American National Standard

ANSI/AAMI/ISO 10993-17:2002

Biological evaluation of medical devices— Part 17: Methods for the establishment of allowable limits for leachable substances

AAMI Association for the Advancement of Medical Instrumentation

The Objectives and Uses of AAMI Standards and Recommended Practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a fume of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards health care professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decisionmaking.

Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

INTERPRETATIONS OF AAMI STANDARDS AND RECOMMENDED PRACTICES

Requests for interpretations of AAMI standards and recommended practices must be made in writing, to the Manager for Technical Development. An official interpretation must be approved by letter ballot of the originating committee and subsequently reviewed and approved by the AAMI Standards Board. The interpretation will become official and representation of the Association only upon exhaustion of any appeals and upon publication of notice of interpretation in the "Standards Monitor" section of the *AAMI News.* The Association for the Advancement of Medical Instrumentation disclaims responsibility for any characterization or explanation of a standard or recommended practice which has not been developed and communicated in accordance with this procedure and which is not published, by appropriate notice, as an *official interpretation* in the *AAMI News.*

Biological evaluation of medical devices— Part 17: Establishment of allowable limits for leachable substances

Approved 15 November 2002 by
Association for the Advancement of Medical Instrumentation

Approved 17 December 2002 by
American National Standards Institute

Abstract: Specifies the method to be used to determine allowable limits for leachable substances in medical devices.

Keywords: biological evaluation, medical devices, leachable substances

AAMI Standard

This Association for the Advancement of Medical Instrumentation (AAMI) standard implies a consensus of those substantially concerned with its scope and provisions. The existence of an AAMI standard does not in any respect preclude anyone, whether they have approved the standard or not, from manufacturing, marketing, purchasing, or using products, processes, or procedures not conforming to the standard. AAMI standards are subject to periodic review, and users are cautioned to obtain the latest editions.

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All AAMI standards, recommended practices, technical information reports, and other types of technical documents developed by AAMI are *voluntary*, and their application is solely within the discretion and professional judgment of the user of the document. Occasionally, voluntary technical documents are adopted by government regulatory agencies or procurement authorities, in which case the adopting agency is responsible for enforcement of its rules and regulations.

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International standards adopted in the United States may include normative references to other international standards. For each international standard that has been adopted by AAMI (and ANSI), the table below gives the corresponding U.S. designation and level of equivalency to the international standard. (Note: Documents are sorted by international designation.)

Other normatively referenced international standards may be under consideration for U.S. adoption by AAMI; therefore, this list should not be considered exhaustive.

International designation	U.S. designation	Equivalency
IEC 60601-1-2:2001	ANSI/AAMI/IEC 60601-1-2:2001	Identical
IEC 60601-2-21:1994 and Amendment 1:1996	ANSI/AAMI/IEC 60601-2-21 & Amendment 1:2000 (consolidated texts)	Identical
IEC 60601-2-24:1998	ANSI/AAMI ID26:1998	Major technical variations
ISO 5840:1996	ANSI/AAMI/ISO 5840:1996	Identical
ISO 7198:1998	ANSI/AAMI/ISO 7198:1998/2001	Identical
ISO 7199:1996	ANSI/AAMI/ISO 7199:1996	Identical
ISO 10993-1:1997	ANSI/AAMI/ISO 10993-1:1997	Identical
ISO 10993-2:1992	ANSI/AAMI/ISO 10993-2:1993/(R)2001	Identical
ISO 10993-3:1992	ANSI/AAMI/ISO 10993-3:1993	Identical
ISO 10993-4:2001	ANSI/AAMI/ISO 10993-4:2001	Identical
ISO 10993-5:1999	ANSI/AAMI/ISO 10993-5:1999	Identical
ISO 10993-6:1994	ANSI/AAMI/ISO 10993-6:1995/(R)2001	Identical
ISO 10993-7:1995	ANSI/AAMI/ISO 10993-7:1995/(R)2001	Identical
ISO 10993-8:2000	ANSI/AAMI/ISO 10993-8:2000	Identical
ISO 10993-9:1999	ANSI/AAMI/ISO 10993-9:1999	Identical
ISO 10993-10:2002	ANSI/AAMI BE78:2002	Minor technical variations
ISO 10993-11:1993	ANSI/AAMI 10993-11:1993	Minor technical variations
ISO 10993-12:1996	ANSI/AAMI/ISO/CEN 10993-12:1996	Identical
ISO 10993-13:1998	ANSI/AAMI/ISO 10993-13:1999	Identical
ISO 10993-14:2001	ANSI/AAMI/ISO 10993-14:2001	Identical
ISO 10993-15:2000	ANSI/AAMI/ISO 10993-15:2000	Identical
ISO 10993-16:1997	ANSI/AAMI/ISO 10993-16:1997	Identical
ISO 10993-17:2001	ANSI/AAMI/ISO 10993-17:2001	Identical
ISO 11134:1994	ANSI/AAMI/ISO 11134:1993	Identical
ISO 11135:1994	ANSI/AAMI/ISO 11135:1994	Identical
ISO 11137:1995	ANSI/AAMI/ISO 11137:1994	Identical
ISO 11138-1:1994	ANSI/AAMI ST59:1999	Major technical variations

International designation	U.S. designation	Equivalency
ISO 11138-2:1994	ANSI/AAMI ST21:1999	Major technical variations
ISO 11138-3:1995	ANSI/AAMI ST19:1999	Major technical variations
ISO TS 11139:2001	ANSI/AAMI/ISO 11139:2002	Identical
ISO 11140-1:1995 and Technical Corrigendum 1:1998	ANSI/AAMI ST60:1996	Major technical variations
ISO 11607:2002	ANSI/AAMI/ISO 11607:2000	Identical
ISO 11737-1:1995	ANSI/AAMI/ISO 11737-1:1995	Identical
ISO 11737-2:1998	ANSI/AAMI/ISO 11737-2:1998	Identical
ISO TR 13409:1996	AAMI/ISO TIR 13409:1996	Identical
ISO 13485:1996	ANSI/AAMI/ISO 13485:1996	Identical
ISO 13488:1996	ANSI/AAMI/ISO 13488:1996	Identical
ISO 14155:1996	ANSI/AAMI/ISO 14155:1996	Identical
ISO 14160:1998	ANSI/AAMI/ISO 14160:1998	Identical
ISO 14161: 2000	ANSI/AAMI/ISO 14161:2000	Identical
ISO 14937:2000	ANSI/AAMI/ISO 14937:2000	Identical
ISO 14969:1999	ANSI/AAMI/ISO 14969:1999	Identical
ISO 14971:2000	ANSI/AAMI/ISO 14971:2000	Identical
ISO 15223:2000	ANSI/AAMI/ISO 15223:2000	Identical
ISO 15223/A1:2002	ANSI/AAMI/ISO 15223:2000/A1:2001	Identical
ISO 15225:2000	ANSI/AAMI/ISO 15225:2000	Identical
ISO 15674:2001	ANSI/AAMI/ISO 15674:2001	Identical
ISO 15675:2001	ANSI/AAMI/ISO 15675:2001	Identical
ISO TS 15843:2000	ANSI/AAMI/ISO TIR15843:2000	Identical
ISO TR 15844:1998	AAMI/ISO TIR15844:1998	Identical
ISO TR 16142:1999	ANSI/AAMI/ISO TIR16142:2000	Identical

Committee representation

Association for the Advancement of Medical Instrumentation

Biological Evaluation Committee

The adoption of ISO 10993-17:2001 as an American National Standard was initiated by the AAMI Biological Evaluation Committee, which also functions as a U.S. Technical Advisory Group to the relevant work in the International Organization for Standardization (ISO). U.S. representatives from the AAMI Allowable Limits for Leachable Substances Working Group (U.S. Sub-TAG for ISO/TC 194/WG 11), chaired by Lawrence H. Hecker, PhD, of Abbott Laboratories, played an active part in developing the ISO standard.

At the time this document was published, the **AAMI Biological Evaluation Committee** had the following members:

Cochairs:	Donald F. Gibbons, PhD
	Donald E. Marlowe
Members:	James M. Anderson, MD, PhD, Case Western Reserve University
	Sumner A. Barenberg, PhD, Bernard Technologies
	Eric R. Claussen, PhD, Becton Dickinson
	Roger Dabbah, PhD, U.S. Pharmacopeial Convention, Inc.
	Donald F. Gibbons, PhD, 3M
	Donald E. Marlowe, FDA Center for Devices and Radiological Health
	Edward Mueller, Consultant, Annapolis, MD
	Barry F. Page, Consultant, Garner, NC
	Melvin E. Stratmeyer, PhD, FDA/CDRH/OST
	Paul Upman, NAmSA
Alternates:	Raju G. Kammula, DVM, PhD, FDA/CDRH/ODE
	Sharon Northup, PhD, U.S. Pharmacopeial Convention, Inc.

At the time this document was published, the **AAMI Allowable Limits for Leachable Substances Working Group** had the following members:

Cochair:	Lawrence H. Hecker, PhD
Members:	Thomas A. Barbolt, PhD, DABT, Ethicon, Inc.
	Leonard S. Berman, PhD, Pall Corporation
	Ronald P. Brown, FDA/CDRH/OST
	Jon Cammack, PhD, Baxter Healthcare Corporation
	Charles Cogdill, Boston Scientific Corporation
	Stephen A. Conviser, Honeywell International
	Kimbrell Darnell, Bard Medical Division
	Lawrence H. Hecker, PhD, Abbott Laboratories
	Sharon J. Northup, PhD, Northup Regulatory Toxicology Services
	Barry F.J. Page, Barry Page Consulting
	Dennis L. Powers, DVM, TYCO Healthcare/Kendall
	James D. Sun, PhD, Becton Dickinson
	Peter William Urbanski, Medtronic World Headquarters Campus
	William T. Young, IBA Medical Sterilization & Analytical Labs
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	Mitchell B. Friedman, PhD , Abbott Laboratories
	Dennis Jenke, PhD, Baxter Healthcare Corporation
	David Porter, PhD, US Pharmacopeia Convention Inc
	Melvin E. Stratmeyer, PhD, FDA/CDRH/OST

NOTE—Participation by federal agency representatives in the development of this standard does not constitute endorsement by the federal government or any of its agencies.

Background of ANSI/AAMI adoption of ISO 10993-17:2002

As indicated in the foreword to the main body of this document (page x), the International Organization for Standardization (ISO) is a worldwide federation of national standards bodies. The United States is one of the ISO members that took an active role in the development of this standard.

International standard ISO 10993-17 was developed by Technical Committee ISO/TC 194, Biological evaluation of medical devices, to provide guidance on the assessment of medical devices and their constituent materials with regard to their potential to produce irritation and delayed-type hypersensitivity.

U.S. participation in this ISO TC is organized through the U.S. Technical Advisory Group for ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation on behalf of the American National Standards Institute. The U.S. made a considerable contribution to this International Standard.

AAMI encourages its committees to harmonize their work with International Standards in the area of biological evaluation of medical devices as much as possible in order to help reduce unnecessary repetition of testing.

Upon review of ISO 10993-17, the AAMI Biological Evaluation Committee and the AAMI Allowable Limits for Leachable Substances Working Group decided to adopt ISO 10993-17:2002 verbatim as a new American National Standard.

AAMI (and ANSI) have adopted other ISO standards. See the Glossary of Equivalent Standards for a list of ISO standards adopted by AAMI, which gives the corresponding U.S. designation and the level of equivalency with the ISO standard.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as technological advances are made and as new data comes to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 1110 N. Glebe Road, Suite 220, Arlington, VA 22201-4795.

NOTE—Beginning with the ISO foreword on page x, this American National Standard is identical to ISO 10993-17:2002.

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 fulfillment 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 the 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 other 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 editions 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 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 with 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, coloring 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 of 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 milliliters, in which case the value must be multiplied by the volume (milliliters) 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 milliliters, in which case the value must be multiplied by the volume (milliliters) 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 modeling (PBPK modeling): System of modeling biological effects taking into account metabolic and pharmacokinetic differences among species of animal.

NOTE—Such data should be utilized whenever it is 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 (L_{TC}): 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 centimeter 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 limits (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).

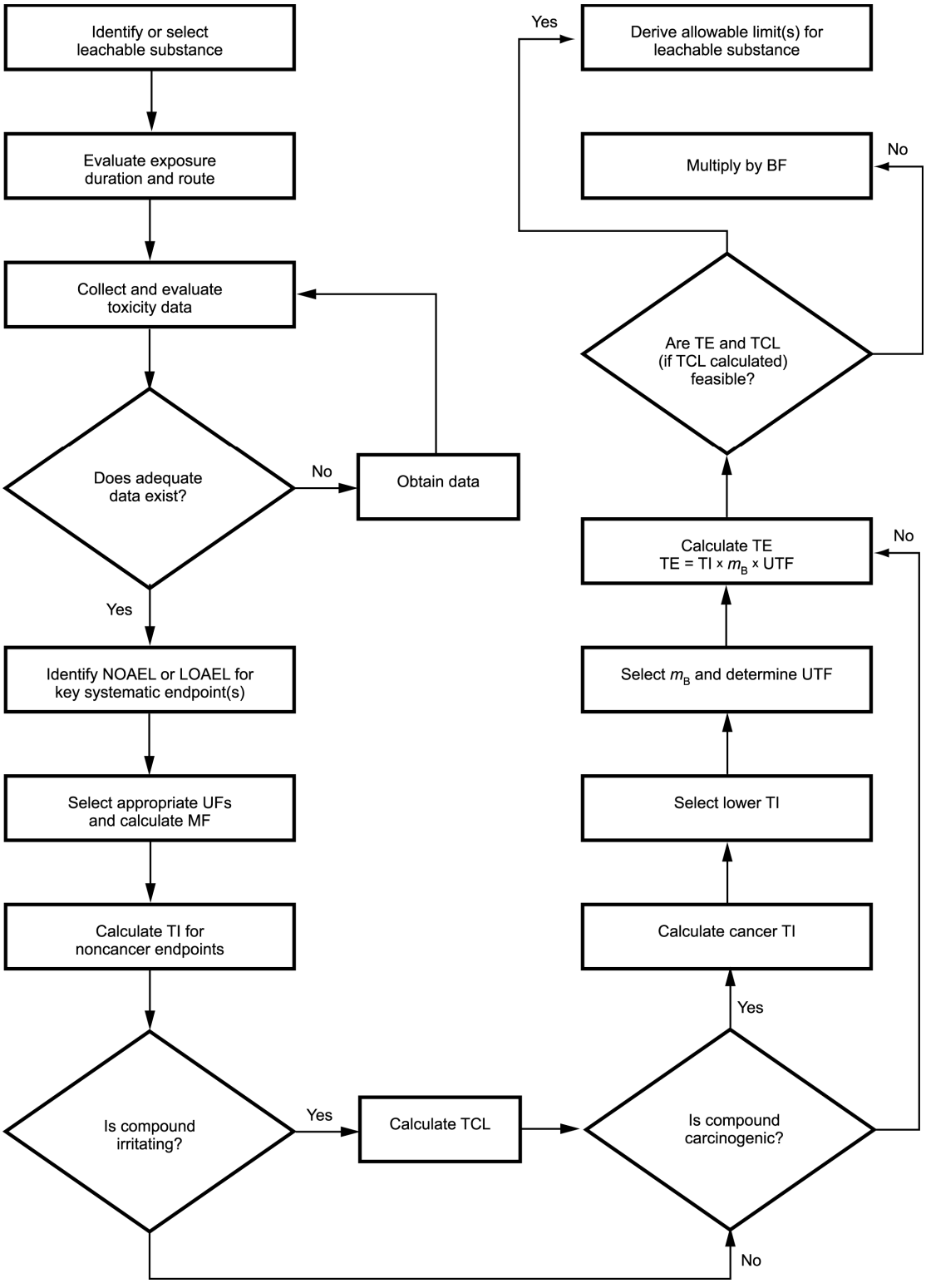

Figure 1—Establishment of allowable limits for leachable substances

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.

5.2 Exposure considerations for TI calculation

5.2.1 Data used

The following data will be used both as a part of the TI calculation in clause 5 and later as a part of determining the appropriate body mass 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 are 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 is available to establish a TI for a specific category, for example, when no chronic data is 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 TI s 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 is 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. This 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 is preferred over animal data.

The data shall be evaluated to identify critical adverse effects and to establish no adverse effect levels NOAELs for these effects. If the data is inadequate to allow a L_{NOAE} 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 is 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, a 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 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 kilograms 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 is 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 a 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 interindividual 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 is 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 is 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.

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

In most cases, a modifying factor between 10 and 1000 should be sufficiently protective. In a few cases, particularly where only poor or inappropriate data is 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 is available, a modifying factor greater than 10,000 may be necessary to establish a TI for permanent contact. Any situation that results in a modifying factor of 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) modeling 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 non-cancer end points 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 tumor types relevant to humans?

— Does 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 tumor 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) modeling 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 limit 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 this data is 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 centimeter, using the modifying-factor approach is:

$$\mathrm{TCL} = \frac{\mathrm{NIL\ or\ MIL}}{\mathrm{MF_{TCL}} \cdot A} \tag{3}$$

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 centimeters.

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 is limited. Hence $\mathrm{UF_6}$ may be 9 or more if both the relevance and quality of the data is poor.

5.6.3.3 Determination of the TCL modifying factor

The TCL modifying factor ($\mathrm{MF_{TCL}}$) shall then be calculated as a product of the uncertainty factors ($\mathrm{UF_4} \cdot \mathrm{UF_5} \cdot \mathrm{UF_6}$) 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 is 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 is preferable when calculating TIs for medical devices intended for use by neonates. When such data is 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 a 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 will 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):

$$UTF = CEF \cdot PEF \quad (4)$$

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

$$\mathrm{CEF} = \frac{\mathrm{TI} \cdot m_B}{\sum \frac{m_{life}}{25{,}000 \text{ days}}} \tag{6}$$

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 releases 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.

$$\mathrm{PEF} = \frac{n_{exp}}{n_{use}} \tag{7}$$

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 can not be determined, use a PEF default of 1.

6.4 Tolerable exposure

The tolerable intake is adjusted to take account of the way the device is used. The tolerable exposure 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 the use of the device and the use 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 the 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 should 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 centimeter.

TE is the tolerable exposure, in milligrams per day;

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

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 maximum amount 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 is available. This default data can serve as the basis for interspecies comparisons unless other data can be shown to be more appropriate. Actual species data varies somewhat in the real world.

A.2 Assumptions

A.2.1 Human

Default parameters for humans:

— 70 year lifetime;

— 2 L/day intake of drinking water;

— 20 m^3/24 h day air intake; 10 m^3/day 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/day of drinking water for males; 0.020 L/day for females;

— 0.29 m^3/24 h day air intake;

— 0.5 kg body mass for adult males; 0.35 kg for adult females;

— 22 day gestation period.

A.2.3 Mouse

Default parameters for mice:

— 2 year lifetime;

— 0.005 L/day 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 day gestation period.

A.2.4 Hamster

Default parameters for hamsters:

— 2 year lifetime;

— 0.015 L/day 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 day gestation period.

A.2.5 Guinea pig

Default parameters for guinea pigs:

— 3 year lifetime;

— 0.085 L/day of drinking water;

— 0.43 m^3/24 h day air intake;

— 0.5 kg body mass;

— 68 day gestation period.

A.2.6 Dog

Default parameters for dogs:

— 11 year lifetime;

— 0.5 L/day of drinking water;

— 7.5 m^3/24 h day air intake;

— 16 kg body mass;

— 63 day gestation period.

A.2.7 Rabbit

Default parameters for rabbits:

— 7 year lifetime;

— 0.33 L/day drinking water;

— 1.44 m^3/24 h day air intake;

— 3 kg body mass;

— 31 day gestation period.

Annex B
(informative)

Risk assessment for mixtures of leachable substances

If the compounds being leached from a device exert their effects via a common toxicological mechanism of action or are structurally similar to one another (e.g., phthalate esters, acrylates, methacrylates), and the dose of these compounds received by a patient is well below the respective TI value for each compound, it can be assumed that any effects will occur in an additive fashion; that is, the combined effects of two or more agents is equal to the sum of the effects of each agent given alone. As a result, a hazard index (HI) approach can be used to estimate the likelihood that adverse effects will occur following exposure to the mixture. An HI can be calculated as follows:

$$HI = \sum_{i=1}^{n} \frac{dose_i}{TI_i} \qquad \text{(B.1)}$$

where

n is the number of components of the mixture;

$dose_i$ is the dose of each compound received by the patient, in milligrams per day;

TI_i is the tolerable intake, in milligrams per day, of each compound.

Annex C
(informative)

Conversion of allowable limits for systemic exposure and for body surface contact to maximum dose to patient from a medical device

C.1 Introduction

This annex describes the method for calculating the maximum amount, i.e. the maximum dose, expressed as a mass, to patient, of a substance leachable from a medical device based upon the ISO allowable limit for the leachable substance.

A leachable substance may have multiple allowable limits. There are allowable limits for systemic exposure which include allowable limits for some or all of the three ISO 10993-1 exposure categories, namely, limited exposure, prolonged exposure and permanent contact. Within each of these exposure categories there may be allowable limits for specific exposure populations, in addition to the allowable limit for adults. There may also be different limits for specific routes of entry. Lastly, there may also be allowable limits for leachable substances that are irritating to body tissues.

Allowable limits for systemic exposure are expressed in units of mass per day (milligrams per day). Allowable limits for body surface contact are expressed in mass per surface area (milligrams per square centimeter).

C.2 Calculation of the maximum dose to patient of a leachable substance from a medical device for systemic exposure

C.2.1 Permanent-contact devices

Medical devices in the permanent-exposure category may be used from 31 days to 25,000 days.

The formula for calculation of the maximum amount of a substance that may be leached from a medical device in the permanent-exposure category follows:

$$m_{dev,\ perm} = AL_{perm} \times 25{,}000 \qquad (C.1)$$

where

$m_{dev,\ perm}$ is the maximum amount per device, i.e. maximum dose to patient in milligrams;

AL_{perm} is the allowable limit for the permanent-exposure category, in milligrams per day.

C.2.2 Prolonged-exposure devices

Medical devices in the prolonged-exposure category may be used from 2 days to 30 days.

The formula for calculation of the maximum dose to patient of a substance leachable from a medical devices in the prolonged-exposure category follows:

$$m_{dev,\ prol} = AL_{prol} \times 30 \qquad (C.2)$$

where

$m_{dev,\ prol}$ is the mass device, i.e. maximum dose to patient, in milligrams;

AL_{prol} is the allowable limit for the prolonged-exposure category, in milligrams per day.

C.2.3 Limited-exposure devices

For medical devices in the limited-exposure category, i.e. use for up to 24 h (one day), the allowable limit for the leachable substance in units of milligrams per day becomes the maximum dose to patient of the leachable substance in units of milligrams (per device).

$$m_{dev,\ lmt} = AL_{lmt} \times 1 \qquad (C.3)$$

where

$m_{dev,\ lmt}$ is the mass per device, i.e. maximum dose to patient, in milligrams;

AL_{lmt} is the allowable limit for the limited-exposure category, in milligrams per day.

C.3 Calculation of the maximum dose to patient of a substance leachable from medical devices from body-surface contact

The formula for calculation follows:

$$m_{dev,\ BSC} = m_A \cdot A \qquad (C.4)$$

where

$m_{dev,\ BSC}$ is the massper device, i.e., maximum dose to patient, in milligrams;

m_A is the tolerable contact level, in milligrams per square centimeter;

A is the surface area of medical device in contact with the body, in square centimeters.

Annex D
(informative)

Risk analysis report

D.1 General

Any thorough documentation of the information and rationale used to establish the allowable limits for leachable substances from medical devices will suffice. The following is offered as a possible report. Either a report may be made for each device, or a report for each substance or any logical report coverage based upon individual circumstances. Minimization of paperwork to the extent possible is desired.

D.2 Contents

The report should contain the following information:

a) the identity of the leachable substance(s);

b) a brief description of the device(s) in question;

c) key NOAEL(s), LOAEL(s), NIL(s), and/or MIL(s) or other endpoints for the leachable substance. Each item should be referenced; modifying factor chosen and its justification (i.e., justifications for UF_1, UF_2, UF_3, etc.);

d) non-cancer TI(s);

e) cancer TIs), if appropriate;

f) TCLs), if appropriate;

g) UTF and its justification (i.e., justifications for CEF and PEF);

h) TE and its justification;

i) feasibility evaluation summary with references for all key data used;

j) if applicable, the BF chosen and its justification, with references to all key data used;

k) allowable limits for the residue(s);

l) statement to the effect that the allowable limits were calculated using the methods described in this part of ISO 10993.

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