

How to sample and to analyse VOCs of respiratory medical devices according to the new ISO 18562-3

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■ ABSTRACT

The ISO 18562 series of standards [14, 15] are being formed to provide additional guidance and standardisation for evaluating the biocompatibility of breathing gas pathways in healthcare applications, e.g. respiratory and ventilation medical devices (MD). Part 3 of ISO 18562 specifies tests for the emissions of volatile organic compounds (VOCs) from the gas pathways of a MD, its parts of accessories, which are intended to provide respiratory care or supply substances via the respiratory tract to a patient in all environments. A thermal desorption (TD) system coupled with gas chromatography-mass spectrometry (GC-MS) is a suitable technique for the analysis of VOCs in a wide range of sample types. Emissions should be sampled using tubes packed with an appropriate adsorbent based on ISO 16000-6 [12]. The VOCs emitted from the MD are sampled and pre-concentrated onto the sorbent-packed tubes followed by thermal desorption of the VOCs and analysis via GC-MS. Following the VOC emission and condensate testing outlined in ISO 18562, the chemical compounds identified must be toxicologically evaluated.

■ ZUSAMMENFASSUNG

Gewinnung und Analyse von VOCs aus Atemtherapieprodukten gemäß der neuen ISO 18562-3

Die neue ISO-Norm 18562 [14, 15] wurde eingeführt, um einen zusätzlichen Leitfaden für eine einheitliche Bewertung der Biokompatibilität von Atemtherapieprodukten wie z. B. Beatmungsgeräte bereitzustellen. Teil 3 der ISO-Norm 18562 legt die Prüfung auf Emissionen von flüchtigen organischen Verbindungen (Volatile Organic Compounds, VOCs) aus den Luftwegen eines Medizinproduktes, seinen Bestandteilen oder seines Zubehörs fest, welche dazu bestimmt sind, einem Patienten unter allen Lebensumständen in der Atemwegspflege und -therapie zu helfen oder ihm Medikamente über die Atemwege zuzuführen. Für die Analyse von VOCs wird das

Verfahren der Thermodesorption angewendet, gekoppelt mit der Gaschromatographie-Massenspektrometrie (GC-MS). Diese Analysetechnik wird für eine Vielzahl von Probenarten als geeignete Technik angesehen, um den

Gehalt an VOCs zu ermitteln. Bei diesem Verfahren, welches in der ISO-Norm 16000-6 [12] beschrieben wird, werden die zu untersuchenden flüchtigen Stoffe, die von den Medizinprodukten abgegeben werden, in speziellen Probenahmeröhrchen (Sorbent Tubes) gesammelt und konzentriert. Anschließend erfolgen die Thermodesorption der VOCs und die Analyse mittels GC-MS. Die identifizierten VOCs müssen infolge der in ISO 18562 beschriebenen Emissionsprüfung einer vollständigen toxikologischen Bewertung unterzogen werden.

■ KEY WORDS

- Volatile organic compounds (VOCs)
- Thermal desorption (TD)
- ISO 18562-3
- ISO 10993
- Respiratory medical devices (RMDs)

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1. Introduction

Respiratory medical devices (RMDs) are widely used to deliver air, oxygen or anaesthetics to patients with a variety of short-, medium- and long-term medical conditions. In the past, materials in RMDs were considered as external communicating devices and these materials were evaluated according to the ISO 10993 series of standards [8]. Until recently, the potential presence of contaminants in the air/gas stream was not questioned, but now there is growing awareness of the potential for polymeric compounds to release harmful VOCs in the gas pathways which are subsequently inhaled by the patient. For this reason, the new ISO series of standards 18562

“Biocompatibility evaluation of breathing gas pathways in healthcare application” [14, 15] was released in March 2017. ISO 18562 comprises 4 parts; each of these sections is designed to address a potential hazard that is specifically associated with the breathing gas pathway of an MD. The scope of devices covered by the new series of standards can range from simple breathing tubes to complex gas mixing stations and ventilators. All MDs, its parts or device accessories, containing gas pathways are addressed by these standards, e.g. 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, mouth pieces, resuscitators, breathing tubes, breathing systems filters, Y-pieces and any breathing accessories, which are intended to provide respiratory care or supply substances via the respiratory tract to a patient in all environments. 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 new ISO series of standard. Further, it includes any and all accessories of these devices that may come in contact with the gas stream before it reaches the patient. According to this, not only the facemask of a breathing device needs to be tested, but also any connectors, filters and tubing that may come into contact with the gas being delivered to the patient. It is not within the scope of the new ISO guideline to address contamination arising from the source of the breathing gases entering such RMDs, but is intended to detect potential contaminations generated from the MD itself. These contaminations might come from the original manufacturing process. Part 3 of ISO 18562 “Tests for emissions of volatile organic compounds (VOCs)” are proposed to protect patients from excessive amounts of VOCs that arise from the interior of the RMD gas pathway. ISO 18562-3 represents the application of the best-known science by addressing the risk from potentially hazardous VOCs conveyed to the patient via the gas stream. The new guideline addresses a major gap in methodology, because the ISO standard 10993, which had been applied so far, does not include the determination of VOCs emissions directly from breathing gas pathways.

VOCs are organic compounds with boiling points ranging from 50–260 °C at a standard atmospheric pressure of 101.3 kPa. Patients could be exposed to VOCs during inhalation of breathing gases. These substances may cause health effects including eye, nose, conjunctival and throat irritation, headaches, loss of coordination, nausea, vomiting, allergic skin reaction, dyspnoea, dizziness and fatigue or damage to liver, kidney and the central nervous system. They might even lead to systemic issues including blood clots, heart problems and cancer [1]. Additionally, VOCs could have an impact on health

by irritating the mucous membranes or causing possible long-term effects in the nervous system. Some VOCs can react with nitrogen oxides or with ozone to produce new oxidation products and secondary aerosols, which can cause sensory irritation symptoms [2]. It is accepted that there is no point in setting limit values that are lower than those found in air that people might breathe every day.

2. Methodology

Major hazards that are associated with breathing gas pathways of RMDs are VOCs that can be dispensed in the gas stream. In a comprehensive description, Part 3 of ISO 18562 defines how the evaluation of RMDs should be conducted but does not recommend specific methods for collecting and sampling VOCs. In general, 2 different analytical methods for testing emissions of VOCs are described: emission sampling by either using sorbent-tubes in accordance with ISO 16000-6 [12] or canisters in compliance with ASTM D5466 [16]. These approaches are well-established and widely used for air-monitoring and related applications; tube-based methods as described in ISO guideline 16000-6 are preferred for analysing emissions from products and materials. The analysis of VOCs emitted from RMDs using the tube-based standard ISO 16000-6 is the focus of this article.

2.1 The principle of thermal desorption (TD) analysis

TD is a suitable technique for the desorption of concentrated VOCs collected from gas streams on sorbent-packed tubes in advance. The desorbed compounds will then be transferred to a gas chromatograph (GC) equipped with a flame ionization detector (FID) and/or a mass spectrometer (MS). This technique can be used to reduce the detection limits of GC methods and to improve chromatographic performance by reducing peak widths [3]. The main principle of TD is the release of adsorbed organic compounds by heating up the sorbent-packed tube. Prior to desorption, a sorbent-packed tube is connected to the gas flow path of the RMD and high-purity air is supplied at a defined flow rate for a specific time. VOCs that are released from the RMDs during the test are adsorbed and pre-concentrated on the sorbent of the tube. The tubes are then placed into the TD, which is essentially a heater cartridge designed to cover the entire area of the adsorbing material. When ready, the heater is activated and the adsorbed components (analytes) are desorbed from the tube and transferred using a carrier gas to a focusing trap, which is held cool during the transfer. After condensation of the analytes, the focusing trap is rapidly heated (“fired”) and the trapped components are transferred to the GC system for analysis. The TD maximises sensitivity for trace-level target compounds and routinely allows analyte detection at ppb level or below.

2.2 Sorbents and Sampling

TD tubes are packed with one or mixtures of different sorbent materials that are designed to attract and trap VOCs. These tubes are placed into the TD. The type and number of sorbents depends on several factors, such as sampling setup, volatility range of analytes, analyte concentration and the humidity of the sample [5, 6]. One of the most versatile and common sorbents for TD is a porous polymer based on 2,6-diphenyleneoxide known by its trademark Tenax®-TA (poly(2,6-diphenylphenylene oxide)) [7]. The described sorbent tubes are 3½ inches long with an outer diameter of ¼ inch containing Tenax®-TA sorbent. Any VOCs which meet the following criteria are compatible with TD: $\leq n\text{-C}_{40}$, boiling point ≤ 525 °C, compatibility with standard GC systems and compatibility of the sorbent or matrix containing compounds with the high temperatures required. Inorganic compounds, most perma-

nent gases (CO₂, Ar, N₂, etc.), compounds with very low boiling points (e.g. methane), compounds with volatility > n-C₄₀ or compounds that are thermally unstable are not compatible with TD.

The following sampling approaches can be applied:

- (I) Passive (diffusive) sampling [4]: A tube is packed with a single sorbent bed that allows adsorbing analytes from the air diffusively. It is suitable for sampling known compounds over a period of hours (for analyte concentrations of 2–10 µg/m³) to weeks (for analyte concentrations of 0.3–300 µg/m³). It is a simple and cost-effective method of collecting large numbers of samples that are required in many air monitoring programs. Vapours migrate across the air gap at a constant "uptake rate". Passive sampling is a slow process, typically taking a few days.
- (II) Active (pumped) sampling [18]: A tube is packed with up to 3 sorbent beds and a flow of the sample gas passes through it. It is suitable for sampling high and low concentrations of known and unknown compounds over timescales of minutes to hours. Typically, the flow rate is 20–100 mL/min. The taken volume is typically in the range of 5 mL up to 100 L, depending on expected concentrations. This technique is much faster compared to diffusive sampling.
- (III) Direct sampling [18]: This method is used for sampling emissions from small pieces of solid or semi-solid materials. The material is placed inside a tube and heated up to release the vapours directly into the focusing trap. The sample needs to be homogeneous and only 50–100 mg of sample is needed. Heating conditions must be gentle to release VOC contents.
- (IV) Dynamic Headspace [19]: The material is placed in a (micro-) chamber or other sampling container. Then a flow of gas passes through to transfer the headspace dynamically onto a sorbent tube.

Methods (II) and (IV) are commonly used for sampling VOCs emitted from RMDs. The method of VOC emission testing according to ISO 18562-3 is specified at the end of this article.

2.3 TD Conditions

Typical desorption conditions for VOC analysis using a secondary cold trap and sampling tube containing 200–250 mg Tenax®-TA are shown in table 1 [12].

3. Discussion¹⁾ – Acceptance criteria and toxicological evaluation

The fundamental consideration in assessing a substance is "what is the dose to the patient of this substance?". Limits for toxicological purposes are most often quoted in µg/d (tolerable exposure (TE)). Limits for environmental purposes and the quantitative amounts determined by test laboratories are usually given as concentrations in µg/m³. To calculate the permitted concentration of a certain substance in the breathing gas, the total volume of gas inhaled in a day should be known. The dose to the patient depends on the concentration of the substances (µg/m³) multiplied by the volume (m³) inhaled by the patient. TE is calculated when the tolerable intake (TI) (in µg/kg body weight/d)²⁾ is multiplied by the body weight of patients or patient groups [8]. The default

body weight values used to calculate TE are the following: neonate 0.5 kg, infant 3.5 kg, paediatric 10 kg and adult 70 kg [14]. The acceptable dose of a certain substance for patients should be below the calculated TI. If the TI cannot be calculated, the threshold of toxicological concern (TTC) (µg/d) [14] should be considered for the toxicological evaluation of the substance. This applies to all values relevant to the exposure category. When the "first 24-h test" reveals a very low value, below that allowed for longer term use, no further tests have to be performed [14].

The acceptance criteria for the dose-to-patient are divided into 3 exposure categories: limited exposure (≤ 24 h), prolonged exposure use (> 24 h but < 30 d) and permanent contact (≥ 30 d) [14]. For MDs intended for limited exposure (≤ 24 h) a TTC value of 360 µg/d can be used for an adult; for MDs with a prolonged exposure use (> 24 h but < 30 d) a TTC value of 120 µg/d is applied. The TTC for the first 24h period is set to 360 µg, for all subsequent 24h periods it is 120 µg. For each identified compound in MDs intended for permanent contact (≥ 30 d) a TTC value of 40 µg/d may be used. For the first 24-h period, the TTC is like the TTC for the first 24-h period at prolonged exposure (360 µg). For the subsequent 29 24-h periods, the TTC is set at 120 µg; beyond 30 d the TTC value is 40 µg.

Part 1 of ISO 18562 specifies default breathing volumes that are used to calculate the dose to the patient in any 24-h period: 0.2 m³/d for neonates, 2.0 m³/d for infants, 5.0 m³/d for paediatrics, and 20 m³/d for adults, equating to rates of 0.15, 1.38, 3.47 and 13.8 L/min (lpm), respectively.

Following the emission and condensate testing outlined in ISO 18562 series [13], the chemical compounds identified in Part 3 of ISO 18562 need to be toxicologically evaluated according to ISO 10993-17 [11]. Therefore, the acute dose of the compounds to the patients must be calculated considering parameters, such as dilution from the amount of gas and the breathing volume of the target patient population. The toxicologists should also consider inhalation toxicity data if available, which are the most relevant to breathing gas pathways. For any compounds that are found to pose a toxicological concern to patients, cytotoxicity and sensitisation according to ISO 10993-5 [9] and ISO 10993-10 [10], respectively, will be required. Finally, all analytical, biological and toxicological data have to be considered for an adequate safety evaluation of RMDs.

ISO standard 18562-3 describes VOC emission testing as follows:

- At the beginning of the test, the RMD, its parts or accessories are set up according to the instructions for use. It can be necessary to use additional accessories to perform this test (e.g. test lung). When using such additional items, care needs to be taken

¹⁾ The specification of results was not possible because the device will not be activated until September in a new laboratory and office building.

²⁾ Note: Declaration according to ISO 18562-3; meant is "µg per kg body weight and day", thus "µg/kg body weight x d".

to prepare them so that they do not interfere with the measurements being made. Alternatively, the test may be run with all the accessories in place, but without the RMD under test to produce a blank value. This blank value is then subtracted from the value obtained when running the test again with the RMD in the circuit. The RMD, its parts or accessories should be representative samples that have been subjected to normal manufacturing, shipping and handling delays. The tests should be performed at a time after manufacturing that represents the shortest reasonable time that could elapse between manufacturing and use with a patient. It may be necessary to use more than 1 RMD in this test to allow the results to be greater than the limits of measurement.

- Maintain the MD, part or accessory at its highest clinically relevant rated ambient temperature until the MD, part or accessory have achieved thermal stability. The test may be performed at higher temperatures to facilitate faster or accelerated testing. However, care has to be taken to ensure that higher temperatures do not alter the chemical composition of the VOCs emitted.
 - A sampling point must be selected which is comparable to the gas that would be inhaled by the patient. It may be inevitable to use a chamber to hold the MD in this test and sample the air in the chamber.
 - The gas flowrate must be characteristic of the clinical use for the MD. At e.g. ventilators or humidifiers the continuous flow should be intended 20 m³/d for adult patients, 5.0 m³/d for paediatric patients, 2.0 m³/d for infant patients and 0.21 m³/d for neonatal patients. MDs such as nebulizer or manual resuscitator, which are intermittently used, must be operated in a clinically relevant manner for the maximum intended period of a treatment. Furthermore an adequate sampling period has to be chosen which allows capturing sufficient gas for a meaningful measurement.
 - The sampling of the breathing gas for limited exposure (≤ 24 h) (e.g. nebulizer, manual resuscitator) should reflect the maximum of a typical treatment period of a patient in a clinically relevant manner. Sampling should be performed continuously or at comparable time intervals throughout the duration of use.
- For MDs with prolonged exposure (> 24 h, < 30 d) 3 sampling points should be examined. For the first period, sampling starts at the beginning of gas flowing through the MD. The second period starts after the first 24 h of gas flowing and the last at the end of use of the medical device. This period reflects the maximum permitted duration of use in a patient, as defined by the manufacturer or upon reaching a value below the tolerable intake (TI) limit for each

substance or the threshold of toxicological concern (TTC), as applicable.

For MDs with permanent exposure (≥ 30 d) the first and second sampling period are equal to sampling period for MDs with limited exposure. The third sampling period for MDs with permanent exposure starts at the end of day 29 or upon reaching a value below the TI limit for each substance or the TTC, as applicable.

- Generally, the sample flow rate shall be low enough to not disturb the normal operation of the MD. The sampling period may be extended to allow quantification down to the required detection limit or reduced to stop overloading of the sampling system. Further sampling periods may then be needed. For small MDs or MDs which emit very low values of VOC it is possible to do the test only at the first sampling point. The amount at the beginning of the testing is most likely higher than at the end. Extrapolating this start value across the whole length of use seriously overestimates the dose the patient takes. If the calculated dose is tolerable, testing has not to be performed continuously during the expected duration of use but may be done only at the beginning. Metals or ceramics, that are known not to produce VOCs, do not need to be tested.
- Methods of ISO 16000-6 [12] or ASTM D5466-01 [17] or an equivalent method should be used to analyse the samples.
- If VOCs are detected these compounds have to be identified and the concentration of each substance has to be determined. Compounds with concentrations below 2 $\mu\text{g}/\text{m}^3$ do not have to be identified.

4. Conclusions

The new ISO 18562 series of standards, especially Part 3, offers the opportunity to evaluate VOCs, which are released from the RMDs into the gas pathway during clinical use and which may be harmful to the patients. VOCs emitted from the materials of RMDs can be sampled and pre-concentrated on sorbent-packed tubes by 2 different approaches:

- active pumped-based sampling or
 - sampling by microchamber (dynamic headspace).
- The first approach is mainly applicable for self-contained systems such as breathing tubes or filters where the gas inlet and outlet can be easily connected to the gas flow whereas the second approach is used for RMDs such as breathing masks or mouth pieces. The combination of TD for desorption of analytes and GC-MS for analysis is the method of choice for the evaluation of the VOCs in RMDs. This procedure is more suitable for imitating the clinical use of the RMDs than applying solvent extraction

■ **Table 1**

Possible thermal desorption parameters.

Desorption temperature	260–280 °C
Desorption time	5–15 min
Desorption gas flow rate	30–50 mL/min
Cold-trap high temperature	260–300 °C
Cold-trap low temperature	–30–+20 °C*
Cold-trap sorbent	Tenax®-TA
Transfer-line temperature	150–225 °C
Split ratio	Split ratio between the sample tube and secondary trap and between the secondary trap and analytic column should be selected dependent on expected analyte concentration.

* Note: It is normal for the focusing trap to be held at or below room temperature. Lower temperatures are not recommended due to the condensation of water inside the trap, which may influence the subsequent chromatographic analysis. Higher temperatures reduce the amount of water in the trap.

as described in the ISO 10993 series of standards which now makes it easier to assess the safety of these types of products. The application of the procedure described in this paper is closer to the clinical use of the RMDs compared to solvent extraction as recommended by ISO 10993 for chemical characterisation of MDs in general. Following this strategy, the safety assessment of these types of products can now be improved.

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