not exceed 0,1 mg/d. In addition, the maximum EO dose shall not exceed:

— 4 mg in the first 24 h;

— 60 mg in the first 30 d;

— 2,5 g in a lifetime.

The average daily dose of ECH to patient shall not exceed 0,4 mg/d. In addition, the maximum ECH dose shall not exceed:

— 9 mg in the first 24 h;

— 60 mg in the first 30 d;

— 10 g in a lifetime.

4.3.3 Prolonged exposure devices

The average daily dose of EO to patient shall not exceed 2 mg/d. In addition, the maximum EO dose shall not exceed:

— 4 mg in the first 24 h;

— 60 mg in the first 30 d.

The average daily dose of ECH to patient shall not exceed 2 mg/d. In addition, the maximum ECH dose shall not exceed:

— 9 mg in the first 24 h;

— 60 mg in the first 30 d.

4.3.4 Limited exposure devices

The average daily dose of EO to patient shall not exceed 4 mg.

The average daily dose of ECH to patient shall not exceed 9 mg.

4.3.5 Tolerable contact limits for surface contacting devices and implants

4.3.5.1 Overview

The tolerable contact limit (TCL) is expressed in units of micrograms per square centimetre for EO and milligrams per square centimetre for ECH. The unit of square centimetre represents the surface area of the patient-device interface.

NOTE The intent of this subclause is to prevent localized irritation due to EO or ECH released from the device.

4.3.5.2 Tolerable contact limit for EO

Either the EO TCL for surface contacting devices and implants shall not exceed 10 µg/cm^2 or it shall exhibit negligible irritation as specified in ISO 10993-10.

4.3.5.3 Tolerable contact limit for ECH for surface contacting devices

Either the ECH TCL for surface contacting devices and implants shall not exceed 5 mg/cm^2 or it shall exhibit negligible irritation as specified in ISO 10993-10.

4.3.6 Special situations

For multi-device systems the limits shall apply to each individual patient-contact device.

Residue of EO in intraocular lenses shall not exceed 0,5 µg EO per lens per day, or 1,25 µg per lens. Prorate limits for other intraocular devices are set on the basis of the mass of the device, with the mass of an intraocular lens taken as 20 mg. The acceptability of ECH levels in intraocular devices made from viscoelastic materials that contain chlorine may need to be evaluated, as the level of ECH that results in ocular toxicity is about four times greater than the corresponding EO level.

For blood cell separators used in patient and donor blood collection, the maximum allowable dose of EO is 10 mg and the maximum allowable dose of ECH shall not exceed 22 mg.

For blood oxygenators and blood separators, the maximum allowable dose of EO to patient is 60 mg and the maximum allowable dose of ECH shall not exceed 45 mg.

For devices used in cardiopulmonary bypass procedures, the maximum allowable limits shall be 20 mg for EO and 9 mg for ECH.

For extracorporeal blood purification devices, the EO and ECH limits specified shall be 4,6 mg/device, but the allowable EO dose for a lifetime may be exceeded.

For drapes that are intended to contact only intact skin, the maximum allowable limits shall be the TCL of 10 µg/cm^2 for EO and 5 mg/cm^2 for ECH, or the drapes shall exhibit negligible irritation as specified in ISO 10993-10.

NOTE The rationale for specifying EO limits for certain devices that are at variance with the general requirements appears in Annex F.

A flowchart providing guidance for the application of this part of ISO 10993 to the determination of EO residuals in medical devices is presented in Annex C.

4.4 Determination of EO and ECH residuals

4.4.1 General

4.4.1.1 Procedure

The procedure for determining compliance with 4.3 consists of extracting the residue from samples, determining the amount of residue, determining the contact surface of the device, and analysing and interpreting the data.

DANGER — Analysts and others who obtain samples should perform all work involving the use of the chemicals and solvents required for these methods in a fume cupboard whilst wearing appropriate protective clothing, and should review the Material Safety Data information for each chemical prior to such use. Healthcare workers using EO-sterilized medical devices shall take appropriate precautions to protect against exposure to residues, which may be required by local occupational health and safety regulations.

4.4.1.2 Ethylene oxide

This is a flammable gas that is irritating to body surfaces and highly reactive. It is mutagenic under many conditions, has fetotoxic and teratogenic properties, can adversely effect testicular function and can produce injury to many organ systems in the body. In cancer studies in animals, inhalation exposure produced several types of neoplastic changes including leukaemia, brain tumours and mammary tumours while ingestion or subcutaneous administration produced tumours only at the site of contact. One investigator has reported higher cancer and mortality rates in some subpopulations of exposed workers. However, the results of several studies in workers have shown even weaker associations. See References [177], [178] and [181]. In 1994 the International Agency for Research on Cancer (IARC) reclassified EO as a human carcinogen (class 1) based mainly on its mechanism of action. See Reference [75].

4.4.1.3 Ethylene chlorohydrin

This is a flammable liquid that is irritating to body surfaces, acutely toxic and readily absorbed through the skin in toxic amounts. It has weak mutagenic potential, has some potential to produce fetotoxic and teratogenic changes and can produce injury to several organ systems in the body including lungs, kidneys, central nervous system and cardiovascular system. It was negative in cancer bioassays in animals.

4.4.2 Determination of residue

A valid method of extraction and measurement shall be used to determine the amount of EO and, where necessary, ECH delivered to the patient.

If ECH is not detected based on the results of analyses performed using the methods given in either K.4.2 or K.4.7, no further monitoring for ECH is required.

NOTE Many gas chromatography (GC) methods that use a capillary column instead of a packed column will produce EO, ECH and EG results during a single sample run.

The guiding principle in selecting appropriate extraction methods (4.4.6) for the quantitative determination of EO and, where necessary, ECH is the evaluation of the dose to the patient in order to show compliance with the requirements set out in 4.3.

Where residues are shown to be within the requirements for products tested by exhaustive extraction, there is no need to further challenge the device by simulated-use extraction, provided all applicable limits in 4.3 are met. When exhaustive extraction is used, particular attention shall be paid to the limits expressed for the first 24 h and for the first 30 days in 4.3.

Many analytical methods for these EO-sterilization residuals have been described and are reviewed in the Bibliography. However, the enormous diversity of materials and methods of construction of sterile medical