INTERNATIONAL STANDARD

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Biological evaluation of medical devices —

Part 17: Establishment of allowable limits for leachable substances

Évaluation biologique des dispositifs médicaux —
Partie 17: Établissement des limites admissibles des substances relargables

Reference number
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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this part of ISO 10993 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 10993-17 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Evaluation and testing*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for in vitro cytotoxicity*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 8: Selection and qualification of reference materials for biological tests*

— *Part 9: Framework for identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and delayed-type hypersensitivity*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

Future parts will deal with other relevant aspects of biological testing.

For the purposes of this part of ISO 10993, the CEN annex regarding fulfilment of European Council Directives has been removed.

Introduction

The determination of the suitability of a medical device for a particular use involves balancing any identified risks with the clinical benefit to the patient associated with its use. Among the risks to be considered are those arising from exposure to leachable substances arising from medical devices.

Risks associated with exposure to hazardous leachable substances are managed by identifying the leachable substances, quantifying the associated risks and limiting exposure within tolerable levels. This part of ISO 10993 provides a method by which maximum tolerable levels can be calculated from available data on health risks. Allowable limits may be based upon health risks that can be systemic or local, immediate or delayed, and range in severity from minor localized adverse effects to life-threatening risks. These allowable limits are intended to be derived, using this part of ISO 10993, by toxicologists or other knowledgeable and experienced individuals, capable of making informed decisions based upon scientific data and a knowledge of medical devices.

The allowable limits derived may be used by anyone. In addition to use by ISO, other standards-developing organizations, government agencies, regulatory bodies, and other users for setting allowable limits as standards or regulations, manufacturers and processors may use the allowable limits derived to optimize processes and aid in the choice of materials in order to protect patient health. Where risks associated with exposure to particular leachable substances are unacceptable, this part of ISO 10993 can be used to qualify alternative materials or processes.

Biological evaluation of medical devices —

Part 17:
Establishment of allowable limits for leachable substances

1 Scope

This part of ISO 10993 specifies a method for the determination of allowable limits for substances leachable from medical devices. It is intended for use in deriving standards and estimating appropriate limits where standards do not exist. It describes a systematic process through which identified risks arising from toxicologically hazardous substances present in medical devices can be quantified.

This part of ISO 10993 is not applicable to devices that have no patient contact (e.g. *in vitro* diagnostic devices).

Exposure to a particular chemical substance may arise from sources other than the device, such as food, water or air. This part of ISO 10993 does not address the potential for exposure from such sources.

2 Normative reference

The following normative document contains provisions which, through reference in this text, constitute provisions of this part of ISO 10993. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent edition of the normative document indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

3 Terms and definitions

For the purposes of this part of ISO 10993, the terms and definitions given in ISO 10993-1 and the following apply.

3.1
allowable limit
AL
largest amount of a leachable substance that is deemed acceptable on a daily basis, when taken into the body through exposure to a medical device

NOTE Allowable limits are expressed in dose to the patient for each applicable exposure period. The units used are mass per unit time, e.g. milligrams per day. These doses represent tolerable risks for medical devices under the circumstances of intended use.

3.2
benefit factor
BF
numerical factor that takes into account the health benefit from use of the medical device(s) containing the leachable substance in question

3.3
concomitant exposure factor
CEF
numerical factor that accounts for patient exposure to many medical devices containing the same leachable substance

NOTE This factor is used to adjust the product of TI and body mass downward.

3.4
default
value to be used, in the absence of data, for an uncertainty or other factor used in the calculation of the allowable limit

3.5
harm to health
physical injury and/or damage to health

3.6
health benefit
likelihood of maintaining or improving health

3.7
health hazard
potential source of harm to health

3.8
health risk
combination of the likelihood of occurrence of harm to health and the severity of that harm

3.9
health risk analysis
use of available information to identify health hazards and to estimate health risk

3.10
leachable substance
chemical removed from a medical device by the action of water or other liquids related to the use of the device

EXAMPLE Additives, sterilant residues, process residues, degradation products, solvents, plasticizers, lubricants, catalysts, stabilizers, anti-oxidants, colouring agents, fillers and monomers, among others.

3.11
lowest observed adverse effect level
LOAEL
lowest concentration or amount of a substance found by experiment or observation which causes detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure

NOTE Alterations in morphology, functional capacity, growth, development or life span of the target organism may be detected which are judged not to be adverse.

3.12
minimally irritating level
MIL
amount of a leachable substance that is minimally irritating to the patient

NOTE It is normally expressed in milligrams, although sometimes as milligrams per millilitre, in which case the value must be multiplied by the volume (millilitres) used to get the mass (milligrams).

3.13
modifying factor
MF
mathematical product of uncertainty factors UF_1, UF_2 and UF_3

3.14
multiple exposure
more than one exposure of the same patient to devices containing the same leachable substance, simultaneously or at different times

3.15
non-irritating level
NIL
largest amount of a leachable substance that is not irritating to the patient

NOTE It is normally expressed in milligrams, although sometimes as milligrams per millilitre, in which case the value must be multiplied by the volume (millilitres) used to get the mass (milligrams).

3.16
no observed adverse effect level
NOAEL
greatest concentration or amount of a substance found by experiment or observation which causes no detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure

NOTE Alterations of morphology, functional capacity, growth, development or life span of the target organism may be detected which are judged not to be adverse.

3.17
physiologically based pharmacokinetic modelling
PBPK modelling
system of modelling biological effects taking into account metabolic and pharmacokinetic differences among species of animal

NOTE Such data should be utilized whenever they are available.

3.18
proportional exposure factor
PEF
numerical factor for patient exposure to a leachable substance that accounts for the fact that a medical device is not typically utilized every day during the entire exposure category of interest

NOTE This factor is used to adjust the product of TI and body mass upwards.

3.19
repeated use
use of the same device by the same patient more than once without reprocessing

3.20
safety
freedom from unacceptable health risk

3.21
simultaneous use
use of more than one device by the same patient at the same time

3.22
tolerable contact level
TCL
tolerable contact exposure to a leachable substance resulting from contact with a medical device

NOTE It is normally expressed in milligrams per square centimetre of body surface.

3.23
TCL **modifying factor**
MF_{TCL}
mathematical product of uncertainty factors UF_4, UF_5 and UF_6

3.24
tolerable exposure
TE
product of the tolerable intake, the body mass and the utilization factor

NOTE It is normally expressed in milligrams per day to the patient.

3.25
tolerable intake
TI
estimate of the average daily intake of a substance over a specified time period, on the basis of body mass, that is considered to be without appreciable harm to health

NOTE It is normally expressed in milligrams per kilogram of body mass per day. It is derived as a part of the overall establishment of allowable limits for a leachable substance in a medical device.

3.26
tolerable risk
risk which is accepted in a given context based upon the current values of society

3.27
uncertainty factor
UF
factor intended to account for the uncertainties inherent in estimating potential effects of a chemical on humans from results obtained in human populations or surrogate species

3.28
utilization factor
UTF
numerical factor used to take into account the utilization of the device in terms of frequency of use and utilization in conjunction with other medical devices that can be reasonably anticipated to contain the same leachable substance

4 General principles for establishing allowable limits

4.1 The process of establishing allowable limits (see Figure 1) for an identified substance leachable from medical devices consists of

a) evaluating the biological risk associated with the leachable substance (see clause 5) by

— collecting data and identifying critical health endpoints,

— determining tolerable intakes (TI) that are specific for the route of entry and duration of exposure, and

— determining tolerable contact levels (TCL) if irritation is an appropriate endpoint;

b) determining the tolerable exposure (TE) of the patient to the leachable substance (see clause 6) by

— determining appropriate patient body mass (m_B), and

— modifying the product of tolerable intake and body mass based upon a device utilization factor (UTF);

c) determining feasibility and applying benefit when appropriate. If the feasibility evaluation determines that the TE is both technically and economically feasible, the TE becomes the allowable limit. In the event that the TE is not technically or economically feasible (see clause 7), further modification of the TE based upon benefit evaluation shall be performed on a case-by-case basis to establish the allowable limit (see clause 8).

4.2 Knowledgeable and experienced individuals, capable of making informed decisions based on the scientific data available, shall implement the requirements of this part of ISO 10993 through the application of professional judgement. This requires experience in the interpretation of toxicological data and toxicological risk assessment of medical devices, together with knowledge of the use and benefit of medical devices and the feasibility of achieving allowable limits determined.

4.3 The safety of medical devices requires an absence of unacceptable health risk. An analysis of the health risks posed by specific leachable substances allows exposure limits to be established that permit an appropriate degree of protection from harm to health in the event that the hazardous leachable substance would be released into the body during the clinical use of the device. The degree of protection deemed appropriate in any situation is dependent upon a number of factors, such as the nature of the hazard identified, the practicality of risk reduction and the magnitude of the benefit derived from the use of the medical device. Assessment of the acceptability of a health risk thus requires several complex factors to be investigated and balanced. Confidence in the risk assessment is a function of the quality and quantity of data evaluated.

4.4 In the broadest sense, substances leachable from medical devices can be introduced into the body by differing routes, ranging from skin absorption to ingestion, to inhalation, to direct systemic administration. In addition, devices can be placed into one of three categories according to their durations of use. In turn, each usage category may have multiple limits based upon multiple routes of exposure, as specified in ISO 10993-1. Thus, the overall allowable limit for a particular leachable substance can have up to three components, a short-term limit, a prolonged limit and a lifetime limit. In turn, each of these limits may need to be protective from multiple routes of exposure. To achieve this, tolerable intake values (TI) are calculated individually for each route of exposure within each applicable use category. That is, there may be multiple TIs, each route-specific, for a given usage category. In many cases the toxicological data may have sufficient consistencies to permit the use of the lowest TI value for either a usage category or a route of entry to best represent the toxicological effects of the leachable substance.

4.5 The first stage in the establishment of an allowable limit is the identification of a substance that may pose a health hazard. Once a hazardous substance is selected, the process of establishing an allowable limit begins with the establishment of tolerable intakes.

NOTE International Standards such as ISO 14971 or other hazard identification schemes may be employed to identify potentially hazardous residues.

5 Establishment of tolerable intake (TI) for specific leachable substances

5.1 General

A review of toxicological data provides the information necessary to establish a “no observed adverse effect level” (NOAEL). A modifying factor approach is then applied to the data for noncancer endpoints (see 5.4) so that an appropriate tolerable intake value can be established. Either modifying factor or quantitative approaches may be applied to determine the tolerable intake from cancer data (see 5.5). The modifying factor takes into account the type, amount and quality of data evaluated, the severity of the hazard identified, the uncertainty inherent in the risk assessment, and the level of safety assurance deemed appropriate, among other considerations.

The nature of the hazard identified shall be characterized by evaluating the toxicity of the substance in terms of the type of toxic effects seen and the dosages at which the toxic effects occur via various routes of exposure.

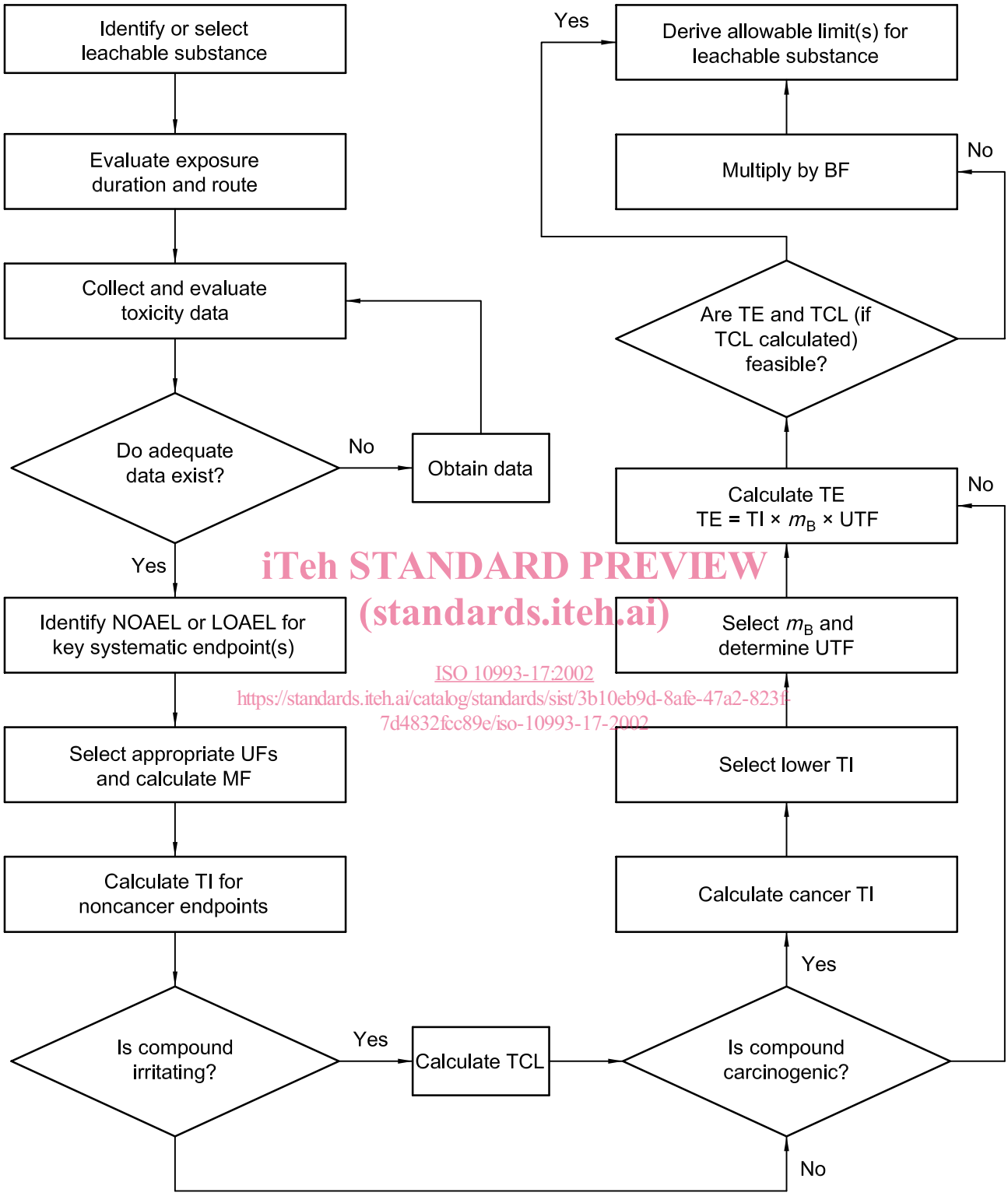

Figure 1 —Establishment of allowable limits for leachable substances