International Standard

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Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 3: Tests for emissions of volatile organic substances

Évaluation de la biocompatibilité des chemins de gaz respiratoire utilisés dans le domaine de la santé —

Partie 3: Essais concernant les émissions de substances organiques volatiles

Reference number
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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 document 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 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 3, *Lung ventilators and related equipment,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 215, *Respiratory and anaesthetic equipment*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO 18562-3:2017), which has been technically revised.

The main changes are as follows:

— added informative mapping annexes to relevant regulatory requirements;

— clarified terms and definitions used in the document;

— broke the term *VOC* (now *VOS*) into parts based on boiling point.

A list of all parts of the ISO 18562 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document is intended to protect *patients* connected to *medical devices* from excessive amounts of *volatile organic substances* that arise from within the *gas pathways* of those *medical devices*. This document represents the application of the best-known science by addressing the *risks* from potentially hazardous *volatile organic substances* being conveyed to the *patient* by the gas stream.

This document is intended to cover the biological evaluation of *gas pathways* of *medical devices* within a *risk management process*, as part of the overall *medical device* evaluation and development. This approach combines the review and evaluation of existing data from all sources with, where necessary, the selection and application of additional tests.

In general, the ISO 10993 series is intended to cover the biological evaluation of *medical devices*. However, the ISO 10993 series does not appropriately address the biological evaluation of the *gas pathways* of *medical devices*. For example, the ISO 10993 series does not provide guidance how to evaluate the presence of *VOSs*.

It is not within the scope of this document to address contamination arising from the source of the breathing gases entering such *medical devices*, but rather only address the potential contamination generated from within the *medical device* itself. This contamination might be from the original manufacturing *process* or generated by the *medical device* itself during use.

This document is concerned with *volatile organic substances* that could be conveyed to the *patient* by the breathing gases. *Volatile organic substances* can have health effects ranging from unpleasant odour and irritation of the mucous membranes to possible long-term effects on the nervous system. It is accepted that there is no point in setting levels that are lower than those found in air that people might breathe every day.

The tests for the presence of *volatile organic substances* generated by respiratory *medical devices* are based on advanced laboratory practice and require specialist training and equipment to generate meaningful results.

The methods to determine the acceptable levels of contamination are contained in ISO 18562-1.

This document has been prepared in consideration of:

— the *Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices,* IMDRF/GRRP WG/N47:2018[7] as indicated in Annex B;

— the *Labelling Principles for Medical Devices and IVD Medical Devices,* IMDRF/GRRP WG/N52:2019[8] as indicated in Annex B;

— the the *essential principles of safety and performance* according to ISO 16142-1:2016 as indicated in Annex C; and

— the general safety and performance requirements of a *medical device* according to regulation (EU) 2017/745[9].

In this document, the following verbal forms are used:

— “shall” indicates a requirement;

— “should” indicates a recommendation;

— “may” indicates a permission;

— "can" indicates a possibility or capability.

Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 3:
Tests for emissions of volatile organic substances

1 Scope

This document specifies tests for the emissions of *volatile organic substances* from the *gas pathways* of a *medical device*, its parts or *accessories,* which are intended to provide respiratory care or supply substances via the respiratory tract to a *patient* in all environments. The tests of this document are intended to quantify emissions of *volatile organic substances* that are added to the respirable gas stream by the materials of the *gas pathway*. This document establishes acceptance criteria for these tests.

NOTE Gaseous emission of *volatile organic substances* includes emissions of *volatile organic compounds*, *semi-volatile organic compounds* and *very volatile organic compounds*.

This document addresses potential contamination of the gas stream arising from the *gas pathways* of *medical devices* or *accessories*, which is then conducted to the *patient*.

This document applies over the *expected lifetime* of the *medical device* in *normal use* and takes into account the effects of any intended *processing*.

This document does not address biological evaluation of the surfaces of *gas pathways* that are in direct contact with the *patient*. The requirements for direct contact surfaces are found in the ISO 10993 series.

Medical devices, parts or *accessories* containing *gas pathways* that are addressed by this document include, but are not limited to, ventilators, anaesthesia workstations (including gas mixers), breathing systems, oxygen conserving devices, oxygen concentrators, nebulizers, low-pressure hose assemblies, humidifiers, heat and moisture exchangers, respiratory gas monitors, respiration monitors, masks, medical respiratory personal protective equipment, mouth pieces, resuscitators, breathing tubes, breathing systems filters, Y-pieces and any breathing *accessories* intended to be used with such devices. The enclosed chamber of an incubator, including the mattress, and the inner surface of an oxygen hood are considered to be *gas pathways* and are also addressed by this document.

This document does not address contamination already present in the gas supplied from the gas sources while *medical devices* are in *normal use*.

EXAMPLE Contamination arriving at the *medical device* from gas sources such as *medical gas pipeline systems* (including the non-return valves in the pipeline outlets), outlets of pressure regulators connected or integral to a medical gas cylinder or room air taken into the *medical device* is not addressed by ISO 18562 series.

This document is intended to be read in conjunction with ISO 18562-1.

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 16000-3:2022, *Indoor air — Part 3: Determination of formaldehyde and other carbonyl compounds in indoor and test chamber air — Active sampling method*

ISO 16000-4:2011, *Indoor air — Part 4: Determination of formaldehyde — Diffusive sampling method*

ISO 16000-6:2021, *Indoor air — Part 6: Determination of organic compounds (VVOC, VOC, SVOC) in indoor and test chamber air by active sampling on sorbent tubes, thermal desorption and gas chromatography using MS or MS FID*

ISO 18562-1:2024, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 1: Evaluation and testing within a risk management process*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 18562-1:2024 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/

NOTE For convenience, an alphabetized index of all defined terms and their sources used in this document are given in Annex D.

3.1
rated
<value> term referring to a value assigned by the *manufacturer* for a specified operating condition

[SOURCE: IEC 60601-1:2005+AMD1:2012+AMD2:2020, 3.97]

3.2
target compounds
compounds that are believed likely to be present and therefore need to be deliberately looked for

3.3
thermal stability
condition under which the temperature of an object does not change by more than 2 °C over a period of 1 h

[SOURCE: IEC 60601-1:2005+AMD1:2012+AMD2:2020, 3.125, modified — "increase" has been changed to "change".]

4 General principles

All *gas pathways* of *medical devices* or *accessories* shall be evaluated using the strategy detailed in ISO 18562-1:2024.

The fundamental consideration in assessing a substance is to determine the *inhalation dose* of this substance to the *patient*.

Limits for toxicological purposes are most often quoted in µg/kg body mass/d (*tolerable intake*). Limits for environmental purposes, and the quantity that is measured by test laboratories, are usually quoted as concentrations in µg/m^3. The *inhalation dose* depends on the concentration of the substance (in µg/m^3) multiplied by the volume inhaled by the *patient* in a day (in m^3/d).

Standard daily breathing volumes are found in ISO 18562-1:2024, 6.2.

5 *Volatile organic substance* emissions

NOTE There is guidance or rationale for this Clause contained in Clause A.2.

5.1 General

a) All *gas pathways* of a *medical device* or *accessory* shall be evaluated for the emission of *volatile organic substances*.

NOTE 1 Gaseous emission of *volatile organic substances* includes emissions of *VOCs*, *SVOCs* and *VVOCs*.

b) In the selection of materials to be used in the *medical device* manufacture, the first consideration should be given for fitness for purpose with regard to characteristics and properties of the material, which include physical, mechanical, chemical and toxicological properties.

1) Knowledge of materials should inform the nature and extent of screening for substances including any *target compounds*.

2) Specific sampling methods may be required for *target compounds*.

EXAMPLE Aldehydes from polyoxymethylene plastics, isocyanates and degradation products from polyurethanes.

c) The evaluation should use the *risk management process* to assess if testing is required.

NOTE 2 The evaluation of some components, which are identical in *formulation*, manufacturing or application *processes* and preparation for use to an existing component of a *medical device* that has been previously tested, might conclude that no further testing is required. Refer to ISO 18562-1:2024, Figure 1. Manufacturing and application *processes* include *processing* (i.e. cleaning/disinfection/sterilization either prior to use or between uses).

d) A *medical device*, part or *accessory* shall not add to the gas that could be inspired by the *patient* substances at levels that create an unacceptable *risk* to the *patient.*

NOTE 3 Parts downstream of the *patient* can be evaluated for emissions if there is a *risk* that the *patient* might inspire gas that has been in contact with them.

e) If the *risk management process* determines that testing is required, the tests of 5.2 shall be performed.

5.2 Test method

Perform emission testing as follows.

a) Set up the *medical device*, part or *accessory* according to the instructions for use.

1) It can be necessary to use additional *accessories* in order to perform this test (for example, hoses or a test lung). When using such additional items, care needs to be taken to prepare them so that they do not interfere with the measurements being made.

2) Alternatively, the test may be run with all the *accessories* in place, but without the *medical device* under test to produce a blank value. This blank value is then subtracted from the value obtained when running the test again with the *medical device* in the circuit.

3) The *medical device*, part or *accessory* should be a representative sample that has been subject to normal manufacturing, shipping and handling delays.

4) The tests should be performed at a time after manufacture that represents the shortest reasonable time that could elapse between manufacture and use with a *patient.*

5) It may be necessary, if needed, to use more than one *medical device* in this test, to allow the results to be greater than the limits of measurement.

b) Maintain the *medical device*, part or *accessory* at its highest clinically relevant *rated* ambient temperature until the *medical device*, part or *accessory* has achieved *thermal stability*.

1) The test may be performed at higher temperatures to facilitate faster or accelerated testing. However, care is needed to ensure that higher temperatures do not alter the chemical composition

of the *VOSs* emitted. In such a case, a supporting rationale, based on composition and *processing* to confirm that this is not expected to result either in thermal changes to chemical composition of the sample, or loss of *VVOC* before the start of sampling, shall be documented in the biological evaluation plan.

c) Choose a sampling site to be representative of the gas that would be inhaled by the *patient.*

1) It may be necessary to use a chamber to hold the *medical device* in this test and sample the air in the chamber.

d) Set the gas flowrate, through the *medical device*, part or *accessory* to a value that is representative of the clinical use for the *medical device* and gives the worst case *inhalation dose*, as follows.

NOTE 1 There is guidance or rationale for this list item contained in Clause A.2.

1) For an active flow *medical device* and its accessories (e.g. ventilator and ventilator breathing system) set the flowrate by selecting the lowest usable setting for delivery to the patient, considering flowrates, volumes and pressures.

i) The sampling pump flowrate shall be less than 80 % of the selected *medical device* flowrate.

2) For a passive flow *medical device* (e.g. where the flowrate is dependent on a spontaneously breathing *patient*) use a flowrate derived from the default daily breathing volume found in ISO 18562-1:2024, Table 1, for the smallest intended *patient* group.

3) The *manufacturer*

i) may justify a different flowrate, but

ii) the justification shall be documented, and

iii) the flowrate shall be clinically relevant.

EXAMPLE 1 Sleep apnoea breathing therapy equipment *patients* are at rest so the resting nominal breathing volume column is appropriate.

EXAMPLE 2 Sleep apnoea breathing therapy equipment and some neonatal ventilators have a very high flow, of which only a portion enters the *patient's* lungs, the rest is vented to atmosphere.

4) For an intermittently used *medical device* operate the *medical device* in a clinically relevant manner, for the maximum intended duration of a use.

5) Ensure that the sampling period enables capturing sufficient gas to make a meaningful measurement.

i) If the clinical maximum duration of operation is insufficient to permit making a meaningful measurement, it can be that a toxicological *hazard* does not exist, and testing is unnecessary. If this is the case, rationale shall documented in the biological evaluation plan.

e) Sample the breathing gas.

NOTE 2 There is guidance or rationale for this list item contained in Clause A.2

NOTE 3 The concentration of emitted volatile organic compounds from plastic materials is highest when the parts are new. The emissions of *VOSs* typically decay over time, as more of them get flushed out of the walls of the *gas pathway* as shown in Figure 1. If a measurement is only made at the start of use, then the total dose to the *patient* can be severely overestimated. Ideally, the sampling could extend over the whole duration of use of the *medical device*, and the total dose the *patient* receives measured directly. However many current sampling techniques do not allow this. To calculate the *inhalation dose* requires calculating the area under the concentration-versus-time curve. To minimize the test burden, the following method for prolonged exposure (>24 h, <30 d) use or long-term exposure (≥30 d) use *medical devices* can be used.

1) For a limited exposure (≤24 h) use *medical device* (e.g. nebulizer, manual resuscitator), do the following.

   i) Sample for a period that reflects the maximum duration of a typical treatment of a *patient* in a clinically relevant manner.

   ii) Either sample continuously or at equally spaced time intervals throughout the duration of use.

2) For prolonged exposure (>24 h, <30 d) use *medical device*, do the following.

   i) For the first sample period, start at the beginning of gas flowing through the *medical device*.

   ii) For the second sample period of 24 h, sample after the first 24 h of gas flowing through the *medical device*.

   iii) For the third sample period, start after the second sample period. Stop sampling upon reaching a value below the *TE* limit for each substance or the allowable limit according to ISO 18562-1:2024, as applicable.

   iv) When the "first 24-h test" returns a very low value, below that allowed for longer term use, then further tests need not be performed.

3) For a long-term exposure (≥30 d) use *medical device*, do the following.

   i) For the first sample period, start at the beginning of gas flowing through the *medical device*.

   ii) For the second sample period, sample after the first 24 h of gas flowing through the *medical device*.

   iii) For additional sampling periods:

      I) upon reaching a value below the *TE* limit for each substance;

      II) a decreasing trend; or

      III) a plateau with no increasing trend.

   iv) When the "first 24-h test" returns a very low value, below that allowed for longer term use, then further tests need not be performed.

4) The sample flowrate shall be low enough so as to not disturb the normal operation of the *medical device*.

5) The sampling duration may be

   i) extended to result in a large enough sample volume to allow quantification down to the required detection limit or

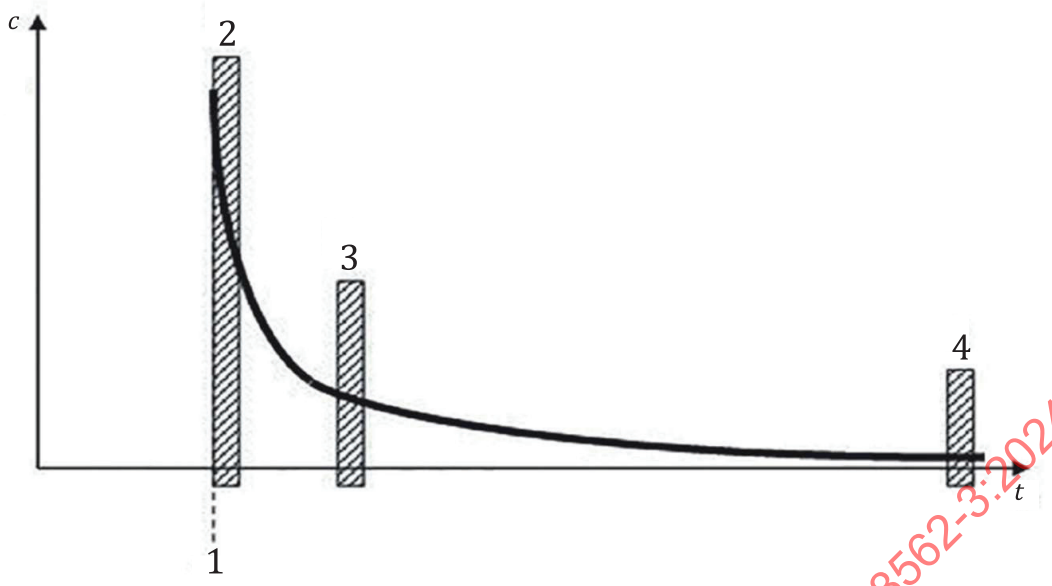
   ii) reduced to prevent overloading of the sampling system.

      I) Additional sampling points may then be needed.

6) For small *medical devices* or others that only emit very low amounts of *volatile organic substances*, it is possible to do a test only at the start. The values at the start are most likely to be higher than the value at the end, so extrapolating the start value across the whole duration of use seriously overestimates the *inhalation dose* the *patient* receives.

   i) If the calculated *inhalation dose* is acceptable, then testing need not be performed throughout the expected duration of use and may be performed only at the start.

7) Components only made of materials that are known not to emit *VOSs*, such as ceramics or metals, need not be tested for gaseous emissions.



Key

c concentration
t time
1 start of test time zero
2 first sampling period
3 second sampling period
4 last sampling period at end of use or at steady state

Figure 1 — Typical decay curve — Concentration as a function of time

f) Perform analysis of the samples using the methods of:

1) ISO 16000-6 utilizing sorbent tubes;

2) ASTM D5466-21 utilizing canisters; or

3) a demonstrably equivalent method.

g) The analysis shall not be limited to target *compounds*.

1) Analysis shall include:

i) all *target* compounds; and

ii) all other compounds detected whether identified or unidentified.

2) Specific assessments for formaldehyde and other carbonyl compounds shall be included.

NOTE 4 If there is an indication that there are *VVOCs* in the analysis according to ISO 16000-6, then further testing using ISO 16000-6:2021, Annex D, can be appropriate.

h) If formaldehyde and other carbonyl compounds are identified they become *target compounds* and the analysis shall conform to ISO 16000-3:2022 and ISO 16000-4:2011.

i) If *VOSs* are detected, identify the compounds and determine the level of each compound present in the samples.

1) *Target compounds* on target lists at concentrations below 1 µg/m^3 need not be reported in chemical analysis or the toxicological *risk assessment*.

2) Non-target compounds and unidentified compounds at concentrations below 2 µg/m^3 need not be reported in chemical analysis or the toxicological *risk assessment*.

3) Compounds, that are not commercially available or identified, should be semi-quantified.

4) If possible for unidentified compounds, information shall be provided on retention index, molecular mass, molecular structure and functional groups as well as the level of confidence for the information.

NOTE 5 ISO 16000-6:2021 contains information regarding satisfactory levels of identification. Compounds are quantified using the response factor of toluene when individual references are not available or the compound is unidentified. Some *authorities having jurisdiction* can require the use of a minimum of 3 surrogate standard materials for external calibration that vary based on their physicochemical properties and elution. For example, if a separation in a gas chromatograph is for about 1 h and most compounds elute prior to 40 min, then a surrogate standard should be analysed between 0 min to 10 min, 10 min to 20 min, and 20 min to 40 min to address compounds that vary in volatility.

NOTE 6 Required detection levels for a specific compound can vary, depending on the allowed *tolerable exposure*. If the *tolerable exposure* is high or the time of exposure is short, then there is no need to use the precise analysis methods necessary for more toxic substances or longer exposures.

5.3 Assessment of *inhalation dose*

a) Limits for environmental purposes, and the quantity that is measured by test laboratories, are usually quoted as concentrations, in µg/m^3. However, in this document doses and limits are expressed in µg/d. The *inhalation dose* to the *patient* depends on the concentration of the substance (in µg/m^3) multiplied by the volume of that gas (in m^3/d) inhaled by the *patient* of the intended *patient* group per day (see ISO 18562-1:2024, Table 1). A neonate *patient* breathes a smaller total daily volume than an adult *patient*.

NOTE 1 In calculating the *inhalation dose* to the *patient*, it is the volume of breathing gas that the *patient* inhales that is of interest — not the volume of gas flowing through the *medical device*. For example, sleep apnoea equipment or neonatal ventilators commonly have high flows, but only a portion of that enters the *patient*'s lungs — most of the flow is bypassed to the atmosphere. For a low flow oxygen giving set, only a portion of the gas breathed by the *patient* is supplied by the *medical device*—most of the breathed volume is room air.

b) The *inhalation dose* calculations for limited exposure use *medical devices*, such as emergency resuscitation equipment (typically used for 20 min), cannot make use of the above approach.

1) The *inhalation dose* should be calculated on the actual clinically relevant delivered volumes. Therefore, the allowable concentrations of contaminants (in µg/m^3) in the breathing gas from short duration of use *medical devices* can be higher than from continuous use *medical devices*.

2) Adjustments may be made for *medical devices* not in continuous use (e.g. sleep apnoea therapy equipment). It is the total dose reaching the *patient* in any 24 h period that is of importance.

c) Other breathing volume values, as appropriate for a specific *medical device*, may be used to calculate *inhalation dose*.

d) Calculate the *inhalation dose* that the *patient* could receive.

1) For a prolonged exposure or long-term exposure use *medical* device, calculate the concentrations of each compound over time (as the concentrations decline with time, as shown in the graph in Figure 1) and combine that with the volumes of gas reaching the lungs of the *patient*, as specified in b) and c).

i) Calculate the *inhalation dose* the *patient* receives in the first 24 h period.

ii) Calculate the *inhalation dose* the *patient* receives in following 24 h periods.

2) For a limited exposure use *medical device*, calculate the *inhalation dose* the *patient* receives of each compound within a 24 h period.

e) Using the method outlined in ISO 18562-1:2024, Clause 7, confirm that the *inhalation dose* the *patient* receives of any individual *VOS*, which has toxicological data, does not exceed the daily *TE* for that compound.

1) For substances without toxicological information, confirm the *inhalation dose* is less than the allowable limit specified in ISO 18562-1:2024 Clause 7.

NOTE 2 ISO 18562-1:2024, Clause 7, contains more guidance on calculating *tolerable exposure* levels and allowable limits for identified and unidentified compounds.

NOTE 3 The *tolerable exposure* for the first 24 h period is higher than for the subsequent 24 h periods.

6 Reporting

The report shall include:

a) a description of the *medical device* or *accessory* subject to evaluation (i.e. the sample or samples tested);

b) the description and rationale for the test article including any differences between it and the final *medical device*;

c) the sampling system components;

d) a description of the testing method utilized and its qualification (e.g., calibration data or accreditation);

e) the detection and quantification limits of the analytical method;

f) any deviations from the *procedure* indicated in this standard;

g) the test parameters (e.g., flow rate, temperature, pressure, run time duration);

h) the testing results with a reference to the subclauses which explain how the results were calculated and including:

1) qualitative data generated (e.g. *VOS* identities, including a description of the identification *procedure*); and

2) quantitative data generated (e.g. *VOS* concentrations, including a description of the quantification *procedures* and providing the classification of the quantitative data as estimated quantitative analysis, semi-quantitative analysis or quantitative analysis);

i) any unusual features observed;

j) derivation of the *inhalation dose* estimates;

k) the acceptance criteria including the data on which they are based;

l) summary comparison of the acceptance criteria and *inhalation doses*;

m) a dated reference to this standard (the standard used for the evaluation); and

n) the dates of the testing.

Annex A
(informative)

Rationale and guidance

A.1 General guidance

This annex provides rationale for some requirements of this document and is intended for those who are familiar with the subject of this document, but who have not participated in its development. An understanding of the reasons for the main requirements is considered to be essential for its proper application. Furthermore, as clinical practice and technology change, it is believed that rationale for the present requirements will facilitate any revision of this document necessitated by those developments.

A.2 Rationale for particular clauses and subclauses

The numbering of the following rationales corresponds to the numbering of the clauses and subclauses in this document. The numbering is, therefore, not consecutive.

— **Clause 5 – Gaseous emissions**

Volatile organic substances should not outgas in excessive amounts from the *gas pathways* into the flow of gases intended to be delivered to the *patient*. The amount delivered to the *patient* should not create an unacceptable *risk*. Table A.1 indicates the typical classifications of organic substances.

Table A.1 — Classification of *volatile organic substances*

Description	Abbreviation	Boiling point range °C	Example compounds
Very volatile organic compounds	*VVOC*	< 50 °C	Propane, butane, formaldehyde, methyl chloride, methylene chloride
Volatile organic compounds	*VOC*	50 °C to < 250 °C	d-Limonene, toluene, acetone, ethanol (ethyl alcohol) 2-propanol (isopropyl alcohol), hexanal
Semi-volatile organic compounds	*SVOC*	250 °C to 400 °C	Pesticides [DDT, chlordane, plasticizers (phthalates), fire retardants (PCBs, PBB)]

VOSs in the body are characterized by rapid uptake and equally rapid elimination. When the compound is absorbed into the blood stream, it is rapidly distributed throughout the body. The elimination half-lives for *VOSs* from the blood are typically a few minutes to a few hours.

The most relevant parameter is the actual *inhalation dose* — the concentration multiplied by the volume the *patient* inhales or ingests.

— **5.2 – Test method**

d)

The sources of the test daily flow volumes in this document are described in ISO 18562-1:2024, 6.2, and the accompanying rationale for the subclause. The first usage is expected to yield the maximum extraction of *VOSs* and therefore conveys the maximum *inhalation dose* of each substance.

In determining the worst case intended *patient* population, the *manufacturer* should consider a number of factors.

— The fraction of the gas that flows through the device evaluated and that is inspired into the *patient's* lungs.

— The fraction of the total volume of gas breathed by the *patient* that has been exposed to the device under evaluation.

In many cases, these fractions differ between *patient* populations, and the *manufacturer* should consider these factors in determining the worst case *patient* population.

For example many infant ventilators set a flowrate through the breathing circuit that is titrated to achieve a desired airway pressure. This flowrate is irrespective of the volume of gas inspired into the lungs, but can differ based on factors such as the size of mask used. Most of the breathing gas delivered to the breathing circuit is not inhaled, but is exhausted to atmosphere, either through one or more exhaust ports, or as leakage around a mask or cannulae.

In this example, all of the inspired gas flows through the *medical device* evaluated, but the fraction of the gas flow that is not inspired varies with the size (and breathed volume) of the *patient*. For this class of equipment, the lowest flowrate that can be set cannot be appropriate for continuous use, as it would deliver the lowest possible airway pressure. For example, this flowrate could be clinically appropriate to provide minimal CPAP during a spontaneous breathing trial, but not to be applied continuously.

A different example would be a low-flow oxygen therapy equipment, where the *patient* is intended to inspire oxygen from the equipment together with room air. In this case, the lowest settable flowrate can be a small fraction of the total breathed volume.

The *manufacturer* should identify the lowest clinically appropriate flowrate setting for each *patient* scenario, and use that to estimate the inhalation dose to the *patient* for any specified *VOS* concentration. This can be used in rationale to support the selection of both the worst case *patient* population and the worst case flowrate.

d) 1)

A low flowrate gives a higher measured concentration of any *VOS* present, but also a lower volume over the period for the measurement. The emission of *VOCs* from a solid material into the *gas pathways* can be divided into three main processes; internal diffusion within the material; partitioning of the compound at the interface to air; and diffusion/convection of the substance within the boundary layer[10][14]. Volatility of representative *VOCs* can be found in Reference [12]. Diffusion in a material and the partition coefficient into gas phase are what control *VOS* release from a material providing that the *VOS* concentration in the boundary condition is negligible. This is true as long as there is any gas flow passing over the surface of the material. Both the diffusion rate of the *VOS* within the solid material, and the partitioning of the *VOS* at the interface between material and air are positively correlated with temperature[14], as well as being dependent on the material itself.

This implies that the amount of *VOS* that is released into the gas phase is independent of the flowrate. Hence, the sensible thing is to determine the amount of *VOS* released from a *medical device* under optimal measurement conditions representative of clinical use and the relevant (maximum) temperature and duration. The exposure to the *patient* is the measured amount of each *VOS* delivered or the concentration derived by using the clinically relevant breathing volume for the *patient* category in question.

— ***e)***

Common sampling durations range from 30 min to 180 min. The sampling duration chosen needs to allow averaging (e.g. of heater control algorithms) and smoothing of any transients in the measurement. The sampling duration might need to be longer to result in a large enough sample volume to allow quantification down to the required detection limit or reduced to prevent overloading of the sampling system. Additional sampling points are then advisable.

The data produced by instrument analyses of *VOS*, etc. can be complex. It can require careful consideration and filtering to provide an accurate representation of *patient* exposure. Data should be reviewed and interpreted by expert assessors prior to the conduct of toxicological *risk assessment*.

Data which contradicts the physical principles of volatiles release from solids can be excluded from consideration, with appropriate rationale.