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# oSIST prEN ISO 10993-17:2022

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**Biološko ovrednotenje medicinskih pripomočkov - 17. del: Toksikološka ocena tveganja glede sestavin medicinskih pripomočkov (ISO/DIS 10993-17:2021)**

Biological evaluation of medical devices - Part 17: Toxicological risk assessment of medical device constituents (ISO/DIS 10993-17:2021)

Biologische Beurteilung von Medizinprodukten - Teil 17: Toxikologische Risikobewertung von Medizinproduktbestandteilen (ISO/DIS 10993-17:2021)

Évaluation biologique des dispositifs médicaux - Partie 17: (ISO/DIS 10993-17:2021)

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**ICS:**

| | | |
|---|---|---|
| 11.100.20 | Biološko ovrednotenje medicinskih pripomočkov | Biological evaluation of medical devices |

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# Biological evaluation of medical devices —

## Part 17:
## Toxicological risk assessment of medical device constituents

ICS: 11.100.20

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# Foreword

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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 (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.

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This second edition cancels and replaces the first edition (ISO 10993-17:2002), which has been technically revised.

The main changes compared to the previous edition are as follows:

— To follow

A list of all parts in the ISO 10993 series can be found on the ISO website.

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# Introduction

A medical device or material that comes in 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 the safety of the medical device. The ISO 10993 standard 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, defines key terms that facilitate a common understanding of biological risk assessment. For example, biological risk is defined as the combination of the probability of harm to health occurring as a result of adverse reactions associated with medical device or material interactions, and the severity of that harm. Toxicological risk is defined as the probability of a specified degree of an adverse reaction occurring in response to a specified level of exposure. Toxicological hazard is defined as the potential for a chemical substance or material to cause an adverse biological reaction, taking into account the nature of the reaction and the dose required to elicit it. ISO 10993-18 includes methods for obtaining the necessary data for the toxicological risk assessment of medical device constituents. Furthermore, ISO 10993-18 specifies when to consider conducting a toxicological risk assessment per this Standard.

This Part of ISO 10993 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 of this Standard. For example, biological risk analysis of a medical device includes obtaining chemical constituent information as described in ISO 10993-1 (Clause 6.1) and ISO 10993-18. The extent to which constituent information can be obtained depends on what is known about the material formulation, manufacturing process (*i.e.* processing aid chemicals, process steps, etc.), what nonclinical and/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 whether or not exposure to a harmful dose(s) of all constituents could occur during the time period that a medical device contacts the body. The process, requirements, criteria and methods specified in this Standard are intended to yield the following information, which are useful in the overall biological risk assessment of the final product.

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— the presence of constituents that are a potential source of harm to health

— a worst-case exposure estimate(s) for each chemical constituent(s) to determine whether or not it could cause appreciable harm to health

— derivation of a tolerable intake or tolerable contact level, to a chemical 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

— an evaluation of exposure data for each chemical constituent(s) that is/are without appreciable harm to health, or alternatively, is or could be a harmful dose

Lastly, this latest revision of ISO 10993-17 extends the previous version by clarifying when a toxicological risk assessment is necessary, how to calculate worst case exposure of a chemical constituent, and when the probability of occurrence of harm to health should be addressed by other means. (e.g. frequency dose-response (if available), probabilistic dose-response, or biological test).

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# Biological evaluation of medical devices —

# Part 17: Toxicological risk assessment of medical device constituents

## 1 Scope

This part of the ISO 10993 specifies the process and requirements for the toxicological risk assessment of medical device constituents to be used within the biological evaluation of the final product described in ISO 10993-1, which includes the methods and criteria used to assess if exposure of a chemical constituent(s) is without appreciable harm(s).

The process described in this document is intended to apply after chemical characterization compositional profiling is performed as required by ISO 10993-18, and thus a toxicological risk assessment of either the compositional information, extractable data or leachable data are required to conclude if the risks related to the constituents are acceptable or not.

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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/excluded chemicals, that are present or extracted at an amount representative of patient exposure below a relevant, toxicologically-based reporting threshold (see 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 ISO 10993-18:2020, Annex C).

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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),

— all biological risks applicable to a medical device (e.g., harm(s) that result(s) from physical interaction (*i.e.*, application of mechanical forces, energy, or surface morphology, etc.) of the medical device with the body), provided that the chemical exposure is unchanged,

— active pharmaceutical ingredients of device-drug combination products or biologic components of device-biologic combination products as additional regulatory considerations may apply,

— exposure to a particular chemical constituent that arises from sources other than the device, such as food, water, or air. This document does not address the potential for exposure from such sources

## 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*

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

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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 terminological 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(s) with similar molecular, physical, chemical and toxicological properties

**3.2**
**benchmark dose low**
$BMD_L$
dose derived from dose-response modelling that is associated with a specified change (*e.g.*, 5% or 10%) in the dose-response relationship

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

[SOURCE: Crump 1984 [1], EPA 2012 [2]]

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**3.3**
**carcinogen**
constituent that causes cancer in humans or animals as determined by valid experimental evidence

[SOURCE: International Agency for Research on Cancer [3]; National Cancer Institute [4]]

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

Note 1 to entry: Constituent is also defined in ISO/TC 21726 and ISO 10993-18, which includes intentionally or unintentionally added chemicals/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), and degradation products. The term also includes side products and intermediates released from a medical device.

**3.5**
**default value**
value or factor used in the derivation of a *tolerable contact level* (3.24) or *tolerable intake* (3.25), in the in the absence of specific data (*e.g.*, an *uncertainty factor* (30))

**3.6**
**dose-response**
relationship of dosage to harm(s) related to exposure

Note 1 to entry: In general, there are two types of dose-response relationships. The first type is the change in response for an individual to a range of doses. The second type is the distribution of a response among individuals to a range of doses.


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**3.7**
**exposure dose**
quantity of a chemical constituent that does, or could contact the body over a specified time period

Note 1 to entry: to entry: Exposure dose is normally expressed as mg/kg/day or as mg/cm$^2$/day.

**3.8**
**harm to health**
an adverse reaction, such as altered morphology, physiology, growth, development, reproduction or lifespan that (a) impairs function of an organ/system, organism, or (sub)population, (b) reduces capacity to tolerate impaired function, or (c) increases susceptibility to other influences that impair function

Note 1 to entry: Examples of (sub) population include, but are not limited to, male versus female, preterm neonates versus adults, etc.

**3.9**
**harmful dose**
dose capable of eliciting appreciable *harm to health* (3.8)

**3.10**
**human carcinogen**
*carcinogen* (3.3) for which human data demonstrates a causal association between exposure to the chemical constituent and occurrence of cancer

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**3.11**
**identified constituent**
*constituent* (3.4) for which molecular structure information is complete

Note 1 to entry: The identity of a medical device constituent can be obtained by information gathering or non-targeted/targeted analytical approaches as described in ISO 10993-18.

Note 2 to entry: Examples of molecular structure information include (e.g., illustration or SMILES code), molecular formula, and CAS registry number (RN) of constituents; molecular structure includes its elements (type, number, arrangement) and bond information.

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**3.12**
**irritation**
localized non-specific inflammatory response to single, repeated or continuous application of a substance/material

[SOURCE: ISO 10993-23]

Note 1 to entry: Skin irritation is a reversible reaction and is mainly characterized by local erythema (redness) of the skin.

**3.13**
**lowest observed adverse effect level**
**LOAEL**
lowest concentration or amount of an identified constituent found by experiment or observation which causes detectable harm to health (3.8) of the target organism under defined conditions of exposure

Note 1 to entry: Lowest observed adverse effect level is normally expressed as mg/kg/day.

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**3.14**
**margin of safety**
**MOS**
ratio of the chemical constituent's *tolerable contact level* (3.24) (numerator), *tolerable intake* (3.25) (numerator), or threshold of toxicological (if applicable) (numerator), and its exposure dose (denominator)

Note 1 to entry: to entry: Margin of Safety (MOS) addresses irritation, genotoxicity, systemic toxicity, carcinogenicity or reproductive/developmental endpoints

**3.15**
**minimally irritating level**
**MIL**
lowest amount of an identified chemical constituent that is irritating to the body

Note 1 to entry: Minimally irritating level is normally expressed as $mg/cm^2$.

**3.16**
**modifying factor**
**MF**
mathematical product of uncertainty factors

**3.17**
**non-irritating level**
**NIL**
greatest amount of an identified chemical constituent that does not elicit irritation to the body

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Note 1 to entry: Non-irritating level is normally expressed as milligram per centimetre squared ($mg/cm^2$).

**3.18**
**no observed adverse effect level**
**NOAEL**
greatest concentration or amount of an identified constituent found by experiment or observation which causes no detectable *harm to health* (3.8) of the target organism under defined conditions of exposure

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Note 1 to entry: No observed adverse effect level is normally expressed as milligram (mg) per kilogram (kg) of body weight per day (*i.e.*, mg/kg/day).

**3.19**
**point of departure**
**POD**
dose used to derive a *tolerable contact level* (3.24) or a *tolerable intake* (3.25)

Note 1 to entry: Note to entry: Examples of a POD include: *non-irritating level* (3.17), or a *minimally irritating level* (3.15), or a *benchmark dose low* (3.2), or a *no observed adverse effect level* (3.18), or *lowest observed adverse effect level* (3.13) for an observed incidence or change in level of response

[SOURCE: EPA Integrated Risk Information System (IRIS) [5]]

**3.20**
**release kinetics**
quantity of a constituent that is released from a medical device as a function of time

Note 1 to entry: Release kinetics data can be obtained experimentally (e.g., simulated use study, leachables study, or other type of extractables study). Alternatively, if supporting chemical and material data are available, a qualified or validated release model can be used. Experimental release kinetics test methods and release models to a subset of medical device constituents and materials have been published in the scientific literature for phthalates and colour additives. [6][7]


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Note 2 to entry: Factors that impact release (e.g., linear versus nonlinear) include, but are not limited to, physicochemical properties of the chemical constituent (e.g., molecular size, solubility, and thermal stability), physicochemical properties of the extracting solvent (e.g., solubility and thermal stability), as well as, impact of the extraction temperature on the device material(s) in the test sample (e.g., increased free volume of a polymer system at elevated temperature).

**3.21**
**slope factor**
upper-bound estimate of risk per increment of dose that can be used to estimate risk probabilities for different exposure levels

Note 1 to entry: Slope factor is expressed as a pre-determined frequency of occurrence (*i.e.*, the number of individuals that the response is expected to occur in a larger population per unit exposure dose. For example, slope factor that represents a frequency of occurrence in a specified population is commonly expressed as 1 in 100 000 for every 1 mg/kg/day increase in exposure to the chemical constituent.

**3.22**
**suspected human carcinogen**
*carcinogen* (3.3) for which toxicological data indicates a causal relationship between exposure to the chemical constituent and cancer

Note 1 to entry: Suspected human carcinogen applies when human data are inadequate to establish an association between exposure to the chemical constituent and cancer. Suspected human carcinogens are established by experts in chemical carcinogenesis based on a weight-of-evidence assessment.

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**3.23**
**systemic toxicity**
harm(s) that occur at a different organ/system other than at the site of contact between the body and the medical device

Note 1 to entry: Systemic toxicity can occur within a few days of a one-time exposure (*i.e.*, acutely) or delayed after repeated/ongoing exposure (subacute and subchronic, and chronic) to a *harmful dose* (3.9) of a chemical constituent released from a single medical device or from use of multiple medical devices.

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**3.24**
**tolerable contact level**
**TCL**
estimate of the daily surface-contact exposure to an *identified constituent* (3.11) over a specified time period that is without appreciable *irritation* (3.12)

Note 1 to entry: Tbolerable contact level is normally expressed as mg/cm$^2$/day of body or tissue surface.

**3.25**
**tolerable intake**
TI
estimate of the daily exposure of an *identified constituent* (3.11) over a specified time period (*e.g.*, acute, subacute, subchronic, or chronic), on the basis of body mass, on the basis of body mass, that is considered to be without appreciable *harm to health* (3.8)

Note 1 to entry: Tolerable intake is normally expressed as milligram (mg) per kilogram (kg) of body weight (bw) per day (*i.e.*, mg/kg/day). It is derived to establish a toxicological exposure limit for a medical device *constituent* (3.4).

**3.26**
**total quantity**
TQ
amount of an *identified constituent* (3.11) present in, or that which can be extracted from, the medical device

Note 1 to entry: Total quantity is normally expressed as milligram per device (mg/device).

Note 2 to entry: The constituent's total quantity and its release rate influences the maximum duration that which an individual can be exposed to the *constituent* (3.4). [8]

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**3.27**
**toxicological risk**
probability of an adverse reaction occurring in response to a specified level of exposure

**3.28**
**toxicological risk assessment**
determination if an *exposure dose* (3.7) of a *constituent* (3.4) will not, or could, elicit appreciable *harm to health* (3.8)

**3.29**
**toxicological screening limit**
TSL
cumulative *exposure dose* (3.7), over a specified time period, to an *identified constituent* (3.11) that will be without appreciable *harm to health* (3.8)

**3.30**
**uncertainty factor(s)**
**UF**
numerical value that accounts for uncertainties when extrapolating a *point of departure* (3.19) to individuals who could be exposed to *constituent(s)* (3.4) of toxicological concern

**3.31**
**worst case exposure dose**
*exposure dose* (3.7) based on the selection of the full range of clinical-use scenario, specific clinical use condition(s), or assumption(s) related to the clinical scenario that results in a maximum exposure value ($EED_{max,}$ Annex E)

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Note 1 to entry: Specific clinical use conditions or assumptions used to establish worst case exposure is not intended to take account of deliberate misuse (*i.e.*, the misuse is not reasonably foreseeable) of a medical device use that results in new constituent toxicological risk(s)

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## 4 Abbreviations and terms

Abbreviations and corresponding terms that are used in this document (Table 1).

**Table 1 — Abbreviations and terms**

| Abbreviation | Term |
|---|---|
| $BMD_L$ | Benchmark Dose Low |
| $EED_{max}$ | Estimated exposure dose (maximum) |
| LOAEL | Lowest observed adverse effect level |
| MOS | Margin of safety |
| MIL | Minimally irritating level |
| MF | Modifying factor |
| NIL | Non-irritant level |
| NOAEL | No observed adverse effect level |
| POD | Point of departure |
| $SF_{ar}$ | Safety factor (assumed release) |
| $SF_{rk}$ | Safety factor (release kinetics) |
| TCL | Tolerable contact level |
| TI | Tolerable intake |
| TQ | Total quantity |
| TSL | Toxicological screening limit |


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**Table 1** *(continued)*

| Abbreviation | Term |
|---|---|
| TTC | Threshold of toxicological concern |
| UF | Uncertainty factor |

## 5 Toxicological risk assessment within the biological evaluation process

Risk assessment is the overall process of risk analysis and risk evaluation. Risk analysis is the systematic use of available information to identify hazards (*i.e.*, potential source of harm) and to estimate the risk (ISO 14971:2019, 3.19). Risk is typically estimated by assigning values to the probability of occurrence of harm and the severity of that harm (ISO 10993-1:2018, B.3.1.3). For toxicological risk, a hazardous situation occurs when exposure to a constituent is (or could be) at a level that results in appreciable harm to health under the intended condition of medical device use. ISO 10993-1 also states the likelihood that harm will occur can be estimated from knowledge of the actual availability of toxic components and the known dose response in relevant tissue(s).

Risk evaluation is the determination of the acceptability of a risk by comparing the risk against documented risk acceptability criteria; thus, enabling identification of risks that require risk control (ISO 10993-1:2018, B.3.1.4 and ISO 14971:2019, 5.5, 5.5 and Clause 6). Criteria for the acceptability of toxicological risks shall be established and documented.

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The approaches described in this document can be used as part of risk analysis in which risks applicable to this Standard that could result from constituent exposure are identified or estimated qualitatively or quantitatively.

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Note 1 For information on relevant risk management concepts and requirements, see ISO 14971:2019, 3.19, 3.20, 4.4, 5.4, 5.5 and Clause 6. For information on application of these concepts to biological evaluation, see ISO 10993-1:2018, B.3.1.2 and B.3.1.3.

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Note 2 Frequency-based dose-response data describes the occurrence of a specific harm in a specified population

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Note 3 ISO 14971 states risk estimation can be qualitative or quantitative. This standard includes qualitative (e.g., a TI or TCL based on a no observed adverse effect level and uncertainty factors) or quantitative (e.g., cancer risk based on a slope-factor) approaches. Specific methods to determine actual availability of a chemical constituent and its dose-response in a specified tissue that which a medical device contacts are not described in this document.

The types of toxicological information used (Clause 6); derivation of tolerable contact level (TCL), tolerable intake (TI), thresholds of toxicological concern (TTC) (Clause 7); exposure dose estimation (Clause 8); and margin of safety (MOS) derivation (Clause 9) are described in this document. The approaches described in this standard can also be used to establish a total quantity of a constituent present in or extracted from a medical device is too low to present a toxicological risk (6.2.1). Chemical characterization and comparison with an appropriate TCL, TI, or TTC (if applicable) can be used to determine if further testing is needed, see ISO 10993-1:2018, 4.3. This process is illustrated in Figure 1.

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