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Biological evaluation of medical devices —

Part 17: Toxicological risk assessment of medical device constituents

Évaluation biologique des dispositifs médicaux —

Partie 17: Appréciation du risque toxicologique des constituants des dispositifs médicaux

Reference number
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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.

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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, *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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ISO 10993-18:2020, *Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process*

ISO/TS 21726:2019, *Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents*

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

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1 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
analogue
substance with similar molecular, physical, chemical or toxicological properties

3.2
benchmark dose low
BMD_L
lower one-sided confidence limit of a dose derived from *dose-response* (3.6) modelling that is associated with a specified change (e.g. 5 % or 10 %) in the dose-response relationship

Note 1 to entry: A specified change of 5 % is applied when a reported harm applies to individual animals. A specified change of 10 % is applied when a reported harm applies to a fraction of animals in a population.

[SOURCE: EPA 2012[2]]

3.3
carcinogen
constituent (3.4) that causes cancer in humans or experimental animals as determined by valid experimental or observational evidence

Note 1 to entry: Carcinogens are either genotoxic carcinogens or non-genotoxic carcinogens. A genotoxic carcinogen is a constituent capable of causing cancer by a mechanism that involves direct alteration of the genetic material of target cells, as a key event at an early stage in tumour development. A non-genotoxic carcinogen is a constituent capable of producing cancer by a mechanism where direct gene damage is not the key event in tumour development (C.3.1).

[SOURCE: International Agency for Research on Cancer[3]]

3.4
constituent
chemical that is present in or on the finished medical device or its materials of construction

Note 1 to entry: Constituents can be intentionally or unintentionally added chemicals or compounds, such as: additives (e.g. plasticizers, lubricants, stabilizers, anti-oxidants, colouring agents, fillers), manufacturing process residues (e.g. monomers, catalysts, solvents, sterilant and cleaning agents), degradation products or impurities (e.g. byproducts or side products) or contaminants[5].

[SOURCE: ISO 10993-18:2020, 3.10, modified — "or on" has been added to the definition and Note 1 to entry has been replaced.]

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