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Introduction

This draft standard is based on national and international discussions. Your comments on this draft are invited and will assist in the preparation of the consequent standard.

For international standards, comments will be reviewed by the relevant UK national committee before sending the consensus UK vote and comments to the international committee, which will then decide appropriate action. If the international standard is approved, it is usual for the text to be published as a British Standard.

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Template for comments and secretariat observations

Date: xx/xx/20xx	Document: ISO/DIS xxxx
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1	2	(3)	4	5	(6)	7
MB	Clause No./ Subclause No./Annex (e.g. 3.1)	Paragraph/ Figure/Table/Note	Type of comment	Comment (justification for change) by the MB	Proposed change by the MB	Secretariat observations on each comment submitted
	3.1	Definition 1	ed	Definition is ambiguous and needs clarifying.	Amend to read '...so that the mains connector to which no connection...'	
	6.4	Paragraph 2	te	The use of the UV photometer as an alternative cannot be supported as serious problems have been encountered in its use in the UK.	Delete reference to UV photometer.	



DRAFT International Standard

ISO/DIS 10993-3

Biological evaluation of medical devices —

Part 3: Evaluation of genotoxicity, carcinogenicity, reproductive toxicity, and developmental toxicity

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Foreword

ISO (the International Organization for Standardization) and IEC (the International Electrotechnical Commission) form the specialized system for worldwide standardization. National bodies that are members of ISO or IEC participate in the development of International Standards through technical committees established by the respective organization to deal with particular fields of technical activity. ISO and IEC technical committees collaborate in fields of mutual interest. Other international organizations, governmental and non-governmental, in liaison with ISO and IEC, also take part in the work. In the field of information technology, ISO and IEC have established a joint technical committee, ISO/IEC JTC 1.

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

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This document was prepared by Technical Committee ISO/TC 194, *Biological and clinical evaluation of medical devices*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 206, *Biocompatibility of medical and dental materials and devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition of ISO 10993-3 cancels and replaces the third edition (ISO 10993-3:2014), which has been technically revised.

The main changes compared to the previous edition are as follows:

- Deletion of the Annex on Cellular Transformation;
- Restructure of [Annex A](#) on Guidance on selecting an appropriate test sample preparation procedure for genotoxicity testing;
- Addition of [Annex C](#) on in vivo carcinogenicity assays that includes the Annex on solid state carcinogenesis;
- Addition of [Annex D](#) on Genotoxicity Assessment of Nanomaterials;
- Expanded [Annex B](#) on genotoxicity test methods;
- Addition of [Annex E](#) on Recipe for S9 mix;
- Addition of [Annex G](#) on the evaluation of reproductive and developmental toxicity;
- Update of normative references and bibliography.

A list of all parts in the ISO 10993 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html

Introduction

The basis for biological evaluation of medical devices is often empirical and driven by relevant concerns for human safety. The risk of serious and irreversible effects, such as cancer or second generation abnormalities, is of particular public concern. It is inherent in the provision of safe medical devices that such risks be minimized to the greatest extent feasible. The assessment of mutagenic, carcinogenic, reproductive, and developmental toxicity hazards is an essential component of the control of these risks. Not all test methods for the assessment of genotoxicity, carcinogenicity, reproductive toxicity, and developmental toxicity are equally well developed, nor is their validity well established for the testing of medical devices.

Significant issues with test sample size and preparation, scientific understanding of disease processes and test validation can be cited as limitations of available methods. Since the previous document revision, many genotoxicity test methods have been updated with revised OECD guidelines. However, these generally provide clearer recommendations but little alteration in test methods. Scientifically sound alternatives to the proposed testing can be acceptable insofar as they address relevant matters of safety assessment.

In the selection of tests needed to evaluate a particular medical device, a careful assessment of expected human uses and potential interactions with biological systems is important, particularly in such areas as reproductive and developmental toxicology.

This document presents test methods and evaluation strategies for the identification of specific biological harms. Testing is not always necessary or helpful in managing toxicological risks associated with exposure to medical device materials but, where it is appropriate, it is important that maximum test sensitivity is achieved.

In view of the multitude of possible outcomes and the importance of factors such as extent of exposure, species differences and mechanical or physical considerations, risk assessment is typically performed on a case-by-case basis. Suggestions for risk consideration and integration of ISO 10993-17 and -18 are provided.

Biological evaluation of medical devices —

Part 3:

Evaluation of genotoxicity, carcinogenicity, reproductive toxicity, and developmental toxicity

1 Scope

This document specifies strategies for risk estimation and selection of biological harms identification tests with respect to the possibility of the following potentially irreversible biological effects arising as a result of exposure to medical devices:

- genotoxicity;
- carcinogenicity;
- reproductive and developmental toxicity.

This document is applicable when the need to evaluate a medical device for potential genotoxicity, carcinogenicity, reproductive toxicity, and developmental toxicity has been established.

NOTE Guidance on selection of relevant endpoints is provided in ISO 10993-1.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1:2018, *Biological evaluation of medical devices — Part 1: Requirements and general principles for the evaluation of biological safety within a risk management process*

ISO 10993-2:2022, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-12:2021, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-16:2017, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Toxicological risk assessment of medical device constituents*

ISO 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process*

ISO 14971:2019, *Medical devices — Application of risk management to medical devices*

OECD 414, *OECD Guideline for the Testing of Chemicals — Prenatal Development Toxicity Study*

OECD 421, *OECD Guideline for the Testing of Chemicals — Reproduction/Developmental Toxicity Screening Test*

OECD 422, *OECD Guideline for the Testing of Chemicals — Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test*

OECD 443, *OECD Guideline for the Testing of Chemicals — Extended One-Generation Reproductive Toxicity Study*
OECD 471, *OECD Guideline for the Testing of Chemicals — Bacterial Reverse Mutation Test*
OECD 473, *OECD Guideline for the Testing of Chemicals — In vitro Mammalian Chromosome Aberration Test*
OECD 474, *OECD Guideline for the Testing of Chemicals — Mammalian Erythrocyte Micronucleus Test*
OECD 475, *OECD Guideline for the Testing of Chemicals — Mammalian Bone Marrow Chromosomal Aberration Test*
OECD 487, *OECD Guideline for the Testing of Chemicals — In vitro Mammalian Cell Micronucleus Test*
OECD 488, *OECD Guideline for the Testing of Chemicals — Transgenic Rodent Somatic and Germ Cell Gene Mutation Assays*
OECD 489, *OECD Guideline for the Testing of Chemicals — In Vivo Mammalian Alkaline Comet Assay*
OECD 490, *OECD Guideline for the Testing of Chemicals — In vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1, ISO 10993-12 and the following apply.

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

- 1) ISO Online browsing platform: available at <https://www.iso.org/obp>
- 2) IEC Electropedia: available at <https://www.electropedia.org/>

3.1 carcinogenicity test

test to determine cancer outcomes after long term or life-span exposure of animals

3.2 developmental toxicity test

test to determine adverse effects on the developing organism during prenatal development, or postnatally to the time of sexual maturation

3.3 genotoxicity test

test using cells, bacteria, yeast, fungi, animals, or other biological systems to determine whether gene mutations, chromosomal alterations, or other genetic changes are caused by the test sample

3.4 reproductive toxicity test

test to evaluate the potential effects of test samples on male or female reproductive function during any stage of development or fertility

3.5 sham-incubated vehicle

vehicle control exposed to the same extraction time and temperature as the test sample extract

3.6 threshold of toxicological concern TTC

level of exposure for constituents, below which there would be no appreciable risk to human health

Note 1 to entry: The constituent is defined as a chemical or compound present in or on a finished medical device or material(s) of construction. Constituents may be intentionally present (e.g., an additive such as an antioxidant) or unintentionally present (e.g., an impurity).

[SOURCE: ISO/TS 21726:2019 3.5, modified — Note 1 to entry has been added.]

4 Assessment strategies

4.1 General

ISO 10993-1 indicates circumstances where the potential for genotoxicity, carcinogenicity, reproductive toxicity, and developmental toxicity are relevant biological harms for consideration in an overall biological safety evaluation. Evaluation of the biological harms shall be conducted with consideration of the following factors:

- whether assessment is necessary based on patient population (e.g. not in the case of <6 months life expectancy); and the anticipated impact of test results on risk management judgements,
- whether assessment is necessary based on the worst-case quantity, type of contact and duration of exposure,

NOTE Quantity can be influenced by device size and number used per patient.

- an analysis of the chemical constituents of the device material(s), including manufacturing process residues and degradation products or metabolites, to identify causes of concern. The identification can be based on chemical-specific toxicity data if available; otherwise, structure-activity relationships or previous demonstration of relevant toxicity in the chemical class can be used,
- existing information relevant to the genotoxicity, carcinogenicity, reproductive toxicity, and developmental toxicity evaluation of the medical device, and
- previous use of equivalent (see ISO 10993-1:2018, 4.1) materials and processing in relevant applications.

The decision to waive in vitro genotoxicity testing shall be justified. The decision to conduct in vivo testing shall be justified.

4.2 Other considerations

Toxicity evaluation can be warranted for additional states of the device, such as wear debris generated from the device, absorbable materials, or materials that cure in situ (e.g. cements, adhesives, and pre-polymer mixtures) unless toxicological risk assessment based on material information determines no cause for concern. For guidance on sample preparation for in situ curing devices see ISO 10993-12.

NOTE Material information can include chemical composition, degradation products, debris size and morphology, pre-polymerization, and post-polymerization products etc.

If exposure to constituents identified in accordance with ISO 10993-18 is determined to be within acceptable levels based on toxicological risk assessment conducted in accordance with ISO 10993-17, no additional testing needs to be performed to address the relevant risks.

5 Genotoxicity assessment

5.1 General

Assessment of genotoxic risk should be made:

- a) by toxicological risk assessment based on chemical characterization in accordance with ISO 10993-17 and ISO 10993-18 or;
- b) by performing genotoxicity testing in the standard test battery in accordance with [5.2.2](#).

In certain cases (e.g. a material which has not been used in a legally marketed device), both toxicological risk assessment and genotoxicity testing can be appropriate.

If the device is made with and releases nanomaterials, additional evaluation shall be considered.

NOTE See ISO/TR 10993-22 and [Annex D](#) for more information.

If the device contains identified genotoxicants which are not easily detected using non-targeted analytical approaches described in ISO 10993-18 (e.g. glutaraldehyde, formaldehyde), targeted analysis of genotoxic residuals shall be conducted. Where compositional profiling or analytical chemistry reveals the presence of chemical constituents with inadequate genotoxicity data and where QSAR (quantitative structure activity relationship) information is inconclusive (see ISO 10993-17), testing of individual chemicals or device components containing the chemical should be considered. In either case the test sample shall be justified.

5.2 Testing strategy

5.2.1 General

No single test is capable of detecting all genotoxic agents. Therefore, the usual approach is to conduct a battery of in vitro and under certain circumstances also in vivo tests.

Genotoxicity tests are designed to detect the two major classes of genetic damage:

- gene mutations (DNA single base pair changes, small deletions or additions), and
- Chromosomal damage (structural aberrations such as translocations, small or large deletions and insertions, and gain or loss of whole chromosomes (aneuploidy) or parts of chromosomes).

NOTE Bacterial reverse mutation assays have been shown to detect relevant small-scale mutational changes produced by the majority of genotoxic carcinogens detected by rodent bioassays.

5.2.2 Test battery

When genotoxicity testing is performed, it shall be conducted in accordance with [Annex B](#) and the test battery shall include:

- 1) a test for gene mutations in bacteria (see OECD 471), modified for medical devices, see [clause B.2](#), and
- 2) one of the following three validated in vitro mammalian cell tests:
 - a) an in vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells (see OECD 473), modified for medical devices, see [clause B.3](#) and [B.4.1.2](#), or
 - b) an in vitro mouse lymphoma tk⁺/₋ assay using L5178Y cells (see OECD 490), modified for medical devices, including detection of small (slow growing) and large colonies, see [clause B.3](#) and [B.4.1.1](#), or
 - c) an in vitro mammalian cell micronucleus test for chromosomal damage and aneugenicity (see OECD 487), modified for medical devices, see [clause B.3](#) and [B.4.1.3](#).

NOTE 1 The OECD 471 can be inappropriate for nanomaterials, see [Annex D](#).

Tests shall be performed in the presence and absence of metabolic activation. Metabolic activation is achieved by addition of a co-factor-supplemented post-mitochondrial fraction (S9).

NOTE 2 An example for a S9 recipe is given in [Annex E](#).

In vitro mammalian tests shall include both a short-term exposure with and without S9 and a long-term exposure without S9.

Results from both chromosomal aberration assays and the in vitro mouse lymphoma tk⁺/₋ assay (MLA) have a relatively high level of congruence for compounds that are regarded as genotoxic but yield negative results in the bacterial reverse mutation assay. The MLA detects the broadest set of genetic damage, including both small-scale and large-scale genetic damage. The micronucleus assay detects chromosomal damage in the form of whole chromosome loss or chromosomal fragments and uniquely detects aneuploidy. The three tests are equally acceptable as an in vitro mammalian genotoxicity test (see OECD 473, OECD 487 and OECD 490).

5.2.3 In vivo genotoxicity testing

- 1) In vivo genotoxicity tests are not part of the recommended genotoxicity test battery because they are relatively insensitive and not likely to detect the concentrations of substances generally found in medical devices or in medical device extracts.^{[52][53]} However, under certain circumstances, an in vivo test can be informative. These circumstances can include assessment of nanomaterial or other particulates suspected of sequestration in particular organs or tissues (see [Annex D](#), [2] and ISO/TR 10993-22); or
- 2) when additional relevant factors e.g. toxico-kinetics (see ISO 10993-16) or organ-specific toxicity need to be considered.

In vivo tests are valid only with data demonstrating the test sample reached the target cells, organs, or tissues. Mutational analysis in target organs of rats or mice can be determined using one of several rodent transgenic mutation assays (see OECD 488); chromosomal damage can be assessed in the erythrocyte micronucleus assay (see OECD 474), the in vivo comet assay (see OECD 489), or the in vivo chromosomal aberration assay (see OECD 475). See [B.5](#) for additional considerations for in vivo assays.

All animal studies shall be performed in a facility approved by a nationally recognized organization and in accordance with all appropriate regulations dealing with laboratory animal welfare to comply with the requirements of ISO 10993-2.

5.2.4 Follow-up evaluation

If genotoxicity tests are performed in accordance with [5.2.2](#) and if the in vitro tests are negative, the test article can be considered non-genotoxic and further testing is not necessary.

When any single in vitro test is positive, then the following options shall be considered:

- a) Identification of genotoxic constituents such as impurities or residues by chemical characterization (information gathering or analytical chemistry testing) or other testing, with appropriate steps taken to eliminate or manage any identified risks.
- b) If confounding factors are suspected to have caused the positive response in an initial genotoxicity test, the dosing and/or test conditions may be altered.
- c) Presume that a genotoxicity risk exists and manage the risk in accordance with ISO 14971. Equivocal results (i.e. elevated results that don't meet criteria for a positive result), can require repeating tests with a modified protocol such as adjusting dilution of the extract or the test chemical in the test system.

5.3 Test sample preparation

Test samples should be extracted in vehicles compatible with the test system (see [Annex A](#)). Use of extraction vehicles that are incompatible with the test system require additional manipulation (e.g. solvent removal) that can alter the composition of the extract and, therefore, affect the results of the test. Use of extraction vehicles that are incompatible with the test system shall be justified.

Extraction shall be performed in accordance with ISO 10993-12 unless otherwise justified.

Tests can be performed on solutions (e.g. soluble or liquid devices), suspensions (e.g. Method A in [Annex A](#)), extracts (e.g. Method B in [Annex A](#)) of the finished product, device components or individual chemicals from the medical device. If individual chemicals are tested, then the appropriate OECD guidelines shall be followed.

NOTE Some authorities having jurisdictions prefer Method C in [Annex A](#) to be used.

6 Carcinogenicity Assessments

6.1 General

The objective of carcinogenicity studies is to determine tumorigenic potential in animals and to evaluate the relevant risk to patients. Mechanisms of carcinogenesis can be genotoxic or non-genotoxic. Medical devices shall be evaluated for both types of carcinogenicity, preferably by alternative approaches, such as chemical characterization and toxicological risk assessment, that do not use in vivo testing.

Animal testing for carcinogenicity is technically challenging. It requires implantation of many medical devices or representative samples of the medical device or the application of concentrated medical device extracts to achieve the elevated doses necessary for a valid test in a reasonable number of animals. For these reasons animal testing is generally not justified when the risks can be adequately assessed by other means.

NOTE For additional information on animal carcinogenicity testing, see [Annex C](#).

Where genotoxicity of a medical device is established, additional evaluation of carcinogenic risk shall be performed (e.g. ISO 10993-17). In this situation, additional factors such as genotoxicity results, history of clinical use, and the indication for use should be considered in determining the risk. It can be informative to identify the genotoxic constituent(s) and focus the evaluation on that chemical.

6.2 Evaluation strategy

6.2.1 General

Carcinogenicity should be evaluated initially using chemical characterization in accordance with ISO 10993-18 and toxicological risk assessment in accordance with ISO 10993-17. In cases where devices or materials are not readily amenable to analytical chemistry testing and adequate material information is available along with genotoxicity testing data on the final finished device, it is always preferable to use chemical information and toxicological risk assessment to determine potential carcinogenicity rather than performing an animal carcinogenicity study.

NOTE 1 Some authorities having jurisdictions can require consideration of carcinogenicity testing for novel materials (e.g. when data are not available to provide an adequate assessment).

If the results of toxicological risk assessment indicate no unacceptable risk of carcinogenicity from the device, then no further assessment is required.

Carcinogenicity testing shall not be performed when risks can be adequately assessed or managed without generating new carcinogenicity test data or when the benefit/risk analysis obviates the need for a carcinogenicity assessment. If the toxicological risk assessment demonstrates an unacceptable risk of carcinogenicity from the device, the risk shall be managed accordingly (see also ISO 14971). Alternatively, if the device contains a chemical with inadequate toxicological data, biological testing shall be justified on the basis of a need for additional information. The assessment should address both genotoxic (see [6.2.2](#)) and non-genotoxic carcinogenicity (see [6.2.3](#)) on the individual chemical identified in the toxicological risk assessment.

NOTE 2 The history of human clinical use can be considered in the risk assessment. The clinical evidence for carcinogenicity risk is generally not monitored over an adequate timeframe and this aspect of device safety can be unknown.

6.2.2 Genotoxic carcinogens

The risk from genotoxic carcinogens can be established by genotoxicity testing or by toxicological risk assessment. Testing will require a battery of tests (see [5.2.2](#)).

Where genotoxicity of a medical device is established, additional evaluation of carcinogenic risk shall be performed in accordance with ISO 10993-17. In these situations, additional factors such as genotoxicity results, history of clinical use, and the indication for use should be considered in determining the risk

assessment. It can be informative to identify the genotoxic constituent and focus the evaluation on that chemical.

NOTE While genotoxic carcinogenicity involves non-threshold mechanisms, there are exposure levels below which impact on lifetime cancer risk is considered acceptable (usually less than 1 in 100 000 additional lifetime incidence).

6.2.3 Non-genotoxic carcinogens

Non-genotoxic carcinogens do not cause direct DNA damage but induce cancer via other mechanisms (see [29], [30] and [31]). These carcinogens predominantly induce their effects (leading to cancer) upon repeated exposure leading to prolonged interference with homeostatic processes that lead to irreversible and uncontrolled cellular proliferation. The prediction of carcinogenic potential of non-genotoxic chemicals is complicated by:

- the diversity of modes of action;
- the tissue and species specificity; and
- the absence of currently validated tests methods.

While a reliable evaluation is to conduct a rodent carcinogenicity test (see [30], [32], [33] and [34]), there are many practical challenges (see 6.1). Therefore, toxicological risk assessment in accordance with ISO 10993-17 should be used.

If the substance is not genotoxic and carcinogenicity data is not available, then a tolerable intake based on subchronic, or chronic systemic toxicity data can be useful for evaluating the risk. If there is insufficient data to set a TI, then the TTC described in ISO/TS 21726 may be used to estimate the risk. Recent publications indicate that the TTCs based on Cramer Class are protective for non-genotoxic carcinogens (see [37]).

NOTE 1 Non-genotoxic carcinogens have thresholds, below which the risk of cancer is unlikely (ECHA 2017^[36]).

NOTE 2 Approaches for prediction of non-genotoxic carcinogenicity are under active investigation (e.g., [33] and [35]).

NOTE 3 Examples for non-genotoxic carcinogens can be found in (see [37], supplementary material).

7 Evaluation of reproductive and developmental toxicity

7.1 General

Reproductive toxicity evaluation shall be considered for devices intended for use in individuals of reproductive age under any of the following conditions:

- devices have prolonged or long-term direct or indirect contact with reproductive organs or gametes;
- devices have prolonged or long-term in vitro contact with gametes/ reproductive tissue;
- devices have prolonged or long-term use and contain known or presumed reproductive toxicants (materials with a known adverse effect on reproduction);
- devices are absorbable or cure in situ, and are in close proximity to the reproductive organs, regardless of duration of contact; or
- materials which have not been used in a legally marketed device, for a similar intended purpose.

NOTE 1 Material means material of construction, intended additives, or process residuals, or any combination of the three.

NOTE 2 Similar use means the nature of contact category and contact-duration category are the same; and the device risk level is considered the same or lower compared to the legally marketed device. In addition to contact category and contact-duration, additional factors to consider in the determination of the device risk level include: the material type and quantity, the material constituent composition, device contact frequency, nature/degree of tissue contact with the device, and user population.

Developmental toxicity evaluation shall be considered for:

- devices with prolonged or long-term direct or indirect contact with embryos or fetuses; and
- devices for prolonged or long-term use on individuals in early childhood and contain known or presumed developmental toxicants [e.g. endocrine disruptors (see [Annex F](#)) and lead]. Potential exposure from a medical device contacting lactating women should also be considered.
- devices are absorbable or cure in situ, and are in close proximity to the reproductive organs, regardless of duration of contact; or
- materials which have not been used in a legally marketed device, for an equivalent intended purpose.

7.2 Evaluation methods

Assessment of reproductive and developmental risk should be made:

- a) by toxicological risk assessment based on chemical characterization in accordance with ISO 10993-17 and ISO 10993-18 or;
- b) by performing developmental and reproductive testing as described in [Annex G](#).

Current biological methods are for single substances and are not validated for mixtures (e.g. medical device extracts). Evaluation for medical devices shall first consider a toxicological risk assessment focusing on reproductive and developmental toxicity in accordance with ISO 10993-17. Exposure estimates can be determined through chemical characterization outlined in ISO 10993-18.

Exposure estimates can be improved with simulated-use extraction studies. If it is determined that the amount of a reproductive and developmental toxicant in the device is above acceptable limits, the presence of the toxicant shall be carefully considered for risk control where possible and in the benefit-risk analysis in the (overall) risk management file in accordance with ISO 14971:2019, 7.4.

The following factors should be considered in the toxicological risk assessment:

- an assessment of reproductive potential of the subject population (devices used in early adulthood, or reproductive age-individuals);
- a specific assessment of reproductive toxicity data, if available;
- the potential for exposure of reproductive tissues, the developing offspring, or nursing child, including available chemical characterization information in accordance with ISO 10993-18 and available toxicokinetic studies in accordance with ISO 10993-16;
- device physical characteristics;
- available device genotoxicity information;
- history of clinical use;
- indication for use; and
- the need for additional information relevant to the reproductive and developmental toxicity risk arising from use of the device (see ISO 10993-1).

NOTE For more information see [Annex G](#).

When the remaining risk is unacceptable due to a lack of robust experimental data, individual chemical substances can be tested with in vitro or in vivo biological test methods (e.g. ICH S5[38]) (see [clause G.2](#)).