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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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 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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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

$\mathrm{MD}_{\mathrm{a.r.s.}}$ Medical device (extraction (i.e. assumed release) study)

$\mathrm{MD}_{\mathrm{b.c.}}$ Medical device (body contact)

$\mathrm{MD}_{\mathrm{r.k.s.}}$ Medical device (release kinetic study)

MF Modifying factor

$\mathrm{MF}_{\mathrm{TCL}}$ Modifying factor (tolerable contact level)

MIL Minimally irritating level

MoS Margin of safety

$\mathrm{MoS}_{\mathrm{com}}$ Margin of safety (combined)

$\mathrm{MoS}_{\mathrm{i}}$ Margin of safety (individual or each)

NIL Non-irritating level

NOAEL No observed adverse effect level

POD Point of departure

R_{d} Release duration

$\mathrm{SA}_{\mathrm{ext}}$ Surface area (extraction)

SIF Slope factor

SVOC Semi volatile organic compound

SF Scaling factor

$\mathrm{SF}_{\mathrm{a.r.}}$ Scaling factor (assumed release)

$\mathrm{SF}_{\mathrm{r.k.}}$ Scaling factor (release kinetics)

TCL Tolerable contact level

TD_{50} Toxic dose (50 %)

TI Tolerable intake

TQ Total quantity (i.e. present or extracted)

$\mathrm{TQ}_{\mathrm{a.r.}}$ Total quantity (assumed release)

$\mathrm{TQ}_{\mathrm{ext}}$ Total quantity (extracted)

$\mathrm{TQ}_{\mathrm{max}}$ Total quantity (maximum)

TRA Toxicological risk assessment

TSL Toxicological screening limit

$\mathrm{TSL}_{\leq 30\ \mathrm{d}}$ Toxicological screening limit (less or equal to 30 days)

$\mathrm{TSL}_{>30\ \mathrm{d}}$ 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.

The relevance of the harm shall be determined from information on the intended use of the medical device, based on its categorization in accordance with ISO 10993-1:2018, Clause 5 and 6.2, taking into account its exposure scenario (see 6.2.1) and reasonably foreseeable sequences or combinations of events related to medical device use that can result in harm to health (refer to the applicable requirements in ISO 14971).

EXAMPLE Types of exposure or contact include, but are not limited to, topical, dermal, oral, gastrointestinal, inhalation, respiratory, subcutaneous, intramuscular, bone, intravenous or blood, neural tissues.

NOTE Reasonably foreseeable means sequences or combinations of events related to medical device use that can result in harm to health (when TTC is applied).

If the harm is not relevant to the intended use of the medical device, the toxicological risk is negligible, and can be evaluated as acceptable.

5.1.3 Risk estimation

The toxicological risk shall be estimated when exposure to a constituent can exceed a pre-determined level that can result in a relevant harm under the anticipated worst-case conditions of medical device use.

The toxicological risk is negligible when the total quantity of a constituent that is present in, on or extracted from the medical device is at or below the toxicological screening limit (see 6.2.2), or worst-case estimated exposure dose is below the applicable TTC value (see 7.2), or the worst-case estimated exposure dose is below the tolerable contact level or tolerable intake (see Clauses 8, 9 and 10).

Toxicological risk estimation includes the following activities:

— a constituent-specific TCL or TI is derived based on conservative assumptions (see 7.1) or, if a constituent-specific POD is not available, a TTC (if applicable) is applied (see 7.2);

— the calculation of the worst-case estimated exposure dose for the constituent (see Clause 8);

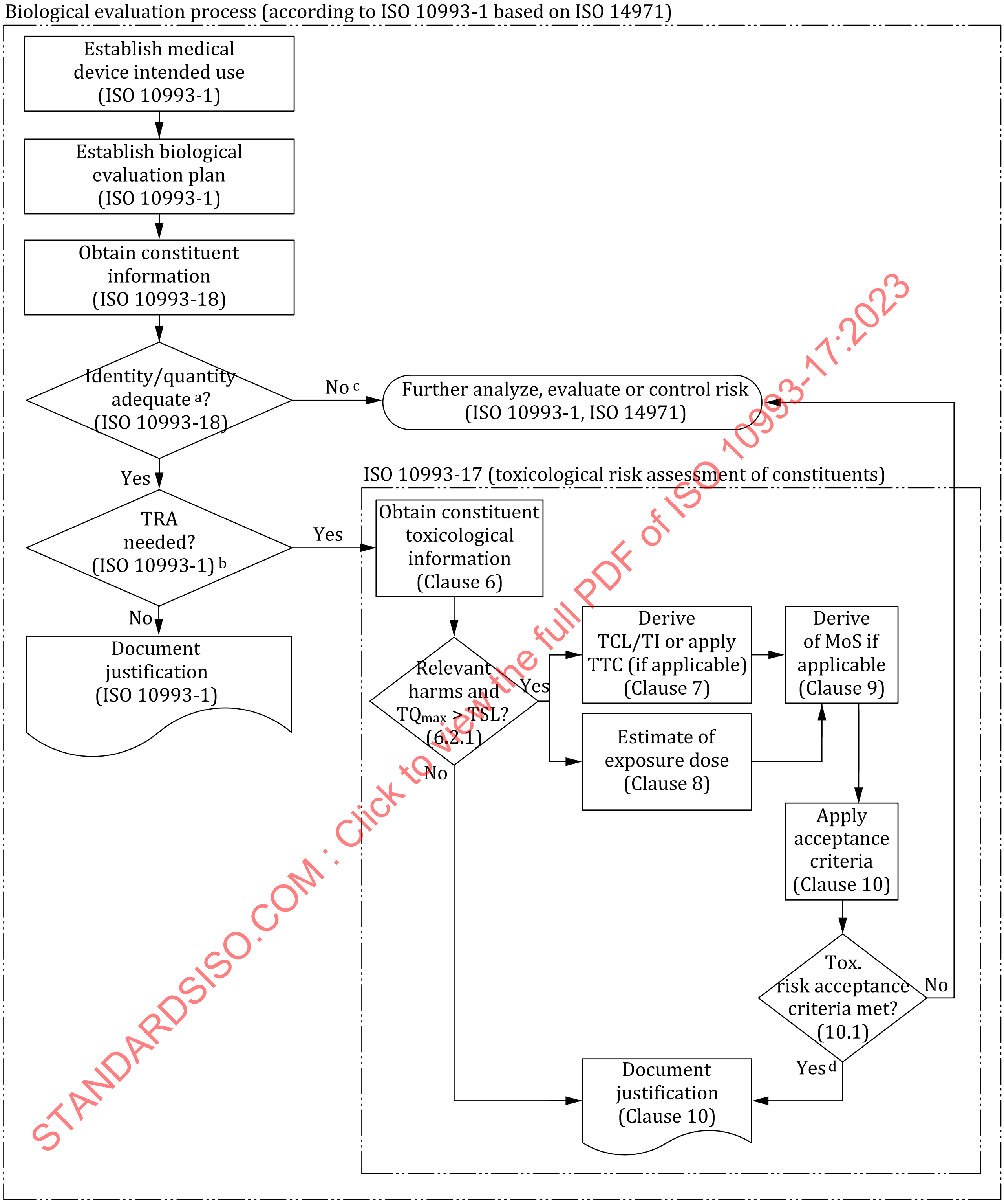
— the calculation of the MoS, where appropriate (see Clause 9).

NOTE Risk estimation is a process used to assign values to the probability of occurrence of harm and the severity of that harm (see ISO 14971:2019, 3.22 and A.2.5.5). For medical devices for which any harm due to toxicity is considered unacceptable, assigning a value for severity is not necessary.

Risk acceptability shall be based on pre-determined risk acceptability criteria in accordance with ISO 14971:2019, 4.4 d) and ISO 10993-1:2018, 7 b).

The MoS can be used to evaluate whether the toxicological risk acceptability criteria are met (see Clause 9 and Clause 10).

When exposure to a constituent does not meet the acceptability criteria, the toxicological risk shall be further addressed (see 10.2).



Key

Tox. toxicological

NOTE TSL or TTC are not applicable to cohort of concern, excluded compounds, irritation or other endpoints (see ISO/TS 21726).

[a] Adequacy of constituent identity for toxicological risk assessment is informed by the experts involved in the toxicological risk assessment.

[b] Harms specified in this document may be addressed by other approaches described in ISO 10993-1 and other applicable parts of the ISO 10993 series.

c When the identity of a reportable constituent cannot be adequately elucidated and its worst-case exposure dose cannot be estimated, biological testing may be necessary to address the applicable biological risk(s).

d The determination that toxicological risk assessment criteria are met is specific to the constituent and endpoint(s) addressed per this document and does not infer that all biological risks associated with a medical device are acceptable.

Figure 1 — Toxicological risk assessment within the biological evaluation process

5.2 Toxicological risk assessment process

Figure 2 shows in detail the toxicological risk assessment process that is shown in Figure 1. Critical toxicological risk assessment activities described in this document are illustrated in Figure 2.

The toxicological risk assessment process requires that[12][13][14]:

a) The following information shall be provided (see Clause 6), in accordance with ISO 10993-1 and ISO 10993-18:

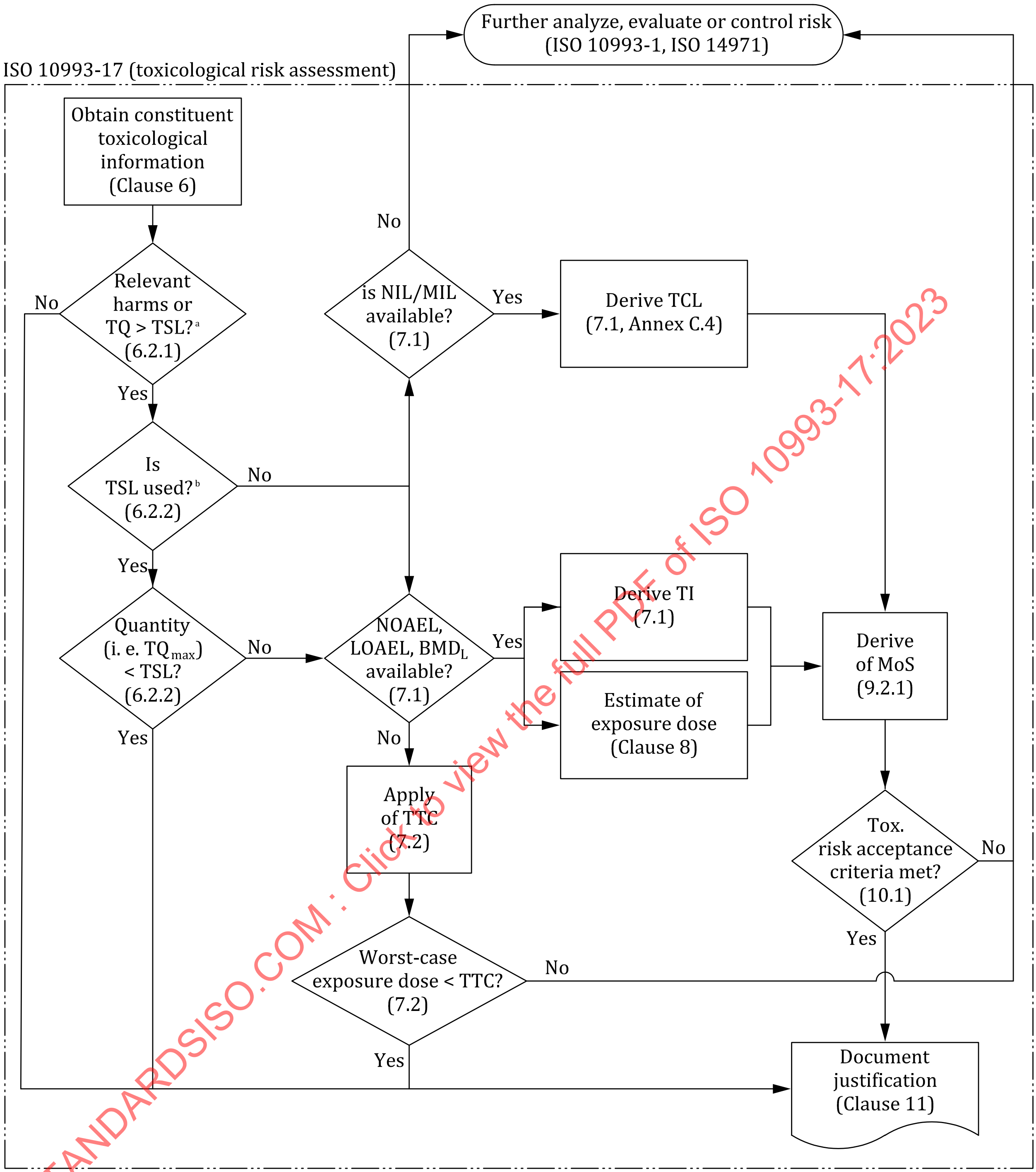
- — a description of the device (e.g. an illustration of the device and identification of its materials of construction that contact the body);
- — a description of the intended use of the medical device (e.g. indications, contraindications, clinical use conditions, route of exposure, patient population, duration and frequency of use), from which the worst-case intended clinical use scenario shall be determined;
- — the identity and quantity of each reportable constituent (e.g. molecular structure or CAS RN) obtained in accordance with ISO 10993-18.

b) The toxicity of each constituent shall be characterized (see 6.1 and 6.2), based on a systematic review of available toxicological information that takes into account:

- — the nature of the harm(s) to health;
- — the relationship between exposure and harm (i.e. dose-response relationship and the influence of the route and duration of exposure).

c) The toxicological risk shall be assessed for each constituent by either:

- — determining that the constituent is not capable of eliciting harm that is relevant to the intended use of the medical device (see 6.2), or
- — determining that the total quantity of a constituent is too low to elicit appreciable harm to health (see 6.2.1 or 6.2.2), or
- — determining that the worst-case estimated exposure dose for each constituent present in, on, or released from the medical device is below its TCL or TI (see Clauses 7, 8 and 9), or
- — determining that the quantity of a constituent released is below the relevant TTC value (if applicable; see 7.2).



a Harm relevant to a toxicological risk assessment of a constituent in, on or released from a medical device of a given categorization are determined in ISO 10993-1.

b TSL or TTC are not applicable to the cohorts of concern, excluded compounds, irritation or other excluded endpoints as described in ISO/TS 21726:2019, 5.3.

Figure 2 — Critical toxicological risk assessment activities

6 Constituent specific toxicological information

6.1 General

After constituents have been identified, the next step in the toxicological risk assessment is understanding the inherent property of a constituent to elicit or induce harm in humans, as well as the conditions (e.g. route, duration, frequency, gender, age) necessary for the constituent to elicit the harm. Knowledge of the conditions that pertain to the clinical use of the device is recommended to determine whether the harm is clinically relevant.

NOTE 1 Toxicity is an inherent property of a constituent's molecular structure and physicochemical characteristics that occurs under specified conditions (e.g. treatment dose, route, duration, frequency, sex, age).

EXAMPLE Clinical conditions include, but are not limited to, the number of medical devices per patient procedure, nature and duration of body contact, and sensitivity of individuals.

The nature or types of harm to health that can be addressed by application of a TCL, TI, TSL or TTC (if applicable) include the following:

— irritation (TCL);

— systemic toxicity (i.e. acute, subacute, subchronic or chronic) (TSL, TI or TTC);

— genotoxicity (TSL, TI or TTC);

— carcinogenicity (TSL, TI or TTC);

— reproductive toxicity (TSL, TI or TTC);

— developmental toxicity (TSL, TI or TTC);

— other toxicity endpoints if relevant based on available toxicological data (i.e. TSL, TI or TTC do not apply).

When toxicological information for a constituent is obtained from the literature or other sources, the information shall be evaluated in accordance with 6.2.1, Clause 7, Clause 8, Clause 9, Clause 10 and Clause 11.

When toxicological information is not available or is inadequate to derive a TI for a constituent, the TTC concept can be used according to 6.2.2 or 7.2.

Toxicological risk assessment of other harms (e.g. skin sensitization) shall be justified, based on adequacy of available constituent and harm specific toxicological data, and documented.

NOTE 2 Skin sensitization is a delayed-type hypersensitivity reaction that comprises induction and elicitation. For constituents that elicit an allergic response in hypersensitive individuals at very low concentrations, the risk of elicitation of an allergic response in these individuals is typically controlled by avoiding exposure to that specific constituent[15][16][17].

6.2 Identification of hazardous constituents

6.2.1 General

Identification of hazardous constituents involves obtaining and evaluating toxicological information for each constituent. Constituent specific toxicological information such as in vitro or in vivo toxicity studies, as well as human epidemiological studies, clinical trials or case reports, can be obtained from primary health effect data, supporting health effect data or secondary health effect sources (published review articles, authoritative reports, databases, etc.).

Toxicological information shall be obtained from a systematic search in multiple information sources or databases in accordance with ISO 10993-1:2018, C.2.3.

The selection of information sources and search criteria shall be documented and justified.

NOTE 1 Toxicological data are typically obtained experimentally or predicted based on a qualified or validated model, and are used to identify hazardous constituents. Examples of toxicological data include, but are not limited to, benchmark dose low, dose-response data, nature of the harm to health, harmful dose, primary health effect data, lowest observed adverse effect level, minimally irritating level, non-irritating level, no observed adverse effect level, slope factor, supporting health effect data and systemic toxicity data.

NOTE 2 Primary health effect data are original reports of direct evidence, in vitro or in vivo, of the potential toxic effect that a constituent does or does not elicit at a specified dose and route and duration of treatment. Examples of primary health effect data include original reports of irritation, systemic toxicity (acute, subacute, subchronic or chronic), genotoxicity, carcinogenicity, or reproductive or developmental toxicity.

NOTE 3 Supporting health effect data are indirect evidence, in vitro, in silico, in chemico, in vivo or clinical data that a constituent does or does not have the potential to elicit harm to health at a specified dose, and route and duration of the treatment. Examples of supporting evidence include, but are not limited to, chemical/physical properties, toxicological structural alerts, toxicokinetics (i.e. absorption, distribution, metabolism, and excretion), mechanism or mode of toxic action, animal studies, human epidemiological studies, clinical trials or case reports.

NOTE 4 A secondary health effect source is a document other than the original report (e.g. a review article published in a scientific journal or a database that summarizes the toxicological findings in one or more original reports) that includes a description of constituent specific toxicological data (i.e. primary health effect or supporting health effect data).

The adequacy and relevance of the obtained toxicological information shall be justified and documented in the context of the intended use conditions of the medical device.

The reliability and quality of the information shall be evaluated and documented in accordance with Annex A.

When systematic review of constituent toxicity by an expert group addresses the availability and quality of toxicological data, the systematic review can be used as a secondary health effect source. The applicability, relevance and quality of such systematic reviews shall be justified and documented.

NOTE 5 Applicability of a systematic review means the reported toxicological information is current and specific to the constituent.

When toxicological information for a constituent indicates that exposure does not result in harm relevant to the intended use of the medical device, further toxicological risk assessment is not necessary (i.e. negligible toxicological risk).

EXAMPLE 1 An example of negligible toxicological risk includes, but is not limited to, when physicochemical characteristics of a constituent indicates it will not absorb into, or interact with, the body (e.g. molecules with molecular weight of >500 Da having direct contact with intact skin)[18].

For constituents where toxicological information is available, the following information shall be documented (if available):

— animal model (species, breed/strain, age, male or female, and number);

— the route of administration;

— the dose range, administration frequency and duration;

— the nature of harm associated with a specified dose;

— the cell(s), tissue(s), organ(s) or systems that are evaluated and whether any harm is observed.

NOTE 6 The relationship between a constituent and its harm is established by demonstrating whether the biological response is dose- and time-dependent, or that sufficient mechanistic information is available to establish a cause-effect relationship.

NOTE 7 In silico analysis can be used to predict the nature of harm when a chemical specific POD is not available.

When nature of harm is not understood, a computer-based model (also known as in silico analysis) can be used to predict the nature of the harm to health for the identified constituent. The validation of the selected in silico model shall be justified and documented.

If a quantitative mathematical model is used to predict the nature of the harm to health (e.g. quantitative structure activity relationship), the model should be validated[18]to[21].

NOTE 8 In silico quantitative mathematical models establish a relationship between one or more quantitative parameters derived from constituent identity information to a measurable property or activity that relates to the harm to health.

Relevance of specific exposure scenarios that are applicable to the constituent and its harm to health shall be established[22].

When constituent harm to health is dependent on a specific exposure scenario, the constituent exposure specific information and the relevance of the information to medical device intended use shall be documented.

EXAMPLE 2 Factors that define exposure specific scenarios include: duration (e.g. acute, subacute, subchronic, chronic), route (e.g. dermal, oral, inhalation, intravenous), tissue, organ or system (e.g. digestive, nervous, hepatic, renal, cardiovascular, or respiratory), sex (i.e. male or female), age of the individuals (e.g. paediatric or geriatric), or species (i.e. human or non-human).

6.2.2 Application of the toxicological screening limit

The toxicological screening limit can be used to establish whether the TQ of an identified constituent, which is present or extracted, is too low to elicit genotoxicity, cancer, systemic toxicity (e.g. acute, subacute, subchronic, chronic), or reproductive or developmental toxicological risk (see Annex B for additional information). When the total quantity of a constituent to which an individual can be exposed for a specified time period (i.e. a cumulative exposure dose) is below the specified TSL, the quantity can be judged to be of negligible toxicological risk and no further risk evaluation is recommended for these systemic harms; this is subject to the exclusions specified in Clause B.1, and conditions and requirements specified in this subclause.

When the toxicological screening limit approach is used for a constituent, the applicable TSL value shall be compared to the TQ_{max} to which an individual can be exposed.

The TQ_{max} shall account for the duration that the medical device contacts the body, the number or quantity of devices extracted, and the number or quantity of medical devices that is in contact with the body in accordance with Clause B.3.

Comparisons between TSL values and TQ_{max} for each constituent shall be documented.

When the TQ_{max} of an identified constituent exceeds the applicable TSL, an exposure dose for the constituent shall be estimated and evaluated as described in Clause 7, Clause 8, Clause 9 and Clause 10.

NOTE 1 ISO 10993-18 describes methods to obtain the total quantity of a constituent present in or on, or that can be extracted from the medical device (e.g. information gathering or generating chemical data by extracting a medical device using exaggerated or exhaustive methods).

NOTE 2 Suitability of the TQ of a constituent that can be extracted from a medical device for comparision to a TSL is dependent on extraction and analytical parameters, such as the number of medical devices used as the test article, the method used in the preparation of the test article, the solvent type(s) and volume, the temperature, the duration of extraction, the number of extraction cycles (i.e. one or more), and the reference standard used for quantification[23].

When the TQ of a constituent that can be extracted is obtained by extraction and quantification methods that are conservative relative to the medical device intended use, the TQ of each reportable constituent may be assumed to represent a cumulative exposure dose suitable for comparing to a TSL.

When the TQ of a reportable constituent that can be extracted does not represent a cumulative exposure dose based on the extraction and quantification methods used, the toxicological risk of a constituent should be addressed according to 6.2.3, 6.2.4, Clause 7, Clause 8, Clause 9, Clause 10 and Clause 11.

When the TQ cannot be obtained, such as when the constituent cannot be identified or when the amount of the constituent cannot be measured, the TSL approach shall not be applied and toxicological risk assessment shall be conducted in accordance with the requirements of this document; otherwise, further biological evaluation is needed in accordance with ISO 10993-1.

6.2.3 Identification of human carcinogens or suspected human carcinogens

A human carcinogen or suspected human carcinogen is identified when human or non-human weight of evidence data that indicates the constituent is a human carcinogen or a suspected human carcinogen[24] to[29].

Cancer risk of a carcinogen shall be estimated, in accordance with Clause C.3, or controlled or managed in accordance with 10.2.

6.2.4 Selection of the point of departure

When the constituent harm to health is relevant to the medical device's intended use and a constituent specific POD is available, the selected POD and source (i.e. primary health effect data, supporting data or secondary health effect source) shall be documented.

Based on the obtained toxicological information, the most critical (e.g. the lowest) clinically relevant POD shall be selected.

NOTE 1 Guidance on selection of a POD is given in 7.1. Guidance on evaluating toxicological data quality is given in Annex A.

When toxicological information is assessed to be inadequate or absent for an identified constituent, the use of TTC or toxicological data from a structural analogue (also known as read-across approach), shall be justified and documented[30]to[38].

NOTE 2 TTC selection is described in ISO/TS 21726.

The following criteria are useful to identify an analogue:

— molecular structure (e.g. the type and arrangement, including bonding, configuration and optical rotation of elements in a specified order);

— physical properties (e.g. molecular weight, boiling point, vapour pressure, density, crystallinity or solubility);

— chemical properties (e.g. reactivity, stability, acidity or alkalinity);

— biological properties (e.g. metabolism or metabolic pathways, lipophilicity or bioaccumulation) as applicable to the constituent and intended use of the medical device.

NOTE 3 The use of a similarity score (e.g. Tanimoto coefficient, Fingerprints) can be useful in combination with physicochemical information for the selection of structural analogues[39][40].

Selection of a structural analogue shall be justified and documented. Alternatively, TTC can be used to address genotoxicity, carcinogenicity, systemic toxicity, or reproductive or developmental toxicity as described in 7.2[41].

7 Tolerable contact level, tolerable intake and threshold of toxicological concern

7.1 Derivation of TCL and TI

Prior to deriving a constituent specific TCL (i.e. for irritation) or TI (i.e. for genotoxicity, systemic toxicity, carcinogenicity, or reproductive or developmental toxicity), availability of a specific and relevant POD for a medical device's intended use shall be determined.

When available, a constituent's POD is used to derive a TCL or TI value for each constituent. The TCL (i.e. for irritation) or TI (i.e. for genotoxicity, systemic toxicity, carcinogenicity, or reproductive or developmental toxicity) used shall account for the duration for which constituent exposure is assessed.

NOTE 1 The underlying objective in selecting the highest NOAEL when multiple NOAELs are available for the same type of harm and same clinically relevant exposure scenario is to prevent over estimation of toxicological risk of the constituent. The underlying objective in selecting the lowest POD for chemicals that induce more than one type of harm is to prevent other clinically relevant harms that can occur at higher doses.

When multiple NILs or NOAELs are available that apply to the same harm and same clinically relevant exposure scenario, the highest NIL or NOAEL can be used to derive the TCL or TI, respectively. When toxicological data are of mixed quality, the TCL or TI shall be based on the study with the highest quality data (see applicable requirements in Annex A).

When different types of PODs (e.g. NIL versus MIL; NOAEL versus LOAEL), or same type of POD for different types of harms, are available for the same constituent and same study quality (see Annex A for additional information), the lowest POD shall be used.

NOTE 2 Derivation of a TCL or TI for select harms is described in Annex C and Annex D.

When a threshold for a constituent is available for use in other applications besides medical device use (e.g. pharmaceutical product, food product, occupational, environmental), the applicability of the threshold for the duration and type of medical device body contact shall be justified and documented. In these situations, additional uncertainty factor(s) should be applied when the approach used to derive the threshold does not address all of the sources of uncertainty that reflect the circumstances of exposure applicable to the intended use of the medical device (see Clause C.2).

NOTE 3 The application of additional uncertainty factors to a TCL or TI not originally intended for medical device use apply when all of the uncertainties applicable to clinical use of the medical device are not addressed, e.g. differences in exposure route or sensitivity of the individual exposed.

7.2 Application of TTC

When the result of the application of 7.1 is the determination that constituent specific toxicological information is not adequate to derive a TI, the TTC approach shall be applied in accordance with this clause to address the following endpoints: genotoxicity, carcinogenicity, systemic toxicity (i.e. acute, subacute, subchronic and chronic), or reproductive or developmental toxicity.

TTC values shall not be used to assess the toxicological risk of cohorts of concern, excluded compounds, or other biological endpoints in accordance with ISO/TS 21726.

NOTE 1 Types and examples of cohort of concern and excluded compounds are described in ISO/TS 21726.

When the worst-case estimated exposure dose is conservative and below the corresponding TTC, the release can be judged to be of negligible toxicological risk.

NOTE 2 Conservative means the estimation of worst-case estimated exposure dose is deliberately higher than the probable true exposure.

When negligible toxicological risk cannot be determined (e.g. underestimation or overestimation of the quantity released), the toxicological risk shall be addressed by other means in accordance with ISO 10993-1 and ISO 14971. Outcomes of further risk analysis or risk evaluation or risk control shall be documented in accordance with ISO 10993-1 and ISO 14971.

Outcomes of the comparison shall be documented (see Clause 11).

NOTE 3 ISO/TS 21726 includes TTC values applicable to constituents that leach from medical devices (except for gas pathway devices).

NOTE 4 The application of TTC for VOCs and SVOCs present or released from a gas pathway device is described in the ISO 18562 series.

8 Exposure dose estimation

The EED_{max} of a constituent that contacts or enters the body per day shall be estimated. The process to determine the quantity of a constituent that contacts or enters the body is described in Figure 3.

NOTE 1 Per day exposure is time-based and occurs on a single day or on multiple days.

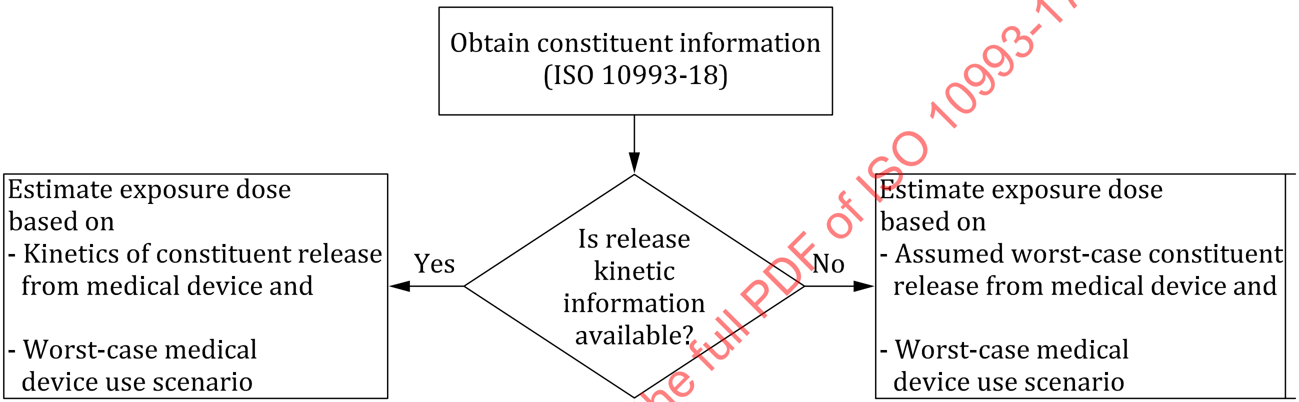


Figure 3 — Exposure dose estimation

The worst-case exposure dose shall be estimated based on worst-case conditions of the use of the medical device.

The following worst-case medical device use assumptions shall be applied:

— the type of chemical exposure information relevant to the medical device intended use (see Clause E.1);

— the largest possible number or quantity of the medical device to which an individual can be exposed in accordance with the medical device intended use, unless otherwise justified (see Clauses E.2 and E.3);

— the lowest body mass of individuals who can be exposed to the constituent (see D.2.1 and Clauses E.2 and E.3).

NOTE 2 ISO 10993-18:2020, Clause 5 includes chemical characterization approaches that vary in relevance to medical device intended use. Information gathering and extraction studies establish the hypothetical worst-case estimated exposure dose based on the total quantity of each chemical constituent released from the medical device, see ISO 10993-18:2020, 5.4. The determination of actual exposure is described in ISO 10993-18:2020, 5.8.

When toxicological risk assessment applies to individuals with unique susceptibilities (see C.2.2.2), additional exposure dose estimates, based on body mass specific to these individuals (see D.2.1) shall be used in the exposure calculation as specified in Annex E, unless justified with supporting evidence.

When accounted for in the reporting of chemical characterization data per ISO 10993-18, the maximum number and quantity of medical devices that simultaneously contact the body shall be accounted for in the calculation of the worst-case estimated exposure dose of each constituent to which an individual can be exposed.

The specific medical device use assumptions that are used to calculate an exposure dose shall be justified and documented.

The method used to calculate an exposure dose shall be in accordance with Annex E. The application of additional assumptions and calculations used in the calculation shall be justified and documented.

NOTE 3 The exposure dose is expressed in the same unit as the TI (i.e. as µg/kg/d) or TCL (i.e. µg/cm^2).

NOTE 4 Exposure on a day can occur intermittently, continuously for a portion of the day or continuously for the entire day. In all these cases, the exposure dose is reported on a per day basis.

NOTE 5 When available, toxicokinetics data can be useful to estimate an internal dose.

9 Margin of safety

9.1 General

For each constituent, the estimated exposure dose shall be assessed to be either

— without appreciable harm to health, or

— a harmful dose.

For this toxicological assessment process, a MoS approach shall be used as described in 9.2.

NOTE 1 An estimated exposure dose can be a harmful dose when the TCL or TI or EED_{max} are not conservative, see 10.1.

NOTE 2 MoS does not apply to 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.

9.2 Calculating the margin of safety

9.2.1 General

The MoS shall be based on the following:

— constituent TI or TCL, in accordance with Clause 7;

— worst-case estimated exposure dose, EED_{max}, in accordance with 3.32 and Clause 8.

The MoS is the ratio of the chemical specific TI or TCL and the worst-case estimated exposure dose (i.e. EED_{max} in µg/kg/d or µg/cm^2), and calculated by Formula (1):

$$MOS = \frac{TI}{EED_{max}} \quad \text{or}$$

$$MOS = \frac{TCL}{EED_{max}} \quad (1)$$

where

EED_{max} is the exposure dose that is a maximum value for a specified intended clinical-use scenario, in µg/kg/d or µg/cm^2;

TI is the estimated daily exposure of an identified constituent over a specified time period (e.g. acute, subacute, subchronic or chronic), on the basis of body mass in µg/kg/d, that is considered to be without appreciable harm to health.

TCL is the estimated the daily tissue surface-contact exposure to an identified constituent at the contact site over a specified time period that is without appreciable irritation, in µg/cm^2;

NOTE 1 Tolerable contact level applies to irritation. Tolerable intake applies to systemic toxicity (acute, subacute, subchronic or chronic), genotoxicity, carcinogenicity or reproductive/developmental toxicity.

NOTE 2 MoS is unitless (i.e. units for EED_{max} are the same as those used for TCL or TI).

The toxicological risk assessment shall address the quantity as a function of duration of exposure to the constituent and associated risks. For example, the ratio of a worst-case estimated exposure dose to a life-time TI is generally protective for acute, subacute, subchronic and chronic systemic toxic effects.

When release kinetics data are available, then the worst-case estimated exposure dose, as described in Clause E.2, shall be used in the derivation of the MoS.

When release kinetics data are not available, acute, subacute, subchronic or chronic exposure can be assumed to occur based on the fewest number of exposure days as described in Clause E.3 [e.g. Formula (E.3)]. MoS values that correspond to acute, subacute, subchronic, and chronic exposure shall be calculated (see Table 1) based on a worst-case exposure for each of these exposure periods (see Table E.4) and compared to the TI or TCL value, unless the approach used is in accordance with E.3.2.

Table 1 — MoS values to consider when constituent release kinetics data are not available

Period of assumed exposure to the constituent	Calculation of MoS value for toxicological endpoints to be addressed[d]			
	Acute[c]	Subacute[c]	Subchronic[c]	Chronic[c]
≤1 d[a]	X	Not applicable	Not applicable	Not applicable
2 d to 30 d[ab]	X	X	Not applicable	Not applicable
31 to 365 d[ab]	X	X	X	Not applicable
≥366 d[ab]	X	X	X	X

X indicates toxicological endpoint shall be addressed unless otherwise justified (see Clause E.1).

[a] This applies when Formula (E.1) is used to estimate an exposure dose.

[b] This applies when Formula (E.3) is used to estimate the worst-case estimated exposure dose for assumed exposure periods.

[c] Acute, subacute, subchronic and chronic refer to the duration of exposure for which the TCL or TI is protective (see 9.2.1 NOTE 1).

[d] See 6.1 for toxicological endpoints to be addressed.

NOTE 3 When a POD is unavailable to derive a TI for limited or prolonged exposure (i.e. acute or subacute exposure), a TI that applies to long-term exposure (i.e. subchronic and chronic exposure) can be used to address limited or prolonged exposure duration, also see example in 9.2.1.

EXAMPLE An example of the calculation of a MoS for a medical device constituent is as follows: an assumed worst-case estimated exposure dose is applied to constituent data obtained by exhaustively extracting the medical device using analytically expedient solvents, see ISO 10993-18:2020, 5.4.

In this example, the medical device intended is an implant in long-term contact with tissue/bone. Worst-case estimated exposure from Clause E.4 and Table E.5 are used in the calculation of the applicable MoS values and two constituent specific TI values are available [i.e. 60 µg/kg/d and 10 µg/kg/d for harm that can occur from limited or prolonged (≤30 d), and long-term (>30 d) exposures].

Table 2 — Calculation example of MoS based on assumed release for a long-term implant and two TI values

Time period d	TI[a] µg/kg/d	EED_{max}[b] µg/kg/d	MoS	**Formula (1)**
≤1	60	500	0,12	0,12 = 60 / 500
2 to 30	60	250	0,24	0,24 = 60 / 250
31 to 365	10	16	0,625	0,625 = 10 / 16
≥366	10	1,4	7,14	7,14 = 10 / 1,4

[a] TI values of 60 µg/kg/d and 10 µg/kg/d are derived based on a NOAEL obtained from a constituent specific subacute and chronic, respectively, systemic toxicity studies. Because constituent specific POD data from acute (<1 d) and subchronic (90 d) systemic toxicity studies are unavailable, the TI value applicable to the longer time periods is used (i.e. subacute TI for 2 d to 30 d and chronic TI for >366 d of assumed exposure, respectively).

[b] EED_{max} values are based on the assumed worst-case estimated exposure from Annex E.

The MoS values in Table 2 are evaluated according to Clause 10.

9.2.2 Combining MoS values to address additivity of harm

MoS values, MoS_i, of two or more constituents shall be combined when the following apply:

— exposure to each constituent can occur simultaneously (e.g. constituents are present in or on, or released from the same medical device);

— the constituents elicit the same harm in the same target organ or system and the same mode of action applies.

The combined MoS value, MoS_{com}, shall be derived in accordance with Formula (2).

$$MOS_{com} = 1 / \sum_{i=1}^{n} \frac{1}{MOS_i} \tag{2}$$

where

MoS_{com} is the result from the summation of reciprocal MoS_i (unitless) values;

MoS_i is the MoS for each (i.e. individual) constituent that results from Formula (1).

When the constituent's critical adverse health effect is not known, then combining MoS values is not required and the MoS value for each constituent is calculated and used individually for toxicological risk assessment.

NOTE 1 Combining MoS values applies to the constituent's critical adverse health effect. The critical adverse health effect is the harm that occurs at the lowest administered POD dose.

NOTE 2 Combining MoS values addresses the harm that can occur in an additive fashion, as well as the harm that occurs by the same or different exposure routes. Formula (2) is adapted from hazard index of mixtures for medical device constituents[42]to[50].

NOTE 3 In some studies, a distinct toxicological mode of action is not always evident, particularly for minor adaptive effects such as small changes in organ mass or reversible changes in blood chemistry, and in such cases, risks are not always additive for a target organ.

10 Toxicological risk acceptance criteria

10.1 General

An exposure dose of a constituent is without appreciable harm to health (i.e. tolerable toxicological risk) when the following apply:

— MoS exceeds 1;

— contributing values to the MoS are demonstrated to be conservative.

NOTE 1 Conservative means the estimation of toxicological risk is deliberately higher (i.e. lower MoS) than the probable true risk.

Examples when the values contributing to the MoS are conservative include, but not limited to:

— The method used in the calculation of EED_{max} represents an overestimate of the probable true worst-case estimated exposure dose;

— For each uncertainty factor used in the derivation of the TI (C.2.2 or C.3.2) or TCL (C.4.3), the default value is used.

When the TCL, TI or EED_{max} are not demonstrated to be conservative, the evaluation of the MoS shall be addressed in accordance with 10.2.

When the TCL, TI or EED_{max} are demonstrated to be conservative and when the MoS does not exceed 1 (i.e. a possible toxicological risk), the toxicological risk shall be further evaluated in accordance with 10.2.

MoS values shall be assessed based on expert judgement when exposure dose is based on assumed release as described in Clause E.3 (i.e. release kinetics data are not available).

For a toxicological risk to be judged acceptable, it shall be supported by evidence that assumed release is conservative in relation to the intended use of the medical device.

NOTE 2 Expert judgement can include assessment of the nature of the harm to health as described in Clause 5 and Clause 6.

MoS values, including how each was calculated, and the conclusion of each exposure dose evaluation shall be justified and documented, in accordance with Clause 11.

10.2 Further risk analysis or risk evaluation or risk control

Toxicological risk shall be further addressed by other means in accordance with ISO 10993-1 and ISO 14971 when any of the following apply:

— the MoS is below 1 based on release kinetics in Clause E.2, and TI or TCL are used,

— the cancer risk of a human carcinogen or suspected human carcinogen exceeds 1 in 100 000, or

— the MoS is judged to represent possible toxicological risk.

NOTE 1 When constituent exposure is understood, an MoS below 1 generally indicates a possible or probable toxicological risk.

Further risk analysis, risk evaluation or risk control can consider information that addresses:

— the dose of a constituent that will elicit harm (e.g. LOAEL),

— the relevance of the exposure dose to the intended use of the medical device (e.g. refinement of the EED_{max}), or

— if risk control is not practical and information is available that demonstrates the expected benefit of the medical device outweighs the toxicological risk.

For example, exposure is reduced as low as reasonably practicable and cancer risk is actively managed using risk management procedures as described in ISO 14971.

Outcomes of further risk analysis or risk evaluation or risk control shall be documented in accordance with ISO 10993-1 and ISO 14971.

11 Reporting requirements

Constituent specific toxicological data, justifications and methods used to apply TSL, TTC, the derivation of TCL or TI values, the estimation of exposure dose, the derivation of MoS values and the evaluations of worst-case exposure shall be documented and reported (see examples in Annex F).

Compliance with the requirements in this document, which includes Clause 6 to Clause 9, and Annexes B, C and E, is verified by inspection of the report.

Annex A
(normative)

Evaluation of toxicological data quality when selecting a point of departure

According to 7.1 and C.2.2.4.3, it is essential that relevant toxicological data are used to evaluate the nature of harm, and to establish the POD value. POD values that can be used in the derivation of a TI value include, but are not limited to, BMD_L, NOAEL or LOAEL.

Toxicological data should be systematically collected and critically assessed for quality. Quality assessment addresses the study design, conduct or data analysis and reporting that can introduce selection, performance, detection, attrition and reporting biases.[51]to[61] Reporting bias can be assessed by confirming that all key information is included in collected studies. Ideally, studies should present sufficient information to allow a knowledgeable reader to understand:

— the toxicological relevance of the study to the constituent;

— that the reported methodological information is adequate for the experiment to be repeated and the dose-response data are reproducible;

— the reliability and validity of the findings based on the data generated.

Evaluation of reporting bias should address whether the quality of the underlying methods used or the generated data can be adversely impacted. Reporting bias can be evaluated when toxicological data are obtained from a secondary health effect source based on expertise of the source (e.g. source is authored by experts in toxicology).

The adequacy of available evidence to support the conclusions of the toxicological risk assessment shall be confirmed.

NOTE Tools for assessing quality are categorized into:

a) checklists of questions that identify sources of bias, or

b) scoring systems that produce a numerical reliability rating for each study (e.g. ToxRTool, ARRIVE Guidelines).

Reducing uncertainty in scores can be addressed by weighing each source of bias[62]to[72].

Annex B
(normative)

Derivation of toxicological screening limits

B.1 General

The total quantity (in µg) of a constituent can be used to assess whether exposure for one or more days can result in a cumulative exposure dose that is at a negligible toxicological risk level (i.e. too low to present a toxicological risk for the applicable harms) and no additional toxicological risk estimation is recommended.

NOTE 1 When TSL is applied, TQ represents the cumulative exposure dose [e.g. the summation of the exposure dose (daily) over the number of exposure days of contact with the device][73].

The TSLs according to this document apply to systemic toxicity (acute, subacute, subchronic and chronic), genotoxicity, carcinogenicity, reproductive or developmental toxicity for oral or parenteral routes, as well as adults, paediatrics (6 months of age or older) and pregnant women[74].

When the TSL approach is used for any medical device, the 120 µg TSL $_{\leq 30\ \mathrm{d}}$ value shall be used for each constituent to address applicable biological endpoints that can result from short-term (i.e. ≤30 d) exposure, see Table B.2.

For long-term body contacting medical devices, the 600 µg TSL $_{>30\ \mathrm{d}}$ value should be used for each constituent, in addition to the TSL $_{\leq 30\ \mathrm{d}}$ value, to address TQ values that exceed the TSL $_{\leq 30\ \mathrm{d}}$ value and applicable biological endpoints that can result from long-term (i.e. >30 d) exposure, see Table B.2.

TSL shall not be applied to harms that the TTC values are not protective in accordance with ISO/TS 21726:2019, Clause 1.

Toxicological screening limits shall apply to the following:

— identified constituent, and

— total quantity of each constituent present in or on or released from the medical device.

NOTE 2 ISO 10993-18 describes information gathering or an extraction study method that results in an estimate of the total quantity of a constituent present in, on or extracted from the medical device.

Toxicological screening limits shall not apply to medical devices used long-term in very young infants or neonates, including preterm, or to the following types of constituents:

— the nature of harm is irritation,

— the cohort of concern substances or excluded compounds, or

— substances that are not identified constituents (i.e. unknown or incomplete chemical identity).

NOTE 3 TSL does not apply to preterm or very young infants (i.e. 6 months of age or younger) because these individuals have unique susceptibilities (Clause 8 and C.2.2.2).

A TSL shall not be applied to volatile compounds from gas pathway devices because inhalation specific TTC values are established in ISO 18562-1 for these constituents.

B.2 Calculation of the TSL

Toxicological screening limits are based on mutagenic TTC values applicable to the duration of exposure to the constituent. The toxicological screening limit can be calculated using Formula (B.1).

$$TSL = TTC \times D \tag{B.1}$$

where

TSL is the toxicological screening limit expressed as the cumulative quantity of exposure, in µg, to a constituent over a specified time period;

D is the duration of exposure, in d, according to ISO 10993-1:2018, 5.3.

When a toxicological screening limit is used, default *TTC* and *D* values in Table B.1 below shall be used to calculate the applicable TSL value and applied in accordance with Clause B.3.

Table B.1 — Default toxicological screening limit *TTC* and *D* for *TSL* calculations

Period of assumed exposure to the constituent d	*TTC* g/d	*D* d	*TSL* µg
≤30	120	1	120 (i.e. 120 µg/d × 1 d)
>30	20	30	600 (i.e. 20 µg/d × 30 d)

NOTE 1 For long-term contact, the duration of exposure is rounded down to 30 d, instead of 31 d.

NOTE 2 The *TTC* and *D* values in Table B.1 are conservative (i.e. lowest values) for dose and time dependent harms (e.g. genotoxicity, cancer, systemic toxicity, reproductive/developmental toxicity, see ISO/TS 21726:2019, 5.1).

B.3 Application of toxicological screening limits

When the TSL approach is used for any medical device, $TSL_{\leq 30\ \mathrm{d}}$ = 120 µg for short-term exposure duration shall be used for each constituent in accordance with Table B.2.

For medical devices in long-term contact with the body, $TSL_{>30\ \mathrm{d}}$ = 600 µg for long-term exposure duration may be used for each constituent in addition to the $TSL_{\leq 30\ \mathrm{d}}$ value, see Table B.2.

Table B.2 — Application of toxicological screening limits for *TQ*

Medical device contact duration	**Periods of assumed exposure to the constituent**		
	1 d	≤30 d	>30 d
Limited (≤1 d)	$TSL_{\leq 30\ \mathrm{d}}$ = 120 µg	Not applicable	Not applicable
Prolonged (≤30 d)	$TSL_{\leq 30\ \mathrm{d}}$ = 120 µg	$TSL_{\leq 30\ \mathrm{d}}$ = 120 µg	Not applicable
Long-term (>30 d)	$TSL_{\leq 30\ \mathrm{d}}$ = 120 µg	$TSL_{\leq 30\ \mathrm{d}}$ = 120 µg	$TSL_{>30\ \mathrm{d}}$ = 600 µg

NOTE Toxicological screening limits are not intended to replace the analytical evaluation threshold (AET) described in ISO 10993-18.

The toxicological screening limit can be used to evaluate the safety of extractables that exceed the AET considering the restrictions defined in Clause B.1.

When the TSL approach is used, the total quantity of each identified chemical constituent to which an individual can be exposed shall be compared to the relevant TSLs in accordance with Table B.2.

For single-use (disposable) medical devices that are repeatedly used and when cumulative duration of body contact is prolonged, the TSL $_{\leq 30\ \mathrm{d}}$ may be used to screen constituents that present negligible toxicological risk for short-term exposure (see EXAMPLE 6). For single-use (disposable) medical devices that are repeatedly used and cumulative duration of body contact is long-term, toxicological risk for each constituent should be assessed in accordance with Clauses 7, 8, 9 and 10.

When the number or quantity of medical devices that contact the body differs from the number or quantity of medical devices used in the extraction study, the total quantity of each identified chemical constituent extracted shall be adjusted by application of a SF using Formula (B.2), unless justified with supporting evidence that the reported total quantity represents a cumulative exposure dose.

$$TQ_{max} = TQ \times SF \tag{B.2}$$

where

TQ_{max} is the maximum total quantity, in µg, to which an individual can be exposed (i.e. cumulative exposure dose);

TQ is the total quantity, in µg, present in or on, or extracted from the medical device (e.g. from an exaggerated or exhaustive extraction study);

SF is the ratio of the quantity (e.g. cm^2, g or ml) of medical devices that are in contact with the body divided by the quantity of medical device(s) used in the extraction study.

When the number of medical devices applies to the intended use (e.g. a hip implant), the maximum number of medical devices that contacts the body and the number of medical devices used in the extractions study shall be used to calculate the SF using Formula (B.3), unless justified with supporting evidence that the reported total quantity represents the cumulative exposure dose.

When the number of medical devices does not apply (e.g. the largest surface area of the medical device that can contact the body is not the same as the surface area of the device which is in contact with the solution during extraction), the maximum quantity (e.g. cm^2, g or ml) of the medical device that is in contact with the body and the quantity of the medical device used in the extraction study shall be used to calculate the SF using Formula (B.3).

$$SF = MD_{\text{b.c.}} / MD_{\text{a.r.s.}} \tag{B.3}$$

where

$MD_{\text{b.c.}}$ is the maximum quantity (e.g. cm^2, g or ml) of medical devices that are simultaneously in contact with the body;

$MD_{\text{a.r.s.}}$ is the quantity of medical devices used in the extraction study.

EXAMPLES 1 to 6 are applications of toxicological screening limits.

EXAMPLE 1 Limited or prolonged contact: When 100 µg of an identified constituent is extracted from a single medical device and a single medical device is in contact with the body for less than or equal to 30 d (not repeatedly used), the application of Formulae (B.1), (B.2) and (B.3) results in a $TSL_{\leq 30\text{ d}}$ of 120 µg.

$$TSL_{\leq 30\text{ d}} = 120 \times 1 = 120\ \mu\text{g}$$

where

120 is the TTC for ≤30 d (see Table B.1), in µg/d;

1 is the number of days for ≤30 d assumed exposure time period (see Table B.1).

$$TQ_{max} = 100 \times 1 = 100\ \mu\text{g}$$

where

100 is the reported total quantity in the extraction solvent (i.e. TQ_{ext}), in µg;

1 is the *SF* where 1 is the maximum number of medical devices that are in contact with the body divided by the single medical device extracted.

Short-term exposure to the constituent is a negligible toxicological risk because TQ_{max} is less than the $TSL_{\leq 30\ d}$.

EXAMPLE 2 Limited or prolonged contact: When 100 µg of an identified constituent is extracted from a single medical device and two medical devices are in contact with the body for less than or equal to 30 d (not repeatedly used), the application of Formulae (B.1), (B.2) and (B.3) results in a $TSL_{\leq 30\ d}$ of 120 µg.

$$TSL_{\leq 30\ d} = 120 \times 1 = 120\ \mu g$$

where

120 is the TTC for ≤30 d (see Table B.1), in µg/d;

1 is the number of days for the ≤30 d assumed exposure time period (see Table B.1).

$$TQ_{max} = 100 \times 2 = 200\ \mu g$$

where

100 is the reported total quantity in the extraction solvent (i.e. TQ_{ext}), in µg;

2 is the *SF* where 2 is the maximum number of medical devices that are in contact with the body divided by the single medical device extracted.

Short-term exposure to the constituent can present a toxicological risk because TQ_{max} is greater than the $TSL_{\leq 30\ d}$.

EXAMPLE 3 Long-term contact: When 300 µg of an identified constituent is extracted from a single medical device and a single medical device is in contact with the body for long-term (i.e. greater than 30 d) (not repeatedly used), the application of Formulae (B.1), (B.2) and (B.3) results in a $TSL_{\leq 30\ d}$ of 120 µg and a $TSL_{>30\ d}$ of 600 µg.

$$TSL_{\leq 30\ d} = 120 \times 1 = 120\ \mu g$$

where

120 is the TTC for ≤30 d (see Table B.1), in µg/d;

1 is the number of days for the ≤30 d assumed exposure time period (see Table B.1).

$$TSL_{>30\ d} = 20 \times 30 = 600\ \mu g$$

where

20 is the TTC for >30 d (see Table B.1), in µg/d;

30 is the number of days for the >30 d assumed exposure time period (see Table B.1).

$TQ_{max} = 300 \times 1 = 300$ µg

where

300 is the reported total quantity in the extraction solvent (i.e. TQ_{ext}), in µg;

1 is the *SF* where 1 is the maximum number of medical devices that are in contact with the body divided by the single medical device extracted.

Short-term exposure to the constituent can present a toxicological risk because TQ_{max} is greater than the $TSL_{\leq 30\ d}$; whereas, long-term exposure to the constituent is a negligible toxicological risk because TQ_{max} is less than the $TSL_{>30\ d}$.

EXAMPLE 4 Long-term contact: When 320 µg of an identified constituent is extracted from a single medical device and two of the same medical devices are in contact with the body at the same time for more than 30 d (not repeatedly used), the application of Formulae (B.1), (B.2) and (B.3) results in a $TSL_{\leq 30\ d}$ of 120 µg and a $TSL_{>30\ d}$ of 600 µg.

$TSL_{\leq 30\ d} = 120 \times 1 = 120$ µg

where

120 is the TTC for ≤30 d (see Table B.1), in µg/d;

1 is the number of days for the ≤30 d assumed exposure time period (see Table B.1)

$\mathrm{TSL}_{>30\ d} = 20 \times 30 = 600$ µg

where

20 is the TTC for >30 d (see Table B.1), in µg/d;

30 is the number of days for the >30 d assumed exposure time period (see Table B.1).

$TQ_{max} = 320$ µg $\times 2 = 640$ µg

where

320 is the reported total quantity in the extraction solvent (i.e. TQ_{ext}), in µg;

2 is the *SF* where 2 is the maximum number of medical devices that are in contact with the body divided by the single medical device extracted.

Short-term and long-term exposure to the constituent can present a toxicological risk because TQ_{max} is greater than the $TSL_{\leq 30\ d}$ and $TSL_{>30\ d}$, respectively.

EXAMPLE 5 Long-term contact: When 300 µg of an identified constituent is extracted from a single medical device (50 cm^2) and two of the same medical devices (200 cm^2 each) are in contact with the body at the same time (i.e. the total device surface area is equal to two devices multiplied by 200 cm^2/device which is 400 cm^2) for more than 30 d (not repeatedly used), the application of Formulae (B.1), (B.2) and (B.3) results in a $TSL_{\leq 30\ d}$ of 120 µg and a $TSL_{>30\ d}$ of 600 µg.

$TSL_{\leq 30\ d} = 120 \times 1 = 120\ \mu g$

where

120 is the TTC for ≤30 d (see Table B.1), in µg/d;

1 is the number of days for the ≤30 d assumed exposure time period (see Table B.1).

$TSL_{>30\ d} = 20 \times 30 = 600\ \mu g$

where

20 is the TTC for >30 d (see Table B.1), in µg/d;

30 is the number of days for the >30 d assumed exposure time period (see Table B.1).

$TQ_{max} = 300 \times 8 = 2\ 400\ \mu g$

where

300 is the reported total quantity in the extraction solvent (i.e. TQ_{ext}), in µg;

8 is the *SF* where 400 cm² is the maximum device surface area, in cm², that is in contact with the body divided by the 50 cm² device surface area extracted.

Short-term and long-term exposure to the constituent can present a toxicological risk because TQ_{max} is greater than the $TSL_{\leq 30\ d}$ and $TSL_{>30\ d}$, respectively.

EXAMPLE 6 Cumulative prolonged contact: When 300 µg of an identified constituent is extracted from a single medical device (50 cm²) that is in contact with the body for less than one day, and a new device is used every day for up to 10 days (i.e. repeat use), the application of Formulae (B.1), (B.2) and (B.3) results in a $TSL_{\leq 30\ d}$ of 120 µg.

$TSL_{\leq 30\ d} = 120 \times 1 = 120\ \mu g$

where

120 is the TTC for ≤30 d (see Table B.1), in µg/d;

1 is the number of days of contact of a single medical device.

$TQ_{max} = 300 \times 10 = 3\ 000\ \mu g$

where

300 is the reported total quantity in the extraction solvent (i.e. TQ_{ext}), in µg;

10 is the *SF* where 50 cm² is the maximum device surface area, in cm², that is in contact with the body divided by the 50 cm² device surface area extracted.

Short-term exposure to the constituent can present a toxicological risk because TQ_{max} is greater than the $TSL_{\leq 30\ d}$.

Annex C
(normative)

Derivation of constituent TI or TCL for select endpoints

C.1 General

The method to derive a non-cancer TI (see Clause C.2), cancer TI (see Clause C.3), or TCL (see Clause C.4) is described in this annex. The methods to derive a TI or TCL shall be applied when toxicological data for a constituent are available, as described in Clause 6 and 7.1.

When toxicological data of a constituent are not available to derive a TI, then TTC shall be applied in accordance with 7.2.

NOTE In this annex, an uncertainty factor approach is described based on References [75] to [85].

C.2 Setting of TI for non-cancer endpoints

C.2.1 General

For each relevant anticipated route and duration of exposure, a TI is calculated from the NOAEL, LOAEL, BMD_L or other value determined to be the POD (see 7.1). Each TI calculation shall account for uncertainty of the data and its extrapolation to intended human exposure.

The TI shall provide protection to the most sensitive individuals with which the medical device is in contact.

NOTE Where a relevant dose-based threshold has been determined by an expert committee or regulatory agency for non-medical device use, it can be adapted for medical device use by applying uncertainty factors to address differences in the circumstances of exposure relevant to the medical device intended use (see C.2.2 for types of uncertainties to consider for medical device uses).

C.2.2 Determination of uncertainty factors

C.2.2.1 General

Sources of uncertainty shall be identified and used in the derivation of the TI. The selection of uncertainty factors that account for sources of uncertainty encompasses many different considerations to meet the requirements in 10.1. These factors consider the uncertainties inherent in estimating the potential effects of a constituent on exposed individual(s) (see Table C.1).

The value of each uncertainty factor shall be documented, with justification for its selection. Some considerations in the selection of the appropriate uncertainty factors include variation among humans, species extrapolations and other uncertainties as described in C.2.2.2 to C.2.2.4[86]to[89].

C.2.2.2 Uncertainty for intraspecies variation, $UF_{(TI)1}$

Intraspecies variation among humans applies to pre-term, paediatric and adults [including elderly or pregnant women, (i.e. including the woman or foetus)] that differ in absorption, metabolism, tissue distribution, excretion, elimination or biological response to constituents of toxicological concern. In the absence of human data to characterize variability among adults or paediatrics (6 months of age or older), a default 10-fold uncertainty factor shall be applied unless otherwise justified with supporting evidence.

NOTE 1 Preterm, neonate, very young infants (i.e. 6 months or younger) and pregnant women (including the woman or foetus) are potentially more vulnerable to constituents of toxicological concern due to differences in developmental (e.g. neurological, immunological, skeletal, reproductive or endocrine) or toxicokinetics (i.e. absorption, metabolism, tissue distribution and excretion)[92] to [95].

When preterm, neonate and very young infants (i.e. 6 months or younger) are exposed to chemical constituents whose main elimination route is hepatic metabolism or renal excretion, an additional threefold uncertainty factor shall be applied to address the immaturity of the metabolic capacity and renal function[90][91].

For infants older than 6 months, a justification of an additional uncertainty factor can be required.

The uncertainty factor that accounts for intraspecies variation shall be justified and documented. An idiosyncratic response shall not serve as the basis for a TI value because justification of an uncertainty factor protective for these individuals is generally not feasible.

NOTE 2 Idiosyncratic means the response is specific to an individual and not the general population[96].

NOTE 3 In some cases, the uncertainty factor for intraspecies variation can be less than 10. For example, when human data indicate intraspecies variation is negligible or when the POD is based on the most sensitive human sub-population.

C.2.2.3 Uncertainty for interspecies differences, $UF_{(TI)2}$

Interspecies uncertainty accounts for extrapolation from data derived in a species other than humans. In the absence of detailed knowledge of interspecies differences in toxicity, a default 10-fold uncertainty factor shall be applied unless otherwise justified with supporting evidence.

When toxicity and toxicokinetics of the constituent are established and similar between human and the experimental model, a smaller uncertainty factor for interspecies differences can be justified with supporting evidence. The uncertainty factor that accounts for interspecies variation shall be justified and documented[89].

C.2.2.4 Uncertainty from the quality and relevance of the experimental data, $UF_{(TI)n}$

$UF_{(TI)n}$ is used in the MF calculation (see C.2.3) when additional uncertainties related to the following apply, which include, but are not limited to:

— use of short-term studies for extrapolation to longer-term exposures or effects (see C.2.2.4.2);

— use of LOAEL data instead of NOAEL data (see C.2.2.4.3);

— use of animal models of uncertain or limited relevance to the medical device user or its intended use (see C.2.2.4.3);

— use of data from different route of exposure (see C.2.2.4.1);

— data quality (see C.2.2.4.3).

Table C.1 provides types of additional uncertainties and ranges to be considered for $UF_{(TI)n}$. Sources and numerical level of uncertainty shall be justified and documented in the report.

Table C.1 — Additional uncertainty factors for consideration in the derivation of a TI

Sources of additional uncertainty	Types of additional uncertainty	$UF_{(TI)n}$	Subclause
Route-to-route	Oral data to dermal application or inhalation to dermal application	1	C.2.2.4.1
	Inhalation to parenteral or inhalation to oral application	1 to 10	
	Oral data to parenteral	1 to 100	
Exposure duration	Subchronic to chronic extrapolation	2 to 6	C.2.2.4.2
	Subacute to chronic extrapolation	6 to 10	
Point-of-departure	LOAEL to NOAEL	3 to 10	C.2.2.4.3
Data applicability	Use of an analogue, state of matter (e.g. gas to solid dose)	1 to 10	
Data quality	Reliability and relevance	1 to 10	

NOTE Accounting for multiple additional uncertainties each at the maximum value (i.e. 10) can result in an excessively high modifying factor, see C.2.3.

C.2.2.4.1 Route-to-route extrapolation

C.2.2.4.1.1 Oral to dermal application or inhalation data to dermal application

When extrapolating a systemic toxicity POD from oral-to-dermal or inhalation-to-dermal exposure routes, a default value of 1 can be justified when absorption and systemic dose by oral or inhalation routes is equivalent or greater than the dermal route. Otherwise, a higher uncertainty factor shall be applied unless justified with supporting evidence[97]to[99].

NOTE For absorbable chemicals, time to C_{max} (i.e. highest concentration) in the systemic circulation is typically shorter for oral exposure compared to dermal exposure[100]to[103].

C.2.2.4.1.2 Inhalation data to parenteral application or inhalation data to oral application

For extrapolation from inhalation to parenteral routes, a default 10-fold uncertainty factor shall be used unless otherwise justified with supporting evidence.

Lower or higher uncertainty factors can be applied when the extent of absorption is known. For volatile and semi-volatile organic constituents, the rate of absorption can be higher than for non-volatile organic constituents and metals. For extrapolation from inhalation to oral routes, an uncertainty factor of 1 can be applied, since lower thresholds derived for inhalation compared to the oral route are due to the lack of a first-pass effect in inhalation studies[104].

C.2.2.4.1.3 Oral data to parenteral application

Oral bioavailability UFs adjust the quantity of constituent in the gastrointestinal tract that is absorbed. When extrapolating an oral POD of a constituent to parenteral exposure route (e.g. intravenous) based on its bioavailability, the impact of pre-systemic metabolism on the systemic dose and nature of harm (e.g. an ingested constituent that is metabolized by the liver to lesser toxic products) shall be justified and documented.

When a POD from an oral toxicity study is extrapolated to parenteral exposure routes (e.g. intravenous), the following uncertainty factors based on oral bioavailability data (if available) can be used[105]:

— $UF_{(TI)n}$ = 100 if oral bioavailability is <1 %,

— $UF_{(TI)n}$ = 10 if oral bioavailability is ≥1 % and <50 %,

— $UF_{(TI)n}$ = 2 if oral bioavailability is ≥50 % and <90 %, or

— $UF_{(TI)n}$ = 1 if oral bioavailability is ≥90 %.

Alternatively, an oral POD can be extrapolated by multiplying by the percent of oral bioavailability. When a range of oral bioavailability data are reported, the lower limit shall be used.

Extrapolation of a POD from an oral toxicity study to parenteral exposure routes based on the above oral bioavailability UF or percent oral bioavailability shall be justified with supporting oral bioavailability data.

If oral bioavailability is not known, a default value of 10 can be used[106]to[108].

C.2.2.4.2 Exposure duration

When short-term repeat exposure studies are used for extrapolation to longer-term exposures, time-dependent toxicities, or accumulation of the constituent in the body can occur. For extrapolation from a subchronic study to chronic exposure, a default sixfold uncertainty factor shall be applied unless otherwise justified with supporting evidence.

For extrapolation from subacute studies to chronic exposure, a default 10-fold uncertainty factor shall be applied unless otherwise justified with supporting evidence.

An uncertainty factor of 10 should be applied when the dose-response curve is shallow or unknown.

NOTE In general, a shallow dose-response curve applies when the magnitude of the harm is only slightly higher at a higher dose compared to the same harm that occurs at a lower dose of the same constituent. A BMD_L value near the origin of the dose-response curve indicates the dose-response curve is shallow.

Higher uncertainty factors may be considered when toxicity increases over time and constituents accumulate in the body[88][89][94][109][110][111][112][113].

C.2.2.4.3 Point of departure, data applicability and data quality

Uncertainty in the applicability of toxicological data from an analogue should also be considered. The magnitude of this UF should account for the extent of structural and biological similarity between the analogue and the extracted compound of interest. When accounting for the quality of constituent specific or analogue toxicological data used to derive the TI, for studies judged to be well designed for their intended purposes and executed properly, a default uncertainty factor of 1 can be selected. A default 10-fold uncertainty factor shall be applied when the selected POD is obtained from a toxicological study with reduced reliability or relevance[114][115].

Examples of when a 10-fold default UF for data quality or relevance can be applied include:

— to account for the absence of clinically relevant toxicity data pertaining to the patient population (e.g. reproductive or developmental toxicity for a device used in pregnant women), or

— when the POD is obtained from an underpowered study (low numbers of animals or only in one sex) or limited number of organs collected for evaluating potential harm.

C.2.3 Determination of the modifying factor

The modifying factor shall be calculated as the product of all uncertainty factors identified in accordance with C.2.2.2 to C.2.2.4, as shown in Formula (C.1).

$$MF = UF_{(TI)1} \times UF_{(TI)2} \times UF_{(TI)n} \quad \text{(C.1)}$$

where MF is the modifying factor.

The application of a large MF (e.g. >10 000 for the general population) can overestimate a toxicological risk. In these cases, toxicological risk shall be assessed by applying TTC in accordance with 7.2, or further analyse or control the toxicological risk, see 10.2.

C.2.4 Derivation of the non-cancer TI value

After the POD (NOAEL, LOAEL, etc.) and the modifying factor are determined, the TI shall be calculated in amount (mg or µg) per kilogram body mass per day, as shown in Formula (C.2).

$$TI = POD / MF \tag{C.2}$$

C.3 Setting of TI for cancer endpoints

C.3.1 General

When human data are inadequate, the determination that a constituent can be a suspected human carcinogen shall be based on the weight of evidence. Types of data used in weight of evidence include:

— carcinogenicity data from long-term in vivo animal studies (e.g. pre-neoplastic lesions or tumour findings in animal studies);

— mechanistic data (e.g. genotoxicity or other modes of action involving other key characteristics).

For constituents that are not human carcinogens or suspected human carcinogens, the approach in Clause 7 shall be applied.

NOTE 1 Mechanistic data can be useful in a weight of evidence assessment to establish whether cancer can be associated with a specified exposure dose (e.g. non-linear)[116][117][118].

NOTE 2 Key characteristics include chemical properties and biological activities that are important elements of the constituent's carcinogenic mode of action. Reported key characteristics include

a) electrophilic or metabolically activated,

b) genotoxic,

c) alters DNA repair or makes the genome unstable,

d) induces of epigenetic changes,

e) induces oxidative stress,

f) induces chronic inflammation,

g) immunosuppressive,

h) modulates receptor-mediated effects,

i) causes cell immortalization, and

j) causes cellular proliferation or cell death, or impairs the supply of nutrients[119].

C.3.2 Cancer risk estimation

C.3.2.1 General

When a chemical constituent is a human carcinogen or suspected human carcinogen, cancer risk shall assess whether an exposure to a human carcinogen or suspected human carcinogen dose is at a tolerable cancer risk level.

When the constituent TI is based on a cancer risk estimate, the MoS calculation shall apply a cancer risk threshold that is protective for a lifetime of exposure (e.g. 70 years), unless otherwise justified.

Other approaches used to evaluate the cancer risk of a constituent shall be justified and documented.

C.3.2.2 Slope-factor approach

Cancer risk can be estimated based on a constituent specific slope factor (if available). The slope factor, which is used to calculate [see Formula (C.3)] the dose that corresponds to a default lifetime cancer risk level of 1 in 100 000 (i.e. cancer risk specific dose), shall be used as the TI value for cancer, unless otherwise justified with supporting evidence[120].

$$CRSD = CRL / SlF \tag{C.3}$$

where

CRSD is the cancer risk specific dose, in mg/kg/d;

CRL is the cancer risk level;

SlF is the slope factor, in $(\text{mg/kg/d})^{-1}$.

NOTE Application of a slope factor means the dose-response relationship at low doses is linear (i.e. non-threshold mode of action). When a slope factor is used to estimate cancer risk, additional uncertainty factors are not applied to derive the cancer risk specific dose.

EXAMPLE The lifetime oral cancer risk specific dose for benzene is:

— $SlF = 0{,}015\ (\text{mg/kg/d})^{-1}$[121];

— $CRL = 1$ in 100 000 (i.e. 1×10^{-5});

— $CRSD = 1 \times 10^{-5} / 0{,}015 = 6{,}667 \times 10^{-4}$ mg/kg/d.

C.3.2.3 TD_{50} approach

When a slope factor for a human carcinogen or suspected human carcinogen is not available, an alternative cancer risk approach can be based on a constituent specific TD_{50} value (if available) as shown in Formula (C.4)[74].

$$CRSD = TD_{50} / 50\ 000 \tag{C.4}$$

where

TD_{50} is the daily dose-rate, in µg/kg body mass/d, for life, to induce tumours in half of test animals that would have remained tumour-free at zero dose;

50 000 is an assumed value for estimating lifetime cancer risk level of 1 in 100 000.

NOTE When a TD_{50} is used to estimate cancer risk, additional uncertainty factors are not applied to derive the cancer risk specific dose.

Other approaches used to evaluate cancer risk of a constituent shall be justified and documented.

C.4 Establishment of tolerable contact levels

C.4.1 General

A review of constituent irritation data provides the information necessary to decide whether estimation of the irritation risk needs to be assessed according to this document. If constituent specific irritation information is available and applicable to the intended use of the medical device, a modifying-factor approach can be used to derive a constituent specific *TCL* that represents acceptable irritation risk[19][20][84][91][103].

NOTE *TCL*s are considered in addition to tolerable intakes unless justified and documented.

This approach is not intended for the derivation of *TCL* values based on allergic contact dermatitis or local effects, except for irritation in anatomically or pharmacokinetically isolated organs (e.g. brain, eye).

C.4.2 Setting of TCL for the irritation endpoint

For each relevant contact tissue, a TCL shall be calculated from the NIL.

Each *TCL* calculation shall consider the degree of irritation from increasing concentrations of non-irritating doses whenever these data are available.

A modifying-factor approach shall be used to calculate the *TCL*. This approach incorporates the use of a modifying factor as described in C.4.4. Formula (C.5) calculates the *TCL*, in µg/cm^2, using the modifying-factor approach.

$$TCL = NIL / MF_{\mathrm{TCL}} \tag{C.5}$$

where

- NIL is the non-irritating level from the study where the threshold was experimentally identified and reported, in µg/cm^2;
- MF_{TCL} is the modifying factor.

NOTE When a NIL is absent, a MIL can be used, see C.4.3.4.

Irritation limits should be established based upon the broadest segment of exposed individuals. When the *TCL* is intended for specific subpopulations, the applicable data (e.g. clinical data) should be used for the specific individuals for which the device is intended.

C.4.3 Determination of TCL uncertainty factors

C.4.3.1 General

The methods used to determine the biological risk of irritation are different from those used to determine the biological risk of systemic toxicity. The chief difference is the degree of uncertainty. Normally, when irritation is not observed in an appropriate test model, irritation is less probable for humans. Hence, there is a more limited use of multiple uncertainty factors and large margins of safety. Nevertheless, the choice of uncertainty factors should encompass several considerations described in C.4.3.2, C.4.3.3 and C.4.3.4.

C.4.3.2 Uncertainty for intraspecies variation, $UF_{(\mathrm{TCL})1}$

Uncertainty among humans shall be addressed when deriving a TCL value. It is always preferable to have actual data to assess human variation.

In the absence of experimental data to characterize individual variability in human response to an irritating leachable substance, a default 10-fold uncertainty factor, $UF_{(\mathrm{TCL})1}$, shall be applied, unless otherwise justified with supporting evidence. For example, other uncertainty factors, $UF_{(\mathrm{TCL})1}$, ranging from 3 to 9 can be used if justified when the MIL or NIL is based on animal studies.

C.4.3.3 Uncertainty for interspecies differences, $UF_{(\mathrm{TCL})2}$

Uncertainty resulting from inherent differences between other species and humans shall be addressed. It is always preferable to have data and detailed knowledge of the relationship between humans and the test species.

In the absence of such information, a default 10-fold uncertainty factor, $UF_{(\mathrm{TCL})2}$, shall be used unless otherwise justified with supporting evidence.

C.4.3.4 Uncertainty from the quality and relevance of experimental data, $UF_{(TCL)n}$

Uncertainty resulting from the quality and relevance of the experimental data shall be addressed.

When a MIL is used, a default threefold uncertainty factor, $UF_{(TCL)n}$, shall be applied unless otherwise justified with supporting evidence.

A UF of 9 shall be applied when conclusions are drawn based upon a poorly designed or executed study, or when the amount of relevant constituent specific irritation data is limited.

C.4.4 Determination of the TCL modifying factor

The TCL modifying factor, MF_{TCL}, shall be calculated as a product of the uncertainty from C.4.3 as given in Formula (C.6).

$$MF_{TCL} = UF_{(TCL)1} \times UF_{(TCL)2} \times UF_{(TCL)n} \tag{C.6}$$

Formula (C.5) shall serve as the basis for the TCL. In most cases, an overall modifying factor of 30 or less should be sufficient but can be larger when non-irritating concentrations have not been established.

Annex D
(informative)

Typical assumptions for biological parameters

D.1 General

This annex provides parameters for use in assessing risk. It specifies the lifespan, daily intake of water, daily intake of air, body mass and gestation period for the human, rat, mouse, hamster, guinea pig, dog and rabbit. These are the most common species for which data are available. This data can serve as the basis for interspecies comparisons unless other data can be shown to be more appropriate. Actual species data vary somewhat in the real world.

D.2 Assumptions

D.2.1 Human

The parameters for humans:

— 70-year lifespan;

— 2 l/d intake of drinking water;

— 20 m^3/24 h day air intake (adult); 10 m^3/d in 8 h workday (adult)[122];

— 70 kg body mass for adult men; 60 kg for adult women, which is also representative of all adults in a worst-case assumption;

— 10 kg for children (>1 year to ≤16 years of age); 3,5 kg for infants (<1 year); 1,5 kg for very low birthweight infants; or 0,5 kg for very low birthweight neonates (e.g. preterm neonate);

— 9-month (normally 40 weeks) gestation period;

— 5 l blood volume (adult).

NOTE 1 Body mass of 70 kg and 60 kg for an adult male, and adult female or unisex, respectively, are conservative for exposure dose estimation because these values are below the average for these sex-based groups (e.g. a medical device use that is intended for all adults)[123]. A body mass of 50 kg, or lower, for adults can be used when a more conservative approach is judged to be necessary (e.g. patients with below average body mass, such as: individuals of low stature or malnutrition due to an eating disorder, cancer or AIDS).

NOTE 2 When the medical devices intended use is for a wide range of general patients, the use of infant body mass (3,5 kg) is sufficiently conservative to calculate the EED_{max} for infants and the general population. When the medical device intended to use is for low birthweight neonates, the use of 0,5 kg is sufficiently conservative to calculate the EED_{max} for this subpopulation.

D.2.2 Rat

The parameters for rats are:

— 2-year lifespan;

— 0,025 l/d of drinking water for males; 0,020 l/d for females;

— 0,29 m^3/24 h day air intake;

— 0,25 kg or 0,5 kg body mass for young and older adult males, respectively; 0,2 kg or 0,35 kg for young and older adult females, respectively[124];

— 22 d gestation period.

D.2.3 Mouse

The parameters for mice are:

— 2-year lifespan;

— 0,005 l/d of drinking water;

— 0,043 m^3/24 h day air intake;

— 0,03 kg body mass for adult males, 0,025 kg for adult females;

— 20 d gestation period.

D.2.4 Hamster

The parameters for hamsters are:

— 2-year lifespan;

— 0,015 l/d of drinking water;

— 0,086 m^3/24 h day air intake;

— 0,125 kg body mass for adult males; 0,110 kg for adult females;

— 15 d gestation period.

D.2.5 Guinea pig

The parameters for guinea pigs are:

— 3-year lifespan;

— 0,085 l/d of drinking water;

— 0,43 m^3/24 h day air intake;

— 0,5 kg body mass;

— 68 d gestation period.

D.2.6 Dog

The parameters for dogs are:

— 11-year lifespan;

— 0,5 l/d of drinking water;

— 7,5 m^3/24 h day air intake;

— 16 kg body mass;

— 63 d gestation period.

D.2.7 Rabbit

The parameters for rabbits are:

— 7-year lifespan;

— 0,33 l/d drinking water;

— 1,44 m^3/24 h day air intake;

— 3 kg body mass;

— 31 d gestation period.

Annex E
(normative)

Estimation of an exposure dose

E.1 General

A worst-case estimated exposure dose, EED_{max}, for each reportable constitutent shall be estimated in accordance with this annex, based on ISO 10993-18 constituent data, unless otherwise justified with supporting evidence.

NOTE 1 Information gathering of constituents intentionally used in the manufacture of the medical device or its materials of construction can be used to represent the total quantity of a constituent present in, on or can be extracted from the medical device. Exaggerated, exhaustive or simulated-use extractions that are conservative relative to the medical device intended use can be assumed to represent a total quantity that can be extracted. Simulated-use extraction or leachable studies, during which data are collected at multiple time-points, can provide (when appropriately justified) release kinetics information for limited, prolonged or long-term contact medical devices.

NOTE 2 ISO 10993-18 describes approaches for obtaining constituent exposure information, which includes when to consider conducting a simulated-use, leachable or other type of extraction study.

NOTE 3 Constituent information from the literature can be used for exposure dose estimation when appropriately justified, see ISO 10993-18:2020, 5.2.2.

NOTE 4 The quantity of a constituent extracted from a medical device and suitable for calculating a worst-case estimated exposure dose is dependent on extraction and analytical parameters, such as the number of medical devices used as the test article, the method used in the preparation of the test article, the solvent(s) type and volume, the temperature, the duration of extraction, the number of extraction cycles (if applicable) and the reference standard used for quantification[23].

When calculating a worst-case estimated exposure dose of a medical device constituent, the following criteria shall be applied.

a) When TSL is not used, worst-case estimated exposure doses shall be estimated for the following time periods and medical device contact categories, unless otherwise justified:

— <1 d for limited, prolonged and long-term contacting medical devices,

— 2 d to 30 d for prolonged and long-term contacting medical devices,

— 31 d to 365 d for long-term contacting medical devices that contact the body for <1 year, and

— >366 d for long-term contacting medical devices that contact the body for >1 year.

b) When TSL is used in accordance with 6.2.1 and the total quantity of a chemical constituent that is present or can be extracted from medical device exceeds the $TSL_{\leq 30\ d}$ value but is less than the $TSL_{>30\ d}$ value, then a worst-case estimated exposure dose shall be estimated for the following time periods and applicable medical device contact categories, unless otherwise justified:

— <1 d for limited, prolonged or long-term contacting medical devices, and

— 2 d to 30 d for prolonged or long-term contacting medical devices.

c) When TSL is used in accordance with 6.2.1 and the total quantity of a chemical constituent that is present or can be extracted from a long-term contacting medical device is above the $TSL_{>30\ d}$ value, then the worst-case estimated exposure dose shall be estimated for all four time periods, unless otherwise justified.

When two or more constituents elicit the same harm at the same target organ or system and have the same TI, the individual estimated exposure doses for each of the applicable constituents shall be summed.

E.2 Exposure dose estimation based on release kinetics information

Exposure dose estimation based on release kinetics information shall be applied to identified constituents using a reference standard suitable for accurate quantification and targeted chemical analysis.

When the medical device is categorized as limited contact with the body, or release kinetics data are available for a prolonged or long-term contact medical device, the exposure dose shall be calculated using Formula (E.1).

$$EED_{max} = (HQ_{r.k.} \times SF_{r.k.}) / BW_L \tag{E.1}$$

where

EED_{max} is the estimated exposure dose that represents worst-case exposure of a constituent;

$HQ_{r.k.}$ is the highest measured quantity, in µg/d, released in a day during a release kinetics study that includes data collection for the time periods from Table E.1;

$SF_{r.k.}$ is the ratio of the number or quantity (in cm^2, g or ml) of medical devices that are in contact with the body divided by the number or quantity of medical devices used in the extraction study;

BW_L is the lowest body mass, in kg, of an individual in contact with the medical device.

When the number of medical devices that contacts the body differs from the number of medical device(s) used in the release-kinetics study, the reported $HQ_{r.k.}$ does not represent the worst-case estimated exposure dose. To account for the difference between medical device intended use and the release kinetics study, the reported $HQ_{r.k.}$ of each constituent assessed shall be adjusted by the application of a scaling factor, $SF_{r.k.}$, using Formula (E.2).

When the number of medical devices does not apply (e.g. the largest surface area of device which can be in contact with the body is not the same as the surface area of the device which is in contact with the solution during extraction), the maximum quantity (in cm^2, g or ml) of the medical device that is in contact with the body and the quantity of the medical device used in the extraction study shall be used to calculate the $SF_{r.k.}$ using Formula (E.2).

$$SF_{r.k.} = MD_{b.c.} / MD_{r.k.s} \tag{E.2}$$

where

$MD_{b.c.}$ is the maximum number or quantity (in cm^2, g or ml) of medical devices that are simultaneously in contact with the body;

$MD_{r.k.s.}$ is the number or quantity of medical devices used in the release kinetic study.

When the quantity of the medical device used varies, the worst-case (highest) $SF_{r.k.}$ to BW_L ratio shall be used, unless otherwise justified with supporting evidence.

The selection of specific time periods used for $HQ_{r.k.}$ evaluation shall be documented and justified with the medical device category and applicable time periods in accordance with Table E.1, unless otherwise justified with supporting evidence. Selection of specific days for analysis within a Table E.1 time period should consider the constituent's expected rate of release, duration of release and quantity extracted at each time point [i.e. above or below a TCL, TI, TTC (if applicable) or analytical limit (if applicable)].

Table E.1 — Selection of time periods for the evaluation of $HQ_{r.k.}$

Medical device category	Time period for obtaining release kinetics data			
	≤1 d	2 d to 30 d	31 d to 365 d	≥366 d
Limited (≤1 d)	X	Not applicable	Not applicable	Not applicable
Prolonged (2 d to 30 d)	X	X	Not applicable	Not applicable
Long-term (31 d to 365 d)	X	X	X	Not applicable
Long-term (≥366 d)	X	X	X	X
X indicates that release data is required, or a justification for excluding it, for this medical device category and time period.				

NOTE 1 Expected rate and duration of release can be based on the constituent's physicochemical characteristics (e.g. solubility, polarity, lipophilicity, and molecular weight), feasibility of release (e.g. diffusivity of an additive embedded in the medical device versus impurity present on device surface), temperature and TQ when such data are available.

The number of time points within an exposure period shall be sufficient to address late bolus release of the constituent(s), unless justified with supporting evidence that late bolus release will not occur.

NOTE 2 Late bolus release of a chemical constituent is the release of a higher quantity after the initial or steady-state release. For example, late bolus release of a chemical constituent can occur when the medical device degrades (e.g. wear/corrosion of a material of construction) over multiple days (e.g. prolonged or long-term).

When the HQ of a constituent is obtained by extraction and quantification methods that are conservative relative to the medical device intended use, the HQ of each constituent may be assumed to be adequate to calculate a worst-case estimated exposure dose, EED_{max}.

When the HQ of a reportable constituent does not represent the highest measured quantity released in a day based on the extraction and quantification methods used, the toxicological risk of a constituent should be addressed by other means according to ISO 10993-1 and ISO 14971.

EXAMPLES 1 and 2 give exposure dose estimation based on release kinetics information.

EXAMPLE 1 Constituent release is quantified for multiple days (i.e. same device is repeatedly extracted for 24 h using fresh solvent). The medical device intended use information includes the following:

— externally communicating and prolonged contact;

— body contact is daily for 25 d;

— a single medical device is in contact with the body of a patient;

— the test article extracted is a single final medical device of largest configuration;

— used in adults only (BW_L = 60 kg, unisex);

— $SF_{r.k.}$ = 1 (i.e. 1 device is used per patient and 1 device was used in the extract).

The quantities extracted each day and calculated daily worst-case exposures, per Formula (E.1), are presented in Table E.2.

Table E.2 — Clause E.2, EXAMPLE 1 — EED_{max} values for a constituent per Formula (E.1)

Time period d	Extraction day	$HQ_{r.k.}$ µg	EED_{max} µg/kg/d	Formula (E.1)
≤1	1	12 000	200	200 µg/kg/d = (12 000 × 1) / 60
2 to 25	2	1 500	25	25 µg/kg/d = (1 500 × 1) / 60
	3	200	3,3	3,3 µg/kg/d = (200 × 1) / 60
	4	<*LOD*	Not applicable	Not applicable
Extraction duration is 24 h at 37 °C. $SF_{r.k.}$ = 1 BW_L = 60 kg				

The EED_{max} values of 200 µg/kg/d and 25 µg/kg/d (i.e. highest in each time period) are used to assess toxicological risk of the constituent for the two time periods (i.e. ≤1 d and 2 d to 25 d, respectively).

EXAMPLE 2 Constituent release is quantified for multiple days (i.e. same device is repeatedly extracted for 24 h using fresh solvent). Device intended use information is the following:

— externally communicating and prolonged contact;

— body contact is daily for 10 d (maximum);

— used in adults only (BW_L = 60 kg, unisex);

— up to 5 devices are in contact with the body of a patient;

— the medical device configuration with the largest surface area is 150 cm^2;

— the test article extracted is representative of the final device with a surface area of 100 cm^2;

— $SF_{r.k.}$ is 7,5 (i.e. 5 × 150 cm^2 / 100 cm^2).

The quantities extracted each day and calculated daily worst-case exposures, per Formula (E.1), are presented in Table E.3.

Table E.3 — Clause E.2, EXAMPLE 2 — EED_{max} values for a constituent per Formula (E.1)

Time period d	Extraction day	$HQ_{r.k.}$ µg	EED_{max} µg/kg/d	Formula (E.1)
≤1	1	12 000	1 500	1 500 µg/kg/d = (12 000 × 7,5) / 60
2 to 10	2	1 500	187	187 µg/kg/d = (1 500 × 7,5) / 60
	3	500	62,5	62,5 µg/kg/d = (500 × 7,5) / 60
	4	200	25	25 µg/kg/d = (200 × 7,5) / 60
	5	<*LOD*	Not applicable	Not applicable
Extraction duration is 24 h at 37 °C. $SF_{r.k.}$ = 7,5 BW_L = 60 kg				

The EED_{max} values of 1 500 µg/kg/d and 187 µg/kg/d are used to assess toxicological risk for the two time periods (i.e. ≤1 d and 2 d to 10 d, respectively).

E.3 Worst-case exposure dose estimation based on maximum release

E.3.1 General

When the medical device contact is categorized as prolonged or long-term contact and release kinetics data are not available, the exposure dose can be calculated using Formula (E.3). For limited contact medical devices, calculation of the worst-case estimated exposure dose shall be performed in accordance with Clause E.2.

$$EED_{max} = (TQ \times SF_{a.r.}) / BW_L / R_d \quad (E.3)$$

where

- EED_{max} is the estimated exposure dose that represents worst-case exposure of a constituent;
- TQ is the total quantity, in µg, present in or on, or extracted from the medical device (e.g. from an exaggerated or exhaustive extraction study);
- $SF_{a.r.}$ is the scaling factor applied when the assumed release is used;
- BW_L is the lowest body mass, in kg, of an individual in contact with the medical device;
- R_d is the assumed release duration, in d, (i.e. lowest number of medical device exposure days), considering the ISO 10993-1 exposure category applicable to the medical device.

Assumed (i.e. default) release durations, R_d, shall be applied based on the shortest duration of constituent exposure of each period of assumed exposure as presented in Table E.4, unless otherwise justified with supporting evidence.

Table E.4 — Selection of default R_d values

Medical device contact duration category	R_d for each time period of assumed constituent exposure d			
	≤1 d	2 d to 30 d	31 d to 365 d	≥366 d
Prolonged (≤30 d)	1	2	Not applicable	Not applicable
Long-term (31 d to 365 d)	1	2	31	Not applicable
Long-term (≥366 d)	1	2	31	366
R_d value indicates when it is used to calculate a worst-case estimated exposure dose unless otherwise justified.				

NOTE 1 Conservatively, chronic exposure for humans ranges from 365 d to a lifetime.

NOTE 2 Selecting the fewest number of days that the medical device contacts the body in each medical device contact category is a conservative approach for exposure dose estimation.

When the number of medical devices that contacts the body differs from the number of medical device(s) used in the extraction study, then the reported $TQ_{a.r.}$ will not represent the worst-case estimated exposure dose. To account for the difference between medical device intended use and the extraction study, the reported $TQ_{a.r.}$ of each constituent assessed shall be adjusted by application of a scaling factor, $SF_{a.r.}$, using Formula (E.4).

When the number of medical devices does not apply (e.g. the largest surface area of device which can be in contact with the body is not the same as the surface area of the device which is in contact with the solution during extraction), the maximum quantity (in cm^2, g, or ml) of the medical device that contacts the body and the quantity of the medical device used in the extraction study shall be used to calculate the $SF_{a.r.}$

$$SF_{a.r.} = MD_{b.c.} / MD_{a.r.s} \quad (E.4)$$

where

$MD_{b.c.}$ is the maximum number or quantity (in cm^2, g, or ml) of medical devices that simultaneously contact the body;

$MD_{a.r.s.}$ is the number or quantity of medical devices used in the extraction study.

When the TQ of a constituent is obtained by extraction and quantification methods that are conservative relative to the medical device intended use, the TQ of each reportable constituent may be assumed to represent a cumulative exposure dose and adequate for calculating a worst-case estimated exposure dose, EED_{max}.

When the TQ of a reportable constituent that can be extracted does not represent a cumulative exposure dose based on the extraction and quantification methods used, the toxicological risk of a constituent should be addressed by other means according to ISO 10993-1 and ISO 14971.

For single-use (disposable) medical devices where the cumulative exposure duration can exceed 30 d, the default R_d value in Table E.4 that applies to the contact duration of a new single-use medical device shall be used for each time period of assumed constituent exposure greater than 1 d, unless otherwise justified with supporting exposure information (i.e. the design of the extraction study and the worst-case exposure scenario), see EXAMPLES 2, 3, and 4.

NOTE 3 The toxicological risk of a medical device constituent can be underestimated when an R_d higher than 2 is used for a repeatedly used single-use (disposable) limited or prolonged contacting medical device where the cumulative exposure duration can exceed 30 d.

When the size or the quantity of the medical devices used varies depends on individual size, the worst-case (highest) $SF_{a.r.}$ to BW_L ratio should be used.

EXAMPLE 1 to 4 give the exposure dose estimation based on the assumed maximum release.

EXAMPLE 1 Constituent TQ is obtained from formulation and manufacturing process data or by exhaustively extracting the medical device using analytically expedient solvents. The medical device intended use information includes the following:

— implanted, tissue or bone, and long-term contact;

— body contact is daily for more than 10 years;

— used in adults only (BW_L = 60 kg, unisex);

— up to 2 medical devices can be implanted during a patient's life;

— the medical device configuration with the largest surface area is 150 cm^2;

— the test article extracted is representative of the final device with a surface area of 100 cm^2;

— $SF_{a.r.}$ is 3 (i.e. 3 = 2 × 150 / 100);

— TQ present or extracted is 10 000 µg.

The calculated daily worst-case estimated exposure doses, per Formula (E.3), and considering that TQ represents the cumulative quantity released daily for all exposure periods, are presented in Table E.5.

Table E.5 — Clause E.3, EXAMPLE 1 — EED_{max} values per Formula (E.3) for long-term tissue/bone implant

Time period d	TQ µg	R_d d	EED_{max} µg/kg/d	Formula (E.3)
≤1	10 000	1	500	500 µg/kg/d = (10 000 × 3) / 60/ 1
2 to 30	10 000	2	250	250 µg/kg/d = (10 000 × 3) / 60 / 2
31 to 365	10 000	31	16	16 µg/kg/d = (10 000 × 3) / 60 / 31
≥366	10 000	366	1,4	1,4 µg/kg/d = (10 000 × 3) / 60 / 366
$SF_{a.r.}$ = 3				

The EED_{max} values of 500 µg/kg/d, 250 µg/kg/d, 16 µg/kg/d, and 1,4 µg/kg/d are used to assess toxicological risk for each time period, respectively, of assumed constituent exposure.

EXAMPLE 2 Constituent TQ is obtained from formulation and manufacturing process data or by exaggerated extraction of five single-use (disposable) medical devices using analytically expedient solvents. The medical device intended use information includes the following:

— body contact is in a breached or compromised surface;

— body contact duration of a new medical device is limited (≤24 h);

— cumulative exposure duration from repeat use is more than 30 days (i.e. long-term);

— used in adults only (BW_L = 60 kg, unisex);

— five new medical devices are used each day;

— the test article extracted is representative of the final device;

— $SF_{a.r.}$ is 1 (i.e. the number of medical devices extracted, 5, is equal to the number of medical devices that are in contact with the body, 5);

— TQ of a constituent present or extracted from the five medical devices is 900 µg.

The calculated daily worst-case estimated exposure doses, per Formula (E.3), and considering that TQ represents the cumulative quantity released daily for all exposure periods, are presented in Table E.6.

Table E.6 — Clause E.3, EXAMPLE 2 — EED_{max} values per Formula (E.3) for a single-use (disposable) device with cumulative long-term exposure from repeat use every 24 h

Time period d	TQ µg	R_d d	EED_{max} µg/kg/d	Formula (E.3)
≤1	900	1	15	15 µg/kg/d = (900 × 1) / 60 / 1
2 to 30	900	1	15	15 µg/kg/d = (900 × 1) / 60 / 1
31 to 365	900	1	15	15 µg/kg/d = (900 × 1) / 60 / 1
≥366	900	1	15	15 µg/kg/d = (900 × 1) / 60 / 1
Exaggerated extraction at 50 °C; $SF_{a.r.}$ = 1; BW_L = 60 kg				

The EED_{max} values of 15 µg/kg/d, 15 µg/kg/d, 15 µg/kg/d and 15 µg/kg/d are used to assess the toxicological risk of the constituent for each time period, respectively, of assumed constituent exposure.

EXAMPLE 3 Constituent TQ is obtained from formulation and manufacturing process data or by exaggerated extraction of the medical device using analytically expedient solvents. The medical device intended use information includes the following:

— single-use (disposable) medical device in a breached or compromised surface;

— contact duration of a new medical device is 3 d;

— cumulative exposure duration from repeat use is more than 30 days (i.e. long-term);

— used in adults only (BW_L = 60 kg, unisex);

— 1 new medical device is used per procedure;

— the test article extracted is representative of the final device;

— $SF_{a.r.}$ is 1 (i.e. the number of medical devices extracted, 1, is equal to the number of medical devices that are in contact with the body, 1);

— TQ of a constituent present or extracted is 1 200 µg.

The calculated daily worst-case estimated exposure doses, per Formula (E.3), and considering that TQ represents the cumulative quantity released daily for all exposure periods, are presented in Table E.7.

Table E.7 — Clause E.3, EXAMPLE 3 — EED_{max} values per Formula (E.3) for a single-use (disposable) device with cumulative long-term exposure from repeat use every 3 d

Time period d	TQ µg	R_d d	EED_{max} µg/kg/d	Formula (E.3)
≤1	1 200	1	20	20 µg/kg/d = (1 200 × 1) / 60 / 1
2 to 30	1 200	2	10	10 µg/kg/d = (1 200 × 1) / 60 / 2
31 to 365	1 200	2	10	10 µg/kg/d = (1 200 × 1) / 60 / 2
≥366	1 200	2	10	10 µg/kg/d = (1 200 × 1) / 60 / 2
Exaggerated extraction for 3 d at 50 °C; $SF_{a.r.}$ = 1; BW_L = 60 kg.				

The EED_{max} values of 20 µg/kg/d, 10 µg/kg/d, 10 µg/kg/d, and 10 µg/kg/d are used to assess toxicological risk of the constituent for each of the time periods, respectively, of assumed constituent exposure.

EXAMPLE 4 Constituent TQ is obtained from formulation and manufacturing process data or by exhaustive extraction of the medical device using analytically expedient solvents. The medical device intended use information includes the following:

— single-use (disposable) medical device in a breached or compromised surface;

— contact duration of a new medical device is 60 days (i.e. long-term);

— cumulative exposure duration from repeat use is more than 2 years;

— used in adults only (BW_L = 60 kg, unisex);

— 1 new medical device is used per procedure;

— the test article extracted is representative of the final device;

— $SF_{a.r.}$ is 1 (i.e. the number of medical devices extracted, 1, is equal to the number of medical devices that are in contact with the body, 1);

— TQ of a constituent present or extracted is 10 400 µg.

The calculated daily worst-case estimated exposure doses, per Formula (E.3), and considering that TQ represents the cumulative quantity released daily for all exposure periods, are presented in Table E.8.