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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.

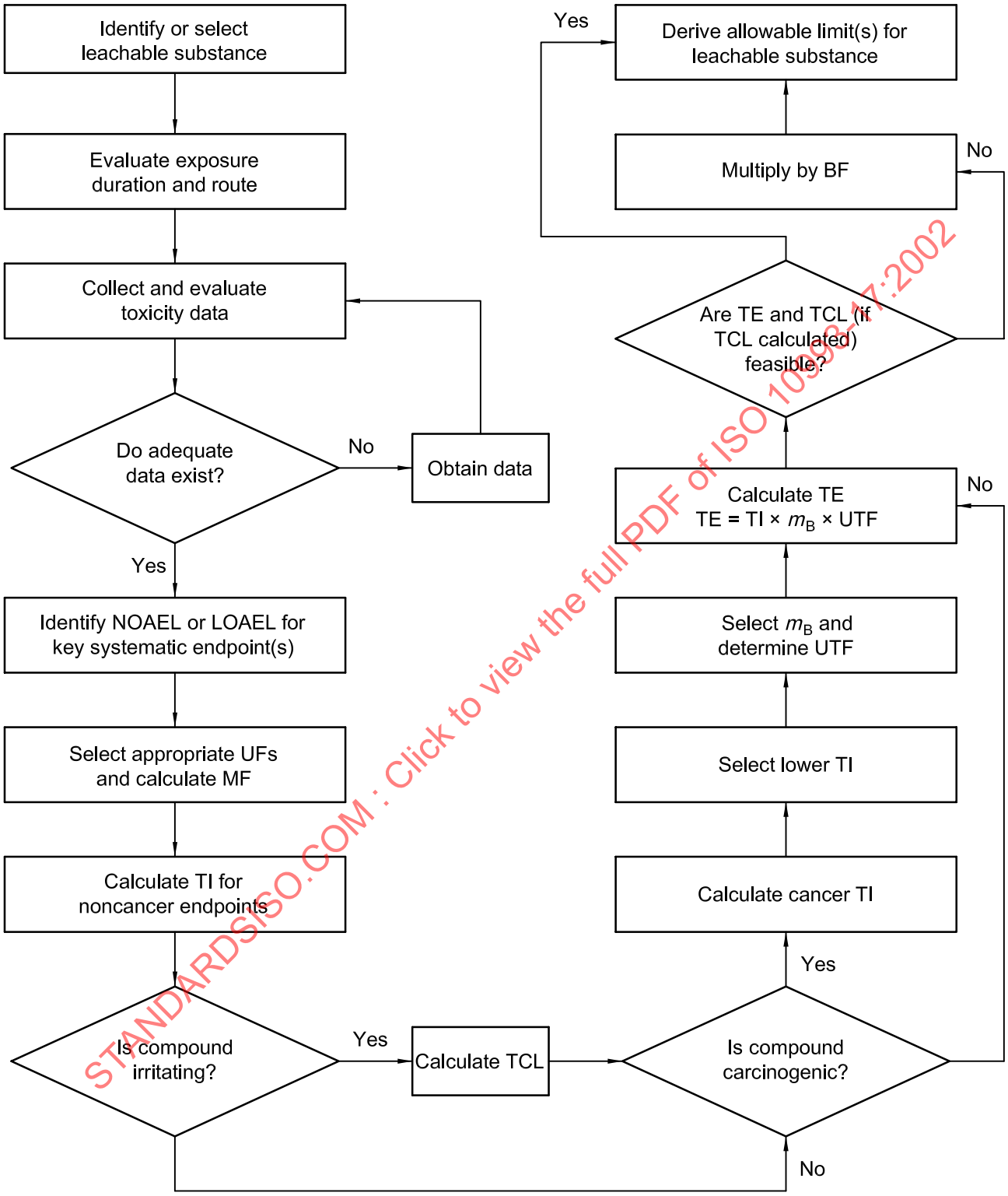

Figure 1 —Establishment of allowable limits for leachable substances

5.2 Exposure considerations for TI calculation

5.2.1 Data used

The following data are used both as a part of the TI calculation in clause 5 and later as a part of determining the appropriate body masses and utilization factors for the calculation of allowable limits in clause 9:

a) duration of patient exposure to a leachable substance (see 5.2.2);

b) normal route(s) of patient exposure to the leachable substance (see 5.2.3).

5.2.2 Exposure duration considerations

The duration of exposure of a specific device is categorized using the provisions of ISO 10993-1, of clause 4, and analysis of appropriate data.

For leachable substances covered by ISO 10993 (all parts), TI for permanent contact, prolonged exposure, and limited exposure may be necessary, e.g. ethylene oxide sterilization residues. If TI is established for a leachable substance with no specific device in mind or to cover all devices, permanent-contact TI is calculated with excursions as binding constraints for prolonged and limited exposures as needed, based upon the biological effect of the residue. If an TI is established for a leachable substance present in a device or class of devices with a specific duration category, the TI is established for that category with shorter term excursions, as necessary, based upon the biological effect of the leachable substance.

If no data are available to establish an TI for a specific category, for example when no chronic data are available to establish permanent contact TI, data from shorter term studies can be used with a larger modifying factor.

If a device can be placed in more than one category, the TI shall be based upon the more rigorous category.

5.2.3 Considerations of route of exposure

When TIs are established for leachable substances with no specific route in mind, or to cover multiple routes, TIs are calculated for each route of potential exposure within a given exposure-duration category to the extent possible according to ISO 10993-1. If the TIs for different routes of exposure within a given exposure-duration category are within a factor of 10, the lowest TI may be used as the TI for all exposure routes for that entire exposure-duration category. However, if the TIs vary by more than ten-fold, it may be necessary to have more than one TI for the exposure-duration category.

When TIs are established for leachable substances from a specific device or class of devices, TIs are calculated only for the intended route of usage of the device for each applicable exposure-duration category.

When no data are available for a specific route, TIs from other routes with data may be used for the route with no data. Such quantitative route-to-route extrapolation is encouraged, with any added uncertainty accounted for as a part of uncertainty factor 3 (UF_3).

5.3 Collection and evaluation of data

Once a leachable substance has been selected for evaluation, relevant available data shall be collected. These data may include

a) chemical and physical properties,

b) occurrence and use,

c) pharmacology,

d) toxicokinetics (absorption, distribution, metabolism and elimination),

e) toxicology, and

f) effects in humans.

Data used to set limits should be of high quality and pertinent. All available data should be considered in the context of understanding the overall toxicity profile of the substance. The basic approach is based on the premise that acute data (for example data from studies of 14 days or less) should be used to set limited exposure or short-term limits; subchronic effects data (for example data from one- to three-month studies) should be the basis for prolonged-exposure limits and chronic or lifetime data (for example data from studies of six months or longer duration) are preferred over subchronic, or short-term, data for setting lifetime permanent-exposure limits. Longer-term data may be useful in establishing shorter-term limits. Where available, human data are preferred over animal data.

The data shall be evaluated to identify critical adverse effects and to establish NOAELs for these effects. If the data are inadequate to allow a NOAEL to be determined, a low adverse effect level (LOAEL) or other value can be used in subsequent calculations, providing appropriate adjustment is made for the additional uncertainty introduced. Where possible, the dose-response relationship should be investigated to assist in determining a NOAEL, so that the magnitude of exposure can be related to the probability of toxic effects occurring in the experimental model. Data from multiple routes of exposure, e.g. oral, dermal or tissue contact, parenteral, and inhalation, shall be evaluated, as appropriate. In the case of potential exposure from only a single route of entry, data relevant to that route are the most relevant, although data from other routes can also be considered.

Taking into account the intended route of human exposure, the adverse effects that are deemed to be most relevant as a basis for limit setting shall be identified as well as the dosages required to produce these adverse effects. The most relevant NOAEL or, exceptionally, a LOAEL or other value shall be selected for use in the calculation of a health-based allowable limit. This selection shall reflect an evaluation of all adverse effects, based upon professional judgement. It should be made on the basis of the highest NOAEL or the lowest adverse effect level for any toxic effect seen, taking into account the applicability and criticality of the toxic effects, the route of experimental exposure, known interspecies differences in susceptibility, confidence in the experimental data, the expected route and duration of human exposure and any other factors considered relevant. The rationale for the choice of dose level shall be documented.

5.4 Set TI for noncancer endpoints

5.4.1 General

For each relevant anticipated route and duration of exposure, an TI shall be calculated from the NOAEL, LOAEL or other value determined. Each TI calculation shall take into account the degree of severity of the hazard identified and the uncertainty inherent in the risk analysis.

A modifying factor approach shall be used whenever possible to calculate TIs. This approach combines the use of uncertainty factors that are determined on the basis of professional judgement, to provide an acceptable margin of safety against the adverse effects of most concern.

The formula for calculating TI values, in milligrams per kilogram body mass per day, using the modifying factor approach, is shown in equation (1) below.

$$\mathrm{TI} = \frac{\mathrm{NOAEL, LOAEL, etc.}}{\mathrm{MF}} \qquad (1)$$

where the modifying factor is $UF_1 \cdot UF_2 \cdot UF_3$ (see 5.4.2 for descriptions of uncertainty factors UF_1, UF_2 and UF_3).

Limits should be established based upon use by the broadest segment of the anticipated user population. For example, if users are predominantly healthy adult males, estimates should be based upon exposure to adult males; if a device is intended for a specific population, such as pregnant women or neonates, estimates should be based upon that population. Typical assumptions for respiration rates, body masses, etc., that should be used in this calculation, are shown in annex A.

5.4.2 Determination of uncertainty factors

5.4.2.1 General

The estimation of uncertainty factors encompasses many different considerations. These factors take into account the uncertainties inherent in estimating the potential effects of a chemical on humans from results obtained in human populations or surrogate species. None of these considerations is easy to quantify in risk analysis. The uncertainty factor for use with human data is smaller than that for use with animal data. The uncertainty factor is smaller when using chronic data to determine TIs for permanent exposure than when subchronic data are used. It is also smaller when using NOAELs than when using LOAELs. The value or degree of influence assigned to 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 below.

5.4.2.2 Uncertainty factor 1 (UF_1)

UF_1 accounts for inter-individual variation among humans. UF_1 should be taken into account when deriving an TI 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 a toxic agent, a default uncertainty factor of 10 has been used historically to allow for the full range of human variability when safety assessment has been based upon effects reported in animals. In consequence, a greatly reduced uncertainty factor, possibly even 1, may be appropriate when the adverse effect has been studied in the patient group which would be exposed.

If variation among humans is judged to be minimal, an uncertainty factor of or approaching 1 should be selected. If variation among humans is judged to be significant, an uncertainty factor of or approaching 10 should be selected. If human variation is judged to be intermediate, an intermediate uncertainty factor should be taken. Idiosyncratic hypersusceptibility shall not normally serve as the basis for a TI value. As a result, the uncertainty factor for inter-individual human variability will not necessarily account for exceptionally sensitive subpopulations. The manner in which the material is handled in the body should also be considered in establishing the relevance and magnitude of any uncertainty factor.

5.4.2.3 Uncertainty factor 2 (UF_2)

UF_2 accounts for extrapolation from data derived in a species other than humans. UF_2 should take into account the inherent differences between the other species and man. It is always preferable to have data and detailed knowledge of the relationship between man and the test species.

In the absence of detailed knowledge of interspecies differences in toxicity, a 10-fold safety factor may be appropriate. If the toxicity and toxicokinetics of the substance are well-known and similar in humans and the experimental model, a smaller uncertainty factor for this difference should be used. Similarly, if differences are judged to be of toxicological significance, larger uncertainty factors should be used. The manner in which the material is handled in the body should also be considered in establishing the relevance and magnitude of any uncertainty factor.

5.4.2.4 Uncertainty factor 3 (UF_3)

UF_3, an uncertainty factor between 1 and 100, accounts for the quality and relevance of the experimental data. If the data are of good quality and relevant, a factor of 1 shall be used. The factor (UF_3) shall be based upon professional judgement that takes into account the quality of the data and the design of the studies.

These considerations should be made for uncertainties such as, but not limited to, the following situations:

a) short-term studies being used for extrapolation to longer-term exposures or effects;

b) having only LOAEL data instead of NOAEL data;

c) absence of supporting studies;

d) use of animal models inappropriate for the endpoint being assessed;

e) inappropriate route of exposure;

f) rate of exposure;

g) confidence in the data base.

The degree of safety assurance deemed appropriate in view of the severity of the health hazard should also be considered when establishing TIs. If the health hazard is such that death, very serious harm or an irreversible target organ effect is an expected outcome or used as an endpoint, an added allowance should be considered. Similarly, if the endpoint is of limited toxicological significance, a reduced allowance should be considered. The manner in which the material is handled in the body should also be considered in establishing the relevance and magnitude of any uncertainty factor.

If the amount or quality of relevant data available is limited, a factor approaching or equal to 100 should be selected. If studies that serve as the basis for the TI are judged to be well designed for their intended purposes and executed properly, a factor approaching or equal to 1 should be selected. Intermediate situations would indicate that intermediate factors should be selected. The upper range of the factor may be extended to over 100 if acute animal data are the only basis for calculation of TI values for permanent exposure.

5.4.3 Determination of the modifying factor

The modifying factor (MF) shall then be calculated as the product of the uncertainty factors ($UF_1 \cdot UF_2 \cdot UF_3$) [see equation (2) below]. This modifying factor shall serve as the basis for the determination of the TI and, in turn, the tolerable exposure (TE) for each usage category.

$$MF = UF_1 \cdot UF_2 \cdot UF_3 \qquad (2)$$

In most cases, a modifying factor between 10 and 1 000 should be sufficiently protective. In a few cases, particularly where only poor or inappropriate data are available and significant hazards are identified, a modifying factor as high as 10 000 may be necessary. In some cases, there may be sufficient human data or sufficiently trivial endpoints to justify a modifying factor less than 10. If only acute lethality data are available, a modifying factor greater than 10 000 may be necessary to establish an TI for permanent contact. Any situation that results in a modifying factor greater than 10 000 is indicative of a high degree of imprecision in the analysis and consideration should be given, in such cases, to the urgent need for additional data. As an alternative to the use of default UFs, physiologically based pharmacokinetic (PBPK) modelling can be used to account for inter-individual variations among humans (UF_1) and to conduct interspecies extrapolation (UF_2) within a species. Use of PBPK models could reduce uncertainty and result in a different MF.

5.5 Set TI for cancer endpoints

5.5.1 Procedure for carcinogenic leachable substances

Once determined, the TI for cancer shall be evaluated along with TI values for noncancer endpoints to determine the appropriate permanent-exposure TI for use in calculations of TE.

For leachable substances considered to be carcinogenic, a weight-of-evidence test shall be applied to determine the appropriate method for the determination of the TI based on cancer. The weight-of-evidence test involves answering the following questions:

— Is the material a genotoxic carcinogen?

— Are the tumour types relevant to humans?

— Do existing biodisposition data support extrapolation to humans?

— Does epidemiological information support relevance to humans?

5.5.2 Options for substances that pass the weight-of-evidence test

If the weight-of-evidence test indicates that the material is a genotoxic carcinogen, the tumour types observed in cancer bioassays are relevant to humans, and biodisposition and/or epidemiological information support relevance to humans, one of the following two approaches shall be used.

a) Determine the cancer TI based upon quantitative risk assessment procedures using statistical models with a significant risk level of 10^{-4}, or

NOTE If a linear multistage model is used, then consideration should be given to the possible nonlinearity of low doses and even possible biological thresholds arising from the presence of DNA repair mechanisms and other homeostatic processes.

b) Do not determine a cancer TI. Reduce patient exposure as low as reasonably practicable and actively manage the cancer risk using risk management procedures.

NOTE For more information see ISO 14971.

5.5.3 Procedure when weight-of-evidence test fails or is equivocal

If the weight-of-evidence test fails, the modifying factor approach shall be used. If the weight-of-evidence test is equivocal, both the modifying factor and quantitative risk assessment techniques should be used for the determination of cancer TI. When the modifying factor approach is used, the methods described in 5.3 shall be followed for tumorogenic responses.

Whenever possible, physiologically based pharmacokinetic (PBPK) modelling should be used to estimate the dose delivered to the target organ in question rather than the applied dose. In turn, the delivered dose is used in the calculation of risks rather than the applied dose.

5.6 Establishment of tolerable contact levels (TCLs)

5.6.1 General

A review of the irritation data provides the information necessary to decide whether irritation needs to be considered and, if necessary, to establish a non-irritating level (NIL). Once it is decided that a NIL needs to be derived, a modifying-factor approach is used so that a tolerable contact level can be developed. It is anticipated that TCLs will be needed for only some leachable substances, and when needed they may only be needed for some devices used in certain applications. The TCLs to be used would become dual binding constraints with the allowable limits in these situations. Furthermore, there may be situations in which the prevention of irritation is sufficiently restrictive that allowable limits based upon systemic toxicity are not necessary.

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

5.6.2 Exposure consideration for TCL calculation

Tolerable contact levels (TCLs) may be required for any leachable substance that produces an irritant response from direct contact with body tissues, e.g. skin, eye, mucous membranes or surfaces breached from a specific device usage pattern. Patient populations should be considered.

Tolerable contact levels (TCLs) may be required for multiple tissue-contact applications. For example, a material may not be irritating at a given concentration following a single application, but may be irritating following repeated application.

5.6.3 Set TCL for irritation endpoint

5.6.3.1 General

For each relevant contact tissue, a TCL shall be calculated from the non-irritating level (NIL), minimally irritating level (MIL) or other similar level. Each TCL calculation should take into account the degree of irritation from multiple exposure to non-irritating concentrations whenever these data are available. A modifying-factor approach shall be used to calculate the TCL. This approach incorporates the use of uncertainty factors that are determined on the basis of professional judgement, to provide an acceptable margin of safety against irritation. The formula for calculating TCL, in milligrams per square centimetre, using the modifying-factor approach is:

$$\mathrm{TCL} = \frac{\mathrm{NIL\ or\ MIL}}{\mathrm{MF_{TCL}} \cdot A} \qquad (3)$$

where

$\mathrm{MF_{TCL}}$ is the modifying factor ($\mathrm{UF_4} \cdot \mathrm{UF_5} \cdot \mathrm{UF_6}$);

NIL is the non-irritating level, in milligrams;

MIL is the minimally irritating level, in milligrams;

A is the body contact surface area, in square centimetres.

Irritation limits should be established based upon the broadest segment of a specific user population. If intended for other than general use, use the subpopulation for which the device is intended.

5.6.3.2 Determination of uncertainty factors

The methods used for determining biological risk of irritation are different than those used for systemic toxicity. The chief difference is the degree of uncertainty. Normally, if irritation is not produced in an appropriate test model, irritation will not be produced in human use. 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.

— **Uncertainty factor 4 ($\mathrm{UF_4}$)**

$\mathrm{UF_4}$ accounts for inter-individual variation among humans. $\mathrm{UF_4}$ should be taken into account 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, an uncertainty factor ranging from 3 to 10 should be used.

— **Uncertainty factor 5 ($\mathrm{UF_5}$)**

$\mathrm{UF_5}$ accounts for extrapolation from data derived in a species other than humans. $\mathrm{UF_5}$ should take into account the inherent differences between the other species and humans. It is always preferable to have data and detailed knowledge of the relationship between man and the test species. In the absence of such detailed knowledge, an interspecies variation uncertainty factor ($\mathrm{UF_5}$) of 3 should be used.

— **Uncertainty factor 6 ($\mathrm{UF_6}$)**

$\mathrm{UF_6}$ accounts for the quality and relevance of the experimental data. Use of MILs versus NILs may require an uncertainty factor ($\mathrm{UF_6}$) of 3 or more. Similarly, a $\mathrm{UF_6}$ up to 3 may be applied if conclusions are drawn based upon a poorly designed or executed study, or if the amount of relevant data were limited. Hence $\mathrm{UF_6}$ may be 9 or more if both the relevance and quality of the data are poor.

5.6.3.3 Determination of the TCL modifying factor

The TCL modifying factor (MF_{TCL}) shall then be calculated as a product of the uncertainty factors ($UF_4 \cdot UF_5 \cdot UF_6$) as given in equation (3). This modifying factor shall serve as the basis for the TCL. In most cases an overall modifying factor of 30 or less should be sufficient, but may be larger if non-irritating concentrations have not been established or if only poor or inappropriate data are available.

5.7 Risk assessment of mixtures

This part of ISO 10993 is to be used to derive allowable limits for individual leachable substances released from medical devices. However, a patient is rarely exposed to one residue at a time. A more likely scenario is one in which exposure occurs to multiple compounds released from the device at the same time. This co-exposure to multiple compounds has the potential to increase or decrease the toxicity of any given substance of interest. However, when the rate at which compounds are released from a medical device is well below the respective TI value for these compounds, then the likelihood of synergistic effects occurring among the mixture constituents is small. Methods to address risk assessment of mixtures are given in annex B.

6 Calculation of tolerable exposure (TE)

6.1 General

Exposure to a given leachable substance may arise from use of a number of medical devices. Once TIs have been developed for a leachable substance, it is necessary to adjust the appropriate TI to determine the amount of exposure arising that would be tolerable, taking into account the way the device is to be used and the potential for exposure to other medical device sources of the leachable substance.

The following factors shall be evaluated to determine the appropriate body mass and utilization factor (UTF) to be used to determine the tolerable exposure (TE):

a) particular populations exposed to the device;

b) the predominant body mass of exposed population;

c) intended usage pattern of the device;

d) potential for patient exposure to the same leachable substance from multiple devices.

A TCL is not adjusted for utilization, since it is a local effect that would not normally be increased or decreased based upon device utilization. Rather, the TCL would be applied as a tolerable exposure for those residues/device combinations where irritation is a factor in setting an allowable limit. When applied, the TCL would normally be treated as a mutually binding TE. In those cases where irritation represents the binding constraint, the TCL would become the TE but be expressed in milligrams per device, since unacceptable irritation should not be tolerated for even one day.

Utilization factors shall reflect the normal routes of residue exposure to the patient from the device or device class. If a single TI was chosen to represent all TIs for an exposure category, some latitude should be allowed in the calculation of utilization factors for route-specific devices. If one TI was used for all routes of entry in a given duration category, a separate TI may be calculated for a device-specific route of entry and used as the basis for the utilization factor for that device or device category.

6.2 Exposure population

6.2.1 Body mass

The bulk of medical devices are used in adults. Thus 70 kg shall be used to calculate TE unless the device is intended for use in another population. In that case, the TE shall be based on the body mass derived from the dominant use pattern, with special consideration given to devices specifically intended for use with uniquely sensitive groups, such as neonates. See annex A for a variety of body masses that may be used.

6.2.2 Devices specifically intended for use in neonates and children

For neonates, consideration should be given to the potential immaturity of the principal routes of elimination of the material and the potential for higher accumulation. Data derived from studies in which neonates are exposed to the hazardous material are preferable when calculating TIs for medical devices intended for use by neonates. When such data are not available for calculating TIs, the TIs calculated from adult data can be used to calculate TE.

TE calculations should be performed using body mass 3,5 kg for neonates and 10 kg for children as the human body mass for that device.

6.3 Calculation of utilization factor from intended use pattern

6.3.1 General

The product of the tolerable intake TI and body mass is adjusted by multiplication with a utilization factor (UTF).

The normal use pattern of a medical device, including its use as a part of a therapy system, shall be determined for the population of interest. Derivation of utilization factors shall, where possible, take account of the anticipated use pattern of medical devices. This entails the calculation of a concomitant exposure factor (CEF) and a proportional exposure factor (PEF). These factors are multiplied together to obtain the utilization factor (UTF) as given in equation (4):

$$\mathrm{UTF} = \mathrm{CEF} \cdot \mathrm{PEF} \tag{4}$$

6.3.2 Concomitant exposure factor (CEF)

Assess the extent of exposure to a specific leachable substance arising from the use of multiple devices. Determine a concomitant exposure factor (CEF) of between 0,2 and 1,0 on the basis of this assessment, in line with the following principles.

a) Use a CEF of 0,2 if the utilization factor is unknown.

b) If many medical devices (i.e. at least 5 % of the devices sold in a calendar year, or more than five devices in any single medical procedure) can release the leachable substance, the CEF shall be calculated as either:

   1) the product of TI and body mass (m_B) divided by the total amount of leachable substance expected to be released by medical devices during a procedure as given in equation (5), or

$$\mathrm{CEF} = \frac{\mathrm{TI} \cdot m_B}{m_{proc}} \tag{5}$$

where

TI is the tolerable intake, in milligrams per kilogram body mass per day;

m_B is the body mass, in kilograms;

m_{proc} is the mass of total leachable substance released during a procedure, in milligrams per day.

2) the product of TI and m_B divided by the anticipated mean daily exposure of an average person to the leachable substance from all devices over a lifetime as given in equation (6), or

$$CEF = \frac{TI \cdot m_B}{\sum \frac{m_{life}}{25\,000 \text{ days}}} \quad (6)$$

where

TI is the tolerable intake, in milligrams per kilogram body mass per day;

m_B is the body mass, in kilograms;

m_{life} is the mass of leachable substance released over a lifetime, expressed as mean daily exposure in milligrams.

3) the default value of 0,2.

c) If few devices that can release the leachable substance are used (i.e. less than 5 % of the devices sold in a calendar year, or less than five devices in any single medical procedure, a CEF of 1,0 shall be used.

6.3.3 Proportional exposure factor (PEF)

A utilization factor (UTF) can be adjusted upwards to account for a situation where a device is not used for the entire duration of an exposure category. To facilitate this, a proportional exposure factor (PEF) shall be calculated as the proportion of the exposure category during which actual exposure to the device is anticipated to occur. Thus, as shown in equation (7), the PEF equals the number of days in the exposure category divided by the number of days a device is used before it is discarded.

$$PEF = \frac{n_{exp}}{n_{use}} \quad (7)$$

where

n_{exp} is the number of days in the exposure category;

n_{use} is the number of days of device use.

If the number of days a device is used varies, a reasonable upper limit should be used. If a reasonable upper limit cannot be determined, use a PEF default of 1.

6.4 Tolerable exposure

The tolerable intake TI is adjusted to take account of the way a device is used. The tolerable exposure TE is the product of the tolerable intake, the body mass and the utilization factor.

$$TE = TI \cdot m_B \cdot UTF \quad (8)$$

where

TE is the tolerable exposure after consideration of patient body mass and factoring in device utilization. It is normally expressed in milligrams per day;

TI is the tolerable intake after modification based upon the device evaluation. It is normally expressed in milligrams per kilogram body mass per day;

m_B is the body mass specific to the intended patient population. In the absence of specific information, use m_B = 70 kg;

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

7 Feasibility evaluation

7.1 Feasibility refers to the ability of a manufacturer or reprocessor to achieve tolerable exposure. Feasibility has two components:

a) technical feasibility; and

b) economic feasibility.

Technical feasibility refers to the ability to achieve the tolerable exposure for a device or device class regardless of cost.

Economic feasibility refers to the ability to meet the tolerable exposure without making provision of the device an unsound economic proposition. Cost and availability implications should be considered in the selection of allowable limits to the extent that these impact upon the preservation, promotion or improvement of human health.

7.2 If achieving the tolerable exposure is feasible, benefit evaluation shall not be performed, the benefit factor defaults to 1 and the allowable limit is the same as the tolerable exposure. If it is either technically or economically infeasible to meet the tolerable exposure, benefit evaluation should be performed. The rationale for the consideration of benefit shall be documented.

8 Benefit evaluation

8.1 The degree of safety assurance deemed appropriate for medical devices acknowledges the fact that the use of all medical devices carries a health benefit. The greater the health benefit anticipated from the use of the device, the greater the health risk that can be accepted. For the purpose of this part of ISO 10993, however, benefit is only considered, on a case by case basis, if the tolerable exposure would be exceeded. In that case only, a factor taking into account health benefit may be introduced to modify the tolerable exposure (TE) if toxicity arising from leachable substances present in the device is deemed to be acceptable when balanced against the particular health benefit anticipated from the therapy and provided that leachable substances have been reduced to the greatest extent possible consistent with the preservation, promotion or improvement of human health in general.

8.2 In applying a risk assessment to a medical device, allowance can be made for the expectation that no medical procedure is without health risk and that risks associated with the use of medical devices are balanced against the health benefits arising from their use.

8.3 In cases where leachable substances that are toxic compounds arising from materials or processes cannot readily be avoided by the use of alternative materials or processing methods, the significance of the benefit arising from the use of the device should be considered. The justification for the necessity and magnitude of the benefit factor used in the calculation of the allowable limit shall be documented. In such cases, the allowable limit is the product of the TE and benefit factor (BF).

9 Allowable limits

9.1 After calculation of the TEs and their modification based upon the feasibility and benefit, an allowable limit is calculated for each TE. Meeting all the allowable limits is required.

9.2 Each allowable limit AL is calculated using the following general formula.

$$AL = TE \cdot BF \quad (9)$$

where

AL is the 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 (see 3.1), expressed in milligrams per day;

NOTE 1 If based upon TCL, TE equals TCL and allowable limit is expressed in milligrams per square centimetre.

TE is the tolerable exposure, in milligrams per day;

NOTE 2 If based upon TCL, it is expressed in milligrams per square centimetre.

BF is the benefit factor.

9.3 Allowable limits can also be expressed in milligrams per device. Conversion methods are found in annex C for allowable limits in terms of mass per device (m_{dev}) based upon either systemic limits, in milligrams per day, or body surface contact limits for irritating substances.

10 Reporting requirements

The key data considered and the rationale for the selection of all factors shall be recorded. See annex D.

Annex A
(informative)

Some typical assumptions for biological parameters

A.1 General

This annex gives the default parameters for use in assessing risk. It specifies the lifetime, 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. These default 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.

A.2 Assumptions

A.2.1 Human

Default parameters for humans:

— 70-year lifetime;

— 2 l/d intake of drinking water;

— 20 m^3/24-h d air intake; 10 m^3/d in 8-h workday;

— 70 kg body mass for adult men; 58 kg for adult women; 10 kg for children; 3,5 kg for neonates (< 1 year);

— 9-month gestation period.

A.2.2 Rat

Default parameters for rats:

— 2-year lifetime;

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

— 0,29 m^3/24-h d air intake;

— 0,5 kg body mass for adult males, 0,35 kg for adult females;

— 22-d gestation period.

A.2.3 Mouse

Default parameters for mice:

— 2-year lifetime;

— 0,005 l/d of drinking water;

— 0,043 m^3/24-h d air intake;

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

— 20 d gestation period.

A.2.4 Hamster

Default parameters for hamsters:

— 2-year lifetime;

— 0,015 l/d of drinking water;

— 0,086 m^3/24-h d air intake;

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

— 15-d gestation period.

A.2.5 Guinea pig

Default parameters for guinea pigs:

— 3-year lifetime;

— 0,085 l/d of drinking water;

— 0,43 m^3/24-h d air intake;

— 0,5 kg body mass;

— 68-d gestation period.

A.2.6 Dog

Default parameters for dogs:

— 11-year lifetime;

— 0,5 l/d of drinking water;

— 7,5 m^3/24-h d air intake;

— 16 kg body mass;

— 63-d gestation period.

A.2.7 Rabbit

Default parameters for rabbits:

— 7-year lifetime;

— 0,33 l/d drinking water;

— 1,44 m^3/24-h d air intake;

— 3 kg body mass;

— 31-d gestation period.