INTERNATIONAL STANDARD

ISO 10993-17

Second edition
2023-09

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
ISO 10993-17:2023(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.

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, *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);

— 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.

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).

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*

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.]

3.5
default value
value or factor used in the derivation of a *worst-case exposure dose* (3.32), *tolerable contact level* (3.25) or *tolerable intake* (3.26), in the absence of specific data [e.g. an *uncertainty factor* (3.31)]

3.6
dose-response
relationship of dosage to observable harm

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

3.7
exposure dose
quantity of a *constituent* (3.4) that does or can contact the body by an exposure route over a specified time period

Note 1 to entry: The exposure dose is expressed in microgram per kilogram of body mass per day (µg/kg/d) or in microgram per centimetre squared (µg/cm^2).

Note 2 to entry: The exposure dose is different from the absorbed dose. The absorbed dose is the quantity of the constituent that traverses the portal of entry, which is dependent on the absorption rate of the constituent.

3.8
harm to health
adverse reaction, such as altered morphology, physiology, growth, development, reproduction or lifespan that

a) impairs function of an organ or system, organism, or (sub)population,

b) reduces capacity to tolerate an 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, female, preterm neonates, adults.

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 *constituent* (3.4) and occurrence of cancer

EXAMPLE Human carcinogens include, but are not limited to, International Agency for Research on Cancer (IARC) Group I carcinogens or US National Toxicology Program (NTP) "known to be a human carcinogen".[6][7]

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

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

EXAMPLE Examples of molecular structure information include molecular structure illustration or simplified molecular input line entry system (SMILES) code, molecular formula, and Chemical Abstract Service Registry Number (CAS RN®[1]). Molecular structure information includes its atomic elements (type, number, arrangement) and bond information.

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

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

[SOURCE: ISO 10993-23:2021, 3.7]

3.13
lowest observed adverse effect level
LOAEL
lowest concentration or amount of an *identified constituent* (3.11) found by experiment or observation which causes detectable *harm to health* (3.8) to the target organism under defined conditions of exposure

Note 1 to entry: The lowest observed adverse effect level is expressed in microgram per kilogram of body mass per day (µg/kg/d).

3.14
margin of safety
MoS
ratio of the constituent's *tolerable contact level* (3.25) (numerator), *tolerable intake* (3.26) (numerator) and its *exposure dose* (3.7) (denominator)

Note 1 to entry: Margin of safety addresses *irritation* (3.12), genotoxicity, *systemic toxicity* (3.23), carcinogenicity or reproductive or developmental endpoints.

3.15
minimally irritating level
MIL
lowest amount per surface area of an identified *constituent* (3.4) that is irritating to the tissue at the contact site as determined by valid experimental or observational evidence

Note 1 to entry: The minimally irritating level is expressed in microgram per centimetre squared (µg/cm^2).

3.16
modifying factor
MF
mathematical product of *uncertainty factors* (3.31)

3.17
non-irritating level
NIL
greatest amount per surface area of an identified *constituent* (3.4) that does not elicit irritation to the tissue at the contact site as determined by valid experimental or observational evidence

Note 1 to entry: The non-irritating level is expressed in microgram per centimetre squared (µg/cm^2).

1) Chemical Abstracts Service (CAS) Registry Number® is a trademark of the American Chemical Society (ACS). This information is given for the convenience of users of this document and does not constitute an endorsement by ISO of the product named. Equivalent products may be used if they can be shown to lead to the same results.

3.18
no observed adverse effect level
NOAEL
greatest concentration or amount of an *identified constituent* (3.11) found by experiment or observation which causes no detectable *harm to health* (3.8) to the target organism under defined conditions of exposure

Note 1 to entry: The no observed adverse effect level is expressed in microgram per kilogram of body mass per day (µg/kg/d).

3.19
point of departure
POD
low point on a toxicological dose-response curve established from experimental or observational data that corresponds to the *benchmark dose low* (3.2), or a *lowest observed adverse effect level* (3.13), or a *minimally irritating level* (3.15), or a *non-irritating level* (3.17), or a *no observed adverse effect level* (3.18)

Note 1 to entry: The POD is used to derive a *tolerable contact level* (3.25) or a *tolerable intake* (3.26).

[SOURCE: EPA Integrated Risk Information System (IRIS)[8]]

3.20
release kinetics
quantity of a *constituent* (3.4) 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. Examples of experimental release kinetics test methods and release models have been published in scientific literature for phthalates and colour additives[9][10].

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

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

Note 1 to entry: The slope factor is expressed in a pre-determined frequency of occurrence (i.e. the number of individuals in which the response is expected to occur) per unit *exposure dose* (3.7). For example, a slope factor for cancer risk that represents a frequency of occurrence in a specified population is expressed as *x* in 100 000 for every 1 µg/kg/d increase in exposure to the constituent.

3.22
suspected human carcinogen
carcinogen (3.3) for which non-human experimental evidence indicates a probable association between exposure to the *constituent* (3.4) and cancer in humans

Note 1 to entry: Suspected human carcinogen applies when human data are inadequate to establish an association between exposure to the constituent and cancer. Suspected human carcinogens can be established by non-human in vivo or in vitro evidence based on a weight of evidence assessment (see C.3.1).

Note 2 to entry: Suspected human carcinogens include, but are not limited to, IARC Group 2A or 2B carcinogens or NTP "reasonably anticipated to be human carcinogen".[6][7]

3.23
systemic toxicity
harm that occurs in an organ or system other than at the contact site

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

Note 2 to entry: The contact site is the specific location at which the medical device interfaces or interacts with the tissue.

3.24
threshold of toxicological concern
TTC
level of exposure for constituents, below which there would be no appreciable risk to human health

[SOURCE: ISO/TS 21726:2019, 3.5]

3.25
tolerable contact level
TCL
estimate of the surface-contact exposure to an *identified constituent* (3.11) that is without appreciable *irritation* (3.12)

Note 1 to entry: The tolerable contact level is expressed in microgram per centimetre squared ($\mu g/cm^2$) of tissue at the contact site.

3.26
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, that is considered to be without appreciable *harm to health* (3.8)

Note 1 to entry: The tolerable intake is expressed in microgram per kilogram of body mass per day (µg/kg/d). It is derived to establish a toxicological exposure limit for a medical device *constituent* (3.4).

3.27
total quantity
TQ
amount of a *constituent* (3.4) present in, or that can be extracted from, the medical device

Note 1 to entry: The total quantity is expressed in microgram (µg).

Note 2 to entry: The constituent's total quantity and its release rate (or kinetics) influence the maximum duration that an individual can be exposed to the *constituent* (3.4)[11].

3.28
toxicological risk
probability of a specified degree of an adverse reaction occurring in response to a specified level of exposure

[SOURCE: ISO 10993-1:2018, 3.24]

3.29
toxicological risk assessment
determination of whether an *exposure dose* (3.7) to a *constituent* (3.4) can or cannot elicit appreciable *harm to health* (3.8)

3.30
toxicological screening limit
TSL
cumulative *exposure dose* (3.7) to an *identified constituent* (3.11) over a specified time period that is without appreciable *harm to health* (3.8)

Note 1 to entry: TSL is expressed in microgram per individual exposed.

3.31
uncertainty factor
UF
numerical value that accounts for uncertainties when extrapolating a *point of departure* (3.19) to individuals that can be exposed to a *constituent* (3.4) of toxicological concern

EXAMPLE Extrapolation types include, but are not limited to: intraspecies (see C.2.2.2), interspecies (see C.2.2.3), dose route (see C.2.2.4) and study duration (see C.2.2.4).

3.32
worst-case estimated exposure dose
EED_{max}
exposure dose (3.7) that is a maximum value for a specified intended clinical-use scenario

Note 1 to entry: EED_{max} is based on the selection of the full range of intended clinical use scenarios, specific clinical use condition or assumption related to the intended clinical scenario (see Annex E for additional information).

Note 2 to entry: Specific clinical use conditions or assumptions used to establish worst-case estimated exposure dose do not include deliberate misuse of a medical device that is not reasonably foreseeable or that results in different *harm to health* (3.8).

4 Abbreviated terms and symbols

The following abbreviated terms and symbols apply in this document.

AET	Analytical evaluation threshold
BMD_L	Benchmark dose low
BW_L	Body mass (low)
CoC	Cohort of concern
C_{max}	Highest concentration
CRL	Cancer risk level
CRSD	Cancer risk specific dose
CRSDE	Cancer risk specific dose estimate
EED_{max}	Estimated exposure dose (maximum)
HQ	Highest quantity
HQ_i	Highest quantity (irritant)
$HQ_{r.k.}$	Highest quantity (release kinetics)
LOAEL	Lowest observed adverse effect level
LOD	Limit of detection

MD	Medical device
$MD_{a.r.s.}$	Medical device (extraction (i.e. assumed release) study)
$MD_{b.c.}$	Medical device (body contact)
$MD_{r.k.s.}$	Medical device (release kinetic study)
MF	Modifying factor
MF_{TCL}	Modifying factor (tolerable contact level)
MIL	Minimally irritating level
MoS	Margin of safety
MoS_{com}	Margin of safety (combined)
MoS_i	Margin of safety (individual or each)
NIL	Non-irritating level
NOAEL	No observed adverse effect level
POD	Point of departure
R_d	Release duration
SA_{ext}	Surface area (extraction)
SIF	Slope factor
SVOC	Semi volatile organic compound
SF	Scaling factor
$SF_{a.r.}$	Scaling factor (assumed release)
$SF_{r.k.}$	Scaling factor (release kinetics)
TCL	Tolerable contact level
TD_{50}	Toxic dose (50 %)
TI	Tolerable intake
TQ	Total quantity (i.e. present or extracted)
$TQ_{a.r.}$	Total quantity (assumed release)
TQ_{ext}	Total quantity (extracted)
TQ_{max}	Total quantity (maximum)
TRA	Toxicological risk assessment
TSL	Toxicological screening limit
$TSL_{\leq 30\ d}$	Toxicological screening limit (less or equal to 30 days)
$TSL_{>30\ d}$	Toxicological screening limit (greater than 30 days)

TTC Threshold of toxicological concern

UF Uncertainty factor

VOC Volatile organic compound

5 Toxicological risk assessment within the biological evaluation process

5.1 General

5.1.1 Risk assessment principles

This document describes an approach for identifying, estimating and evaluating toxicological risks that can arise from exposure to medical device constituents. According to ISO 14971, risk assessment comprises risk analysis and risk evaluation. Risk analysis is the systematic use of available information to identify hazards (potential sources of harm) and to estimate the risk. The process of risk estimation assigns values to the probability of occurrence of harm and the severity of that harm. Risk evaluation is the process of comparing risk estimates to acceptability criteria to determine the acceptability of risk. ISO 10993-1 states that the likelihood that harm will occur can be estimated from the knowledge of the actual availability of toxic components and the known dose response in relevant tissue.

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.

This document describes a systematic approach to toxicological risk assessment based on:

— toxicological information on constituents that describes potential harms and the circumstances in which harm can occur (see Clause 6);

— the derivation of a tolerable contact level or tolerable intake, or the selection of a threshold of toxicological concern (see Clause 7);

— exposure dose estimation (see Clause 8);

— the derivation of a MoS, where appropriate (see Clause 9).

This process is illustrated in Figure 1.

Toxicological risk assessment shall be conducted by experienced individuals, knowledgeable in toxicology, medical devices (i.e. clinical use conditions, materials, manufacturing process, etc.) and exposure dose estimation.

NOTE 2 Assessment of toxicological risk typically involves close collaboration of experts in medical device manufacturing or clinical use or design, material science, analytical chemistry and toxicology.

This document shall not be used for commercially marketed medical devices to mandate a reassessment of historical ISO 10993-18 chemical constituent data assessed previously using the appropriate edition of this document at the time of the assessment. Compliance with this document (i.e. ISO 10993-17:2023) may be shown by providing a justification for the adequacy of the historical toxicological risk assessment. This includes confirmation that none of the issues identified in ISO 10993-1:2018, 4.9 have occurred; otherwise, a new toxicological risk assessment is needed for any of the relevant endpoints in 6.1 of this document.

5.1.2 Hazard identification

A hazard is identified when a medical device constituent that is capable of causing a harm that is relevant to the circumstances of exposure to the medical device is found to be present in or on, or released from a medical device.