INTERNATIONAL STANDARD

ISO 13959

Third edition
2014-04-01

Water for haemodialysis and related therapies

Eau pour hémodialyse et thérapies apparentées

Reference number
ISO 13959:2014(E)

COPYRIGHT PROTECTED DOCUMENT

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

Published in Switzerland

Contents

Page

Foreword

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

The 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).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This third edition cancels and replaces the second edition (ISO 13959:2009), which has been technically revised.

Introduction

Assurance of adequate water quality is one of the most important aspects of ensuring a safe and effective delivery of haemodialysis, haemodiafiltration, or haemofiltration.

This International Standard contains minimum requirements, chemical and microbiological, for the water to be used for preparation of dialysis fluids, concentrates, and for the reprocessing of haemodialysers and the necessary steps to ensure compliance with those requirements.

Haemodialysis and haemodiafiltration can expose the patient to more than 500 l of water per week across the semi-permeable membrane of the haemodialyser or haemodiafilter. Healthy individuals seldom have a weekly oral intake above 12 l. This over 40-fold increase in exposure requires control and monitoring of water quality to avoid excesses of known or suspected harmful substances. Since knowledge of potential injury from trace elements and contaminants of microbiological origin over long periods is still growing and techniques for treating drinking water are continuously developed, this International Standard will evolve and be refined accordingly. The physiological effects attributable to the presence of organic contaminants in dialysis water are important areas for research. At the time this International Standard was published it was not possible to specify threshold values for organic contaminants permitted in water used for the preparation of dialysis fluids, concentrates, and reprocessing of haemodialysers. The issue of organic contaminants will be reassessed on the next revision of this International Standard.

Within this International Standard, measurement techniques current at the time of publication have been cited. Other standard methods may be used, provided that such methods have been appropriately validated and compared to the cited methods.

The final dialysis fluid is produced from concentrates or salts manufactured, packaged, and labelled according to ISO 13958 mixed with water meeting the requirements of this International Standard. Operation of water treatment equipment and haemodialysis systems, including ongoing monitoring of the quality of water used to prepare dialysis fluids, and handling of concentrates and salts are the responsibility of the haemodialysis facility and are addressed in ISO 23500. Haemodialysis professionals make choices about the various applications (haemodialysis, haemodiafiltration, haemofiltration) and should understand the risks of each and the requirements for safety for fluids used for each.

The verbal forms used in this International Standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this International Standard, the auxiliary verb

- "shall" means that compliance with a requirement or a test is mandatory for compliance with this International Standard,
- "should" means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this International Standard, and
- "may" is used to describe a permissible way to achieve compliance with a requirement or test.

This International Standard is directed towards manufacturers and providers of water treatment systems and also to haemodialysis facilities.

Water for haemodialysis and related therapies

1 Scope

This International Standard specifies minimum requirements for water to be used in haemodialysis and related therapies.

This International Standard includes water to be used in the preparation of concentrates, dialysis fluids for haemodialysis, haemodiafiltration and haemofiltration, and for the reprocessing of haemodialysers.

The operation of water treatment equipment and the final mixing of treated water with concentrates to produce dialysis fluid are excluded from this International Standard. Those operations are the sole responsibility of dialysis professionals. This International Standard does not apply to dialysis fluid regenerating systems.

2 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

2.1
action level
concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

2.2
chlorine, combined
chlorine that is chemically combined, such as in chloramine compounds

Note 1 to entry: There is no direct test for measuring combined chlorine, but it can be measured indirectly by measuring both total and free chlorine and calculating the difference.

2.3
chlorine, free
chlorine present in water as dissolved molecular chlorine (Cl), hypochlorous acid (HOCl), and hypochlorite ion (OCl−)

Note 1 to entry: The three forms of free chlorine exist in equilibrium.

2.4
chlorine, total
sum of free and combined chlorine

Note 1 to entry: Chlorine can exist in water as dissolved molecular chlorine, hypochlorous acid, and/or hypochlorite ion (free chlorine) or in chemically combined forms (combined chlorine). Where chloramine is used to disinfect water supplies, chloramine is usually the principal component of combined chlorine.

2.5
colony-forming unit
CFU
measure of bacterial or fungal cell numbers that theoretically arise from a single cell when grown on solid media

Note 1 to entry: Colonies can also form from groups of organisms when they occur in aggregates.

2.6
device
individual water purification unit, such as a softener, carbon bed, reverse osmosis unit, or deionizer

Note 1 to entry: This term is synonymous with the term "component" as used by the US Food and Drug Administration (see Reference [49]).

2.7
dialysis fluid
dialysate
dialysis solution
aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during haemodialysis

Note 1 to entry: The term "dialysis fluid" is used throughout this International Standard to mean the fluid made from dialysis water and concentrates that is delivered to the dialyser by the dialysis fluid delivery system. Such phrases as "dialysate" or "dialysis solution" are used in place of dialysis fluid in some countries; however, that usage is discouraged to avoid confusion.

Note 2 to entry: The dialysis fluid entering the dialyser is referred to as "fresh dialysis fluid", while the fluid leaving the dialyser is referred to as "spent dialysis fluid."

Note 3 to entry: Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and haemofiltration.

2.8
dialysis fluid delivery system
device that prepares dialysis fluid online from dialysis water and concentrates or that stores and distributes premixed dialysis fluid, circulates the dialysis fluid through the dialyser, monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow and blood leaks, and prevents dialysis during disinfection or cleaning modes

Note 1 to entry: The term includes reservoirs, conduits, proportioning devices for the dialysis fluid, and monitors and associated alarms and controls assembled as a system for the purposes listed above.

Note 2 to entry: The dialysis fluid delivery system can be an integral part of the single-patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

Note 3 to entry: Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

2.9
dialysis water
water that has been treated to meet the requirements of this International Standard and which is suitable for use in haemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialysers, preparation of concentrates, and preparation of substitution fluid for online convective therapies

2.10
disinfection
destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

Note 1 to entry: Disinfection is a less lethal process than sterilization because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

2.11
endotoxin
major component of the outer cell wall of gram-negative bacteria

Note 1 to entry: Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, leading to a syndrome characterized by fever, shaking, chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose [see also *pyrogen* (2.20)].

2.12
endotoxin units
EU

units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

Note 1 to entry: Because activity of endotoxins depends on the bacteria from which they are derived, their activity is referred to as a standard endotoxin.

Note 2 to entry: In some countries, endotoxin concentrations are expressed in international units (IU). Since the harmonization of endotoxin assays, EU and IU are equivalent.

2.13
feed water

water supplied to a water treatment system or an individual component of a water treatment system

2.14
haemodiafiltration

form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane

Note 1 to entry: Diffusive solute removal is achieved using a dialysis fluid stream as in haemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing a replacement solution into the blood either before the dialyser (predilution haemodiafiltration), after the dialyser (postdilution haemodiafiltration), or a combination of the two (mixed dilution haemodiafiltration).

2.15
haemodialysis

form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

Note 1 to entry: Fluid removal that is sufficient to obtain the desired weight loss is achieved by establishing a hydrostatic pressure gradient across the membrane. This fluid removal provides some additional waste solute removal, particularly for solutes with higher molecular weight.

2.16
haemofiltration

form of renal replacement therapy in which waste solutes are removed from blood by convection

Note 1 to entry: Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the haemofilter (predilution haemofiltration), after the haemofilter (postdilution haemofiltration), or a combination of the two (mixed dilution haemofiltration).

Note 2 to entry: There is no dialysis fluid stream in haemofiltration.

2.17
Limulus amoebocyte lysate test
LAL test

assay used to detect endotoxin

Note 1 to entry: The detection method uses the chemical response of an extract from blood cells of a horseshoe crab (*Limulus polyphemus*) to endotoxins.

Note 2 to entry: Amebocyte lysate from a second horseshoe crab, *Tachypleus tridentatus*, can also be used to detect endotoxin.

2.18
manufacturer

entity that designs, manufactures, fabricates, assembles, or processes a finished device

Note 1 to entry: Manufacturers include, but are not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development, and initial distributions of foreign entities performing these functions. The term does not cover preparation of concentrates from prepackaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility after responsibility for the concentrate is transferred from the manufacturer to the user.

2.19
microbiological contamination

contamination with any form of microorganism (e.g. bacteria, yeast, fungi, and algae) or with the by-products of living or dead organisms such as endotoxins, exotoxins, and cyanobacterial toxins (derived from blue-green algae)

2.20
pyrogen

fever-producing substance

Note 1 to entry: Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also *endotoxin* (2.11)].

2.21
source water

water entering a dialysis facility from an external supplier, such as a municipal water supply

Note 1 to entry: Source water is sometimes referred to as feed water.

2.22
sterile

free from viable microorganisms

Note 1 to entry: “Sterile” can be used to describe a packaged solution that was prepared using a terminal sterilization process validated according to the methods of the applicable pharmacopoeia. A terminal sterilization process is commonly defined as one that achieves a sterility assurance level (SAL) of 10^{-6}, i.e. assurance of less than one chance in a million that viable microorganisms are present in the sterilized article.

Note 2 to entry: Alternatively, “sterile” can be used to describe a solution prepared for immediate use by a continuous process, such as filtration, that has been validated according to the methods of the applicable pharmacopoeia to produce a solution free from microorganisms for the validated life of the filter.

2.23
substitution fluid

fluid used in haemofiltration and haemodiafiltration treatments which is infused directly into the patient’s blood as a replacement for the fluid that is removed from the blood by filtration

Note 1 to entry: Substitution fluid is also referred to as substitution solution or replacement solution.

Note 2 to entry: Substitution fluid can also be used for bolus administration, for priming of an extracorporeal blood circuit, and for returning blood to the patient at the end of a treatment.

2.24
total dissolved solids

TDS

sum of all ions in a solution, often approximated by means of electrical conductivity or resistivity measurements

Note 1 to entry: TDS measurements are commonly used to assess the performance of reverse osmosis units. TDS values are often expressed in terms of $CaCO_3$, NaCl, KCl, or 442 equivalents, in milligrams per litre (mg/l). [442 is a solution of sodium sulfate (40 %), sodium bicarbonate (40 %), and sodium chloride (20 %) that closely represents the conductivity to concentration relationship, on average, for naturally occurring fresh water.]

2.25
user
physician or physician's representative or healthcare professional with a responsibility for the prescription, production, and delivery of dialysis fluid

2.26
water treatment system
collection of water treatment devices and associated piping, pumps, valves, gauges, etc., that together produce water meeting the requirements of this International Standard for haemodialysis applications and deliver it to the point of use

3 Dialysis water requirements

3.1 Dialysis water verification and monitoring

The quality of the dialysis water, as specified in 3.2 and 3.3, shall be verified upon installation of a water treatment system. Monitoring of the dialysis water quality shall be carried out thereafter.

3.2 Microbiological requirements

Total viable microbial counts in dialysis water shall be less than 100 CFU/ml, or lower if required by national legislation or regulations. An action level shall be set based on knowledge of the microbial dynamics of the system. Typically, the action level will be 50 % of the maximum allowable level.

Endotoxin content in dialysis water shall be less than 0,25 EU/ml, or lower if required by national legislation or regulations. An action level shall be set, typically at 50 % of the maximum allowable level.

NOTE See A.1 for a history of these requirements.

3.3 Chemical contaminants

Dialysis water shall not contain chemicals at concentrations in excess of those listed in Tables 1 and 2, or as required by national legislation or regulations.

NOTE 1 See A.2 for an explanation of values supplied.

NOTE 2 The maximum allowable levels of contaminants listed in Tables 1 and 2 include the anticipated uncertainty associated with the analytical methodologies listed in Table 3.

Where the dialysis water is used for the reprocessing of haemodialysers (cleaning, testing, and mixing of disinfectants), the user is cautioned that the dialysis water shall meet the requirements of this International Standard. The dialysis water should be measured at the input to the dialyser reprocessing equipment.

Table 1 — Maximum allowable levels of toxic chemicals and dialysis fluid electrolytes in dialysis water[a]

Contaminant	Maximum concentration mg/l[b]
Contaminants with documented toxicity in haemodialysis	
Aluminium	0,01
Total chlorine	0,1
Copper	0,1
Fluoride	0,2
Lead	0,005
Nitrate (as N)	2
Sulfate	100
Zinc	0,1
Electrolytes normally included in dialysis fluid	
Calcium	2 (0,05 mmol/l)
Magnesium	4 (0,15 mmol/l)
Potassium	8 (0,2 mmol/l)
Sodium	70 (3,0 mmol/l)

[a] A dialysis facility’s Medical Director has the ultimate responsibility for ensuring the quality of water used for dialysis.

[b] Unless otherwise noted.

Table 2 — Maximum allowable levels of other trace elements in dialysis water

Contaminant	Maximum concentration mg/l
Antimony	0,006
Arsenic	0,005
Barium	0,1
Beryllium	0,000 4
Cadmium	0,001
Chromium	0,014
Mercury	0,000 2
Selenium	0,09
Silver	0,005
Thallium	0,002

4 Tests for compliance with microbiological and chemical requirements

4.1 Microbiology of dialysis water

Samples shall be collected where a dialysis machine connects to the water distribution loop, from a sample point in the distal segment of the loop or where such water enters a mixing tank.

Microbial analysis of water should be conducted as soon as possible after sample collection to avoid unpredictable changes in the microbial population. If samples cannot be assayed within 4 h of collection, follow the laboratory’s instructions for sample storage and shipping. Samples intended for colony counts should not be frozen.

Total viable counts (standard plate counts) shall be obtained using conventional microbiological assay procedures (pour plate, spread plate, membrane filter techniques). Membrane filtration is the preferred method for this test. Other methods may be used, provided that such methods have been appropriately validated and compared to the cited methods. The calibrated loop technique is not accepted.

Culture media shall be tryptone glucose extract agar (TGEA), Reasoner's 2A (R2A), or other media that can be demonstrated to provided equivalent results. Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C and an incubation time of 168 h (7 d) are recommended. Other incubation times and temperatures may be used if it can be demonstrated that they provide equivalent results. No method will give a total microbial count.

The presence of endotoxins shall be determined by the *Limulus* amoebocyte lysate (LAL) test. Other test methods may be used if it can be demonstrated that they provide equivalent results.

4.2 Chemical contaminants test methods

Compliance with the requirements listed in Table 1 can be shown by using chemical analysis methods referenced by the ISO, the American Public Health Association[3] or the US Environmental Protection Agency[47] methods referenced in applicable pharmacopoeia, or by any other equivalent validated analytical method.

Compliance with the requirements listed in Table 2 can be shown in one of three ways.

- Where such testing is available, the individual contaminants in Table 2 can be determined using chemical analysis methods referenced by ISO, the American Public Health Association[3] or the US Environmental Protection Agency,[47] or other equivalent analytical methods.
- Where testing for the individual trace elements listed in Table 2 is not available, and the source water can be demonstrated to meet the standards for potable water as defined by the WHO or local regulations, an analysis for total heavy metals can be used with a maximum allowable level of 0,1 mg/l.
- If neither of these options is available, compliance with the requirements of Table 2 can be met by using water that can be demonstrated to meet the potable water requirements of the WHO (see Reference [53]) or local regulations and a reverse osmosis system with a rejection of >90 % based on conductivity, resistivity, or TDS. Samples shall be collected at the end of the water purification cascade or at the most distal point in each water distribution loop.

Table 3 lists suitable test methods for each contaminant, along with an appropriate reference.

Table 3 — Analytical test methods for chemical contaminants

Contaminant	Analytical technique	Reference, method number
Aluminium	Inductively coupled plasma mass spectrometry or Atomic absorption (electrothermal)	ISO 17294-2:2003 American Public Health Assn, #3113
Antimony	Inductively coupled plasma mass spectrometry or Atomic absorption (platform)	ISO 17294-2:2003 US EPA, #200.9
Arsenic	Inductively coupled plasma mass spectrometry or Atomic absorption (gaseous hydride)	ISO 17294-2:2003 American Public Health Assn, #3114
Barium	Inductively coupled plasma mass spectrometry or Atomic absorption (electrothermal)	ISO 17294-2:2003 American Public Health Assn, #3113
Beryllium	Inductively coupled plasma mass spectrometry or Atomic absorption (platform)	ISO 17294-2:2003 US EPA, #200.9
Cadmium	Inductively coupled plasma mass spectrometry or Atomic absorption (electrothermal)	ISO 17294-2:2003 American Public Health Assn, #3113

Table 3 *(continued)*

Contaminant	Analytical technique	Reference, method number
Calcium	Inductively coupled plasma mass spectrometry or EDTA titrimetric method or atomic absorption (direct aspiration) or ion specific electrode	ISO 17294-2:2003 American Public Health Assn, #3500-Ca D American Public Health Assn, #3111B
Total chlorine	DPD ferrous titrimetric method or DPD colourimetric method TMK/MTK colourimetric method	American Public Health Assn, #4500-Cl F American Public Health Assn, #4500-Cl G
Chromium	Inductively coupled plasma mass spectrometry or Atomic absorption (electrothermal)	ISO 17294-2:2003 American Public Health Assn, #3113
Copper	Inductively coupled plasma mass spectrometry or Atomic absorption (direct aspiration) or neocuproine method	ISO 17294-2:2003 American Public Health Assn, #3111 American Public Health Assn, #3500-Cu D
Fluoride	Ion chromatography or Ion selective electrode method or sodium 2-(parasulfophenylazo)-1,8-dihydroxy-3,6-naphthalenedisulfonate (SPADNS) method	ISO 10304-1:2007 ISO 10359-1:1992 American Public Health Assn, #4500-F^- C American Public Health Assn, #4500-F^- D
Lead	Inductively coupled plasma mass spectrometry Atomic absorption (electrothermal)	ISO 17294-2:2003 American Public Health Assn, #3113
Magnesium	Inductively coupled plasma mass spectrometry or Atomic absorption (direct aspiration) Ion chromatography	ISO 17294-2:2003 American Public Health Assn, #3111 EPA 300.7:1986
Mercury	Flameless cold vapour technique (atomic absorption)	American Public Health Assn, #3112
Nitrate	Ion chromatography or Spectrophotometric method using sulfosalicylic acid or Cadmium reduction method	ISO 10304-1:2007 ISO 7890-3:1988 American Public Health Assn, #4500-NO3 E
Potassium	Inductively coupled plasma mass spectrometry or Atomic absorption (direct aspiration) or flame photometric method or ion specific electrode	ISO 17294-2:2003 American Public Health Assn, #3111 American Public Health Assn, #3500-K D American Public Health Assn, #3500-K E
Selenium	Inductively coupled plasma mass spectrometry or Atomic absorption (gaseous hydride) or atomic absorption (electrothermal)	ISO 17294-2:2003 American Public Health Assn, #3114 American Public Health Assn, #3113
Silver	Inductively coupled plasma mass spectrometry or Atomic absorption (electrothermal)	ISO 17294-2:2003 American Public Health Assn, #3113
Sodium	Inductively coupled plasma mass spectrometry or Atomic absorption (direct aspiration) or flame photometric method or ion specific electrode	ISO 17294-2:2003 American Public Health Assn, #3111 American Public Health Assn, #3500-Na D
Sulfate	Ion chromatography or Turbidimetric method	ISO 10304-1:2007 American Public Health Assn, #4500-SO_4^{2-} E

Table 3 *(continued)*

Contaminant	Analytical technique	Reference, method number
Thallium	Inductively coupled plasma mass spectrometry or Atomic absorption (platform)	ISO 17294-2:2003 US EPA, 200.9
Total heavy metals	Colourimetric	European Pharmacopoeia, 2.4.8 US Pharmacopoeia, < 231 >
Zinc	Inductively coupled plasma mass spectrometry or Atomic absorption (direct aspiration) or dithizone method	ISO 17294-2:2003 American Public Health Assn, #3111 American Public Health Assn, #3500-Zn D

Annex A
(informative)

Rationale for the development and provisions of this International Standard

A.1 Microbiology of dialysis water

NOTE The information in this clause is intended to give the reader a historical perspective of how the microbial limits were developed for this International Standard.

Originally, it was considered that the water used to prepare dialysis fluid need not be sterile. However, several studies had demonstrated that the attack rates of pyrogenic reactions were related directly to the number of bacteria in dialysis fluid.[14][18][19] These studies provided the rationale for setting the maximum level of bacteria in dialysis water at 200 CFU/ml in the original AAMI standard for water quality published in 1982. Later, the European community chose to use a slightly lower level of 100 CFU/ml as their bacterial limit for dialysis water and that value has been adopted in this International Standard. Because 7 d can elapse between sampling water for the determination of microbiological contamination and receiving results, and because bacterial proliferation can be rapid, action levels for microbial counts and endotoxin were introduced into this International Standard. These action levels allow the user to initiate corrective action before levels exceed the maximum levels established by this International Standard.

Several groups of investigators have shown convincingly that pyrogenic reactions are caused by lipopolysaccharides or endotoxins that are associated with gram-negative bacteria. Furthermore, gram-negative water bacteria have been shown to be capable of multiplying rapidly in dialysis water prepared by distillation, deionization, reverse osmosis, and softening. Dialysis fluid made with this water likewise provides a very good growth medium for these types of bacteria. Even at low levels of bacterial contamination, pyrogenic reactions have been reported when the source of endotoxin was exogenous to the dialysis system (i.e. present in the community water supply).[21] Consequently, it was thought prudent to impose an upper limit on the endotoxin content of dialysis water. A level of 2 EU/ml was chosen by AAMI in 2001 as the upper limit for endotoxin, since compliance with that level could be easily achieved with contemporary water treatment systems using reverse osmosis, ultrafiltration, or both. At the same time, the European community chose to use an upper limit of 0,25 EU/ml for endotoxin. During the revision for the second edition of this International Standard in 2008, the 0,25 EU/ml limit was included as the upper limit for endotoxin in dialysis water.

A.2 Chemical contaminants in dialysis water

NOTE This historical review is provided to help the reader understand the considerations given to the chemical contamination of water used for dialysis treatments.

Contaminants identified as needing restrictions on the allowable level that can be present in water for dialysis are divided into three groups for the purposes of this International Standard. The first group includes chemicals shown to cause toxicity in dialysis patients. These chemicals include fluoride, aluminium, chloramine, sulfate, nitrate, copper, zinc, and lead. Chlorine is included here because of its potential toxicity.

Toxicity of fluoride in dialysis patients at the levels usually associated with fluoridated water, 1 mg/l, is questionable. In the absence of a consensus on fluoride's role in uraemic bone disease, it was initially thought prudent to restrict the fluoride level of dialysis fluid.[40] Subsequently, illness in all of eight dialysis patients, with the death of one patient, was reported as a result of accidental overfluoridation of a municipal water supply.[12] Fluoride levels of up to 50 mg/l were found in water used for dialysis that was treated only with a water softener. Probably, these illnesses would have been less severe, if not prevented, if the dialysis water had been treated with deionization or reverse osmosis. In one case, where deionizers were allowed to exhaust, 12 of 15 patients became acutely ill from fluoride intoxication.[5] Three of the patients died from ventricular fibrillation. Fluoride concentrations in the water used to prepare the dialysis fluid were as high as 22,5 mg/l.

The suggested maximum aluminium level has been specified to prevent accumulation of this toxic metal in the patient.[30][33] Aluminium is particularly likely to increase suddenly to high levels caused by changes in the method of water treatment to include aluminium-containing compounds. As with fluoride, water treatment would provide a measure of safety even if the aluminium levels should increase dramatically between chemical tests of the dialysis water.

The toxicity of chloramine is undisputed.[15] Although the role of free chlorine in oxidative blood damage is unclear, its high oxidation potential and ability to form chloramines suggests the avoidance of highly chlorinated water in preparation of dialysis fluid. Chlorine can be present in water as both free chlorine and chlorine in chemically combined forms. Chloramine is a form of chemically combined chlorine. Determining the level of chloramine typically involves measuring both total chlorine and free chlorine and assigning the difference in concentrations to chloramine. During the edition for the second revision of this International Standard in 2008, the working group chose to simplify this situation by setting a maximum allowable level for total chlorine at the same value used previously for chloramine (0,1 mg/l), thus permitting a single test to be used.

Sulfate at levels above 200 mg/l has been related to nausea, vomiting, and metabolic acidosis. The symptoms disappear when the level remains below 100 mg/l.[13] Nitrates are a marker for bacterial contamination and fertilizer runoff and have caused methaemoglobinaemia.[11] They should, therefore, be permitted only at very low levels. Both copper and zinc toxicity have been demonstrated when these substances are present in dialysis fluid at levels below those permitted by the US Environmental Protection Agency (EPA) standard.[22][36] Hence, a lower level has been chosen.

Dialysis fluid lead levels of 52 µg/l to 65 µg/l have been associated with abdominal pain and muscle weakness.[25] There is no evidence of lead toxicity when lead levels in water or dialysis fluid are below 5 µg/l.

The second group of substances addressed in 3.3 and Table 1 consists of physiological substances that can adversely affect the patient if present in the dialysis fluid in excessive amounts. Calcium, magnesium, potassium, and sodium are examples of these substances.

Of the physiological substances that can be harmful when present in excessive amounts, calcium has been reduced from the 10 mg/l originally selected to 2 mg/l on the basis of the critical role of calcium in bone disorders associated with renal disease. A level of 10 mg/l would have allowed a potential 20 % error in dialysis fluid calcium, whereas a level of 2 mg/l reduces that error risk to less than 5 %.

The third group of chemical contaminants addressed in 3.3 is based on the US EPA maximum allowable levels for drinking water.[48] When the AAMI standard ANSI/AAMI RD5[55] was initially developed, the US EPA *Safe Drinking Water Act*[48] included maximum allowable levels for barium, selenium, chromium, silver, cadmium, mercury, and arsenic. Selenium and chromium levels in dialysis water were set at the "no-transfer" level.[28] The "no-transfer" level was chosen even though it is above the US EPA limit for selenium and 28 % of the US EPA limit for chromium, because a restriction is not needed below the level at which there is no passage from the dialysis fluid to the blood. The International Standard specified the maximum allowable limits for the other contaminants in this group to be one tenth of the US EPA maximum allowable limits because the volume of water used for dialysis far exceeds that used for drinking water, because protein binding of these solutes could occur in the blood, and because there is reduced renal excretion of these substances. These reduced limits were selected using the following assumptions: 1) feed water entering dialysis systems typically meets the US EPA *Safe Drinking Water Act*; 2) typically, reverse osmosis treatment removes 90 % to 99 % of dissolved inorganic solids; and 3) reverse osmosis-treated water is a suitable standard for safety of water used in dialysis. These assumptions are based on the recommendations of Keshaviah et al..[26] Although these assumptions can be questioned, it was reasoned that setting standards in this way would cause little or no economic impact, even though some feed water exceeds the US EPA maximum allowable levels. It should be noted that the level for arsenic, 0,05 mg/l in the Keshaviah report, is a typographical error. The correct value is 0,005 mg/l as given in Table 2 of this International Standard (E. Klein, personal communication). It should also be noted that the EPA maximum allowable level for arsenic in drinking water was reduced to 0,01 mg/l, effective from January 26th, 2006.

Several changes occurred in the *Safe Drinking Water Act* after these levels were established. Specifically, antimony, beryllium, free cyanide, and thallium were added to the list of contaminants covered by the Act and the maximum allowable level for cadmium had been decreased. For consistency, antimony, beryllium, and thallium were added to the list of contaminants in the United States. The maximum allowable levels of antimony and thallium were set at values above one-tenth of the US EPA maximum allowable level because of limitations in the sensitivity of commonly available analytical methods for these two contaminants. After considerable discussion, it was decided not to add free cyanide to the list of contaminants. There was concern that special requirements for sample collection and shipment, together with the need to pre-treat the sample before analysis to eliminate interfering substances, would impose a burden on dialysis facilities that could not be justified in the absence of specific toxicity data. It was also decided not to decrease the maximum allowable level of cadmium in the list of contaminants. This decision was based on the absence of toxicity data in dialysis patients treated with water that meets this International Standard and the minimum detection levels of currently used analytical methods.

Little, if any, data exist to indicate that haemodialysis patients are at particular risk from any of the third group of contaminants, which are included in the AAMI standard solely by virtue of their inclusion in the *Safe Drinking Water Act.* In the United States, there was discussion about eliminating the third group of contaminants from Table 2 and moving discussion of them to this Annex. This discussion was prompted by the ongoing addition of contaminants to the US *Safe Drinking Water Act*. As was the case with antimony, beryllium, and thallium, in general no data exist to indicate that these new contaminants are of particular concern in the setting of haemodialysis. On the other hand, adding new contaminants to Table 2 has the potential to increase the operating constraints to dialysis facilities for testing water samples for compliance. There was enough discomfort about removing the third category of contaminants from Table 2 that it was decided to leave the list of contaminants unchanged but to reorganize the table into three clear sections and not to add new contaminants to the table unless there was accompanying evidence of toxicity in the setting of haemodialysis. During the revision for the second edition of this International Standard in 2008, a decision was made to separate the third group of contaminants into a separate table. One reason for this change was to allow alternative approaches to monitoring these contaminants to facilitate use of this International Standard in areas lacking the appropriate analytical tools for measuring trace elements at the levels listed in Table 2. Three options are provided. The preferred option is to measure concentrations of the individual trace elements. If this option is not available, two other approaches may be used. The first, and preferred alternative, is to measure total heavy metals. The second, and least preferred alternative, is to use reverse osmosis with a demonstrated rejection of at least 90 %. Both these alternative approaches are based on the use of feed water meeting applicable potable water standards and it is the responsibility of the dialysis facility to ensure that its water supply routinely meets potable water standards. Finally, it should be evident from the discussion in this Annex that the maximum allowable levels for the contaminants listed in Tables 1 and 2 are not precisely determined values but represent reasonable estimates based on sparse clinical data. As a result, any uncertainty in the analytical methods listed in Table 3 is likely to be small compared to the uncertainty involved in establishing the maximum allowable level and, for that reason, analytical uncertainty is considered to be included in the values listed in Tables 1 and 2.

Tables 1 and 2 of this International Standard should not be taken as a definitive list of harmful substances but as a partial listing of those that might reasonably be expected to be present and have clinical implications. Iron is not included because it does not enter the patient's blood in sufficient quantities to cause toxicity. Iron can, however, cause fouling of water purification devices or dialysis fluid supply systems. While no specific limit has been set, water treatment equipment suppliers are encouraged to consider the iron content of the feed water when recommending suitable equipment. A concern was raised regarding the injection of formulated phosphates (known as polyphosphates) primarily to bind iron and manganese to avoid the staining of fixtures and clothing. The concern was raised that this practice could cause significant problems in water purification. Some municipal water suppliers were considering the use of chlorine dioxide as a disinfectant for potable water supplies. Chlorine dioxide breaks down in water to yield chlorite, chlorate, and chloride ions. Little information could be found about the potential for chlorine dioxide and its daughter products to be toxic to haemodialysis patients. A limited study of 17 patients unknowingly treated with dialysis water prepared by carbon and reverse osmosis from water disinfected with chlorine dioxide showed no evidence of adverse effects.[4] In that study, the dialysis water used to prepare dialysis fluid contained 0,02 mg/l to 0,08 mg/l of chlorite ions and no detectable chlorate ions. However, the patient population was small, and potentially important haematological parameters were not measured. Further, there were only sparse data included on the removal of chlorine dioxide, chlorite ions, and chlorate ions by carbon and reverse osmosis, and it was not clear that sufficiently sensitive methods were available for their analysis in a dialysis facility. Therefore, there was no basis for setting maximum allowable levels of chlorine dioxide, chlorite ions, or chlorate ions in water to be used for dialysis applications, or for making recommendations on methods for their removal at that time. However, in specifying water purification systems, manufacturers of such systems should be aware of the possibility that municipal water suppliers may add chlorine dioxide to the water.

Limits could not be determined for toxic organic substances or for radioactive materials.[26] However, the US EPA drinking water standard[48] lists maximum contaminant levels (MCL) for more than 50 toxic organic substances. Following the rationale used in establishing levels for other potentially toxic contaminants that have not been shown to be harmful to dialysis patients (see previous paragraph), it is reasonable that these levels should be reduced tenfold if they are monitored. These data are provided for information purposes only, because these substances are only representative of a vast number of contaminants that occur in tap water, all of whose toxic effects are largely unknown.[26] In agreement with the Keshaviah report, it is thought that systems including reverse osmosis and carbon filtration would adequately remove most organics. In support of this position, reverse osmosis has been demonstrated to remove 92 % to 98 % of 14 different pesticides during water treatment for dialysis.[7]

Bibliography

[1] ISO 13958, *Concentrates for haemodialysis and related therapies*

[2] ISO 23500, *Guidance for the preparation and quality management of fluids for haemodialysis and related therapies*

[3] American Public Health Association. *Standard Methods for the Examination of Water and Wastewater*. APHA, Washington, D.C., Twenty first Edition, 2005

[4] Ames R.G., & Stratton J.W. Effect of chlorine dioxide water disinfection on hematologic and serum parameters of renal dialysis patients. *Arch. Environ. Health*. 1987, **42** pp. 280–285

[5] Arnow P.M., Bland L.A., Garcia-Houchins S., Fridkin S., Fellner SK An outbreak of fatal fluoride intoxication in a long-term hemodialysis unit. *Ann. Intern. Med.* 1994, **121** pp. 339–344

[6] Baz M., Durand C., Ragon A. et al. Using ultrapure water in hemodialysis delays carpal tunnel syndrome. *Int. J. Artif. Organs*. 1991, **14** pp. 681–685

[7] Becker F.F., Janowsky U., Overath H., Stetter D. The removability of pesticides during the production of dialysis water. *Biomed. Tech. (Berl.)*. 1989, **34** pp. 215–220

[8] Bernick J.J., Port F.K., Favero M.S., Brown D.G. Bacterial and endotoxin permeability of hemodialysis membranes. *Kidney Int.* 1979, **16** pp. 491–496

[9] Bommer J., Becker K.P., Urbaschek R., Ritz E., Urbaschek B. No evidence for endotoxin transfer across high-flux polysulfone membranes. *Clin. Nephrol.* 1987, **27** pp. 278–282

[10] Bommer J., Becker K.P., Urbaschek R. Potential transfer of endotoxin across high-flux polysulfone membranes. *J. Am. Soc. Nephrol.* 1996, **7** pp. 883–888

[11] Carlson D.J., & Shapiro F.L. Methemoglobin from well water nitrates. A complication of hemodialysis. *Ann. Intern. Med.* 1970, **73** pp. 757–759

[12] Centers for Disease Control (CDC). Fluoride intoxication in a dialysis unit—Maryland. *Morbidity and Mortality Weekly*. 1980, **29** p. 134

[13] Comty C., Luehmann D., Wathen R., Shapiro F. Prescription water for chronic hemodialysis. *Trans. Am. Soc. Artif. Intern. Organs*. 1974, **10** pp. 189–196

[14] Dawids S.G., & Vejlsgaard R. Bacteriological and clinical evaluation of different dialysate delivery systems. *Acta Med. Scand.* 1976, **199** pp. 151–155

[15] Eaton J.W., Koplin C.F., Swofford H.S., Kjellstrand C.M., Jacob H.S. Chlorinated urban water: A cause of dialysis-induced hemolytic anemia. *Science*. 1973, **181** pp. 463–464

[16] European Pharmacopoeia Commission. *European Pharmacopoeia*. Strasbourg, Eighth Edition, 2014

[17] Evans R.C., & Holmes C.J. *In vitro* study of the transfer of cytokine-inducing substances across selected high-flux hemodialysis membranes. *Blood Purif.* 1991, **9** pp. 92–101

[18] Favero M.S., Peterson N.J., Boyer K.M., Carson L.A., Bond WW. Microbial contamination of renal dialysis systems and associated risks. *Trans. Am. Soc. Artif. Intern. Organs*. 1974, **20** pp. 175–183

[19] Favero M.S., Peterson N.J., Carson L.A., Bond W.W., Hindman S.H. Gram-negative water bacteria in hemodialysis systems. *Health Lab. Sci.* 1975, **12** pp. 321–334

[20] Gazenfeldt-Gazit E., & Eliahou H.E. Endotoxin antibodies in patients on maintenance hemodialysis. *Isr. J. Med. Sci.* 1969, **5** pp. 1032–1036

[21] Hindman S.H., Carson L.A., Peterson N.J., Schonberger L.B., Solano N.J. Pyrogenic reactions during hemodialysis caused by extramural endotoxin. *Lancet*. 1975, **2** pp. 732–734

[22] Ivanovich P.A., Manzler A., Drake R. Acute hemolysis following hemodialysis. *Trans. Am. Soc. Artif. Intern. Organs*. 1969, **15** pp. 316–320

[23] Japan Water Works Association. *Test Methods for Tap Water*, 2001

[24] Jones D.M., Tobin B.M., Harlow G.R., Ralston A.J. Bacteriological studies of the modified Kiil dialyser. *BMJ*. 1970, **3** pp. 135–137

[25] Kathuria P., Nair B., Schram D., Medlock R. Outbreak of lead poisoning in a hemodialysis unit. *J. Am. Soc. Nephrol.* 2004, **15** p. 617A

[26] Keshaviah P., Luehmann D., Shapiro F., Compty C. *Investigation of the Risks and Hazards Associated with Hemodialysis Systems*, (Technical report, Contract #223-78-5046) Silver Spring, MD: U.S. Dept. of Health and Human Services, Public Health Service/Food and Drug Administration/Bureau of Medical Devices, June 1980

[27] Kidd E.E. Bacterial contamination of dialysing fluid of artificial kidney. *BMJ*. 1964, **1** pp. 880–882

[28] Klein E., Holland F.F., Gidden H. et al. *Membrane and Material Evaluation*. (Annual progress report, N01-8M-2221, PB299021-AS) Gulf South Research Institute, March 15, 1979

[29] Kleophas W., Haastert B., Backus G., Hilgers P., Westhoff A., van Endert G. Long-term experience with an ultrapure individual dialysis fluid with a batch type machine. *Nephrol. Dial. Transplant.* 1998, **13** pp. 3118–3125

[30] Kovalchik M.T., Kaehny W.D., Hegg A.P., Jackson J.T., Afrey A.C. Aluminum kinetics during hemodialysis. *J. Lab. Clin. Med.* 1978, **92** pp. 712–720

[31] Laude-Sharp M., Caroff M., Simard L., Pusineri C., Kazatchkine M.D., Haeffner-Cavaillon N. Induction of IL-1 during hemodialysis: Transmembrane passage of intact endotoxin (LPS). *Kidney Int.* 1990, **38** pp. 1089–1094

[32] Lonnemann G., Behme T.C., Lenzer B., Floege B. Permeability of dialyzer membranes to TNF-inducing substances derived from water bacteria. *Kidney Int.* 1992, **42** pp. 61–68

[33] Masuyama J., & Tachibana Y. Effects of water purification on renal osteodystrophy in the patients with regular hemodialysis therapy, *J. Japan. Soc. Kidney Dis.* 1984, **26** pp. 407–416

[34] Matsuhashi N., & Yoshioka T. Endotoxin-free dialysate improves response to erythropoietin in hemodialysis patients. *Nephron*. 2002, **92** pp. 601–604

[35] McKane W., Chandna S.M., Tattersall J.E., Greenwood R.N., Farrington K. Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. *Kidney Int.* 2002, **61** pp. 256–265

[36] Petrie J.J.B., & Row P.G. Dialysis anemia caused by subacute zinc toxicity. *Lancet*. 1977, **1** pp. 1178–1180

[37] Quellhorst E. Methods of hemodialysis. *Nieren- Hochdruckkr.* 1998, **27** pp. 35–41

[38] Rahmati M.A., Homel P., Hoenich N.A. et al. The role of improved water quality on inflammatory markers in patients undergoing regular dialysis. *Int. J. Artif. Organs*. 2004, **27** pp. 723–727

[39] Raij L., Shapiro F.L., Michael A.F. Endotoxemia in febrile reactions during hemodialysis. *Kidney Int.* 1973, **4** pp. 57–60

[40] Rao R.K.S., & Friedman E.A. Fluoride and bone disease in uremia. *Kidney Int.* 1975, **7** pp. 125–129

[41] Schiffl H., Fischer R., Lang S.M., Mangel E. Clinical manifestations of AB-amyloidosis: Effects of biocompatibility and flux. *Nephrol. Dial. Transplant.* 2000, **15** pp. 840–845

[42] Schiffl H., Lang S.M., Stratakis D., Fischer R. Effects of ultrapure dialysis fluid on nutritional status and inflammatory parameters. *Nephrol. Dial. Transplant.* 2001, **16** pp. 1863–1869

[43] Schiffl H., Lang S.M., Fischer R. Ultrapure dialysis fluid slows loss of residual renal function in new dialysis patients. *Nephrol. Dial. Transplant.* 2002, **17** pp. 1814–1818

[44] Schindler R., Lonnemann G., Schäffer J. et al. The effect of ultrafiltered dialysate on the cellular content of interleukin-1 receptor antagonist in patients on chronic hemodialysis. *Nephron*. 1994, **68** pp. 229–233

[45] Sitter T., Bergner A., Schiffl H. Dialysate related cytokine induction and response to recombinant human erythropoietin in haemodialysis patients. *Nephrol. Dial. Transplant.* 2000, **15** pp. 1207–1211

[46] Tokars J.I., Alter M.J., Favero M.S. et al. National surveillance of dialysis associated diseases in the United States, 1993. *ASAIO J.* 1996, **42** pp. 219–229

[47] U.S. Environmental Protection Agency, *Methods for the determination of metals in environmental samples, Supplement 1 (EPA-600-R-94-111).* Cincinnati (Ohio): Environmental Monitoring Systems Laboratory

[48] U.S. Environmental Protection Agency. *Safe Drinking Water Act, 1996* (Public law 104–182). Washington (DC): EPA. (See also *National Primary and Secondary Drinking Water Regulations*. U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water)

[49] U.S. Food And Drug Administration. *Guidance for the Content of Premarket Notifications for Water Purification Components and Systems for Haemodialysis*. U.S. Food and Drug Administration, Rockville, MD, 1997

[50] United States Pharmacopeial Convention, Inc. *United States Pharmacopoeia—National Formulary*. Rockville, MD: United States Pharmacopeial Convention Inc.

[51] Ureña P., Herbelin A., Zingraff J. et al. Permeability of cellulosic and non-cellulosic membranes to endotoxin subunits and cytokine production during *in-vitro* haemodialysis. *Nephrol. Dial. Transplant.* 1992, **7** pp. 16–28

[52] Vanholder R., Van Haecke E., Veys N., Ringoir S. Endotoxin transfer through dialysis membranes: small- versus large-pore membranes. *Nephrol. Dial. Transplant.* 1992, **7** pp. 333–339

[53] World Health Organization. *Guidelines for drinking-water quality*. Geneva, Fourth Edition, 2011 http://www.who.int/water_sanitation_health/publications/2011/dwq_guidelines/en/

[54] Yamagami S., Adachi T., Sugimura T. et al. Detection of endotoxin antibody in long-term dialysis patients. *Int. J. Artif. Organs*. 1990, **13** pp. 205–210

[55] ANSI/AAMI RD5:2003, *Hemodialysis systems*

ICS 11.040.40

Price based on 16 pages