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I.S. EN ISO 10993-11:2009

# Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO 10993-11:2006)

## I.S. EN ISO 10993-11:2009

*Incorporating amendments/corrigenda issued since publication:*

<i>This document replaces:</i> I.S. EN ISO 10993-11:2007	<i>This document is based on:</i> EN ISO 10993-11:2009 EN ISO 10993-11:2006	<i>Published:</i> 29 April, 2009 15 June, 2007
This document was published under the authority of the NSAI and comes into effect on: 21 August, 2009		ICS number: 11.100.20
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I.S. EN ISO 1093-11:2009

EUROPEAN STANDARD

**EN ISO 10993-11**

NORME EUROPÉENNE

EUROPÄISCHE NORM

April 2009

ICS 11.100.20

Supersedes EN ISO 10993-11:2006

English Version

## Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO 10993-11:2006)

Évaluation biologique des dispositifs médicaux - Partie 11:  
Essais de toxicité systémique (ISO 10993-11:2006)

Biologische Beurteilung von Medizinprodukten - Teil 11:  
Prüfungen auf systemische Toxizität (ISO 10993-11:2006)

This European Standard was approved by CEN on 12 April 2009.

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 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 Management Centre has the same status as the official versions.

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## **Foreword**

The text of ISO 10993-11:2006 has been prepared by Technical Committee ISO/TC 194 “Biological evaluation of medical devices” of the International Organization for Standardization (ISO) and has been taken over as EN ISO 10993-11:2009 by 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of an identical text or by endorsement, at the latest by October 2009, and conflicting national standards shall be withdrawn at the latest by March 2010.

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 10993-11:2006.

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 93/42/EEC on Medical Devices and 90/385/EEC on Active Implantable Medical Devices.

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, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.

### **Endorsement notice**

The text of ISO 10993-11:2006 has been approved by CEN as a EN ISO 10993-11:2009 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 Communities 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 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 — Correspondence between this European Standard and Directive 93/42/EEC on medical devices**

Clause(s)/sub-clause(s) of this EN	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
4, 5, 6	Annex I: 7.1, 7.2, 7.5	

**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 Communities 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 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 — Correspondence between this European Standard and Directive 90/385/EEC on active implantable medical devices**

Clause(s)/sub-clause(s) of this EN	Essential Requirements (ERs) of Directive 90/385/EEC	Qualifying remarks/Notes
4, 5, 6	Annex I : 9	

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

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I.S. EN ISO 1093-11:2009

# INTERNATIONAL STANDARD

**ISO**  
**10993-11**

Second edition  
2006-08-15

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## **Biological evaluation of medical devices —**

### **Part 11: Tests for systemic toxicity**

*Évaluation biologique des dispositifs médicaux —*

*Partie 11: Essais de toxicité systémique*



Reference number  
ISO 10993-11:2006(E)

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Published in Switzerland

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 10993-11 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO 10993-11:1993) which has been technically revised.

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

- *Part 1: Evaluation and testing*
- *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 delayed-type hypersensitivity*
- *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*
- *Part 20: Principles and methods for immunotoxicology testing of medical devices*

## **Introduction**

Systemic toxicity is a potential adverse effect of the use of medical devices. Generalized effects, as well as organ and organ system effects can result from absorption, distribution and metabolism of leachates from the device or its materials to parts of the body with which they are not in direct contact. This part of ISO 10993 addresses the evaluation of generalized systemic toxicity, not specific target organ or organ system toxicity, even though these effects may result from the systemic absorption and distribution of toxicants.

Because of the broad range of medical devices, and their materials and intended uses, this part of ISO 10993 is not overly prescriptive. Whilst it addresses specific methodological aspects to be considered in the design of systemic toxicity tests, proper study design must be uniquely tailored to the nature of the device's materials and its intended clinical application.

Other elements of this part of ISO 10993 are prescriptive in nature, including those aspects that address compliance with good laboratory practices and elements for inclusion in reporting.

While some systemic toxicity tests (e.g. long term implantation or dermal toxicity studies) can be designed to study systemic effects as well as local, carcinogenic or reproductive effects, this document focuses only on those aspects of such studies, which are intended to address systemic effects. Studies which are intended to address other toxicological endpoints are addressed in ISO 10993-3, ISO 10993-6, ISO 10993-10 and ISO/TS 10993-20.

Pyrogenicity (see Annex F) represents an additional systemic effect which has historically been included in this part of ISO 10993. However, efforts are being taken to address pyrogenicity in a dedicated, stand-alone standard.

Finally, toxicology is an imperfect science. The outcome of any single test should not be the sole basis for making a determination of whether a device is safe for its intended use.

# Biological evaluation of medical devices —

## Part 11: Tests for systemic toxicity

### 1 Scope

This part of ISO 10993 specifies requirements and gives guidance on procedures to be followed in the evaluation of the potential for medical device materials to cause adverse systemic reactions.

### 2 Normative references

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.

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

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

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

### 3 Terms and definitions

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

#### 3.1

##### **dose**

##### **dosage**

amount of test sample administered (e.g. mass, volume) expressed per unit of body weight or surface area

#### 3.2

##### **dose-effect**

relationship between the dosage and the magnitude of a defined biological effect either in an individual or in a population sample

#### 3.3

##### **dose-response**

relationship of dosage to the spectrum of effects related to the exposure

**NOTE** There are two types of dose-response relationships. The first type is the response of an individual to a range of doses. The second type is the distribution of responses of a population of individuals to a range of doses.

#### 3.4

##### **leachable substance**

chemical removed from a device or material by the action of water or other liquids related to the use of the device

**NOTE** Examples of leachable substances are additives, sterilant residues, process residues, degradation products, solvents, plasticizers, lubricants, catalysts, stabilizers, anti-oxidants, colouring agents, fillers and monomers.

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