

# Elastomeric parts for parenterals and for devices for pharmaceutical use —

## Part 1: Extractables in aqueous autoclavates

The European Standard EN ISO 8871-1:2004 has the status of a  
British Standard

ICS 11.040.20

## National foreword

This British Standard is the official English language version of EN ISO 8871-1:2004. It is identical with ISO 8871-1:2003. Together with Parts 2 and 3, it partially supersedes BS EN ISO 8871:1997 which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/212, IVDs, which has the responsibility to:

- aid enquirers to understand the text;
- present to the responsible international/European committee any enquiries on the interpretation, or proposals for change, and keep the UK interests informed;
- monitor related international and European developments and promulgate them in the UK.

A list of organizations represented on this committee can be obtained on request to its secretary.

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The British Standards which implement international or European publications referred to in this document may be found in the *BSI Catalogue* under the section entitled “International Standards Correspondence Index”, or by using the “Search” facility of the *BSI Electronic Catalogue* or of British Standards Online.

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### Summary of pages

This document comprises a front cover, an inside front cover, the EN ISO title page, the EN ISO foreword page, the ISO title page, pages ii to v, a blank page, pages 1 to 19, the Annex ZA page, an inside back cover and a back cover.

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English version

**Elastomeric parts for parenterals and for devices for  
pharmaceutical use - Part 1: Extractables in aqueous  
autoclavates (ISO 8871-1:2003)**

Eléments en élastomère pour administration parentérale et  
dispositifs à usage pharmaceutique - Partie 1: Substances  
extractibles par autoclavage en milieu aqueux (ISO 8871-  
1:2003)

This European Standard was approved by CEN on 15 July 2004.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the Central Secretariat or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the Central Secretariat has the same status as the official versions.

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**Management Centre: rue de Stassart, 36 B-1050 Brussels**

## **Foreword**

The text of ISO 8871-1:2003 has been prepared by Technical Committee ISO/TC 76 "Transfusion, infusion and injection equipment for medical and pharmaceutical use" of the International Organization for Standardization (ISO) and has been taken over as EN ISO 8871-1:2004 by CMC.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by March 2005, and conflicting national standards shall be withdrawn at the latest by March 2005.

This document supersedes EN ISO 8871:1997.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland and United Kingdom.

### **Endorsement notice**

The text of ISO 8871-1:2004 has been approved by CEN as EN ISO 8871-1:2004 without any modifications.

NOTE Normative references to International Standards are listed in annex ZA (normative).

INTERNATIONAL  
STANDARD

**ISO**  
**8871-1**

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**Elastomeric parts for parenterals and for  
devices for pharmaceutical use —**

Part 1:  
**Extractables in aqueous autoclavates**

*Éléments en élastomère pour administration parentérale et dispositifs à  
usage pharmaceutique —*

*Partie 1: Substances extractibles par autoclavage en milieu aqueux*





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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 8871-1 was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection equipment for medical and pharmaceutical use*.

Together with the other parts (see below), this part of ISO 8871 cancels and replaces ISO 8871:1990, which has been technically revised.

ISO 8871 consists of the following parts, under the general title *Elastomeric parts for parenterals and for devices for pharmaceutical use*:

- *Part 1: Extractables in aqueous autoclavates*
- *Part 2: Identification and characterization*
- *Part 3: Determination of released-particle count*
- *Part 4: Biological requirements and test methods*
- *Part 5: Functional requirements and testing*



## **Introduction**

The elastomeric parts specified in the various parts of this International Standard are produced from a material which is usually called "rubber". However, rubber is not a unique entity, since the composition of rubber materials may vary considerably. The base elastomer and the type of vulcanization have a major influence on the principle characteristics of an individual rubber material, as do additives such as fillers, softeners and pigments. These may have a significant effect on the overall properties. The effectiveness, purity, stability and safe handling of a drug preparation may be affected adversely during manufacture, storage and administration if the rubber part used has not been properly selected and validated (approved).



# Elastomeric parts for parenterals and for devices for pharmaceutical use —

## Part 1: Extractables in aqueous autoclavates

### 1 Scope

**1.1** This part of ISO 8871 defines procedures for classifying elastomeric parts for primary packs and medical devices used in direct contact with preparations for parenteral use, including both aqueous preparations and dry preparations which have to be dissolved before use.

It specifies a series of comparative test methods for chemical evaluation by the determination of extractables in aqueous autoclavates (see Clause 4) and describes the various fields of application for elastomeric parts. Dimensions and functional characteristics are specified in the relevant International Standards. Required properties as specified in this part of ISO 8871 are regarded as minimum requirements.

**1.2** This part of ISO 8871 is applicable for the categories of elastomeric parts given in Clause 3; specific requirements, however, are laid down in the relevant International Standards dealing with the items or devices listed in Clause 3.

Elastomeric parts for empty syringes for single use are excluded from the scope of this part of ISO 8871 as they are not in contact with the injected preparation for a significant length of time.

**1.3** Compatibility studies with the intended preparation have to be performed before the approval for final use can be given; however, this part of ISO 8871 does not specify procedures for carrying out compatibility studies.

### 2 Normative references

The following referenced documents are indispensable for the application 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 8362-2:1988, *Injection containers for injectables and accessories — Part 2: Closures for injection vials*

ISO 8362-5:1995, *Injection containers for injectables and accessories — Part 5: Freeze drying closures for injection vials*

ISO 8536-2:2001, *Infusion equipment for medical use — Part 2: Closures for infusion bottles*

ISO 8536-6:1995, *Infusion equipment for medical use — Part 6: Freeze drying closures for infusion bottles*

ISO 11040-2:1994, *Prefilled syringes — Part 2: Plungers and discs for dental local anaesthetic cartridges*

ISO 11040-5:2001, *Prefilled syringes — Part 5: Plungers for injectables*

### **3 Classification**

Elastomeric parts exist in various designs and sizes depending on the intended end-use. These parts serve different purposes depending on the item or device in which they are incorporated. Elastomeric parts have, therefore, been classified into the following categories:

- elastomeric parts for injection vials (see ISO 8362-2);
- elastomeric parts for infusion bottles (see ISO 8536-2);
- elastomeric parts for prefilled syringes (see ISO 11040-2 and ISO 11040-5);
- elastomeric parts for medical devices for pharmaceutical use (excluding gloves and probes);
- elastomeric parts for freeze-dried products (see ISO 8362-5 and ISO 8536-6).

### **4 Requirements**

#### **4.1 Resistance to steam sterilization**

Elastomeric parts shall not lose their required biological, chemical and physical properties after being sterilized twice in saturated steam at  $(121 \pm 2)$  °C for 30 min each time.

#### **4.2 Chemical requirements**

Elastomeric parts shall comply with the chemical requirements specified in Table 1.

Elastomers are divided into the following types:

- Type I elastomer: this meets the strictest requirements and is the preferred type.
- Type II elastomer: this does not meet these severe requirements as a result of its different chemical composition which is necessary to give the mechanical properties required for special applications (e.g. multiple piercing).

The methods to be used to determine the chemical characteristics of the elastomeric parts are specified in Annex A to Annex J.

### **5 Sampling**

Take a random sample of the elastomeric parts which is representative of each delivery, with the parts in their original state. The number of elastomeric parts taken shall be as specified in the relevant International Standards (see Clause 3).

Table 1 — Chemical requirements for testing aqueous autoclavates

Characteristic	Requirements	Test as described in Clause/Annex
Turbidity	Type I: Not more turbid than reference suspension II	A.1
	Type II: Not more turbid than reference suspension III	
Colour	Type I and II: Not more intensely coloured than reference solution GY <sub>5</sub>	A.2
Acidity/alkalinity	Type I and II: ≤ 0,3 ml sodium hydroxide solution, $c(\text{NaOH}) = 0,01 \text{ mol/l}$ or ≤ 0,8 ml hydrochloric acid, $c(\text{HCl}) = 0,01 \text{ mol/l}$	B
Absorbance	Type I: ≤ 0,2 AU across the whole range from 220 nm to 360 nm	C
	Type II: ≤ 4,0 AU across the whole range from 220 nm to 360 nm	
Reducing substances	Type I: ≤ 3,0 ml sodium thiosulfate solution, $c(\text{Na}_2\text{S}_2\text{O}_3) = 0,01 \text{ mol/l}$	D
	Type II: ≤ 7,0 ml sodium thiosulfate solution, $c(\text{Na}_2\text{S}_2\text{O}_3) = 0,01 \text{ mol/l}$	
Extractable heavy metals	Type I and II: ≤ 2,0 mg/l	E
Extractable zinc	Type I and II: ≤ 5,0 mg/l	F
Extractable ammonia	Type I and II: ≤ 2,0 mg/l	G
Residue on evaporation	Type I: ≤ 2,0 mg/50 ml	H
	Type II: ≤ 4,0 mg/50 ml	
Volatile sulfides	Type I and II: Black stain on acetate paper shall not be larger or darker than reference (0,154 mg Na <sub>2</sub> S for every 20 cm <sup>2</sup> of stopper surface area.)	I
Conductivity (optional)	Type I: ≤ 15 μS/cm	J
	Type II: ≤ 30 μS/cm	

A blank may be prepared where appropriate for system control, but correction of the result using the blank result is only allowed if mentioned in the corresponding annex.

## 6 Apparatus and reagents

**6.1** Use only reagents of recognized analytical grade. For the preparation of standard solutions, see the relevant annex.

**6.2** Use purified water prepared by distillation or by any other suitable means.

Its conductivity shall be less than 3,0 μS/cm.

NOTE Purified water as specified in various national pharmacopoeias corresponds to grade 1 and grade 2 water as specified in ISO 3696.

**6.3** Glassware shall be made from borosilicate glass.

## 7 Preparation of test solutions

7.1 Closures shall be processed in the as-delivered condition.

7.2 Place a suitable number of complete elastomeric parts in a wide-necked flask and add 300 ml of purified water for every 150 cm<sup>2</sup> of surface area of the elastomeric parts. Cover the mouth of the flask, e.g. with aluminium foil or an inverted borosilicate glass beaker. Weigh the flask plus contents. Heat in an autoclave so that a temperature of  $(121 \pm 2)$  °C is reached within 20 min to 30 min and maintain this temperature for 30 min. Cool to room temperature over about 30 min. Make up to the original mass with purified water if necessary (if tightly closed containers are not used).

Shake this solution (solution S<sub>1</sub>) and immediately separate it from the elastomeric parts. Shake solution S<sub>1</sub> before each test.

7.3 Prepare a blank solution (solution S<sub>0</sub>) in the same way as for solution S<sub>1</sub> except that 300 ml of purified water are used without the elastomeric parts.

7.4 Use solutions S<sub>1</sub> and S<sub>0</sub> obtained as described to carry out the chemical tests.

## Annex A (normative)

### Appearance of solution

#### A.1 Turbidity of solution S<sub>1</sub>

##### A.1.1 General

The determination may be carried out instrumentally using a turbidimeter or by visual comparison.

##### A.1.2 Visual comparison with standards

###### A.1.2.1 Reagents

###### A.1.2.1.1 Hydrazine sulfate solution

Dissolve 1,0 g of hydrazine sulfate in water and dilute to 100 ml with water. Allow to stand for 4 h to 6 h.

###### A.1.2.1.2 Hexamethylenetetramine solution

Dissolve 2,5 g of hexamethylenetetramine in 25,0 ml of water in a glass-stoppered 100 ml flask.

###### A.1.2.1.3 Stock suspension

To the solution of hexamethylenetetramine in the flask add 25,0 ml of hydrazine sulfate solution. Mix and allow to stand for 24 h. This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. Discard if the suspension adheres to the glass. Mix well before use.

###### A.1.2.1.4 Standard suspension

Dilute 15,0 ml of the stock suspension to 1 000 ml with water. This suspension shall be freshly prepared and may not be stored for longer than 24 h.

###### A.1.2.1.5 Reference suspensions

Prepare reference suspensions in accordance with Table A.1. Mix well before use.

**Table A.1**

	I	II	III
Standard suspension	5,0 ml	10,0 ml	30,0 ml
Water	95,0 ml	90,0 ml	70,0 ml

**A.1.2.2 Procedure**

Use identical test tubes made of colourless, transparent, neutral glass, and with a flat base and an internal diameter of 15 mm to 25 mm. Fill one tube to a depth of 40 mm with solution  $S_1$  and three others to the same depth with the reference suspensions (see Table A.1). Compare the solutions in diffuse daylight 5 min after preparation of the reference suspensions, viewing vertically against a black background. The light conditions shall be such that reference suspension I can be readily distinguished from water, and that reference suspension II can be readily distinguished from reference suspension I.

**A.1.3 Instrumental determination by turbidimeter**

The reference suspensions prepared in A.1.2.1.5 represent the following limits:

Reference suspension II: 6 FTU<sup>1)</sup> (type I elastomers)

Reference suspension III 18 FTU (type II elastomers)

Check the instrument on a regular basis to ensure that it defines these limits correctly.

**A.1.4 Expression of results**

Report the result as “complies”/“does not comply” with type I or type II requirements (see Table 1).

**A.2 Colouration of solution  $S_1$** **A.2.1 Reagents****A.2.1.1 Stock yellow solution**

Dissolve 46 g of ferric chloride in about 900 ml of a mixture of 25 ml of concentrated hydrochloric acid (~ 36 %) and 975 ml of water and make up to 1 000 ml with the same mixture. Titrate (see A.2.1.2) and adjust the concentration of the solution to 45,0 mg of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  per millilitre by adding the same mixture. Protect the solution from light.

**A.2.1.2 Titration**

Into a 250 ml conical flask fitted with a ground-glass stopper, place 10,0 ml of the stock solution, 15 ml of water, 5 ml of concentrated hydrochloric acid and 4 g of potassium iodide. Close the flask, allow to stand in the dark for 15 min and then add 100 ml of water. Titrate the liberated iodine with 0,1 mol/l sodium thiosulfate, using 0,5 ml of starch solution (A.2.1.8), added towards the end of the titration, as indicator.

1 ml of 0,1 mol/l sodium thiosulfate is equivalent to 27,03 mg of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ .

**A.2.1.3 Stock red solution**

Dissolve 60 g of cobalt chloride in about 900 ml of a mixture of 25 ml of concentrated hydrochloric acid and 975 ml of water and make up to 1 000 ml with the same mixture. Titrate (see A.2.1.4) and adjust the concentration of the solution to 59,5 mg of  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$  per millilitre by adding the same mixture.

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1) Formazine turbidity units.



**A.2.1.4 Titration**

Into a 250 ml conical flask fitted with a ground-glass stopper, place 5,0 ml of the stock solution, 5 ml of dilute hydrogen peroxide solution and 10 ml of a 300 g/l solution of sodium hydroxide. Boil gently for 10 min, allow to cool and add 60 ml of dilute sulfuric acid (A.2.1.7) and 2 g of potassium iodide. Close the flask and dissolve the precipitate by shaking gently. Titrate the liberated iodine with 0,1 mol/l sodium thiosulfate, using 0,5 ml of starch solution (A.2.1.8), added towards the end of the titration, as indicator. The end-point is reached when the solution turns pink.

1 ml of 0,1 mol/l sodium thiosulfate is equivalent to 23,79 mg of  $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ .

**A.2.1.5 Stock blue solution**

Dissolve 63 g of copper sulfate in about 900 ml of a mixture of 25 ml of concentrate hydrochloric acid and 975 ml of water and make up to 1 000 ml with the same mixture. Titrate (see A.2.1.6) and adjust the concentration of the solution to 62,4 mg of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  per millilitre by adding the same mixture.

**A.2.1.6 Titration**

Into a 250 ml conical flask fitted with a ground-glass stopper, place 10,0 ml of the stock solution, 50 ml of water, 12 ml of dilute acetic acid (~ 12 %) and 3 g of potassium iodide. Titrate the liberated iodine with 0,1 mol/l sodium thiosulfate, using 0,5 ml of starch solution (A.2.1.8), added towards the end of the titration, as indicator. The end-point is reached when the solution shows a slight pale-brown colour.

1 ml of 0,1 mol/l sodium thiosulfate is equivalent to 24,97 mg of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ .

**A.2.1.7 Sulfuric acid, dilute**

Prepare a solution containing 98 g of sulfuric acid per litre of water.

**A.2.1.8 Starch solution**

Triturate 1,0 g of soluble starch with 5 ml of water and, whilst stirring, pour the mixture into 100 ml of boiling water containing 10 mg of mercuric iodide.

**A.2.1.9 Standard solution**

From the three stock solutions, prepare a standard solution as follows:

**Table A.2 — Standard solution GY**

Volumes in millilitres

Standard solution	Stock yellow solution	Stock red solution	Stock blue solution
GY (greenish-yellow)	9,6	0,2	0,2

**A.2.1.10 Reference solution**

From the standard solution, prepare a reference solution as follows:

**Table A.3 — Reference solution GY<sub>5</sub>**

Volumes in millilitres

Reference solution	Standard solution GY	Hydrochloric acid (10 g/l HCl)
GY <sub>5</sub>	3,0	97,0

Prepare the reference solution immediately before use.

**A.2.2 Procedure**

Use identical test tubes made of colourless, transparent, neutral glass, and with a flat base and an internal diameter of 15 mm to 25 mm. Fill one tube to a depth of 40 mm with solution S<sub>1</sub> and another to the same depth with the reference solution (see Table A.3). Compare the solutions in diffuse daylight, viewing vertically against a white background.

Using identical tubes of colourless, transparent, neutral glass with a flat base and an external diameter of 15 mm to 25 mm, compare the liquid to be examined with the reference solution (see Table A.3). The depth of the layer being 40 mm. Compare the colours in diffuse daylight, viewing vertically against a white background.

**A.2.3 Expression of results**

Report the result as “complies”/“does not comply” with the requirement (see Table 1).

## Annex B (normative)

### Acidity or alkalinity

#### B.1 General

Depending on their composition, some types of closure formulation contain ingredients which may act as acids or alkalis. If acidic or alkaline material is extracted, a change in the pH-value, which may adversely affect the stability of a pharmaceutical product, may occur. Such a change in the pH-value can be determined by potentiometric measurement of the aqueous extract using a pH electrode. However, the potentiometric determination may lead to misleading results when measurements are performed in unbuffered systems around pH 7. Therefore, it is recommended that a titration method be used to determine acidity or alkalinity.

#### B.2 Reagents

##### B.2.1 Bromothymol blue solution

Dissolve 50 mg of bromothymol blue in a mixture of 4 ml of 0,02 mol/l sodium hydroxide and 20 ml of ethanol (~ 96 %) and dilute to 100 ml with water.

##### B.2.2 Colour change

From pH 5,8 (yellow) to pH 7,4 (blue) or *vice versa*.

##### B.2.3 Test for sensitivity

To 0,3 ml of bromothymol blue solution add 100 ml of carbon-dioxide-free water. The solution shall be yellow. Not more than 0,1 ml of 0,02 mol/l sodium hydroxide shall be required to change the colour to blue.

#### B.3 Procedure

Add 0,1 ml of bromothymol blue solution to 20 ml of test solution  $S_1$ . Titrate against 0,01 mol/l sodium hydroxide or 0,01 mol/l hydrochloric acid.

Calculate the result as the number of millilitres of sodium hydroxide or hydrochloric acid consumed by 20 ml of test solution  $S_1$  (to one place of decimals). Not more than 0,3 ml of 0,01 mol/l sodium hydroxide or 0,8 ml of 0,01 mol/l hydrochloric acid shall be required to obtain a blue or yellow colour, respectively.

#### B.4 Expression of results

Report the result as “complies”/“does not comply” with the requirement (see Table 1).

## Annex C (normative)

### Absorbance

#### C.1 General

The ultraviolet (UV) spectrum obtained on extracts of elastomeric materials is primarily a function of the kind of accelerator or antioxidant present in the individual elastomeric formulation. This type of test is applicable to all vulcanized rubber products and is usually performed using an aqueous extract.

#### C.2 Procedure

Carry out the test within 5 h of preparation of solution  $S_1$ .

Filter test solution  $S_1$  through a membrane filter (pore size approx. 0,45  $\mu\text{m}$ ) if necessary to filter out particles which could cause stray light interference. Place the solution in a 1 cm quartz cell in a scanning UV spectrometer, with a blank solution  $S_0$  in the reference cell, and obtain the spectrum over the wavelength range from 220 nm to 360 nm.

If dilution is necessary, record the dilution factor.

Use this factor when estimating compliance.

#### C.3 Expression of results

Report the result as the recorded curve showing the absorbance (extinction coefficient) plotted versus the wavelength and also as “complies”/“does not comply” with type I or type II requirements (see Table 1).

## Annex D (normative)

### Reducing substances

#### D.1 General

When subjected to extraction processes in aqueous media, a given elastomeric material may release oxidizable matter, depending on its composition. Probably the most common of the possible extractables from elastomeric parts are the vulcanizing agents, the accelerators and their reaction products. This category of materials might include one or more of the following constituents: sulfur, thiurams, sulfenamides, thiazoles, dithiocarbamates, complex organic amines, phenolic resins and organic peroxides.

The extraction of the reducing matter is performed under conditions which simulate those to which elastomeric parts are usually exposed during sterilization in a steam autoclave.

#### D.2 Reagents

##### D.2.1 Sulfuric acid, dilute

Prepare a solution containing 98 g of sulfuric acid per litre of water.

##### D.2.2 Starch solution

Triturate 1,0 g of soluble starch with 5 ml of water and, whilst stirring, pour the mixture into 100 ml of boiling water containing 10 mg of mercuric iodide.

#### D.3 Procedure

Carry out the test within 4 h of preparation of solution  $S_1$ . To 20,0 ml of solution  $S_1$ , add 1 ml of dilute sulfuric acid and 20,0 ml of 0,002 mol/l potassium permanganate. Boil for 3 min. Cool. Add 1 g of potassium iodide or 2 ml of 10 % potassium iodide solution in water and titrate immediately with 0,01 mol/l sodium thiosulfate, using 0,25 ml of starch solution as indicator. Also carry out a titration using 20,0 ml of blank solution  $S_0$ .

Calculate the result as the difference, in millilitres, between the volumes of titrant required by solution  $S_1$  and solution  $S_0$  (to one place of decimals).

#### D.4 Expression of results

Report the result as “complies”/“does not comply” with type I or type II requirements (see Table 1).

## Annex E (normative)

### Extractable heavy metals

#### E.1 General

The extraction of metal ions, due to the presence of mineral fillers and certain metal oxides used as cure boosters, is common. The levels of these metals can be controlled by the rubber manufacturer by careful selection of material and thorough inspection of supplies.

The extraction of the heavy metals is performed under conditions which simulate those to which elastomeric parts are usually exposed during sterilization in a steam autoclave.

#### E.2 Reagents

##### E.2.1 Standard lead solution

Prepare an aqueous solution containing 2,0 mg/l of Pb from lead nitrate [Pb(NO<sub>3</sub>)<sub>2</sub>].

##### E.2.2 Thioacetamide reagent

To 0,2 ml of a 40 g/l thioacetamide solution in water, add 1 ml of a mixture of 5 ml of water, 15 ml of 1 mol/l sodium hydroxide and 20 ml of glycerol (85 %). Heat in a water-bath for 20 s. Prepare immediately before use.

##### E.2.3 Buffer solution, pH 3,5

Dissolve 25,0 g of ammonium acetate in 25 ml of water and add 38,0 ml of hydrochloric acid (E.2.4). Adjust the pH if necessary with dilute hydrochloric acid (E.2.5) or dilute ammonia (E.2.6). Dilute to 100 ml with water.

##### E.2.4 Hydrochloric acid

Dilute 70 g of concentrated hydrochloric acid [35,0 % to 37,0 % (by mass) of HCl] to 100 ml with water.

##### E.2.5 Hydrochloric acid, dilute

Dilute 20 g of concentrated hydrochloric acid [35,0 % to 37,0 % (by mass) of HCl] to 100 ml with water.

##### E.2.6 Ammonia, dilute

Dilute 41 g of concentrated ammonia [25,0 % to 30,0 % (by mass) of ammonia] to 100 ml with water.

#### E.3 Procedure

To 12 ml of solution S<sub>1</sub>, add 2 ml of pH 3,5 buffer solution (E.2.3). Mix and add to 1,2 ml of thioacetamide reagent (E.2.2). Mix immediately. Prepare a reference solution in the same manner by mixing 10 ml of standard lead solution (E.2.1), as prescribed, and 2 ml of solution S<sub>1</sub>.

After 2 min, any brown colour in the test solution shall not be more intense than that of the reference solution, which corresponds to a heavy metal concentration of 2 mg/l.

#### **E.4 Expression of results**

Report the result as “complies”/“does not comply” with the requirement (see Table 1).

## Annex F (normative)

### Extractable zinc

#### F.1 Procedure

Most rubber formulations require a small portion of zinc oxide to support the vulcanization process and to improve certain physical characteristics. Consequently zinc ions may be extracted by aqueous fluids.

#### F.2 Procedure

**F.2.1** Add 1 ml of 0,01 mol/l hydrochloric acid to 20 ml of solution  $S_1$ .

**F.2.2** Prepare at least three calibration solutions from a standard zinc solution (1 g/l Zn) by diluting with 0,1 mol/l hydrochloric acid and water to give an acid concentration similar to that in the test solution. Prepare calibration solutions of concentrations which span the expected zinc concentration in the test solution.

**F.2.3** Measure the absorbance of the test solution and the calibration solutions at 213,9 nm using a zinc hollow-cathode lamp as the radiation source and an air/acetylene flame.

If dilution of the test solution is necessary, record the dilution factor.

Consider the dilution factor, if applicable, in the calculation of the results.

Calculate the result as mg/l of Zn in solution  $S_1$  (to one place of decimals).

#### F.3 Expression of results

Report the result as “complies”/“does not comply” with the requirement (see Table 1).



## Annex G (normative)

### Extractable ammonia

#### G.1 General

The leaching of traces of ammonia is mostly observed with conventional natural-elastomer formulations. It is usually caused by the presence of protein material or amines in the natural isoprene polymer.

The extraction of ammonia is performed under conditions which simulate those to which elastomeric parts are usually exposed during sterilization in a steam autoclave.

#### G.2 Reagents

##### G.2.1 Sodium hydroxide

Prepare a dilute sodium hydroxide solution (8,5 g of NaOH per 100 ml).

##### G.2.2 Alkaline potassium tetraiodomercurate

Dissolve 11 g of potassium iodide and 15 g of mercuric iodide in water and make up to 100 ml with water.

Immediately before use, mix one volume of this solution with an equal volume of 250 g/l sodium hydroxide solution.

#### G.3 Procedure

Make 5 ml of solution  $S_1$  alkaline, if necessary, by the addition of a measured volume of dilute sodium hydroxide solution and dilute to 15 ml with water. To the solution, add 0,3 ml of alkaline potassium tetraiodomercurate solution. Prepare a reference solution by adding to 10 ml of a standard ammonium solution (containing 1 mg/l  $NH_3$ ) the same volume of dilute sodium hydroxide solution as for solution  $S_1$ , diluting to 15 ml with water and adding 0,3 ml of alkaline potassium tetraiodomercurate solution. Place the solutions in test tubes and stopper the tubes.

After 30 s, any yellow colour in the test solution shall not be more intense than that in the reference solution, which corresponds to 2 mg/l  $NH_3$  in solution  $S_1$ .

#### G.4 Expression of results

Report the result as “complies”/“does not comply” with the requirement (see Table 1).

## Annex H (normative)

### Residue on evaporation

#### H.1 General

Depending on their composition, rubber formulations may release various quantities of non-volatile solids on extraction.

The extraction of non-volatile solids is performed under conditions which simulate those to which elastomeric parts are usually exposed during sterilization in a steam autoclave.

They are determined from the mass remaining after evaporation to dryness.

#### H.2 Procedure

Dry an evaporating dish at 105 °C max., allow to cool in a desiccator and weigh. Introduce a known volume (at least 50,0 ml) of solution S<sub>1</sub> and evaporate to dryness at 105 °C max. Allow to cool in the desiccator and reweigh.

Calculate the result as the number of milligrams of residue per 50 ml of solution S<sub>1</sub> (to one place of decimals).

#### H.3 Expression of results

Report the result as “complies”/“does not comply” with type I or type II requirements (see Table 1).

## Annex I (normative)

### Volatile sulfides

#### I.1 General

Conventional cure systems use sulfur or sulfur-containing compounds for cross-linking purposes. Rubber materials vulcanized using such compounds may form volatile sulfides when exposed to aqueous extraction media, especially at acid pH-values. The sulfides released can be detected visually by reaction with lead acetate paper.

#### I.2 Reagents

##### I.2.1 Citric acid

Prepare a 20 g/l aqueous solution.

##### I.2.2 Lead acetate paper

Immerse filter paper weighing about 80 g per square metre in a mixture of 1 volume of dilute acetic acid [(120 ± 5) g/l] and 10 volumes of lead acetate solution (containing 95 g/l lead acetate). After drying, cut the paper to fit the size of the mouth of the flask used.

##### I.2.3 Sodium sulfide (Na<sub>2</sub>S·9H<sub>2</sub>O)

##### I.2.4 Lead acetate solution

Prepare a 95 g/l solution in carbon-dioxide-free water.

##### I.2.5 Acetic acid, dilute

Dilute 12 g of glacial acetic acid to 100 ml with water.

The solution contains not less than 115 g/l and not more than 125 g/l of C<sub>2</sub>H<sub>4</sub>O<sub>2</sub> (molecular mass 60,1).

#### I.3 Procedure

Place rubber, cut into pieces if necessary, with a total surface area of (20 ± 2) cm<sup>2</sup> in a 250 ml conical flask and add 50 ml of 20 g/l citric acid solution. Place a piece of lead acetate paper over the mouth of the flask and maintain the paper in position by placing an inverted glass beaker over it. Heat in an autoclave at (121 ± 2) °C for 30 min. Any black stain on the paper shall not be more intense than that produced by a reference prepared at the same time and in the same manner using 0,154 mg of sodium sulfide (Na<sub>2</sub>S·9H<sub>2</sub>O) and 50 ml of 20 g/l citric acid solution. Special care is necessary to avoid errors due to the extremely hygroscopic nature of sodium sulfide.

#### I.4 Expression of results

Report the result as “complies”/“does not comply” with the requirement (See Table 1).

## Annex J (informative)

### Conductivity

#### J.1 General

When exposed to aqueous extraction media, elastomeric parts may release substances which increase the conductivity of the extraction medium.

#### J.2 Procedure

**J.2.1** Perform the following test within 4 h of preparing test solution  $S_1$ .

**J.2.2** Use only borosilicate glass containers that have been specifically reserved for conductivity determinations.

**J.2.3** Rinse the measurement electrodes (platinum electrodes or electrodes covered with platinum black) several times with purified water, and then twice with blank solution  $S_0$ .

**J.2.4** Measure the conductivity of blank solution  $S_0$ . It shall be less than  $3,0 \mu\text{S}/\text{cm}$  at  $(20 \pm 1) ^\circ\text{C}$ .

**J.2.5** Rinse the measurement electrodes at least twice with test solution  $S_1$  and then measure the conductivity of solution  $S_1$ .

**J.2.6** If the measurements are not taken at the temperature of  $(20 \pm 1) ^\circ\text{C}$ , temperature corrections shall be made.

#### J.3 Expression of results

Report the conductivity of solutions  $S_1$  and  $S_0$  in microsiemens per centimetre ( $\mu\text{S}/\text{cm}$ ).

## Bibliography

- [1] ISO 48:1994, *Rubber, vulcanized or thermoplastic — Determination of hardness (hardness between 10 IRHD and 100 IRHD)*
- [2] ISO 247:1990, *Rubber — Determination of ash*
- [3] ISO 2781:1988, *Rubber, vulcanized — Determination of density*
- [4] ISO 3696:1987, *Water for analytical laboratory use — Specification and test methods*
- [5] ISO 7886-1:1993, *Sterile hypodermic syringes for single use — Part 1: Syringes for manual use*
- [6] ISO 8871-2:2003, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 2: Identification and characterization*
- [7] ISO 8871-3:2003, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 3: Determination of released-particle count*

**Annex ZA**  
(normative)

**Normative references to international publications  
with their relevant European publications**

This European Standard incorporates by dated or undated reference, provisions from other publications. These normative references are cited at the appropriate places in the text and the publications are listed hereafter. For dated references, subsequent amendments to or revisions of any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies (including amendments).

NOTE Where an International Publication has been modified by common modifications, indicated by (mod.), the relevant EN/HD applies.

<u>Publication</u>	<u>Year</u>	<u>Title</u>	<u>EN</u>	<u>Year</u>
ISO 8362-2	1988	Injection containers for injectables and accessories - Part 2: Closures for injection vials	EN 28362-2	1993



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