International Standard

ISO 10993-3

Fourth edition
2026-08

Biological evaluation of medical devices —

Part 3: Evaluation of genotoxicity, carcinogenicity, reproductive toxicity and developmental toxicity

Évaluation biologique des dispositifs médicaux —

Partie 3: Évaluation de la génotoxicité, de la cancérogénicité, de la toxicité sur la reproduction et de la toxicité sur le développement

Reference number
ISO 10993-3:2026(en)

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ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

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.

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).

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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).

This fourth edition of ISO 10993-3 cancels and replaces ISO 10993-3:2014 and ISO/TR 10993-33:2015.

The main changes are as follows:

— this document has been entirely revised to emphasize evaluation of genotoxicity, carcinogenicity, reproductive toxicity and developmental toxicity instead of testing;

— chemical characterization and toxicological risk assessment have been added as an approach to address genotoxicity, carcinogenicity, reproductive toxicity and developmental toxicity;

— the follow-up evaluation has been changed when an in vitro genotoxicity test is positive and the flowchart for follow-up evaluation has been removed;

— reproductive toxicity and developmental toxicity have been described separately;

— the annex on cellular transformation has been deleted;

— ISO/TR 10993-33 has been merged into this document as Annex B on genotoxicity test methods.

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

The basis for biological evaluation of medical devices is often empirical and driven by 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 minimized to the greatest extent feasible. The assessment of mutagenic, carcinogenic, reproductive toxicity and developmental toxicity hazards is an essential component of the control of these risks. Not all test methods for the assessment of genotoxicity, carcinogenicity, reproductive toxicity and developmental 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. Since the previous edition of this document, many genotoxicity test methods have been updated with revised OECD guidelines. However, these generally provide clearer recommendations but little alteration in test methods. Scientifically sound alternatives to the proposed testing can be acceptable insofar as they address relevant matters of safety assessment of the medical device.

In the selection of tests needed to evaluate a particular medical device, a careful assessment of expected human uses and potential interactions with biological systems is important, particularly in such areas as reproductive toxicity and developmental toxicity.

This document presents test methods and evaluation strategies for the identification of specific biological harms. Testing is not always necessary or appropriate in evaluating biological 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 is typically performed on a case-by-case basis. Suggestions for risk consideration and integration of ISO 10993-17 and ISO 10993-18[7] are provided.

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Biological evaluation of medical devices —

Part 3:
Evaluation of genotoxicity, carcinogenicity, reproductive toxicity and developmental toxicity

1 Scope

This document specifies strategies for risk estimation and evaluation of biological harms with respect to:

— genotoxicity;

— carcinogenicity;

— reproductive toxicity; and

— developmental toxicity.

This document is applicable when the need to evaluate a medical device for potential genotoxicity, carcinogenicity, reproductive toxicity and developmental toxicity has been established.

This document is not applicable to active pharmaceutical ingredients of device-drug combination products or biological components of device-biologic combination products which are covered by regulations.

NOTE Guidance on selecting relevant biological effects for medical devices is covered in ISO 10993-1.

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 10993-1:2025, *Biological evaluation of medical devices — Part 1: Requirements and general principles for the evaluation of biological safety within a risk management process*

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

ISO 10993-12:2021, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Toxicological risk assessment of medical device constituents*

ISO 14971:2019, *Medical devices — Application of risk management to medical devices*

OECD 471:2020, *OECD Guideline for the Testing of Chemicals — Bacterial Reverse Mutation Test*

OECD 473:2016, *OECD Guideline for the Testing of Chemicals — In vitro Mammalian Chromosome Aberration Test*

OECD 487:2016, *OECD Guideline for the Testing of Chemicals — In vitro Mammalian Cell Micronucleus Test*

OECD 490:2016, *OECD Guideline for the Testing of Chemicals — In vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene*

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3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1, ISO 10993-12 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
carcinogenicity test
test to determine cancer outcomes after long term or life-span exposure of animals

Note 1 to entry: Outcomes are typically based on tumorigenic potential and other factors.

3.2
developmental toxicity evaluation
methods to determine adverse effects on the developing organism during prenatal development or postnatally to the time of sexual maturation

3.3
genotoxicity test
test using cells, bacteria, yeast, fungi, animals or other biological systems to determine whether gene mutations, chromosomal alterations or other genetic changes are caused by the test sample

3.4
reproductive toxicity evaluation
methods to evaluate the potential effects of test samples on male or female reproductive function during any stage of development or fertility

3.5
sham-incubated vehicle
vehicle control exposed to the same extraction time and temperature as the test sample extract

3.6
threshold of toxicological concern
TTC
level of exposure for constituents, below which there would be no appreciable risk to human health

Note 1 to entry: The constituent is defined as a chemical or compound present in or on a finished medical device or material(s) of construction. Constituents can be intentionally present (e.g. an additive such as an antioxidant) or unintentionally present (e.g. an impurity).

[SOURCE: ISO/TS 21726:2019, 3.5[11], modified — Note 1 to entry has been added.]

4 Assessment strategies

4.1 General

ISO 10993-1 indicates circumstances where the potential for genotoxicity, carcinogenicity, reproductive toxicity and developmental toxicity are relevant biological harms for consideration in an overall biological safety evaluation. Evaluation of the biological harms shall consider the following factors:

— whether assessment is necessary based on patient population (e.g. life expectancy, sensitive population) and the anticipated impact of test results on risk management judgements,

— whether assessment is necessary based on the worst-case quantity, type of contact and duration of exposure,

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