SLOVENSKI STANDARD
SIST EN ISO 10993-7:2000

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Biološko ovrednotenje medicinskih pripomoļkov - 7. del: Ostanki po sterilizaciji z etilenoksidom (ISO 10993-7:1995)

Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals (ISO 10993-7:1995)

Biologische Beurteilung von Medizinprodukten - Teil 7: Ethylenoxid-Sterilisationsrückstände (ISO 10993-7:1995)

Evaluation biologique des dispositifs médicaux - Partie 7: Résidus de stérilisation a l'oxyde d'éthylene (ISO 10993-7:1995)

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Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals (ISO 10993-7:1995)

Evaluation biologique des dispositifs médicaux - Partie 7: Résidus de stérilisation à l'oxyde d'éthylène (ISO 10993-7:1995)

Biologische Beurteilung von Medizinprodukten - Teil 7: Ethyleoxid-Sterilisationsrückstände (ISO 10993-7:1995)

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CEN

European Committee for Standardization
Comité Européen de Normalisation
Europäisches Komitee für Normung

Central Secretariat: rue de Stassart,36 B-1050 Brussels

Foreword

The text of the International Standard ISO 10993-7:1995 has been prepared by the Technical Committee ISO/TC 194 "Biological evaluation of medical devices" in collaboration with the CEN/TC 206 "Biocompatibility of medical and dental materials and devices".

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

Part 1:	Guidance on selection of tests
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 cytotoxicity: *in vitro* methods
Part 6:	Tests for local effects after implantation
Part 7:	Ethylene oxide sterilization residuals
Part 9:	Degradation of materials related to biological testing
Part 10:	Tests for irritation and sensitization
Part 11:	Tests for systemic toxicity
Part 12:	Sample preparation and reference materials
Part 13:	Identification and quantification of degradation products from polymers
Part 14:	Identification and quantification of degradation products from ceramics
Part 15:	Identification and quantification of degradation products from coated and uncoated metals and alloys
Part 16:	General guidance on toxicokinetic study design for degradation products and leachables
Part 17:	Glutaraldehyde and formaldehyde residues in industrially sterilized medical devices

Future parts will deal with other relevant aspects of biological testing.

Annexes A and B form an integral part of this part of ISO 10993. Annexes C, D, E and F are for for information only.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by April1995, and conflicting national standards shall be withdrawn at the latest by April 1995.

This European Standard has been prepared under a madate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

According to the CEN/CENELEC Internal Regulations, the following countries are bound to implement this European Standard: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom.

Endorsement notice

The text of the International Standard ISO 10993-7:1995 was approved by CEN as a European Standard without any modification.

NOTE: Normative references to International Standards are listed in annex ZA (normative).

Annex ZA (normative)
Normative references to international publications with their relevant European publications

This European Standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies.

Publication	Year	Title	EN	Year
ISO 10993-1	1992	Biological evaluation of medical devices - Part 1: Guidance on selection of tests	EN 30993-1	1994
ISO 10993-3	1992	Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity	EN 30993-3	1993

INTERNATIONAL STANDARD

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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

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Contents

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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.

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.

International Standard ISO 10993-7 was prepared jointly by Technical Committees ISO/TC 194, *Biological evaluation of medical devices* and ISO/TC 198, *Sterilization of health care products*.

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

— *Part 1: Evaluation and testing*

— *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 cytotoxicity: in vitro methods*

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

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Degradation of materials related to biological testing* [Technical Report]

— *Part 10: Tests for irritation and sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymers*

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

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

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

— *Part 17: Glutaraldehyde and formaldehyde residues in industrially sterilized medical devices*

Annexes A and B form an integral part of this part of ISO 10993. Annexes C, D, E and F are for information only.

Introduction

Requirements for the quality system for validation and routine monitoring of sterilization of medical products with gaseous ethylene oxide 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 under development by ISO/TC 194. The specific requirements 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.

When determining the suitability of ethylene oxide (EO) for sterilization of medical devices, it is important to ensure that the levels of residual EO and ethylene chlorohydrin (ECH) pose a minimal risk to the patient in normal product use. 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 ethylene glycol (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.

Product development and design should have considered the use of alternative materials and sterilization processes with the aim of minimizing exposure to residuals. Requirements herein are in addition to the biological testing requirements for each individually designed medical device as indicated in ISO 10993-1. The biological testing requirements, combined with the EO-sterilization process residue limits, form the justification that an EO-sterilized device is acceptable for use.

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 and guidance also is included in informative annexes.

EO-sterilized devices that have no patient contact (e.g. *in vitro* diagnostic devices) are not covered by this International Standard.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 10993-1:1992, *Biological evaluation of medical devices — Part 1: Guidance on selection of tests.*

ISO 10993-3:1992, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity.*

ISO 10993-10:1995, *Biological evaluation of medical devices — Part 10: Tests for irritation and sensitization.*

3 Definitions

For the purposes of this part of ISO 10993, the definitions given in ISO 10993-1 and the following definitions 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 using an extraction method using water that simulates product use.

NOTE 1 The burden of validation on the analytical laboratory is to demonstrate that the simulated-use extraction is carried out under conditions that provide the greatest challenge to the intended use. Product use simulation should be carried out assuming the device is assigned to the most stringent category probable for duration of exposure and should take into consideration both tissue(s) exposed and temperature of exposure.

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

4 Requirements

NOTE 3 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 part of ISO 10993 are contained in informative annexes.

4.1 General

This clause specifies maximum allowable residues for ethylene oxide (EO) for each individual medical device sterilized with EO. Maximum allowable residues for ethylene chlorohydrin (ECH) when ECH has been found to be present in medical devices sterilized with EO also are specified.

No exposure limits are set for ethylene glycol (EG) because risk assessment indicates that when EO residues are controlled as required by this part of ISO 10993, it is unlikely that biologically significant residues of EG would be present (see E.1).

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 by 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 EO residual level at 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. For example, irritation effects shall be considered for all devices, particularly small devices (see E.2). This International Standard does not take account of the possibility of acute localized effects, for which insufficient data are available. Particularly for small devices, attention should be paid to the potential for such effects and the concentration of EO per unit of surface area.

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 duration of contact.

Devices shall be placed into one of three exposure categories in accordance with ISO 10993-1:1992, subclause 5.2:

a) limited exposure: devices whose single or multiple use or contact is likely to be up to 24 h;

b) prolonged exposure: devices whose single, multiple or long-term use or contact is likely to exceed 24 h but not 30 days;

c) permanent contact: devices whose single, multiple or long-term use or contact exceeds 30 days.

NOTES

4 If a material or device may be placed in more than one duration category, the more rigorous testing requirements 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.

5 As it is applied in this part of ISO 10993, "multiple use" is defined to mean repeated use of the same device.

4.3 Allowable limits

For each medical device, the maximum allowable doses of EO and ECH that are 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.

NOTE 6 The limits for permanent contact and prolonged contact devices are expressed as maximum average daily doses. These limits also 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. The procedure that was used to establish the allowable limits is described in E.2.

4.3.1 Permanent contact devices

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

20 mg in the first 24 h;

60 mg in the first 30 days;

2,5 g in a lifetime.

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

12 mg in the first 24 h;

60 mg in the first 30 days;

50 g in a lifetime.

4.3.2 Prolonged exposure devices

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

20 mg in the first 24 h;

60 mg in the first 30 days.

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

12 mg in the first 24 h;

60 mg in the first 30 days.

4.3.3 Limited exposure devices

The average daily dose of EO to patient shall not exceed 20 mg.

The average daily dose of ECH to patient shall not exceed 12 mg.

NOTE 7 The simultaneous use of more than one device or the use of devices in the treatment of neonates may result in additional exposure as described in E.2.1.1.

4.3.4 Special situations

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

Residue of EO in intraocular lenses shall not exceed 0,5 µg EO per lens per day, nor 1,25 µg per lens.

For blood oxygenators and blood separators, the average daily dose of EO to patient shall not exceed 60 mg.

For extracorporeal blood purification set-ups, the EO and ECH limits specified above for the prolonged and limited duration category apply, but the allowable EO dose for a lifetime may be exceeded.

NOTE 8 The rationale for specifying EO limits for certain devices that are at variance with the general requirements appears in E.2.1.3.

4.4 Determination of EO and ECH residuals

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

4.4.1 Safety considerations

DANGER — Analysts and others obtaining samples should perform all work involving the use of the chemicals and solvents required for these methods under the fume hood with appropriate protective clothing, and should review the Material Safety Data information for each chemical prior to such use.

4.4.1.1 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 affect 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 exposed workers. However, the results or several recent studies in workers have not been consistent with this finding.

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

NOTE 9 If ECH is not detected based on the results of analyses performed using the methods given in B.5.2 and B.5.7, no further monitoring for ECH is required.

Validated methods that meet this requirement are described in annex B. However, any method which has been shown to be analytically sound may be used provided it has been validated by demonstrating that the system meets the requirements set out in annex A, and has been evaluated against the referee methods contained in annex B.

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 dose to the patient in order to show compliance with 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 further to challenge the device by simulated-use extraction, provided all applicable limits in 4.3 are met. When exhaustive extraction is used,