

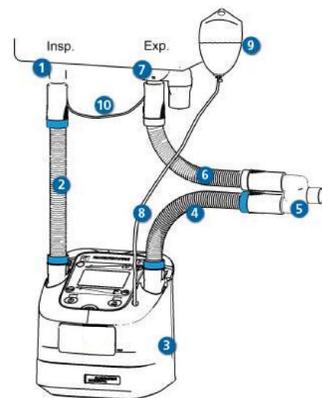
Risk Assessment of Semivolatile Compounds in a Respiratory Breathing Circuit: A Comparison of Three Data Sources

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INTRODUCTION

A case study is presented for a toxicological risk assessment of the trace chemicals released from a **respiratory gas humidifier**, which has an intended use for adult, pediatric, and neonatal patients where mechanical ventilation is required. Data from an **air pathway analysis** for volatile organic compounds (VOCs) as per ISO 18562 were compared against data from an **extractable/leachable (E/L) analysis** as per ISO 10993-18 and a **headspace gas analysis** of VOCs. VOCs, SVOCs, and NVOCs were identified by these analyses. Data from the three analyses were compared to understand how differences in the analytical approach, along with chemical/physical properties of the analytes, may affect the estimates of release.

MEDICAL DEVICE DESCRIPTION



The **heated breathing circuit** includes a humidifier chamber and connectors, and is intended to provide **conditioning of respiratory gases** during medical procedures. It can be used for a prolonged duration, depending on clinical needs, but a single device is recommended to be replaced after 28 days of use. It is classified according to ISO 10993-1 as an external communicating device that makes permanent patient contact (i.e., > 30 days).

- 1 Inspiratory Port (ventilator)
- 2 Connection tube from ventilator to humidifier
- 3 Humidifier chamber
- 4 Inspiratory tube from humidifier to patient
- 5 Y-piece
- 6 Expiratory tube from patient to ventilator
- 7 Expiratory port (ventilator)
- 8 Water feed line with spike
- 9 Water reservoir (bag or bottle)
- 10 Cable between connection tube and expiratory tube

Component:	Plug	Refill Tube	Chamber w/colorant	Gasket PermaBond	Y-piece Adult	Pressure Line + T
Weight (g):	0.4	18.6	101	2.6	28	27.8
Weight % of Device:	0.2 %	10.4 %	56.6 %	1.5 %	15.7 %	15.6 %
Polymer Composition:	Silicone	PVC	Styrene-Butadiene copolymer	PermaBond 4 UV 80 HV	Polyethylene	PVC plus Polypropylene

ANALYTICAL METHODS

Headspace Gas GC/MS Analysis: A sample (~2 g) of each component of the breathing circuit was excised from the device and placed into a separate headspace vial. Internal standard was added, then each sample was heated at 90°C for 60 minutes. Headspace gas was transferred and desorbed into the GC/MS. Analytes were identified by retention time and mass spectral matching.

Detection Limits: 0.1 µg per aliquot. Because each component has a different weight and is analyzed separately, DLs range from 0.1 µg for the plug to 5 µg for the colorant chamber.

Gas Flow Analysis by Tedlar Bag Sampling, Tenax Tube Desorption, and GC/MS Analysis: The assembled device was heated to 41°C, while maintaining a 1.38 L/minute oxygen flow to simulate clinical use conditions over a continuous 48-hour period. At intervals of 0-1, 3-4, 17-18, 23-24, and 47-48 hours, gas flow effluent was collected into pre-cleaned 100 L Tedlar bags. A 5 L aliquot of each 1-hour sample was transferred to a Tenax sorbent tube, which was then desorbed and analyzed by GC/MS for target and non-target compounds.

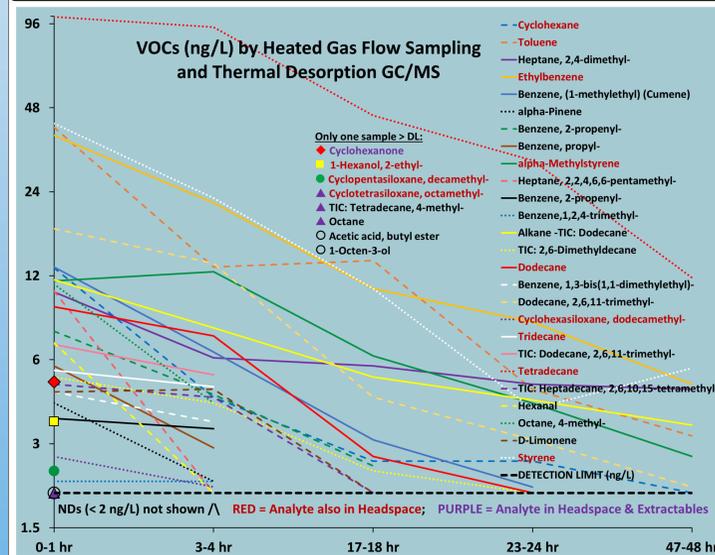
Detection Limits: 2 ng/L air. Using a 5 L injected aliquot taken from an 83 L one-hour gas flow sample, the time-weighted DL = 0.17 µg/hour. Using fitted emission curves for several VOCs, an average ratio of 12.2:1 was estimated for cumulative emissions divided by 0-1 hour emissions. Therefore, a threshold level detection of 0.17 µg in the 0-1 hour sample equates to a cumulative emissions DL of 2 µg per 48 hours.

Extractable/Leachable Analysis: Components were combined and extracted with 20% and 50% Ethanol/Water solutions at 50°C for 72 hours. A 1:100 dilution was performed to reduce ethanol interference prior to VOC analysis by GC/MS. Solutions were extracted with methylene chloride and concentrated 100:1 prior to analysis by GC/MS (SVOCs) and LC/MS (NVOCs).

Detection Limits: VOC = 10 µg/L, which equates to 1700 µg/device

Detection Limits: SVOC and NVOC = 10 µg/mL, which equates to 170 µg/device

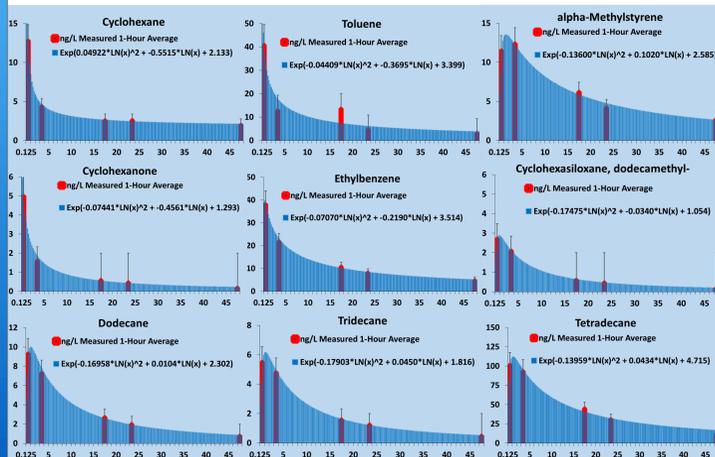
ANALYTICAL RESULTS: HEATED GAS FLOW



ESTIMATED CUMULATIVE RELEASE: GAS FLOW

28 Compounds were detected in the first two consecutive gas flow samples. **13 VOCs were observed in both the gas flow and headspace gas analysis.** To enable data comparison, the **cumulative release over 48-hours** of gas flow was first estimated by integrating a **curve fit to the data.** Two-Parameter equations ($y = a \times e^{(-bx)}$; $y = a \times x^{(-b)}$; $y = a \times \ln(x) + b$) adequately fit the data only if there was a steeply descending initial trend, but did not yield a good fit if the second data point was similar to or greater than the first point. However, a **3-parameter exponential-quadratic-log model** fit well in nearly all cases. Modeling was performed by a quadratic least squares method applied to the log-transformed data. A numerical minimization of residuals was done to verify optimized quadratic coefficients. Curve integration was done by Simpson's method.

Several VOC data sets included both positive and non-detected values. For a rough estimate of cumulative release, non-detected results (< 2 ng/L) were imputed as positive values equal to a fraction of the DL or a fraction times the previous imputed value adjusted for different time intervals, using low/high estimates of 0.3/0.8. This was done because statistical models cannot accurately impute data points with < 5 positive values.



ONLY FOUND IN HEADSPACE

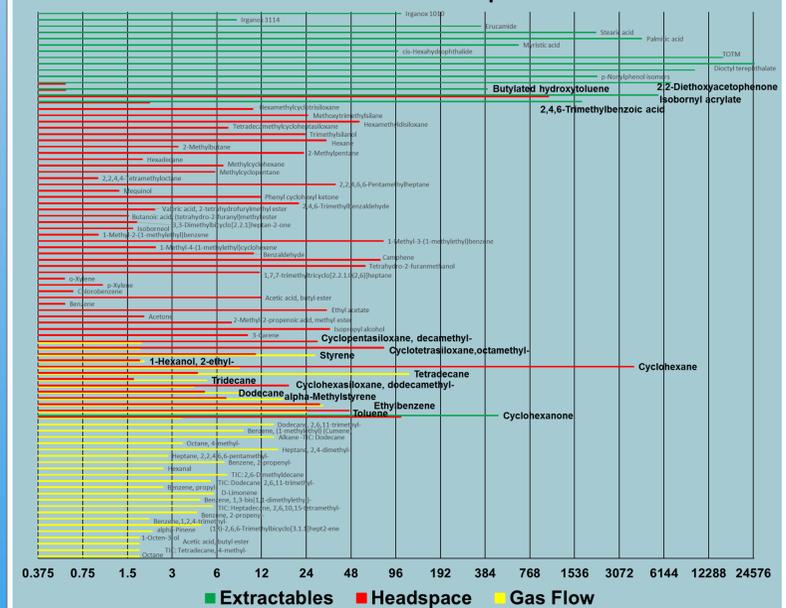
Acetone	2-Methylbutane	Hexamethylcyclotrisiloxane
Benzene	2-Methylpentane	Tetradecamethylcycloheptasiloxane
Ethyl acetate	Hexadecane	1-Methyl-4-(1-methylethyl)cyclohexene
Chlorobenzene	Methylcyclopentane	2,2,4,4-Tetramethylcyclohexane
o- and p-Xylene	Methylcyclohexane	Hexamethylsiloxane
Hexane	Acetic acid, butyl ester	Phenyl cyclohexyl ketone
3-Carene	2,2,4,6,6-Pentamethylheptane	2,4,6-Trimethylbenzaldehyde
Camphene	1-Methyl-3-(1-methylethyl)benzene	3,3-Dimethylbicyclo[2.2.1]heptan-2-one
Mequinol	1-Methyl-2-(1-methylethyl)benzene	Tetrahydro-2-furranmethanol
Isoborneol	Trimethylsilanol	2-Methyl-2-propenoic acid, methyl ester
Benzaldehyde	Methoxytrimethylsilane	Valeric acid, 2-tetrahydrofurfurylmethyl ester
1,7,7-trimethylbicyclo[2.2.1.0(2,6)]heptane		Isopropyl alcohol
Butanoic acid, (tetrahydro-2-furanyl)methyl ester		

ONLY IN EXTRACTS

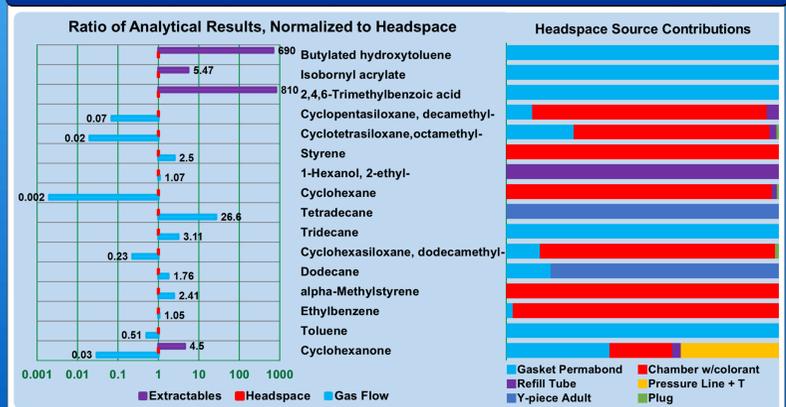
Myristic acid
Palmitic acid
Stearic acid
Erucamide
Irganox 3114
TOTM
Irganox 1010
cis-Hexahydrophthalide
Diethyl terephthalate
p-Nonylphenol isomers
(1-Hydroxycyclohexyl)phenylmethanone

Total Micrograms per Device by 3 Analytical Methods

Each analytical method provides a distinct data set of detected substances with some overlap between methods.



COMPOUNDS DETECTED BY MULTIPLE METHODS:



PHYSICAL/CHEMICAL PROPERTIES AFFECTING RELEASE

Gas Flow Analysis by Tedlar Bag Sampling: Emission of VOCs from the breathing circuit involves three migration processes: (1) diffusion of VOCs through a polymer material, (2) volatilization from the polymer surface, and (3) air dispersion controlled by pressure differentials, turbulence, and convection. Physical constants affecting migration include the polymer diffusion coefficient, the material/air partition coefficient, and a dilution/attenuation factor related to flow rate.¹ The gas flow analytical data reflect a trend consistent with the general polymer emission profiles studied by other investigators, in which initial heating causes air concentrations to spike quickly due to the immediate release of VOCs from the surficial layers of the polymer, then emission rates drop off, as might be expected whenever the near-surface solid phase concentrations in the polymer become depleted. A gradual transition towards a slower rate of decay then occurs, presumably at the point where diffusion through the polymer becomes the rate-limiting factor. This is generally consistent with findings reported by investigators who have measured and modeled polymer-to-air VOC emissions in various settings.^{2,3,4,5,6} In the gas flow analytical system, it is critical to verify that VOCs are not lost due to absorption onto the walls of the sampling bag.⁷ For this project, Tedlar bags were spiked with target compounds to verify acceptable analyte recoveries.

Headspace Gas GC/MS Analysis: A strong temperature dependence exists for the surface/air equilibrium constant applicable to VOC headspace analysis in a closed system. As shown by the comparison of analytical results, the higher temperature of headspace analysis (90°C) versus gas flow analysis (41°C) enhances the release of various VOCs. This is consistent with the findings of other investigators and with mathematical predictions of the diffusion coefficient as a function of temperature.^{8,9,10,11,12} Preparation of samples by cutting components, separating parts previously glued with adhesives, and exposing both the inner and outer surfaces of tubes and fittings further facilitates release of VOCs from polymer surfaces that are not exposed under clinical conditions.

Extractable/Leachable Analysis: Solvent extraction of VOCs, SVOCs, and NVOCs from polymers involves several physical processes: (1) diffusion of VOCs through a polymer material; (2) potential swelling of the polymer due to penetration of certain extraction solvents; and (3) partitioning and dissolution into the extraction solvent. The choice of extraction solvent significantly affects polymer swelling and compound solubility. In addition to affecting diffusion rate, temperature also affects the polymer-liquid partition coefficient, although if equilibrium were able to be achieved, practically the entire amount of a compound in a polymer could migrate into a nonpolar solution.^{10,13,14,15} Many organic substances can be efficiently solvent-extracted, including low-volatility compounds that are hard to detect by headspace or gas flow analysis. As expected, the amounts released by extraction were observed to be much greater than headspace results for analytes detected by both methods.

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USE OF AIR PATHWAY METHODS IN RISK ASSESSMENT

Headspace Gas GC/MS Analysis: This analysis yielded several VOCs that were not observed in gas flow analysis, despite having similar detection limits. While headspace analysis is an established method under ISO 10993-18, the conditions of analysis involve elevated temperatures well outside the range that could be encountered during clinical use and exposures to outer surfaces and cut surfaces that are not part of the actual exposure pathway. For example, several of the headspace compounds that were elevated above levels in gas flow analysis are associated with the gasket PermaBond material, and headspace sample preparation increases the available emission surfaces for this material much more than the configuration used in gas flow analysis.

Gas Flow Analysis by Tedlar Bag Sampling: Analytical results were used to generate an estimate of cumulative emissions that approximates patient exposures to gas phase VOCs. Sampling was conducted under realistic operating temperatures, oxygen flow rates, and utilizing a configuration that included gas flow across the inside surfaces of tubes and chambers, which reflects clinical conditions. Despite these advantages, gas flow analysis is only mentioned in draft guidance ISO 18562, and is not yet accepted by FDA. While this method does not account for patient inhalation/ingestion of humidified vapor condensate, since the walls of the connection tubing are heated during operation, this could minimize the contact of water droplets with device surfaces.

Extractable/Leachable Analysis: Analytical data represent chemicals released by aggressive solvent extraction at elevated temperatures. FDA currently advises use of extractables data to estimate vapor condensate exposure. However, as approved, this ISO 10993-18 method was designed to determine leachable constituents from a device in contact with blood or other biological fluids. Thus, it is uncertain how extract exposure assumptions can apply to the respiratory pathway.