MEDITSIINISEADMETE BIOLOOGILINE HINDAMINE. OSA 23: KONTAKTÄRRITUSKATSED

Biological evaluation of medical devices - Part 23: Tests for irritation (ISO 10993-23:2021 + ISO 10993- 23:2021/Amd 1:2025)

EVS • EESTI STANDARDIMIS- JA AKREDITEERIMISKESKUS
ESTONIAN CENTRE FOR STANDARDISATION AND ACCREDITATION

EESTI STANDARDI EESSÕNA

NATIONAL FOREWORD

See Eesti standard EVS-EN ISO 10993-23:2021 +A1:2025 sisaldab Euroopa standardi EN ISO 10993-23 ja selle muudatuse A1:2025 ingliskeelset teksti.	This Estonian standard EVS-EN ISO 10993-23:2021+A1:2025 consists of the English text of the European standard EN ISO 10993-23 and its amendment A1:2025.
Standard on jõustunud sellekohase teate avaldamisega EVS Teatajas. Euroopa standardimisorganisatsioonid on teinud Euroopa standardi rahvuslikele liikmetele kättesaadavaks 31.03.2021, muudatus A1 27.08.2025.	This standard has been endorsed with a notification published in the official bulletin of the Estonian Centre for Standardisation and Accreditation. Date of Availability of the European standard is 31.03.2021, for A1 27.08.2025.
Muudatusega A1 lisatud või muudetud teksti algus ja lõpp on tekstis tähistatud sümbolitega ⟨A1⟩ ⟨A1⟩. Standard on kättesaadav Eesti Standardimis-ja Akrediteerimiskeskusest.	The start and finish of text introduced or altered by amendment A1 is indicated in the text by tags ⟨A1⟩ ⟨A1⟩. The standard is available from the Estonian Centre for Standardisation and Accreditation.

Tagasisidet standardi sisu kohta on võimalik edastada, kasutades EVS-i veebilehel asuvat tagasiside vormi või saates e-kirja meiliaadressile standardiosakond@evs.ee.

ICS 11.100.20

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 10993-23 + A1

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English Version

Biological evaluation of medical devices - Part 23: Tests for irritation (ISO 10993-23:2021 + ISO 10993- 23:2021/Amd 1:2025)

Évaluation biologique des dispositifs médicaux - Partie 23: Essais d'irritation (ISO 10993-23:2021, Version corrigée inclus 2021-02 + ISO 10993- 23:2021/Amd 1:2025)

Biologische Beurteilung von Medizinprodukten - Teil 23: Prüfungen auf Irritation (ISO 10993-23:2021 + ISO 10993- 23:2021/Amd 1:2025)

This European Standard was approved by CEN on 1 October 2020. Amendment A1 was approved by CEN on 19 January 2025.

EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Rue de la Science 23, B-1040 Brussels

Ref. No. EN ISO 10993-23:2021 E
+ EN ISO 10993-23:2021/A1:2025 E

European foreword

This document (EN ISO 10993-23:2021) has been prepared by Technical Committee ISO/TC 194 "Biological and clinical evaluation of medical devices" in collaboration with Technical Committee CEN/TC 206 “Biological and clinical evaluation of medical devices” the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by September 2021, and conflicting national standards shall be withdrawn at the latest by September 2021.

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

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

For the relationship with EU Directive(s) see informative Annex ZA, ZB and ZC, which are integral parts of this document.

The following referenced documents are indispensable for the application of this document. For undated references, the latest edition of the referenced document (including any amendments) applies. For dated references, only the edition cited applies. However, for any use of this standard ‘within the meaning of Annex ZA’, the user should always check that any referenced document has not been superseded and that its relevant contents can still be considered the generally acknowledged state-of-art.

When an IEC or ISO standard is referred to in the ISO standard text, this shall be understood as a normative reference to the corresponding EN standard, if available, and otherwise to the dated version of the ISO or IEC standard, as listed below.

NOTE The way in which these referenced documents are cited in normative requirements determines the extent (in whole or in part) to which they apply.

Table — Correlations between undated normative references and dated EN and ISO standards

Normative references as listed in Clause 2 of the ISO standard	Equivalent dated standard	
	EN	ISO or IEC
ISO 10993-1	EN ISO 10993-1:2021 [a]	ISO 10993-1:2018
ISO 10993-2	EN ISO 10993-2:2006	ISO 10993-2:2006
ISO 10993-9	EN ISO 10993-9:2021[a]	ISO 10993-9:2019
ISO 10993-12	EN ISO 10993-12:2021 [a]	ISO 10993-12:2020
ISO 10993-13	EN ISO 10993-13:2010	ISO 10993-13:2010
ISO 10993-14	EN ISO 10993-14:2001	ISO 10993-14:2009
ISO 10993-15	EN ISO 10993-15:2021[a]	ISO 10993-15:2019
ISO 10993-18	EN ISO 10993-18:2021[a]	ISO 10993-18:2020
ISO 14155	EN ISO 14155:2020	ISO 14155:2020
[a] Under preparation at European level.		

NOTE This part of EN ISO 10993 refers to ISO 10993-1 which itself refers to ISO 14971. In Europe, it should be assumed that the reference to ISO 14971 is to EN ISO 14971:2012.

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Republic of North Macedonia, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 10993-23:2021 has been approved by CEN as EN ISO 10993-23:2021 without any modification.

[A1] Amendment A1 European foreword

This document (EN ISO 10993-23:2021/A1:2025) has been prepared by Technical Committee ISO/TC 194 "Biological and clinical evaluation of medical devices" in collaboration with Technical Committee CEN/TC 206 “Biological and clinical evaluation of medical devices” the secretariat of which is held by DIN.

This Amendment to the European Standard EN ISO 10993-23:2021 shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by February 2026, and conflicting national standards shall be withdrawn at the latest by February 2026.

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

This document has been prepared under a standardization request addressed to CEN by the European Commission. The Standing Committee of the EFTA States subsequently approves these requests for its Member States.

For the relationship with EU Legislation, see informative Annex ZA, which is an integral part of this document.

Any feedback and questions on this document should be directed to the users’ national standards body/national committee. A complete listing of these bodies can be found on the CEN website.

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Endorsement notice

The text of ISO 10993-23:2021/Amd 1:2025 has been approved by CEN as EN ISO 10993-23:2021/A1:2025 without any modification. [A1]

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Foreword

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

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

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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

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

This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biological and clinical evaluation of medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

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.

Amendment A1 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.

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Introduction

This document assesses possible contact hazards from medical devices, which can produce irritation.

Some materials that are included in medical devices have been tested, and their skin or mucosal irritation potential has been demonstrated. Other materials and their chemical components have not been tested and can induce adverse effects when in contact with human tissue. The manufacturer is thus obliged to evaluate each device for potential adverse effects prior to marketing.

The irritation potential of a medical device or its components can be predicted either by an *in vivo* animal irritation test or by an *in vitro* irritation test if qualified for use with medical devices.

ISO 10993-2 describes animal welfare aspects for performing animal studies for the biological evaluation of medical devices thereby also emphasizing the 3R's for replacement, reduction, and refinement of animal studies. This document describes tests to determine the irritancy of medical devices, materials or their extracts either by *in vitro* tests or *in vivo* tests. *In vitro* tests have preference over *in vivo* tests when appropriately validated and providing equally relevant information to that obtained from *in vivo* tests (see ISO 10993-1 and ISO 10993-2).

〚A1〛 Traditionally, tests in small animals have been performed prior to testing on humans to help predict human responses. More recently, in vitro tests as well as human tests have been added as adjuncts or alternatives. For skin irritation testing of neat chemicals, in vitro tests were developed using reconstructed human epidermis (RhE) models[31]. The method was adapted for detection of irritant chemicals in medical device extracts. The results of a large interlaboratory study that tested two types of RhE models showed that these models can also be used to detect the presence of irritant chemicals extracted from polymeric materials [polyvinylchloride (PVC) and silicone] commonly used in the manufacture of medical devices[6]. This method was found to be equally sensitive in the detection of low concentrations of some strong irritant compounds when compared to the human patch testing and intracutaneous rabbit test[14]. Therefore, a stepwise approach for irritant testing can start with the in vitro RhE model.

In 2023, two new type RhE models listed in OECD 439 were adopted for medical devices after they demonstrated equivalent predictive capacity compared to the two other RhE models in interlaboratory studies[42][43][44]. 〚/A1〛

The developed and validated RhE models are appropriate to predict skin tissue irritation response. It is recommended to explore the use of other alternative *in vitro* models to assess the irritation potential for mucosal or eye epithelial applications.

It is intended that, for regulatory submission, these studies be conducted using GLP or ISO/IEC 17025 as applicable to the respective country and comply with regulations related to animal welfare. Statistical analysis of data is recommended and can be used whenever appropriate.

This document is intended for use by professionals, appropriately qualified by training and experience, who are able to interpret its requirements and judge the outcomes of the evaluation for each medical device, taking into consideration all the factors relevant to the device, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous clinical experience.

The tests included in this document are important tools for the development of safe products, provided that they are executed and interpreted by trained personnel.

This document is based on numerous standards and guidelines, including OECD Test Guidelines (TG), U.S. Pharmacopoeia[40] and the European Pharmacopoeia[39]. It is intended to be the basic document for the selection and conduct of tests enabling evaluation of irritation responses relevant to the safety of medical materials and devices.

Instructions are given in normative Annex A for the preparation of materials specifically in relation to the above tests. In normative Annex D several special *in vivo* irritation tests are described for application of medical devices in areas other than skin. In addition, normative Annex E provides information for conducting human skin irritation testing.

Biological evaluation of medical devices — Part 23: Tests for irritation

1 Scope

This document specifies the procedure for the assessment of medical devices and their constituent materials with regard to their potential to produce irritation. The tests are designed to predict and classify the irritation potential of medical devices, materials or their extracts according to ISO 10993-1 and ISO 10993-2.

This document includes:

— pre-test considerations for irritation, including *in silico* and *in vitro* methods for dermal exposure;

— details of *in vitro* and *in vivo* irritation test procedures;

— key factors for the interpretation of the results.

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, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-9, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products*

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

ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices*

ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics*

ISO 10993-15, *Biological evaluation of medical devices — Part 15: Identification and quantification of degradation products from metals and alloys*

ISO 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

OECD 404, *Acute Dermal Irritation/Corrosion*

OECD 439, *In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method*