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**Meditsiinivahendite bioloogiline hindamine.
Osa 5: Katsed tsütotoksilisuse hindamiseks
- in vitro meetodid**

Biological evaluation of medical devices - Part 5:
Tests for cytotoxicity - in vitro methods

EESTI STANDARDI EESSÕNA

NATIONAL FOREWORD

<p>Käesolev Eesti standard EVS-EN ISO 10993-5:1999 sisaldab Euroopa standardi EN ISO 10993-5:1999 ingliskeelset teksti.</p> <p>Käesolev dokument on jõustatud 23.11.1999 ja selle kohta on avaldatud teade Eesti standardiorganisatsiooni ametlikus väljaandes.</p> <p>Standard on kättesaadav Eesti standardiorganisatsioonist.</p>	<p>This Estonian standard EVS-EN ISO 10993-5:1999 consists of the English text of the European standard EN ISO 10993-5:1999.</p> <p>This document is endorsed on 23.11.1999 with the notification being published in the official publication of the Estonian national standardisation organisation.</p> <p>The standard is available from Estonian standardisation organisation.</p>
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<p>Käsitlusala: Standardi käesolev osa kirjeldab testimismeetodeid meditsiinivahendite tsütotoksilisuse vastasmõjude hindamiseks in vitro.</p>	<p>Scope:</p>
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ICS 11.100

Võtmesõnad: bioloogilised testid, hambaraviaparatuur, hambaravimaterjalid, kirurgiline instrumentarium, kirurgilised implantaadid, meditsiiniaparatuur, testimine, tsütotoksilisus

English version

Biological evaluation of medical devices

Part 5: Tests for *in vitro* cytotoxicity
(ISO 10993-5 : 1999)

Évaluation biologique des
dispositifs médicaux – Partie 5:
Essais concernant la cytotoxicité *in
vitro* (ISO 10993-5 : 1999)

Biologische Beurteilung von
Medizinprodukten – Teil 5: Prüfungen
auf *in vitro*-Zytotoxizität
(ISO 10993-5 : 1999)

This European Standard was approved by CEN on 1999-04-16.

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 Central Secretariat or to any CEN member.

The European Standards exist 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 Central Secretariat has the same status as the official versions.

CEN members are the national standards bodies of Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.

CEN

European Committee for Standardization
Comité Européen de Normalisation
Europäisches Komitee für Normung

Central Secretariat: rue de Stassart 36, B-1050 Brussels

Foreword

International Standard

ISO 10993-5 : 1999 Biological evaluation of medical devices – Part 5: Tests for *in vitro* cytotoxicity, which was prepared by ISO/TC 194 'Biological evaluation of medical devices' of the International Organization for Standardization, has been adopted by Technical Committee CEN/TC 206 'Biocompatibility of medical and dental materials and devices', the Secretariat of which is held by NNI, as a European Standard.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, and conflicting national standards withdrawn, by November 1999 at the latest.

In accordance with the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard:

Austria, Belgium, the Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and the United Kingdom.

Endorsement notice

The text of the International Standard ISO 10993-5:1999 was approved by CEN as a European Standard without any modification.

NOTE: Normative references to international publications are listed in Annex ZA (normative).

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Introduction

Due to the general applicability of *in vitro* cytotoxicity tests and their widespread use in evaluating a large range of medical devices and materials, it is the purpose of this part of ISO 10993, rather than to specify a single test, to define a scheme for testing which requires decisions to be made in a series of steps. This should lead to the selection of the most appropriate test.

Three categories of test are listed: extract test, direct-contact test, indirect-contact test.

The choice of one or more of these categories depends upon the nature of the sample to be evaluated, the potential site of use and the nature of the use.

This choice then determines the details of the preparation of the samples to be tested, the preparation of the cultured cells, and the way in which the cells are exposed to the samples or their extracts.

At the end of the exposure time, the evaluation of the presence and extent of the cytotoxic effect is undertaken. It is the intention of this part of ISO 10993 to leave open the choice of type of evaluation. Such a strategy makes available a battery of tests, which reflects the approach of many groups which advocate *in vitro* biological tests.

The numerous methods used and end-points measured in cytotoxicity determination can be grouped into categories of evaluation type:

- a) assessments of cell damage by morphological means;
- b) measurements of cell damage;
- c) measurements of cell growth;
- d) measurements of specific aspects of cellular metabolism.

There are, therefore, several alternative means of producing results in each of these four categories. The investigator should be aware of the categories of test and into which a particular technique fits, in order that comparisons may be made with other results on similar medical devices or materials, and in order that interlaboratory tests may be conducted.

1 Scope

This part of ISO 10993 describes test methods to assess the *in vitro* cytotoxicity of medical devices.

These methods specify the incubation of cultured cells either directly or through diffusion

- a) with extracts of a device, and/or
- b) in contact with a device.

These methods are designed to determine the biological response of mammalian cells *in vitro* using appropriate biological parameters.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

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

ISO 10993-12:1996, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*.

3 Terms and definitions

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

3.1

negative control material

material which, when tested in accordance with this part of ISO 10993, does not produce a cytotoxic response

NOTE The purpose of the negative control is to demonstrate background response. For example, high-density polyethylene¹⁾ for synthetic polymers, and aluminium oxide ceramic rods for dental material, have been used as negative controls.

1) High-density polyethylene can be obtained from the U.S. Pharmacopeia (Rockville, Maryland, USA) and Food and Drug Safety Center, Hatano Research Institute (Ochiai 729-5, Hadanoshi, Kanagawa 257 - Japan). This information is given for the convenience of the user of this part of ISO 10993 and does not constitute an endorsement by ISO of these products.