Doctoral Dissertation
Doctoral Program in Chemical Engineering (29th Cycle)

Scale down of a dynamic generator of VOC reference gas mixtures

By

Maricarmen Lecuna
B.S Chemical Engineering

Supervisor:
Prof. Guido Sassi

Doctoral Examination Committee:
Elena Amico di Meane, Referee, National Physic Laboratory UK (NPL)
Valter Maurino, Referee, Università di Torino
Aimè Lay- Ekuakille, Referee, Università del Salento
Claudio Minero, Referee, Università di Torino

Politecnico di Torino

2017

Declaration

I hereby declare that, the contents and organization of this dissertation constitute my own original work and does not compromise in any way the rights of third parties, including those relating to the security of personal data.

Maricarmen Lecuna

2017

* This dissertation is presented in partial fulfillment of the requirements for **Ph.D. degree** in the Graduate School of Politecnico di Torino (ScuDo).

To my beloved parents.

"Cuando alguien se da cuenta del misterio insondable que es vivir le da la espalda a todas las ideas, se queda con ese solo hecho, vivir. Es suficiente para colmar una vida"

"When someone realizes the unfathomable mystery that is to live, he turns his back on all ideas, he stays with that single fact, to live, it is enough to fill a life"

Rafael Cadenas

ABSTRACT

Scale down of a dynamic generator of VOC reference gas mixtures

by Maricarmen Lecuna

Submitted on 25th November 2016 to the Department of Applied Science and Technology (DISAT) – Politecnico di Torino in partial satisfaction of the requirements for the degree of

Doctor of Philosophy

Supervisor: Prof. Guido Sassi

A system for the dynamic preparation of reference gas mixtures based on the diffusion technique has been developed by the National Metrology Institute of Italy i.e. the Istituto Nazionale di Ricerca Metrologica (INRIM). The gravimetric method used for the estimation of the diffusion rate and consequent concentration, gives the system the property to be a primary standard. The system can generate mixtures with low uncertainty and high stability in the 20 nmol.mol^{-1} - 2.5 μmol.mol^{-1} concentration range with a 5% (k = 2) expanded uncertainty for mixtures of acetone in air. Based on this system, a transportable device for the generation of VOC reference gas mixtures to be used as calibration standard was designed and developed.

The methodology used for the scale down included several steps. An initial characterization and modelling of the primary device was done using computational tools. Based on the response of the computational model to the different physical quantities, a set of design parameters was identified. The thresholds for this set of parameters were established and translated into a set of design criteria to consider in order to keep the metrological performance target.

After the design and development of the transportable device, a metrological characterization was carried out, to verify its capabilities. The metrological characterization of the generator was done in the Dutch National Metrology Institute i.e. the Van Swinden Laboratory (VSL) trough Cavity Ring Down Spectroscopy (CRDS) analyses to evaluate the linearity, the reproducibility and the short term stability. The results for the generation of methanol mixtures with molar fractions in the 80-150 nmol.mol^{-1} range, were 99.6% linear, with a reproducibility after 3 days within 2,9% and a short term stability better than 1% per hour. Repeatable measurements of the generated concentration were

obtained for three different molar fractions, with the use of both CRDS (VSL) and the GC/FID (INRIM).

A flow of the desired dry pure carrier gas can be connected to the device. The presence of water in the system has not been taken into account and further analyses should be done before introducing it to the system. Water presence might affect the adsorption rate, and consequently the flushing time before normal operation. This transportable device is able to perform in-situ calibration of instruments and has been designed to generate gas mixtures of up to four species at a time.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

Introduction

Volatile organic compounds (VOCs) are a wide group of substances that include hydrocarbons, alcohols, aldehydes and organic acids. Biogenic sources are the biggest sources of VOCs, followed by anthropogenic sources of VOCs that include fuel production, distribution, and combustion (especially in motor vehicles due to either evaporation or incomplete combustion of fuel). Anthropogenic emissions occur in heavily populated, industrialized regions (95% in the northern hemisphere), where natural emissions are relatively low, so they have significant impacts on regional chemistry despite small global emissions [1].

1.1. IMPORTANCE OF MONITORING VOLATILE ORGANIC COMPOUNDS

VOCs monitoring has become important in different levels. Being such a wide group of substances, the species of interest and their relative concentrations vary depending on the type of application. The most relevant and challenging applications are going to be illustrated, and their requirements will be considered in the development of the present work.

1.1.1. Environment and Atmospheric Models

VOCs influence climate through the production of organic aerosols and their involvement in the production of O_3 in the presence of NO_x and light. After 1700s, the amount of greenhouse gases released into the atmosphere increased, especially due to the intensification of industrial activities. Over time, these gases can be removed from the atmosphere by chemical reactions or by emission sinks, such as the oceans and vegetation. However, as a result of human activity, these gases enter the atmosphere more quickly than they are being removed, consequently increasing their concentrations. Carbon dioxide, methane, nitrous oxide, and certain manufactured gases become well mixed throughout the global atmosphere because of their relatively long lifetimes and because of transport by winds. Ozone is also a greenhouse gas, but its effects depend on its altitude, or where the gas is located vertically in the atmosphere [2]. At the surface, ozone is an air pollutant that adversely impacts human health, natural vegetation and crop yield and quality [3] [4].

Tropospheric ozone is a major component of urban photochemical smog, and a highly reactive oxidant which, when inhaled, can worsen bronchitis and emphysema, trigger asthma, and permanently damage lung tissue and has been recognized as a threat to human health [5] [6]. Also, its deleterious effects on plants pose a large-scale risk to crop production and forest vitality in many regions of the world, especially in the north hemisphere [3]. Together with other gases found in the atmosphere, it plays a role in the deterioration of building materials (e.g. steel, stone, concrete, brick and wood) exposed in outdoor environments [7]. Unlike the other major greenhouse gases, tropospheric ozone only lasts for days to weeks, so levels often vary by location and by season, which makes difficult the modelling of concentrations and its long-term effects.

The increase on the levels of VOCs and NOx, have led to an approximate doubling of ozone in the lower troposphere over the past couple of centuries, making tropospheric ozone the third most important anthropogenic greenhouse gas after carbon dioxide (CO_2) and methane (CH_4) [8]. Efforts on monitoring VOCs in atmosphere have been made to model climate change and predict the formation of tropospheric ozone.

1.1.2. Industry

Besides the effects on the atmosphere, Volatile Organic Compounds (even at trace level) represent a threat to some manufacturing processes, such as such as semiconductor, nanotechnology, photovoltaic and high brightness and organic LED industries [9]. After the initial problem of airborne chemical contamination was reported by IBM researchers in 1994 [10], other semiconductor companies began to examine the damage caused by the Airborne Molecular Contaminants (AMCs) during manufacturing processes.

According to the ISO 14644-8 classification of airborne molecular contamination; *“the product or process can be sensitive to, or can be destroyed by, molecular contamination resulting from airborne molecules due to external, process, or otherwise generated sources”* [11]. Airborne Molecular Contaminants includes a wide group of chemical substances, including Volatile Organic Compounds. AMCs are different from particles, as they exist in gaseous or vapour forms with average dimensions of only 0.2-3.0 nm, therefore AMCs can penetrate and pass through ULPA (ultra-low particulate air) filters.

Industrial micro-fabrication processes and other manufacturing processes at even smaller scale, bring new challenges regarding environmental control, especially cleanliness. Trace organics have an increasingly detrimental impact on the performance, yield, and reliability of ever smaller semiconductor devices [12]. The challenge addressing the development of on-site detection devices brings the necessity of proper reference mixtures at trace level to be used as calibration standards.

1.1.3. Indoor Air Quality

Human exposure to Volatile Organic Compounds was first addressed as a health issue by the World Health Organisation [13]. Organic compounds in indoor air can produce sensory effects, such as perceptions of odour and irritation, which can severely affect human health and wellbeing. Organic compounds may cause odours, mucosal and sensory irritation and airway effects at levels encountered indoors.

In the European Community, population exposure to air pollution by VOCs inside buildings is much larger than outdoor exposure, because (a) the concentrations of most VOCs are higher indoors than outdoors, (b) on average the time spent indoors is about tenfold greater than the time spent outdoors and (c) susceptible subpopulations such as infants, elderly and people of poor health spend most of their time indoors [14].

The first two types of health reactions are typical for the sick building syndrome (SBS) and therefore, VOCs are often suspected to be a cause of SBS. A few VOCs that may be emitted by flooring materials are human carcinogens and some VOCs are potential sensitizers [15]. Since no global thresholds has been defined, the type of VOCs considered and their limit values, can vary depending on the region or country of analysis. Lowest Concentration of Interest (LCI) are threshold values based on the determination of concentration levels below which there is no reason to expect adverse effects.

In 2006, Italy published a decree on the labelling of solvents and other products containing VOCs. However the thresholds published for total VOCs are not clearly defined [16]. Some other Europeans thresholds were evaluated and considered, in order to determine the target concentrations in Europe.

In Germany the Committee for Health-related Evaluation of Building Products (AgBB) publishes a list every 1 - 2 years, containing limit values for different organic compounds (the number of substances rose to 196 in the 2015 issue [17]). German LCI values are derived from European and German occupational exposure limit values (OEL) by division with safety factors [18]:

- 10 times if the exposure involves sensitive population (e.g. children, old persons, sick persons) in indoor setting.
- Another factor of 10, for longer exposition in indoor environments aside from workplace (up to 24 hours all days, whole life), compared to 40 h 5 days a week and only during working life time,
- An additional factor of 10 is added for suspected carcinogens.
- Proven carcinogens should not be emitted into indoor air at all.

In France, the French Health and Environmental Protection Agency (AFSSET) published a list in 2006, containing French LCI values for some of the 190 VOCs [19]. In 2011, a VOC French regulation was published, with norms for labelling and thresholds for emissions in indoor air. For each substance or group of substances, the emission scenarios, the characterization method, the method for measuring exposure concentration, the limit values and the corresponding classes were reported [20]. The LCI values shall serve as criterion for acceptance of emission into indoor air, and are considered to correspond to the A+ criterion on the aforementioned decree [19].

Chronic Reference Exposure Level (CREL) values are defined by toxicology based on health risk assessment studies with respect to indoor air exposure, normally related to a period of time (i.e. a working day of 8h). Their definition is under the responsibility of the Californian Environmental Protection Agency.

Not all VOCs are common for the countries that were reviewed, but for those common substances, the lowest concentrations of interest where compiled. It is evident that different references and different assessment methods lead to very different limit values, as shown in Table 1. This is explained by the lack of a global framework to establish targets based on actual clinical evaluations, more than economic issues.

Table 1. Lowest Concentration of Interest for different countries (in µg/m³)

Substance	LCI (D)	LCI (F)	CREL (CA)
1-Butanol	3100	1500	-
2-Ethoxyethanol	19	70	70
Crotonaldehyde	1	1	-
Formaldehyde	120	10	33
n-Hexane	72	700	7000
Terpenes	1500	450	-
Toluene	1900	300	300
Xylene	2200	200	700

1.1.4. Biomarkers for disease detection

VOCs are also emitted constantly by human body, from different parts of the body. They mostly accumulate in the breath, urine, skin, blood, sweat and faeces. Some VOCs are secreted from lung cells and exhaled; some, however, are secreted into the blood and then emitted to the external environment via the breath. [21] This introduces the possibility for using them as biomarkers for different diseases.

First measurements of VOC biomarkers in breath were performed by Gordon et al. in 1985, to detect lung cancer using GC/MS analyses [22]. With the help of modern instruments, VOCs can be detected and analysed in the form of ‘fingerprints’ that are disease specific.

Recently, a sensitive artificial olfactory system called ‘NA-NOSE’ was used for detection of VOCs in breath samples, to detect head and neck cancer. The dispositive is a nanoscale artificial nose based on an array of highly cross-reactive gas sensors, mainly chemiresistors (based on different monolayer-capped metal nanoparticles) that can identify and separate different organic compounds with $\mu mol.mol^{-1}$ level sensitivity.[23]

While the responses to the same compound at a certain concentration are individually different among the constituent sensors, the signals to the mixture compounds that are present in the breath sample are additive, so that the overall signal of one sensor stems from a total 10-100 $nmol.mol^{-1}$ of cancer volatile biomarkers. Hence, the sensors' responses are less affected by noise and consequently, allow a lower uncertainty than the detected (sub) $nmol.mol^{-1}$ concentrations of the separate compounds in the GC–MS/SPME analysis.[23]

With worldwide 1.59 million deaths per year, lung cancer it is the most common cancer related to death among men and women and the major reason for its high fatality is the late diagnosis [24]. After an accurate literature review and consolidation, Saalberg obtained some conclusions about the best suited biomarkers for lung cancer. [25] According to his findings, five research groups confirmed 2-butanone and 1-propanol as best suited discriminators for lung cancer. The next group of substances, each revealed by four research teams, comprises isoprene, ethylbenzene, styrene and hexanal.

1.2. METROLOGY FOR VOLATILE ORGANIC COMPOUNDS MONITORING: EUROPE’S EFFORTS

Different worldwide and European institutions are committed with the monitoring of VOCs at trace level for different applications: environment, indoor quality, industrial and most recently, medical fields.

With lower concentrations, detection and measuring techniques are updated to improve sensitivity. This has led to greater efforts in creating metrological frameworks and better standards, to ensure the quality of the measurements and their metrological traceability.

1.1.1. Atmosphere

The Global Atmosphere Watch (GAW) Programme was born in 1989, after that the World Meteorological Organization (WMO) members recognized the importance of the atmospheric chemistry in their weather, climate and air quality programmes and activities [26]. One of the focal areas of VOCs in recent years, is the monitoring and control of reactive gases, a group that includes surface ozone, carbon monoxide, volatile organic compounds (VOCs), oxidized nitrogen compounds, hydrogen and sulphur dioxide.

A global network for a defined set of VOCs that uses discrete air samples from the NOAA/ESRL/GMD cooperative air sampling network is now affiliated with GAW-VOC. The global stations Jungfraujoch, Cape Verde and Hohenpeissenberg continue to measure a larger range of these compounds.

Among the tasks to reach by 2015, it was considered the increase of the frequency of measurements and the creation of further Central Calibration Laboratories (CCLs) for core VOCs. A core set of molecules was identified, taking into account their ease of measurement in a flask network, and their usefulness in providing information on many processes such as emissions from defined sources, long-range transport, and chemical loss processes [26]. This group represents the focal variables for climate change monitoring and is compose by Ethane, Propane, Acetylene, Isoprene, Terpenes, DMS, Formaldehyde, Acetonitrile, Methanol, Ethanol, Acetone, Benzene, Toluene, *Iso-/n*-Butane and *Iso-/n*-Pentane.

The project requires the monitoring of 10 pmol.mol^{-1} – 10nmol.mol^{-1} with a maximum uncertainty of 5% (k = 2). The data quality objectives for this project are the lowest of measurable concentrations among all the other possible applications, setting the state of the art for VOC measurements.

1.2.1. Industry

The metrological framework of industrial monitoring of VOCs has also been addressed by a European project. “Metrology for airborne molecular contamination in manufacturing environments” (MetAMC) is a project that has been developed since 2013 until the present year. The project encompassed a multitude of European national metrology institutes, including the Italian NMI, INRIM, and other stakeholders. For MetAMC, the state-of-the-art techniques for practical airborne molecular contamination monitoring where used to develop portable ultra-sensitive monitoring equipment for use in manufacturing environments. This project contemplated also the investigation on novel generation methods to produce reference materials that will help to improve the reliability of industrial calibration [9],[27].

1.2.2. Indoor Air Quality

The influence of volatile organic compounds (VOCs) on health and indoor air quality has been investigated by European countries for many decades. In 1982, a strategy for the reduction of total volatile organic compounds (TVOCs) was already proposed [28]. However, in the last decade, a new concept called “organic compounds in indoor air” (OCIA) with a compound-by-compound approach, has been introduced, as well as the consideration of other substances that were not considered in the initial report of WHO [13]. The new broader definition includes all biologically relevant organic compounds, non-proteins, non-glucans, etc. (i.e., organic compounds tentatively with molecular weights <500–1000 Da) in the indoor environment [28].

For more than 22 years the European Collaborative Action ECA "Indoor Air Quality & It's Impact on Man" has been implementing a multidisciplinary collaboration of European scientists the ultimate goal of which was the provision of healthy and environmentally sustainable buildings. To accomplish this task ECA is dealing with all aspects of the indoor environment including thermal comfort, pollution sources, quality and quantity of chemical and biological indoor pollutants, energy use and ventilation processes which all may interact with indoor air quality.

Possible health risks from indoor air pollution and aspects of risk assessment have been also addressed recently in European and international working groups and projects [29]. INDEX Project in Europe was developed to define the type and levels of chemicals in indoor air and the available toxicological information, to allow the assessment of the impact on health and comfort [30]. In California, in 2005, a law regarding indoor air pollution was also presented [31].

The most recent project, ”Metrology for VOC indicators in air pollution and climate change” [32], focuses on the VOC key compounds (indicators) that are regulated by the European legislation and are relevant for indoor air monitoring and for air quality and climate monitoring programmes like the VOC programme established by the World Meteorological Organization (WMO) – Global Atmosphere Watch (GAW) and the UNECE's European Monitoring and Evaluation Programme (EMEP). This project has combined the Data Quality Objectives (DQOs) of the GAW, with uncertainties in the range of 2-7%.

1.2.3. Biomarkers for disease detection

Back in 2010, the Breath analysis project (T2.J02) was carried out in collaboration with the NMIs of Denmark, Portugal, France, Netherlands and the German Physikalisch-Technische Bundesanstalt (PTB). The project addressed the analysis of breath for early disease detection, aiming to make reliable identification of the species and reduction of the measurement uncertainty of the molar concentration. The target was to reduce the current typical 10% uncertainty to at least 1-2%, taking into consideration the presence of interfering components in breath [33]. The substances of interest were Acetone, Ammonia, Carbon dioxide, Carbon monoxide, Ethane, Ethanol, Formaldehyde, Methane, Methanol, Nitrogen monoxide and Pentane, all in the presence of water.

A project on the development and validation of sensitive instrumentation for key reactive biomarkers was chosen as Selected Research Topic by EURAMET in late 2015. The project was intended to develop novel methods of detection and preparation of validated and reliable reference standards for the calibration of breath sampling instrumentation. [34]

1.3. CHALLENGES IN THE PREPARATION OF REFERENCE GAS MIXTURES FOR CALIBRATION

The calibration is a process that assigns values to the response of a device or instrument relative to a reference standard or a designated process [35]. The International Vocabulary of Metrology, defines the calibration as an operation that establishes a relation between the quantity values (and uncertainties) provided by measurement standards corresponding to indications with associated measurement uncertainties [36]. In the process, the collected information is used to establish a relation that allows to obtain a measurement result from an indication.

Calibration guarantees that the readings from an instrument are consistent with other measurements, and are important for the determination of the accuracy of a measurement. Depending on the type and number of the analysers, it is conceivable that an auditor might need as many as 24 separate cylinders of expensive reference standards. Cylinders are not only expensive, but pose the problem of long term stability, affecting the uncertainty of the reference mixture, especially in the case of handling reactive gases, as VOCs. To comply with environmental regulations and quality standards, a shelf life must be reported on the certificate of analysis of a gas standard. For many reactive gas species at concentrations less than 1,000 μmol.mol^{-1}, the mixture stability depends on the technology of the supplier and can vary significantly [37]. Some suppliers may base their certifications on the mass weighed into the cylinder only. However, is important to consider that gravimetric certifications have limitations associated to [37]:

- Loss of reactive minor components due to surface absorption (example: chlorine in a steel cylinder)
- Presence or addition of impurities in multi-component mixtures (example: isobutene impurity in propane, adding to the isobutane weight in a propane/ isobutane mixture)
- Reaction of impurities in the mixture with certified minor components
- Mistakes, which may include addition of the wrong component.

For this reasons, dynamic systems have been developed to generate fresh mixtures at a lower cost, and with a better metrological performance. Many techniques have been developed and will be reviewed in the Chapter 2.

A primary dynamic system based on the diffusion technique is operative at INRIM. It is able to generate up to 18 substances (VOCs) in parallel, dosed in a carrier stream of up to 50 Sml.min^{-1}. Concentrations down to 1 nmol.mol^{-1} can be generated, with a 2.5% uncertainty (k=1), depending on the conditions of generation and the substance of interest. However the operation of the system is bounded to the physical space where it is set. This system can be employed for the calibration of different devices as long as they are transported to the laboratory. This might be convenient for commercial uses and whenever the expected targets of uncertainty are much higher.

Even if the primary dynamic system is able to generate reference mixtures that meet the requirements of GAW, it does not address the need for the calibration of remote atmospheric stations that require in situ calibration. The compactness target for a transportable device is constrained to different requirements. But a scale down considering those requirements and the targets, would lead to a compact and dynamic system that not only produces mixtures in respect of the highest quality objectives of GAW, but can be actually transported to where it is needed.

An important requirement for portability is related to the volume occupied by the whole device. In a portable gas standard mixtures generator is desirable to have dimensions compatible with commercial racks commonly used in gas analysis laboratories. This implies that both generation and dilution system should be adapted to enter inside a case of 19” (482.8 x 177 x 192.5 mm).

The capacity of generation of mixtures in terms of mass flow rate, is defined by the air source. Commercial zero air generation system operates at maximum 3-5 SL.min^{-1} depending on field facilities. The diffusion rate is limited by the dilution ratio and the target concentration. To get a portable device diffusion rates must be kept lower than those in a main laboratory system.

VOCs are a very wide family of substances and the interest on a specific species and its target concentrations depends mainly on the application. In this work, several applications where reactive VOCs need to be monitored at trace level, are described.

The key substances common for the different applications will be identified. Later they will be used for the characterization of the primary system and further validation of the transportable device. The generation conditions for all cases will be carefully chosen so they represent the most conservative case.

1.4. SCOPE OF THE WORK

This dissertation deepens into the detail of the modelling and design carried out to develop a transportable device for generation of VOC standard gas mixtures. The definition of the system, the phenomena involved and the identification and quantification of the uncertainty sources are addressed.

The performance of the device developed will be evaluated while generating trace level standard mixtures of Acetone and Methanol. However, the generator designs considers the possibility to change pressure and temperature in order to diffuse other mixtures, using VOC compounds with vapour pressure above 70kPa. The idea of a transportable device that is traceable to the primary system is to give a response to the need of accurate and stable transfer standards. The system could be used for calibration in situ in the atmospheric stations of GAW or as point of care for breath analysis in the hospitals, improving the quality of the measurements and providing more accurate measurements for early disease detection, indoor quality monitoring and atmospheric monitoring and modelling.

1.4.1. General objective

A primary system based on diffusion technique was developed by the National Metrology Institute of Italy (INRIM). The system is operative and generates mixtures of up to 18 substances, from 100 nmol.mol^{-1} to $2.5\mu\text{mol.mol}^{-1}$ with 1% of uncertainty (k=1), handling dilution air flow rates up to 25Nl.min^{-1}. The main objective of this project is to scale down the primary system, to reproduce its performances in a transportable device. The VOC dosed by the transportable device is traceable to the primary and also stable, having the capability to be a transfer standard (dynamic) in the VOC calibration chain.

1.4.2. Specific objectives

To achieve the main objective, it is necessary to follow a series of steps, based on a methodology that is going to be studied in Chapter 3.

The first step is the characterization of the primary device that includes the development of a predictive model of the system and its uncertainty. Once a model is obtained, it is possible to identify the most important parameters, and find a set of design criteria to perform the scale down.

After combining the design criteria and the transportability requirements, the next step is to design and construct the new device. At last, a metrological characterization of the transportable device will be done to obtain insights onto its performance.

1.5. THESIS OUTLINE

In Chapter 2, a description of the phenomena involved in the generation process is carried out, including the definition of concepts and methods necessary for the development of this work.

The methodology followed to achieve the proposed objective is discussed and defined in Chapter 3.

Chapter 4 addresses the process and metrological characterization of the primary system, allowing to evaluate its actual performance. A model to simulate the performance is developed and validated in this section.

Based on the sensitivity analyses made over the system with the help of the models developed, the design criteria, to be considered in the design of the transportable device, are identified and defined. Insights into this particular are given in Chapter 5.

Chapter 6 shows the process of the scale down, from the application of the above models, to construction and metrological characterization, including the validation of the performance with GC – FID and cavity ring down spectroscopy (CRDS) measurements of the concentration.

Finally, a summary is presented, with the contributions from this research and the opportunities for the future. Special emphasis is given to the next steps to be taken towards a better performance and the parallel generation of an increased number of substances.

CHAPTER 2

Methods for preparation of gas mixtures

The preparation of gas mixtures contemplates the dilution of one or more pure substances of interest into a carrier gas that can be pure air or an inert gas. Two approaches exist to prepare gas mixtures: static and dynamic. These different techniques have been developed in an effort to improve both the accuracy of the estimation of the molar fraction of the mixtures and their stability to meet the targets of each application, so they can be used for calibration purposes.

2.1. STATIC METHODS OF PREPARATION

Currently, the most common and popular technology to prepare reference gas mixtures is the gravimetric method. High - pressurized cylinders are prepared gravimetrically, putting a known amount inside a pressurized cylinder [11]. The concentrations handled are typically 1 $\mu mol.mol^{-1}$ and their uncertainties usually 5–15 % depending on the compound and the preparation method [38]. Cylinders of reference VOC mixtures at high accuracy are commercially available and behave well at the concentrations mentioned above and in the short term (less than 1 year).

However, studies have demonstrated several drawbacks, including the lack of accuracy for particular cases such as polar compounds, like formaldehyde, and hydrocarbons beyond C10–C11 like sesquiterpenes [39]. The high cost of the cylinders, low field portability, dangers associated with their use and long term instability are among the disadvantages of this technology. The challenge is to have high metrological performances at low concentrations of the order of $nmol.mol^{-1}$ and $pmol.mol^{-1}$. Providing quality standards would fulfil the needs of the different applications that involve the use of these mixtures in environmental, industrial and medical fields [40][9][32].

Dynamic methods continuously provide fresh mixtures with stable VOC amounts of substance fraction and short time VOC interaction with the internal tube walls. For this reason, this type of technology is the best candidate to fulfil the needs and to be developed in the future of production of generation standards [9][32].

Several calibration standard suppliers agree that the most important factors to consider when manufacturing or ordering a reference mixture (liquid or gaseous) are the following [41] [37] [42] [43]:

- Blend tolerance
- Accuracy and Stability
- Metrological Traceability

The mixture refers to the desired type of calibration standard the customer requires, such as a liquid or a gas blend.

Blend tolerance is the acceptable concentration range for each of the components of the reference mixture. Example: Oxygen requested at 100 $\mu mol.mol^{-1}$ in nitrogen with ± 2% blend tolerance will allow an acceptable concentration of 98-102 $\mu mol.mol^{-1}$ for oxygen.

In the International Vocabulary of Metrology, accuracy has been defined as *“the closeness of agreement between a measured quantity value and a true quantity value of a measurand”* [36]. Accuracy is typically reported as percentage relative to the mean of the concentration or an absolute value, i.e.: If a component is certified at 100 $\mu mol.mol^{-1}$ with ±1% accuracy, the end user should yield an analytical value of 99 - 101 $\mu mol.mol^{-1}$ for that component. The stability, on the other hand is the ability to maintain a constant concentration value over a defined time within given uncertainty. The mixture stability also has a significant impact on the accuracy and long-term usability of the reference mixture.

The metrological traceability positions the measurement inside a calibration chain. Mixtures that are calibrated against a National Metrology Institute (NMI) standard or a lab standard directly traceable to an NMI standard, are traceable. Traceable instrument calibration is required for environmental regulation, analyses in legal proceedings and other metrological applications.

- *Sources of Uncertainty in cylinders*

When a gas mixture is needed, the cylinder can release a continuous stream of mixture at a fixed pressure. The output of the cylinder can then be connected to the device that needs to be calibrated. However not every substance and every concentration range is suitable to be generated using cylinders. For generation of standard gas mixtures with reactive gases, the dynamic technologies could represent a better approach than the conventional gas cylinders. This is especially important at low concentrations, where a high accuracy is more difficult to maintain [44].

The reasons for a decrease in concentration in the long term may be explained by several reasons. The first and most probable cause of instability is the presence of active sites on the walls of either the cylinder or the system which delivers the gas from the cylinder to the analyser (regulating valve, sample line and sample loop). Consequently sorption of the components on the walls through either chemical or physical bonding can occur.

Another reason for VOC losses may be the interaction of two or more components of the mixture. A bias between the standards used for one analysis and those used for a subsequent analysis can also provide a difference in the measurements from a year to another [45].

Analyses performed on different cylinders with more than 40 VOCs at low concentration over 6 years, were carried out at NIST. They have figured out some reasons for possible cylinder dependency. Either poor quality control during the cylinder passivation process or incompatibility of the passivation process with the alloy used to make the cylinder may alter the stability of the mixture in the long term. Exposure of the treated cylinder to a compound which could neutralize the treatment process (e.g. water) was also found to be a reason of possible instability, along with the polarity of the substances which exhibited instability [45].

2.2. DYNAMIC METHODS OF PREPARATION

Different dynamic methods exist and can be used to generate fresh mixtures of VOCs at trace level. In the dynamic methods, VOCs are dosed in continuous mode into a stream of purified carrier gas, followed by a homogenization of the mixture. However, the principle used to generate the mixtures can be different, and so is the complexity of the model used to estimate the concentration. The presence of more parameters most of the times involves a higher uncertainty. A list of techniques employed is briefly described below.

2.2.1. Dilution from cylinder

A method to achieve high dilution is mixing a VOC mixture contained in a gas cylinder with a zero gas stream, both being accurately measured with flow meters. When low concentrations are required, accurate low – flow meters are necessary and if they are not available, a double or multiple dilution stage can be necessary. Using this method, the initial contaminant can be diluted by four to nine orders of magnitude [46]. However, the introduction of different stages promote pressure instabilities in the system, which can affect the uncertainty of the standard mixture generated. The use of mass flow controllers (MFC) for each step of dilution, was early introduced as a solution [46].

MFCs were found to be appropriate for the dynamic preparation of diluted gas mixtures as long as they are calibrated prior to each use. The reason is that their calibration is not stable over long time periods.

The uncertainty of the dilution flow rate resulted mainly from the limited short-term stability of the MFC at either low dilution flow rate or short generation time.

Consequently, MFCs can provide highly accurate dilution flow rates with a 0.2 % relative uncertainty , for flow rates larger than 70 % of the MFC’s full scale and generation times longer than 5 min [47].

Using the MFC to adjust the flow rate of pure air might be a good option, however to dose the reference mixture into such air stream using a MFC is not feasible. VOCs in the reference mixture may interact with the inner walls of the instrument. It might not be easy to take into account VOC losses due to these phenomena as they depend on the particular configuration and materials used by the manufacturer of the instrument.

Even if a good method for dilution is developed, the uncertainty of the diluted mixtures depends on the composition uncertainty of the cylinder and the realization of the dilution process. Reaching low concentrations by means of dynamic dilution is possible, but with an uncertainty and stability directly related to those of the initial gas cylinder.

2.2.2. Diffusion method

Diffusion generation systems can release a reproducible, accurate, and stable amount of VOC in a flushing carrier gas. Dynamic generation of reference VOC mixtures by diffusion is described by standards [48],[49]. The system consists of a set of vials, with a reservoir containing the liquid substance to be generated and a long neck of small diameter. With simple assumptions, the geometry of the neck and the thermodynamic properties of the substance are the only parameters necessary to estimate the transported mass.

The accuracy, reproducibility and stability of the diffusion flow rate generated depends on the variability and stability of temperature and pressure. Both parameters must be considered at the gas-liquid interphase -where phase change occurs- and inside of the vial neck -where controlling diffusive transport phenomena occurs. The pressure in the vial pipe and on gas-liquid interphase depends on pressure drops of the line connecting the diffusion cell to the drain and on the atmospheric pressure. A controlled temperature is kept in the thermal bath where the cells are partially immersed. The quality of the temperature control, as well as the heat transferred from the controlled zone to the target zones and the detection of possible heat sinks or sources, have a key role to keep a low variability of the temperature.

2.2.3. Permeation method

This method is one of the most common and effective dynamic methods for producing trace level mixtures. The heart of the system is the permeation device, which is usually a short polymer tube [46]. The device is sealed at both ends by glass plugs and filled with the analyte of interest. The analyte vapour dissolves into the polymer, diffuses through it, and finally mixes into the carrier gas stream [50]. Permeation devices, can be filled only with compounds having vapour pressures below 1 bar at ambient temperatures i.e. which are liquid. That is to say a permeation device cannot be used for alkanes and low number (≤C4) alkenes [38].

For most analytes, the permeation rate is strongly dependent on temperature. A common rule of thumb states that for every degree Celsius of temperature increase, the permeation rate increases by 5– 10 % [50].

A generic permeation device could be used as a working standard that has to be checked once in a while by a laboratory standard. The reason is that the permeation rate has to be measured before use over the entire range of possible temperatures (usually 15 to 35 ◦C) with an independent calibration device and should be cross-checked every few months to confirm the initially measured permeation rate.

One of the main disadvantages is that an accurate modelling of the diffusion through the polymeric material is complicated. But also the limited commercial availability of the compounds, their high prices (typically $200–$1000 for a single permeation tube) and the changes in the permeation characteristics of the diffusion membranes over time make this technique less appealing with respect to other methods of generation [51].

2.2.4. Injection method

For the technique based on liquid injection, the liquid VOC is directly injected into a carrier gas (such as air or nitrogen) at a known rate. In this approach, it is assumed that the liquid standard injected into the carrier stream is completely evaporated [46]. After the injection, the mixture is homogenized in a mixing chamber. Different configurations have been developed over time.

At the beginning of the development of such technology, liquid VOCs where sprayed into a stream of warm carrier as described by Jaouen et al [52]. An automatized syringe was later introduced, to inject pure liquids into a dilution gas flow, as well as a heating system capable of improving the evaporation of the injected liquid.

However, even if it is a simple technique, this system lacks the ability of continuous operation (due to the need of a syringe-fill cycle) and requires a heated liquid injection manifold (to promote evaporation of the liquid standard at higher flowrates) and a separate mixing chamber [51].

2.2.5. Evaporation method

In the evaporation technique, a stream of gas passes in close proximity to the liquid to be vaporized. The amount of liquid evaporated will depend on the bubble size, the rate of the temperature increase in the liquid phase and the height of the column of liquid. Evaporation is an excellent method for generating a single VOC mixture into a relatively high volume of gas (10-100NL.min^{-1}). But the major disadvantage is that the effluent gas mixture must be independently analysed as the uncertainty of the estimation is usually high (due to the high number of parameters).

2.2.6. Diffusion in comparison with other techniques

Stable gases such as carbon monoxide, carbon dioxide, propane, methane, hydrogen and oxygen have been extensively studied, so their behaviour in calibration mixtures, in sampling systems and in analytical instrumentation is well understood [53]. Some other substances, especially semi VOCs and oxygenated VOCs, still receive attention in metrology research, since their behaviour prevents the generation of highly accurate stables mixtures, especially at trace level concentrations. Based on Taylor's compilation of the D-22 American Society for Testing and Materials (ASTM) symposium, the most important techniques for gas mixture preparation were reviewed. A comparative table, based on the one reported in the aforementioned publication, was prepared and updated to the current state of art (See Table 2) [53]. It shows the maximum expected extended uncertainty (k = 2) for different generation techniques. Electrolytic and chemical reaction techniques were not considered as they might be irrelevant for the group of substances of interest.

Table 2. Accuracy targets for different dynamic generation methods

Method	Molar fraction	Expected uncertainty
Dilution from cylinder [46]	> 1 nmol.mol^{-1}	up to 10%

Diffusion [54] [46]	> 100 pmol.mol^{-1}	up to 2%
Permeation [46]	> 200 pmol.mol^{-1}	up to 3%
Injection [51]	> 500 pmol.mol^{-1}	up to 7%

2.2.7. Existing devices operating

A prototype system based on diffusion technique was developed in 1999 by Gautrois et al. [55]. The system allowed the generation of mixtures at pmol.mol-1 level (not traceable), of different VOCs, including halogenated hydrocarbons, alkanes and aromatics, within a range of boiling points from 305 (1,1-dichloroethene) to 418 K (1,2-dimethylbenzene).

However, even if the system was stable, having a good reproducibility (2.2 - 12.7%), the calculation of the generated diffusion rate was made based on two assumptions. The first, the concentration at the tip of the vial which was equal to zero and a concentration equal to the saturation value at the entrance of the tube [55]. These assumptions can widely affect the uncertainty of the estimated diffusion rate, especially for particular cases. A low carrier velocity, brings as consequence a higher concentration at the tip of the tube, decreasing the actual rate of diffusion.

On the other hand, if the substance generated has a high vapour pressure, the mass transferred via diffusion through the tube may compete with the evaporation process. In this case, the concentration at the entrance of the diffusion tube would be lower than the saturation concentration. A set of refillable diffusion tubes was developed in 2009 by Tracer Measurement Systems, Ltd. They can be calibrated gravimetrically in a few weeks and are useful for generating µmol.mol^{-1} and nmol.mol^{-1} concentrations of VOCs and SVOCs. Even if they are easy to operate, the influence of leakages or interactions should be accounted for, due to the presence of a polymeric cap, especially at low concentrations.

CHAPTER 3

Methodology for scale down of the primary system

The scope of this chapter is to define the methodology to apply in order to scale down the primary device of INRIM. Special attention is given to the transportability and the metrological performances of the resulting device. The reference mixtures produced by the scaled device should be comparable to those of the primary one, as their final application is the calibration of instruments [56].

To identify whether it is necessary or not to take into account the metrological traceability, it is necessary to address the quality of the estimation of the combined uncertainty that is evaluated. To guarantee a low uncertainty in a combined measurement, it is necessary to identify and minimize the influence quantities that represent the major sources of uncertainty. Traceable measurements provide a well estimated uncertainty that will be smaller than any conservative uncertainty considered. Using a traceable measurement of the parameters that represent the major sources of uncertainty is therefore a helpful resource in the minimization of the uncertainty of a combined measurement [37].

3.1. METROLOGICAL TRACEABILITY

According to the International Vocabulary of Metrology, *metrological traceability* is *"the property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty"* [36].

Being a property of the measurement, it means that only the result of the measurement can be considered traceable, not the equipment or devices used.

However, by calibrating an equipment in a proper way, it is possible to obtain a device that potentially produces traceable measurement results [56]. To lay within a metrological traceability framework, a calibration hierarchy should be defined and respected. The uncertainty of the traceable measurement considers the uncertainty propagation of each step of the chain of calibration.

A measurement standard has been defined by the International Vocabulary of Metrology as "*realization of the definition of a given quantity, with stated quantity value and associated measurement uncertainty, used as a reference"* [36] .

Is important to clarify that to accomplish the realization of the definition of a given quantity, a measuring system, a material measure (like a ruler or a 1kg mass) or a reference material (like a standard solution for calibration) can be used. Depending on the definition of the measurement standard, there is a BIPM classification which is useful in the establishment of the metrological traceability chain. International measurement standards are recognized by signatories of an international agreement and intended to serve worldwide, while national standards serve as a basis for calibration within a state. A primary standard is a measurement standard for which a primary measurement procedure has been used, that is to say, without making reference to another measurement standard. It is chosen by agreement after international comparisons to guarantee that it meets the requirements of reproducibility, repeatability and stability defined for the application of interest [36].

When a primary standard is used to calibrate a measurement standard, it becomes a reference standard and the result is a secondary standard. In terms of application, a working standard is routinely used to calibrate instruments and differs from a transfer standard in the fact that the latter, is employed as intermediary to compare two reference standards [36].

The definitions above, can represent steps in the metrological traceability chain, and can be linked in different ways to provide a metrological framework to any kind of activity involving direct or indirect measurements.

3.2. CONSTRUCTION OF A CALIBRATION CHAIN

The GAW-VOC network has structured a Quality Assurance (QA) and Quality Control (QC) framework that illustrates how a calibration chain works [26]. This configuration achieves universally common, coherent, traceable and verifiable climate observations [57]. A calibration chain can have any size, but every additional step increases the uncertainty of the measurement.

In the case of the GAW-VOC network, the World Calibration Center for VOCs (WCC-VOC) develops QA/QC procedures to guarantee the quality of the data reported in long-term [26]. Each link in the metrological traceability chain will be formed by a measurement standard. The QA/QC procedures contemplate the exchange of transfer standards for VOC measurements amongst the laboratories involved in the VOC network. The Central Calibration Laboratories (CCL) provide the VOC transfer standards to the WCC-VOC. The CCL prepare the cylinders filled with the reference mixtures of interest, to be used as transfer standards at the ambient air levels of the target VOCs (in general at low nmol.mol^{-1} level). The transfer standards are traceable to the CCL's primary VOC standards. The CCLs are also responsible for maintaining the standard scale for the species under consideration.

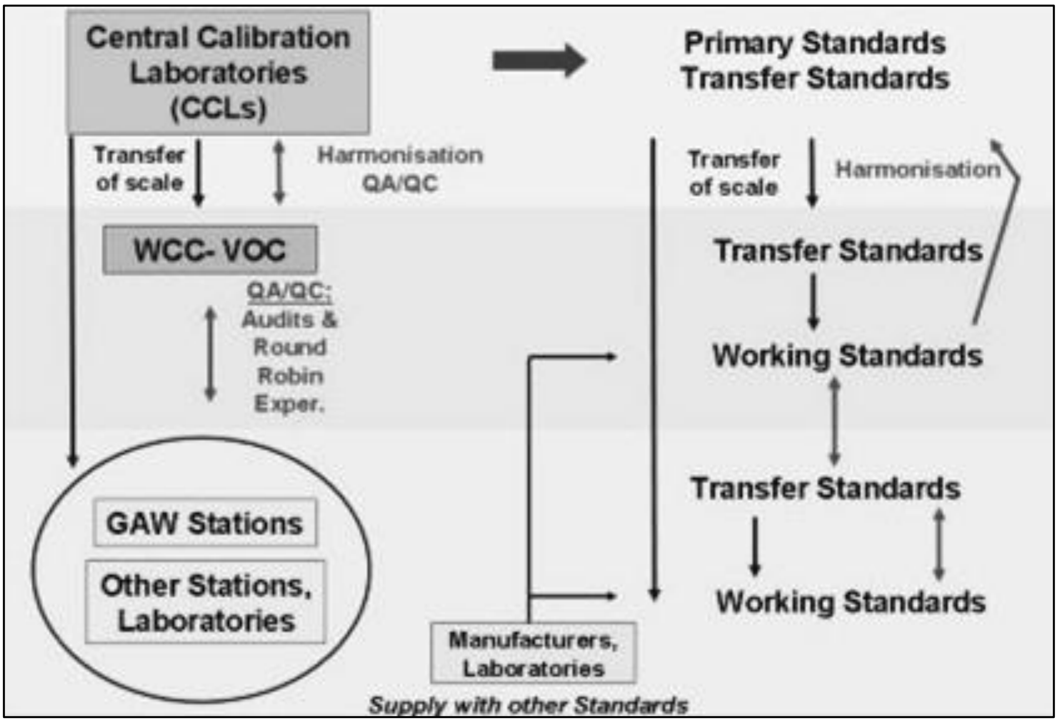

Fig. 1. Metrological traceability chain in GAW network [58]

3.3. TRANSPORTABILITY MEETS METROLOGICAL TRACEABILITY

In Italy, a system capable of generating a primary standard has been developed by the National Metrology Institute (INRIM). The measurement of the concentration is indirect and based on the gravimetric method to know the amount of liquid VOC transferred to the mixture during a period of time. The system is formed by two parts, the generator containing the vials where the diffusion takes place and another other part for the subsequent dilution (details on Chapter 4).

The uncertainty of the measurement is highly dependent on the time between each mass measurement. However, even if the uncertainty of this system is very low, the device is not transportable. Sampling the gas mixture entails the introduction of additional sources of uncertainty that have proved to be relevant, limiting the applications of the standard. A transportable device, following the same principles of the INRIM's primary system, and calibrated against it, would become a secondary or reference standard. Being directly traceable to the dynamic primary standard, it can become a transfer standard that can be moved between laboratories and stations providing a real VOC in air reference mixture. The CCL will develop, produce, calibrate and sell the required generators.

Given the operating principle, this device is able to work at considerably low concentrations, keeping a low uncertainty and high stability. This characteristic broads the range of applications to processes where low detection of volatile organic compounds is required. In - situ calibrations, points of care for breath analysis in hospitals or use as transfer standards are a few of the possible applications of the device.

3.4. SCALE DOWN METHODOLOGY

Three major steps will be considered to pass from the dynamic primary system to a prototype of the transportable device.

3.4.1. Step 1: Characterization of the primary device

In order to keep the same metrological performance, it is necessary to accurately characterize the primary device. For this purpose, two approaches will be considered:

the metrological and the process characterization. The first one corresponds to the definition of the uncertainty and stability associated with the reference mixture generated. While the second one, corresponds to the analysis of the phenomena involved in the generation and dilution processes. Combining both approaches, allows to define the targets to be achieved and the identification of the considerations to take into account into the design and construction of the secondary transportable device.

- *Uncertainty estimation*

Measuring is an important step of science and engineering. Performing a measurement allows to quantify changes and states in objects. To establish a relation between a number and an object or state is a process that consider many details. A property becomes measurable when there is a defined operation that allows the observation of the property of interest and its isolation from other phenomena. A fundamental measurement is direct, while a derived measurement relies on another property to quantify the value.

The quantification depends on a scale and the uncertainty of the measured value will depend on the instrument, its capacity to identify changes in the system and the reproducibility of the measurement itself.

However, if the property or value is measured as a function of other properties (derived measurement) then the estimation of the uncertainty will be different and dependent on the uncertainty of its influence quantities [59].

The procedure used in this thesis, summarizes the GUM procedure for Type A evaluation of the uncertainty into a table called uncertainty budget (See Table 3) [60]. The construction of the budget contemplates N rows, one per each influence quantity considered. The columns in the table collect the information of mean X_i and uncertainty $u(X_i)$ of each input quantity. The sensitivity coefficients $C(X_i)$ can be calculated from the mathematical model of the property, as the partial derivative with respect to each input quantity. For the estimation of the uncertainty of the model, the sensitivity coefficients are the equations obtained through a sensitivity analysis with respect to each variable. The combined uncertainty sums the contribution of each input quantity.

Table 3. Uncertainty budget for combined uncertainty estimation.

$\boldsymbol{X_i}$	**[X_i]**	**u(X_i)**	**C(X_i)**	$[\boldsymbol{u}(\,\boldsymbol{Xi}\,)\cdot\boldsymbol{C}(\boldsymbol{Xi})]^{\boldsymbol{2}}$	**SI [%]**
Input Quantity X_i	*Units* X_i	$u(\,Xi\,)$	$\frac{dF}{dx_i}$	$\left(\frac{dF}{dx_i}\right)^2\cdot u(\,Xi\,)^2$	$\frac{[u(\,Xi\,)\cdot C(Xi)]^2}{\max([u(\,Xi\,)\cdot C(Xi)]}$
Combined Uncertainty			$U(\,Y\,)^2=\sum_{i=0}^{N}\left(\frac{dF}{dx_i}\right)^2\cdot u(\,Xi\,)^2$		

The significance index SI, is a way to identify the largest source of uncertainty of the model. Negligible sources of uncertainty are associated to a SI below 1%, while input quantities with SI equal to 100% are the main sources of uncertainty. The latter have a key role in the minimization of the uncertainty of the property estimation.

- *Stability estimation*

The uncertainty of non-stationary processes needs to consider also the stability of the measurements. A stability analysis may be concerned with both the stochastic (noise) and deterministic (systematic) properties of the device under test. The stochastic characteristics of the device are usually considered to be constant. Any possible environmental effect is often best handled by eliminating it from the test conditions. It is also assumed that the frequency reference instability and instrumental effects are either negligible or removed from the data. This approach intends to isolate the stability of the process of interest, as best as possible.

The problem with the deviation stems from its use of the deviations from the average, which is not stationary for most of the divergence noise types. That problem can be solved by instead using the first differences of the fractional frequency values (the second differences of the phase), as described for the Allan variance.

The Allan variance is the most common time domain measure of frequency stability (in clocks, oscillators and amplifiers). Similar to the standard variance, it is a measure of the fractional frequency fluctuations, but has the advantage of being convergent for most types of noise [61]. Data sets for chemical system have usually low density (less than 100 points per interval) and for this reason, a theoretical approach was not developed previously. For high density data set, the analysis is usually based on the frequency domain while the time domain based analysis is reserved for low density data sets by an analogous model [62].

The original non-overlapped Allan, or two-sample, variance (AVAR) is the standard time domain measure of frequency stability.

$$\sigma_y^2(\tau) = \frac{1}{2(M-1)} \sum_{i=1}^{M-1} [y_{i+1} - y_i]^2 \qquad (1)$$

Where y_i is the ith value of the M fractional frequency values averaged over the measurement interval (observation time), τ. The result is usually expressed as the square root, $\sigma_y(\tau)$, best known as the Allan deviation [61]. Calculating the Allan deviation of the different operation conditions of the system, for different observation times, allows to construct a map, where it is possible to observe the magnitude of the stability for different measurement intervals.

- *Process characterization through mathematical modelling*

The modelling and simulation in Computational Fluid Dynamics (CFD) allows the analysis of engineering problems involving transport phenomena by using computer-based simulation [63]. However, the steps to obtain results for an engineering problem are subject to the stages of pre-processing, involving the geometry definition, the grid generation (meshing) and model selection, and then they are followed by the solution and analysis of results.

The theoretical models involved in the process characterization of each part of the primary device, will be created using the CFD software ANSYS Fluent, to analyse the variables of influence that can affect the diffusion rate and the role each variable plays in the diffusion rate and the generator concentration. The CFD modelling involve a series of considerations that can be summarized as shown in Fig. 2 .

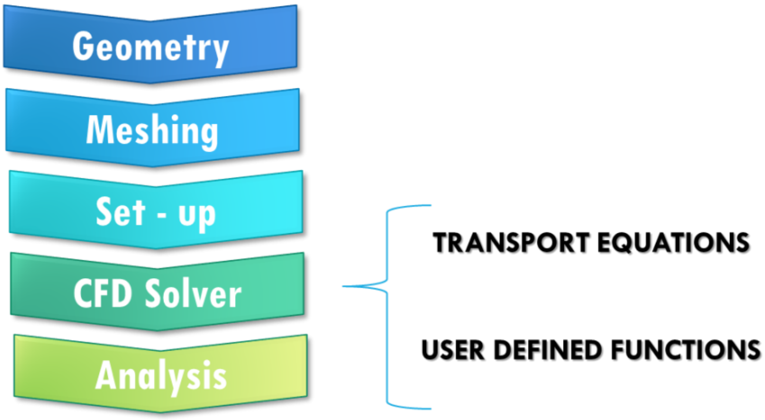

Fig. 2. Methodology involved in the CFD analysis

The considerations for each part of the model development are going to be discussed in the following chapter. On the other hand, to model the adsorption effects, MATLAB was used in combination with CFD to evaluate the dynamic of the system in a simplified way. The use of a mathematical model is not free from uncertainty. In order to verify the results, the uncertainty of the models will be evaluated according to their input quantities variables and eventually compared to the experimental results.

3.4.2. Step 2: Identification of the criteria of interest

Understanding the phenomena involved into every part of the process is key to identifying the variables that need to be considered during the operation of the primary device. After that, through experimental observation and modelling, it is possible to perform sensitivity analysis over the parameters that may affect the performance of the primary device. The main concern in this work, beyond precision and accuracy of the model, is to obtain the sensitivity coefficients of each influence quantity. Quantifying the ratio of change of the diffusion flowrate with respect to every influence quantity is fundamental to identify the major sources of uncertainty. The ability to evaluate the uncertainty can result into a better accuracy of the reference standard, that matches the targets mentioned early [26].

3.4.3. Step 3: Realization and Performance Evaluation

In order to design a new device, it is necessary to start by defining the limitations or requirements to be considered. In this case, it is important to meet the size, capacity and target concentrations imposed at the beginning of the project. With these considerations in mind, the design of the different parts can be done.

The vial system, is where the generation takes place. To meet the requirements imposed, it should be refillable, sealable to guarantee zero leakages and kept at a constant temperature. The dilution system, that allows to obtain low concentration mixtures, should guarantee a good quality mixing of the VOC generated into the carrier stream.

With the procedures defined to obtain the design criteria, it will be possible to define every part of the device. A subsequent metrological characterization and evaluation of the reproducibility will give us insights into the performance of the constructed device, with respect to the primary one.

CHAPTER 4

Characterization of the dynamic primary preparation of reference VOC mixture

The first step is the characterization of the dynamic primary system. A scheme has been prepared to illustrate the way it works, followed by the modelling process, the uncertainty analysis and the stability. Evaluating the metrological performance and identifying how the operational conditions influence the preparation of the mixtures, sets the targets to be considered in the design of each part of the transportable device.

4.1. DESCRIPTION OF THE SYSTEM

The dynamic preparation device can be used to generate fresh references mixtures based on the diffusion method. The device can be separated into two main sections, the generator and the dilutor. The generation is based on the diffusion through stagnant flow phenomenon and is done with the use of a carrier stream through a calibrated diffusion cell containing the VOC, while the dilution is made in a single stage with purified air.

The Fig. 3 in the next page represents a scheme of the whole VOC standard preparation system, which can be separated into two sections, generation and dilution, being the first one the objective of this work. A purified air stream (ϕ_1 of 10 – 25 Sl.min^{-1}) with an initial VOC concentration ω_A, is mixed with the VOC diffusion flow rate (D_R of 0.1 – 1 µg.min^{-1}) from the cells, which is carried by purified air (ϕ_C around 50 Sml.min^{-1}).

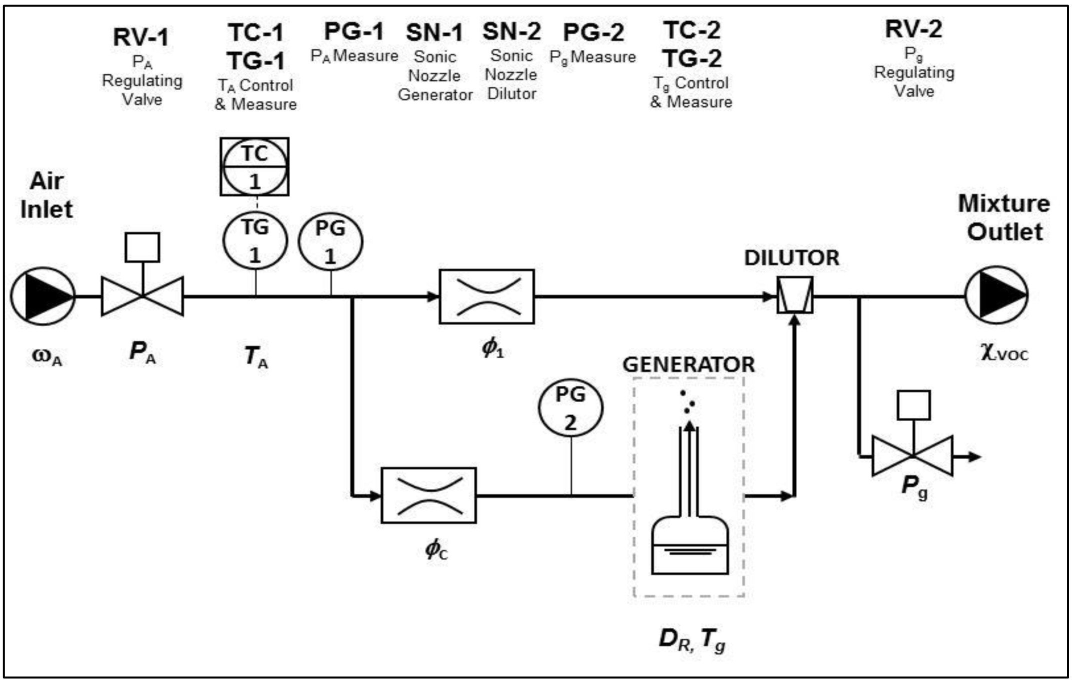

Fig. 3. Dynamic standard preparation scheme

The air flow rate to the system is controlled in pressure (RV-1) and temperature (TC-1) to regulate flow rates (ϕ_1 and ϕ_C) across sonic nozzles, while liquid VOC and the diffusion vial are controlled in temperature (TC-2) to regulate diffusion flow rate D_R. The generator pressure (PG of 45-800 Pa as relative pressure) is regulated by a valve (RV-2) at the end of the dilutor line.

4.2. PROCESS CHARACTERIZATION OF THE GENERATION SECTION

The Fig. 4 shows a cell scheme, with air carrier at the inlet and the VOC mixture at the outlet, and the detail of the limit conditions set in the diffusion vial. The molar fraction of VOC at the inlet of the vial neck is calculated as the ratio between the vapour pressure P_V and the generator pressure P_G, based on the assumption that the gas phase inside the VOC reservoir is saturated at the generator temperature.

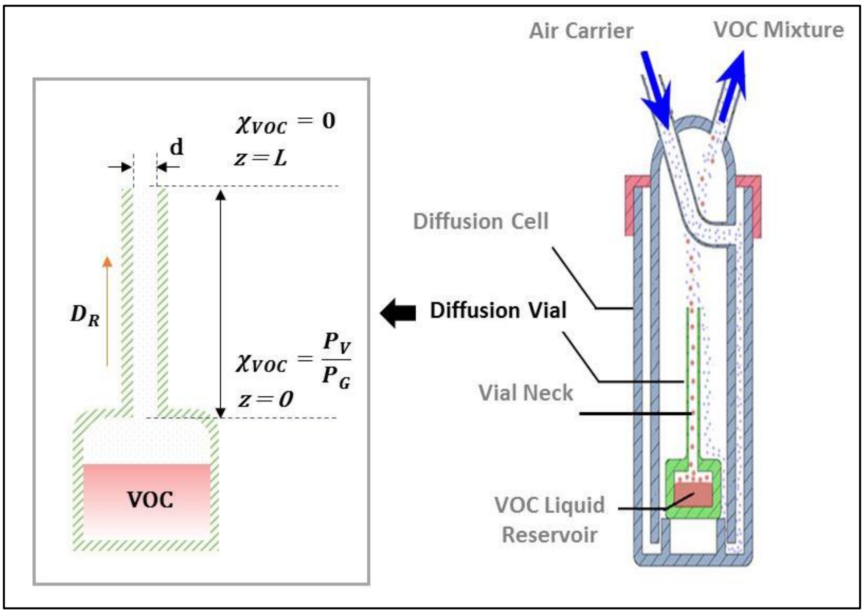

Fig. 4. Generator Cell Detail: Diffusion across Vial Neck

The carrier flow rate is kept stable and constant by means of a calibrated sonic nozzle. The temperature of the thermal bath, in which all the diffusion cells are immersed, is controlled to be at 25°C, with a variability below 0.01 K.

The liquid VOC contained in the reservoir is stagnant and kept at constant temperature. The gas phase on the liquid reservoir is considered to be saturated of the VOC. The VOC transfer from the liquid reservoir obeys diffusion laws, and takes place from the liquid surface to the tip of the vial. The carrier flow entering into the cell, "cleans" the tip of the vial, and creates the generated mixture, as it exits the cell-vial system.

4.3. MODELLING OF THE GENERATION SECTION

To model the generator section, along with the transport equations system of the CFD software (including the continuity, energy and momentum balance), a mass balance was applied across the vial neck between the entrance and the exit, where the Fick's law was used [64]. The gas phase on the liquid reservoir is considered to be saturated, and the model corresponds to a VOC diffusion through stagnant air. The species model with inlet diffusion was applied, defining the gas body as a mixture, while the liquid body was defined as pure liquid acetone.

At the gas-liquid interface, the mass transfer from the liquid phase to the gas phase had to be taken into account, with the respective thermal effect over the liquid reservoir. In this case, the boundary condition was defined as a set of coupled walls, with a molar fraction χ_i for the gas side and a heat flow rate set in the liquid side.

The definition of a molar fraction corresponding to the saturation condition at the wall, allowed the software to perform the calculation of the species balance considering Fickian diffusive transport. The following equation is the result of applying the Fick's Law across the vial neck, as a function of the partial pressures in each point, where the diffusion flow rate D_R is written as a function of geometrical parameters such as diameter of the neck d, the length of the neck*:* the properties of the VOC, including the diffusion coefficient D_{VOC}, the molecular weight MW_{VOC} and the vapour pressure p_v; and the conditions of pressure and temperature, both inside of the vial (p_G and T_G respectively) and at the exit of the vial neck (*pL)*, where the molar fraction χ_{VOC} has been defined theoretically as 0. The universal gas constant *R* and π are also included in the equation.

$$D_R = \frac{D_{VOC}\,\pi\,d^2 MW_{VOC}\,p_G}{4\,L\,R\,T_G} \cdot \ln\left(\frac{p_G - p_L}{p_G - p_v}\right) \tag{2}$$

The parameters needed to calculate the diffusion flow rate – interphase temperature, molar fractions at the inlet and outlet of the neck – were read using a User Defined Function (UDF). The resulting diffusion rate was used to calculate the heat transferred from the liquid due to the phase change.

The diffusion flowrate was also used to define a mass source term, used to close the continuity balance. The reason is that the diffusive transport given by the molar fractions is calculated by the species transport equation and is not included into the continuity equation of the CFD software.

At each iteration, the heat transferred from the liquid and the diffusion flowrate were assigned. The first one, at the liquid side of the wall-wall boundary condition, while the source term was included in the cell layer adjacent to the gas side of the wall.

With this conditions, the solver of the CFD software performed further heat and mass transfer calculations over the whole domain. This process continued until convergence of all the balances. Fig. 5 represents a simplified flowchart on how the UDFs are integrated into the CFD solver (ANSYS Fluent). The use of this method gives as result a CFD model that considers the combined effect of the premises considered by the theoretical model showed above and the fluid dynamics calculations made by the software.

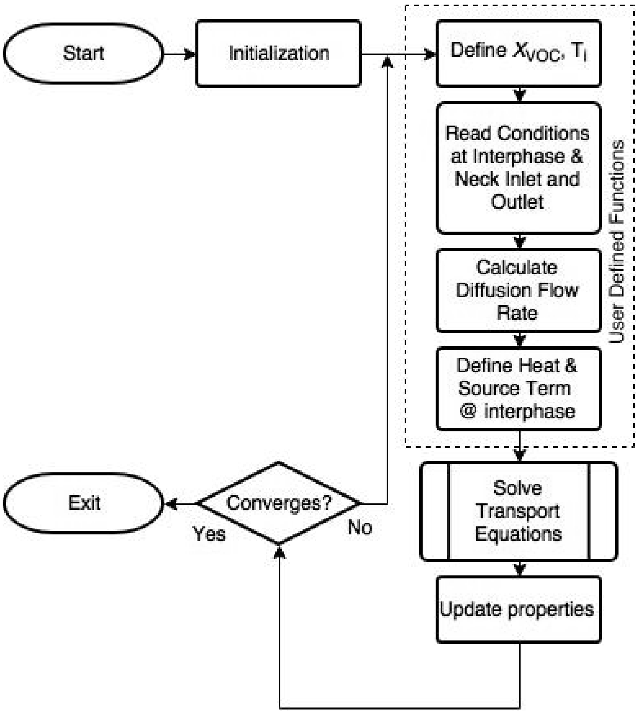

Fig. 5. Simplified Flowchart for ANSYS Fluent Calculation

4.4. VALIDATION OF THE MODEL

To validate the model for the generation, six vials with two different nominal sizes were considered (See Table 4). The chosen VOC for this case study was Acetone.

Table 4. Vials used in experimental data generation

Vial Size	Neck (Nominal) [mm]	Reservoir (Nominal) [mm]	D_R @ 26°C (Nominal) [$\mu g.min^{-1}$]	# Vials
1	Length 100 Diameter 0.55	Length 30 Diameter 25	1	3
2	Length 50 Diameter 1.2	Length 60 Diameter 25	15	3

Three vials (nominal size 1) were designed to generate 1 μg min^{-1}, while the other three (nominal size 2) were designed to generate 15 μg min^{-1} of Acetone (nominal diffusion flow rates at 26 °C). These vials were weekly weighed for 10 month at 26°C and 35°C. Diffusion rate was calculated as a mean over 5 months of 4 weeks each. The standard deviation was calculated to be 1% and 0.2% for 1 and 15 μg min^{-1} nominal diffusion rate respectively. The characterization of the two existing vials was made and the results were used to evaluate the performance of the theoretical model. The effects of the temperature and geometry on the diffusion flow rate were calculated using the CFD model and compared with the experimental results.

Four experimental set ups were considered for validation (Vials sizes 1 and 2 (See Table 4) with acetone at 26°C and 35°C). For the comparison, a sensitivity analysis of the CFD model over the temperature was made for each vial size. The comparison between experimental and CFD model results for each vial configuration, are shown in the validation charts (see Figures Fig. 6 and Fig. 7).It can be observed that the simplified CFD model developed is able to predict the diffusion rate considering the thermal effects for different geometries.

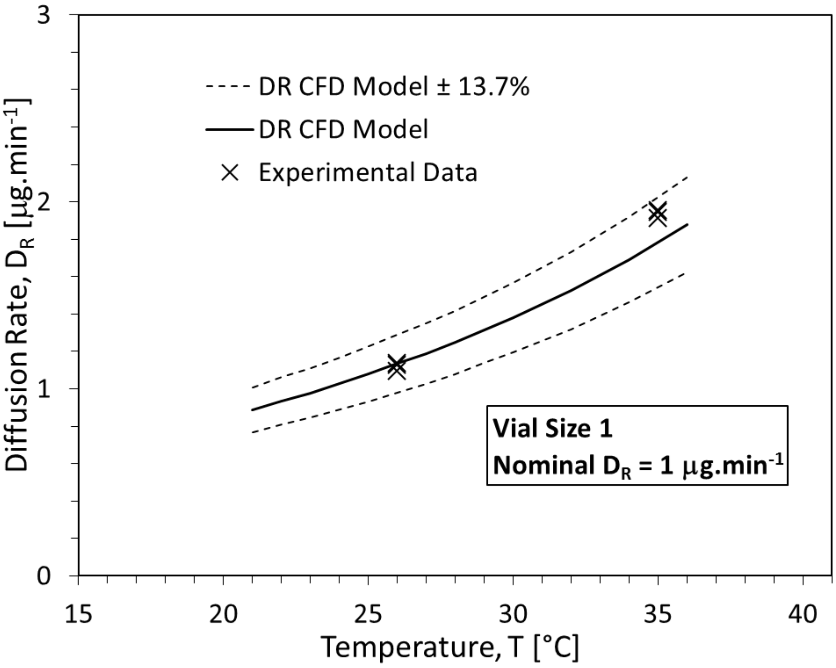

Fig. 6. Model validation for Vial Size 1.

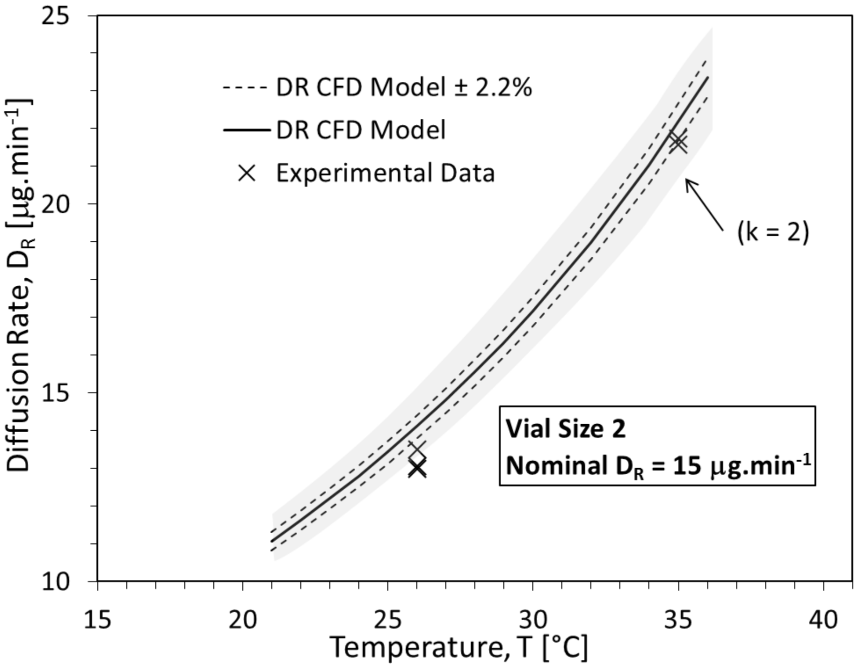

Fig. 7. Model validation for Vial Size 2.

The uncertainty evaluation of the CFD model was performed over the four cases. The sensitivity coefficients calculated from the CFD model and the conditions of each generation were used to determine the uncertainty of each predicted value. The influence quantity with the highest contribution to the uncertainty was the diameter of the vial neck. Its contribution to the combined uncertainty of the diffusion rate D_R was due to the uncertainty of the measurement. Using an instrument with a resolution of the order of 1 µm would minimize the combined uncertainty of the diffusion rate D_R to 5.2% and 0.5%, for vial size 1 and 2 respectively.

4.5. PROCESS CHARACTERIZATION OF THE DILUTION SECTION

As shown in Fig. 3 in section 4.1, a purified air stream (ϕ_1 of 10 – 25 Sl.min^{-1}) with an initial VOC concentration of ω_A, conditioned the system to have a constant and stable flowrate. After, the sonic nozzle is used to dilute the generated mixture coming from the generator, which represents the VOC diffusion flow rate (D_R of 0.1 – 1ug.min^{-1}) from the cells, carried by purified air (ϕ_C around 50 ml.min^{-1}).

The mixture of the two streams can be modelled and defined from the global species mass balance. The Fig. 8 shows the scheme of the whole generation system, where the dilution section is represented by the volume of control 2. The mass balance made over the whole system, allows to obtain an equation of the mass fraction of the VOC in the standard mixture, which is considered as measurand for the analysis of the mixing.

The mass balance allows to determine the molar fraction of each species in the mixture stream in steady state.

In the "Generation" section, the diffusion rate D_R is the amount of pure VOC per unit time that is transferred by diffusion to the carrier flow ϕ_C. The "Dilution" section, receives the mixture ϕ_G and the dilution air flow ϕ_1, to obtain the final mixture ϕ_D. The leak flow rate ϕ_L, is considered as a single stream for the whole system with the maximum concentration of VOC (ω_G) [54]. The VOC losses due to wall interactions (specifically adsorption) are also considered in the form of a global loss, ϕ_W.

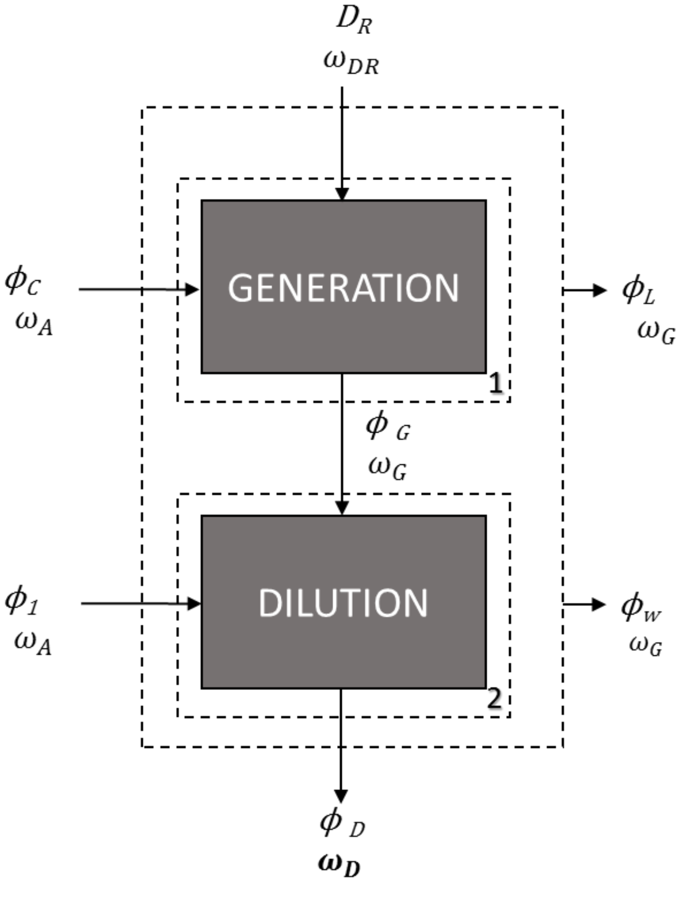

Fig. 8. Mass Balance of standards mixtures generation system [54]**.**

The molar fraction of VOC in the prepared standard mixture is the measurand, i.e., the quantity to be measured. The analysis of the influence quantities can be performed by the sensitivity analysis of a model based on material balance. Separated generation and dilution sections were considered as sketched in Fig. 8 in which Diffusion rate, carrier flow rate, air flow rate, air purity, leakage flow rate and VOC adsorption rate on walls were included. The “Generation” part is where the diffusion rate D_R is transferred by diffusion to the carrier flow ϕ_C. ω_{VOC} is the VOC concentration in the diffusive flow. In the “Dilution” part, the mixture ϕ_G is diluted to obtain the reference mixture, with a flow rate equal to ϕ_D. A leak can occur at any point of the system, but the flow rate ϕ_L in the material balance is considered as a single stream for the whole system even if the amount of VOC in the leak flow rate depends on the point of emission (and its local molar fraction). For a conservative approach the highest concentration of VOC (ω_G) is considered as worst case, i.e. the concentration in the generator section.

The global mass balances for the generation and dilution sections are respectively:

$$\left(\frac{D_R}{\omega_{VOC}}\right) + \phi_C = \phi_G \qquad (3)$$

$$\phi_G + \phi_1 = \phi_D + (\phi_W + \phi_L) \qquad (4)$$

The diffusion rate (D_R) and the amount of VOC adsorbed per unit time (ϕ_W), are much smaller than the air flow rates ϕ_C and ϕ_1 respectively, so the terms in the brackets can be neglected in the global mass balance equations.

The VOC mass balances for the generation and dilution sections are respectively:

$$D_R + \omega_A\phi_C = \omega_G\phi_G \qquad (5)$$

$$\omega_G\phi_G + \omega_A\phi_1 = \omega_D\phi_D + \phi_W + \omega_G\phi_L \qquad (6)$$

Where ω are the VOC concentration in air ($_A$), in the generator downstream ($_G$) and in the dilutor downstream ($_D$), expressed as mass fraction [g g^{-1}]. In the last two equations D_R and ϕ_W are not negligible.

Inclusion of mixing effects

The application of the global and component balances, gives as result the equation of the measurand, the molar fraction of VOC in the standard mixture, which in this case has been multiplied by a factor M_P, representing the quality of the mixing as a probability (perfect mixing being 1). This factor provides the whole range of molar fraction that can be observed in a section of tube, according the degree of mixing. The following measurand equation results

$$\chi_{VOC} = M_P \left[\frac{MW_M}{MW_{VOC}} \cdot \frac{(D_R + \omega_A \cdot \phi_C) \cdot (\phi_C - \phi_L) + (\omega_A \cdot \phi_1 - \phi_W) \cdot \phi_C}{\phi_C \cdot (\phi_C + \phi_1 - \phi_L)} \right] \tag{7}$$

It can be used to evaluate the uncertainty and validate the results of the CFD model but does not provide information about the mixing. A detailed study can be carried out from Navier-Stokes equations [64], to determine the concentration profile across the pipe, a tedious calculation that can be easily done using software and CFD tools.

The typical time of the dilution remains below 1 min, so it is recommended to clean the system for 20-30 min to reach the equilibrium before the sampling is made. This way, the possible VOC losses can be minimized, assuring the stability of the VOC molar fraction of the sample.

Leakages quantification

Leakages can be usually reduced to a negligible value as different kind of seals can be used to guarantee non reactivity, closure and reliability of closure. The seal introduces a new surface for wall interactions and an opportunity of leakage. If the seal must be opened/closed during operations it represents a very important source of risk of leakage. A leakage can represent an important source of uncertainty [3] especially in the connections and lines downstream the outlet of the diffusion vial.

The use of glass as inert material to avoid VOC losses due to wall interaction, can carry leakages problems and should be cautiously considered. An option to assure reliable seals is the use of metallic elements for connections but this increases the risk of wall interactions. However, in such a case, the absence of reactions between the VOC and the wall material must be guaranteed. Reactions between different metals and VOCs under the generation conditions are not well documented and for this reason the choice of any metallic material should be subject to further analysis.

A good compromise for this case, can be reached by using treated steel, like Siltek® / Sulfinert® treatments, which provide an inert silicon-based coating that reduces surface adsorption in stainless steel till a level close to the one of glass.

The determination of the leakage flowrate ϕ_L is based on an experimental test, which detail has been explained by Sassi et al (2015) [54]. The average leakage flow rate ϕ_{L} is related to the pressure decrease by a mass balance done over the reference volume between the start and the end of the test. Since leakage flow rate is proportional to relative pressure, the test value was multiplied by the relative pressure ratio at test and working conditions to refer the test results to working conditions.

$$\phi_{L,w} = \frac{V}{t}\left(\frac{P_i}{T_i} - \frac{P_f}{T_f}\right) \cdot \frac{P_w}{P_i} \cdot \frac{MW_M}{R} \tag{8}$$

Where V is the reference volume on which the test is performed, t is the test period, P and T are the absolute pressure and temperature, $_i$ and $_f$ subscripts refer to initial and final values respectively, $_w$ subscript refers to working conditions, MW_M is the molecular weight of the mixture, which in this case (due to the low molar fraction) can be approximated to the molecular weight of air MW_A, and R the universal gas constant. The reference volume was calculated, from the pressure variation due to the injection of a known amount of gas by a syringe, by the mass balance on the reference volume before and after injection:

$$\mathrm{V} = \frac{P_i V_i}{T_i} \cdot \left[\frac{T_{sf} T_{si}}{P_{sf} T_{si} - P_{si} T_{sf}}\right]_s \tag{9}$$

The reference volume V is the amount of air in the system volume at initial system conditions T_{si} and P_{si}. V_i is the amount of air in the syringe volume at initial syringe conditions T_i and P_i. T_{sf} and $\underline{P_{sf}}$ represent the system final conditions. The dead volume of the measuring system was considered as a part of the total system volume. To perform the leakage flow rate measurement, the reference volume V have to be isolated by ball valves and connected to the pressure measurement device. The reference volume must be measured and the initial pressure have to be reached by air inflation.

Leakage is generally very low and over a short time a pressure decrease cannot be observed, only accidental leakage can be observed and should be reduced before generation [54]. The conditions of the leakage test are: specific test pressure, duration and volume have to be chosen in order to quantify the leakage flow rate by the previously described method. Since the generator performances are affected by the pressure variation, two reference volumes were considered to avoid high pressure exposure of the generator over a long time, i.e., generator volume and dilutor volume.

In a closed system, no pressure drop should be observed over the test duration. The minimum possible pressure reduction should be equal to the uncertainty of the pressure measurement of the system. The maximum possible leakage flow rate at test conditions can be calculated by Equation (9), and introduced into the equation 10 as the uncertainty of the leakage flow rate. To set a negligible contribution to the total uncertainty of VOC molar fraction in the mixture, a threshold value was calculated for the uncertainty of leakage flow rate, i.e., leakage flow rate significance index equal to 1%. The minimal test duration t can be calculated from the Equation (9) at the threshold value for the flow rate uncertainty $u(\phi_L)$. For an isothermal test:

$$t = \frac{u(p)}{u(\phi_L)} \cdot \frac{V}{T} \cdot \frac{p_w}{p_{test}} \cdot \frac{MW_A}{R} \tag{10}$$

where $u(p)$ is the uncertainty of the pressure measurement system; p_{test} is the relative pressure at which the test is performed; p_w is the working relative pressure; $u(\phi_\mathrm{L})$ is the target uncertainty for the leakage flow rate. The initial relative pressure must be much higher than the working pressure to assure a conservative value for the measured leakage flow rate. Nevertheless, the test pressure must be chosen to avoid perturbations to the system devices and their performance. If no pressure drop is observed over the test duration *t*, the leakage contribution is negligible [54].

Effects of wall interactions in the dynamic generation of standard gas

---

Wall interactions can be of physical nature, such as adsorption with the consequent permeation or sink effects, and/or chemical reactions. Sorption phenomena, depends on many factors, including properties of VOCs, properties of the substrate, VOC concentration, temperature, humidity and air velocity [65]. The effect of wall interactions can be relevant for this section [66]. A specific study is necessary to quantify interactions because few data are available in literature [54]. Among these factors, the characteristic time in which the sorption phenomena occurs is particularly important. It can help to define whether the phenomenon should be considered or neglected, with respect to the time in which the process of interest takes place.

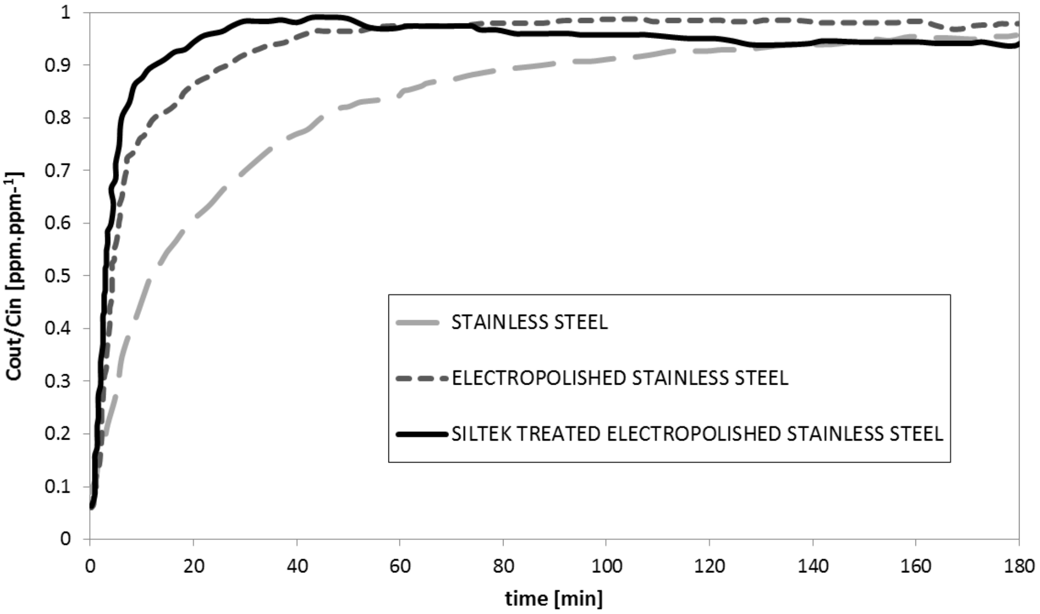

Fig. 9. Adsorption kinetics of treated and untreated steel with moisture air (1 μmol.mol^{-1} of water) [67]**.**

Fig. 9 shows data for wet up process (adsorption of water) for different materials, such as untreated stainless steel, electro polished stainless steel and Siltek® treated stainless steel.

From the figure, it can be noted that the time required to arrive to the saturation condition at the wall can vary from approximately 30 min to 140 min for Siltek® treated steel and untreated stainless steel, respectively. The model of the dilutor considers the use of Siltek® treated steel and does not take into account the effect of wall interactions, even if they can be relevant for this section, [66] as the characteristic time of the dilution remains below 1 min. As mentioned before, to avoid undesirable effects, it is recommended to clean the system with zero air for 20-30 min to reach the equilibrium before the sampling is made. This way, the possible VOC losses can be minimized, assuring the stability of the VOC molar fraction of the generated gas mixture.

Additional considerations should be taken into account in the design process if a different material is used. The maximum adsorbed mass can be estimated using the concentration profiles inside the system and the properties of the VOCs generated. The estimation of the maximum rate of adsorption can help in defining the maximum area of contact that minimizes the contribution of this phenomenon to the molar fraction uncertainty [66].

Investigate the adsorption/desorption effect that occurs when a stream of VOCs gas mixtures passes on the surface of various materials is important to minimize the uncertainty. Especially in the walls of the pipes used for sampling and in the dynamic generation system. This section describes the principles of the model developed, using a case study to illustrate the results obtained and how they can be applied in the estimation of the uncertainty associated to wall effects during sampling or generation.

4.6. MATHEMATICAL MODEL

The system to be modelled is a simple cylindrical pipe that carries a gas stream containing the VOC of interest, at a certain concentration, mass flow rate and temperature. The pipe surface is considered to be smooth, making the area of contact equal to the geometrical surface area of the cylinder. The same pipe, was modelled in two ways: following a CFD approach that considers all the transfer phenomena that affects the stream, and a simplified unidimensional model. Different considerations were taken for each case. Fig. 10, shows a diagram of the geometry of interest in this case.

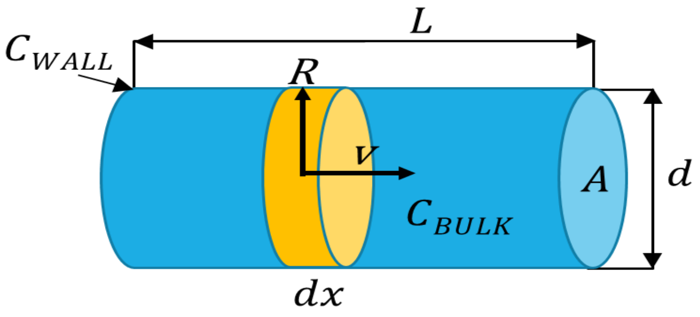

Fig. 10. Geometry considered for modelling of VOC-surface interactions.

The fluid dynamics inside the pipe, can be solved by applying the differential balances of momentum, mass and energy inside of the tube. The Computational Fluid Dynamic software ANSYS Fluent allows to solve the balances inside the pipe in a rigorous way. The numerical error depends mainly on the choice of the mesh, the maximum residual allowable and the integration time in the case of transient simulation.

The gas stream inside the pipe carries a concentration of VOC that is subject to different VOC-surface interactions. The interaction starts with a surface adsorption and depending on the conditions and nature of the wall material, can lead to another type of interaction, as permeation through the porous wall and/ or reaction. Adsorption, reactions and permeation/sink effects involve a loss of VOC that needs to be quantified, as it represents a source of uncertainty on the generated mixture concentration.

Considering the adsorbed mass as the product of a first order reaction, the rate of VOC loss can be expressed as in Eq. (11) [68]:

$$R = \frac{\partial C}{\partial t} = K_{ads}\,(C_{VOC} - C'_{VOC}) \qquad (11)$$

Where R, which is the rate of adsorption, depends on both the concentration difference between the bulk and the wall and a constant of adsorption K_{ads}.

The quantification of the adsorption can be done in a rigorous way by introducing a source term in the differential mass balance of CFD [63]. In this way, the evaluation of the differential mass balance can be done at every element of the mesh, providing a profile of concentration along the tube that changes with time as the wall reaches the saturation. Equation 12, shows the partial derivative equation (PDE) that represent the mass balance in two dimensions applied by CFD for the problem of interest.

$$\frac{\partial \rho}{\partial t} = -\frac{\partial (v_x \rho)}{\partial x} - \frac{\partial (v_r \rho)}{\partial r} - \frac{v_r \rho}{r} + R \cdot dV \qquad (12)$$

However, the computational cost of solving the problem with CFD is high, and to optimize the time a simplified solution has been developed. The mass balance in one dimension showed in Eq.(13) introduces the term of effective diffusion as a measure of the back mixing inside of the pipe. The adsorption rate is calculated with the same kinetic equation. The combination of CFD capabilities and the numerical solution of Eq. (13) allows the simulation of the adsorption phenomena that takes considerably less time. The solution obtained from the model can be used to determine the value of the constant of adsorption K_{ads} from a regression with experimental data.

$$\frac{\partial y}{\partial x} = -v\frac{\partial y}{\partial x} + \mathcal{D}eff\frac{\partial^2 y}{\partial x^2} - R \tag{13}$$

4.6.1. *Estimation of parameters: Effective diffusion and Adsorption constant*

The unidimensional model considers that a single block of fluid moves at a certain velocity and does not interact with the adjacent fluid. The term of effective diffusion introduces the back mixing effect that takes place inside the real pipe. The CFD offers a reliable solution for this problem and for this reason is used to determine the fluid dynamics effect without any wall interaction. Using the real geometry and conditions of the experiment, a CFD simulation is performed and the concentration at the outlet as function of time is obtained.

An initial value of effective diffusion is used to generate a solution of Eq. (13) (with $R = 0$). At this point a regression to minimize the sum of squares of the result of Eq. (13) and CFD is done, changing the parameter of effective diffusion until the error is minimized. The Fig. 11 represents the analysis involved in the estimation of both parameters, D_{eff} and K_{ads}.

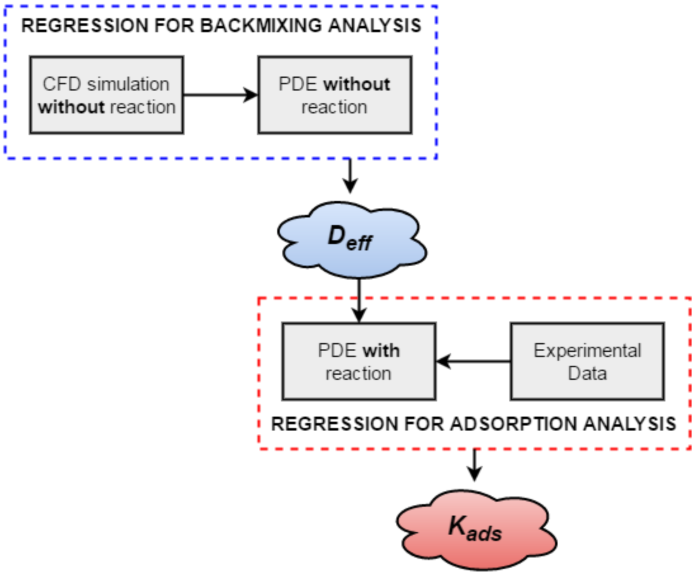

Fig. 11. Simplified Model for estimation of the VOC-surface adsorption.

After an effective diffusion is obtained, the simplified model is instructed to reproduce the fluid dynamic behaviour of the pipe, and at this point an estimation of K_{ads} is possible. A similar procedure to estimate the effective diffusion is done. Experimental data is directly compared to the results of the simplified model, changing the K_{ads} to minimize the sum of the squares of the concentration at the outlet of the pipe. When the error is minimized (below a value of tolerance defined), the value of K_{ads} is considered to be the right value.

4.6.2. Experimental setup for adsorption analysis and case study

The data used as input for the model is the measurement of concentration at the outlet of the test tube. Different conditions should be considered: the quality of air, the frequency of measurement, the stability of the conditions, the internal area of the test tube and the observation time and system. The latter two have the greatest influence on the quality of the data generated, as a short tube, for which the area is small and the time of observation is short, reaches the saturation immediately. This results in a steep saturation curve that decreases the amount of points available for the regression and the accuracy of the K_{ads} estimation.

Fig. 12 shows the typical experimental setup, with the influence quantities considered as input variables for the model.

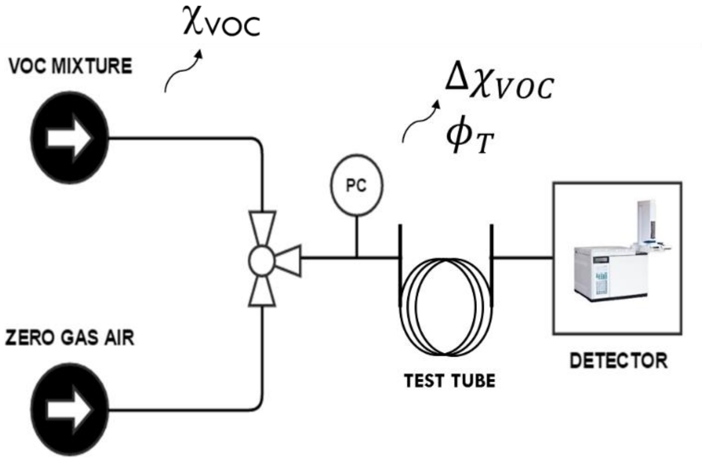

Fig. 12. Typical setup for wall interaction analysis.

As case study, a preliminary analysis of data generated by the system of Deutscher Wetterdiens (DWD) was done. Specifically, the results of an experiment of adsorption over Sulfinert® were analysed. The conditions of the experiment that are considered as input data for both the CFD analysis and the K_{ads} estimation, are summarized in the Table 5.

Table 5. Input parameters for the case study

Parameter	Value
Material	Sulfinert ® passivated 304 stainless steel
Internal Diameter	2.159 mm
Length of test tube	10 m
Temperature	50°C
Pressure	inlet 925 mbar, outlet 905 mbar
Mole Fraction @ inlet	3 µmol mol^{-1}
Mass Flow Rate	15 SmL min^{-1}

The CFD simulation under the conditions shown above was performed. The obtained results were compared to the simplified model results. Fig. 13 shows the result of the regression, where the curve plotted represent the better approximation to the CFD results. In the process of regression the curve of CFD was compared with those generated by the simplified model after minimization of the error. The error function to be minimized was the sum of the squared difference between the CFD and the corresponding "Simplified" concentration at a particular time.

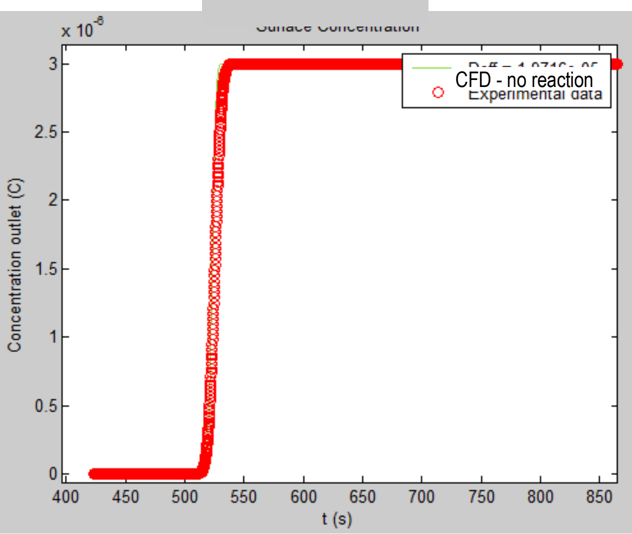

Fig. 13. Outlet concentration: CFD Simulation (no reaction) vs Simplified Model response.

After the calculation of the effective diffusion i.e. the experimental results (without data treatment) were compared to a simplified model including the reaction term. The result from the regression can be observed in Fig. 14. The regression process was similar to the one used for obtaining the effective diffusion. The error function to be minimized was the sum of the squared difference between the simplified model and the experimental data at a particular time. The quality of the regression for both cases depends on the value of the tolerance and other conditions such as the maximum change allowable of the parameter that is being calculated. Another important issue is the quality of data. A proper data treatment for suppression of noise could improve the process of regression at a cost, in terms of uncertainty, that should be evaluated.

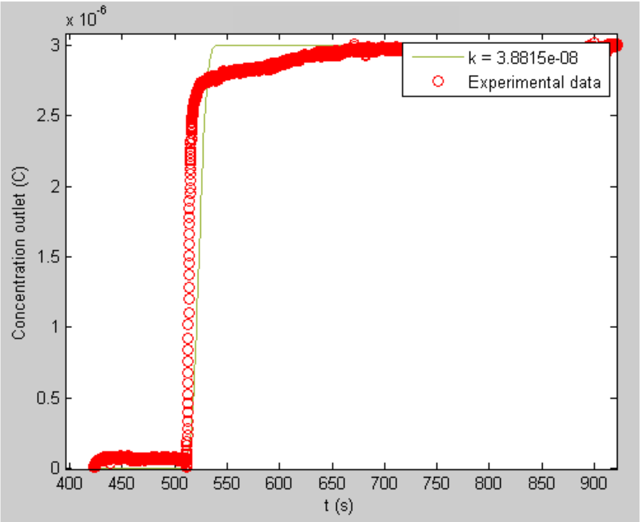

Fig. 14. Outlet Concentration: Experimental data vs Simplified model with reaction.

Purity of zero gas stream

INRIM provided the measurements of the purity of the zero-gas used in the generation and dilution. Zero gas stream corresponds to an air stream that is purified and compressed in the laboratory. Measurements were carried out by gas chromatographic measurements. The measured methanol impurity was used as mean value and the standard deviation of consecutive zero-gas analysis is considered as standard uncertainty. The analytical signal is the peak area of the interfering impurity, at methanol retention time, filtered by the system blank. For the purpose of this work, a null mean value for methanol impurity was considered, 300 pmol.mol^{-1} is obtained as standard uncertainty. For the only purpose of comparison, in Fig. 15 a typical GC analysis of a mixture of Methanol-Ethanol-Acetone at different molar fraction, prepared in cylinder zero-air flow with the dilution system previously described, is reported.

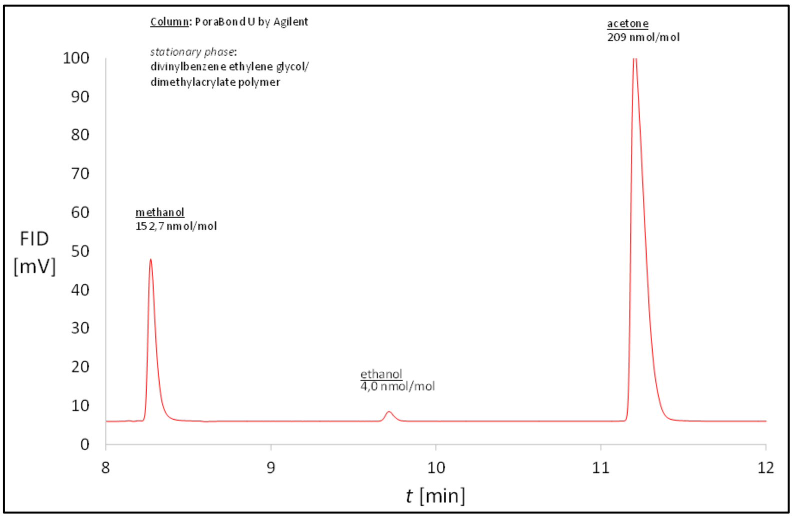

Fig. 15. Typical GC analysis of a mixture of Methanol-Ethanol-Acetone prepared in cylinder zero-air flow with the dilution system previously described

Uncertainty analysis

The uncertainty analysis has been done over the diffusion rate and the molar fraction of the mixture, separately. Preparing an uncertainty budget for the generation and the dilution part, allows to identify the most relevant contributions to the uncertainty. The highest source of uncertainty of the reference mixture molar fraction was the diffusion rate. For this reason, an uncertainty analysis over the diffusion rate allows to identify the most significant contributions in the minimization of the uncertainty of the reference mixture.

4.7. UNCERTAINTY BUDGET OF THE DIFFUSION RATE

As described in Chapter 3, the uncertainty budget is a tool used to provide insights on the uncertainty of a measurand. The contribution of each uncertainty source is reported and the evaluation of the combined standard measurement uncertainty is done following the GUM method [60].

For the diffusion rate analysis, an experimental model based on previous work [69], including the effect of buoyancy and vial cooling during the weighing process (see Eq. (16)), was used. The CFD model sensitivity coefficients were used to propagate the uncertainty of each source, as the computational model was able to model the thermal effects in a precise way. The following tables, correspond to two uncertainty budgets for the generation of acetone in dry air. In both cases, the gravimetric method was used, however, different vials and consequently, different sensitivity coefficients were employed.

Table 6. Uncertainty budget for low diffusion rate.

X	[X]	x	u(x)	u(x)/(x)	I_S [%]
Δm	g	0.01	3.81E-04	3.8%	100.0%
Δt	s	604800	255	0.0%	0.0%
Δm_B	g	-3.87E-04	8.25E-05	0.8%	4.2%
Δm_C	g	0	6.32E-07	0.0%	0.0%

X	[X]	x	u(x)	u(x)/(x)	I_S [%]
p_{mean}	Pa	98000	58.3	0.1%	63.9%
p_{actual}	Pa	101325	58.3	0.1%	0.0%
p_{VOC}	Pa	32153.7	642.5	2.0%	0.0%
ω_{VOC}	$g.g^{-1}$	1.0	0.0	0.1%	4.7%
dp_{actual}	Pa	0	50	0.0%	0.0%
dT_{actual}	K	0	0.02	0.0%	2.7%
D_R	$\mu g.min^{-1}$	**0.96**	**0.048**	**5.0%**	(k = 1)

Table 6 (Cont.). Uncertainty budget for low diffusion rate.

Table 6 is the uncertainty budget of the generation of 1μg.min^{-1}. The main source of uncertainty is given by the mass measured every 7 days (*Δm*), followed by the vapor pressure of the substance (p_{VOC}) and the buoyancy correction (Δm_B). The uncertainty of the mass measurement and of the pressures (p_{mean}, p_{actual}) depend on the available instruments, while the purity of the acetone (ω_{VOC}) is given by the reference material supplier. The vapour pressure instead, is a value calculated using Antoine equation based on Ambrose [70]. Since the uncertainty of the value given by the calculation was not reported, it has been calculated from the experimental data using a non linear regression, obtaining a 2% uncertainty when the uncertainty of the liquid temperature is 0.2%.

The correction for the thermal effect (Δm_c) included in this case, is the corresponding for the expression of high diffusion rate. This gives a conservative estimate of the mass perturbation.

Table 7. Uncertainty budget for high diffusion rate.

X	[X]	x	u(x)	u(x)/(x)	I_S% [%]
Δm	g	0.15	3.81E-04	0.3%	100.0%
Δt	s	604800	255	0.0%	0.0%
Δm_B	g	-3.87E-04	8.25E-05	0.1%	4.2%
Δm_C	g	0	6.32E-07	0.0%	7.7%
p_{mean}	Pa	98000	58.3	0.1%	63.9%
p_{actual}	Pa	101325	58.3	0.1%	7.9%
p_{VOC}	Pa	32153.7	642.5	2.0%	0.0%

X	[X]	x	u(x)	u(x)/(x)	I_S% [%]
ω_{VOC}	$g.g^{-1}$	1.0	0.0	0.1%	4.7%
dp_{actual}	Pa	0	50	0.0%	0.0%
dT_{actual}	K	0	0.02	0.0%	2.7%
D_R	$\mu g.min^{-1}$	**14.37**	**0.1**	**0.3%**	(*k* = 1)

Table 7 (Cont.). Uncertainty budget for high diffusion rate.

A higher diffusion rate is reported in Table 7. Also in this case the two greatest sources of uncertainty correspond to the mass measurement (Δm) and the vapor pressure (p_{VOC}), however in this case a relevant contribution is given by the mass perturbation due to the thermal effect (Δm_c). At even conditions of cooling velocity, the vial with the greatest diffusion flowrate shows a higher uncertainty that needs to be taken into account.

The variability of the temperature for both cases includes the effect of the stability in the observation time and a maximum variability associated to the liquid level. The latter has been calculated as the temperature variability between the minimum and maximum liquid level of a vial filled with acetone. The pressure variability accounts only for the variability of the atmospheric pressure calculated with the Allan algorithm [71], which is dependent on the time of observation.

A summary of the uncertainty analysis made for the generation system is presented in Fig. 16. For different diffusion rates, an uncertainty budget was carried out. The contribution that each source has on the overall uncertainty can be observed as a function of the diffusion rate. The most important uncertainty sources to consider to improve the accuracy of the diffusion rate are the mass and the vapour pressure. However, the accuracy and stability of the atmospheric pressure become relevant beyond 15 $\mu g.min^{-1}$. It is important to notice that increasing the days between mass measurements improves the accuracy of the mass but is detrimental to the stability of the pressure and temperature measurements.

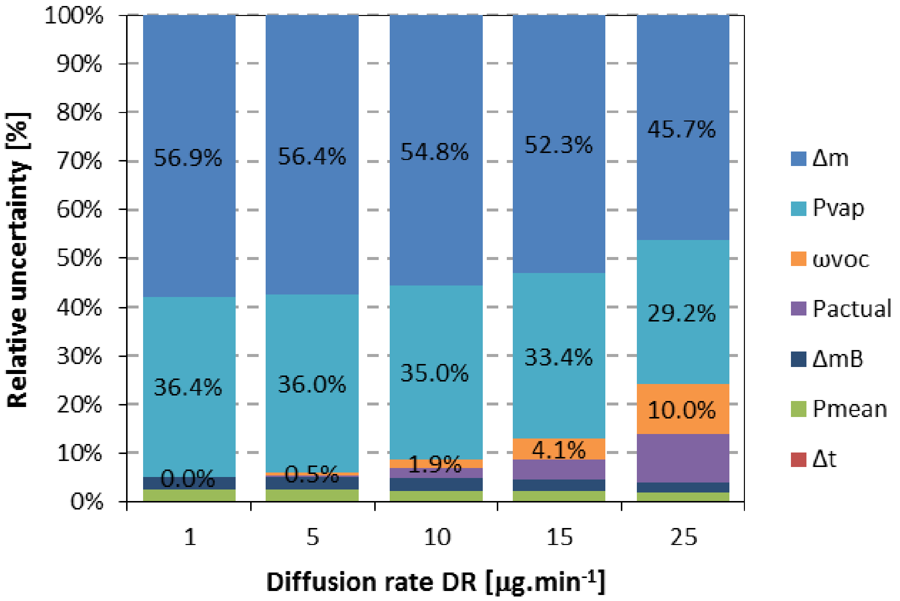

Fig. 16. Summary of the uncertainty budget for the generation system for different diffusion rate (mass measurement every 7 days)

Besides the effect that the mass measurement and the vapor pressure have on the uncertainty of the diffusion rate, the perturbation of mass due to the cooling appeared to be important at high diffusion rates. In the case of the buoyancy correction, even if the relative uncertainty of the calculated mass is high and its estimation is difficult, the effect on the overall uncertainty is not negligible and should be analysed in more detail.

The vapor pressure estimation was improved by performing a regression directly over the available data. A detailed calculation of the uncertainty was also made, however the changes on this variable did not improve significantly the diffusion rate uncertainty. However, for the cases of study, all the evaluated uncertainties were below the required target, even for the nominal diffusion rate of 1 µg.min^{-1}.

4.8. UNCERTAINTY BUDGET OF THE CONCENTRATION OF THE STANDARD MIXTURE

An uncertainty budget was prepared for the case study. Table 8 contains the information obtained using the model developed, which introduces VOC – wall interactions and leakages as sources of uncertainty. Leakages and adsorption mass flow rates threshold uncertainties were calculated and a negligible significance over the total uncertainty i.e. I_S = 1% was obtained.

The carrier and dilution air mass flow rates were chosen to obtain a reference VOC mixture of 40 nmol.mol^{-1} based on a diffusion rate of 1 µg·min^{-1}. The uncertainty of the diffusion flow rate was evaluated as in Table 6. The dilution air flow rate uncertainty is the 0.5% sonic nozzle uncertainty mainly dependent on the upstream pressure accuracy [72].

Table 8. Target Uncertainty budget of the molar fraction of the reference mixture.

X	[X]	x	u(x)	u(x)/(x)	I_S% [%]
D_R	µg·min^{-1}	1	0.05	5.0%	100%
ϕ_c	Sml·min^{-1}	50	10	20.0%	< 1%
ϕ_I	Sl·min^{-1}	9.307	0.047	0.5%	0.5%
ϕ_W	ng·min^{-1}	0	1.00	-	< 1.0%
ϕ_L	Sml·min^{-1}	0	50.0	-	< 1.0%
ω_A	nmol·mol^{-1}	0.096	0.056	58.3%	< 1.0%
χ_{VOC}	nmol·mol^{-1}	40.00	2.01	5.02%	*k*=1

The carrier flow rate (ϕ_c) was left with a high uncertainty because its value does not contribute to the final uncertainty in a relevant way. The air purity uncertainty (ω_A) was evaluated considering a uniform distribution from 0 to the double of the measured air purity value. With these experimental conditions, the targets for leakages and wall interaction flowrate were calculated, allowing to minimize the uncertainty of the concentration down to 5%.

4.9. EVALUATION OF THE SHORT TERM STABILITY OF THE DYNAMIC SYSTEM

The stability of the operational conditions, for generation and dilution, was calculated by the Allan deviation algorithm from the experimental data. The stability $\sigma_{exp,i}(\tau)$ is reported in Fig. 17 for each operative quantity over a range of 1 – 1000 min of observation time and referred to the mean value of the quantity over the whole period.

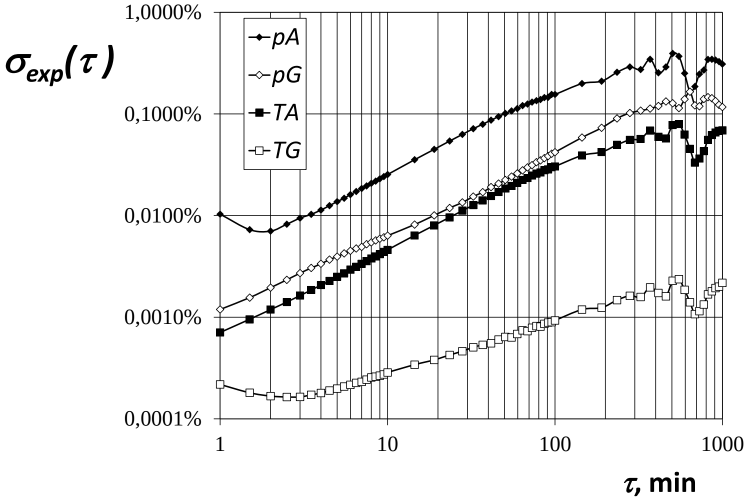

Fig. 17. Experimental stability of the operational conditions, calculated with relative Allan deviation at different observation times.

All the stabilities increased with observation time, and the slope of the logarithm to base 10 of the operative quantities with respect to the logarithm to base 10 of t, was 0.7 for inlet pressure of the dilution system (*pA*), the generation pressure (*pG*), the air temperature (*TA*) and 0.3 for the generation temperature (*TG*). The lower slope was associated to a more stable and less time dependent quantity, which in this case is *TG*. Even if in general the pressure terms are less stable than the temperature ones, the less stable quantity was found to be the air inlet pressure of the main dilution flow *pA*. These results were published by Demichelis et al (2016) [73].

The influence of the fluctuation of the operational conditions on the uncertainty of the molar fraction was also analysed. The VOC molar fraction stability issues were negligible for times below 10 min (fast sampling e.g. mixture sampling in gas chromatograph or spectrometers). However, the VOC molar fraction stability issues cannot be neglected for slow sampling, such as the filling of canisters for long-term exposure measurements or online calibration of gas sensors for long time. A better control of the air inlet pressure p_A can reduce instabilities at a negligible level.

The stability of the air inlet pressure gave the main stability contribution, so it must be considered in the uncertainty calculation. The stability contribution to the total uncertainty resulted to be negligible for observation times below 60 and 200 min and for VOC molar fraction uncertainty of 2% and 5% at 30 nmol.mol^{-1} level [73].

CHAPTER 5

Design criteria of a dynamic generator based on the diffusion technique

The characterization of the generator is important to understand the phenomena involved in the diffusion/dilution process and to give information about the specific performances of the system when it is subject to changes in the influence quantities of the diffusion rate.

5.1. DIFFUSION RATE MODEL

A model was developed [69] to determine the actual diffusion rate, $D_{R,actual}(t)$, using the gravimetric method. The vial containing the liquid VOC is weighed initially and after a fixed period of time. The mass obtained corresponds to the "apparent" diffusion rate, and must be corrected for the purity of the liquid VOC and the difference between weighing and generation conditions as in Eq. (14):

$$D_{R,actual}(t) = \omega_{VOC}\left(\frac{\Delta m + \Delta m_B}{\Delta t}\right)\beta + \delta D_{R,actual}(t) \tag{14}$$

where ω_{VOC} represents the purity of the liquid VOC, Δm is the mass of VOC equal to the difference between the filled and the empty vial, Δm_B is the correction due to buoyancy effect, Δt is the period of time between weighing and β is the correction factor to pressure. The differential term $\delta D_{R,actual}(t)$ is a time dependant value that corresponds to a short-term variability of the diffusion rate, calculated from the variability of pressure and temperature and the sensitivity coefficients of each quantity as follows:.

$$\delta D_{R,actual}(t) = c_T \cdot (\delta T_{TB}(t) + \delta T_W) + c_P \cdot \delta P_{LAB}(t) \tag{15}$$

where c_T and c_P are the sensitivity coefficients for temperature and pressure respectively, $\delta P_{LAB}(t)$ is the stability function of the environmental pressure and $(\delta T_{TB}(t) + \delta T_W)$ is the stability function of the environmental temperature, defined as the sum of the stability of the thermal bath, $\delta T_{TB}(t)$, plus the variability of the temperature due to the cooling effect of the vial when it is removed from the thermal bath for weighing, δT_W.

The contribution from the environmental temperature and pressure to the value of diffusion rate is null, as the mean value of this variations can be considered to be equal to zero. However, the influence over the uncertainty of diffusion rate is different from zero and depends on the stability of both conditions over time.

5.2. DESIGN CRITERIA OF THE GENERATION PART

The parameters that have an influence on the uncertainty of the diffusion rate generated in the vial/cell system where analysed. The major sources of uncertainty are associated to the mass measurement, the temperature control and the conditions of generation. This section describes in more detail their influence and accounting into the uncertainty budget of the measurand.

5.2.1. Mass measurement

The mass of the VOC measured from the difference between the filled and the empty vial, is subject to different phenomena involved in the weighing process. In the uncertainty analysis of the diffusion rate, the effect of buoyancy and vial cooling were considered.

- *Buoyancy*

The term Δm_B in Eq. (14) corresponds to the correction for the buoyancy effect which has been introduced into the model for this procedure. This factor was introduced to take into account the force balance resulting on the vial/VOC system, where the net force, which give us the mass reading of the system, is the difference between the weight of the vial and its buoyancy.

From this balance, the mass is measured at the beginning of the generation and after a period of time. The difference Δm, between the two masses, calculated at each moment by Eq. (16), is the mass of the VOC evaporated that gives us the diffusion rate of the system.

$$\Delta m = (m_2 - V_2 \cdot \rho_{A2}) - (m_1 - V_1 \cdot \rho_{A1}) \tag{16}$$

where $m1\ and\ m2$ are the mass readings at the first and second measurement respectively, ρ_A is the air density at each measurement, V_1 is the initial vial/VOC volume and V_2 is the vial/VOC volume after the generation. The difference between V_1 and V_2 is the volume of liquid VOC evaporated, V_{vapor}, which can be calculated transforming Δm into a volume with the density of the liquid VOC. Combining these relations together, the evaporated VOC corrected mass, Δm, can be rewritten as follows:

$$\Delta m = \frac{1}{1 - {\rho_{A2}}/{\rho_{VOC.l}}} [m_2 - m_1 - V_1 \cdot (\rho_{A1} - \rho_{A2})] \tag{17}$$

- *Temperature variability during weighing*

The variability of the temperature of the vial during the generation process is related to the temperature control of the thermal bath and also must include the perturbation of the vial temperature during weighing. The environment temperature is usually lower than the thermal bath, so the vial will be disturbed with a cooling effect during the weighing process.

An analysis on the dynamics of the cooling was performed, aiming to minimize the effect on the overall uncertainty. Using the CFD model of the vial, dynamic simulations were made to reproduce the effects of cooling in different conditions. A previous validation of the model was made before by comparing the simulation with experimental results of a known cell filled with water, results are reported in Fig. 18.

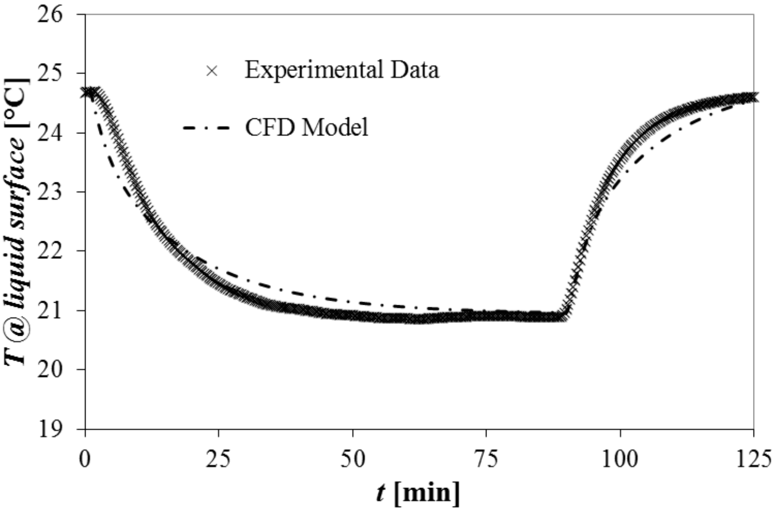

Fig. 18 Validation of the model for the dynamics of the vial cooling

After validating the model, simulations with acetone were performed, at high (15µg.min^{-1}) and low (1µg.min^{-1}) diffusion rate, changing the time of weighing to observe the overall change in the temperature and diffusion rate. The steady state was reached after approx. 125 min, for each case, as it happened also for the validation shown in Fig. 18. However, when comparing the results of the dynamic simulation against the steady state simulation, there is a consistent difference of 4% for both cases (high and low diffusion rate). This difference is related to the increase of the convergence tolerance used in the case of the dynamic simulation that has been increased in order to obtain the results in less time. Fig. 19 shows the dynamics of the cooling, when the vial is extracted from the thermal bath, for low diffusion rate. To improve the readability of the plot, only the input step that corresponds to a time of weighing of 10 min is reported.

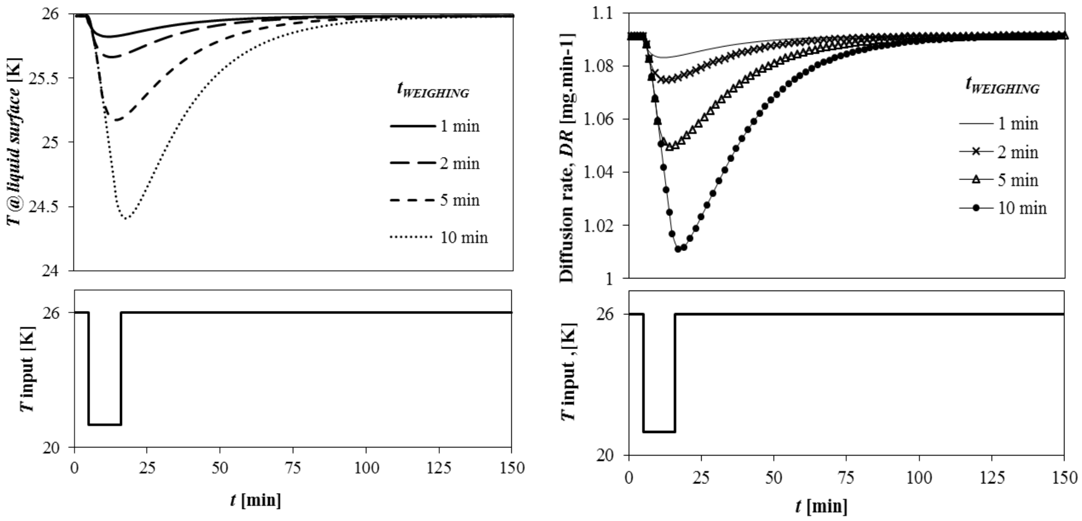

Fig. 19. Dynamic of cooling during weighing process for low diffusion rate

Additional to the step in the temperature, there is a step in the air carrier flowrate, that is limited to 1% of the carrier original flowrate (50 Sml.min^{-1}) when the vial is out of the cell. This change has been done to simulate the natural convection phenomenon to which the vial is subject during the weighing. The new value of the carrier flowrate is used as it represents a compromise between convergence and precision of the results. It has been chosen after changing the carrier flowrate from 0.01% to 10% of the original value to evaluate convergence and thermal effect. Below 5%, no significant changes in the thermal effect were observed - since the flowrate was very small - however the convergence significantly decreases with the flowrate due to the complexity of the natural convection phenomenon.

The variability of the temperature due to the cooling effect is a function of the time of weighing and the thermal capacity of the vial/liquid set, which is assumed to remain constant during the weighing period.

With the response of the diffusion rate over time, the overall mass perturbation during weighing was calculated as a numerical integral in the period of time corresponding to weighing time. The points for low and high diffusion rate calculated, are plotted in Fig. 20. A regression over the data calculated gives an expression for the mass perturbation due to the cooling effect, which can be included in the uncertainty estimation and used to estimate the maximum weighing time.

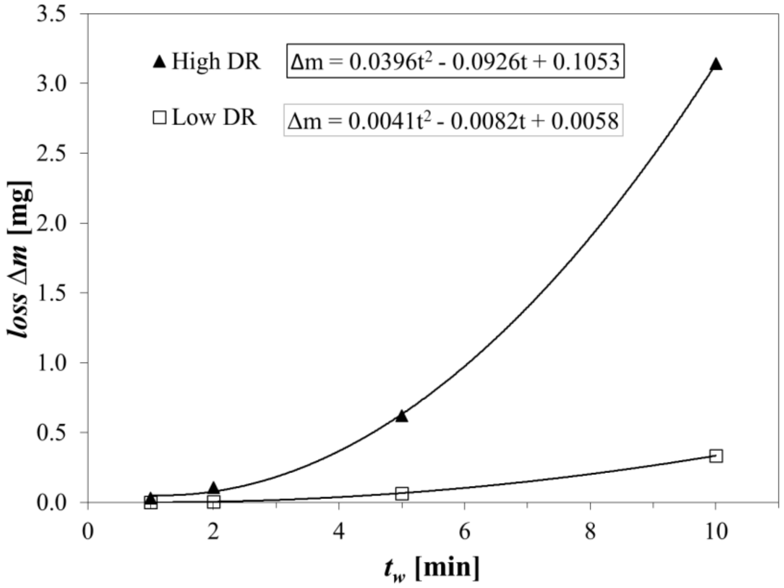

Fig. 20. Mass perturbation associated to different weighing times

- *Frequency of mass measurement*

The time between each measurement must be considered to improve the accuracy of the mass measurement. Frequent measurements lead to a greater uncertainty of the diffusion rate, as the mass evaporated decreases.

This effect becomes more important at lower diffusion rates. In Fig. 21 the diffusion rate uncertainty over time between the mass measurements is shown. The uncertainty analysis was carried out over three vials.

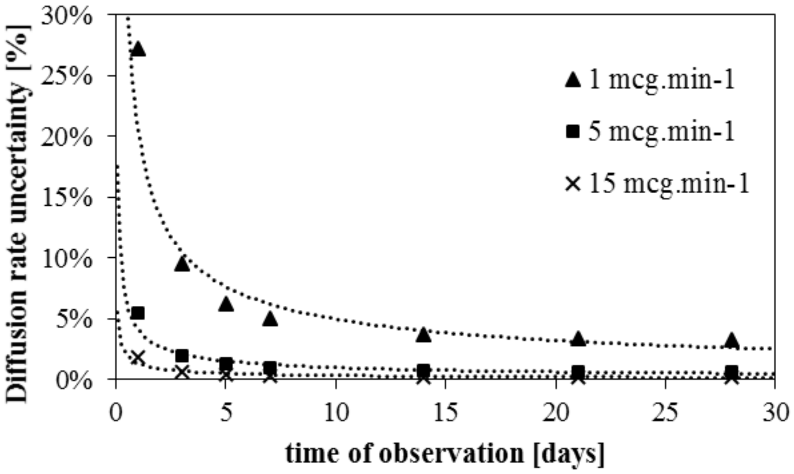

Fig. 21. Diffusion rate uncertainty over time between mass measurements

- *Maximum time of weighing*

The maximum time of weighing t_W at a given ΔT, guarantees a minimal increase in the temperature variability. Exposing the vial to the cooling effect for a time equal or below the maximum t_W, assures the minimal variability and keeps the contribution to the diffusion rate uncertainty below a negligible level (IS 1%). The maximum time of weighing can be calculated from the dynamics of the vial cooling, using the expressions corresponding to the regression curves reported in Fig. 20.

5.2.2. Density of air uncertainty

To properly correct the diffusion rate for buoyancy, it is necessary a good estimation of the density of air. The NIST (simplified) equation [74] used to calculate the air density, depends on the pressure, humidity and temperature of the air. The simplified correlation can be applied over a range of air density equal to 1.2 ± 10% kg m^{-3}, with a typical uncertainty of $4x10^{-4}$ kg m^{-3}.

The uncertainty of the air density is evaluated as a combined uncertainty, using the NIST equation considering the measurement uncertainty of the operating conditions and the uncertainty of the estimation itself. If the variability in the laboratory is high, the uncertainty of the correction factor can increase up to a point where it becomes a relevant source of uncertainty of the diffusion rate, making the correction unreliable and consequently unnecessary.

Table 9, shows the uncertainty budget of air density, based on the available instruments used in the environment where the mass is measured.

Table 9. Uncertainty of the air density

X	[X]	x	u(x)	u(x)/(x)	I_S [%]
T_{LAB}	K	293.15	0.10	3.41E-04	70%
$\%H_R$	%	40	5.00	1.25E-01	100%
P_{LAB}	Pa	97000	40.00	4.12E-04	87%
ρ_{air}	kg m-3	**1.149**	**0.001**	**0.1%**	(*k*=1)

5.2.3. VOC vapour pressure

A sensitivity analysis was made over each influence quantity of the CFD model to obtain the coefficients representing the ratio of change of the diffusion rate. For the design process, understanding the influence of both theoretical and operating conditions over the diffusion flowrate and its uncertainty is necessary. However, to evaluate the uncertainty of the existing system, the experimental parameters that influence the generation process should be taken into account.

The following figures show the results of the sensitivity analysis done over the experimental parameters for the CFD model and experimental results. They serve to validate the results of the model which can be used for the design of the process and also provide the coefficients applied in the propagation of the uncertainty in the next section.

Fig. 22 shows the sensitivity of the diffusion flow rate to the vapour pressure of the vial with the maximum uncertainty estimated. For a given substance with known vapour pressure, results from CFD model are validated with experimental results, showing a substantial agreement within the estimated range of uncertainty. The experimental points correspond to the gravimetric estimation of the diffusion rate using equal nominal vials for different substances. Even if the vials are designed to generate 50µg.min^{-1}, individual modelling based on the specific dimensions of each vial was made for simulation purposes.

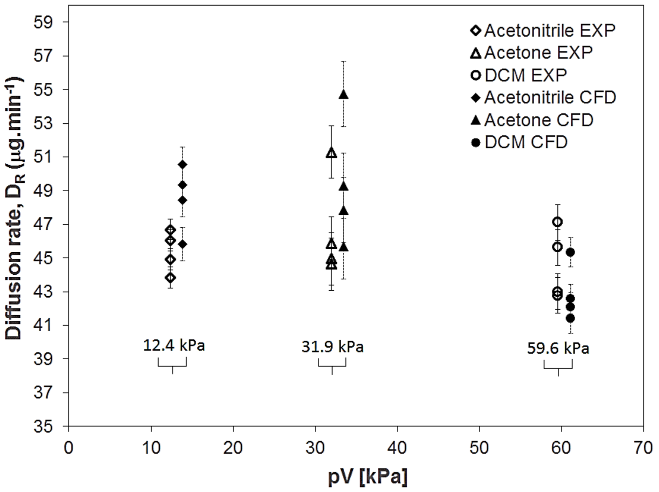

Fig. 22. Sensitivity of the Diffusion rate to the vapour pressure

5.2.4. Thermal bath temperature

Fig. 23 shows the sensitivity of the diffusion flow rate to the temperature of the vial with the maximum uncertainty evaluated. For each temperature, the corresponding vapour pressure value was calculated for acetone. The plot shows the simulation results against the experimental points. The uncertainty was evaluated influence applying the Guide to the expression of uncertainty in measurement (GUM) procedure over the quantities that affect the CFD model.

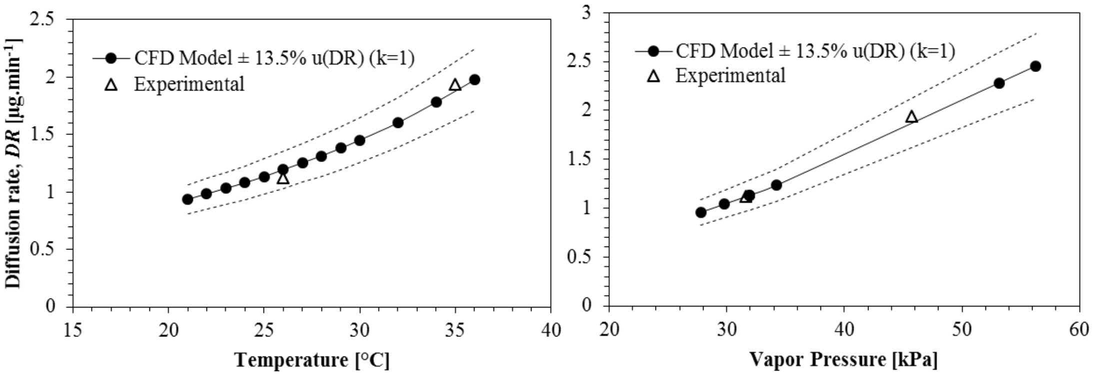

Fig. 23. Sensitivity of the Diffusion rate to the thermal bath temperature and corresponding vapour pressure for acetone.

5.2.5. VOC liquid Mass

The mass of liquid in the reservoir has an influence over the diffusion flowrate and its uncertainty. The liquid level can be used as indicator of the remnant VOC inside of the vial, along with the time of operation of the generation cell.

With higher diffusion rate, the variation of the VOC liquid mass with time increases and affects the thermal balance of the vial. The change obeys to the decrease in the thermal capacity of the liquid reservoir, which is an extensive property depending on the VOC liquid mass. Fig. 24, shows the temperature profile of the cell / vial system. A stable thermal bath at $T_{\infty,}$ provides a temperature at the outer wall of the cell that is equal to T_{ow1}. The heat is transferred by conduction to the inner face T_{ow2}. The heat is then transferred by convection into the inner wall, which reaches the temperatures T_{iw1} and T_{iw2} at the outer and inner faces respectively. Inside the vial, the liquid body gets colder as it provides the energy necessary to evaporate the mass of VOC that is transferred to the gas phase via diffusion.

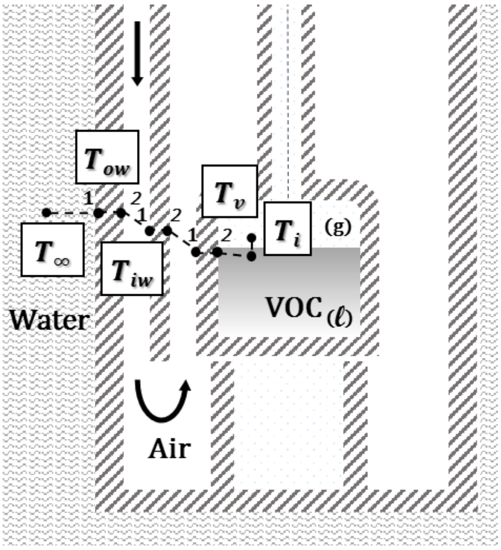

Fig. 24. Temperature Profile across the Cell/Vial System

This effect introduces a new source of uncertainty and the definition of a minimum liquid volume, above which the rate of change of the diffusion rate with time remains constant.

5.2.6. *Carrier gas flow rate*

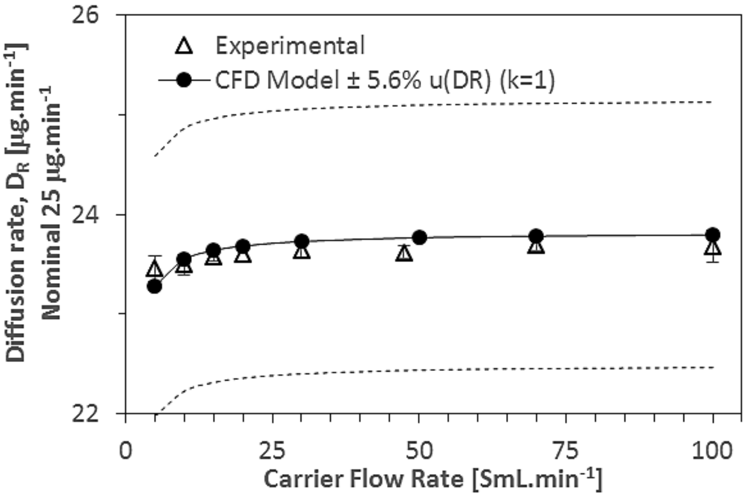

Fig. 25. Sensitivity of the Diffusion rate to the carrier gas flow rate

The carrier flow rate effect on the diffusion rate is related to the increase in the velocity inside the cell, which “cleans” the tip of the diffusion neck of the vial. A lower concentration of VOC at the end of the neck is a way to get closer to the theoretical maximum diffusion flow rate, as it provides a larger difference in concentration.

For the CFD model of the generator, the carrier flow rate effect was analysed and it was observed an increase of the diffusion rate value until a maximum. In Fig. 25, the CFD model results for an acetonitrile generation of 25µg.min^{-1}, are compared with the experimental results.

5.3. DESIGN CRITERIA OF THE DILUTION PART

To generate standard gas mixtures at nmol.mol^{-1} level a dilution is expected over the diffusion flow rate from the generation section. A mixing tee can perform an online dilution of the two streams. However, a set of parameters should be considered in the design, construction and operation in order to obtain reproducible and stable results with the desired uncertainty.

The evaluation of the different parameters was made over a CFD Model that reproduces the behaviour of the experimental device. According to the results, the main considerations from the geometrical point of view are decreasing the diameters to obtain a turbulent profile and adjusting the injection of the streams in case no further decrease of the diameter can be done. Since the CFD calculation calculates the concentrations at every node of the mesh, an average and its standard deviation can be calculated at a given cross section. The minimum length of tube can be the estimated, once a target superficial standard deviation has been defined. This can be done calculating a target uncertainty budget from the consideration of perfect mixing.

To properly evaluate the uncertainty of the standard gas mixture, not only the mixing has to be considered. The possibility of VOC losses from wall interactions should be minimized using treated steel or keeping the contact area below the thresholds defined for different wall materials. In both cases, a proper cleaning cycle with flushing times adequate to the characteristic time of adsorption of the material is important. The cleaning would allow to reach the equilibrium at the surface and minimize the effect of the adsorption on the molar fraction of the mixture.

5.3.1. *Mixing factor*

In order to generate a gaseous standard that is reproducible and stable, a proper mixing of the species in the gas should be achieved. The perfect mixing consideration implies that there are no spatial gradients of molar fraction. A good quality of mixing should then be as close as possible to this ideal condition. A factor to define the degree or the quality of mixing was introduced into the model of the molar fraction of VOC, χ_{VOC}.

The Mixing factor *(M_P)* can be defined as the relation between the *spatial* molar fraction, $\chi_{VOC}(x,y,z)$, with respect to the *mean* molar fraction, $\overline{\chi_{VOC}}$, at the current time, according to the following equation:

$$M_P = \frac{\chi_{VOC}(x,y,z)}{\overline{\chi_{VOC}}} \tag{18}$$

The probability of having perfect mixing between the VOC diffusion rate stream into the zero air, can be considered as a normal distribution with standard deviation σ, as shown in Fig. 26.

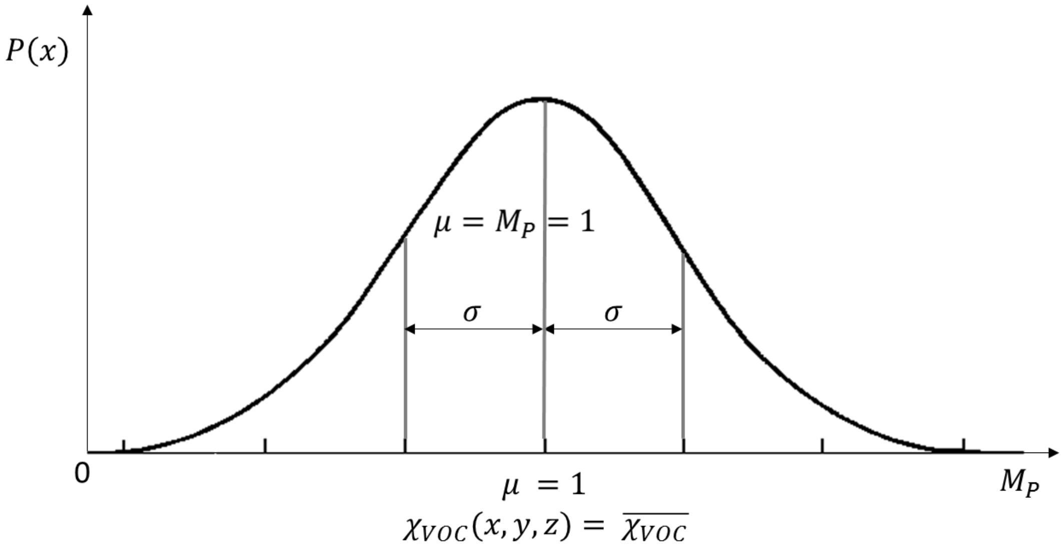

Fig. 26. Mixing Factor Probability Density Function

There is no way to know the exact profile of concentration inside the tube and to determine the degree of mixing. However, an estimation of the influence of the mixing on the measurand can be done using the profile calculated numerically by the CFD model.

For the metrological evaluation, the condition of perfect mixing is assumed, associating all the possible changes to the uncertainty of M_P. This leaves the measurand value equal to the mean molar fraction and introduces a new uncertainty, defined as the superficial standard deviation over the cross section, divided by the mean value of χ_{VOC}.

The contribution to the uncertainty is evaluated following the guidelines of the Guide to the expression of uncertainty in measurements (GUM) [60]. The significance index [69] is the index used to find out the major source of uncertainty. This index allows to identify major, relevant and negligible sources of uncertainty. Based on this principle, the maximum uncertainty that provides a negligible contribution can be set, providing a reference to the target superficial standard deviation.

5.3.2. Minimum Length of Mixing

The minimum length of mixing for a tube, should be calculated at the minimum expected flow rate, to assure the performance over the whole flow rate range. From the target uncertainty, for which the mixing factor of 1 was considered, the target superficial standard deviation can be calculated.

Checking the superficial standard deviation over cross sections of tube across the tube length allows to observe at which point the target of mixing is reached. If some stratification is expected, another indication of the degree of mixing can be considered by adding a tee at the end of the tube. The tee exits correspond to the sampling and vent outlet lines. The definition of the tube length can be done with a CFD simulation in steady state. With the tee at the end, VOC molar fractions at both outlets should be equal to the expected mean (from mass conservation) within a defined tolerance. This guarantees the absence of VOC losses through the vent, when the difference in flow rate with the respect to the sample line is wide.

In the dynamic set up, the mixing effect as source of uncertainty should depend on the time of sampling. This time affects directly the volume of the gas standard sample, making possible the estimation of a temporal mean $\overline{\chi_{VOC}}(V(t))$ over the volume *(V)* collected at the time, *t*. The ratio between the temporal mean and the expected mean give us an indication of the evolution of the degree of mixing contribution to the uncertainty, for different sampling times.

5.3.3. Shape and Geometry

The most important parameter to consider for the dilutor performance is the shape and geometry of the device. Shape and geometry act by two separate mechanisms: any acceleration and deceleration, i.e., momentum transfer, enhance mixing; the average relative directions of the streams at the contact point play a main role in the effectiveness of reciprocal contact between streams. A tee connection was considered as a mixing device, for a specific diameter, to select different angles of injection of the air and diffusion rate streams to evaluate the influence over mixing performance. Flow rates strongly affect mixing performances of an equipment and devices. Reynolds number couples geometrical dimension of device with flow rate and material properties. It gives the ratio between total disrupting forces (kinetic energy) and structural forces (viscous resistance of fluids) which work in opposite direction for mixing. Local high Reynolds Number values can supply a concentrate mixing energy reducing the mixing length. Local Reynolds Number can be modified by the shape of the device.

To increase the velocity and turbulence, having small diameters is desirable, however when generating at low mass flow rates, where the flow regimes tend to be laminar, changing the angle of injection might help to create zones of higher turbulence.

The Fig. 27, shows the geometrical configurations around a cross tee that were analysed. The injection positions of air and VOC were changed to form angles of either 90° or 180°, splitting both diffusion rate and dilution air. The latter showed a better performance, especially when splitting the dilution stream, as a more regular profile inside the tube could be observed. The configuration at 90 degrees instead, showed a stratified flow, with a layer near the region of injection with a higher concentration.

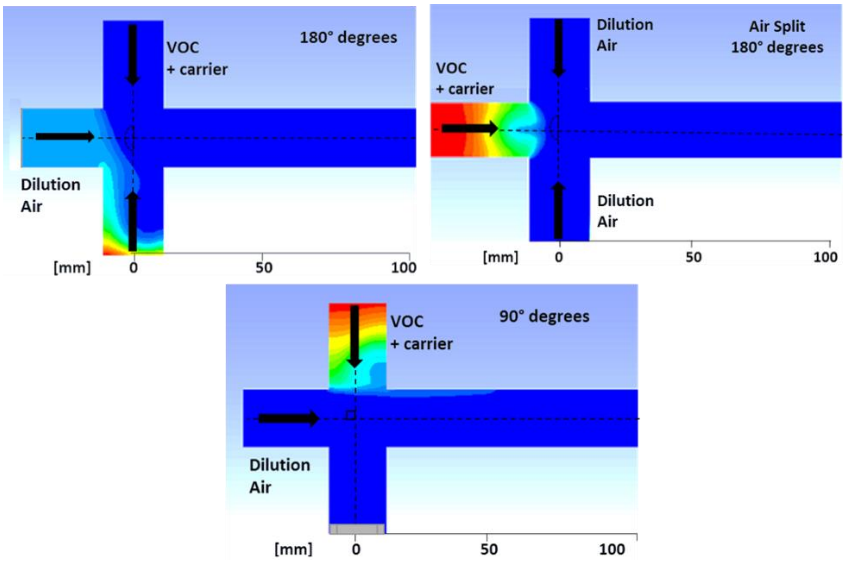

Fig. 27. Injection configurations for the dilution cross tee.

The results shown in the figure above, are more evident in Fig. 28 where the relative superficial standard deviation is plotted against the distance from injection. The values are relative to the superficial mean molar fraction. For all the cases the most conservative condition was considered, which corresponded to a generation in a 50Sml.min^{-1} flow and a dilution with 10Sl.min^{-1} (nominal molar fraction equal to 40 nmol.mol^{-1} of Methanol).

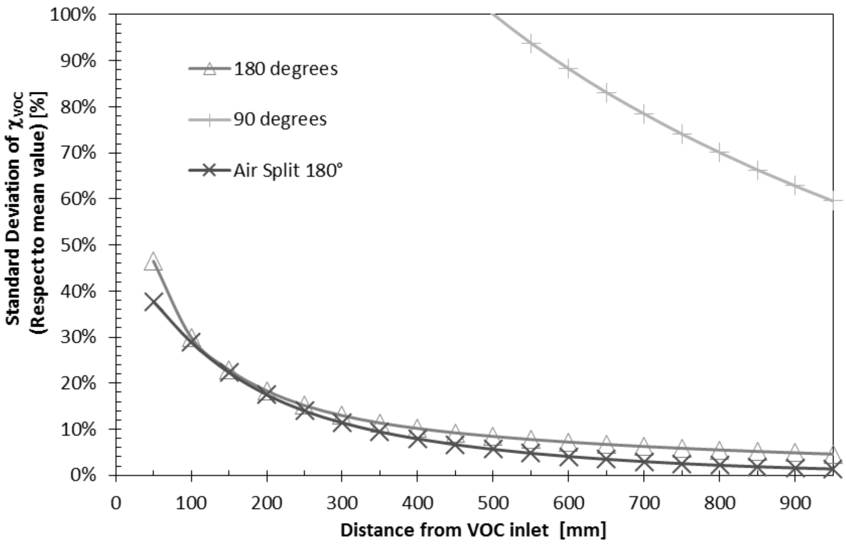

Fig. 28. Superficial standard deviation of the Molar Fraction for the 3 different injection configurations considered above

5.3.4. *Adsorption Effect*

The choice of the material is important to avoid wall interaction effects, especially in the dilution part where wall interaction is relevant for this section. The reason is that the characteristic time of adsorption and the dilution process itself are on the same order of magnitude. The dilution characteristic time remains below 1 min while the characteristic time for Siltek® treated steel and untreated stainless steel varies from 30 to 140min.

For this reason, when working with Siltek® treated steel, it is recommended to clean the system with zero air for 20-30 min to reach the equilibrium before the sampling of the standard is made. In this way, the possible VOC losses can be minimized, assuring the stability of the VOC molar fraction of the sample. In case the treated steel is unavailable, maximum contact area should be defined for different materials. Fig. 29 shows the adsorbed mass for different materials and different areas.

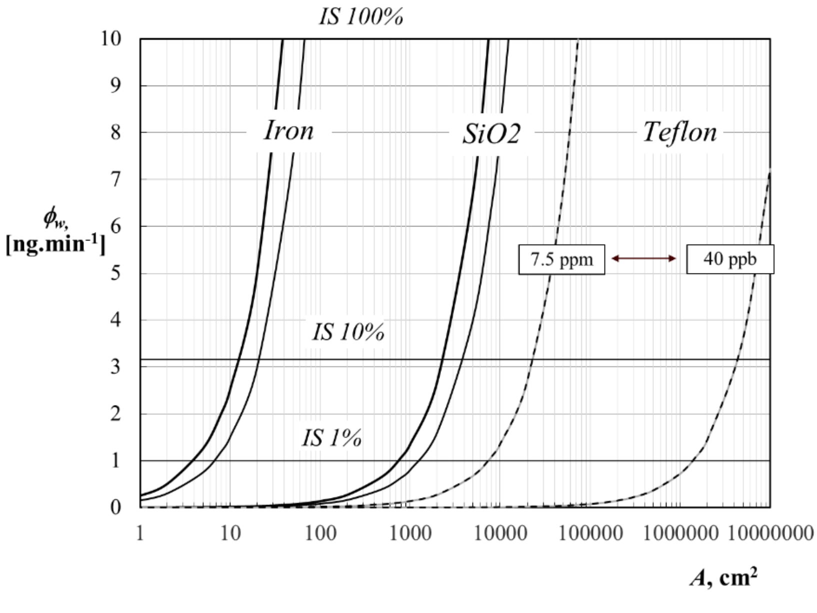

Fig. 29. Thresholds for Acetone wall - adsorption for different wall materials [54]

Following the same principle, the target uncertainties associated to the VOC losses due to wall adsorption were quantified. The labels “IS 1%”, “IS 10%” and “IS 100%” represent the maximum VOC loss in ng.min^{-1} to have a negligible, relevant and major contribution, respectively. The curve was calculated based on the interaction with Acetone, however polar VOCs with similar structure can be considered to have a similar behaviour.

5.3.5. Maximum allowable leakage flow rate

The model based on the mass balance presented in Chapter 4 (Eq. 7), was used to evaluate the uncertainty over the standard mixture molar fraction. The methodology for the propagation of the uncertainty was based on the Guide to the expression of uncertainty in measurement (GUM) [60]. The significance index of the leakage flow rate was minimized to evaluate the different thresholds of influence: negligible, relevant and main contribution. This procedure allows to obtain the maximum allowable leakage flow rate in order to minimize the uncertainty.

The effect of the leakages on the uncertainty of the molar fraction of the VOC was analysed for a particular case on the whole device. A generation of 40 nmol.mol^{-1} of acetone in air was considered. The test duration was calculated according to the equation (10), with an uncertainty of the pressure sensor and a leakage flow corresponding to a negligible contribute.

The procedure described in the methods was followed in order to calculate the volume of the system and, 500 mL was calculated as a conservative value (the higher is the value, the higher is the calculated leakage flow rate). A test duration of 4 min was calculated at a test relative pressure equal to working pressure (0.5 kPa), while 2.3 kPa and 4.5 kPa were calculated as test relative pressure to have a test duration of 1 min and 30 s respectively. In any case pressure and time are compatible with the performances of the generator, a single leakage test can be done on the whole volume of the device. More detailed information of the conditions of the leakage test are reported in the aforementioned publication by Sassi et al [54].

A flowrate of leakages equal to zero was considered, however, the uncertainty of such assumption was evaluated, introducing an absolute value of ϕ_1 to the mass balance. After compiling the data of the generation, the uncertainty of the molar fraction was equal to 1.13%. Changing the leakage uncertainty, resulted on different accuracy of the standard mixture, as shown in Table 10.

Table 10. Maximum allowable leakage flow rate ϕ_L.

$u(\phi_L)$ Sµl·min^{-1}	Contribution	$u(\chi_{VOC})$ % of 40 nmol.mol^{-1}
538.4	I_S = 100% Main	1.55%
158.9	I_S> 10% Relevant	1.17%
50.0	I_S < 1% Negligible	1.13%

CHAPTER 6

Realization and characterization of the portable device

The procedures shown in Chapter 5 where applied to determine the dimensions of every part of the transportable device. The resulting system is very similar to the primary one, with the difference that no cells are used. The air stream enters into the system and its temperature is conditioned. The determination of the minimum length of tube was done to ensure that the temperature of the air inside was constant. After the air is conditioned, it passes through a flow control device to guarantee a stable flow. The following part is a manifold that receives the diffusion rates from the different cells. The manifold and the subsequent mixing line where designed using the CFD to guarantee that the vial closest to the outlet gets completely mixed at the lowest expected flowrate.

6.1. MATERIALS AND METHODS

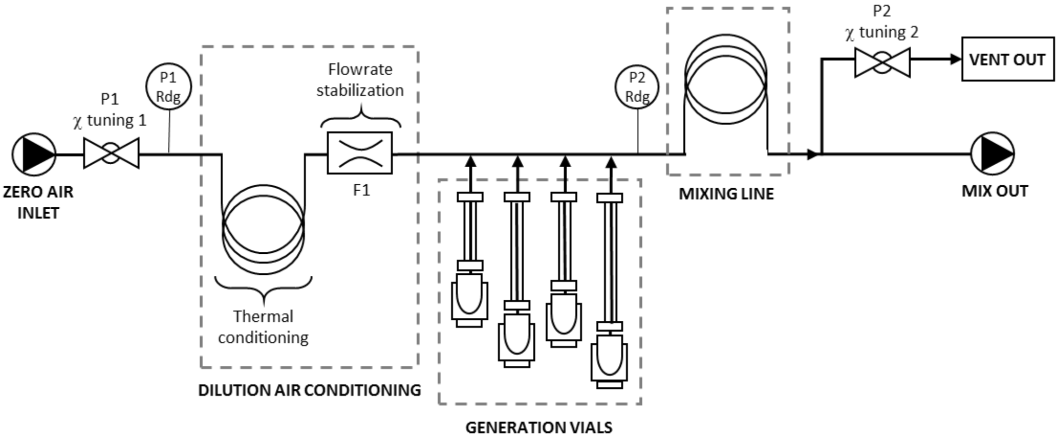

Fig. 30. Scheme of the portable generator

The operation scheme of the portable generator is reported in Fig. 30. From the rear side of the generator, the zero air flow comes in through the port "Air In". The inlet pressure is regulated by the pressure regulator P1, through the external knob "χ *tuning 1*", and measured by a pressure sensor P1_Rdg. The air flow entering into the system is thermally conditioned and the flow rate controlled by a flow rate stabilization system F1. The controlled flow is mixed with the methanol diffusion flow D_R coming out from a conditioned diffusion vial, the temperature of which is displayed in the generator screen. The pressure in the mixing line is controlled by a back pressure regulator P2, through the external knob "χ *tuning 2*", and measured by a pressure sensor P2_Rdg.

The outputs of both pressure measurements are displayed on the device screen. A part of the mixture flow is sampled in the "Mix Out" sampling line and the rest is vented out through the "Vent out" port. The sampling line, visible in Fig. 31 consists in a 2.5 m 1/8" Siltek tubing. The generator operates at a constant diffusion vial temperature, around 30°C, i.e. at the same diffusion rate, and at a constant mixing chamber pressure P2, around ambient pressure. The methanol molar fraction in the sampling line changes according to the air pressure P1, the mixture flow rate in the sampling line is around 1 $Sl.min^{-1}$.

The generator doses the VOCs of choice (up to 4 substances) into the provided zero gas stream. The air, or gas of interest must be clean and available at 7 bar absolute with a maximum consumption of 5 $Sl.min^{-1}$.

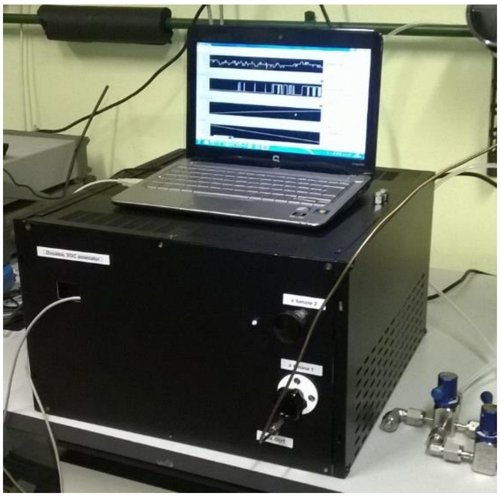

Fig. 31. Picture of the portable generator

6.1.1. *INRIM measurement with Cryo-GC-FID*

A generation using methanol was performed at INRIM to evaluate the performance of the device. The molar fraction of the methanol mixtures generated by the portable device were measured by the INRIM's GC-FID. These measurements were traceable to the primary INRIM methanol/air mixtures prepared by the diffusion technique in the primary device described in Chapter 4.

INRIM measurements were done using a gas chromatograph with cryogenic pre-concentration and flame ionization detection Cryo-GC-FID. A total sample of 400 ml of mixture was pre-concentrated at -50°C in the cryo trap. Cycle of measurements of 30 min were obtained with the FID. The signal, the peak area for methanol, was then converted to molar fraction with the known GC calibration function.

The calibration of the GC was made against primary methanol in air mixtures in the 10 – 500 nmol.mol^{-1} range. These primary mixtures were prepared with the INRIM primary diffusion generator and a 5% expanded uncertainty is considered for each calibration point and is reported as error bar in Fig. 32. The final methanol molar fraction is obtained by subtracting from the generator measures the mean of zero-air measures done before and after the measurement set.

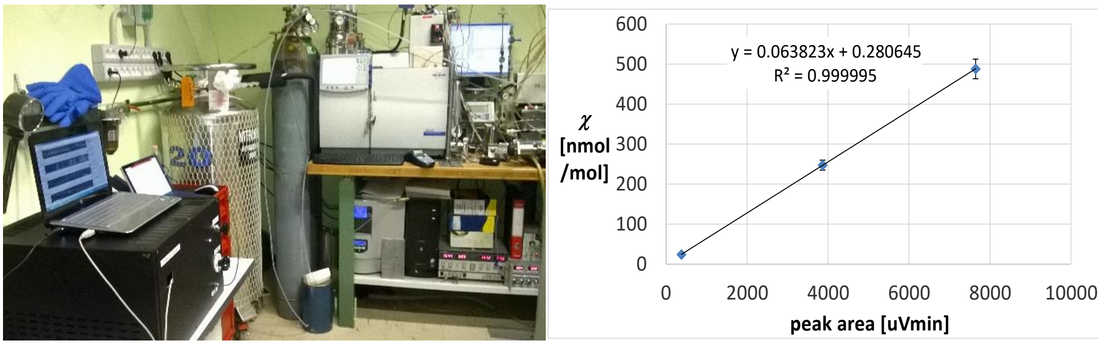

Fig. 32. Picture of the INRIM measurement setup (Cryo-GC-FID) for testing the portable generator (left). Calibration of GC measurement system with primary dynamic methanol mixtures (right).

For the calibration of the portable device, measurements were done in three different days at three different P1 of the portable generator. After each change in pressure, corresponding to a change in the molar fraction of the mixture, a time of 24h was considered for stabilization. The calibration function of the portable device was obtained as function of P1, for constant mixing chamber parameters (P2 and T) and the geometry defined.

6.1.2. VSL measurement with CRDS

In the framework of the Key-VOCs Project, a visit to the Netherlands' National Metrology Institute, VSL was carried out in April 2016. In a similar way to the above measures carried out at INRIM, another generation from the portable device, using methanol, was performed at VSL. The molar fraction of the generated methanol mixtures were measured in this case by the VSL home-built Cavity Ring Down Spectroscopy (CRDS) apparatus operating in the mid-infrared wavelength region.

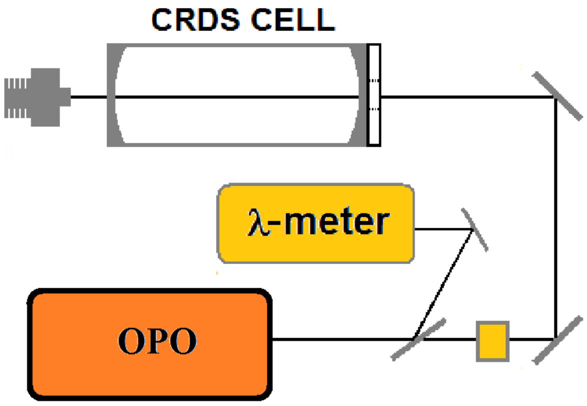

Fig. 33. Schematics of the measurement set-up at VSL

A schematic of the experimental set-up [75] is shown in Fig. 33 which encompasses a widely tuneable infrared light source known as continuous wave optical parametric oscillator (OPO) in combination with cavity ring down spectroscopy (CRDS). In addition the wavelength is monitored using a wavelength meter. In the CRDS cell an effective absorption path length of nearly 3 km is obtained. For the monitoring of methanol, the strong absorption feature around 2982 cm^{-1} was selected. In this range, there is a very low spectral interference from other compounds that might be present in the gas mixture. The pressure in the measurement cell was kept constant at 1030 mbar using a pressure controller. Methanol measurements were referred to internal gravimetric primary standards.

In Fig. 34 is reported a picture of the VSL measurement setup (CRDS) for testing the portable generator and a reference methanol spectra, for different concentrations in the range of nmol/mol.

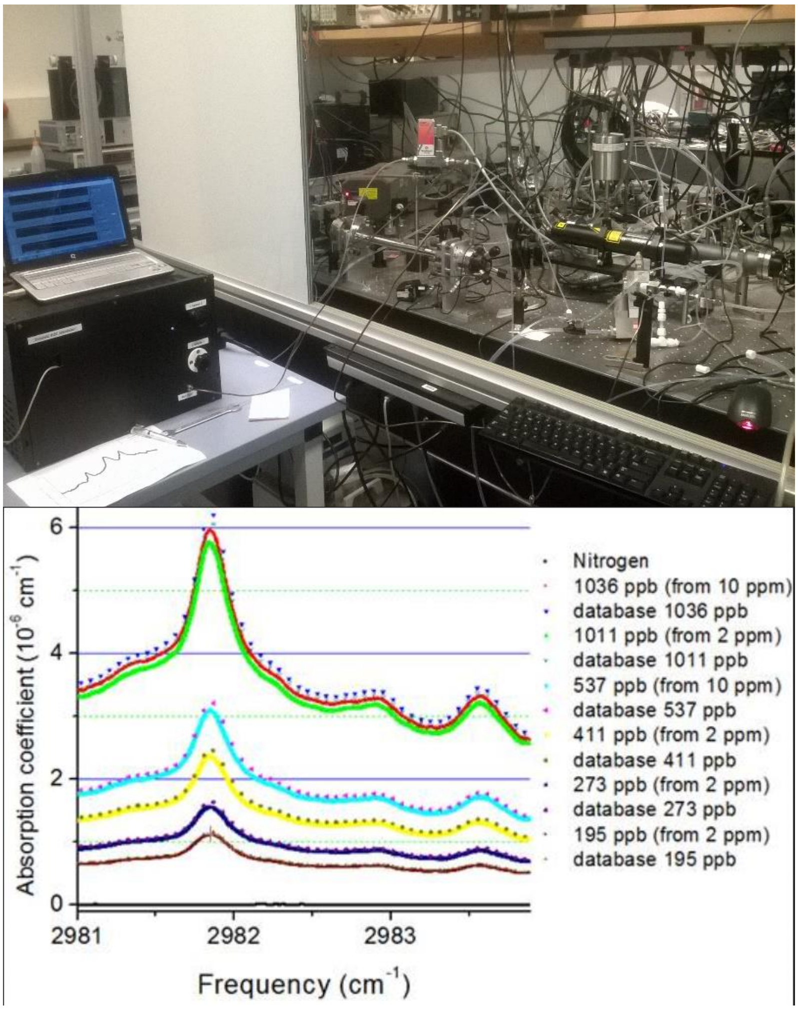

Fig. 34. Picture of the VSL measurement setup (CRDS) for the testing of the portable generator (top) and a reference methanol spectra (bottom)

VSL measurements were done continuously with an acquisition time of around 1 min for 5 days. During this time period the generator’s molar fraction was set at 3 different levels. Zero-air measurements were done typically before and after one generation setting, to verify the zero VOC level.

6.1.3. Experimental measurements of metrological performances

The metrological characteristics of the generator, such as short-term stability, reproducibility and linearity, were calculated from the CRDS measures. The reason to choose the CRDS measures instead of the Cryo-GC-FID was the higher frequency of measurements that can be achieved with the first system.

For the short-term stability evaluation, the Allan algorithm was applied to the CRDS data at 80 nmol.mol^{-1} nominal molar fraction. The results were compared with the mixture stability calculated by the generator. The main instability source of the generator was the vial temperature. For this reason, the molar fraction stability (i.e. mixture stability) was calculated multiplying the Allan deviation points calculated over the vial temperature data during operation, by the appropriate sensitivity coefficients to the molar fraction.

For the generator reproducibility evaluation, two measurements at nominal 80 nmol.mol^{-1} were performed with CRDS, and the percentage bias between the two obtained means was considered as generator reproducibility. Finally, to check the generator linearity, the CRDS points were plotted against the values of 1/P1 of the generator and the correlation coefficient of the obtained trend line was computed as a measurement of linearity.

6.2. MEASUREMENT RESULTS

The measurement results obtained during the visit at VSL institute, are reported in Fig. 35. They are filtered using as reference the stability data at the beginning of the experiment. On the left axis the device generation quantities such as P1 and a quantity (voltage) proportional to the vial temperature are reported, and on the right axis the CRDS measures are displayed. All quantities are plotted over the 100 hours measurement time.

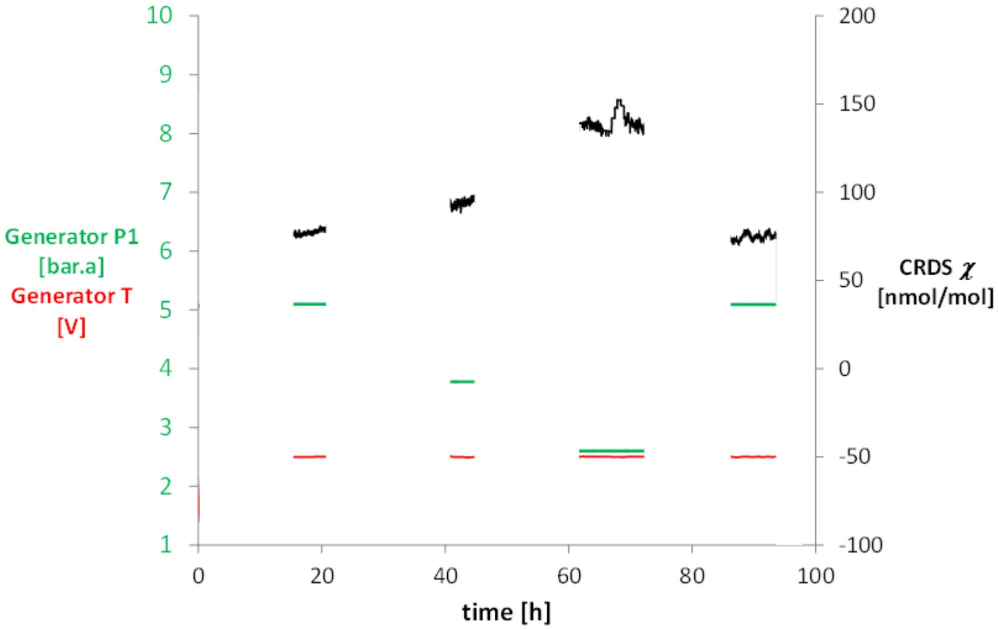

Fig. 35. Measurement results obtained at VSL, filtered by early instability at each nominal molar fraction point

The generations made at VSL and INRIM are compared and reported in the Table 11. The VSL and the INRIM measured values of the molar fraction of methanol generated, χ, by the portable generator with their respective preliminary uncertainties, are reported. It is noticeable a slight discrepancy in measured values that increases with increasing molar fraction, however with both CRDS (VSL) and the GC/FID (INRIM), repeatable measurements of concentration were obtained for the three different molar fractions.

Table 11. CRDS and Cryo-GC-FID measured values of the molar fraction generated by the INRIM portable generator

Nominal χ [nmol.mol^{-1}]	***VSL***			***INRIM***		
	χ [nmol.mol^{-1}]	$e(\chi)$ [nmol.mol^{-1}]	$e(\chi)/\chi$ %	χ [nmol.mol^{-1}]	$e(\chi)$ [nmol.mol^{-1}]	$e(\chi)/\chi$ %
80	76.0	1.6	2%	78.0	1.5	2%
100	94.3	8.4	8%	105.5	7.5	8%
150	138.5	30.0	17%	176.3	23.5	17%

6.3. METROLOGICAL CHARACTERIZATION OF THE PORTABLE GENERATOR

6.3.1. Generator short-term stability

In Fig. 36, the characterization of the generator stability from 1 to 1000 min is reported. At short observation times, it is evident a higher instability using the CRDS detector with respect to the generator. This effect can be explained by the instability contribution of the CRDS measurement itself. However, it is possible to state that the generator provides mixtures with a molar fraction stability better than 1% per hour.

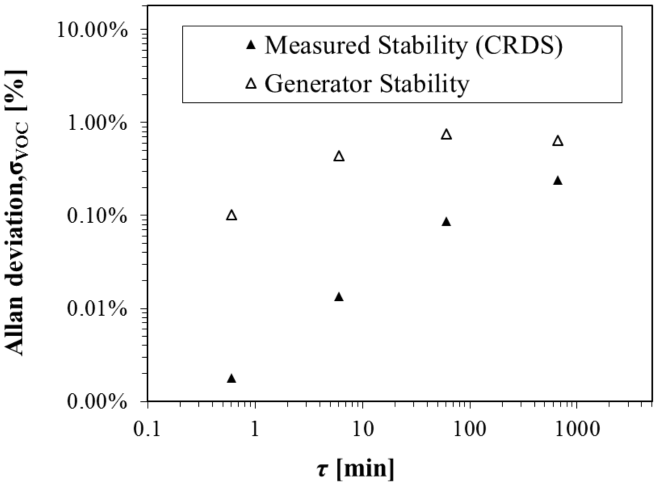

Fig. 36. Allan standard deviation of measured molar fraction (CRDS) and generator at 80 nmol.mol^{-1} nominal, at different observation times

6.3.2. Generator reproducibility

Fig. 37 reports two sets of continuous measurement of the methanol molar fraction using the CRDS detector. Firstly, the grey line was obtained and after three days of operation the same conditions of pressure were set to verify the reproducibility of the concentration (black line). It is noticeable that the generator is able to reproduce the same molar fraction of methanol with 2.9% at a nominal concentration of 80 nmol.mol^{-1} after three days of continuous operation.

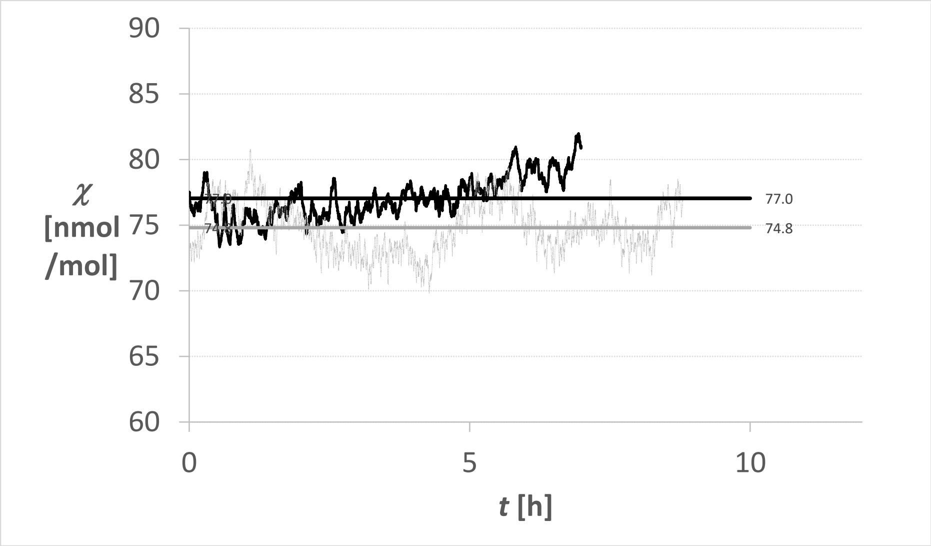

Fig. 37. Reproducibility of the same molar fraction of methanol after three days

6.3.3. *Generator linearity*

A measurement system that is linear can be calibrated easily with two or three points, instead of requiring tedious calibration procedures. The linearity was verified with the points generated in Netherlands by the VLS (See Fig. 38).

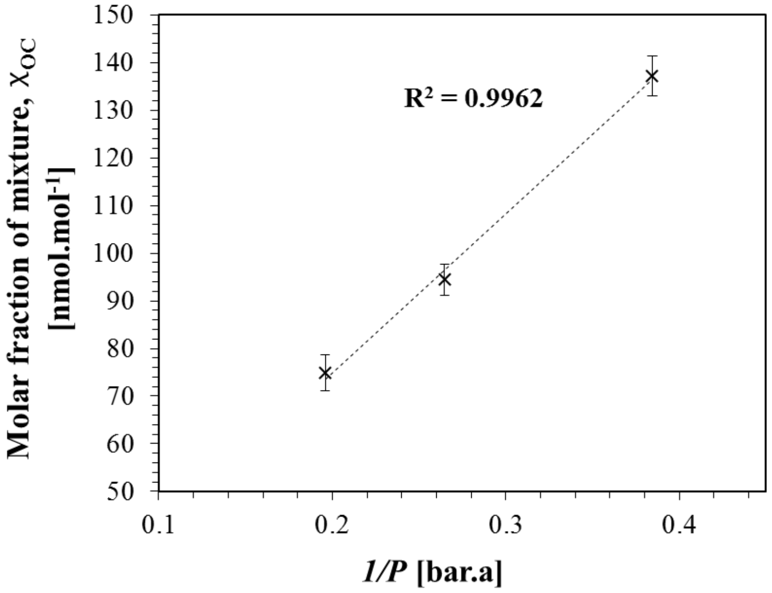

Fig. 38. Linearity of the methanol molar fraction provided by the generator

The generator was found to produce molar fraction mixtures in the 80-150 nmol.mol^{-1} range with a 99,6% linearity. The error bars reported in the graph represents the VSL measurement repeatability.

CONCLUSIONS

The metrological characterization of the primary dynamic system of INRIM was carried out. It included the development of a predictive model of the system and the evaluation of the metrological performance through uncertainty, stability and reproducibility. The first step was to obtain a model for the cells/vials system with uncertainty and precision comparable to those of the experimental results. A set of design criteria was defined and ultimately used to determine the size of the diameter and length of the vial's neck the VOC reservoir and to choose the materials to be used inside of the transportable device.

The methodology developed to evaluate the mixing was applied to define the minimum length of mixing of the portable device. The dimensions of the tubes were decided by the precision of the models and were not based on their contribution to the uncertainty. The reason is that as secondary standard the transportable device is metrological traceable to the primary system, thus its uncertainty budget follows/depends on the one built for the primary device. After assembling all the pieces in the rack box with the thermal control, an evaluation of the metrological performance of the transportable device was done.

A generation using methanol was performed at INRIM to evaluate the performance of the portable device. The molar fraction of the methanol mixtures, generated in the 80-150 nmol.mol^{-1} range, were measured by the INRIM's GC-FID. These measurements were metrological traceable to the methanol/air reference mixtures prepared by the INRIM primary dynamic device. In a similar way, another generation from the portable device, using methanol, was performed at VSL where the molar fraction of the generated mixtures were measured by their CRDS, previously calibrated with VSL cylinders. Slight differences were found among both techniques, and the deviation among them increased proportionally with the molar fraction.

The metrological characterization of the portable generator was based on the CRDS measurements carried out at VSL with the portable device producing molar fraction mixtures in the 80-150 nmol.mol^{-1} range with a 99,6 % linearity, a reproducibility after 3 days within 2,9 % and a short term stability better than 1% per hour.

The future work involves study of the VSL CRDS stability with a stable dynamic standard in order to verify the stability of the VSL measurement system. This comparison gives more insight into the stability of the portable device, since no short-term stability study can be performed with the INRIM GC/FID. The characteristic time of the measurements with the GC/FID does not allow an evaluation of the stability but more reproducibility points can be carried out with this techniques. Even if repeatable measurements were obtained, further analyses with the GC/FID system of INRIM are desirable, to understand the bias observed during the comparison.

The gravimetric estimation of the diffusion rate, however is still the best way to guarantee the minimal uncertainty. In this case, the vials geometry are constructed in such a way that are sealed to the system, assuring the absence of leakages in the system. Modifying the vials to make them removable, in such a way that a mass measurement can be easily performed, is the only way to make the device primary.

Another improvement would be the addition of a purifier to the portable system. Currently the generator/vial-cell system is able to dose VOCs into the carrier gas. A pure dry air or inert gas stream can be either generated at INRIM or obtained directly with a cylinder. But even with a calibrated transportable device, in the case of lack of either purification facilities or gas cylinders, the molar fraction and purity of the mixture generated would not be guaranteed.

REFERENCES

1. Intergovernmental Panel on Climate Change. *IPCC TAR: Climate Change - The Scientific Basis*. (2001).
2. US EPA, O. Climate Change Indicators: Atmospheric Concentrations of Greenhouse Gases.
3. Fowler, D. *et al.* Atmospheric composition change: Ecosystems–Atmosphere interactions. *Atmos. Environ.* **43,** 5193–5267 (2009).
4. Cooper, O. R. *et al.* Global distribution and trends of tropospheric ozone: An observation-based review. *Elem. Sci. Anthr.* **2,** 29 (2014).
5. WHO Working Group. *Health Aspects of Air Pollution with Particulate Matter, Ozone and Nitrogen Dioxide*. (2003).
6. Lim, S. S. *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380,** 2224–2260 (2012).
7. Kumar, P. & Imam, B. Footprints of air pollution and changing environment on the sustainability of built infrastructure. *Sci. Total Environ.* **444,** 85–101 (2013).
8. Helmig, D. *et al.* Volatile Organic Compounds in the Global Atmosphere. *Eos, Trans. Am. Geophys. Union* **90,** 513–514 (2009).
9. Consortium, M. IND63 - MetAMC: The Project. *2016* Available at: https://www.ptb.de/emrp/ind63-project.html.
10. MacDonald, S. A. *et al.* Airborne contamination of a chemically amplified

resist. 1. Identification of problem. *Chem. Mater.* **5,** 348–356 (1993).

11. *ISO 14644-1:2015 - Cleanrooms and associated controlled environments -- Part 1: Classification of air cleanliness by particle concentration*. (2015).
12. Hattori, T. Chemical contamination control in ULSI wafer processing. in *AIP Conference Proceedings* **550,** 275–284 (AIP, 2001).
13. World Health Organization. Indoor air quality: Organic pollutants. *Environ. Technol. Lett.* **10,** 855–858 (1989).
14. Balaras, C. A. *et al.* Report 22: Risk Assessment In Relation To Indoor Air Quality. *URBAN AIR, INDOOR Environ. Hum. Expo.* 139 (2000).
15. Anderson, S. E. *et al.* Evaluation of the contact and respiratory sensitization potential of volatile organic compounds generated by simulated indoor air chemistry. *Toxicol. Sci.* **97,** 355–63 (2007).
16. Decreto Legislativo n. 161: 'Attuazione della direttiva 2004/42/CE, per la limitazione delle emissioni di composti organici volatili conseguenti all'uso di solventi in talune pitture e vernici, nonche' in prodotti per la carrozzeria'. *Gazzetta Ufficiale* (2006).
17. Committee for Health-related Evaluation of Building Products. AgBB - Evaluation procedure for VOC emissions from building products. Part 1: Introduction Ausschuss zur gesundheitlichen Bewertung von Bauprodukten Committee for Health-related Evaluation of Building Products Updated List of LCI values 2015 in Part 3 Heal. 26 (2015).
18. Oppl, R. & Neuhaus Eurofins Product Testing, T. A. Emission specifications in Europe and the US – Limit values (TVOC, LCI, CREL, ...) in critical discussion. in *Indoor Air* 4 (2008).
19. AFSSET. Procédure de qualification des émissions de composés organiques volatils par les matériaux de construction et produits de décoration. (2009).
20. Arrêté du 19 avril 2011 relatif à l'étiquetage des produits de construction ou de revêtement de mur ou de sol et des peintures et vernis sur leurs émissions de polluants volatils | Legifrance. (2011). Available at:

https://www.legifrance.gouv.fr/eli/arrete/2011/4/19/DEVL1104875A/jo. (Accessed: 6th October 2016)

21. Buljubasic, F. & Buchbauer, G. The scent of human diseases: a review on specific volatile organic compounds as diagnostic biomarkers. *Flavour Fragr. J.* **30,** 5–25 (2015).

22. Gordon, S. M., Szidon, J. P., Krotoszynski, B. K., Gibbons, R. D. & O'Neill, H. J. Volatile organic compounds in exhaled air from patients with lung cancer. *Clin. Chem.* **31,** 1278–82 (1985).

23. Hakim, M. *et al.* Diagnosis of head-and-neck cancer from exhaled breath. *Br. J. Cancer* **104,** 1649–55 (2011).

24. WHO | Cancer - Fact sheet N°297. *WHO* (2016).

25. Saalberg, Y. & Wolff, M. VOC breath biomarkers in lung cancer. *Clin. Chim. Acta* **459,** 5–9 (2016).

26. Organization, (WMO) World Meteorological. *WMO Global Atmosphere Watch (GAW) Strategic Plan: 2008-2015 - a contribution to the Implementation of the WMO Strategic Plan: 2008-2011*. (WMO, 2007).

27. EURAMET. Metrology for airborne molecular contamination in manufacturing environments -MetAMC Project Details. (2013). Available at: https://www.euramet.org/research-innovation/search-research-projects/details/?eurametCtcp_project_show%5Bproject%5D=1169&eurametCtcp_project%5Bback%5D=511&cHash=d3f6b40a1de3464c12f84f06134afd67.

28. Wolkoff, P. Trends in Europe to reduce the indoor air pollution of VOCs. *Indoor Air* **13 Suppl 6,** 5–11 (2003).

29. Autrup, H. *et al.* Scientific Committee on Health and Environmental Risks SCHER Opinion on risk assessment on indoor air quality Indoor air RA.

30. JOINT RESEARCH CENTRE: Institute for Health and Consumer Protection Physical and Chemical Exposure Unit. *The INDEX project (Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU)*

Summary on recommendations and management options. (2004).

31. Shimer, D., Phillips, T. & Jenkins, P. *INDOOR AIR POLLUTION IN CALIFORNIA California Air Resources Board Air Resources Board*. *Pursuant to Health and Safety Code* (2005).

32. European Metrology Research Programme, ENV56 KEY-VOCs research project 2014 – 2017. Available at: http://www.key-vocs.eu/.

33. Werhahn, O. *iMERA-Plus project T2.J02. "Breath Analysis as a tool for early desease detection"* (2011).

34. EMPIR Call 2015 – Health, SI, Normative and Research Potential Title: Key reactive molecules as exhaled breath biomarkers for disease diagnostics and monitoring Background to the Metrological Challenges.

35. Lipták, B. G. *Instrument engineers' handbook*. (CRC Press, 2003).

36. Corrections), J. 200:2012 (JCGM 200:2008 with minor. *International Vocabulary of Metrology – Basic and General Concepts and Associated Terms (VIM) with informative annotations*. (JCGM, 2016).

37. Geib, R. C. Calibration Standard Gases Are Key to Reliable Measurements. *Spec. Gas Rep.* **Third Quar,** 4 (2005).

38. Brito, J. & Zahn, A. An unheated permeation device for calibrating atmospheric VOC measurements. *Atmos. Meas. Tech* **4,** 2143–2152 (2011).

39. Jayanty, R. K. M., Albritton, J. R., Straley, Y. H. & Von Lehmden, D. J. Journal of the Air & Waste Management Association Stability of PPB and PPM Organic Cylinder Gases Used for Calibration and Audits Stability of PPB and PPM Organic Cylinder Gases Used for Calibration and Audits. *J. Air Waste Manag. Assoc. J. Air Waste Manag. Assoc* **42,** (1992).

40. Penkett, S. & Barrie, L. *WMO/GAW Expert Workshop on Global Long-term Measurements of Volatile Organic Compounds, WMO TD No. 1373*. (WMO, 2007).

41. Martinez, S. Calibration Standards. *American School of Gas Measurement Technology* 4 (2013).

42. Linde-gas. Quality in Specialty Gases Mixtures:Mixture tolerances. Available at: http://hiq.linde-gas.com/en/quality_safety/quality/mixture_tolerances.html.

43. Matheson Tri-Gas. The Gold Standard in Calibration Mixtures.

44. Taylor, J. R. *Introduction To Error Analysis: The Study of Uncertainties in Physical Measurements*. (University Science Books, 1982).

45. Miller, W. R. & Rhoderick, G. C. Stability of compressed gas mixtures containing low level volatile organic compounds in aluminum cylinders. *Fresenius. J. Anal. Chem.* **351,** 221–229 (1995).

46. Nelson, G. O. *Gas mixtures : preparation and control*. (Lewis Publishers, 1992).

47. Demichelis, A., Sassi, @bullet G & Sassi, @bullet M P. Metrological performances of mass flow controllers for dynamic gas dilution. *Accredit. Qual. Assur.* 181–186 (2013). doi:10.1007/s00769-013-0974-y

48. International Organization for Standardization (ISO). *ISO 6145-8:2005 - Gas analysis -- Preparation of calibration gas mixtures using dynamic volumetric methods -- Part 8: Diffusion method*. (2003).

49. International Organization for Standardization (ISO). *ISO 6145-7:2009 - Gas analysis -- Preparation of calibration gas mixtures using dynamic volumetric methods -- Part 7: Thermal mass-flow controllers*. (2003).

50. VICI Metronics Inc. Generating Calibration Gas Standards with Dynacal ® Permeation Devices Calibration Systems Basic U-Tube Holder Additional System Considerations (Technical Note 1001). (2004).

51. Jardine, K. J., Henderson, W. M., Huxman, T. E. & Abrell, L. Dynamic Solution Injection: a new method for preparing pptv–ppbv standard atmospheres of volatile organic compounds. *Atmos. Meas. Tech* **3,** 1569–1576 (2010).

52. Jaouen, P., Gonzalez-Flesca, N. & Carlier, P. Dynamic polluted atmosphere generator at low ppbv levels for validating VOC sampling methods. *Environ. Sci. Technol.* **29,** 2718–2724 (1995).

53. John K. Taylor. Sampling and Calibration for Atmospheric Measurements. A Symposium Sponsored by ASTM Committee D-22 on Sampling and Analysis of Atmospheres. in (ed. ASTM) (1985).

54. Sassi, G., Demichelis, A., Lecuna, M. & Sassi, M. P. Preparation of standard VOC mixtures for climate monitoring. *Int. J. Environ. Anal. Chem.* **95,** 1195–1207 (2015).

55. Gautrois, M. & Koppmann, R. Diffusion technique for the production of gas standards for atmospheric measurements. *J. Chromatogr. A* **848,** 239–249 (1999).

56. Nielsen, H. S. What is Traceability and Why Do We Calibrate? in *ASQ Midwest Conference* (1999).

57. Demichelis, A., Sassi, G. & Sassi, M. Overcoming a Metrological Need in Climate Change Monitoring. in *13th SGEM GeoConference on Energy And Clean Technologies* (2013). doi:10.5593/SGEM2013/BD4/S19.027

58. Demichelis, A., Lecuna, M., Sassi, G. & Sassi, M. P. Diffusion Vials for generation of traceable gas standards of Volatile Organic Compounds (VOC). in *Proceedings of the XXI IMEKO World Congress 'Measurement in Research and Industry'* (2015).

59. Riordan, S. The objectivity of scientific measures. *Stud. Hist. Philos. Sci. Part A* **50,** 38–47 (2015).

60. Joint Committee for Guides in Metrology (JCGM). Evaluation of measurement data: Guide to the expression of uncertainty in measurement. 120 (2008). doi:10.1373/clinchem.2003.030528

61. Riley, W. & Howe, D. A. *Handbook of Frequency Stability Analysis | NIST*. (Special Publication (NIST SP) - 1065, 2008).

62. Rutman, J. & Walls, F. L. Characterization of Frequency Stability In Precision Frequency Sources. *Proc. IEEE* **79,** (1991).

63. ANSYS. *ANSYS Fluent Theory Guide. Release 15.0*. (2013).

64. Bird, R. B. (Robert B., Stewart, W. E. & Lightfoot, E. N. *Transport*

phenomena. (J. Wiley, 2007).

65. Zhang Jianshun Zhang, J., Chen, Q. & Yang, X. A Critical Review on Studies of Volatile Organic Compound (VOC) Sorption by Building Materials (RP-1097). *ASHRAE Trans.* **108,** 162–174 (2002).

66. SEMI International Standards. *SEMI F21-1102 - Classification of Airborne Molecular Contaminant Levels in Clean Environments*. (1995).

67. Harris, P., Senior, M., Calgary, S. & Canada, A. *Relative Response Time of TrueTube^{TM} when Measuring Moisture Content in a Sample Stream Haritec Scientific & Engineering Support*. (2004).

68. Fogler, H. S. *Essentials of chemical reaction engineering*. (Prentice Hall, 2011).

69. Sassi, G., Demichelis, A. & Sassi, M. P. Uncertainty analysis of the diffusion rate in the dynamic generation of volatile organic compound mixtures. *Meas. Sci. Technol.* **22,** 105104 (2011).

70. Ambrose, D., Sprake, C. H. S. & Townsend, R. Thermodynamic properties of organic oxygen compounds. XXXVII. Vapour pressures of methanol, ethanol, pentan-1-ol, and octan-1-ol from the normal boiling temperature to the critical temperature. *J. Chem. Thermodyn.* **7,** 185–190 (1975).

71. Sassi, G., Demichelis, A. & Sassi, M. P. Air flow rate thermal control system at low pressure drop. *Flow Meas. Instrum.* **35,** 44–47 (2014).

72. Wright, J. D., Kayl, J.-P., Johnson, A. N. & Kline, G. M. Gas Flowmeter Calibrations with the Working Gas Flow Standard NIST Special Publication 250-80. (2009).

73. Demichelis, A., Sassi, G., Lecuna, M. & Sassi, M. P. Molar fraction stability in dynamic preparation of reference trace gas mixtures. *IET Sci. Meas. Technol.* **10,** 414–419 (2016).

74. National Physical Laboratory (NPL). Good Practice Guidance: Buoyancy Correction and Air Density Measurement. (2002).

75. Persijn, S., Harren, F. & van der Veen, A. Quantitative gas measurements

using a versatile OPO-based cavity ringdown spectrometer and the comparison with spectroscopic databases. *Appl. Phys. B* **100,** 383–390 (2010).