SLOVENSKI STANDARD
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Biološko ovrednotenje medicinskih pripomočkov - 7. del: Ostanki po sterilizaciji z etilenoksidom (ISO/DIS 10993-7:2024)

Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals (ISO/DIS 10993-7:2024)

Biologische Beurteilung von Medizinprodukten - Teil 7: Ethylenoxid-Sterilisationsrückstände (ISO/DIS 10993-7:2024)

Évaluation biologique des dispositifs médicaux - Partie 7: Résidus de stérilisation à l'oxyde d'éthylène (ISO/DIS 10993-7:2024)

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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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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*.

This third edition cancels and replaces the second edition (ISO 10993-7:2008, ISO 10993-7:2008/Cor 1:2009 and ISO 10993-7:2008/Amd 1:2019), which has been technically revised. This edition shall be implemented within 3 years of publication.

The main changes compared to the previous edition are as follows:

— manufacturer to define allowable limits and extraction conditions, based on the patient population and the duration of use;

— allow for the use of a risk assessment to establish allowable limits;

— provide additional guidance on product release;

— provide additional guidance on determining residuals and the factors that affect residual.

A list of all parts in the ISO 10993 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user’s national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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. The general requirements relating to biological evaluation and testing of medical devices, selection of tests, and the allocation of devices to categories are dealt with in 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 11135:2014, 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 intended product use. Therefore, it is important that the use of alternative materials and sterilization processes are considered during product design and development. EO is known to exhibit a number of biological effects. In the development of this document, consideration was given to these effects, which include irritation, organ damage, mutagenicity, carcinogenicity, and reproductive effects in humans and animals. Similar consideration was given to the harmful effects of ECH and ethylene glycol (EG). ECH can be formed when EO comes into contact with free chloride ions, whereas EG is a hydrolytic reaction product of EO and water. In practice, for most devices, exposure to EO and ECH is considerably lower than the maximum allowable limits established according to this document. No allowable limits are set for ethylene glycol because risk assessment indicated that when EO residuals are controlled, it is unlikely that biologically significant residuals of EG would be present.

Requirements herein are in addition to the biological evaluation requirements as indicated in ISO 10993-1. The biological evaluation, combined with the EO-sterilization process residual limits, form the justification that an EO-sterilized device is safe for its anticipated contact duration. Maximum allowable residuals 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 level (TCL) as given in 4.3.6.2 and Annex D for EO, and in 4.3.6.3 and Annex E for ECH.

In this edition of ISO 10993-7 an uncertainty factor approach based on ISO 10993-17:2023 is used to derive EO and ECH exposure duration-specific tolerable intake (TI) values (expressed in µg/kg/d). Unique in this version of ISO 10993-7 is the conversion of each EO and ECH TI value into subpopulation-specific cumulative exposure-allowable limit values (expressed in mg/device), which are used to determine the extent that EO and ECH, extracted under clinically relevant conditions and time-periods, needs to be reduced post-sterilization.

This edition of ISO 10993-7 applies a different approach as compared to ISO 10993-17:2023 to establishing allowable limits to make it useful for development, validation, and routine control of ethylene oxide sterilization in the manufacture of finished medical devices with focus on the risk assessments associated with 3 chemical constituents that are potentially left in medical devices sterilized with ethylene oxide. ISO 10993-7 extends this knowledge further by calculating the largest amount of EO, ECH or EG that can be present in a medical device such that it would always meet the requirements of ISO 10993-17 when that device has been exposed to the validated sterilization cycle parameters. This maximum amount or allowable limit is expressed in mg/device deemed acceptable when taken into the body through exposure to that medical device. These allowable limits will help determine the appropriate sterilization parameters such as sterilant gas concentration and dwell, as well as aeration temperature and hold time when validating the sterilization process to be used for a product or group of products. Further the allowable limits may be used by regulatory bodies, manufacturers, and processors to optimize processes and aid in the selection and qualification of alternative materials in order to protect patient health.

Biological evaluation of medical devices —

Part 7: Ethylene oxide sterilization residuals

1 Scope

This document specifies allowable limits for residual ethylene oxide (EO) and ethylene chlorohydrin (ECH) in 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 or components that have neither direct nor indirect patient contact (*e.g.*, *in vitro* diagnostic devices) are out of scope of this document. This document does not apply to devices that have been demonstrated to not absorb or retain EO or its degradation product ECH, such as medical devices made exclusively of metal alloys and glass, see Annex C.5[228].

NOTE This document does not specify limits for ethylene glycol (EG). No device limits are specified for EG because the risk assessment in Annex F indicates that calculated allowable levels are higher than those likely to occur in a medical device.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 10993-1:2018, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-23, *Biological evaluation of medical devices — Part 23: Tests for irritation*

3 Terms and definitions

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

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
aeration
part of the sterilization cycle during which the sterilizing agent and/or its reaction products desorb from the health care product until predetermined levels are reached

[SOURCE: ISO 11139:2018, 3.7]

3.2
allowable limit
AL
amount of residual EO or ECH on a single device that is without appreciable *harm to health* (3.10) for the patient's whole exposure to the device

Note 1 to entry: Allowable limits are expressed in mg/device for each applicable exposure period. These limits represent acceptable biological risks for medical devices under the circumstances of their anticipated contact duration.

3.3
cumulative exposure
total quantity of EO and ECH that contacts the body for a specified period of time

Note 1 to entry: Cumulative exposure applies when multiple uses of the same device for same patient or user applies. For example, when more than one device is used simultaneously or repeatedly over a specified period of time.

Note 2 to entry: If a device usage period is less than limited or prolonged contact exposure category, but intended for repeated or multiple usages that exceed another exposure (prolonged or long-term) category, the total residuals are combined and the additional categories apply, *e.g.*, dialyzer cartridges used for less than 24 hours, but repeatedly used long-term.

3.4
concomitant exposure factor
CEF
numerical safety factor that accounts for patient exposure to the simultaneous use of other EO sterilized medical devices different from the subject medical device

Note 1 to entry: CEF is calculated from the reciprocal of the number of devices (1/device) used during a procedure. The default value of 0,2 assumes five other devices are used during a procedure, see Clause 4.4.5. Annex A.2.4 and Annex D.3.2 for further details.

3.5
cycle
set of parameters that make up the sterilization process

3.6
default value
value or factor used in the derivation of a *tolerable contact level* (3.24) or *tolerable intake* (3.26), in the absence of specific data [*e.g.*, an *uncertainty factor* (3.28)]

[SOURCE: ISO 10993-17:2023, 3.5, modified to remove worst case exposure dose and replace with tolerable contact level]

3.7
dose-response
relationship of dosage to observable harm

Note 1 to entry: In general, there are two types of dose-response relationships. The first type is the change in response for an individual to a range of doses. The second type is the distribution of a response among individuals to a range of doses.

[SOURCE: ISO 10993-17:2023, 3.6]

3.8
exhaustive extraction
multi-step extraction conducted until the amount of material extracted in a subsequent extraction step is less than 10 % of that determined in the initial extraction step

Note 1 to entry: Based upon the boiling point of EO (10,7 °C) and the knowledge that substances, other than EO and ECH, may be extracted from the device under evaluation, gravimetric analysis may not be appropriate for determining the exhaustivity level.

[SOURCE: ISO 10993-18:2020, 3.15, modified – removal of gravimetric analysis and addition of Note 1 to entry]

3.9
externally communicating medical device
medical device or medical device component that is partially or wholly located outside the body but has either direct or indirect contact with the internal body fluids and/or tissues

[SOURCE: ISO 10993-1:2018, 3.7]

3.10
harm to health
adverse reaction, such as altered morphology, physiology, growth, development, reproduction or lifespan that

a) impairs function of an organ or system, organism, or (sub)population,

b) reduces capacity to tolerate impaired function, or

c) increases susceptibility to other influences that impair function

Note 1 to entry: Examples of (sub) population include, but are not limited to: male, female, preterm neonates, adults.

[SOURCE: ISO 10993-17:2023, 3.8]

3.11
load
product, equipment, or materials to be processed together within an operating cycle

Note 1 to entry: Frequently referred to as a sterilization batch or sterilization load.

[SOURCE: ISO 11139:2018, 3.155]

3.12
implant
medical device which is intended to be totally introduced into the human body or to replace an epithelial surface or the surface of the eye by means of clinical intervention and which is intended to remain in place after the procedure

[SOURCE: ISO 10993-1:2018, 3.10]

3.13
irritation
localized non-specific inflammatory response to single, repeated, or continuous application of a substance/material

[SOURCE: ISO 10993-17:2023, 3.12]

3.14
lowest observed adverse effect level
LOAEL
lowest concentration or amount of an identified constituent found by experiment or observation which causes detectable *harm to health* (3.10) to the target organism under defined conditions of exposure

[SOURCE: ISO 10993-17:2023, 3.13, modified – Note 1 to entry deleted.]

3.15
minimally irritating level
MIL
lowest amount per surface area of an identified constituent that is irritating to the tissue at the contact site as determined by valid experimental or observational evidence

Note 1 to entry: Minimally irritating level is normally expressed as microgram per centimetre squared ($\mu g/cm^2$).

[SOURCE: ISO 10993-17:2023, 3.15]

3.16
modifying factor
MF
mathematical product of *uncertainty factors* (3.28)

[SOURCE: ISO 10993-17:2023, 3.16]

3.17
non-irritating level
NIL
greatest amount per surface area of an identified constituent that does not elicit *irritation* (3.13) to the tissue at the contact site as determined by valid experimental or observational evidence

Note 1 to entry: non-irritating level is normally expressed as microgram per centimetre squared (μg/cm^2).

[SOURCE: ISO 10993-17:2023, 3.17]

3.18
no observed adverse effect level
NOAEL
greatest concentration or amount of an identified constituent found by experiment or observation which causes no detectable *harm to health* (3.10) to the target organism under defined conditions of exposure

Note 1 to entry: No observed adverse effect level is normally expressed as microgram per kilogram of body weight per day (μg/kg/d).

[SOURCE: ISO 10993-17:2023, 3.18]

3.19
physiologically based pharmacokinetic (PBPK) modelling
system of modelling biological effects taking into account metabolic and pharmacokinetic differences among species of animals

Note 1 to entry: Such data should be utilized whenever available and applicable to medical device anticipated contact duration.

3.20
Residual
quantity of EO or ECH that remains in or on the product after EO sterilization

3.21
safety
freedom from unacceptable risk

[SOURCE: ISO 14971:2019, 3.26]

3.22
simulated-use extraction
extraction using a method that simulates clinical use

Note 1 to entry: A simulated-use extraction is performed to estimate the type and amount of substances that are expected to be released from a medical device during its clinical use. A simulated-use extraction is designed to produce an extractables profile that represents the worst-case leachables profile, meaning that all leachables are also extractables and the levels of all individual extractables are at least equal to the level of all individual leachables.

[SOURCE: ISO 10993-18:2020, 3.35]

3.23
surface contacting medical device
device that contacts intact skin, mucosal membrane or breached or compromised surfaces

3.24
tolerable contact level
TCL
estimate of the surface-contact exposure to an identified constituent that is without appreciable *irritation* (3.13)

Note 1 to entry: Tolerable contact level is normally expressed as microgram per centimetre squared (μg/cm^2) of tissue at the contact site.

[SOURCE: ISO 10993-17:2023, 3.25]

3.25
tolerable exposure
TE
product of the *tolerable intake* (3.26), the body mass, and the concomitant exposure factor

Note 1 to entry: It is normally expressed in milligrams per day to the patient.

3.26
tolerable intake
TI
estimate of the daily exposure of an identified constituent over a specified time period (*e.g.*, acute, subacute, sub-chronic, or chronic), on the basis of body weight, that is considered to be without appreciable *harm to health* (3.10)

Note 1 to entry: Tolerable intake is normally expressed as microgram per kilogram of body weight per day (μg/kg/d). It is derived to establish an allowable limit for a medical device constituent.

[SOURCE: ISO 10993-17:2023, 3.26]

3.27
toxicological risk assessment
determination of whether an exposure dose to a constituent can or cannot elicit appreciable *harm to health* (3.10)

[SOURCE: ISO 10993-17:2023, 3.29]

3.28
uncertainty factor
UF
numerical values that account for uncertainties when extrapolating a point of departure to individuals who can be exposed to a constituent of toxicological concern

EXAMPLE Examples of extrapolation types include, but are not limited to: intraspecies, interspecies, dose route and study duration.

[SOURCE: ISO 10993-17:2023, 3.31]

4 Requirements

4.1 General

This clause specifies maximum allowable residuals for ethylene oxide (EO) and ethylene chlorohydrin (ECH) for each individual medical device sterilized with EO. Local (acute) effects (*e.g.*, irritation) have been considered and are incorporated in the tolerable contact level (TCL).

The requirements in this document are in addition to the requirements set out in ISO 10993-1. 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 might lead to other limits than those specified in 4.3, which are designed to protect against local irritation and systemic effects.

This document shall not be used for commercially marketed medical devices to mandate a reassessment of historical residuals data assessed previously using the appropriate edition of this document at the time

of the assessment. This includes confirmation that none of the issues identified in ISO 10993-1:2018, 4.9 have occurred; otherwise, a new assessment to demonstrate compliance to allowable limits is needed. This assessment may also include re-testing.

NOTE 1 The previous versions of this standard reported a limit of 4 mg for EO and 9 mg for ECH for adults with limited contact (with CEF = 0,2) for 70 kg adult population and a UF1 of 10 for intra-species variability. From a toxicological point of view these values are not significantly different from the values calculated in the current revision of this standard and thus, these changes in allowable limits do not warrant re-evaluating product that met the limits of the previous version of this standard.

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

NOTE 2 Information on the derivation of the limits in this document as well as other background information and guidance relevant to the use of this document is contained in the informative annexes.

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, the medical device shall be categorized according to the duration of body contact in accordance with ISO 10993-1:

a) Limited contact – medical devices whose cumulative sum of single, multiple, or repeated duration of contact is up to 24 h.

b) Prolonged contact – medical devices whose cumulative sum of multiple, or repeated contact time is likely to exceed 24 h but not exceed 30 d.

c) Long-term contact – medical devices whose cumulative sum of multiple, or repeated contact time 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 shall apply. With multiple exposures, the decision into which category a device is placed shall take into account the potential cumulative effect, bearing in mind the period of time over which these exposures occur.

EO or ECH testing is not required for devices with transitory body contact in line with ISO 10993-1:2018, 5.3.2. However, for products made with materials that could be left in contact with body, such as coatings or lubricants, after the device is removed, a more detailed biocompatibility assessment can be necessary. Cumulative use should also be considered.

4.3 Allowable limits

4.3.1 General

For each medical device, the maximum exposure of EO and ECH to patients shall not exceed the allowable limit (see Table 1) for any of the applicable exposure categories (see 4.2). Alternative limits may be calculated based on risk assessment that accounts for device usage and patient population. The procedure that was used to establish the tolerable intake (TI) is described in Annex D for EO, in Annex E for ECH.

Prolonged contact devices carry additional limits for the first 24 h exposure period and, in the case of the long-term contact devices, for the first 24 h period and the first 30 d period. These limits place constraints on the amount of EO and ECH that can be delivered to the patient during these early time periods.

The concomitant exposure factor (CEF) uses a default value of 0,2 based on 5 devices used simultaneously. If data are available on the number of devices used at one time, e.g., in multi-device systems, convenience kits, long-term contact devices, then the default CEF of 0,2 may be modified (see 4.4.5, A.2.4 and D.3.2 for further justification).