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IANR24-001_v01

ISO 18562 Biocompatibility evaluation of breathing gas pathways in healthcare applications

Part 2: Tests for emissions of particulate matter

Part 3: Tests for emissions of volatile organic substances

Results Report for:

Paediatric Nebulizer Set

Art no: ONP 101-02

18 Mar 2024

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Part A – Analytical results

1 Description and use of the application.

A medical device (consisting of the components as shown in Table 1), has been tested regarding to ISO18562 part 2 and part 3.

The Paediatric Nebulizer kit is used to aerosolize medication approved for nebulization and prescribed by a physician for delivery to the airways. The Nebulizer kit is intended for adult patients consistent with the indication for aerosol medication in hospitals and sub-acute institutions.

The device is intended for the following patient groups: adult and paediatric.

There is no difference between the tested device and the final device.

The device has no defined usage time and it has a contact duration categorized as: limited usage < 24 hours. The test time has been chosen to be 24 hours.

2 Materials used during the testing

This product has been provided from: ANATOMİ PLASTİK SAĞLIK ÜRÜNLERİ TEKSTİL SAN. VE TİC. A.Ş.

Address: Organize Sanayi Bölgesi Mah. 1.Cad. No:11 ONİKİŞUBAT/KAHRAMANMARAŞ/TURKEY

Contact person: ÜMMÜGÜLSÜM JÜLİDE TEKEREK

E-mail to contact person: info@anatomisaglik.com.tr

Purchase order: signed quote 781

Table 1. The medical device evaluated in this study.

Product name	Article number	Lot number	Included in blank
Paediatric Nebulizer Set	ONP 101-02	10102231133	Yes ☐ No ☒

Table 2. Sampling system components.

Device	Range	Calibrated	Included in blank
Flow meter A	0–300 lpm	Yes ☒ No ☐	Yes ☒ No ☐
Flow meter B	0–30 lpm	Yes ☒ No ☐	Yes ☒ No ☐
Particle sensor R02	0.2–0.3 µm	Yes ☒ No ☐	Yes ☒ No ☐
Particle sensor R03	0.3–2.5 µm, 2.5–5.0 µm, 5.0–10.0 µm	Yes ☒ No ☐	Yes ☒ No ☐

All product information in section 1 and 2 is based on information from the client.

3 Exposure evaluation according to ISO 18562

The device was tested for 24 hours at 21–22°C and 25–30% RH, during which a constant air flow of 7,0 lpm was pulled through the medical device for analysis of PM (Particulate Matter) and VOCs (Volatile Organic Compounds).

The flow rate of gas passed through the device is equivalent to a total breathing volume of 10 m^3 per day. As a reference, the corresponding values for normal paediatric and adult breathing patterns are 5,0 m^3 (3,5 lpm) and 20 m^3 (14 lpm) per day, respectively.

4 Method and documentation

Emmace method IM-001, was used for the measurement of PM and VOC.

The analysis was documented and archived by Emmace Assignment number IAN24-001.

Johan Häkkinen was responsible for the testing and report writing and Lars Magnus Bjursten performed the data evaluation and made overall conclusions.

The sample(s) were analysed in the same condition as they arrived at Emmace.

4.1.1 Measurement uncertainty

VOC method:

The expanded measurement uncertainty of the method is 20–30%. The uncertainty is calculated according to the definition in "Evaluation of measurement data - Guide to the expression of uncertainty in measurement", JCGM 100:2008 Corrected version 2010", with a coverage factor equal to 2, which gives a confidence level of approximately 95%.

PM method:

The method has an expanded uncertainty factor of +/- 0,89 µm for the sizes 0,2–2,5 µm with an acceptance criterion of 12 µg/m^3. The expanded uncertainty factor is +/- 1,1 µm for the sizes 0,2–10 µm with an acceptance criterion of 150 µg/m^3.

4.2 Test details and description of generated test samples.

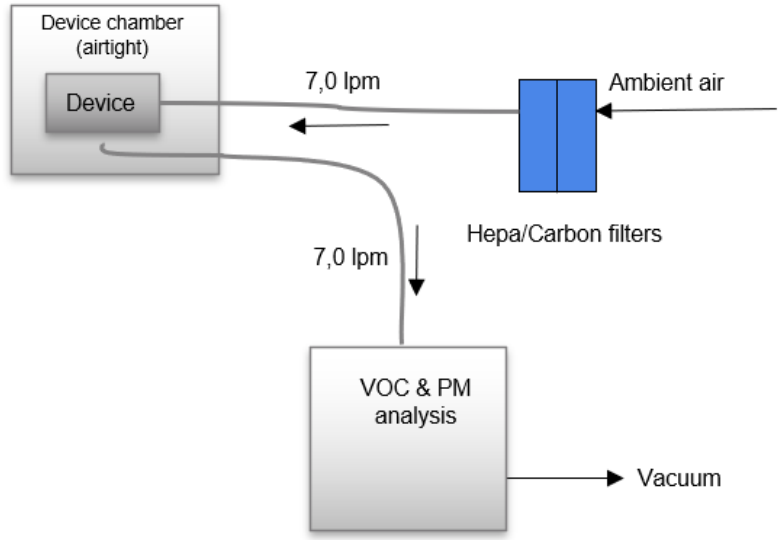
All analyses include the complete test system with all parts and with the chosen sample chamber and accessories, as specified in table 3 below.

Table 3. Test details and sample labelling.

Sample-ID	Details	Test dates	Test time
Blank	Plastic chamber with connectors and tubing.	2024-Jan-29 to 2024-Jan-30	16h 30 min
Test 1	Blank + 1 device inside the plastic chamber	2024-Jan-30 to 2024-Jan-31	24h
Test 2	Duplicate of test 1	2024-Jan-31 to 2024-Feb-01	24h

4.3 The test setup and description of the testing

During the testing the Paediatric Nebulizer Set was placed in a 20 litres airtight chamber, that was supplied with filtered air. Air was pulled by vacuum for analysis from the chamber via a tubing that was airtightly connected to the tubing associated with the device.The air entered in the opposite end of the device, that is where the face mask is located, via an open inlet that was positioned loosely next to the mask. See the setup schematically illustrated in figure 1.



When fully assembled, the narrow inner diameters of a couple of the subcomponents of the device did not allow the pulling of 7,0 lpm through them. Consequently, to enable a representative testing of the device, those subcomponents were disassembled and placed inside the mask, in the centre of the airstream flowing through the device. See the device fully assembled and how it was mounted in the chamber during the testing, in figure 2 and 3, respectively.

Figure 2 & 3. The medical device that was tested in this study, in the left-hand figure (2) and how it was mounted in the airtight chamber during the testing, in the right-hand figure (3). The device is partially disassembled, to thus allow the pulling of 7 lpm through it. The air enters the device via an open outlet that is positioned next to the face mask and exits via its associated tubing, that is airtightly connected to the silicone tube seen on the right-hand side.

The device was excluded during the blank testing, apart from that the setup was identical to when testing the device.

4.4 Evaluation of AET (Analytical Evaluation Threshold)

The reported AET (Analytical Evaluation Threshold) value for the sorbent tubes is 0,1 µg/m^3 assuming a volume of at least 100 litres which is met in this analysis. The exposure AET to patient is thus 2 µg/day with 20 m^3 air to the patient.

5 Results

5.1 Deviations

The testing was performed according to the method with no deviation.

5.2 Air sampling data

See the air sampling data from the combined VOC and PM testing in table 4.

Table 4. Air sampling data from the combined VOC and PM testing.

Sample-ID	Average flowrate through device (lpm)	Total volume through device (L)	Sampled volume for VOC (L)
Test 1	7,0	10090	366
Test 2	7,0	10030	367
Blank	7,0	6900	236

5.3 Particulate matter data

The particle counters give the results in particles/m^3. The mass concentration is calculated by the software and is done by calculating the volume of a sphere for the corresponding size channel (0.2–0.3, 0.3–2.5, 2.5–5 and 5–10 µm). This sphere is multiplied by the density of the sampled material. This number represents the mass of one particle. It is multiplied by the number of measured particles to give the mass concentration of that size channel.

The density used is for an average of all polymers with a density of 1 g/cm^3.

The summary of the test results is shown in Table 5.

Table 4. Summary of the PM results and acceptance criteria according to ISO18562-2.

	Particle size category, average result in µg/m^3	
Sample-ID	0,2–2,5µm	0,2–10µm
Test 1 (individual value)	0,0406	0,0408
Test 2 (individual value)	0,0173	0,0177
Blank	0,0807	0,0808
Average both tests:	0,029	0,029
Average both tests with blank subtracted	0,0	0,0
Limit according to ISO18562-2	≤ 12	≤ 150
Pass/ fail:	Pass	Pass

5.4 VOC data

ALS Control, Danderyd, Sweden, was used as external supplier for VOC analysis of adsorbent tubes. The VOC sampling tubes (samplers) have been analysed by GC-MS method at SGS Institut Fresenius GmbH Dresden. The volumes sampled according to table 4 were used for converting the results from µg/sampler to µg/m^3 air. All values are expressed as toluene equivalents.

Duplicate testing has been performed and the average results from the two tests have been corrected with blank. All substances from the VOC analysis with a result equalling or above the reporting level of 1,0 µg/m^3 in at least one of the tests are presented in table 6.

Substances with a final result (after average calculation and blank is subtracted) equalling or above the reporting level of 1,0 µg/m^3 according to the standard are further evaluated in part B.

Table 5. Individual and total VOC results."<1,0" = below the reporting level.

CAS	Substance	Test 1 (µg/m^3)	Test 2 (µg/m^3)	Blank (µg/m^3)	Average with blank subtracted (µg/m^3)
13475-82-6	2.2.4.6.6-Pentamethylheptane	12	18	-	15
75-69-4	Trichlorofluoromethane	4,4	-	3,0	<1,0
64-17-5	Ethanol	81	94	170	<1,0
67-63-0	iso-Propanol	14	5,1	7,1	2,5
75-65-0	tert. Butanol	6,2	5,3	3,9	1,9
104-76-7	2-Ethyl-1-hexanol	140	220	4,5	176
111-87-5	1-Octanol	3,2	6,7	-	5,0
66-25-1	n-Hexanal	0,6	1,1	0	<1,0
124-19-6	n-Nonanal	-	2,2	1,1	<1,0
67-64-1	Acetone	24	49	6,6	30
78-93-3	2-Butanone	370	410	1,6	388
106-35-4	3-Heptanone	1,1	2,6	-	1,9
Total VOC in the analysis*		659	818	216	624

** Includes all VOCs detected in the GC analysis.*

Part B – Evaluation

Note that this section is optional and not included in the scope of the accreditation. This part of the report is Emmace Consulting's preliminary evaluation of the biological safety of the device according to ISO 18562. The final assessment and risk analysis must be performed by the legal entity responsible for the marketing of the device.

6 Overall Toxicological evaluation

6.1 Particulate matter

All exposure values for particles are below the values given in ISO 18562-2.

6.2 VOC data with respect to exposure limits and TTC (Threshold of Toxicological Concern)

The long-term inhalation toxicological data were obtained as indicated in the footnotes to Table 7.

Table 6 DNEL levels for the VOC substances to be evaluated.

CAS no	Substance	Exposure limits (µg/m³)
13475-82-6	2.2.4.6.6-Pentamethylheptane	104 000 [1]
67-63-0	iso-Propanol	7000 [2]
75-65-0	tert. Butanol	5000 [3]
104-76-7	2-Ethyl-1-hexanol	530 [4]
111-87-5	1-Octanol	10 000 [5]
67-64-1	Acetone	200 000 [6]
78-93-3	2-Butanone	5000 [7]
106-35-4	3-Heptanone	300 000 [8]

[1] NOAEC (rat): 10 400 mg/m³ air (nominal), https://echa.europa.eu/registration-dossier/-/registered-dossier/2110/7/6/3. => 104 mg/m^3 NOAL human (AF=100, 10 species, 10 data).

[2] Subchronic p-RfC = NOAE ÷ UFC = 661.8 mg/m^3 ÷ 100 = 7 mg/m^3 [EPA/690/R-14/009F Final 9-16-2014: Provisional Peer-Reviewed Toxicity Values for Isopropanol].

[3] RfC = 5 mg/m^3 [EPA/635/R-20/370Fa: www.epa.gov/iris Toxicological Review of tert-Butyl Alcohol (tert-Butanol)]. 500 µg/m³ Inhalation repeated dose toxicity, 159.8 mg/m³ acute /short term: (DNEL) repeated dose toxicity [ECHA]

[4] NOAL Mice 10 ppm (8h/d 3 months) = 53,2 mg/m^3 => 530 µg/m^3 (UF=100, 10 race, 10 data) [Wakayama T, Ito Y, Sakai K, Miyake M, Shibata E, Ohno H, Kamijima M. Comprehensive review of 2-ethyl-1-hexanol as an indoor air pollutant. J Occup Health. 2019 Jan;61(1):19-35. doi: 10.1002/1348-9585.12017. PMID: 30698348; PMCID: PMC6499367]. Note that lower concentrations may cause sensory irritation in humans (8 mg/m^3 for 1 hour). PubChem/NioSH: Inhalation/rat Dose: lowest published toxic concentration: 1.5 mg/m^3/90D- continuous exposure. Effect: Liver: Other changes; Kidney, Ureter, and Bladder: Other changes; Nutritional and Gross Metabolic: Weight loss or decreased weight gain. Date: December 2018. The assessment factor determines the allowable exposure concentration. Using AF=10 (species) and 10 (data uncertainty) gives 15 µg/m^3.

[5] 1 Octanol poses a low level of toxicity, but it can be irritating to the skin and eyes. Nonetheless, it is considered safe to use under normal conditions because of its low vapor pressure. [Chemical book]. Overall, the available reproductive and developmental toxicity data for the long chain alcohols indicate no developmental toxicity and minimal maternal toxicity with repeated exposure.

A developmental toxicity study with CASRN 111-87-5 (C8) shows dose-related increases in systemic toxicity (CNS depression, decreased bodyweight gain, pneumonia) in treated dams following oral gavage at 1300 mg/kg-day (highest dose tested), but no evidence of developmental toxicity; the NOAELs for maternal and developmental toxicity are 130 and 1300 mg/kg-day, respectively.[U.S. Environmental Protection Agency Hazard Characterization Document, Dec. 2009]
OEL-RUSSIA:STEL **10 mg/m^3** JAN 1993

[6] 250 ppm NOAL => 592 mg/m^3 EPA/635/R-03/004 www.epa.gov/iris, 200 mg/m³ DNEL (ECHA) From EPA/635/R-03/004 www.epa.gov/iris.

[7] 5mg/m^3 RfC [EPA 635/R-03/009: TOXICOLOGICAL REVIEW OF METHYL ETHYL KETONE; https://iris.epa.gov/static/pdfs/0071tr.pdf]. Long-term: (DNEL) 106 mg/m³ repeated dose toxicity.

[8] NOAEL = 1087 mg/kg/day. Api AM et al: RIFM fragrance ingredient safety assessment, 3-heptanone, CAS Registry Number 106-35-4. Food Chem Toxicol. 2019 Aug;130 Suppl 1:110452.
1087 mg/kg/day => 60000 mg/d (adult) => 3000 mg/m^3 (20 l/d)

Table 7 Dose to patient.

CAS no	Substance	Measured concentration (µg/m^3)	Exposure limits (µg/m^3)
13475-82-6	2.2.4.6.6-Pentamethylheptane	15	13910
67-63-0	iso-Propanol	2,5	7000
75-65-0	tert. Butanol	1,9	5000
104-76-7	2-Ethyl-1-hexanol	176	530
111-87-5	1-Octanol	5,0	10 000
67-64-1	Acetone	30	200 000
78-93-3	2-Butanone	388	5000
106-35-4	3-Heptanone	1,9	300 000

7 Conclusions

Results of the samples tested show:

- The measurement of particulates is well below the established limits.
- The detected VOC result above 1,0µg/m^3 poses no toxicological concern. *
- The AET level gives sufficient margin of safety for the substance below the detection limit.
  *Note: 1-Octanol is considered of low toxicity. The listed exposure limit is however not well established.

8 References

1) Emmace method IM-001, *version 7*.
2) ISO 18562-1:2024 Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 1: Evaluation and testing within a risk management process.
3) ISO18562-2:2024 Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 2: Tests for emissions of particulate matter.
4) ISO18562-3:2024 Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 3: Tests for emissions of volatile organic substances.

9 Version History

Version	Date	Changes
1	2024-03-18	First edition

10 Contact information.

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