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Biološko ovrednotenje medicinskih pripomočkov - 11. del: Preskusi sistemske toksičnosti (ISO/DIS 10993-11:2026)

Biological evaluation of medical devices - Part 11: Tests for systemic toxicity (ISO/DIS 10993-11:2026)

Biologische Beurteilung von Medizinprodukten - Teil 11: Prüfungen auf systemische Toxizität (ISO/DIS 10993-11:2026)

Évaluation biologique des dispositifs médicaux - Partie 11: Essais de toxicité systémique (ISO/DIS 10993-11:2026)

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11.100.20	Biološko ovrednotenje medicinskih pripomočkov	Biological evaluation of medical devices

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ISO/DIS 10993-11.2

Biological evaluation of medical devices —

Part 11: Tests for systemic toxicity

Évaluation biologique des dispositifs médicaux —

Partie 11: Essais de toxicité systémique

ICS: 11.100.20

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Foreword

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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).

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This fourth edition cancels and replaces the third edition (ISO 10993-11:2017), which has been technically revised with the following changes:

— emphasized risk assessment based on available data as a first step;

— added rabbits to Table 1 for group sizes;

— provided guidance on exaggeration of the human dose for toxicity studies;

— provided additional examples of clinical signs and observations in Annex C;

— revision of Annex G;

— provided clarification on study duration for studies described in Annex H;

— the Bibliography was updated.

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

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Introduction

Systemic toxicity is a potential adverse effect of the use of medical devices. Generalized effects, as well as organ and organ system effects can result from absorption, distribution and metabolism of constituents from the device or its materials to parts of the body with which they are not in direct contact. This document addresses the evaluation of generalized systemic toxicity, not specific target organ or organ system toxicity, even though these effects may result from the systemic absorption and distribution of toxicants.

Given the broad range of medical devices, and their materials and intended uses, this document is not overly prescriptive. While it addresses specific methodological aspects to be considered in the design of systemic toxicity tests, proper study design should be uniquely tailored to the nature of the device's materials and its intended clinical application.

Other elements of this document are prescriptive in nature, including those aspects that address conformity with good laboratory practices and elements for inclusion in reporting.

While some toxicity tests (e.g. long-term implantation or dermal toxicity studies) can be designed to study systemic effects as well as local, carcinogenic or reproductive effects, this document focuses only on those aspects of such studies, which are intended to address systemic effects. Studies which are intended to address other biological effects are addressed in ISO 10993-3, ISO 10993-4, ISO 10993-5, ISO 10993-6, ISO 10993-10, ISO 10993-23 and ISO/TS 10993-20.

Prior to conducting a systemic toxicity study, all reasonably available data and scientifically sound methods in the planning and refinement of the systemic toxicity study design should be reviewed. This includes the suitability of use of existing toxicological data, chemistry data or other biological test data (including from in vitro tests and less invasive in vivo tests) for the refinement of study design (dose selection, or selection of pathological endpoints). For the long-term exposure systemic toxicity study in particular, the use of scientifically sound study design, the use of pilot studies and statistical study design and the use of unbiased, quantitative endpoints or methods in the pathological assessment (including clinical pathology, gross pathology and histopathology) are important so as to obtain data which have sufficient scientific validity.

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The outcome of any single test should not be the sole basis for making a determination of whether a device is safe for its intended use.

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Biological evaluation of medical devices —

Part 11:
Tests for systemic toxicity

1 Scope

This document specifies requirements and gives guidance on procedures to be followed in the evaluation of the potential for medical device materials or final products to cause adverse systemic reactions.

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, *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, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

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

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

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3 Terms and definitions

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

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

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
biological harm
injury to humans from one or more adverse biological effects associated with a medical device or material

[SOURCE: ISO 10993-1:2025, 3.6]

3.2
constituent
chemical that is present in or on the finished medical device or its materials of construction

Note 1 to entry: Constituents can be intentionally or unintentionally added chemicals or compounds, such as: additives (e.g. plasticizers, lubricants, stabilizers, anti-oxidants, colouring agents, fillers), manufacturing process residues (e.g. monomers, catalysts, solvents, sterilant and cleaning agents), degradation products, reaction products, or impurities or contaminants.

[SOURCE: ISO 10993-1:2025, 3.15]

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3.3
dose
amount of test sample administered (e.g. mass, volume) per unit of body weight or surface area

3.4
dosage
refers to a specific amount of drug administered at a specific frequency (and over a certain duration

3.5
dose-response effect
relationship of dosage to the spectrum of effects related to the exposure either in an individual or in a population of individuals to a range of doses

3.6
leachable
substance that is released from a medical device or material during its clinical use

[SOURCE: ISO 10993-1:2025, 3.24]

EXAMPLE Additives, sterilant residues, process residues, degradation products, solvents, plasticizers, lubricants, catalysts, stabilizers, anti-oxidants, colouring agents, fillers and monomers.

Note 1 to entry: Leachable substances related to the use of gas pathway devices can be evaluated according to the ISO 18562-4.

3.7
limit test
use of a single group treated at a suitably high dosage of test sample in order to delineate the presence or absence of a toxic hazard

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Note 1 to entry: If the group is not toxic at this high dose, further testing at higher dosages is generally not necessary.

3.8
Long-term exposure
medical device that has a total exposure period of more than 30 d

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Note 1 to entry: More information can be found in ISO 10993-1:2025, 6.4.2 c).

3.9
systemic toxicity
harm that occurs in an organ or system other than at the contact site

Note 1 to entry: Systemic toxicity can occur after a one-time exposure (i.e. acutely) or after repeated or ongoing exposure (e.g. subacute or subchronic or chronic) to a harmful dose of a constituent released from a single medical device or from use of multiple medical devices.

Note 2 to entry: The contact site is the specific location at which the medical device interfaces or interacts with the tissue.

3.10
acute systemic toxicity
adverse effects occurring within 72 h following a single or repeated administration of a test sample for a period of up to 24 h

3.11
subacute systemic toxicity
adverse effects occurring after repeated exposure or continuous exposure of a test sample for a period of up to 28 d

Note 1 to entry: Exposure by implantation or topical application can be viewed as continuous exposure, Subacute repeated intravenous and intraperitoneal studies are generally defined as exposure durations of ≤14 to 28 d for rodents

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3.12
subchronic systemic toxicity
adverse effects occurring after long-term or continuous exposure of a test sample for a period of 90 d

3.13
chronic systemic toxicity
adverse effects occurring after long-term or continuous exposure of a test sample for a major part of the life span

Note 1 to entry: Chronic toxicity studies usually have a duration of at least six months in rodents and rabbits[35] or nine months in large animal species[36].

3.14
test sample
medical device, component or material (or a representative sample thereof, manufactured and processed by equivalent methods), or an extract or portion thereof that is subjected to biological evaluation testing

[SOURCE: ISO 10993-12:2021, 3.14]

4 General considerations

4.1 General

Before a decision to perform a systemic toxicity test is made, a biological evaluation as described in ISO 10993-1 shall be conducted. To evaluate potential systemic toxicity risks of medical devices, consideration should first be given to the availability and applicability of chemical characterization and toxicological risk assessment data before pursuing systemic toxicity testing using an animal model. When there is not sufficient data to estimate the risk of systemic toxicity using either relevant existing information or chemical characterization according to ISO 10993-18 followed by a toxicological risk assessment according to ISO 10993-17, then in vivo systemic toxicity studies should be considered. For example, when the outcome of chemical characterization and toxicological risk assessment is inconclusive to assess tolerable risk and worst-case exposure dose of extractable constituent is not well understood, then an in vivo systemic toxicity test can be considered.

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NOTE 1 Some devices can contain such low concentrations of extractable or leachable constituents that it is unlikely to result in an observed adverse effect in a systemic toxicity test (see ISO 10993-18 and ISO 10993-17). Chemical analysis of test sample extracts can provide information on whether in vivo systemic toxicity testing is potentially useful to the overall biological evaluation.

EXAMPLE 1 The analytical results from a water extract can provide a reasonable estimate of the composition and concentration of device constituents in the saline extract used for dosing an in vivo study, if:

— extraction conditions are similar and

— identification and quantitation are adequate.

EXAMPLE 2 The analytical results from all extracts in an exhaustive extraction study can provide a reasonable estimate of the potential systemic exposure from a systemic toxicity study performed using implantation as the route of exposure.

If available, such information shall be considered when designing a systemic toxicity study. Where constituent concentrations correspond to a dose to the animal are less than approximately 0,015 mg/kg/day to 0,15 mg/kg/day, in vivo effects are unlikely to be observed. Particularly, chemical characterization according to ISO 10993-18 should inform whether the study will be useful for the overall biological evaluation[4].

NOTE 2 A reasonable estimate of very low levels of extractables is that which would equate to a dose to the animal of approximately 0,015 to 0,15 mg/kg/day. The high end of the range is based on the 5th percentile of the oral NOAELs used to calculate the lowest Cramer Class TTC value.[5] The low end of the range accounts for a potential 10-fold difference in toxicity between oral NOAELs used to derive the TTC and parenteral routes used in most medical device extract testing.

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EXAMPLE 3 A long-term medical device with a surface area of 300 cm^2 was exhaustively extracted according to ISO 10993-18. The water extract of the device contained a single extractable that was identified, and the total quantity was reported to be 10 µg. For a systemic toxicity test using a saline extract, the 300-cm^2 device would be extracted at 6 cm^2/ml with a total extraction volume of 50 ml. Assuming the extraction efficiency of the extractable from the device remains the same between water and saline and the same extraction conditions are used, the resulting saline extract would contain the extractable at a concentration of 0,2 µg/ml. At a dose volume of 50 ml/kg IP, the dose to the animal would be 10 µg/kg. If given daily, the dose would be 10 µg/kg/day (0,01 mg/kg/day), which is less than 0,015 mg/kg/day. This calculation indicates that a systemic toxicity test using a saline extract would be unlikely to result in adverse effects and would not be useful for the overall biological evaluation of the device.

Testing shall be performed on the final product or representative component samples, or materials of the final product. Test samples shall reflect the conditions under which the device is normally manufactured and processed. If modifications to the manufacturing and processing conditions are necessary, these should be documented by the manufacturer, together with their justification and captured in the biological evaluation plan. For hazard identification purposes, it can be necessary to exaggerate exposure to the test samples. It could also be necessary to determine the dose for implantation-based systemic toxicity studies, including, but not limited to calculation of dose based on animal weight and worst-case clinical use, and accounting for a safety factor.

Physical and chemical properties of the test sample including, for example, pH, stability, viscosity, osmolality, buffering capacity, solubility and sterility, are some factors to consider when designing the study.

When animal tests are considered, all reasonably and practically available replacement, reduction and refinement (3Rs) alternatives should be identified and implemented to satisfy the provisions of ISO 10993-2. Animal studies should be tailored to address the specific type of systemic toxicity for which data or information are lacking. For instance, if sufficient data exists for chronic toxicity but not for acute toxicity, in vivo studies should be limited to acute toxicity designs.

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4.2 Selection of animal model

There is no absolute criterion for selecting a particular animal species for systemic toxicity testing of medical devices. However, the species used shall be scientifically justified and in line with the provisions of ISO 10993-2. For acute oral, intravenous, dermal and inhalation studies of medical devices, rodents (mouse or rat) are preferred. Rabbits, which are lagomorphs, are an option in dermal studies and preferred in the case of implantation studies where a larger model is needed due to the size of the implant. Other non-rodent species can be considered for testing, recognizing that a number of factors might dictate the number or choice of species for study.

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It is preferred that a single animal species and strain are used when a series of systemic toxicity studies of different durations are performed, e.g. subacute, subchronic and chronic systemic toxicity. This minimizes the variability between species and strains and facilitates an evaluation based primarily on study duration. Should multiple species or strains be used, justification for their selection shall be documented.

4.3 Animal status

Generally, healthy purpose-bred young adult animals, as determined by qualified veterinary personnel, and, of known species, strain, substrain, age, sex, source and with defined microbiological and pathogen health status should be used. At the commencement of the study, the weight variation of animals used within a sex should not exceed ±20 % of the mean weight. When females are used, they should be nulliparous and non-pregnant. Animal selection shall be justified.

4.4 Animal care and husbandry

Care and handling of animals shall be in accordance with the animal care guidelines of the country in which the test facility is located. Animals shall be acclimatized to the laboratory conditions prior to treatment and the period of time documented. Control of environmental conditions and proper animal care techniques are essential to animal well-being, minimization of stress-related physiological responses and the quality of the results. Dietary constituents and bedding materials that are known to produce or influence toxicity should be properly characterized and their potential to influence test results taken into account.

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The temperature and the relative humidity in the experimental animal rooms should be appropriate for the species, e.g. (22 ± 3) °C and relative humidity of 30 % to 70 %, for rodents. Typically, the artificial lighting sequence should be 12 h light, 12 h dark.

For feeding, standardized commercial laboratory diets may be used with an unlimited supply of drinking water. Animals should be caged in-groups by sex or individually, as appropriate; for group housing not more than five animals shall be housed per cage.

4.5 Size and number of groups

4.5.1 Size of groups

The study should use the least number of animals to detect meaningful differences in biological responses and provide meaningful interpretation of the data (see ISO 10993-2). Recommended minimum group sizes, with all routes of test sample administration considered, are given in Table 1.

Table 1 — Recommended minimum group sizes[a]

Study type	Rodent	Non-rodent
Acute	5	3
Subacute	10 (5 per sex)	6 (3 per sex)
Subchronic	20 (10 per sex)	8 (4 per sex)
Chronic	30 (15 per sex)	12 (6 per sex)[b]

[a] Testing in a single sex is typical for acute and pharmacopeia-type testing. When a device is intended for use in only one sex, testing should be done in that sex.

[b] Expert statistical consultation for chronic study non-rodent group size is recommended. The number of animals tested should be based on the minimum required to provide meaningful data. Enough animals shall remain at the termination of the study to ensure proper statistical evaluation of the results.

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When the testing is designed to address both systemic toxicity and implantation endpoints, group sizes shall meet both ISO 10993-11 and ISO 10993-6 requirements. If both sets of requirements can't be met, justification shall be provided and documented.

4.5.2 Number of groups

One dose group treated at a suitable dosage of test sample in a single species could delineate the presence or absence of a hazard (i.e. limit test). However, other multi-dose or dose response studies require multiple groups to delineate the toxic response.

The number of treatment groups may be increased when attempting to characterize a dose response using exaggerated doses. The following examples for exaggerating the dose should be considered:

— multiples of the human dose based on device mass or number/per patient body weight;

— multiples of the surface area of human exposure per patient body weight;

— multiples of the duration of exposure;

— multiples of the amounts of extractable fraction or individual chemicals from the device per patient body weight;

— multiple administrations within a 24-h period.

Other methods to exaggerate the dose may be acceptable. The method used shall be justified.

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4.5.3 Treatment controls

Depending on the objective of the study, the nature of the test sample and the route of exposure, negative control, vehicle control, or sham-treated controls, shall be incorporated into all systemic toxicity studies. These controls shall mimic the test sample preparation and treatment procedure.

4.6 Route of administration

Medical devices or their leachable constituent s may gain access to the body by multiple routes of exposure. The test route of administration for a systemic toxicity test should be chosen based on the ability to exaggerate the systemic dose balanced with clinical relevance. Sometimes parenteral dosing with device extracts can exaggerate the dose more readily than implantation. However, there is limitation in repeated administration of extracts into animals due to their inherent stress and physiological tolerance. Therefore, extract studies (via intravenous and intraperitoneal administration) are typically limited to systemic toxicity up to 28 d, see Annex H. The route of administration shall be justified. Examples of routes of administration can be found in Annex A.

4.7 Sample preparation

The test and control samples and their preparation (such as pH, stability, homogeneity, osmolality, and sterility, as appropriate) shall be described and justified. All samples and vehicles for parenteral delivery should be prepared aseptically. Further guidance on sample preparation is given in ISO 10993-12.

4.8 Dosing

4.8.1 Test sample administration considerations

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Procedures should be designed to avoid physiological changes or animal welfare problems not directly related to the toxicity of the test material. Current proper handling and restraint techniques that minimize aversion and anxiety levels in animals shall be practiced (for example, picking up mice through tunnel or cupped hand instead of by the tail). If a single daily dose of a sufficient volume or concentration is not possible, the dose may be given in smaller fractions over a period not exceeding 24 h.

Test samples shall be delivered at a physiologically acceptable temperature. Aseptic techniques shall be used when samples are given parenterally. In general, test samples are used at or near room temperature (e.g. 25 °C) or body temperature (e.g. 37 °C), with the temperature documented and justified.

Vehicles administered by a parenteral route should be physiologically compatible. When necessary, if gravimetric sedimentation is ineffective, extract centrifugation or filtration to remove particulates can be used. These post-extraction manipulations shall be documented, and justified. In addition, alternate administration routes (e.g. intraperitoneal injections) can be considered and shall be justified. When medical devices or test samples in the form of nanomaterials are to be evaluated, special considerations may be necessary for the sample preparation (e.g. the use of nano-object dispersions instead of extracts).

NOTE For more information, see ISO/TR 10993-22:2017, Clause 6.

Prolonged restraint of animals in long-term exposure systemic toxicity studies should be scientifically justified and performed in a manner that is as humane as possible. Animals shall have adequate room for thoracic and abdominal expansion during breathing, and comfortable surface for resting the head and body. The nature and the duration of restraint should be the minimum required to meet the scientific objectives and should not of themselves compromise the welfare of the test animals. Deviations shall be justified.

Further guidelines on prolonged restraint can be found in the Guide for the Care and Use of Laboratory Animals.[22] When restraint is required animals should be acclimatized to the restraint device prior to test sample administration. Minimal effective restraint of test animals is a key factor to be considered for prolonged infusion.

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4.8.2 Dose

Guidance on dose volume is summarized in Annex B. Multiple dose volume groups and use of dose volumes greater than those given in Annex B shall be justified.

Large dose volumes administered by the oral route should be avoided because they have been shown to overload the stomach capacity and pass immediately into the small bowel. Large volumes may also reflux into the oesophagus.

Intramuscular administration is also volume-limited, depending on size of the animal and the muscular site. Species-specific intramuscular administration volumes are addressed in Annex B.

Bolus intravenous injection volumes are usually given over a period of time dependent on the species. The rate of injection is an important factor and a maximum of 2 ml/min is suggested for rodents.

Slow or timed injection, or intravenous infusion, may be required for large volume administration. Regardless of the calculated rate, the rate of fluid administration shall be stopped or decreased if the animal demonstrates a marked change in clinical condition.

Slow intravenous injection rates may be necessary for test samples limited by solubility or irritancy.

Continuous infusion may be used if clinically indicated. The volume and rate of administration will depend on the substance being given and take into account standard fluid therapy practice.

For subcutaneous administration of test sample, refer to Annex B. The rate and extent of absorption depends on the test sample formulation.

For implantable devices, often the most clinically relevant route of exposure is by implantation. Where practical, the route of administration should mimic the clinical route or tissues of exposure. When possible, the implanted sample should represent an exaggeration of the human clinical dose on a mg/kg body weight basis. In some cases, a surface area (cm^2/kg body weight) or volume (ml/kg body weight) basis of exaggeration may be used based on what is most appropriate for the subject device and its indication(s). Other bases of providing an exaggerated dose may be used with justification. A suggested exaggeration is 10 to 100 times the proportional human dose unless not technically achievable. Ideally, the highest exaggeration factor is to be considered when feasible, e.g. 100X. Additionally, this exaggeration should consider the worst case human population for use, e.g. – adult, children, or infants, as appropriate. When the 10X minimum exaggerated dose is impractical, the dose <10X should be justified. Depending on the nature and size of the device an exaggerated dose, it may not be feasible to implant in the clinical location of use or tissues of exposure. Implantation in alternative tissue(s) may be considered with justification. For example, while relevant route of exposure is preferred, subcutaneous implant sites have the advantage of being able to accommodate proportionately large doses, allowing for exaggeration of the typical clinical dose. This could be a consideration when the most clinically relevant route of exposure is not possible, and an alternative exposure route needs to be selected. For devices that are in contact with internal tissues or reside in the vascular system (e.g. hemodialysis filter), intravenous or intraperitoneal administration of extracts may be an appropriate means to provide exposure (see Annex H). For devices in which the patient is exposed to leachables via inhalation, see the ISO 18562-4 for additional guidance.

Sample document

For studies where the route of administration is via implantation, the amount/volume of a final finished device, portion thereof, or material implanted should be compatible with the test system and not be excessively large. If a large device or a device with multiple components is being implanted, the entire device shall be implanted in the same animal so that systemic toxicity of the entire device can be assessed. If it is not technically feasible to implant the entire device, representative portions of the entire device should be implanted in each test animal. If the test sample has sharp edges/corners this could potentially result in skin perforations in a subcutaneous implant study. In cases where toxic effect may be expected, multiple dose levels may be advisable rather than a single limit type dose.

4.8.3 Dosing frequency

The dosing frequency should be based on clinical relevancy. Exaggerated dose volumes shall be clearly specified and justified. Single or repeated dosing or extract delivery should consider technique refinements that can enhance animal comfort and to prevent compromising test results due to undue stress,[13] including,

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