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STN	**Biologické hodnotenie zdravotníckych pomôcok. Časť 3: Skúšky genotoxicity, karcinogenity a reprodukčnej toxicity (ISO 10993-3: 2014).**	**STN EN ISO 10993-3** 85 6510

Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity (ISO 10993-3:2014)

Táto norma obsahuje anglickú verziu európskej normy.
This standard includes the English version of the European Standard.

Táto norma bola oznámená vo Vestníku ÚNMS SR č. 02/15

Obsahuje: EN ISO 10993-3:2014, ISO 10993-3:2014

Oznámením tejto normy sa ruší
STN EN ISO 10993-3 (85 6510) z októbra 2009

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 10993-3

October 2014

ICS 11.100.20

Supersedes EN ISO 10993-3:2009

English Version

Biological evaluation of medical devices - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity (ISO 10993-3:2014)

Évaluation biologique des dispositifs médicaux - Partie 3: Essais concernant la génotoxicité, la cancérogénicité et la toxicité sur la reproduction (ISO 10993-3:2014)

Biologische Beurteilung von Medizinprodukten - Teil 3: Prüfungen auf Gentoxizität, Karzinogenität und Reproduktionstoxizität (ISO 10993-3:2014)

This European Standard was approved by CEN on 6 September 2014.

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

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Foreword

This document (EN ISO 10993-3:2014) 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 evaluation of medical devices” the secretariat of which is held by NEN.

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 April 2015, and conflicting national standards shall be withdrawn at the latest by April 2015.

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

This document supersedes EN ISO 10993-3:2009.

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 Directives.

For relationship with EU Directives, see informative Annex ZA and ZB, which are integral parts of this document.

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, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 10993-3:2014 has been approved by CEN as EN ISO 10993-3:2014 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 93/42 EEC on medical devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 93/42 EEC on medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in Table ZA.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZA.1 — Correspondence between this European Standard and Directive 93/42/EEC on medical devices

Essential Requirements (ERs) of Directive 93/42/EEC	Clause(s)/sub-clause(s) of this EN	Qualifying remarks/Notes
7.1 (First and second indent)	4, 5, 6 and 7	ER 7.1 is only partly covered by ISO 10993-3, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to evaluate genotoxicity, carcinogenicity or reproductive toxicity risks associated with the materials which are used.
7.2	4, 5, 6 and 7	ER 7.2 is not covered by ISO 10993-3, since the standard does not provide requirements on design and manufacture and does not oblige to minimize risk. However, this standard provides a means to evaluate genotoxicity, carcinogenicity or reproductive toxicity. This evaluation can be a preliminary step for risk minimization. Other forms of toxicity and flammability are not dealt with in this standard.
7.5 (First paragraph)	4, 5, 6 and 7	ER 7.5 is not covered by ISO 10993-3, since the standard does not provide requirements on design, manufacture and packaging and does not oblige to minimize risk.

		However, this standard provides a means to evaluate genotoxicity, carcinogenicity or reproductive toxicity. This evaluation can be a preliminary step for risk minimization. Other forms of toxicity and flammability are not dealt with in this standard.

General Note: Presumption of conformity depends on also complying with all relevant clauses/subclauses of ISO 10993-1.

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

Annex ZB
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 90/385/EEC on active implantable medical devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 90/385 EEC on active implantable medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in Table ZB.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZB.1 — Correspondence between this European Standard and Directive 90/385/EEC on active implantable medical devices

Essential Requirements (ERs) of Directive 90/385/EEC	Clause(s)/sub-clause(s) of this EN	Qualifying remarks/Notes
9 (First and second indent)	4, 5, 6 and 7	ER 9 is only partly covered by ISO 10993-3, since the standard does not provide requirements on design and manufacture. However, this standard provides a means to assess genotoxicity, carcinogenicity or reproductive toxicity used in the manufacture of medical devices. Other forms of toxicity are not covered.

General Note: Presumption of conformity depends on also complying with all relevant clauses/subclauses of ISO 10993-1.

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

INTERNATIONAL STANDARD

ISO 10993-3

Third edition
2014-10-01

Biological evaluation of medical devices —

Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity

Évaluation biologique des dispositifs médicaux —

Partie 3: Essais concernant la génotoxicité, la cancérogénicité et la toxicité sur la reproduction

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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. 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. 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.

The committee responsible for this document is ISO/TC 194.

This third edition of ISO 10993-3 cancels and replaces the second edition (ISO 10993-3:2003), which has been technically revised.

The major technical changes are the following:

a) test strategy changed by inclusion of a *in vivo* test and a follow-up evaluation;

b) new Annex A " Guidance on selecting an appropriate sample preparation procedure in genotoxicity testing" included;

c) Inclusion of further *in vitro* and *in vivo* test for evaluating the genotoxic potential of medical devices;

d) new Annex B "Flowchart for follow-up evaluation" included;

e) Annex E changed to "Considerations for carcinogenicity studies performed as implantation studies" and made normative;

f) new Annex F "*In vitro* tests for embryo toxicity" included.

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

— *Part 1: Evaluation and testing within a risk management process*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for in vitro cytotoxicity*

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

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Framework for identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and skin sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

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

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

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

— *Part 17: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials [Technical specification]*

— *Part 20: Principles and methods for immunotoxicology testing of medical devices* [Technical specification]

The following part is under preparation:

— *Part 33: Supplement to* ISO 10993-3:— *Guidance on tests to evaluate genotoxicity* [Technical Report]

The following definitions apply in understanding how to implement an ISO International Standard and other normative ISO deliverables (TS, PAS, IWA):

— "shall" indicates a requirement;

— "should" indicates a recommendation;

— "may" is used to indicate that something is permitted;

— "can" is used to indicate that something is possible, for example, that an organization or individual is able to do something.

ISO/IEC Directives, Part 2 (sixth edition, 2011), 3.3.1, defines a requirement as an "expression in the content of a document conveying criteria to be fulfilled if compliance with the document is to be claimed and from which no deviation is permitted."

ISO/IEC Directives, Part 2 (sixth edition, 2011), 3.3.2, defines a recommendation as an "expression in the content of a document conveying that among several possibilities one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action is deprecated but not prohibited."

Introduction

The basis for biological evaluation of medical devices is often empirical and driven by the relevant concerns for human safety. The risk of serious and irreversible effects, such as cancer or second generation abnormalities, is of particular public concern. It is inherent in the provision of safe medical devices that such risks be minimised to the greatest extent feasible. The assessment of mutagenic, carcinogenic and reproductive hazards is an essential component of the control of these risks. Not all test methods for the assessment of genotoxicity, carcinogenicity or reproductive toxicity are equally well developed, nor is their validity well established for the testing of medical devices.

Significant issues with test sample size and preparation, scientific understanding of disease processes and test validation can be cited as limitations of available methods. For example, the biological significance of solid state carcinogenesis is poorly understood. It is expected that on-going scientific and medical advances will improve our understanding of and approaches to these important toxicological effects. At the time this document was prepared, the test methods proposed were those most acceptable. Scientifically sound alternatives to the proposed testing may be acceptable insofar as they address relevant matters of safety assessment.

In the selection of tests needed to evaluate a particular medical device, there is no substitute for a careful assessment of expected human uses and potential interactions of the medical device with various biological systems. These considerations will be particularly important in such areas as reproductive and developmental toxicology.

This part of ISO 10993 presents test methods for the detection of specific biological hazards, and strategies for the selection of tests, where appropriate, that will assist in hazard identification. Testing is not always necessary or helpful in managing toxicological risks associated with exposure to medical device materials but, where it is appropriate, it is important that maximum test sensitivity is achieved.

In view of the multitude of possible outcomes and the importance of factors such as extent of exposure, species differences and mechanical or physical considerations, risk assessment have to be performed on a case-by-case basis.

INTERNATIONAL STANDARD **ISO 10993-3:2014(E)**

Biological evaluation of medical devices —

Part 3:
Tests for genotoxicity, carcinogenicity and reproductive toxicity

1 Scope

This part of ISO 10993 specifies strategies for risk estimation, selection of hazard identification tests and risk management, with respect to the possibility of the following potentially irreversible biological effects arising as a result of exposure to medical devices:

— genotoxicity;

— carcinogenicity;

— reproductive and developmental toxicity.

This part of ISO 10993 is applicable when the need to evaluate a medical device for potential genotoxicity, carcinogenicity, or reproductive toxicity has been established.

NOTE Guidance on selection of tests is provided in ISO 10993-1.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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 10993-6, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

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

ISO 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of materials*

OECD 414, *Prenatal Development Toxicity Study*

OECD 415, *One-Generation Reproduction Toxicity Study*

OECD 416, *Two-generation Reproduction Toxicity*

OECD 421, *Reproduction/Developmental Toxicity Screening Test*

OECD 451, *Carcinogenicity Studies*

OECD 453, *Combined Chronic Toxicity/Carcinogenicity Studies*

OECD 471, *Bacterial Reverse Mutation Test*

OECD 473, *In vitro Mammalian Chromosome Aberration Test*

OECD 476, *In vitro Mammalian Cell Gene Mutation Test*

OECD 487, *In Vitro Mammalian Cell Micronucleus Test*