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BSI Standards Publication

Biological evaluation of medical devices

Part 17: Toxicological risk assessment of medical device constituents

bsi.

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National foreword

This British Standard is the UK implementation of EN ISO 10993-17:2023. It is identical to ISO 10993-17:2023. It supersedes BS EN ISO 10993-17:2009, which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/194, Biological evaluation of medical devices.

A list of organizations represented on this committee can be obtained on request to its committee manager.

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This publication has been prepared under a mandate given to the European Standards Organizations by the European Commission and the European Free Trade Association. It is intended to support requirements of the EU legislation detailed in the European Foreword. A European Annex, usually Annex ZA or ZZ, describes how this publication relates to that EU legislation.

For the Great Britain market (England, Scotland and Wales), if UK Government has designated this publication for conformity with UKCA marking (or similar) legislation, it may contain an additional National Annex. Where such a National Annex exists, it shows the correlation between this publication and the relevant UK legislation. If there is no National Annex of this kind, the relevant Annex ZA or ZZ in the body of the European text will indicate the relationship to UK regulation applicable in Great Britain. References to EU legislation may need to be read in accordance with the UK designation and the applicable UK law. Further information on designated standards can be found at www.bsigroup.com/standardsandregulation.

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UK Government is responsible for legislation. For information on legislation and policies relating to that legislation, consult the relevant pages of www.gov.uk.

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Published by BSI Standards Limited 2023

ISBN 978 0 539 01332 0

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ICS 11.100.20

Compliance with a British Standard cannot confer immunity from legal obligations.

This British Standard was published under the authority of the Standards Policy and Strategy Committee on 30 November 2023.

Amendments/corrigenda issued since publication

Date	Text affected

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EUROPEAN STANDARD **EN ISO 10993-17**

NORME EUROPÉENNE

EUROPÄISCHE NORM

November 2023

ICS 11.100.20

Supersedes EN ISO 10993-17:2009

English Version

Biological evaluation of medical devices - Part 17: Toxicological risk assessment of medical device constituents (ISO 10993-17:2023)

Évaluation biologique des dispositifs médicaux - Partie 17: Appréciation du risque toxicologique des constituants des dispositifs médicaux (ISO 10993-17:2023)

Biologische Beurteilung von Medizinprodukten - Teil 17: Toxikologische Risikobewertung von Medizinproduktbestandteilen (ISO 10993-17:2023)

This European Standard was approved by CEN on 2 July 2023.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

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Ref. No. EN ISO 10993-17:2023 E

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European foreword

This document (EN ISO 10993-17:2023) 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 May 2024, and conflicting national standards shall be withdrawn at the latest by May 2024.

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 supersedes EN ISO 10993-17:2009.

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

For the relationship with EU Directive(s) / Regulation(s), 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.

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, Türkiye and the United Kingdom.

Endorsement notice

The text of ISO 10993-17:2023 has been approved by CEN as EN ISO 10993-17:2023 without any modification.

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Annex ZA
(informative)

Relationship between this European Standard and the General Safety and Performance Requirements of Regulation (EU) 2017/745 aimed to be covered

This European standard has been prepared under M/575 to provide one voluntary means of conforming to the General Safety and Performance Requirements of Regulation (EU) 2017/745 of 5 April 2017 concerning medical devices [OJ L 117] and to system or process requirements including those relating to quality management systems, risk management, post-market surveillance systems, clinical investigations, clinical evaluation or post-market clinical follow-up.

Once this standard is cited in the Official Journal of the European Union under that Regulation, compliance with the normative clauses of this standard given in Table ZA.1 and application of the edition of the normatively referenced standards as given in Table ZA.2 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding General Safety and Performance Requirements of that Regulation, and associated EFTA Regulations.

Where a definition in this harmonised standard differs from a definition of the same term set out in Regulation (EU) 2017/745, the differences shall be indicated in the Annex Z. For the purpose of using this standard in support of the requirements set out in Regulation (EU) 2017/745, the definitions set out in this Regulation prevail.

Where the European standard is an adoption of an International Standard, the scope of this document can differ from the scope of the European Regulation that it supports. As the scope of the applicable regulatory requirements differ from nation to nation and region to region the standard can only support European regulatory requirements to the extent of the scope of the European Regulation for medical devices ((EU) 2017/745).

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Regulation (EU) 2017/745. This means that risks have to be 'reduced as far as possible', 'reduced to the lowest possible level', 'reduced as far as possible and appropriate', 'removed or reduced as far as possible', 'eliminated or reduced as far as possible', 'removed or minimized as far as possible', or 'minimized', according to the wording of the corresponding General Safety and Performance Requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with General Safety and Performance Requirements 1, 2, 3, 4, 5, 8, 9, 10, 11, 14, 16, 17, 18, 19, 20, 21 and 22 of the Regulation.

NOTE 3 When a General Safety and Performance Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

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Table ZA.1 — Correspondence between this European Standard and Annex I of Regulation (EU) 2017/745 [OJ L 117] and to system or process requirements including those relating to quality management systems, risk management, post-market surveillance systems, clinical investigations, clinical evaluation or post-market clinical follow-up

General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s)/subclause(s) of this EN	Remarks/Notes
10.1 a), b), d), e), and h)	5, 6, 7, 8, 9, 10 and Annex A, Annex B, Annex C and Annex E	*EN ISO 10993-17 addresses the choice of materials as regards toxicity, but 10.1 is only partly covered. Flammability and mechanical or physical (e.g., surface) properties are not covered. This standard provides requirements for a toxicological risk assessment process for constituents present in or on, or released from, a medical device.* *This risk assessment process involves the identification of substances that have the capacity to interact with biological tissues, cells or body fluids and the assessment of the nature and likelihood of any associated harm to health arising as a result of the intended use of the medical device. While such an assessment can confirm the absence of appreciable toxicological risk, it does not necessarily demonstrate the ability of a medical device or material to perform with an appropriate host response in a specific application.* *The toxicological risk assessment is based on the composition of the finished medical device, which is dependent, in part, on the processing materials used and the impact of processes on the materials of manufacture.* *Where appropriate and necessary for the risk assessment, quantitative structure-activity relationships or mathematical models can be used as part of the process specified.* *The standard provides requirements for a process for specifying a level of exposure to a constituent of a medical device that is without appreciable harm to health and for confirming that a medical device meets the specification so defined.*

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10.2	5, 6, 7, 8, 9, 10 and Annex A, Annex B, Annex C and Annex E	*EN ISO 10993-17 addresses risks posed by contaminants and residues. However, 10.2 is only partly covered by this standard, since the standard does not provide requirements for design, manufacture and packaging. Although this standard does not oblige manufacturers to minimize the risk posed by contaminants and residues in medical devices, it provides a means to estimate those risks and demonstrate that they have been minimized.* *The primary focus of this standard is the risk to patients, but risks to users coming into contact with a medical device are also addressed. However the standard is not applicable to medical device constituents that do not contact the body, so risks to persons involved in the transport or storage of medical devices would not normally be addressed.*
10.4.1	5, 6, 7, 8, 9, 10 and Annex A, Annex B, Annex C and Annex E	*EN ISO 10993-17 addresses risks posed by substances, including degradation products and processing residues. However, 10.4.1 is only partly covered by this standard, since the standard does not provide requirements for design and manufacture, nor does it address risks associated with particles, including wear debris, from medical devices. Although this standard does not oblige manufacturers to minimize the toxicological risk posed by substances in medical devices, it provides a means to estimate those risks and demonstrate that they have been minimized.* *The process specified by this standard includes the identification of substances which are carcinogenic, mutagenic or toxic to reproduction or that have endocrine-disrupting properties. Where such substances are identified, it provides a means for estimation of potential patient or user exposure to the substance that can form a basis for a justification regarding the presence of the substance and for appropriate labelling. However the standard does not include acceptability criteria or labelling requirements.*

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Table ZA.2 — Applicable Standards to confer presumption of conformity as described in this Annex ZA

Column 1 Reference in Clause 2	Column 2 International Standard Edition	Column 3 Title	Column 4 Corresponding European Standard Edition
ISO 10993-1:2018	ISO 10993-1:2018	Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process	EN ISO 10993-1:2020
ISO 10993-18:2020	ISO 10993-18:2020	Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process	EN ISO 10993-18:2020
ISO/TS 21726:2019	ISO/TS 21726:2019	Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents	For applicable standard edition see Column 2
ISO 14971:2019	ISO 14971:2019	Medical devices — Application of risk management to medical devices	EN ISO 14971:2019 EN ISO 14971:2019/A11:2021

The documents listed in the Column 1 of table ZA.2, in whole or in part, are normatively referenced in this document, i.e. are indispensable for its application. The achievement of the presumption of conformity is subject to the application of the edition of Standards as listed in Column 4 or, if no European Standard Edition exists, the International Standard Edition given in Column 2 of table ZA.2.

WARNING 1 — Presumption of conformity stays valid only as long as a reference to this European standard is maintained in the list published in the Official Journal of the European Union. Users of this standard should consult frequently the latest list published in the Official Journal of the European Union.

WARNING 2 — Other Union legislation may be applicable to the product(s) falling within the scope of this standard.

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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 document 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).

ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

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, *Biocompatibility of medical and dental materials and devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO 10993-17:2002), which has been technically revised.

The main changes are as follows:

— the title has been changed;

— the scope has been revised and a new statement on its applicability has been added;

— the following terms have been removed: allowable limit, benefit factor, concomitant exposure factor, health benefit, health hazard, health risk, health risk analysis, leachable substance, multiple exposure, physiologically based pharmacokinetic modelling, proportional exposure factor, repeated use, simultaneous use, TCL modifying factor, tolerable exposure, and tolerable risk, utilization factor;

— the following terms have been added: *analogue* (3.1), *benchmark dose low* (3.2), *carcinogen* (3.3), *constituent* (3.4), *dose-response* (3.6), *exposure dose* (3.7), *harmful dose* (3.9), *human carcinogen* (3.10), *identified constituent* (3.11), *irritation* (3.12), *margin of safety* (3.14), *point of departure* (3.19), *release kinetics* (3.20), *slope factor* (3.21), *suspected human carcinogen* (3.22), *systemic toxicity* (3.23), *threshold of toxicological concern* (3.24), *total quantity* (3.27), *toxicological risk*, (3.28), *toxicological risk assessment* (3.29), *toxicological screening limit* (3.30) and *worst-case estimated exposure dose* (3.32);

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— the following clauses have been removed: former Clause 4 on the general principles for establishing allowable limits, former Clause 5 on the establishment of tolerable intake for specific leachable substances, former Clause 6 on the calculation of tolerable exposure, former Clause 7 on the feasibility evaluation, former Clause 8 on benefit evaluation, and former Clause 9 on allowable limits;

— the following clauses have been added: Clause 4 on abbreviated terms and symbols, Clause 5 on toxicological risk assessment within the biological evaluation process, Clause 6 on constituent toxicological information, Clause 7 on the tolerable contact level, tolerable intake and the threshold of toxicological concern, Clause 8 on the exposure dose estimation, and Clause 9 on margin of safety;

— former Annex A has been moved to Annex D;

— Annex B and Annex C have been deleted;

— the following annexes have added: Annex A on evaluating toxicological data quality when selecting a POD, Annex B on derivation of toxicological screening limits, Annex C on deriving constituent TI or TCL for select endpoints, Annex E on estimating an exposure dose, and Annex F on reporting toxicological risk assessment information.

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.

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Introduction

A medical device or material that has direct or indirect contact with the patient's body or the user's body is expected to perform its intended use while being free from unacceptable risks, including biological and toxicological risks. For this reason, medical devices are typically subject to a biological evaluation within a risk management process to assess their safety. The ISO 10993 series specifies a process through which the manufacturer of a medical device can identify biological hazards associated with the medical device, estimate and evaluate the risks associated with these hazards, control these risks, and monitor the effectiveness of the controls throughout the life cycle of the medical device.

ISO 10993-1, in line with ISO 14971, facilitates a common understanding of biological evaluation within a risk management process. ISO 10993-18 includes methods for identifying and quantifying hazardous medical device constituents so that their toxicological risk can be evaluated. Furthermore, ISO 10993-18 specifies when to consider conducting a toxicological risk assessment per this document.

This document specifies requirements for a toxicological risk assessment process for specific medical device constituents that is used within the biological evaluation process specified by ISO 10993-1 and Clause 1. For example, the biological risk analysis of a medical device includes obtaining constituent information as described in ISO 10993-1:2018, 6.2 and ISO 10993-18. The extent to which constituent information is needed depends on what is known about the material formulation, manufacturing process (i.e. processing aid chemicals, process steps, etc.), what nonclinical or clinical information exist, and on the nature and duration of body contact with the medical device. This toxicological risk assessment process is based on the principle that the biological evaluation and risk assessment process is most efficient and effective when the minimum information necessary is used to assess if exposure to a harmful dose of any medical device constituent can occur. The process, requirements, criteria and methods specified in this document are intended to yield the following information, which is useful in the overall biological risk assessment of the final product:

— whether constituents present in, on or extracted from the medical device are at a quantity that can be a potential source of harm to health;

— derivation of a tolerable intake or tolerable contact level, for a constituent over a specified time period, on the basis of body mass or surface area, that is considered to be without appreciable harm to health;

— a worst-case estimated exposure dose for each constituent and subsequent toxicological risk estimation;

— a toxicological risk estimate based on the tolerable intake or tolerable contact level, and on the worst-case estimated exposure dose for each constituent.

This document is intended for use by toxicologists or other knowledgeable and experienced professionals, appropriately qualified by training and experience, capable of making informed decisions based upon scientific data and a knowledge of medical devices.

Lastly, this latest revision of this document is more extensive that the previous edition as it clarifies when a toxicological risk assessment is recommended, how to calculate the worst-case estimated exposure dose of a constituent and when the probability of occurrence of harm to health should be addressed by other means (e.g. frequency based dose-response (if available), probabilistic dose-response, or biological testing).

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Biological evaluation of medical devices —

Part 17: Toxicological risk assessment of medical device constituents

1 Scope

This document specifies the process and requirements for the toxicological risk assessment of medical device constituents. The methods and criteria used to assess whether exposure to a constituent is without appreciable harm are also specified. The toxicological risk assessment can be part of the biological evaluation of the final product, as described in ISO 10993-1.

The process described in this document applies to chemical characterization information obtained in line with ISO 10993-18. When a toxicological risk assessment of either the compositional information or analytical chemistry data (e.g. extractable data or leachable data) are required to determine whether the toxicological risks related to the constituents are negligible or tolerable.

The process described in this document is not intended to apply to circumstances where the toxicological risk has been estimated by other means, such as:

— constituents, excluding cohort of concern or excluded chemicals, that are present in or extracted from a medical device at an amount representative of patient exposure below a relevant, toxicologically-based reporting threshold (see applicable requirements in ISO 10993-18:2020, Annex E and ISO/TS 21726);

— a new or changed medical device for which chemical or biological equivalence has been established with an existing biocompatible or clinically established medical device (see applicable requirements in ISO 10993-18:2020, Annex C).

The process described in this document is also not applicable to:

— medical device constituents that do not contact the body (e.g. in vitro diagnostics);

— biological risks associated with physical interactions of the medical device with the body (i.e. application of mechanical forces, energy or surface morphology, etc.), provided that the chemical exposure is not changed;

— active pharmaceutical ingredients of device-drug combination products or biologic components of device-biologic combination products as additional regulatory considerations can apply;

— exposure to a particular constituent that arises from sources other than the device, such as food, water or air.

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*

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