List of Titles

American National Standard

ANSI/AAMI 10993-11:1993

Biological evaluation of medical devices, Part 11: Tests for systemic toxicity

AAMI Association for the Advancement of Medical Instrumentation

List of Titles

Association for the Advancement of Medical Instrumentation
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10993-11 Biological Evaluation—Part 11: Tests for Systemic Toxicity

American National Standard

ANSI/AAMI 10993-11:1993

Biological evaluation of medical devices—Part 11: Tests for systemic toxicity

Approved 2 November 1993 by
Association for the Advancement of Medical Instrumentation

Approved 29 December 1993 by
American National Standards Institute, Inc.

Abstract:

This standard covers methodologies for the evaluation of the systemic toxicity potential of medical devices which release constituents into the body. It also covers pyrogenicity.

Committee representation

Association for the Advancement of Medical Instrumentation

The proposed adoption of ISO/DIS 10993-11 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 Systemic Toxicity Working Group (U.S. Sub-TAG for ISO/TC 194/WG 7), chaired by Wava Truscott, PhD, of Baxter Healthcare Corporation, played an active part in developing the ISO standard.

The AAMI **Biological Evaluation Committee** has the following members:

Members:
James M. Anderson, MD, PhD, Case Western Reserve University
Arthur J. Coury, PhD, Society for Biomaterials
Roger Dabbah, PhD, U.S. Pharmacopeial Convention, Inc.
Paul Didisheim, MD, National Heart, Lung, and Blood Institute
Robert L. Fuson, MD, Bristol-Myers Squibb
Donald F. Gibbons, 3M Life Sciences Sector
John G. Miller, DVM, National Institutes of Health
Sharon Northup, PhD, Baxter Healthcare Corporation
Barry F. Page, Health Industry Manufacturers Association
John Paulson, PhD, Ethicon, Inc.
Adelbert L. Stagg, PhD, Cato Research, Ltd.
John W. Stanford, PhD, American Dental Association
Mel Stratmeyer, PhD, FDA Center for Devices and Radiological Health

Alternates:
Stephen Hilbert, Society for Biomaterials
Ed Mueller, FDA Center for Devices and Radiological Health
Harold Stanley, DDS, American Dental Association
Wava Truscott, PhD, Baxter Healthcare Corporation

The AAMI **Systemic Toxicity Working Group** has the following members:

Chairman:
Wava Truscott

Members: Robert Abodeely, Pfizer Hospital Products Group
Jonathan Black, PhD, Clemson University
Dennis Goupil, PhD, American Cyanamid Company
Walter R. Greif, C.R. Bard, Inc.
Willard D. Larson, 3M Medical Surgical Division
Michael McCulley, PhD, Johnson & Johnson
Katharine Merritt, PhD, Case Western Reserve University
Daniel L. Prince, PhD, Gibraltar Biological Labs
Thomas Reichert, PhD, MD, Becton Dickinson & Company
Adelbert L. Stagg, PhD, Cato Research, Ltd.
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Alternates: Herbert N. Prince, PhD, Gibraltar Biological Labs

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/DIS 10993-11

As indicated in the foreword to the main body of this document (page vi), 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 the first edition of the standard for systemic toxicity.

AAMI and ANSI procedures require that standards be reviewed and, if necessary, revised every five years to reflect technological advances that may have occurred since publication. AAMI also encourages its committees to harmonize their work with international standards as much as possible.

The 10993 series of standards was created by Technical Committee ISO/TC 194, Biological evaluation of medical devices, to fill a need for the international harmonization of test methods for various kinds of biological aspects of medical devices.

This document was developed to provide methodologies for the evaluation of systemic toxicity potential of medical devices.

U.S. participation in this ISO activity is through the U.S. Technical Advisory Group for ISO/TC 194, administered by the Association for the Advancement of Medical Instrumentation. The United States had a very proactive role in drafting and negotiating the approval of this standard.

The AAMI Biological Evaluation Committee (U.S. Technical Advisory Group for ISO/TC 194) supports international harmonization of methods used in evaluating biocompatibility of medical devices in order to help reduce unnecessary repetition of testing. The committee recommended in 1992 that AAMI initiate adoption of ISO/DIS 10993-11 in the United States as a new American National Standard. During the ballot of this document, comments were received resulting in some minor technical variations from the original text but for the most part, this document is the same as ISO/DIS 10993-11.

The concepts incorporated in this document should not be considered inflexible or static. This document, 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 come to light.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201.

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.

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 percent of the member bodies casting a vote.

International Standard ISO 10993 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: 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 8: Clinical investigation*
- *— Part 9: Degradation of materials related to biological testing*
- *— Part 10: Tests for irritation and sensitization*
- *— Part 11: Tests for systemic toxicity*
- *— Part 12: Sample preparation and reference materials*

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

Annex A of this part of ISO 10993 is for information only.

Introduction

When a device releases constituents into the body, the constituents may, in sufficiently large concentrations, lead to systemic toxicity. Clinical and experimental evidence of the systemic effects in this area is extremely sparse.

This part of ISO 10993 provides methodologies for the evaluation of systemic toxicity potential of medical devices. In addition, it includes pyrogenicity testing.

Systemic toxicity is a developing experimental science and it is expected that each expert, in carrying out tests, will exercise judgement in the selection of a procedure from the lists of standards and documents

quoted, thereby ensuring that the document that will best suit the needs of a particular device is chosen. It is assumed that, in selecting the most appropriate test method from the list, the individual method(s) may have to be adapted, to evaluate the device under test more appropriately.

It must be borne in mind that subchronic and/or chronic systemic toxicity testing is not always necessary for a risk assessment. Such assessment might be made on the basis of qualitative and quantitative analytical measurements to evaluate the exposure of possible leachables from the device.

This adaptation is international because of the developing nature of the science and because excessive rigidity or over-detailed specifications of methods could prevent application of more appropriate test methods. It is indeed intended that toxicological skill and judgement be applied during the course of study. However, it is equally necessary that, where changes from proposed methodologies are implemented, the rationale should be fully explained and supported scientifically. (See 6.4.)

It is essential, when evaluating the results of toxicological tests, to bear in mind the limitations and the potential variability of the tests. Similarly, it may not always be appropriate to extrapolate from animal studies to the human situation. While *in vivo* testing is designed to indicate possible health hazards, it does not eliminate the need for continuing monitoring and observation in humans.

ANSI/AAMI deviations from ISO/DIS 10993-11

General

American English spelling is used in the ANSI/AAMI standard, and periods are used as decimal points.

Section 3.7

"Subacute toxicity" has been replaced with "subacute toxicity (repeat dose toxicity)."

Rationale: Current standard terminology and more literally correct.

Section 4.6.1

The word "conductive" has been replaced with "conducive."

Rationale: Misspelled word.

Section 5.3**,** Table 1

Row e) has been added to Table 1 in Section 5.3.

Rationale: At the time the ISO standard was voted on as a draft International Standard, part 12 of the ISO series of standards on biological evaluation of medical devices concerning sample preparation and reference materials was still a working draft and undergoing change. The proposed U.S. adoption of ISO/DIS 10993-11 took place somewhat later, when the part 12 draft was further along, and the United States decided that table 1 should be changed to be consistent with section 8.8.2 of the 10993-12 draft that was current at the time.

Section 6.4

In line 3, the word "toxicity" has been replaced with "toxicology."

Rationale: Incorrect word for the science.

Section 6.6

The title has been changed from "Subacute systemic toxicity" to "Subacute systemic toxicity (Repeat dose systemic toxicity)."

Rationale: Current standard terminology and more literally correct.

Sections 6.6.1.1 **and** 6.6.2.1

The word "close" has been replaced with "dose."

Rationale: Incorrect word, typographical error.

Sections 6.6.4 **and** 6.6.5

The word "dermal" has been replaced with "oral."

Rationale: Incorrect subject reference.

Biological evaluation of medical devices—Part 11: Tests for systemic toxicity

1 Scope

This part of ISO 10993*) specifies methodologies for the evaluation of the systemic toxicity potential of medical devices which release constituents into the body. In addition, it includes pyrogenicity testing.

The test methods cited in this part of ISO 10993*) are from International Standards, national standards, directives and regulations. This part of ISO 10993*) is concerned with either the actual product or its leachables. It is intended that tests for extracts or leachables be conducted by choosing appropriate extraction vehicles to yield a maximum extraction of leachable materials, in order to conduct biological testing.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993*). At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this part of ISO 10993*) 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 10993-2:1992, Biological evaluation of medical devices—Part 2: Animal welfare requirements

ISO 10993-3:1992, *Biological evaluation of medical devices—Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

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

Organization for Economic Cooperation and Development (OECD) guidelines for testing of chemicals

Official Journal of the European Communities 84/449

Official Journal of the European Communities 79/831

Official Journal of the European Communities 87/302

ASTM F750 Standard Practice: *Evaluation of material extracts by systemic injection in mice*

ANSI/ADA no. 41: *Biological evaluation of dental materials*

U.S./EPA PB 86/108958

U.S./EPA PB 89/124077

European Pharmacopoeia XXII, 1990

U.S./FDA Toxicological principles for the safety assessment of direct food additives, 1982

U.S. Code of Federal Regulation 1500.40: Method of Testing Toxic Substances

United States Pharmacopoeia XXII: *Biological Reactivity Tests, In-Vivo;* The National Formulary XVII, Rockville, MD; Pharmacopoeial Convention, 1990, pp. 1497-1500

Practice for Extraction of Medical Plastics. ASTM, F-619-87, Annual Book of ASTM Standards, Vol. 13.01, Medical Devices, American Society for Testing and Materials, Philadelphia, PA

Swiss Standard on Biological Evaluation of Dental Materials, Swiss Association for Standardization. SN 119 800

British Standard, B.S. 5736, Part 5, *Pyrogen Tests*

3 Definitions

For the purposes of this part of ISO 10993[*)], the definitions in ISO 10993-1 and the following definitions apply.

3.1 extraction vehicle: Liquid for use in the extraction of leachables from a device.

3.2 extract liquid: Liquid which is tested for biological response after the device has been extracted within it.

3.3 specimen: Unit(s) of device placed into the extraction vehicle.

3.4 blank: Extraction vehicle not containing the specimen under test which is used for comparison with the extract liquid.

3.5 systemic toxicity: Toxicity involving the entire organism.

3.6 acute toxicity: Adverse effects occurring after administration of a single dose or multiple doses of a test sample given within 24 hours.

3.7 subacute toxicity (repeat dose toxicity): Adverse effects occurring after administration of a single dose or multiple doses of a test sample per day given during a period of from 14 days to 28 days.

3.8 subchronic toxicity: Adverse effects occurring after administration of a single dose or multiple doses of a test sample per day given during a part of the lifespan (usually 90 days but not exceeding 10% of lifespan).

3.9 test sample: Device or extract thereof used for systemic toxicity testing.

4 Test sample requirements and recommendations

4.1 General

The patient may be exposed to a variety of conditions or states of the device. Test samples shall be selected primarily for the conditions under which the device is normally used. If deviations are necessary, they shall be recorded in the test report, together with their justification.

Testing should be performed on the final product and/or representative component samples of the final product and/or materials. In some cases, it may be advisable also to test the individual components separately or immediately after the final product has been assembled.

4.2 Use of mold

If a mold is used for the preparation of samples, it shall not interact with or negatively influence the sample material. If appropriate, a suitable insulation medium should be used.

4.3 Polished materials

If the final device is generally polished, then the sample surface shall be similarly treated. The polishing medium shall be carefully and completely removed. Sharp edges should be rounded as appropriate for the application.

4.4 Production conditions

The component or device utilized in the sample preparation shall be exposed to the same conditions and substances as it would encounter during production, such as washing, packaging and sterilization.

4.5 Sterilization

Devices which are intended for sterilization shall be used after sterilization by the intended procedures.

4.6 Physical state of sample

4.6.1 Materials which are conducive to direct application (e.g., liquid, paste or gel) may be tested without modification in dermal and oral studies.

4.6.2 Powders (e.g., products classed as superabsorbents) may be tested by direct deposition or by making a paste in an appropriate solvent or liquid dispersant and then applying it.

4.6.3 Liquids may be tested by direct deposition or after dilution.

For liquid materials such as sprays or inks which will be used by the end-user in a dried form, thin layers are prepared on slides, dried and then extracted.

4.6.4 Solid materials may be used directly on the skin. If it is considered necessary, the solid may be pulverized or moistened sufficiently with water or a suitable non-irritating vehicle to ensure good contact with the tissues. Appropriate solvents are listed in 5.4.

5 Method for extraction from medical devices

5.1 Rationale

5.1.1 The following procedure outlines the basis to obtain extracts from medical devices for testing. This procedure may supplement but does not supersede methods contained in specific study protocols.

5.1.2 Extraction conditions may attempt to exaggerate the clinical-use conditions so as to define the potential toxicological hazard without causing significant changes. Alternatively, because of well defined clinical exposure and actual commercial product-processing parameters, it may be more appropriate for product testing to simulate in-use exposure time and temperature.

5.2 Specimen preparation

The specimen may be prepared by subdividing it into portions; it may also be tested as a whole entity, if appropriate.

For materials that cannot be subdivided without loss of specimen character, identity or integrity, and for which the calculated volume of extraction solvent will not cover the entire specimen (i.e., complex devices, metal objects, interiors of bags, etc.), use the minimum amount of extraction vehicle which will cover the test surfaces. When individual devices are small, it may be necessary to extract multiple units to provide enough sample for necessary testing. Depending on the type of sample, designate either the mass (to the nearest 0.1 g) or the exposed surface area (to the nearest 1 cm^2) extracted. Record the volume of extract.

5.3 Specimen requirements

5.3.1 The recommended sample surface area to volume of extraction vehicle ratio is given in **table 1**. In many

cases, however, other ratios may be appropriate.

5.3.2 Specimens shall be of such dimensions as to fit conveniently within the extraction container and their total surface area shall be completely covered by the extraction vehicle.

5.3.3 The majority of devices are provided sterile and/or cleanly packaged. Extra manipulations and exposure to the drying temperatures are not usually warranted and, in fact, may adversely affect the outcome of some studies.

Table 1

Form of material area vehicle	Thickness mm	Ratio/surface/extraction
a) Film or sheet (separate or coated on glass slides)	<0.5	6 cm^2 per 1 ml1)
	0.5 to 1	3 cm^2 per 1 ml1)
b) Tubing	<0.5 (wall)	6 cm^2 per 1 ml2)
	0.5 to 1 (wall)	3 cm^2 per 1 ml2)
c) Slabs, tubing and molded items	>1	3 cm^2 per 1 ml 3)
d) Irregular shapes (powders, pellets, etc.)	--	0.2 g sample per 1 ml
e) Natural elastomer	>1	1.25 cm^2 per 1 ml

NOTE 1—Additional explanations are given in part 12 of this standard.
1) Both sides combined
2) Sum of internal and external surfaces
3) All exposed surfaces combined

5.3.4 Conduct rinsing and drying procedures when the specimen to be extracted does not appear free of surface contaminants or when otherwise required. Rinse the material using purified water for injection. Repeat rinsing if necessary and dry prior to extraction if required for extracting vehicle compatibility. Omission of the rinsing procedure is recommended for apparently clean specimens as it may permit a more realistic evaluation of the manufacturing process and material.

5.3.5 Ensure that the extraction vessels do not adulterate the extract of the test materials.

5.4 Extraction vehicle

5.4.1 Use an extraction vehicle representative of the extremes of the solubility spectrum for extracting substances from materials (recommended in 5.4.1.1 to 5.4.1.3).

NOTE 2—Pay special attention to the biocompatibility of the extraction vehicle.

5.4.1.1 Polar extraction vehicle: physiological saline.

5.4.1.2 Non-polar extraction vehicle: Oleum neutrale (e.g., DAC, Fract. Coconut, BP 73) or vegetable oil (e.g., cottonseed oil or sesame oil, EP or USP) are deemed acceptable for the following procedure.

Sesame oil or cottonseed oil should, if possible, be freshly refined oil.

5.4.1.3 Additional extraction vehicles: e.g., alcohol/water, alcohol/saline, Polyethylene glycol 400, Dimethylsulfoxide (DMSO), Minimum Essential Media with 5% to 10% calf serum, dilute surfactant, water, dispersion agents, etc.

5.5 Preparation of extracts

Place a properly prepared specimen to be exposed in an extraction container, and add the appropriate extracting medium. Repeat these directions for each extraction vehicle required for testing. At the same time, prepare one blank for each medium for parallel administration and comparisons.

5.6 Extraction conditions

5.6.1 Use an appropriately calibrated autoclave, oven, waterbath or incubator. Extraction at 37°C ± 2°C for periods of up to 72 hours is suitable for most devices. Shorter extraction times at higher temperatures might be considered. Extraction conditions are as follows:

a) 37°C ± 2°C for 72 h ± 2 h

b) 50°C ± 2°C for 72 h ± 2 h

c) 70°C ± 2°C for 24 h ± 2 h

d) 121°C ± 2°C for 1 h ± 0.2 h

If agitation is employed, this shall be noted.

5.6.2 The ideal evaluation of a material should employ times and temperatures that simulate the intended use of a device. The prescribed temperature and duration should not be so severe as to affect the character of the device (i.e., there should be no gross physical change).

Upon removal from the heat source, cool the containers to room temperature. When cool, shake the containers vigorously for 30 seconds and decant the extract liquid into a dry sterile container.

WARNING—For safety reasons, sealed, unvented containers used at a temperature of 121°C, must not be handled until the internal temperature and pressure have reached ambient conditions.

6 Selection of test procedures for systemic toxicity

6.1 Selection of test procedures

Decide upon selection of the appropriate number of test(s) and test procedure(s) for a device in accordance with the Guideline ISO 10993-1 on Biological Evaluation of Medical Devices, giving due consideration to mode and duration of patient contact.

6.2 Preparation

Prepare test samples based on the most appropriate methodologies as selected from those in clause 2.

6.3 Choice of test

The following test procedures for toxicity testing are sufficiently well defined to enable them to be carried out in a similar manner in different countries. The recommended test procedures are well established national and international guidelines, standards and regulations.

6.4 Design and interpretation of test

The test procedures presented in most cases do not approach the level of detail found in standard operating procedures or similar documents. This is intentional because toxicology is a developing experimental science and excessive rigidity or over-detailed specification of methods could inhibit scientific initiative and be counterproductive. It is imperative that there be provision for the exercise of toxicological skill and judgement during the course of the study. Even where this forms part of a prescribed set of test requirements, the rationale behind changes in procedure shall be explained and supported scientifically.

6.5 Acute systemic toxicity

For reasons of animal welfare and because new methods for the testing of acute toxicity have been developed it is not necessary to determine the LD_{50} for the present purpose. Fixed dose procedures provide adequate acute toxicity data for classification, labelling and risk assessment of potentially dangerous substances and preparations.

6.5.1 Acute oral application

The tests in the following documents are recommended:

6.5.1.1 Organization for Economic Cooperation and Development (OECD) guidelines No. 401: Acute Toxicity (Oral).

6.5.1.2 U.S. FDA, Bureau of Foods: Toxicological Principles for the Safety Assessment of Direct Food Additives, 1982, Appendix II, p. 1 ff.

6.5.1.3 Official Journal of the European Communities (EC) September 19, 1984, 84/449/B1. Acute Toxicity (oral).

6.5.1.4 Acute Toxicity (oral) - Fixed Dose Method, EC: 79/831/EEC, Annex V, Updating Feb. 1990.

6.5.2 Acute dermal application

The tests in the following documents are recommended:

6.5.2.1 OECD 402: Acute Dermal Toxicity.

6.5.2.2 U.S. Code of Federal Regulations (CFR) 1500.40: Method of Testing toxic substances - Acute Dermal Toxicity (single exposure).

6.5.2.3 U.S. EPA: Acute Exposure Dermal Toxicity, EPA, Washington, DC, Nov. 84, PB 86-108958, p. 39 ff.

6.5.2.4 EC: 84/449/EEC/B3. Acute Toxicity (dermal) 19. Sept. 1984.

6.5.3 Acute application by inhalation

The tests in the following documents are recommended:

6.5.3.1 OECD No. 403: Acute Inhalation Toxicity.

6.5.3.2 U.S. EPA: Acute and Subchronic Inhalation Toxicity Testing, EPA Washington DC, Oct. 88, PB 89-124077.

6.5.3.3 EC: 84/449/EEC/B2. Acute Toxicity (inhalation). 19. Sept. 1984.

6.5.4 Acute intravenous application

The tests in the following documents are recommended:

6.5.4.1 ASTM F750: Standard Practice Evaluation Material Acts by Systemic Injection in Mice (Method A), Intravenous.

6.5.4.2 USP XXII NF XVII <88> Biological Reactivity Tests, *In-Vivo*.

6.5.5 Acute intraperitoneal application

The tests in the following documents are recommended:

6.5.5.1 ASTM F750: Standard Practice Evaluation Material Extracts by Systemic Injection in Mice (Method B), Intraperitoneal.

6.5.5.2 USP XXII NF XVII <88> Biological Reactivity Tests, *In-Vivo*.

6.5.5.3 ANSI/ADA no. 41: Biological Evaluation of Dental Materials: Acute Systemic Test by IP Route.

6.6 Subacute systemic toxicity (Repeat dose systemic toxicity)

6.6.1 Subacute oral application

The tests in the following documents are recommended:

6.6.1.1 OECD 407: Repeated Dose Oral Toxicity—Rodent: 28-Day or 14-Day Study.

6.6.1.2 U.S. FDA; Bureau of Foods: Toxicological Principles for the Safety Assessment of Direct Food Additives, 1982, Appendix II, p. 8 ff.

6.6.1.3 EC: 84/449/EEC, Nr. L 251/118/B7, Subacute Toxicity (oral).

6.6.2 Subacute dermal application

The tests in the following documents are recommended:

6.6.2.1 OECD 410: Repeated Dose Dermal Toxicity: 21/28-Day Study.

6.6.2.2 EC: 84/449/EEC/B9. Nr. L 251/127 Subacute Toxicity (dermal).

6.6.2.3 U.S. EPA: Repeated Dose Dermal Toxicity: 21-Day Study. EPA, Washington DC, Nov. 84, PB 86-108958.

6.6.3 Subacute application by inhalation

The tests in the following documents are recommended:

6.6.3.1 OECD 412: Repeated Dose Inhalation toxicity: 28-Day or 14-Day Study.

6.6.3.2 EC: 84/449/EEC/B8. Subacute Toxicity (inhalation), 19. Sept. 1984.

6.6.3.3 U.S. EPA: Acute and Subchronic Inhalation Toxicity Testing, EPA Washington DC, Oct. 88, PB 89-124077.

6.6.4 Subacute intravenous application

The test in the following document is recommended:

Adapt OECD 409, "Subacute Toxicity", changing the treatment of animals from oral to intravenous in compliance with one of the tests listed in 6.5.4.

6.6.5 Subacute intraperitoneal application

The test in the following document is recommended:

Adapt OECD 409, "Subacute Toxicity", changing the treatment of animals from oral to intraperitoneal in compliance with one of the tests listed in 6.5.5.

6.7 Subchronic systemic toxicity

6.7.1 Subchronic oral application

The tests in the following documents are recommended:

6.7.1.1 OECD 408: Subchronic Oral Toxicity—Rodent: 90-Day Study.

6.7.1.2 OECD 409: Subchronic Oral Toxicity—Non-Rodent: 90-Day Study.

6.7.1.3 U.S. FDA, Bureau of Foods: Toxicological Principles for the Safety Assessment of Direct Food Additives, 1982, Appendix II, pp. 19 ff.

6.7.1.4 EC: 87/302/EEC, No. L 133/8: 90-Day Repeated Oral Dose Using Rodent Species.

6.7.2 Subchronic dermal application

The test in the following document is recommended:

OECD 411: Subchronic Dermal toxicity: 90-Day Study.

6.7.3 Subchronic application by inhalation

The test in the following document is recommended:

OECD 413: Subchronic Inhalation Toxicity: 90-Day Study.

6.7.4 Subchronic intravenous application

The test in the following document is recommended:

Adapt OECD 408, "Subchronic Oral Toxicity", changing the treatment of animals from oral to intravenous in compliance with one of the tests listed in 6.5.4.

6.8 Chronic toxicity and carcinogenicity

Chronic toxicity or carcinogenicity testing for medical devices seems to be very rarely appropriate in relation to the health risk involved which arises from the exposure. In cases where it seems nevertheless necessary to answer such questions, experts should decide on a case-to-case basis on a proportionate test procedure (see ISO 10993-3).

In the special case of the chronic oral exposure of dental materials, a health risk estimate can be made based on a single elution test: see SN 119 800.

7 Selection of test procedures for pyrogenicity

Pyrogens may cause febrile reactions in patients. Pyrogenicity has been traditionally ascribed to bacterial endotoxin contamination of devices. However, there is now evidence that some materials contain material-related pyrogens. Pyrogenicity testing should be considered in the evaluation of devices/materials.

7.1 Testing for pyrogenic substances of either endotoxin or non-endotoxin origin

USP XXII, NF XVII <151>, Pyrogen Test, p 1515

7.2 Testing for pyrogenic substances of endotoxin origin

7.2.1 USP XXII; NF XVII <85> Bacterial Endotoxin Tests, p. 1493 ff.

7.2.2 European Pharmacopoeia Part V.2.1.9. Pyrogens, 1990.

8 Assessment of results

When assessing the results of toxicological testing on any device, good scientific judgement should be applied. However, the limitations of the tests should be kept in mind. There are various opinions as to the number of animals and duration of test exposure. There are a myriad of substances that may contact the product and many possibilities of product misuse. General pass-fail criteria in biological testing are inappropriate for two main reasons:

Firstly, it is not possible from such experiments to guarantee freedom from harmful effects of a device in humans.

Secondly, the benefits of the use of a device have to be balanced against recognized harmful effects identified in such experiments.

Consequently, although the results of toxicity testing will, in most cases, give good indication of possible hazards, they do not eliminate the need for continuing careful observations of humans, nor abrogate the need for judgement.

9 Test report

9.1 The test report shall be in accordance with the specific test procedure used.

9.2 In addition to the requirement in 9.1, the test report shall include the following:

a) type of device;

b) complete identification of the device tested;

c) dimensions, sample and specimen portion mass;

d) manufacturer's code, catalogue, or formulation number, batch number or date of manufacture, trade-name, etc.

9.3 If extraction methods are used, the report shall include the following:

a) extraction vehicle volume to specimen surface ratio or specimen portion mass to extraction vehicle volume;

b) extraction conditions in accordance with 5.6.1;

c) extraction vehicle identification, including an adequate description such that the vehicle formulation can be duplicated.

d) any observations on gross physical changes of the specimen portions or extract liquid. Such observations may include, but are not restricted to, specimen color change, extract liquid color change and potential multiphase separation.

Annex A
(informative)

Addresses

List of addresses where users may obtain the documents referred to in this part (ISO 10993-11*)):

EUROPEAN PHARMACOPOEIA (EP)

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OECD GUIDELINES FOR TESTING OF CHEMICALS

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U.S./FDA TOXICOLOGICAL PRINCIPLES FOR THE SAFETY ASSESSMENT OF DIRECT

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NOTE 3—Copies of the mentioned national standards (as e.g.: ANSI/ADA, SWISS STANDARD, BS British Standard etc.) may be obtained from the national standard organization in each ISO-member state.