

TECHNICAL REPORT

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Biological evaluation of medical devices — **Part 9:** Degradation of materials related to biological testing

Évaluation biologique des dispositifs médicaux —

Partie 9: Dégradation des matériaux relative à l'évaluation biologique



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Foreword

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

The main task of technical committees is to prepare International Standards, but in exceptional circumstances a technical committee may propose the publication of a Technical Report of one of the following types:

- type 1, when the required support cannot be obtained for the publication of an International Standard, despite repeated efforts;
- type 2, when the subject is still under technical development or where for any other reason there is the future but not immediate possibility of an agreement on an International Standard;
- type 3, when a technical committee has collected data of a different kind from that which is normally published as an International Standard ("state of the art", for example).

Technical Reports of types 1 and 2 are subject to review within three years of publication, to decide whether they can be transformed into International Standards. Technical Reports of type 3 do not necessarily have to be reviewed until the data they provide are considered to be no longer valid or useful.

ISO/TR 10993-9, which is a Technical Report of type 2, was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This document is being issued in the type 2 Technical Report series of publications (according to subclause G.4.2.2 of part 1 of the ISO/IEC Directives, 1992) as a "prospective standard for provisional application" in the field of degradation of materials because there is an urgent need for guidance on how standards in this field should be used to meet an identified need.

This document is not to be regarded as an "International Standard". It is proposed for provisional application so that information and experience of its use in practice may be gathered. Comments on the content of this document should be sent to the ISO Central Secretariat.

A review of this type 2 Technical Report will be carried out not later than two years after its publication with the options of: extension for another two years; conversion into an International Standard; or withdrawal.

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

- *Part 1: Guidance on selection of tests*
- *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 cytotoxicity: in vitro methods*
- *Part 6: Tests for local effects after implantation*
- *Part 7: Ethylene oxide sterilization residuals*
- *Part 9: Degradation of materials related to biological testing [Technical Report]*
- *Part 10: Tests for irritation and sensitization*
- *Part 11: Tests for systemic toxicity*
- *Part 12: Sample preparation and reference materials*
- *Part 13: Identification and quantification of degradation products from polymers*
- *Part 14: Identification and quantification of degradation products from ceramics*
- *Part 15: Identification and quantification of degradation products from coated and uncoated metals and alloys*
- *Part 16: General guidance on toxicokinetic study design for degradation products and leachables from medical devices*
- *Part 17: Glutaraldehyde and formaldehyde residues in industrially sterilized medical devices*

Annexes A, B and C of this part of ISO 10993 are for information only.

Introduction

Attention is drawn to the definition of “medical device” (see 3.1).

When the material of an implanted device experiences a decrease in its mechanical properties and/or mass, it is referred to as degradation for polymers and ceramics, and corrosion for metals and alloys. For those medical devices and materials which experience repeated stress cycles during use, the biological environment may reduce their anticipated fatigue life or endurance limit.

The stability of materials and devices in the biological environment is influenced by the conditions of the service environment as well as the chemical composition, additives, processing aides, impurities, manufacturing processes and decontamination/sterilization.

In addition to the principal components, most polymers contain additives such as antioxidants and stabilizers and all materials contain either minor components or impurities which may be leachable and enter the biological environment and induce a tissue response even if the principal component is stable. Most devices rely upon their stability to ensure safe and efficacious performance. Others, such as resorbable sutures, are designed intentionally to degrade.

While the ability to predict the stability of materials and medical devices *in vivo* is of great importance, the extrapolation of *in vitro* data to the clinical service environment remains a difficult, yet-to-be resolved problem. *In vitro* methods for assessing degradation of materials and medical devices range from the very simple, e.g. exposure to 0,9 % isotonic saline solution, to more complex exposure to solutions containing enzymes, phospholipids, etc. In addition, the material/device can be subjected to external mechanical stress/load during testing. A sequential approach to *in vitro* degradation testing of medical devices and materials involving both accelerated and real-time testing techniques is shown in figure 0.1.

Selection of methods for accelerating degradation testing in a manner which is representative of the service environment remains the responsibility of the designers of the *in vitro* test schemes used. Currently, there are no standard practices, methods or guidelines for the assessment of the degradation of medical devices and materials, and of the degradation products formed, from degradation of these materials and devices in the biological environment. There are, however, methods used for extracting leachable fractions from materials and devices to be used in biological response testing (see, for example, ISO 10993-3, ISO 10993-5, ISO 10993-6 and ISO 10993-7).

The extraction media used may be selected to be compatible with the biological test and may not necessarily represent an adequate extraction of the material. There is a need for additional research to develop accelerated methods for evaluating materials degradation in the human body.

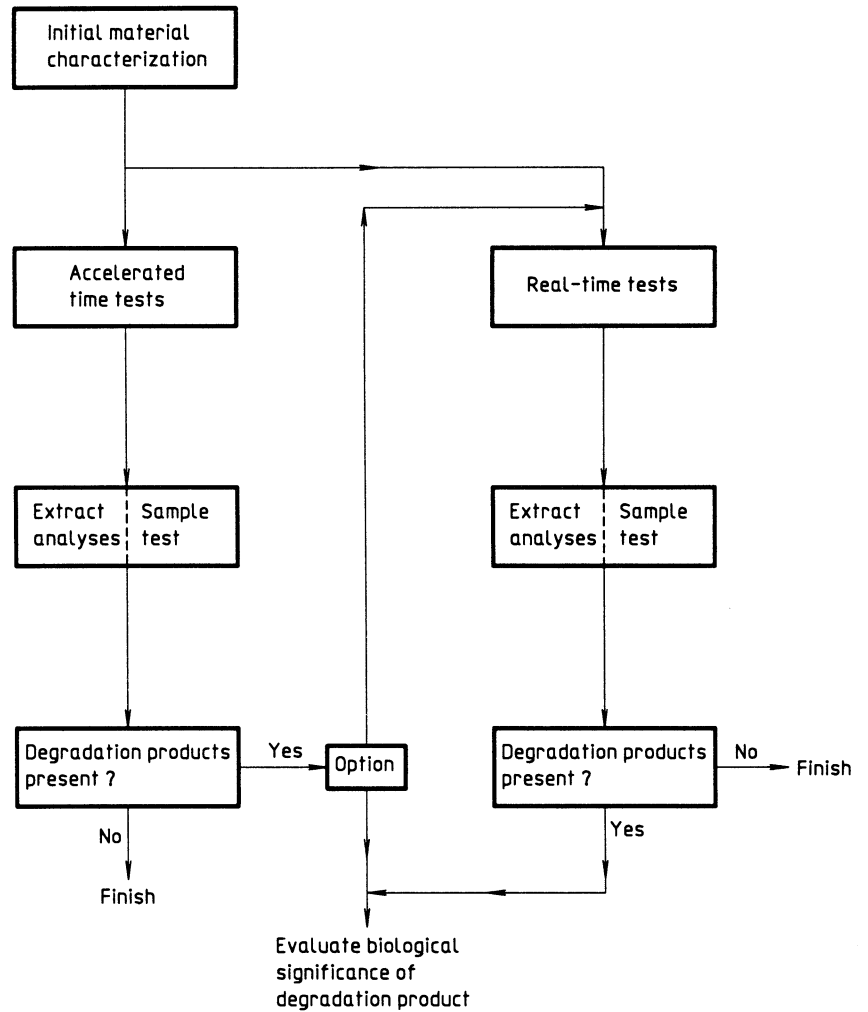


Figure 0.1 — Degradation product evaluation scheme

Biological evaluation of medical devices —

Part 9:

Degradation of materials related to biological testing

1 Scope

This Technical Report aims to facilitate the design of test procedures which are used to evaluate the biological responses to degradation products released from medical devices. Following brief descriptions of each major class of material used for medical devices, this Technical Report focuses on the likely mechanisms of degradation of these materials when they are used in a biological service environment. Accelerated time and real-time degradation testing environments for devices and materials are suggested along with characterization techniques for the degradation products. Finally, an approach for identifying and quantifying degradation products obtained from explanted devices and tissues is proposed.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this Technical Report. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this Technical Report are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 10993-1:1992, *Biological evaluation of medical devices — Part 1: Guidance on selection of tests*.

ISO 10993-3:1992, *Biological evaluation of medical*

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

ISO 10993-5:1992, *Biological evaluation of medical devices — Part 5: Tests for cytotoxicity: in vitro methods.*

ISO 10993-6:1994, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation.*

ISO 10993-7:—¹⁾, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals.*

ISO 10993-12:—¹⁾, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials.*

3 Definitions

For the purposes of this Technical Report, the definitions in ISO 10993-1, ISO 10993-3 and 10993-5, and the following definitions apply.

3.1 medical device: Any instrument, apparatus, appliance, material or other article, including software, whether used alone or in combination, intended by the manufacturer to be used for human beings solely or principally for the purposes of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease, injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;

1) To be published.

— control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means. (Repeated for convenience from ISO 10993-1:1992, definition 3.1.)

3.2 accelerated time test: Laboratory test designed to speed up the degradation of a material/device which would normally take place in the service environment.

3.3 aluminium oxide ceramic: High density, high purity Al_2O_3 which may be a fine-grained polycrystalline, semicrystalline, amorphous or single crystal material.

3.4 amorphous polymer: Macromolecules which do not form crystalline structures.

3.5 antistatic agent: Additive which increases surface conductivity of the material and thus reduces the buildup of charge on the surface.

3.6 bioabsorption: Dynamic process involving the interaction of the body with a biomaterial which results in the breakdown and dissolution or uptake of the material in the physiological environment.

3.7 bioadsorption: Deposition of components of tissue and body fluids on the surface of a material/device.

3.8 bioceramic: Ceramic which upon implantation is transformed into less soluble minerals.

3.9 biodegradation: Alteration undergone by the biomaterial or medical device involving loss of their integrity or performance when exposed to a physiological or simulated environment.

3.10 bioerosion: Dissolution or fragmentation of a biomaterial implanted in the body occurring as a result of surface reactions.

3.11 bioglass; bioglass ceramic: Glass based on SiO_2 which has a specific surface reactivity that enhances the interaction with surrounding tissue due to the action of additives, primarily alkali oxides.

3.12 biomaterial: Synthetic, natural or modified natural material intended to be in contact and interact with the biological system.

3.13 bioresorption: Process by which biomaterials are degraded in the physiological environment and the byproducts eliminated or completely bioabsorbed.

3.14 biostability: Quality of a biomaterial or a medical device of which the physical, chemical and mechanical or other changes are not modified with respect to its behaviour, function or performance within the biological environment.

3.15 biotransformation: Any change which a biomaterial undergoes in the body due to the interaction between the material and the physiological constituents.

3.16 branched polymer: Long-chain molecules with side chains attached to the backbone of the polymer. Often soluble in the same solvents as the corresponding linear polymers.

3.17 calcium phosphate ceramic: Ceramic based on calcium and phosphorus oxide containing one or more calcium phosphate phases.

3.18 coating: Deposited layer or covering on a biomaterial or medical/dental device which is intended to protect or enhance the performance of the device or biomaterial.

3.19 [random] [regular] [block] [graft] copolymer: Polymer consisting of different repeating units (made from two or more different monomers), having different degrees of order.

3.20 corrosion: Chemical reaction of a solid material (usually a metal or alloy) with the environment which causes measurable material property changes.

3.21 crevice corrosion: Usually accelerated chemical reaction in a small fissure, pit or crack of a metal or alloy within a corrosive environment.

3.22 crosslinked [network] polymer: Polymer with chemical linkages between the chains.

3.23 degradation product: Byproduct of a material which is generated by the breakdown or decomposition of the material.

3.24 depolymerization: Reversion of a polymer to its monomer(s) or to a polymer of lower relative molecular mass.

3.25 deposit: Layer or covering laid down on a biomaterial or medical device.

3.26 elastomer: Polymer which maintains its elastic properties in the temperature range between glass

transition temperature and the temperature at which the elastomer begins to flow.

3.27 electrolyte: Substance, usually in solution, which will transmit an electric current by ions.

3.28 environmental stress-cracking: Cracking of stressed materials subjected to certain conditions: the stress may be externally applied, or internally introduced during processing.

3.29 enzymatic degradation: Degradation of materials enhanced and/or initiated by enzymes.

3.30 extraction medium: Liquid which does not dissolve a material or device, but does induce the release of one or more extractable components.

3.31 fatigue corrosion: Combined effect of dynamic loads and chemical attack on metal or alloy properties within a corrosive environment.

3.32 fretting corrosion: Combined interaction of wear and chemical attack on a metal or alloy within a corrosive environment.

3.33 fibre: Arrangement of molecules into a long tubular shape where the length is of the order of 100 times the diameter. Fibre can be continuous or specific lengths.

3.34 filler: Various forms of inorganic or organic materials added to alter material properties.

3.35 final product: Medical device in its "as-used" state.

3.36 homopolymer: Polymer consisting of identical repeating units (made from a single monomer).

3.37 hydrolysis: Chemical bond-cleavage which involves attack by neutral or ionized water in acidic, neutral or basic aqueous media.

3.38 implant coating interface: Zone between the substrate and the coating.

3.39 implant tissue interface: Zone between the implant material and the tissue.

3.40 inert bioceramic: Bioceramic which undergoes no measurable chemical change during long-term contact with the biological environment.

3.41 interface: Zone of contact between two surfaces.

3.42 *in vitro* degradation: Changes in a material exposed to an environment simulating *in vivo* conditions.

3.43 *in vivo* degradation: Structural, physical, mechanical and chemical changes in a material that are induced by the organism.

3.44 leachable: Extractable component, such as additives, monomers and low relative molecular mass constituents in polymeric materials.

3.45 linear polymer: Long chains of uncrosslinked backbone atoms which form a macromolecule.

3.46 lubricant: Substance added to enhance material flow and handling characteristics (e.g. during injection-moulding, extrusion, etc.).

3.47 matrix: Embedding material for fibres or fillers.

3.48 monomer: Any molecule that can be converted into a polymer.

3.49 natural polymer: Macromolecules of natural origin, such as collagen, cellulose, polyaminoacids, rubber, etc.

3.50 oxidative degradation: Reaction occurring due to air (oxygen) or oxidizing agents leading to chain cleavage of chemical bonds.

3.51 pigment: Insoluble colorant added to a material.

3.52 plasticizer: Substance added to polymers which modifies their forming properties and increases the flexibility of products made from these polymers.

3.53 plastics: Synthetic polymers containing additives which enhance polymer processing and/or the final properties of the resulting products.

3.54 polymer blend: Two or more polymers mixed together or in solution to form a product which has properties very often different from those of individual polymers.

3.55 potentiostatic polarization method: Method equal to chronoamperometry with a constant potential: the time-dependent measurement of the current density going through a material/solution interface at a definite potential.

3.56 potentiodynamic polarization method: Method equal to voltamperometry with a linear variation of the potential: the potential-dependent

measurements of the current densities going through a material/solution interphase.

3.57 real-time test: Laboratory test performed to assess degradation of devices or materials which does not employ accelerating factors such as temperature, rapid cycling, etc.

3.58 resorbable bioceramic: Ceramic which upon implantation is dissolved into the surrounding body fluids and tissues.

3.59 resorbable cement: Cement formed from a mixture of inorganic powders, which sets upon mixing with water or dilute acidic or basic solutions and when implanted is dissolved into the surrounding body fluids and tissues.

3.60 resorbable polymer: Polymer deliberately designed to be biotransformed *in vivo* to a non-harmful byproduct which is subsequently eliminated from the organism.

3.61 semicrystalline polymer: Macromolecules able to crystallize partially from the melt or solution.

3.62 solvent: Substance which causes a gas, solid or liquid to dissolve without altering its (chemical)/(molecular) identity.

3.63 stabilizer: Additive added to materials to prevent chemical reactions.

3.64 stable polymer: Polymer which does not undergo any measurable changes when exposed to its service environment.

3.65 stress corrosion: Combined effect of static and/or dynamic stress and chemical attack on metal or alloy properties within a corrosive environment.

3.66 substrate: Material covered by a coating.

3.67 surface-reactive bioceramic: Ceramic which upon implantation shows a surface reaction which may lead to formation of chemical bonding at the implant/tissue interface.

3.68 surgical implant: Medical device implanted in the body by surgical means.

3.69 synthetic polymer: Man-made polymer.

3.70 thermoplastics: Polymers capable of undergoing repeated flow and solidification upon heating/cooling.

3.71 thermoset: Polymer that exists initially as a reactive compound, which upon heating, undergoes a reaction to form a solid, highly crosslinked insoluble matrix.

4 Classification of materials

Biomedical devices are constructed from a wide variety of materials, representing each of the major material classes. These classes include polymers, metals and alloys, ceramics, composites and coatings. A brief introduction to each class as related to its application as a biomedical material is given below.

4.1 Polymers

Polymers are long-chain molecules composed of small, simple repeating units called monomers. The repeating unit is usually equivalent, or nearly equivalent, to the monomer from which the polymer was obtained. Frequently, polymeric materials with relative molecular masses of approximately 20 000, and/or consisting of less than 1 000 to 2 000 repeating units in the chain, are called low molecular mass polymers, while polymeric materials above 20 000 and/or consisting of more than 2 000 repeating units in the chain are called high molecular mass polymers. The term polymer usually refers to the pure material which results from the polymerization process.

Depending on the structure of the polymer chain, polymers are called homopolymers, copolymers, or linear, branched or crosslinked polymers. Another class of polymeric materials is polymer blends consisting of a physical mixture of two or more polymers. Furthermore, depending on the material properties and behaviour, polymers can be divided into thermoplastics or thermosets. In relation to their origin, polymers can be further categorized as natural or synthetic.

4.2 Ceramics

Ceramics are inorganic materials prepared by high temperature thermal processes which form ionic bonds.

The use of ceramics as materials for medical devices originated from research in the early 1970's, which led to the introduction of a variety of bioceramics such as aluminium oxide, glass ceramics and calcium phosphate ceramics. This discussion mainly focuses on four types of ceramics, namely, aluminium oxide, glass ceramics, calcium phosphate ceramics and carbons. These types exhibit three different material responses, i.e. minimally reactive (aluminium oxide), surface reactive (glass ceramics) and resorbable

(calcium phosphate ceramics). The classification of calcium phosphate as a resorbable material is, at present, controversial since the degradation rate of the different types of calcium phosphate varies with changes in its stoichiometry and crystal structure. Wide differences of opinion exist on degradation of hydroxyapatite, a calcium phosphate ceramic, with some investigators classifying it as resorbable, while others consider it nonresorbable. A brief description of each of the major classes of ceramic materials is provided below.

4.2.1 Aluminium oxide is used in high purity form. Devices are, usually, fabricated from fine-grained polycrystalline material and used in load-bearing applications because of its high compressive strength, flexural strength and fatigue resistance. Both strength and fatigue resistance may decrease when it is exposed to physiological fluids.

4.2.2 Glass ceramics can be produced in various compositions. The basis of these ceramics is SiO_2 and P_2O_5 . Depending on the type, CaF_2 , K_2O , MgO , Al_2O_3 , TiO_2 and B_2O_3 can also be found. The surface reactivity is dependent on the composition of the material. For some compositions, hydroxyapatite crystals are expected to nucleate at the implant surface, causing a firm bond with surrounding collagen and bone.

4.2.3 The calcium phosphate ceramics, hydroxyapatite $[\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2]$, tricalcium phosphate $\text{Ca}_3(\text{PO}_4)_2$, and a biphasic combination of these two crystal structures are currently commercially available for use on surgical implants. Other calcium phosphates are currently being investigated for application as biomaterials as well: for example, fluorapatite, magnesium whitlockite and tetracalcium phosphate. The starting material for most hydroxyapatite ceramics is a powder with hydroxyapatite lattice, whereas hydrothermally processed coral materials such as porites are also used.

4.2.4 Ceramics can be fabricated in dense and porous forms. Dense ceramics are used as blocks, granules or coatings. An increase in porosity decreases compressive strength and increases surface area and rate of dissolution. High sintering temperatures tend to reduce the microporosity (pore size less than $3 \mu\text{m}$) of ceramics and may relate to the controversy surrounding the degradability of hydroxyapatites, the non-degradable form approaching theoretical density.

NOTE 1 A more complete listing of specific ceramic materials used medically is provided in table 1.

Table 1 — Classification of ceramic materials

Class	References	Form and composition
Ceramic based on alumina	ISO 6474	Dense sintered crystalline alumina (A1203)
	—	99,9 % pure porous alumina
	—	97 % pure porous alumina
	—	Zirconia reinforced alumina
	—	Calcium phosphate alumina
	—	Single crystal of alumina
Ceramic based on silicate glass	—	Porous vitroceraic
	—	Dense vitroceraic
Ceramic based on calcium phosphate	—	Dense sintered hydroxyapatite
	—	Porous sintered hydroxyapatite
	—	Dense sintered beta TCP
	—	Porous sintered beta TCP
	—	Other types
Ceramic based on calcium carbonate	—	Porous sintered calcium carbonate
	—	Natural porous calcium carbonate
Ceramic based on zirconia	—	Alumina stabilized zirconia
	—	Yttria partially stabilized zirconia
	—	Stabilized zirconia
	—	Ceria partially stabilized zirconia
Dental ceramic based on feldspar	ISO 6872 ISO 9693	Reinforced with leucite
	—	Reinforced with alumina
	—	Reinforced with mica

4.3 Carbons

Carbons include graphite, diamond, and vitreous and pyrolytic carbons. They can be prepared in high purity and are generally considered stable in the physiological environment. Examples of the different carbon forms used as medical non-reactive materials follow.

4.3.1 Pyrolytic carbon: low temperature isotropic and high temperature isotropic carbon materials have a laminar, isotropic, granular or columnar structure and may be pure carbon or alloyed with various carbides, usually silicon. The structure is generally described as turbostratic and consists of poorly defined crystallites.