



DPC: 24/30453916 DC

BSI Group Headquarters

389 Chiswick High Road London W4 4AL

Tel: +44 (0)20 8996 9000

Fax: +44 (0)20 8996 7400

www.bsigroup.com

Date: 17 June 2024

Origin: International

Latest date for receipt of comments: 10 August 2024

Project No. 2022/00656

Responsible committee: CH/194 Biological evaluation of medical devices

Interested committees:

Title: Draft BS EN ISO 10993-7 Biological evaluation of medical devices. Part 7: Ethylene oxide sterilization residuals.

Please notify admin.start@bsigroup.com if you are aware of any keywords that might assist in clarifying or identifying the standard or of the content of this standard:

- i) has any issues related to 3rd party IPR, patent or copyright
- ii) affects other national standard(s)
- iii) requires additional national guidance or information

WARNING: THIS IS A DRAFT AND MUST NOT BE REGARDED OR USED AS A BRITISH STANDARD. THIS DRAFT IS NOT CURRENT BEYOND 10 August 2024

This draft is issued to allow comments from interested parties; all comments will be given consideration prior to publication. No acknowledgement will normally be sent. **See overleaf for information on the submission of comments.**

No copying is allowed, in any form, without prior written permission from BSI except as permitted under the Copyright, Designs and Patent Act 1988 or for circulation within a nominating organization for briefing purposes. Electronic circulation is limited to dissemination by e-mail within such an organization by committee members.

Further copies of this draft may be purchased from BSI Shop <http://shop.bsigroup.com> or from BSI Customer Services, Tel: +44(0) 20 8996 9001 or email cservices@bsigroup.com. British, International and foreign standards are also available from BSI Customer Services.

Information on the co-operating organizations represented on the committees referenced above may be obtained from <https://standardsdevelopment.bsigroup.com/>.

Introduction

This draft standard is based on national and international discussions. Your comments on this draft are invited and will assist in the preparation of the consequent standard.

For international standards, comments will be reviewed by the relevant UK national committee before sending the consensus UK vote and comments to the international committee, which will then decide appropriate action. If the international standard is approved, it is usual for the text to be published as a British Standard.

For national standards, comments will be reviewed by the relevant UK national committee and the resulting standards published as a British Standard.

UK Vote

Please indicate whether you consider the UK should submit a negative (with supporting technical reasons) or positive vote on this draft. Please indicate if you are aware of any reason why this draft standard should not be published as a British Standard.

Submission of Comments

- **Annotated drafts are not acceptable and will be rejected.**
- All comments should be submitted online at <https://standardsdevelopment.bsigroup.com/>. You will need to register in order to comment.

Template for comments and secretariat observations

Date: xx/xx/20xx	Document: ISO/DIS xxxx
------------------	------------------------

1	2	(3)	4	5	(6)	7
MB	Clause No./ Subclause No./Annex (e.g. 3.1)	Paragraph/ Figure/Table/Note	Type of comment	Comment (justification for change) by the MB	Proposed change by the MB	Secretariat observations on each comment submitted
	3.1	Definition 1	ed	Definition is ambiguous and needs clarifying.	Amend to read '...so that the mains connector to which no connection...'	
	6.4	Paragraph 2	te	The use of the UV photometer as an alternative cannot be supported as serious problems have been encountered in its use in the UK.	Delete reference to UV photometer.	



DRAFT International Standard

ISO/DIS 10993-7

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*

ICS: 11.100.20

ISO/TC 194

Secretariat: **DIN**

Voting begins on:
2024-06-17

Voting terminates on:
2024-09-09

This document is circulated as received from the committee secretariat.

ISO/CEN PARALLEL PROCESSING

Reference number
ISO/DIS 10993-7:2024(en)

Full document details: 24/30453916 DC

THIS DOCUMENT IS A DRAFT CIRCULATED FOR COMMENTS AND APPROVAL. IT IS THEREFORE SUBJECT TO CHANGE AND MAY NOT BE REFERRED TO AS AN INTERNATIONAL STANDARD UNTIL PUBLISHED AS SUCH.

IN ADDITION TO THEIR EVALUATION AS BEING ACCEPTABLE FOR INDUSTRIAL, TECHNOLOGICAL, COMMERCIAL AND USER PURPOSES, DRAFT INTERNATIONAL STANDARDS MAY ON OCCASION HAVE TO BE CONSIDERED IN THE LIGHT OF THEIR POTENTIAL TO BECOME STANDARDS TO WHICH REFERENCE MAY BE MADE IN NATIONAL REGULATIONS.

RECIPIENTS OF THIS DRAFT ARE INVITED TO SUBMIT, WITH THEIR COMMENTS, NOTIFICATION OF ANY RELEVANT PATENT RIGHTS OF WHICH THEY ARE AWARE AND TO PROVIDE SUPPORTING DOCUMENTATION.

© ISO 2024  **Documents**
Document Sharing Hub



COPYRIGHT PROTECTED DOCUMENT

© ISO 2024

All rights reserved. Unless otherwise specified, or required in the context of its implementation, no part of this publication may be reproduced or utilized otherwise in any form or by any means, electronic or mechanical, including photocopying, or posting on the internet or an intranet, without prior written permission. Permission can be requested from either ISO at the address below or ISO's member body in the country of the requester.

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

Foreword	iv
Introduction	v
1 Scope	1
2 Normative references	1
3 Terms and definitions	1
4 Requirements	5
4.1 General	5
4.2 Categorization of devices	6
4.3 Allowable limits	6
4.3.1 General	6
4.3.2 Limited contact devices	7
4.3.3 Prolonged contact devices	8
4.3.4 Long-term contact devices	8
4.3.5 Special situations	9
4.3.6 Tolerable contact level	10
4.4 Determination of EO and ECH residuals	11
4.4.1 Procedure	11
4.4.2 Test method validation	11
4.4.3 Product sampling	11
4.4.4 Product extraction	11
4.4.5 Multi-device Systems	12
5 Product release	12
5.1 General	12
5.2 Batch release of products	12
5.3 Release of products at defined minimum aeration time	12
5.4 Procedure for product release using residual dissipation curves	13
6 Adoption of products into established aeration family	14
7 Requalification	14
Annex A (informative) Guidance for the application of this document for the determination of EO and ECH residuals in medical devices	15
Annex B (informative) Factors influencing product residuals	25
Annex C (informative) Rationale for the provisions of this document	28
Annex D (informative) Establishment of allowable limits for EO	33
Annex E (informative) Establishment of allowable limits for ECH	50
Annex F (informative) Ethylene Glycol	60
Annex G (normative) Evaluation of gas chromatograms	64
Annex H (informative) Gas chromatographic determination for EO and ECH	68
Annex I (informative) Preparation of EO and ECH standards	72
Annex J (informative) Ethylene oxide and ethylene chlorohydrin residual measuring methods	76
Annex K (informative) Examples of product release methods	84
Annex ZA (informative) Relationship between this European Standard the General Safety and Performance Requirements of Regulation (EU) 2017/745 aimed to be covered	102
Bibliography	105

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 $\mu\text{g}/\text{kg}/\text{d}$). 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 ($\mu\text{g}/\text{cm}^2$).

[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 ($\mu\text{g}/\text{cm}^2$).

[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 ($\mu\text{g}/\text{kg}/\text{d}$).

[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 ($\mu\text{g}/\text{cm}^2$) 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 ($\mu\text{g}/\text{kg}/\text{d}$). 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).

The Tolerable Exposure (TE) shall be calculated based on the tolerable intake (TI) multiplied by body mass (m_b) and CEF.

$$TE = TI \times m_b \times CEF \quad (1)$$

The allowable limit shall be determined based on tolerable exposure multiplied by the days in the category unless an alternative limit can be justified.

$$AL = TE \times \left(\frac{\text{number of days of the medical device contact duration}}{\text{number of devices used during this duration}} \right) \quad (2)$$

The intended population shall be documented.

NOTE Cumulative limits (total quantity per period of use) are protective for inhalation and parenteral routes of exposure because the lowest point of departure (POD) is selected, which is protective of these exposure routes.

Table 1 — Default values for [formulae \(1\)](#) and [\(2\)](#)

Contact Category	TI for EO mg/kg/d	TI for ECH mg/kg/d	CEF default	Anticipated contact duration d
Limited	0,3	0,64	0,2	1
Prolonged	0,3	0,27		No more than 30
Long-term	0,02	0,029		Default 25 000 d No more than [5 840 d (0 to 16 years)] Default [19 160 d (> 16 years)]

4.3.2 Limited contact devices

The allowable limits (AL) for limited contact devices are based on the tolerable intake (TI) value of 0,3 mg/kg/d for EO, 0,64 mg/kg/d for ECH, with CEF = 0,2 (default) as established in [clause D.3](#) and [clause E.4](#) respectively. The total EO and ECH cumulative exposure estimate obtained by simulated-use or exhaustive extraction shall be compared to the limited contact allowable limit, unless otherwise justified. Alternatively, an assessment targeted to evaluate toxicological risk associated with exposure to EO or ECH from the anticipated contact duration of a specific device can be used to determine the appropriate limits.

$$TE = TI \times m_b \times CEF \quad (3)$$

$$AL \text{ for EO} = 0,3 \text{ mg / kg / d} \times m_b \times 0,2 \times \left(\frac{1}{\text{number of devices used during this duration}} \right) \quad (4)$$

$$AL \text{ for ECH} = 0,64 \text{ mg / kg / d} \times m_b \times 0,2 \times \left(\frac{1}{\text{number of devices used during this duration}} \right) \quad (5)$$

Examples of allowable limits in [Table 2](#) are based on selected patient populations. Based on the device usage and intended patient population(s), other allowable limits may be more appropriate.

Table 2 — Examples of limited contact allowable limits

Patient Population	Patient Weight kg	EO mg/device	ECH mg/device
Adult – Unisex (> 16 years)	60	3,6 mg/device	7,7 mg/device
Adolescent (10 to 16 years)	25	1,5 mg/device	3,2 mg/device
Child (1 to 9 years)	10	0,6 mg/device	1,3 mg/device
Infant (< 1 year)	3,5	0,21 mg/device	0,45 mg/device

NOTE The lowest patient population weight, based on the anticipated contact duration for the device, should be used, see [C.4](#).

4.3.3 Prolonged contact devices

The allowable limits for prolonged contact devices are based on TI value of 0,3 mg/kg/d for EO, 0,27 mg/kg/d for ECH, body mass m_b , and with CEF = 0,2 (default) as established in [clause D.3](#) and [clause E.4](#). The cumulative exposure estimate obtained by simulated use extraction or exhaustive extraction shall be compared to the applicable prolonged duration limit for up to 30 d, unless otherwise justified. Cumulative allowable limits in [Table 3](#) are based on a CEF of 0,2 and 10 d of anticipated contact. Alternatively, an assessment targeted to evaluate toxicological risk associated with exposure to EO or ECH from the anticipated contact of a specific device can be used to determine the appropriate limits.

$$AL = TI \times m_b \times CEF \times \left(\frac{\text{number of days of the medical device contact duration}}{\text{number of devices used during this duration}} \right) \quad (6)$$

$$AL \text{ for EO} = 0,3 \text{ mg / kg / d} \times m_b \times 0,2 \times \left(\frac{\text{number of days of the medical device contact duration}}{\text{number of devices used during this duration}} \right) \quad (7)$$

up to 30 d

$$AL \text{ for ECH} = 0,27 \text{ mg / kg / d} \times m_b \times 0,2 \times \left(\frac{\text{number of days of the medical device contact duration}}{\text{number of devices used during this duration}} \right) \quad (8)$$

up to 30 d

Prolonged-contact devices shall meet Limited Contact allowable limits in [4.3.2](#) during the first 24 h period.

Table 3 — Examples of prolonged contact allowable Limits for 10 d anticipated contact

Patient Population	Patient Weight kg	EO mg/device	ECH mg/device
Adult – Unisex (> 16 years)	60	36	32
Adolescent (10 to 16 years)	25	15	14
Child (1 to 9 years)	10	6,0	5,4
Infant (< 1 year)	3,5	2,1	1,9

NOTE The lowest patient population weight, based on the anticipated contact duration for the device, should be used, see [C.4](#).

4.3.4 Long-term contact devices

4.3.4.1 Ethylene oxide

For EO, the tolerable exposure for long-term use devices is based on TI value of 0,02 mg/kg/d. The allowable limit is determined by multiplying the TE with the number of days of anticipated contact from a single or repeated use of a device for general populations (adults).

$$\text{Adult TE}_{EO} = TI \times m_b \times CEF = 0,02 \times 60 \text{ kg} \times 0,2 = 0,24 \text{ mg / d} \quad (9)$$

$$\text{Adult AL}_{EO} = 0,24 \text{ mg / d} \times \left(\frac{\text{number of days of the medical device contact duration}}{\text{number of devices used during this duration}} \right) \quad (10)$$

For devices to be used for paediatric patients during a specific time frame (age), the TE value can be calculated based upon the values given in [Table D.9](#). For a device intended to be used throughout paediatric time frame (age 0 to 16 y) and through adulthood, the TE value is 0,11 mg/d, see [D.5.7](#). The cumulative exposure estimate should be compared to the applicable allowable limit, unless otherwise justified.

$$\text{Paediatric TE}_{EO} = TI \times m_b \times CEF \quad (11)$$

$$\text{Paediatric AL}_{\text{EO}} = \text{TE} \times \left(\frac{\text{number of days of the medical device contact duration}}{\text{number of devices used during this duration}} \right) \quad (12)$$

Long-term contact devices shall also meet limited and prolonged allowable limits in [4.3.2](#) and [4.3.3](#) during the first 24 h period and the first 30 d, respectively.

4.3.4.2 Ethylene chlorohydrin

For ECH, the tolerable exposure for long-term use devices is based on TI value of 0,029 mg/kg/d. The allowable limit is determined by multiplying the TE with the number of days of anticipated contact from a single or repeated use of a device for general populations (adults) based on the anticipated contact duration.

$$\text{Adult TE}_{\text{ECH}} = 0,029 \text{ mg/kg/d} \times 60 \text{ kg} \times 0,2 = 0,35 \text{ mg/d} \quad (13)$$

$$\text{Adult AL}_{\text{ECH}} = \text{TE} (0,35 \text{ mg/d}) \times \left(\frac{\text{number of days of the medical device contact duration}}{\text{number of devices used during this duration}} \right) \quad (14)$$

For devices to be used for paediatric patients during a specific time frame, the TE value can be calculated based upon the values given in [Table E.5](#). For a device intended to be used for throughout the paediatric time frame (age 0 to 16 years) and through adulthood the TE value is 0,16 mg/d, see [E.4.2.3](#). The cumulative exposure estimate should be compared to the applicable allowable limit, unless otherwise justified.

$$\text{Paediatric TE}_{\text{ECH}} = \text{TI} (0,029 \text{ mg/kg/d}) \times m_b \times \text{CEF} \quad (15)$$

$$\text{Paediatric AL}_{\text{ECH}} = \text{TE} \times \left(\frac{\text{number of days of the medical device contact duration}}{\text{number of devices used during this duration}} \right) \quad (16)$$

Long-term contact devices shall also meet limited and prolonged allowable limits in [4.3.2](#) and [4.3.3](#) during the first 24 h period and the first 30 d, respectively.

4.3.5 Special situations

4.3.5.1 General

For certain medical devices, the default allowable limits for EO and ECH are not appropriate. The rationale for special situation EO and ECH limits that are at variance with the general requirements are in [Annex C](#). When special situations apply to sensitive special populations, the limits presented in [4.3.5.1](#) through [4.3.5.7](#) shall be adjusted, see [clause C.4](#). Examples of limits for sensitive populations are provided in [Table 4](#) — below.

4.3.5.2 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.

4.3.5.3 For blood cell separators used in patient and donor blood collection, the limited contact limit for adults is 9 mg EO and 19 mg ECH. Prolonged and long-term EO and ECH limits apply, see [4.3.3](#) and [4.3.4](#).

4.3.5.4 For extracorporeal blood purification devices, the limited contact EO and ECH limits are 4,6 mg/device. The EO and ECH limits for prolonged and long-term may be exceeded, see [4.3.3](#) and [4.3.4](#).

4.3.5.5 For peritoneal dialysis blood purification devices, the dose of EO shall not exceed 4 mg per device and ECH shall not exceed 3 mg/device during any 24 h period or 90 mg for 30 d. The EO limits for a long-term may be exceeded, see [4.3.4](#).

4.3.5.6 For blood oxygenators and blood reservoirs, the limited contact dose to the patient shall not exceed 54 mg EO and 38 mg ECH. The prolonged contact dose of residuals shall not exceed 108 mg EO and 97 mg ECH. The default long-term limits apply, see [4.3.4](#).

4.3.5.7 For devices used in cardiopulmonary bypass procedures (other than blood oxygenators and blood reservoirs), the limited contact limits shall be 18 mg for EO and 38 mg for ECH. Prolonged and long-term EO and ECH limits apply, see [4.3.3](#) and [4.3.4](#).

4.3.5.8 For any device, such as drapes, that are intended to have loose contact with only intact skin, only the TCL limits apply or the device shall be non-irritating as specified in ISO 10993-23, see [4.3.6](#).

Table 4 — Example of special situation limited contact allowable limits (mg/device)

Patient Population	Patient weight (kg)	Blood cell separators (EO)	Blood cell separators (ECH)	Cardio-pulmonary bypass device (EO)	Cardio-pulmonary bypass device (ECH)	Blood oxygenators and blood reservoirs (EO)	Blood oxygenators and blood reservoirs (ECH)
Adult – Unisex (> 16 years)	60	9,0	19	18	38	54	38
Adolescent (10 to 16 years)	25	3,8	8,0	8	16	23	16
Child (1 to 9 years)	10	1,5	3,2	3,2	6,4	9,0	6,4
Infant (< 1 year)	3,5	0,53	1,1	1,1	2,2	3,2	2,2

NOTE Body weights associated with other sub population age groups which shall require justification, see [clause C.4](#)

4.3.6 Tolerable contact level

4.3.6.1 Overview

The Tolerable Contact level (TCL) is designed to ensure that surface contacting devices, portions of externally communicating medical devices that directly contact tissue/bone/dentin, and implants that directly contact tissue/bone/dentin do not cause local irritation. The TCL is based on the amount of EO and ECH per unit surface area of a device. Except in special situations, these limits shall be considered in addition to the limits in [4.3.2](#). The 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 device. Additional details on the TCL can be found in [Annex D](#) (EO) and [Annex E](#) (ECH).

NOTE 1 ISO 10993-1:2018 includes information on categorization and examples for surface contacting devices [5.2.2], implants [5.2.4], and externally communicating medical devices that contact tissue/bone/dentin [5.2.3 b)].

NOTE 2 These limits apply to all patient contacting devices independent from their category, but only during the limited contact period.

NOTE 3 As TCL is based on amount of EO or ECH per unit surface area or ECH, adjustments for special populations (i.e., paediatrics) is not required.

4.3.6.2 Tolerable contact level for EO

The TCL_{EO} value shall not exceed $10 \mu\text{g}/\text{cm}^2$ for the duration of use up to 24 h, or the device shall be non-irritating as specified in ISO 10993-23.

NOTE Irritation test samples should be representative of the shortest time between sterilization and patient contact, unless data indicate that EO residuals are not decreasing, see [4.4.3](#).

4.3.6.3 Tolerable contact level for ECH

The TCL_{ECH} value shall not exceed 5 mg/cm^2 for the duration of use up to 24 h, or the device shall be non-irritating as specified in ISO 10993-23.

NOTE Irritation test samples should be representative of the shortest time between sterilization and patient contact, unless data indicate that ECH residuals are not decreasing, see [4.4.3](#).

4.4 Determination of EO and ECH residuals

4.4.1 Procedure

The procedure for determining compliance with allowable limits (see [4.3](#)) consists of extracting the residual from samples, determining the amount of residual, determining the contact surface area of the device, and analysing and interpreting the data. Additional guidance on evaluating residuals is provided in [Annex A](#), [Annex B](#), [Annex C](#) and [Annex J](#).

4.4.2 Test method validation

A valid method of extraction and measurement shall be used to determine the amount of EO and, where necessary, ECH delivered to the patient. EO and ECH residuals analysis is normally conducted by gas chromatography (GC). Minimum requirements for such validation include system suitability, demonstration of accuracy, precision (repeatability, intermediate precision, and reproducibility), specificity (sensitivity and selectivity), detection and quantification limits, linearity and range. Validation in accordance with the ICH Harmonized Tripartite Guideline^[209] is sufficient to meet these minimum requirements.

The guiding principle in selecting appropriate extraction methods (see [Annex A](#)) for the quantitative determination of EO and ECH is the evaluation of the dose to the patient in order to show compliance with the requirements set out in [4.3](#). Where residuals 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 that all applicable limits in [4.3](#) are met. If ECH is not detected based on the results of analyses performed using the methods described in either [I.4.7](#) or [I.4.8](#), then no further testing for ECH is required.

When exhaustive extraction is used for prolonged or long-term contact to a medical device, particular attention shall be paid to the limits expressed for the limited and/or prolonged contact periods.

4.4.3 Product sampling

Samples to be used for residual analysis shall be representative of the finished product as presented to the sterilization process and regard shall be given to worst-case sterilization conditions (e.g., allowed double or triple sterilization, minimum aeration time). When selecting samples, attention shall be given to the many factors described in [Annex A](#) and [Annex B](#). Since these factors influence the initial levels of residuals in device components and the rate of residual dissipation, they shall also be considered when samples are retrieved from a processed load and sent to the laboratory for analysis.

4.4.3.1 Sample/fluid ratios

The volume of fluid used to extract residuals from devices, or representative sections of them, shall be sufficient to maximize extraction efficiency while maintaining detection sensitivity, see [Annex A](#), [Annex C](#) and [Annex K](#) for more information on product extraction.

4.4.4 Product extraction

The aim of product extraction is to determine the worst-case amount that could be delivered to the patient in actual use of the device: on a daily basis for limited contact items; on a daily and up to monthly basis for prolonged contact items; on a daily, monthly, and up to a lifetime basis for long-term contact items. Sample preparation shall be performed according to any applicable instructions for use. The worst-case extraction time shall be justified and documented.

EO-sterilization residuals in medical devices can be determined by simulated-use extraction or exhaustive extraction. Only the components of the finished product with direct or indirect patient contact are relevant for testing. The choice of extraction method shall be based on the anticipated contact duration of the device and the following criteria:

- The extraction method chosen shall represent the anticipated contact duration of the product with the greatest exposure to the patient and not solely expeditious analysis or to minimize the apparent concentration of residuals.
- Extraction temperatures and times shall be determined based on the nature of the patient's exposure and the patient's duration of exposure with the device as described in [4.2](#) and [4.3](#).

Guidance on product extraction can be found in [Annex A](#).

4.4.5 Multi-device Systems

A multi-device system is a set of components in a packaging system that are assembled as a product and used together in clinical practice. Due to the potentially complex nature of a multi-device system, an assessment may be appropriate to determine if products should be tested individually or assembled. Additional guidance is provided in [clause A.7](#).

A convenience kit is comprised of procedure-related health care products in which each health care product is used independently in clinical practice. For convenience kits, the limits for the products may be applied independently using the appropriate CEF or the allowable limit calculated for the entire kit. If the number of devices used is different from the default of five (5) devices, then the CEF shall be adjusted to the number of devices in the kit. See [clause A.7](#).

5 Product release

5.1 General

Product is in compliance with this document when it meets the requirements for EO and ECH. For batch release of EO-sterilized product, data shall be documented to demonstrate compliance to the requirement. [5.2](#), [5.3](#) and [5.4](#) provide methods for demonstrating compliance. Other methods may also be appropriate. If sufficient experimental data on residual diffusion kinetics are available, it may be possible to group devices into families based on similarity of materials, manufacturing processes, sterilization process, or clinical use. The rationale or data that justifies this decision shall be documented.

It is also feasible to establish a worst-case master product representing different products, see [clause A.4](#). The selection of a worst-case master product device shall be documented and justified. The amount of EO and ECH as well as the rate of dissipation should be considered when completing this comparison if the products are above the release limits. The product aeration concerns documented in [Annex B](#) are to be considered.

5.2 Batch release of products

Product may be released based on a batch-by-batch basis if the results are in compliance with this document and the data were obtained from testing carried out according to appropriate procedures delineated in [Annex J](#) and meet the requirements for EO and, if applicable, ECH set out in [4.3](#).

5.3 Release of products at defined minimum aeration time

Data collected at the same time point (aeration time) can be used to establish the minimum aeration time. Subsequent product may be released when data from three separate sterilization batches tested at the same time point (aeration time) were obtained from testing carried out according to appropriate procedures with a 95 % upper confidence limit which meets the requirements for EO and, if applicable, ECH set out in [4.3](#). [Annex K](#) provides worked examples of product release calculations.

5.4 Procedure for product release using residual dissipation curves

Dissipation curves are used to estimate the post-sterilization time required for products, or families of products. Products shall be released to the marketplace according to predetermined post-sterilization times and conditions defined by experimental dissipation curves so that the target EO residual levels for the device, as set out in 4.3, are ensured. Annex K provides worked examples of product release calculations.

Dissipation of EO from most materials and devices follows first-order kinetics, i.e., $(\log [EO]) \propto (\text{time after sterilization})$. A plot of the logarithm of the experimentally determined EO concentration against time after sterilization is linear. Release shall then be based on the time after sterilization when the mean regression line intersects the maximum allowable residual. When the plot of the logarithm of the experimentally determined EO concentration against time after sterilization is determined not linear, or results are below detection limits, alternative methods may be applied, such as batch release testing (see 5.2), or defined minimum aeration time (see 5.3), or application of non-linear regressions analysis. Use of non-linear regressions analysis shall be documented and justified.

Regression analysis of pooled data from sufficient time points for at least three sterilization batches of the same product to establish the nature of the dissipation curve will enable product to be released at the calculated upper 95 % prediction limit, L_p , for the allowed residual limit for the product. Time-concentration curves for devices made from combinations of dissimilar materials may not fit this simple pattern over the entire range and may need to be handled differently.

Formulae for calculating the prediction limit, L_p :

$$x_0 = \frac{y_0 - a}{b} \quad (17)$$

$$L_p = x_0 + t_\alpha \times \sqrt{\frac{(S_\alpha)^2}{b^2} \times \left[1 + \frac{1}{n} + \frac{(y_0 - y_\mu)^2}{b^2 \times \sum (x_i - x_\mu)^2} \right]} \quad (18)$$

where

x_0	is the calculated average value of the release time corresponding to the EO limit
y_0	is the logarithmic value of the EO limit
a	is the intercept of the linear regression line obtained from the plot $\log [EO] \propto \text{time}$
b	is the slope of the regression line
L_p	is the prediction limit for a single individual of the product
t_α	is the student t value at significance α with $n-2$ degrees of freedom
$(S_\alpha)^2$	is the residual variance of the regression line
y_μ	is the average of logarithmic EO values
n	is the number of values
x_i	is the individual time after sterilization at which measurements are made
x_μ	is the average of the times after sterilization
$\sum (x_i - x_\mu)^2$	is the sum of squares for x (time)

NOTE 1 The 95 % prediction limit may not apply to ECH as at atmospheric pressure ECH remains in liquid phase between -67°C and 129°C .

NOTE 2 $\log_{10}$ or natural log (ln) can be used with the same outcome. However, consistency must be maintained in which logarithm is used within a set of calculations.

6 Adoption of products into established aeration family

A product may be added to a validated process if deemed equivalent to or a lesser challenge than an existing qualified product. A technical review shall be performed comparing the candidate product with the existing qualified product used to demonstrate compliance to the allowable limits. This review may include evaluation of characteristics noted in [5.1](#) (residual data) and [clause A.5](#). The outcome of the technical review, including the rationale for decisions reached, shall be documented.

7 Requalification

Changes to product, packaging, anticipated contact duration or sterilization process shall be evaluated for their potential impact on residuals. When this assessment indicates a potential increase in the level of residual EO or ECH, data to confirm compliance shall be obtained to ensure continued product acceptability. When this assessment indicates a decrease in the level of residual EO or ECH, consideration can be given to qualifying a new minimum aeration time.

Annex A (informative)

Guidance for the application of this document for the determination of EO and ECH residuals in medical devices

The guidance given in this annex is neither intended as a checklist for assessing conformance with this document nor is it intended to infer that this guidance is the only means of achieving compliance. This guidance is intended to assist in obtaining a uniform understanding and implementation of this document. Guidance is provided to improve understanding for implementation of the requirements by providing explanations and acceptable methods for achieving conformance with specified requirements. Methods other than those given in this guidance can be used, providing their performance achieves conformance with the normative requirements in this document.

A.1 Background

This annex provides guidance on the application of certain parts of the ISO 10993 series to the biological evaluation of medical devices that have been sterilized with ethylene oxide (EO). This annex primarily addresses the application of this document, but limited guidance is also given for other parts of the ISO 10993 series.

When EO and ECH residual limits cannot be met within a required timeframe, then the risk of harm should be estimated and evaluated in accordance with ISO 10993-1 and ISO 14971. If the risk of harm is estimated to be at an unacceptable level, then the risk should be controlled, unless risk control is not practical. When risk control is not practical, benefit-risk analysis should be applied. If there are device-specific standards that address the risk analysis (e.g., ISO 11979-5), the recommendations in the device-specific guidance or standard should be followed.

This annex includes a flow chart that is intended to assist a user in understanding the steps necessary to apply this document. The flow chart shows the decision points and provides guidance for choosing the appropriate actions where alternatives are given in the document. Some of the guidance represents a practical means of applying the document to different products based on factors such as: nature of exposure; duration of exposure; frequency of use; special situations of use (e.g., as cited in [4.3.5](#)); product size.

[4.4](#) gives the requirements for determining EO and, if applicable, ECH residuals, with additional guidance in this Annex. Analytical procedures are described in [Annex G](#), [Annex H](#), [Annex I](#) and [Annex J](#). Extraction conditions for the determination of residual EO are given in [Annex A](#). Guidance on developing an appropriate simulated-use extraction procedure is described in [clause A.3](#). This enables users to develop and document the rationale for an appropriate simulated-use extraction procedure for their EO-sterilized products.

The analytical laboratory should work with the device manufacturer to demonstrate that the simulated-use extraction is carried out under conditions that provide the greatest challenge based on the anticipated contact duration (i.e., worst-case). Product use simulation should be carried out assuming that the device is assigned to the most stringent category probable for the duration of exposure and should take into consideration both tissue(s) exposed and temperature of exposure.

A.2 Guidance

A.2.1 Use of alternative materials and sterilization methods should have been considered during product development and design with the aim of minimizing exposure to residuals. The rationale and basis for this decision should be documented. [Figure A.1](#) assists with the process of evaluating a device.

A.2.2 If the device has no patient contact, such as *in vitro* diagnostic devices, back table covers, Mayo stand covers, device handles, etc., this document does not apply.

NOTE Employee exposure limitations may be required by local occupational health regulations.

A.2.3 Establish the patient population and determine the limits based on the highest potential residual EO and ECH exposure as a ratio to the limits. Typically, the lowest body mass patient special population will have the highest potential exposure, though if the CEF varies with patient body mass, another population can have a higher potential exposure. If the device is in a special category, use the limits in [4.3.5](#). Additional guidance can be found in [clause A.4](#), [clause A.5](#), [clause A.6](#), and [clause C.4](#).

If the device is in a special category use the limits in [4.3.5](#). In some situations, a device specific TI/TE/AL may be appropriate, see [clause A.8](#).

A.2.4 The decision to test batch by batch, at a defined minimum aeration time, or via dissipation curve will be dependent on the several factors:

A.2.4.1 If a defined aeration time has not yet been established, the use of batch release allows for the release of product while the required aeration time is established.

A.2.4.2 If an established minimum aeration time is anticipated to be sufficient to meet the release limit, testing at the defined minimum aeration time testing may be appropriate. End point testing has the disadvantage that if the allowable limits are exceeded, additional testing is required, the amount of aeration time is still unknown, or the minimum established aeration time can be greater than required for the product in question.

A.2.4.3 Use of a dissipation curve, with data collected from a minimum of 3 different sterilization batches with data at different time points (minimum of 1 sample per batch), is useful for new products/processes, to define the minimum aeration time or when the existing minimum aeration time is not sufficient, see [clause K.2](#).

A.2.5 For prolonged and long-term contact devices, exhaustive extraction using repeated 24 h simulated-use extractions ([A.3.2.2](#) and [J.4.2](#)) can be used for estimating limited, prolonged, and long-term exposures, but does not extract all residuals from the device – only the clinically relevant levels. Exhaustive extraction using thermal extraction has the benefit of estimating the total amount of EO in a single extraction, and if these results meet limited contact limits, prolonged and long-term contact limits are also confirmed.

A.2.6 When it has been confirmed that a particular limit will result in a worst-case aeration time, it is possible to reduce subsequent testing to focus on just the variable that results in the worst-case aeration time. For example, if the data from the first sterilization batch for a long-term contact device confirms that the 24-hour EO TCL results result in a worst-case aeration time in dissipation curve calculations, testing of samples from subsequent sterilization batches can be performed via a single 24-hour extraction in lieu of an exhaustive extraction.

A.2.7 The following decision tree in [A.2.8](#) through [A.2.10](#) is based on exhaustive extraction first, followed by simulated-use exhaustive 24 h extractions, for prolonged and long-term devices. Exhaustive thermal extraction is not required in all circumstances.

A.2.8 For long-term contact devices (those contacting the patient for longer than 30 d to a lifetime):

When exhaustive extraction is used and the total measured EO and ECH are not more than the established limited contact limit, prolonged and long-term limits are also confirmed and generating simulated-use extraction data is not needed; go to [A.2.10](#). When exhaustive extraction is used and the total measured EO and ECH exceeds either the established limited, prolonged, or long-term limits, then simulated-use extraction data should be generated (see [A.3.2.2](#)).

This exhaustive extraction may not be necessary for devices which are long-term contact devices due to repeated use or when exhaustive extraction is used and the total measured EO and ECH exceeds either the established limited, prolonged, or long-term limits, then simulated-use extraction data should be generated or generate additional exhaustive extraction data at extended aeration time points.

A.2.9 For prolonged contact devices (those contacting the patient for more than 24 h up to 30 d):

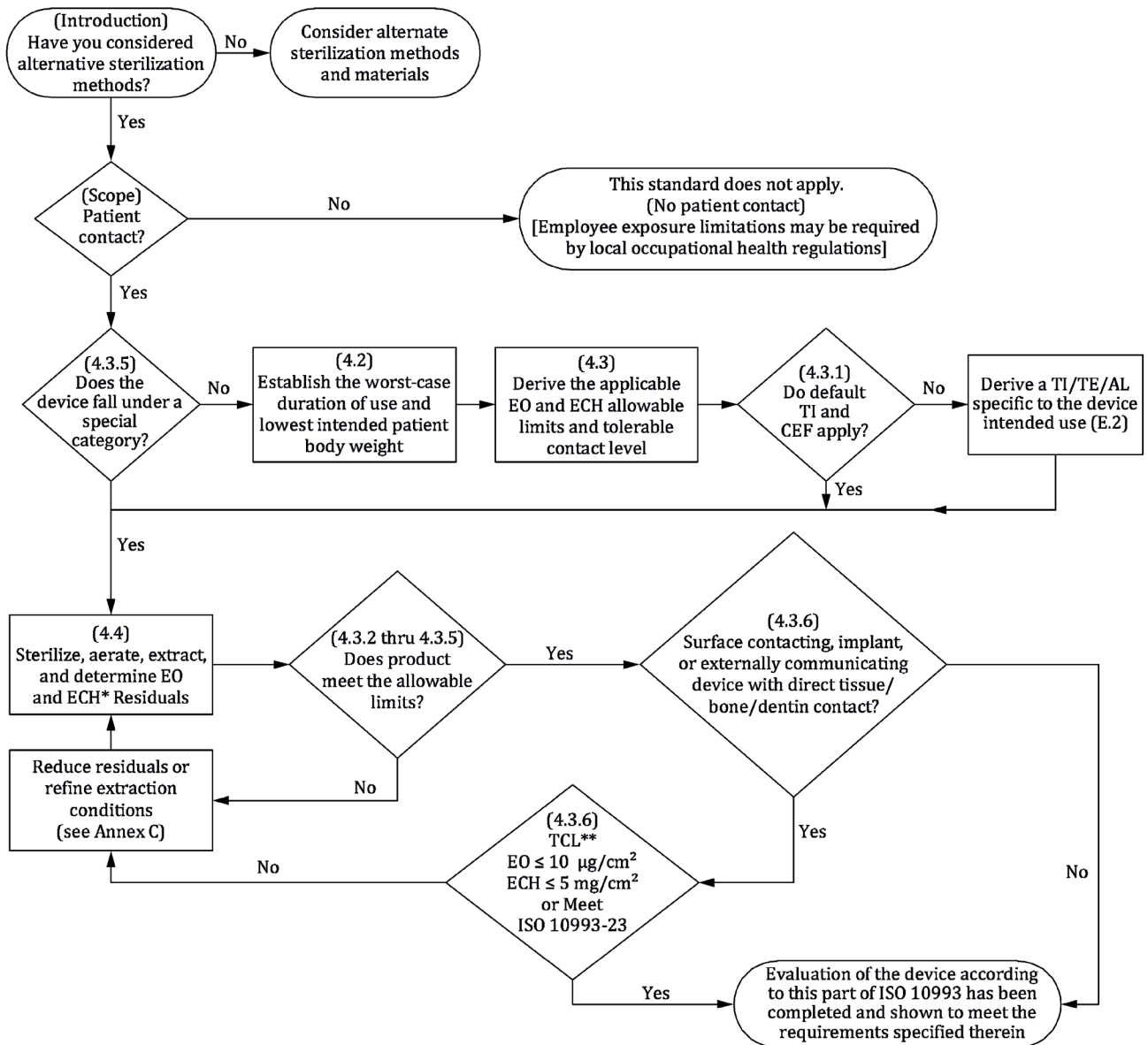
When exhaustive extraction is used and the total measured EO and ECH are not more than the established limited contact limits, prolonged contact limits are also confirmed and generating simulated-use extraction data is not needed and go to [A.2.10](#). When exhaustive extraction is used and the total measured EO and ECH exceeds either the established limited or prolonged limits, then simulated-use extraction data should be generated (see [clause A.3](#)).

This exhaustive extraction may not be necessary for devices which are prolonged contact devices due to repeated use or when exhaustive extraction is used and the total measured EO and ECH exceeds either the established limited, prolonged, or long-term limits, then simulated-use extraction data should be generated or generate additional exhaustive extraction data at extended aeration time points.

A.2.10 Irritation testing/tolerable contact level:

When EO or ECH are released from the device at a concentration that exceeds the applicable limit in [4.3.6](#), demonstration that the medical device does not elicit irritation at the time of release may be used to address this biological endpoint in accordance with ISO 10993-23. Care should be taken to minimize the potential off-gassing of EO between the end of the defined aeration period and irritation testing.

Unnecessary in vivo irritation testing should be avoided in order to comply animal welfare regulations (see ISO 10993-2).



* When chlorine is used as, or part of, a manufacturing material and it is demonstrated that residual levels of ECH is not detectable on the surface of the medical device made of only non-absorbent materials (e.g., glass or metal), routine testing for residual ECH may not be necessary, see [Clause 1](#), NOTE 2.

** TCL does not apply to ocular devices, see [4.3.5.2](#).

Figure A.1 — Flowchart to assist in understanding steps necessary to apply this document

A.3 Determining EO and ECH residuals

A.3.1 Sample handling

A.3.1.1 Sample retrieval

Samples should be removed from the load at the time(s) defined in the protocol for establishing aeration hold time. The residual extraction should be initiated as soon as possible after removal of the sample from the load, or the sample may be kept frozen for extraction later. If shipping the samples to the lab, samples should remain frozen during shipping. This may be done by shipping in controlled environment or on

a quantity of dry ice sufficient to prevent further off-gassing. Caution should be exercised when product samples are removed from the sterilization load soon after the sterilization process is completed due to the risk of employee exposure to EO off-gassing from the product loads.

A.3.1.2 Sample handling after processing

Samples should be stored frozen ($< 0\text{ }^{\circ}\text{C}$) when analysis is delayed. Samples should remain frozen during shipment or shipped on dry ice. Dry ice should remain in the shipping container throughout the shipment and be present when the package is opened in the laboratory (if used), which could require overnight delivery. As an alternative, samples can be extracted after the designated aeration interval and immediately placed in a non-porous container, and the extraction fluid shipped to the analytical laboratory for analysis. If the extraction fluid is water, then shipment should be done such that the fluid is kept at less than $10\text{ }^{\circ}\text{C}$ until arrival. Testing should be carried out to measure hydrolysis of EO to EG.

A.3.1.3 Sampling considerations at the lab

Delayed removal of the product samples from the processed load or lengthy shipment to a laboratory or extended storage in the laboratory for later analysis can jeopardize correlations of residual levels on the samples with those on the rest of the load. Moreover, if samples cannot be drawn from the load and handled so that the effect on aeration conditions for the sample will be negligible, an experiment to establish the relationship between the sample aeration and load aeration should be carried out and include seasonal variation if applicable.

Precautions should be taken to minimize or control the effects of laboratory conditions on the rate of aeration for test samples that have been removed from a product load (see [B.1.5](#)). In addition, operator and analyst safety should be considered. Samples should remain with the product load until the day of analysis or until test samples are retrieved and immediately frozen. The time between removal of samples from a controlled aeration area and the beginning of extraction should be held to a minimum.

Ensure operator safety when handling or working with samples that have been processed with ethylene oxide. Samples should be processed promptly after removal from the freezer to prevent unintended off-gassing. Samples should be prepared according to any applicable pre-use instructions in the product labelling. Extractions should be started as soon as possible after the device has been removed from the packaging or pre-use preparations have been completed.

A.3.1.4 Sample “blank”

In some instances, sample matrix components with the same retention time as the residuals being determined can be detected, resulting in higher EO or ECH results. If the results do not follow first order dissipation kinetics or results are above the detection limit, a “blank” sample may be evaluated for the possible presence of such interferences by the extraction of a non-sterilized sample using the identical procedure being applied to the EO-sterilized samples. In the event of materials being extracted from such a “blank” with conflicting or overlapping retention times in the GC analysis, chromatographic conditions can be modified to separate the interfering peak from the analyte peak, or an alternative analytical procedure can be used.

A.3.1.5 Sample/fluid ratios

The volume of fluid used to extract residuals from devices, or representative sections of them, should be sufficient to maximize extraction efficiency while maintaining detection sensitivity. The nature and size of the device sample therefore determines what constitutes the optimal fluid volume for extraction. Therefore, to maximize analytical sensitivity, a minimum amount of extraction fluid should be used depending on the extraction method required and size of the sample. Devices composed of highly absorbent materials or those from which residuals are extracted by filling might require sample/extraction fluid ratios reflecting increased fluid volume. In any case, sample/extraction fluid ratios should not undermine detection sensitivity.

For example, worst-case anticipated contact duration of many blood-contacting and parenteral devices can be simulated by filling or flushing the blood or fluid path components with water (whichever is appropriate) considering worst-case time and worst-case temperature.

When a device is too large to be extracted in its entirety, it might be necessary to extract several representative portions of the device components in order to ensure confidence in the data derived. These representative portions may be selected in one of two ways. If several varied materials are used, the proportion of each component, as compared with the total sample mass, should parallel the ratio of that component to the total mass of the device being tested. An alternative method would be to select one of the components for testing, subsequent to an evaluation demonstrating that it represented the worst-case with regard to residual content.

A.3.2 Extraction methods

A.3.2.1 General

The dose of residuals that the patient receives from the use of EO-sterilized devices is the critical parameter in the regulation of EO-sterilization residuals. In order to assess this patient or user dose, extraction procedures are required which simulate normal product use. In some cases, this can be achieved by simply filling the product with water, whereas in other cases more complicated simulations including continuous fluid flow might be required. It is recognised that there is no need to simulate product use, if the requirements for EO residuals are already met by determination of the total amount of residuals in the product by exhaustive extraction.

The guiding principle in selecting appropriate extraction methods for the determination of EO is the evaluation of the dose to the patient in order to show compliance with the requirements set out in this document, using simulated-use wherever possible. For devices in the prolonged contact category, it is important to note that the device should also meet the residual requirements of the limited contact category, and that devices in the long-term contact category should also meet the residual requirements of the prolonged contact and limited contact categories, whichever extraction condition is used. Where residuals are shown to be within these requirements for products tested by exhaustive extraction, there is no need to further challenge the device by simulated-use extraction.

Table A.1 — Suggested extraction conditions

Device contact duration (Clause 4.2)		
Long-term contact (> 30 d)	Prolonged contact (24 h to 30 d)	Limited contact (< 24 h)
Simulated-use extrac- tion and Exhaustive extraction	Simulated-use extraction and Exhaustive extraction	Simulated-use extrac- tion

For single use devices used for several days, where repeat use of new devices would result in categorization as prolonged or long-term contact a simulated-use extraction may be an appropriate alternative. When an exhaustive extraction procedure is specified, it could be impractical for large and/or complex devices. In such cases it could be necessary to extract representative portions of the device, then extrapolate the results to the entire device, see [Annex A](#).

A.3.2.2 Simulated-use extraction

A.3.2.2.1 General

Simulated-use aqueous extraction is the reference method in that it is the only method that produces results directly comparable to the limits specified in [4.3](#). These limits are expressed in terms of delivered worst-case dose of EO and ECH to patients. Simulated-use extraction should be carried out under conditions that

represent worst-case medical device anticipated contact duration. When blood is returned from the device to the patient, it should be assumed that any EO residuals will remain in the body.

Because of its polarity and its ability to extract EO and ECH,^[92] water is commonly used for the recovery of residual EO and ECH in simulated-use extractions. Water is used for elution of EO residuals from the sample rather than to dissolve the sample material itself. If the intent is to simulate product use by filling the device, the device should be filled so as to eliminate any air pockets.

A.3.2.2.2 Extraction time and temperature

Samples should be extracted for a time equivalent to or exceeding the maximum time for single use, and at temperatures that provide the greatest realistic simulated challenge. Devices that are used at body temperature should be extracted at 37+/-2 °C (body temperature); extract devices used at ambient temperature (e.g., hypodermic syringes) at 20-25 °C (room temperature). Extraction temperature lower than 37 °C should be justified and documented. For prolonged and long-term use devices, exhaustive extraction or repeated simulated use extractions should be used to estimate the total amount of residuals, see [clause A.2](#) and [I.4.2](#).

The recommended minimum extraction time is one hour.

NOTE 1 Examples of heated medical devices include intravenous fluid warmers and atrial fibrillation ablation catheters.

NOTE 2 The amounts of EO or ECH extracted by simulating intended product use are not necessarily the same as the total product residual content.

A.3.2.2.3 Pre-treatment conditions

Where pre-treatment of the device is required prior to use, this pre-treatment may be conducted before the device is extracted. Where the device is filled for extraction, do this in a manner that eliminates entrained air pockets. Extract the device with water at the temperature and for the time established. Where use of the device involves circulation of fluids (e.g., blood, dialyser fluid), extract the device using water to simulate the fluid's circulating in a manner consistent with product use. Document the rationale for the conditions established. Portions of the device that are not in contact with the body should be excluded, if possible. If non-patient contact portions of the device cannot be excluded from testing, assessment of the patient exposure can be appropriate.

If the assay is not performed immediately after extracting the medical device, the extract should be decanted from the sample and sealed in a vial that is impervious to EO, e.g., poly-(tetrafluoroethylene) (PTFE)-lined, septum-capped vial. The headspace in the vial of any standard solution or extract should be less than 10 % of the total volume. The extract can be stored in the refrigerator for several days (see [clause I.3](#)). If high levels of ECH or EG are detected, the analyst could evaluate the possibility of EO conversion to EG and/or ECH when extracting the sample with water.

A.3.2.3 Exhaustive extraction

A.3.2.3.1 General

Exhaustive extraction is intended to obtain a total quantity of EO or ECH.

A.3.2.3.2 EO and ECH simulated use exhaustive extraction

Exhaustive extraction methods include the concept of repeated simulated-use extractions (generally 24 h each) that continue until the last extraction step performed produces a yield of the analyte which is less than 10 % of the yield of the analyte in the first extraction of the sample, see [Annex J](#). The concept of repeated extractions can fail when the yield of the first extraction is very small, as in the case of a device with little residual or a sample that releases the analyte at a very slow rate. In such cases, extraction should continue until the increase in the cumulative total of the analyte extracted in the several extraction steps is small

relative to the analytical uncertainties. This method has the benefit of providing both the limited, prolonged, and long-term residual data points.

A.3.2.3.3 EO headspace exhaustive extraction

Extraction procedures include thermal extraction followed by headspace gas analysis, solvent extraction procedures, with either headspace gas analysis of the solvent extract, chromatography of the solvent extract, or preparation of the bromohydrin derivative of EO which is determined using a more sensitive GC detector such as an electron capture detector (see [Annex J](#)).

It can produce results that can represent a dose greater than or equal to one the patient can receive. Exhaustive extraction does not generate clinically relevant exposure data; however, when all applicable limits in [4.3](#) are met and residuals are demonstrated to be within the requirements for products tested by exhaustive extraction, there is no need to further challenge the device by simulated-use extraction.

For solvent extraction procedures, selection of a suitable extraction vehicle depends on the material composition of the device and its components. To facilitate complete recovery of EO from the sample, fluids that dissolve the sample material are generally preferred in an exhaustive extraction, provided that interfering substances are not also put into solution by the procedure. Solvent extraction procedures that are combined with headspace gas analysis are described in [J.4.4](#) and such procedures might be able to separate EO from co-extracted interfering chemicals from the sample matrix. Several extraction fluids have been evaluated through interlaboratory comparison testing^{[112],[113]} and^[114].

When conducted as described, headspace methods are considered exhaustive since they are designed to estimate the total quantity of residual EO that is present in the sample. However, headspace methods might not be feasible or preferred for intact testing of large or complex devices. The analyst should exercise caution in the execution of exhaustive extraction methods when evaluating residual levels in high durometer polymer materials such as poly-(methylmethacrylate) to ensure total recovery of EO^[216].

A.3.2.3.4 ECH exhaustive extraction

Water is typically used to extract residual ECH from medical devices using methods similar to those described for determining residual EO. Extract for 24 h at the appropriate temperature, repeating extractions until less than 10 % of the initial amount is recovered, see [J.4.8](#).

A.4 Grouping of devices

Given sufficient experimental evidence on residual diffusion kinetics (e.g., the rate of EO gas dissipation from the packaging for the range of given devices), it might be possible to group devices based on similarities of materials, manufacturing processes and clinical use. For such a classification system to work, the variables discussed above should be controlled. Lack of control can yield data about residual levels that are applicable only to the samples analysed.

Devices of similar design but different sizes may be grouped, and the worst-case selected for testing as representative of the group. Comparison of results from different device groups can establish a worst-case product device that can be used for reverification of compliance. Care should be taken when comparing EO residuals results to account for both EO levels and the rate of dissipation if results are above the established limits resulting in a device with lower initial levels requiring more aeration time to reach allowable limits.

A.5 Worst case product

It is feasible to establish a worst-case master test article representing different devices or families. Comparable EO residual test data including the dissipation kinetics should be considered, i.e., a medical device with initial higher levels of residuals could dissipate faster based on the materials of construction or packaging resulting in a device with lower levels of residuals after sterilization to require more aeration to reach allowable limits. Device surface area, device mass, and device materials can be relevant considerations. A worst-case device might be a smaller device with a special population allowable limit (i.e., lowest body mass patient) when considering the residual results as a percentage of the allowable limit. Alternatively, it is

also acceptable to test a product of a smaller size and extrapolate what the results would be for the product of the largest size (e.g., based on surface area, volume, or mass).

A.6 Adoption of products into established aeration family

Products may be grouped into families (see ISO 11135:2014, D.12.5.11.1). For EO residuals, products can be grouped into families based on device characteristics that allow them to be aerated to safe residual levels using the same defined aeration conditions. Candidate product may be adopted into an existing aeration family in compliance with this document by a documented review of relevant characteristics and/or by qualification studies on samples retrieved after worst-case aeration (e.g., minimum time and temperature).

A.7 Multi-device systems (kits and trays) and convenience kits

For a multi-device system, an understanding of the different components, how they are used and how they are assembled into a product is important. The components that do not have patient contact, do not need to be tested. Due to the potentially complex nature of a multi-device system or convenience kit, a risk assessment could be needed to determine how to apply the limits. Multi-device systems, or kits, may be tested as single assembled device or each device tested individually. Testing components individually would allow for a worst-case device to be established. Testing an assembled product can allow for the application of a single allowable limit with adjustment to the CEF, if appropriate.

For a convenience kit, understanding the use of each product in clinical practice is important. If products can be placed in multiple exposure categories (i.e., limited, prolonged, long-term), then the products in the kit should be grouped according to their exposure category and limits should be applied to each of those products for each category using the appropriate CEF.

A.8 Risk assessment

A toxicological risk assessment may be useful when the EO/ECH cumulative residual quantity exceeds the allowable limit. ISO 10993-17 provides a process, requirements, criteria, and guidance that device manufacturers can use for conducting a toxicological risk assessment.

Medical device anticipated contact duration could indicate the need for medical device specific CEF values that differ from 0,2 if more or fewer devices are used. For example: adjusting the default CEF to 0,25 when the number of medical devices used concomitantly is 4.

Medical device anticipated contact duration could also indicate the need for refinement of the scope and extraction conditions that are more representative of its anticipated contact duration (i.e., in terms of nature of exposure and exposure duration).

For example, it can be deemed sufficient to extract only the inner surface of an administration set tubing where the inner diameter (ID) of the tubing is in fluid/patient contact and not extracting the whole tubing with inner and outer diameter which would most likely yield overestimated EO residuals regarding patient contact.

In the case of a limited contact device used for less than 24 h, the worst-case extraction time can be adjusted from the typical 24 h to the longest clinically relevant exposure time. The risk assessment should not assume that the risk will be acceptable, rather, risk assessment could indicate the need for further risk evaluation or risk control, which includes benefit-risk analysis if risk control is not practical.

A.9 Data analysis and interpretation

A.9.1 Calculation of amount of residual extracted

The concentration of residual observed in the extracts, C_e , is converted into the amount delivered to a patient, in milligrams, M_d , as follows.

Residual extracted by simulated use may be calculated as follows:

$$M_d = \sum_1^n (C_{en} \times V_{en}) \quad (A.1)$$

Residual extracted by exhaustive extraction of representative portion(s) of a device may be calculated as follows:

$$M_d = \sum_1^n (C_{en} \times V_{en}) \times \frac{m_d}{m_s} \quad (A.2)$$

where

M_d is the extract residual, in milligrams;

n is the number of extractions;

C_e is the amount of EO in milligrams per millilitre of extract as derived from the standard curve;

V_e is the extract volume, in millilitres;

m_d is the entire device mass, in grams;

m_s is the mass of sample, in grams;

I_d is the days of anticipated contact duration.

NOTE $\frac{m_d}{m_s}$ only applies if a portion of the device is extracted.

A.9.2 Calculation of average delivered dose, M_{add}

For long-term contact devices, the average delivered dose, M_{add} , in milligrams per day, is as follows:

$$M_{add} = \frac{M_d}{I_d} \quad (A.3)$$

where

I_d is the anticipated contact duration, which is a maximum of 5 840 d for 0 to 16 years and 19 160 d for adulthood, totalling 25 000 d per lifetime;

M_d is the extract residual, in milligrams.

For prolonged contact devices

$$M_{add} = \frac{M_d}{I_d} \quad (A.4)$$

where I_d is the anticipated contact duration, with a maximum of 30 d M_d is the extract residual, in milligrams.

Annex B (informative)

Factors influencing product residuals

The guidance given in this annex is neither intended as a checklist for assessing conformance with this document nor is it intended to infer that this guidance is the only means of achieving compliance. This guidance is intended to assist in obtaining a uniform understanding and implementation of this document. Guidance is provided to improve understanding for implementation of the requirements by providing explanations and acceptable methods for achieving conformance with specified requirements. Methods other than those given in this guidance can be used, providing their performance achieves conformance with normative requirements in this document.

B.1 Sterilization process considerations

B.1.1 General overview

Sterilization process parameters are defined in ISO 11135. However, to properly analyse residuals in EO sterilized devices, it is necessary to recognise those parameters that have an effect on residual content. An understanding of EO kinetics can make it possible to address a family of like devices through the analysis of a “worst-case” representative. Recognition of a family of similar products (that is, similar in size and use, material composition, packaging, EO exposure, water content, and exposure to environmental conditions) can preclude the necessity of analysing each item of the product line. The following parameters affect residual content and can allow analysis of one or more “worst-case” representatives.

B.1.2 Material composition

Materials vary considerably in their ability to absorb, retain and release EO. When conversion of EO to ECH is possible, two similar devices made of different materials are likely to have very different residual profiles. For example, materials that contain a source of free chloride ions exhibit a wide degree of variation in the concentration of ECH formed.

Similarly, a single device composed of two dissimilar materials can require a representative sample of both materials to ensure accurate analysis. Composition and size can be particularly important when considering the simulation of normal product use.

B.1.3 Packaging

Packaging materials vary widely in their abilities to allow penetration and dissipation of both EO gas and the other possible residuals, which can in turn affect EO and ECH residual levels. Packing density and the density of the sterilization container or pallet are other sources of variability. The total number of layers of packaging should also be considered as each layer can act as a barrier to aeration of EO off devices.

B.1.4 Ethylene oxide sterilization cycle

Process conditions under which the device is exposed to EO will affect the residual levels. These conditions include humidity, gas concentration, dwell time, temperature, type of cycle (deep or shallow vacuum), number of post exposure re-evacuations and washes, and the product and load density or the configuration of the product load in the sterilizer. For processes with sufficient controls, the nominal routine processing parameters can be used, and the 95 % confidence interval of the residual results can be used to establish the acceptable aeration time. The impact of the upper tolerances for exposure time and EO inject pressure rise on EO residuals should be considered if greater than 10 % of the nominal value.

B.1.5 Aeration

Residuals in devices can vary as a function of aeration temperature, fresh air intake, load density and configuration, air flow, loading pattern, surface area of products being aerated, and aeration time. If the aeration room/chamber has not demonstrated consistency in air flow and temperature, cold spots in the chamber should be addressed when determining where to place residual samples, see [B.1.6](#). Placement of samples in the worst-case load, pallet and location in the aeration room is best practice when validating aeration time and temperature.

When aeration is carried out at ambient temperature, consideration of data from sterilization loads taken from aeration or quarantine storage at different times of the year may be required.

When using ambient aeration and samples are not frozen until testing, analysts should be aware of seasonal variations in aeration rates when samples are stored under laboratory conditions which differ from the ambient warehouse conditions. Under certain circumstances, which can best be determined by experience, it could be necessary to hold samples prior to analysis under conditions that approximate the lowest temperature at which the product is likely to be stored during ambient aeration, if used.

NOTE Degassing behaviour over the whole room, over the pallet, recorded with seasonal variations of aeration, when validating aeration time and temperature can be forecast under consideration of recorded warehouse conditions affecting aeration time taken into account the variation of load density and configuration, air flow, loading pattern, surface area of products being aerated in a justification for the appropriateness of the used sterilization process.

B.1.6 Aeration location considerations

Residual levels on the product can be impacted by various factors including the temperature, air flow, and location on the pallet, and configuration of the pallet, i.e., chimney in the centre, shrink wrap, etc. A rationale can be made to determine the most appropriate location for product sample placement based on an assessment of these factors. EO concentrations in the aeration area could retard off-gassing, especially when low allowable limits are required for certain subpopulation.

B.1.7 Load configuration

Consideration of the load configuration used for residual qualification should take into account the product, packaging and pallet configuration. This load could be the same as the most challenging load used for the MPQ or a different load configuration. Samples for EO residual testing should be placed in the load that is worst-case for EO residual dissipation. Loads that vary greatly in density or volume may be assessed to determine which presents a greater challenge to EO dissipation since the overall temperature of the load, EO absorption and airflow patterns could impact residual levels.

B.1.8 Repeat sterilization

Re-sterilization of product and the presence of other EO-sterilized medical devices in adjacent areas should be considered when obtaining experimental data. It is common to qualify products for repeat sterilization cycles. Studies suggest that EO residuals are not significantly impacted by multiple sterilizations^[217].

If product is qualified for multiple sterilizations, the time between sterilization cycles should be considered during the qualification. Testing of a limited number of samples from a single batch is typically sufficient to demonstrate that EO and ECH residual levels after multiple sterilization exposures are comparable to samples exposed to a single sterilization exposure. However, if EO and ECH residuals appear to be higher, it might be necessary to test three batches after double or triple sterilization in accordance with [5.3](#) or [5.4](#).

This time between cycles can reflect what would typically happen during routine reprocessing or the samples can be frozen between runs to represent worst-case off-gassing between cycles. Where repeat sterilization has been demonstrated for a worst-case product to have negligible impact on EO residuals, qualification of EO residuals for may be performed after 1 (one) cycle where appropriately justified.

B.1.9 Multiple processes or equipment

If two or more different EO sterilization cycles are approved for a product or product family, product samples from each cycle should be evaluated for testing and a release time determined for each process. When cycle

parameters only differ by gas exposure dwell time or gas concentration, testing on the cycle with the longest gas exposure or the highest gas concentration is sufficient to determine the aeration time for the different cycles.

If more than one cycle is to be approved for a product or product family and the processes differ by more than just the exposure period, gas concentration, equipment, and facility then a worst-case cycle/process may be used if data exists demonstrating which cycle/process is worst-case.

If more than one chamber/aeration area is to be approved for a product or product family, product samples from each chamber should be taken for testing and a release time determined for each chamber/aeration area unless process equivalence is established, or the worst-case equipment is used.

Annex C (informative)

Rationale for the provisions of this document

The guidance given in this annex is neither intended as a checklist for assessing conformance with this document nor is it intended to infer that this guidance is the only means of achieving compliance. This guidance is intended to assist in obtaining a uniform understanding and implementation of this document. Guidance is provided to improve understanding for implementation of the requirements by providing explanations and acceptable methods for achieving conformance with specified requirements. Methods other than those given in this guidance can be used, providing their performance achieves conformance with the normative requirements this document.

C.1 General

This annex specifies the rationale for establishing allowable limits for ethylene oxide sterilization residuals in medical devices based on duration of contact. Included is the basis for establishing limits for ethylene oxide (EO) and ethylene chlorohydrin (ECH).

C.2 Rationale for special situations

C.2.1 General

There are certain circumstances, for example major surgery, where the life-saving nature of the therapy significantly alters the risk-benefit analysis. The allowable limits given per device are based on risks and benefits associated with less critical circumstances. Therefore, ISO 10993-1 and ISO 14971 allow for device benefit alterations in allowable limits on a case-by-case basis for a specific device and its use. In consequence, there is scope for derivation of limits specific to a device used in life-threatening situations where it is not possible to meet the general limits derived in this document. Similarly, there could also be a need to tighten limits when warranted by risks in specific situations.

During the development of this document, six special situations were recognized in which the limits of 4.3 would not be practical due to limitations of the devices themselves, or in which human data indicated that the dose levels shown in 4.3 are not applicable. Human data are available from patient exposure to intraocular lenses which should be addressed by revision of the residual requirements for such devices. Blood cell separators used in donor and patient blood collection can be used multiple times and donors and patients have been shown to become sensitized to EO. Allowable limits for EO for these devices must be lowered to minimize the possibility of sensitization. During treatment of blood with oxygenators or blood separators or cardiopulmonary bypass devices it is recognised that the medical benefit outweighs the risk. This is addressed in considering the allowable Limited Contact limits for these devices. In the case of extracorporeal blood purification set-ups, long-term use could potentially lead to the maximum lifetime dose requirement being exceeded and this is also addressed. In the case of devices like drapes, that are intended to have loose contact with only intact skin, no systemic toxicity is anticipated, and patient safety should be adequately protected by meeting the TCL or irritation test requirements.

C.2.2 Intraocular devices

The residue limits for intraocular contacting lens is 0,5 µg EO and 2 µg per ECH per lens per day, or 5,0 µg ECH per lens. This limit is not based on the long-term contact limit with an average daily dose of 0,1 mg (100 µg) per day for a lifetime. Rather, it is a special case in which the maximum delivered dose cannot exceed a ceiling value of 0,5 µg per lens per day. This is necessary to prevent documented irritation responses of EO to ocular tissue.^{[43][118][119][167]} Prorate limits are used for other intraocular devices based on the mass of the device, with the mass of an intraocular lens taken as 20 mg.

When EO residuals are controlled as specified here for intraocular devices, it is unlikely that significant amounts of ECH will be present. This may not be true for intraocular devices made from viscoelastic materials that contain chlorine. In such cases, studies indicate that the level of ECH that results in ocular toxicity is about four times greater than the corresponding EO level.^{[43][117][118][119]} This should be taken into account when evaluating the acceptability of ECH levels associated with these devices.

C.2.3 Blood cell separators used in donor or patient blood collection

For blood cell separators, the maximum allowable limit for EO is 10 mg per device and the maximum allowable limit for ECH should not exceed 22 mg per device. These devices are used for apheresis collection. The limits take into account the multiple use of such devices in individual donors or patients.

In this case the default assumption of five devices used simultaneously appears somewhat conservative. If one were to assume only two devices as a reasonable worst-case, the CEF would increase from 0,2 to 0,5. This would raise the allowable limit to 9 mg EO.

For EO

$$TE = TI \times m_b \times CEF = 0,3 \text{ mg/kg/d} \times 60 \text{ kg} \times 0,5 = 9 \frac{\text{mg}}{\text{d}} \quad (\text{C.1})$$

For ECH

$$TE = TI \times m_b \times CEF = 0,64 \text{ mg/kg/d} \times 60 \text{ kg} \times 0,5 = 19 \frac{\text{mg}}{\text{d}} \quad (\text{C.2})$$

C.2.4 Blood oxygenators and blood reservoirs

The limits for blood oxygenators and blood reservoirs are 54 mg EO per device and 38 mg ECH per device in a 24 h period. These devices are used in life saving operations such as open-heart surgery. Such procedures are used on individual patients no more than once or twice in a lifetime. Since these devices are used for a day or less, the limits are relaxed. Under such circumstances a further fifteen-fold relaxation of the EO limit and a five-fold relaxation of the ECH limit is warranted. For prolonged contact, the EO limit is 108 mg/device and ECH is 97 mg/device, see [D.5.4](#) and [E.4.2.2](#).

For Limited Contact EO

$$TE = TI \times m_{Bb} \times CEF = 0,3 \text{ mg/kg/d} \times 60 \text{ kg} \times 0,2 \times 1 \text{ d} = 3,6 \frac{\text{mg}}{\text{device}} \times 15 = 54 \frac{\text{mg}}{\text{device}} \quad (\text{C.3})$$

For Limited Contact ECH

$$TE = TI \times m_{Bb} \times CEF = 0,64 \text{ mg/kg/d} \times 60 \text{ kg} \times 0,2 = 7,7 \frac{\text{mg}}{\text{device}} \times 5 = 38 \frac{\text{mg}}{\text{d}} \quad (\text{C.4})$$

For Prolonged Contact EO

$$TE = TI \times m_{Bb} \times CEF \times 30 \text{ d} = 0,3 \text{ mg/kg/d} \times 60 \text{ kg} \times 0,2 \times 30 \text{ d} = 108 \text{ mg} \quad (\text{C.5})$$

For Prolonged Contact ECH

$$TE = TI/MF \times m_b \times CEF = 0,27 \text{ mg/kg/d} \times 60 \text{ kg} \times 0,2 = 3,8 \frac{\text{mg}}{\text{d}} \times 30 \text{ d} = 97 \text{ mg} \quad (\text{C.6})$$

C.2.5 Devices used in cardiopulmonary bypass procedures

The limit for devices used in cardiopulmonary bypass procedures is 18 mg EO per device and 38 mg ECH per device in a 24 h period. These devices are used in severe operations such as open-heart surgery. Such procedures are used on individual patients no more than once or twice in a lifetime and the default CEF of

0,2 appears overly conservative. A CEF of 1,0 appears more reasonable and the allowable limit would be 18 mg EO and 38 mg ECH. The default prolonged contact limit applies.

For Limited Contact EO

$$TE = TI \times m_b \times CEF = 0,3 \text{ mg/kg/d} \times 60 \text{ kg} \times 1 = 18 \frac{\text{mg}}{\text{d}} \quad (\text{C.7})$$

For Limited Contact ECH

$$TE = TI \times Mm_b \times CEF = 0,64 \text{ mg/kg/d} \times 60 \text{ kg} \times 1 = 38,4 \frac{\text{mg}}{\text{d}} \quad (\text{C.8})$$

C.2.6 Extracorporeal blood purification devices

Extracorporeal blood purification devices are used in patients multiple times often over many years. In setting the allowable limits for these devices, consideration is given to the benefit derived from blood purification. The maximum allowable EO dose of 7,2 g for a lifetime may be exceeded, provided that the allowable limit for EO of 3,6 mg for each use is met. In addition, the allowable ECH dose for a lifetime may be exceeded, provided that the allowable limit for ECH of 7,7 mg for each use is met. To exceed the lifetime dose of EO, a patient undergoing blood purification would need to be exposed to 3,6 mg of EO thirteen times every month and such exposure would need to continue for 5,5 years. Similarly, ECH lifetime exposure could be exceeded after 3,7 years of use by end-stage renal disease patients.

For EO:

- Allowable limit for EO of 3,6 mg for each use.
- Lifetime dose of 7,2 g (7 200 mg) may be exceeded.
- It will take about 5,5 years (7 200 mg / 3,6 mg/d / 365) to reach the maximum allowable lifetime EO dose for the use of such devices.

For ECH:

- Allowable limit for ECH of 7,7 mg for each use.
- Lifetime dose of 10 440 mg may be exceeded.
- It will take about 3,7 years (10 440 mg / 7,7 mg/d / 365) to reach the maximum allowable lifetime ECH dose for the use of such devices.

C.2.7 Other blood purification devices

In addition to extracorporeal blood purification using a dialyzer, other dialysis approaches are known, one of which is peritoneal dialysis. Peritoneal dialysis is a therapy that infuses and stores dialysate into the abdominal cavity surrounded by the peritoneum that covers the viscera and removes unnecessary waste products and water in the blood through the peritoneum. Like extracorporeal haemodialysis, peritoneal dialysis has been used clinically for a long time. Since the benefits of peritoneal dialysis are equivalent to the extracorporeal haemodialysis described in [C.2.6](#), acceptable risks of peritoneal dialysis are also considered to be equivalent to extracorporeal haemodialysis. However, unlike extracorporeal haemodialysis, peritoneal dialysis performs multiple dialysate changes during a day. There are various usage forms among the peritoneal dialysis related devices such as a long-term indwelling port in the body, a connecting tube from the port to bags that change every week, and tubing sets that change every day, etc. Therefore, the allowable limits for EO of the peritoneal dialysis related devices should be set in consideration of their usage number in one month. For a 60-kg adult and assuming a CEF = 0,2, the value for EO is 108 mg per 30 d which is the maximum allowable value defined by the extracorporeal haemodialysis device.