TECHNICAL SPECIFICATION

ISO/TS 21726

First edition
2019-02

Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents

Évaluation biologique des dispositifs médicaux — Application du seuil de préoccupation toxicologique (TTC) pour évaluer la biocompatibilité des substances extractibles des dispositifs médicaux

Reference number
ISO/TS 21726:2019(E)

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Published in Switzerland

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*.

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.

Biological evaluation of medical devices — Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents

1 Scope

This document describes the basis for, selection of, and general applicability of a threshold of toxicological concern (TTC) value for a constituent present in/on a medical device or released from a medical device. The TTC values in this document can be used for:

— comparing to a maximum concentration of an identified or unidentified constituent in an extract (see ISO 10993-18);

— supporting toxicological equivalence;

— comparing to a maximum exposure dose estimate of an identified constituent (see ISO 10993-17).

NOTE Constituent is defined in 3.1.

ISO 10993-18 specifies how to convert TTC (µg/d) into a concentration (µg/ml).

TTC is not applicable to constituents with adequate toxicity data for deriving a tolerable intake (TI) value (see ISO 10993-17).

The TTC values established in this document are protective for carcinogens, systemic toxicants, and reproductive toxicants (see Clause 5). This document does not include TTC values for other biological endpoints assessed as part of the biological evaluation of a medical device, per ISO 10993-1, for example:

— cytotoxicity;

— irritation;

— sensitization;

— hemocompatibility;

— material mediated pyrogenicity;

— local effects that occur in tissues at the site of contact between a medical device and the body (e.g. the observations from implantation studies).

The TTC values in this document do not apply to potential exposure via gas pathways of medical devices. For application of TTC for constituents present/released from these devices, see the ISO 18562 series.

The TTC values presented in this document are not applicable for the safety assessment of cohort of concern (see 5.3).

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 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of materials*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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

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

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

3.1
constituent
chemical or compound present in or on a finished medical device or material(s) of construction

Note 1 to entry: Constituents may be intentionally present (e.g. an additive such as an antioxidant) or unintentionally present (e.g. an impurity).

Note 2 to entry: When applying TTC to an extractable or leachable, the identity of the extractable/leachable represents a constituent to which individual(s) are potentially exposed due to medical device use.

3.2
extractable
constituent released when the medical device or material of construction is extracted using laboratory extraction conditions and vehicles

Note 1 to entry: When applying TTC to an extractable, the extracted amount is assumed to potentially contact the individual(s) to whom the medical device contacts during clinical use, see ISO 10993-17.

3.3
identified constituent
constituent assigned a full chemical structure

3.4
leachable
constituent released from a medical device and potentially contacts the individual(s) during its clinical use

Note 1 to entry: When applying TTC to a leachable, the leached amount is assumed to potentially contact the user(s) of the medical device during its clinical use, see ISO 10993-17.

3.5
threshold of toxicological concern
TTC
level of exposure for constituents, below which there would be no appreciable risk to human health[1]

4 Background

4.1 General

The Threshold of Toxicological Concern (TTC) was originally developed for evaluating the toxicological risk of impurities present at low levels when impurity toxicity data are not available[2]. The concept was developed to address impurities present in food contact materials, and was then adapted for impurities in pharmaceutical products[3]to[16][20][21]. The TTC concept can be used to evaluate constituents present, or released, at low amounts from a medical device.

4.2 Protectiveness of TTC values

Separate threshold values have been developed to be protective for cancer-based and non-cancer effects. Threshold values for non-cancer effects are stratified into Cramer Class categories and identified constituents can be assigned to a specific Cramer Class based on their chemical structure[2][16]. Although some evaluation schemes that employ the TTC concept use both non-cancer- and cancer-based threshold values, only one set of TTC values is described in Table 1 to simplify the application of TTC values for the safety assessment of constituents that may be released from medical devices.

The TTC values defined in this document are based on the Acceptable Daily Intake values derived in ICH M7 (R1) (2017) for individual mutagenic impurities in pharmaceuticals[9][17]. The threshold value derived by ICH for mutagenic impurities in the longest exposure duration category (1,5 µg/d) is lower than the threshold value assigned to the most protective Cramer Class non-carcinogenic TTC value (90 µg/d), which is intended to be protective for chronic exposure to non-carcinogens[2][9].

Carcinogens elicit cancer via genotoxic or non-genotoxic mechanisms [19]. The TTC values in Table 1 are intended to be protective for exposure to carcinogens that exert their effect via either mechanism.

5 Applicability of TTC to medical device constituents

5.1 General

The applicability of the threshold values established by ICH for mutagenic impurities is presumed to be protective for both the potential carcinogenic and non-cancer effects that occur following patient exposure to a constituent released from a medical device. ICH M7 TTC values were established for oral or parenteral routes, as well as adults, paediatrics and pregnant women; therefore, the TTC values in this document are considered generally applicable for medical device use(s)[9].

Prior to applying TTC to medical device constituents, the appropriate TTC value is selected based on the medical device contact category, see 5.2. TTC does not apply to highly potent toxicants (i.e. cohort of concern constituents, see 5.3). Applicability of TTC to mixtures is specified in 5.4.

5.2 Selection of TTC value based on duration of body contact

TTC values for medical devices are presented in Table 1 and selected based on duration of body contact. For limited and prolonged contacting medical devices, the recommended TTC value is 120 µg/d. The remaining TTC values (i.e. 20 µg/d, 10 µg/d, and 1,5 µg/d) apply to medical devices categorized as long-term contacting. When a medical device is categorized as long-term body contacting, but actual body contact is uncertain/plausible/actual, then the TTC value for > 10 years (1,5 µg/d) should be selected. The selection of a TTC value based on duration of body contact shall be justified.

Table 1 includes TTC values for two body contact durations (i.e. > 1 month to 12 months and > 1 year to 10 years) not specified in ISO 10993-1:2018, Table A.1, which are different from those normally used for the biological evaluation of medical devices. A less than 10 year TTC value (i.e. 10 µg/d or 20 µg/d) shall be based on medical device use conditions that limits the maximum duration of body contact to less than 12 months or to less than 10 years.

NOTE 1 Maximum means that the absolute or estimated total number of body contacting days is determined by factors (e.g. instructions for use) that limit (or prevent) longer duration of body contact.

NOTE 2 A medical device that contacts the body once per week for a life-time (i.e. 9,9 years = 1 contact d/week × 52 weeks/year × 70 years) ÷ 365 d/year) would result in the selection of 10 µg/d as the TTC value.

When experimental data or model-derived predictions suggest that an identified constituent is not likely to have carcinogenic effects (e.g. negative mutagenicity data or negative results in at least two computational models that operate using different approaches; system-based and statistically based), then categorizing the constituent into its appropriate Cramer Class and use of the corresponding TTC value is recommended[2][16][23][24]. Assignment of identified constituents to Cramer Classes, and the

use of this approach to assess constituent mediated systemic toxicity and reproductive/developmental toxicological risk are found in References [2] and [16].

Table 1 — Recommended ICH M7(R1) (2017) TTC values based on ISO 10993-1 medical device contact category

Medical device contact category	Limited (<24 h)	Prolonged (24 h to 30 d)	Long-term[a] (>30 d)		
Duration of body contact	≤ 1 month		> 1 month to 12 months	> 1 year to 10 years	> 10 years to lifetime
Daily intake (µg/d) of any one constituent	120		20	10	1,5[b]

[a] Long-term includes devices commonly described as permanent contacting (see ISO 10993-1).

[b] The 1,5 µg/d value is based on 10^{-5} cancer risk and 60 kg (adult) body weight[6][17].

5.3 Cohort of concern constituents

5.3.1 General

The TTC approach does not apply to constituents belonging to classes that were excluded from the set of constituents used to originally derive the TTC values[2][6]. If a cohort of concern (CoC) constituent is identified through information gathering or analytically in an extract of the medical device, then a toxicological risk assessment based on cohort of concern specific toxicity data is recommended. Cohorts of concern are highly potent toxicants (i.e. cohort of concern specific TI value is below TTC). Examples of chemical classes known to contain cohorts of concern include, but not limited to, the following:

— Aflatoxin-like compounds;

— *N*-Nitroso compounds;

— Azo compounds;

— Polyhalogenated –dibenzodioxins, -dibenzofurans, and -biphenyls;

— Strained heteronuclear rings;

— Heavy metals (e.g. elemental, ionic, or compounds) ;

— Alpha-nitro furyl compounds;

— Hydrazines/triazenes/azides/azoxy compounds;

— Polycyclic amines;

— Steroids;

— Organophosphorous compounds.

In addition, the use of TTC values is not applicable for the safety assessment of high molecular weight polymeric constituents, particles (including nanoparticles), ceramics, proteins, and radioactive constituents because these types of substances were not included in the original data used to establish the TTC approach.

Constituents (including cohorts of concern – see 5.3.2) are identified through information gathering, which includes, but is not limited to, obtaining information on manufacturing materials, materials of construction, manufacturing processes/steps or constituent chemical composition (including possible impurities) of the medical device, component, or material.

5.3.2 Identification of cohort of concern constituents

When information gathering indicates a manufacturing material or material(s) of construction contains a CoC constituent, further evaluate in accordance with ISO 10993-1, ISO 10993-17 and ISO 10993-18.

An example of CoC constituents reported to be present in a medical device material of construction include, but is not limited to, the following:

— N-nitrosamines are reaction products between specific organic precursor molecules, secondary amines and a "nitrosating agent". In the compounding of rubber, secondary amines are likely formed from certain vulcanization accelerators such as thiurams and dithiocarbamates[22].

5.4 Applicability to mixtures

Since multiple constituents are used to manufacture, process, and sterilize medical devices, medical devices and their materials of construction are likely to contain, and may release, complex mixtures of constituents. The TTC values defined in this document are applicable to individual constituents whether they exist singly in an extract or as one of many constituents in a complex mixture extracted from the medical device. Additional steps are not needed to account for the aggregate effects of multiple constituents in a mixture, since toxicological interactions are not expected at the low exposure levels that correspond to the TTC values[18].

NOTE Guidance on conducting a toxicological risk assessment for mixtures is provided in ISO 10993-17.