NOVA SCHOOL OF
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DEPARTMENT OF PHYSICS

DEVELOPMENT OF METHODOLOGY FOR AUTOMATIC ON-LINE MONITORING OF VOCS IN AN AUTOMOTIVE PLANT AND DIRECT EVALUATION OF ITS IMPACT ON EMPLOYEES

Pedro Rafael Catalão Moura

Master in Biomedical Engineering

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Pedro Rafael Catalão Moura

Master in Biomedical Engineering

Adviser: Valentina Borissovna Vassilenko
Assistant Professor, NOVA School of Science and Technology, NOVA University of Lisbon

Examination Committee:

Chair: Paulo Manuel Assis Loureiro Limão-Vieira,
Full Professor, NOVA School of Science and Technology, NOVA University of Lisbon

Rapporteurs: Regina Maria Brandão de Oliveira Duarte,
Principal Researcher, University of Aveiro
Ana Luísa Marques Paixão de Carvalho Maulvault,
Assistant Researcher, Instituto Português do Mar e da Atmosfera

Adviser: Valentina Borissovna Vassilenko,
Assistant Professor, NOVA School of Science and Technology, NOVA University of Lisbon

Members: Hugo Filipe Silveira Gamboa,
Full Professor, NOVA School of Science and Technology, NOVA University of Lisbon

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Development of Methodology for Automatic On-Line Monitoring of VOCs in an Automotive Plant and Direct Evaluation of Its Impact on Employees

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Quand nous sommes très forts, — qui recule?
Très gais, — qui tombe de ridicule?
Quand nous sommes très méchants, — que ferait-on de nous?
Arthur Rimbaud

ABSTRACT

Proper working conditions must be one of the employers’ main concerns in any type of company but particularly in work locations where the employees are chronically exposed to hazardous compounds. Volatile organic compounds (VOCs) are among the main contributors to the degradation of air quality. Their presence, even at trace concentration levels, may represent a serious risk to human health so, an accurate identification and quantification Is crucial to ensure proper work conditions.

The present doctoral thesis explores the complex scenario of a car factory painting line and assesses the exposure of the employees to the VOCs emitted by the products utilised during the coating processes. To do so, several dedicated studies and protocols were developed and implemented. The most relevant locations of the painting line were evaluated, and the most relevant VOCs were identified. All the coatings used in the line were studied regarding their emissions. GC-IMS was defined as the most suitable technique for indoor air monitoring and quality control due to its outstanding sensitivity and selectivity, analytical flexibility, simplicity, and almost real-time monitoring capacity. A database of analytes and a calibration protocol were developed for identification and quantification purposes. Theoretical considerations on the impacts of continuous exposure on the employees' health were addressed.

The developed protocols and results achieved enabled to create accurate and suitable procedures to continuously monitor and control the indoor air quality at the car factory painting line and at any industrial site. These tools can be used and applied as a proper way of ensuring work conditions of quality for their employees while monitoring the overall state of the factory's indoor air. Finally, this doctoral project allowed to understand the putative impacts on employees' health and assess the necessity to implement further systems of pollutants extraction, air purification and body protection.

Keywords: Air Quality, Car Factory Painting Line, Employees Health, Gas Chromatography, Health Impacts, Indoor Air, Ion Mobility Spectrometry, Volatile Organic Compounds.

RESUMO

Condições de trabalho ideais devem ser uma das principais preocupações dos empregadores em qualquer tipo de empresa, mas, particularmente, em locais de trabalho onde os funcionários estão expostos de forma crónica a compostos perigosos. Compostos voláteis orgânicos (VOCs) estão entre os principais contribuidores para a degradação da qualidade do ar. A sua presença, mesmo em níveis vestigiais de concentração, pode representar um risco sério para a saúde humana, logo, uma correta identificação e quantificação é crucial para assegurar condições de trabalho adequadas.

A presente tese doutoral explora o cenário complexo de uma linha de pintura de uma fábrica automotiva e avaliar a exposição dos trabalhadores aos VOCs emitidos pelos produtos utilizados durante os processos de pintura. Para tal, vários estudos dedicados e protocolos foram desenvolvidos e implementados. As localizações mais relevantes da linha de pintura foram avaliadas, e os VOCs mais relevantes foram identificados. Todas as tintas usadas na linha foram estudadas em função das suas emissões. GC-IMS foi definida como a técnica mais adequada para monitorização do ar interior e controlo de qualidade devido à sua fantástica sensibilidade e seletividade, flexibilidade analítica, simplicidade e capacidade de medição quase em tempo real. Uma biblioteca de compostos e um protocolo de calibração foram desenvolvidos para propósitos de identificação e quantificação. Considerações teóricas sobre o impacto da exposição contínua na saúde dos trabalhadores foram incluídas.

Os protocolos desenvolvidos e resultados conseguidos permitiram criar procedimentos adequados e precisos para monitorizar e controlar continuamente a qualidade do ar interior da linha de pintura da fábrica automotiva e de qualquer localização industrial. Estas ferramentas podem ser usadas e aplicadas como uma forma adequada de garantir condições de trabalho de qualidade para os funcionários enquanto monitorizam o estado geral da qualidade do ar da fábrica. Finalmente, este projeto doutoral permitiu perceber os impactos putativos na saúde dos trabalhadores e avaliar a necessidade de implementar sistemas adicionais de extração de poluentes, purificação do ar, e proteção corporal.

Palavas chave: Ar Interior, Compostos Voláteis Orgânicos, Cromatografia Gasosa, Espetrometria de Mobilidade Iónica, Impactos na Saúde, Linha de Pintura de Fábrica Automotiva, Qualidade do Ar, Saúde dos Trabalhadores.

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ACRONYMS

BTEX	Benzene, Toluene, Ethylbenzene, Xylenes
CAS	Chemical Abstracts Service
CGFU	Circular Gas Flow Unit
CKD	Chronic Kidney Diseases
CLD	Chronic Liver Diseases
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease - 2019
COx	Carbon Oxides
CRC	Colorectal Cancer
CT	Computed Tomography
DIMS	Differential Ion Mobility Spectrometry
E-Nose	Electronic Nose
FAIMS	Field Asymmetric Ion Mobility Spectrometry
FDA	Food and Drug Administration
FENO	Fractional Exhaled Nitric Oxide
GC	Gas Chromatography
GO	Graphene Oxide
IDE	Interdigitated Electrodes

IMS	Ion Mobility Spectrometry
IR	Infrared
LbL	Layer by Layer
MCC	Multi Capillary Column
MOS	Metal Oxide Sensors
MS	Mass Spectrometry
NI	Not Identified
NIOSH	National Institute for Occupational Safety and Health
NOx	Nitrogen Oxides
PC1	Principal Component 1
PC2	Principal Component 2
PC3	Principal Component 3
PCA	Principal Component Analysis
PEI	Polyethyleneimine
PIDS	Photoionization Detector Sensors
PLS	Partial Least Squares
PTFE	Polytetrafluoroethylene
PTR	Proton Transfer Reaction
QCMS	Quartz Crystal Microbalance Sensors
RIP	Reactant Ion Peak
SAWS	Surface Acoustic Wave Sensors
SD	Standard Deviation
SSES	Solid-State Electrochemical Sensors
SOx	Sulphur Oxides
SPME	Solid-Phase Micro Extraction
SWOT	Strengths, Weaknesses, Opportunities, Threats

t_d	Drift Time
TGA	Thermogravimetry
TLV	Threshold Limit Value
r_d	Retention Time
tVOCs	Total Volatile Organic Compounds
UV	Ultraviolet
v_d	Drift Velocity
VOCs	Volatile Organic Compounds
WHO	World Health Organization

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INTRODUCTION

This chapter addresses the primordial issues that led to the creation and development of the doctoral project here explored. In specific, this chapter contains information on the context and motivation behind the doctoral project, the problems and objectives drawn for the project, the approach to accomplish those objectives, and the contributions given. Additionally, the structure of this dissertation and the list of the papers on which it is based can also be consulted.

1.1 Context and Motivation

The attention given by the contemporary society to the public health is on the rise. Public health is, in generic terms, the application of scientific knowledge with the aim of organise systems and/or developing medical services that enable to monitor, prevent, and tackle health-disease processes, control incidents in populational groups, and thwart major dangerous scenarios.

A large number of factors can contribute to affect and degrade public health. Pollution (air, soil and water contamination), contagious diseases (viruses and bacteria), weather conditions (heat and cold waves), and even lifestyle (escalation of the number of cardiovascular, neurological and other diseases) are a few examples of those factors.

The quality of the air existent in both indoor and outdoor locations can significantly contribute to maintaining public health or, in scenarios of poor air quality, contribute to the degradation of specific populational groups health. In fact, air quality is such a preponderant factor in worldwide public health that even the World Health Organization (WHO) has devoted a lot of time to address it and study it. According to the WHO, 99% of the world population lives or often attends locations where the quality of the air is lower than the acceptable level. In addition, the WHO states that around 2.6 billion people are exposed, on a daily basis, to scenarios in which the lack of air quality represents a serious risk to their health. Perhaps the most shocking number provided by the WHO corresponds to the casualties. It is estimated that 4.6 million of precocious deaths occur every year caused by health conditions directly related to the lack of air quality [1]. In addition, WHO has provided annual recommendations on the guidelines in regard to the most hazardous pollutants [2].

Among all the pollutants responsible for the degradation of the air quality, one can list common compounds like carbon oxides (COx), nitrogen oxides (NOx), sulphur oxides (SOx) and even inhalable particulate matters (PM). The presence and the concentration levels of these compounds in the air can often represent a risk to both the human health and the environment. Another well-known group of pollutants is the volatile organic compounds (VOCs). VOCs can greatly affect air quality and be particularly hazardous to human beings due to their characteristics. Exposure to VOCs can lead to a vast range of pathologies and health conditions that spread from simpler problems, like allergies, pruritus, and headaches, to life-threatening pathologies like lung or oral cancer. In addition to the risks to human health of both short- and long-term exposure to VOCs, this category of compounds is known for being present in the composition of many daily-use objects and activities. Furniture, cleaning products, disinfectants and pesticides, perfumes and creams, building and coating materials, food and cooking, smoking, and driving are a few examples of vulgar sources responsible for the emission of VOCs. In this way, VOCs often populate the indoor air of most locations including personal homes, public spaces and even work locations [3, 4].

Considering all the aforementioned facts, the assessment of VOCs is a mandatory and contemporary topic that deserves additional attention in scenarios of chronic exposure. At work locations where exists a vast range of products known for their emissions of VOCs, and where the employees are chronically exposed to those same compounds, their detection, identification, and quantification are even more important and mandatory in order to maintain a suitable quality of the air and provide a safe work environment to the employees.

1.2 Problems and Objectives

The air quality at work locations is of special relevancy since the employees often spend at least eight hours per day at these locations, especially if one is talking about worksites rich in VOCs-emitting sources. An example of such scenario is a car factory painting line.

In order to fully coat a car body, an automotive factory needs to employ a vast diversity of solutions and coatings. The majority of these coatings have, in their composition, organic compounds that are often added as solvents. Since they are rich in these compounds, a considerably elevated amount of VOCs is emitted into the indoor air of the painting line during the automatized application of the coatings to the metallic surface of the vehicles. Consequently, the indoor air of the factory can be extremely toxic and hazardous to the employees of the line who are chronically exposed to this scenario, not to mention the impacts on the environment once the VOCs are released to the exterior.

Considering the aforementioned facts, the present doctoral project was developed as an outcome of a partnership between the Volkswagen car factory in Portugal, Volkswagen AutoEuropa, and NOVA School of Science and Technology – NOVA University of Lisbon. AutoEuropa is the largest foreign investment in Portuguese territory and directly employs more than 5000 people, not to mention the parallel employment in third-party companies. As in any Volkswagen factory, AutoEuropa leaders look forward to providing the best work conditions for all the thousands of employees in terms of safety and health preservation. Being aware of the potential toxicity existent in the painting line of the factory, the leaders of the factory intend to fully address and fix this issue, if that is the case.

Aiming to completely characterise the scenario in regard to the air quality in the indoor of the painting line, a methodology was intended to be developed. Then, this doctoral project intended to develop a complete methodology that enables to assess the indoor air quality of the car factory painting line considering three overall goals: identify the main pollutants, isolate the main emitting sources and evaluate the impacts on the health of the employees.

Under the first goal, this doctoral project aims to identify all the main volatile organic compounds existent in the indoor air of the main locations from the painting line. To do so, one must select an analytical procedure capable of detecting the VOCs at the concentration levels that they are usually present in the air. Then, one must completely evaluate the suitability of the selected technique for both *in-situ* and long-term analyses. Protocols to identify and quantify the analytes detected in the air must equally be developed. The locations of interest of the entire painting line must be defined and properly evaluated with the protocol developed. A full characterisation of the air content in terms of VOCs must be achieved.

In order to complete the second set of goals, one must identify all the possible emitting sources of VOCs. As mentioned, the painting of a car involves several steps and the use of many coating solutions. In this way, one must evaluate all the potential emitting sources of VOCs and identify the most relevant ones for further analysis. Then, a protocol to analyse the identified sources must be developed, and all the VOCs present in the composition of the coatings later emitted into the air must be identified. A comparison of the VOCs emitted by the coatings and the VOCs existent in the air must be performed to complete the second set of goals.

Finally, under the third set of goals, one must evaluate the impacts on the health of the employees. To do so, theoretical considerations regarding the eventual impacts of chronic exposure on the health of the employees must be included in this doctoral project. These considerations aim to compare the compounds emitted by the coatings and existent in the indoor air, with the bibliography in regard to known impacts of those compounds on human health. In addition, they may reveal the necessity of further studies with biological samples collected from the employees.

1.3 Approach and Contributions

As mentioned in the previous chapter, three sets of goals were defined for this doctoral project. In this chapter, a more detailed view on each study developed aiming to successfully achieve all three sets of goals is provided.

The first set of goals includes several topics. The first goal consists of defining a proper analytical procedure that allows to fully study all the samples and assess all the target compounds. To do so, a theoretical analysis is intended to be developed on all the main techniques capable of detecting volatile organic compounds. This approach will enable to select the most suitable technique for the target analyses. Laboratory studies are equally intended to be developed in order to compare ion a practical way the most relevant methodologies available.

Once theoretically selected the analytical technique to be used throughout the entire project, practical experiments are intended to be developed in order to assess the suitability of the technique for *in-situ* and long-term analysis capacity. The capability of the technique to perform analyses *in-loco*, at the target locations, and for long periods of time is crucial to fully characterise the indoor air of the car factory painting line.

Since the project defines the identification and quantification of VOCs as the main and final goal, a database of analytes must be developed for purposes of identification, and a calibration protocol must be developed for purposes of quantification. To do so, pure samples of the target compounds are intended to be analysed with the selected technique and registered in a database of analytes. This database can be later used to identify all the compounds eventually detected throughout the entire doctoral project. Since the characterisation of the indoor air of the factory requires que quantification of the detected analytes, then, pure samples of the target analytes are intended to be analysed with the selected techniques at distinct and known concentration levels. This approach will enable the plotting of calibration curves and the development of an overall calibration procedure.

As the next step, it is intended to develop the protocol for the analyses to be implemented *in-loco* at the car factory painting line. Here, the selected analytical technique and respective methodology are intended to be assembled at the locations of interest, and *in-situ* analyses of the indoor air are intended to be performed. The target locations must be selected after a careful *in-situ* visual analysis of the entire location and considering the information collected near the employees. Then, all the detected analytes must be identified. To do so, the developed database will act as a cross-checking tool, enabling to know all the compounds existent in the air of the painting line and, specifically, in the air of all the locations of interest. In addition, it is expected to quantify the main compounds detected at those same locations using the previously developed protocol of calibration.

Having in mind the identification of the origin of the VOCs, one must list all the potential sources of emission existent in the interior of the painting line. From all the possible sources, the most relevant must be selected for further studies. Then, a protocol for the analysis of the selected VOCs-emitting sources is intended to be developed aiming to characterise all the compounds emitted into the air by the coatings during the painting process. These studies will take place in a laboratory, in this way, samples of the emitting sources must be carefully collected, stored and transported for further analyses. Once defined and applied the measurement protocol, one intends to identify all the VOCs emitted by all types of sources, namely, the basecoats, clearcoats and varnish used in the line, by utilising the previously developed database of compounds.

The identification of all the VOCs existent in the air of the locations of interest, as well as, of all the VOCs emitted by the main emitting sources will enable a direct comparison between both sets of analytes. This comparison can prove the direct connection between the pollutant solutions used in the factory line, and the hazardous analytes detected in the indoor air whose presence represents a threat to the environment and to the health of the employees.

In regard to the evaluation of the impact on the health of the employees, one intends to theoretically assess the potential impacts of the detected VOCs on human health by reviewing the most relevant literature. Considerations on the potential diseases caused by chronic exposure are intended to be given. The necessity of performing analyses with biological samples collected from the employees may arise from these considerations.

It is important to state that for all the mentioned analyses and studies, additional protocols must be developed regarding the preparation of the different types of samples, the period of analysis, the way of collecting, transporting, and storing the samples, and any other details that require eventual preparation prior to the studies.

Once concluded all the tasks of the doctoral project, one aims to be capable of providing the car factory a complete methodology to monitor the indoor air quality of the painting line, control the main solutions responsible for the emission of toxic compounds, and evaluate the impacts of the health of the employees. Furthermore, one intends to grant the factory deep knowledge on the compounds existent in the air, their identity and characteristics, a full description of the composition of the emitting sources and potential issues related to the employees, enabling the factory to act in accordance with the results achieved. One expects that all the work here addressed, and all the results listed in due time can be used in practical terms to improve the work conditions to the employees and help the factory leaders to ensure the maintenance of proper conditions of their facilities.

1.4 Document Organization

Aiming to ensure full transparency of the results achieved throughout the entire doctoral project, every developed study was promptly published in international, peer-reviewed, and indexed journals. Then, all the published material was rearranged in a coherent order to build this dissertation. In this way, the document is divided into four main sections: theoretical framework, materials and methods, results and discussion, and conclusions.

The theoretical framework chapter addressed the state of the art of all the fields relevant to the scope of the doctoral project. In Material and Methods, the list of all developed procedures, used equipment, analysed samples, and used software can be consulted. All the results and respective discussion achieved during the studies developed throughout the doctoral project can be consulted in the chapter Results and Discussion. Finally, overall conclusions and considerations on future work were included in the fourth section of the document.

1.4.1 Published Papers

All the data obtained during the doctoral project and respective results were published in international, indexed and peer-reviewed scientific journals. It is worth stating that, since all the work developed is already published in the form of scientific articles, this dissertation is completely based on those same papers. Each chapter includes a disclaimer on the articles used to write it. A list of these papers is listed considering their reference number below.

[5] **P. C. Moura**, M. Raposo, V. Vassilenko. Breath Biomarkers in Non-Carcinogenic Diseases. *Clinica Chimica Acta,* 117692, 2023. https://doi.org/10.1016/j.cca.2023.117692.

[6] **P. C. Moura**, F. Santos, C. Fujão, V. Vassilenko. Towards the Characterization of the Coatings Used in a Car Factory Painting Line. *Journal of Coatings Technology and Research*, 2023. https://doi.org/10.1007/s11998-023-00847-7.

[7] **P. C. Moura**, P. A. Ribeiro, M. Raposo, V. Vassilenko. The State of the art on Graphene-Based Sensors for Human Health Monitoring through Breath Biomarkers. *Sensors*, 23, 9271, 2023. https://doi.org/10.3390/s23229271.

[8] V. Vassilenko, **P. C. Moura**, M. Raposo. Diagnosis of Carcinogenic Pathologies through Breath Biomarkers: Present and Future Trends. *Biomedicines*, 11, 3029, 2023. https://doi.org/10.3390/biomedicines11113029.

[9] **P. C. Moura**, F. Santos, C. Fujão, V. Vassilenko. In Situ Indoor Air Volatile Organic Compounds Assessment in a Car Factory Painting Line. *Processes*, 11, 2259, 2023. https://doi.org/10.3390/pr11082259.

[10] P. H. C. Santos, **P. C. Moura**, V. Vassilenko. Suitability of Short- and Long-Term Storage of Volatile Organic Compounds Samples in Syringe-Based Containers: A Comparison Study. *Metabolites*, 13, 903, 2023. https://doi.org/10.3390/metabo13080903.

[11] P**. C. Moura**, V. Vassilenko. Long-Term *In Situ* Air Quality Assessment in Closed Environments: A Gas Chromatography – Ion Mobility Spectrometry Applicability Study. *European Journal of Mass Spectrometry*, 29, 231-239, 2023. https://doi.org/10.1177/14690667231187502.

[12] **P. C. Moura**, M. Raposo, V. Vassilenko. Breath Volatile Organic Compounds (VOCs) as Biomarkers for the Diagnosis of Pathological Conditions: A Review. *Biomedical Journal*, 46, 100623, 2023. https://doi.org/10.1016/j.bj.2023.100623.

[13] **P. C. Moura**, V. Vassilenko, P. A. Ribeiro. Ion Mobility Spectrometry Towards Environmental Volatile Organic Compounds Identification and Quantification: A Comparative Overview Over Infrared Spectroscopy. *Emission Control Science and Technology*, 9, 25-46, 2023. https://doi.org/10.1007/s40825-022-00220-x.

[14] **P. C. Moura**, V. Vassilenko. Contemporary Ion Mobility Spectrometry Applications and Future Trends Towards Environmental, Health and Food Research: A Review. *International Journal of Mass Spectrometry*, 486, 117012, 2023. https://doi.org/10.1016/j.ijms.2023.117012.

[15] **P. C. Moura**, T. P. Pivetta, V. Vassilenko, P. A. Ribeiro, M. Raposo. Graphene Oxide Thin Films for Detection and Quantification of Industrially Relevant Alcohols and Acetic Acid. *Sensors*, 23, 462, 2023. https://doi.org/10.3390/s23010462.

[16] **P. C. Moura**, V. Vassilenko. Gas Chromatography – Ion Mobility Spectrometry as a Tool for Quick Detection of Hazardous Volatile Organic Compounds in Indoor and Ambient Air: A University Campus Case Study. *European Journal of Mass Spectrometry*, 28, 113-126, 2023. https://doi.org/10.1177/14690667221130170.

[17] J. M. Fernandes, V. Vassilenko, **P. C. Moura**, V. Fetter. Gas Chromatography-Ion Mobility Spectrometry Instrument for Medical Applications: A Calibration Protocol for ppb and ppt Concentration Range. In: 12th Advanced Doctoral Conference on Computing, Electrical and Industrial Systems, DoCEIS 2021. Costa da Caparica, Portugal: Springer, 349-357, 2021. https://doi.org/10.1007/978-3-030-78288-7_34.

[18] **P. C. Moura**, V. Vassilenko, J. M. Fernandes, P. H. C. Santos. Indoor and Outdoor Air Profiling with GC-IMS. In: 11th Advanced Doctoral Conference on Computing, Electrical and Industrial Systems, DoCEIS 2020. Costa de Caparica, Portugal: Springer, 437-444, 2020. https://doi.org/10.1007/978-3-030-45124-0_43.

A complete list of all the published papers, besides the ones used in this dissertation, can be consulted in Appendix A.

2

THEORETICAL FRAMEWORK

This chapter addresses all the theoretical concepts, state of the art of several fields of interest, useful scenarios and details the aims of the doctoral project. In specific, the chapter offers an overall point of view on the importance of air quality and details on the main factors for the degradation of air quality. A careful description of an industrial scenario can be consulted as well as the topics that lead to its relevance for the present doctoral project. Then, thorough information on the impacts of the lack of air quality on human beings and forms of monitoring that same health is addressed. Finally, information on the main analytical techniques and procedures often used in the mentioned fields is provided.

2.1 Air Quality

Nowadays, most of modern life and social interactions often occur in closed spaces and indoor environments at both private and public locations. Among these, one can mention work facilities [19], personal homes and hotels [20], private cars and public transportation [21], stores and shopping centres [22], schools [16], hospitals [23], and many others. In fact, this predominance of time spent indoors has been addressed and statistically described in several scientific studies.

Klepeis et al., for instance, developed a statistical study whose results showed that the survey respondents spend 87% of their daily time in some kind of indoor location [24]. Brasche et al., in their turn, were able to conclude that German citizens spend 15.7 hours per day in indoor environments. Similar values were registered by the authors for the United States of America (15.6 hours per day) and Canada (15.8 hours per day), which means that the average percentage of time spent in indoor spaces is more than 65% of the day [25]. The addressed results were corroborated by Schweizer et al., in a more recent study. The authors gathered a cohort of 1427 volunteers from seven different countries and assessed the time spent in indoor areas by all the subjects. They were able to determine that the average time spent in indoor locations ranges from 13.5 to 15.8 hours per day, meaning that the citizens spend between 56 to 66% of their daily time in the interior of some kind of building, transportation, work location, or public facilities [26]. Since most of our life is spent indoors, a truly relevant issue arises which must be carefully deemed: indoor air quality.

The degradation of indoor conditions and the lack of air quality are triggered by several known causes. Chemical compounds like carbon monoxide (CO), sulphur dioxide (SO_2), nitrous oxide (N_2O), and volatile organic compounds (VOCs), for example, are among the main contributing factors to the loss of safety conditions in indoor locations [23, 22, 27]. The presence of these polluting compounds, especially at hazardous concentration levels, originates the well-known syndrome of "sick building" and, consequently, causes a vast range of pathologies and health conditions in the humans who frequently populate those buildings [28, 29, 30].

As mentioned, public and heavily populated spaces should receive further attention to what air quality concerns. An example of potential risks to populational groups is the clinical environment. In hospitals, air quality assessment is critical since the presence of toxic compounds can have direct consequences on the health of both medical staff and patients under treatment. An eventual continued exposure to these compounds existing in the air may, not only, worsen the diseases of the patients, but also, lead to the development of additional health conditions [31, 23]. In another context, the presence of pollutants at toxic levels of concentration in kindergartens and primary schools, for example, may represent an unnecessary danger for younger children. Taking into consideration the fact that the pulmonary/respiratory system of children is under development, possible health problems at such young ages can be even more critical [32, 33, 34, 35]. Similar considerations can be applied to public spaces like train and bus stations, airports, malls, restaurants, stores, and other heavily populated locations. These locations require a correct and accurate air quality assessment to prevent public health problems and minimise the risks of large-scale diseases [36, 37, 20]. Finally, work locations where the employees' exposure to VOCs occurs on a daily basis, such as factories, production lines, painting lines, and large-scale facilities, are also scenarios of interest and should have protocols for air quality monitoring and control, to mitigate potential health risks during the work shifts [38, 39, 40, 41].

2.1.1 Volatile Organic Compounds

Volatile Organic Compounds (VOCs) are among the main factors responsible for air quality degradation in both indoor and outdoor environments. Due to their idiosyncrasies, VOCs deserve and have been receiving special attention from the academic community [3]. Evidence of that is the evolution of the number of published papers under the scope "Volatile Organic Compounds" and indexed in one of the main scientific databases, specifically, Web of Science. This evolution is visible in Figure 1, where the growth in the number of published articles is evident.

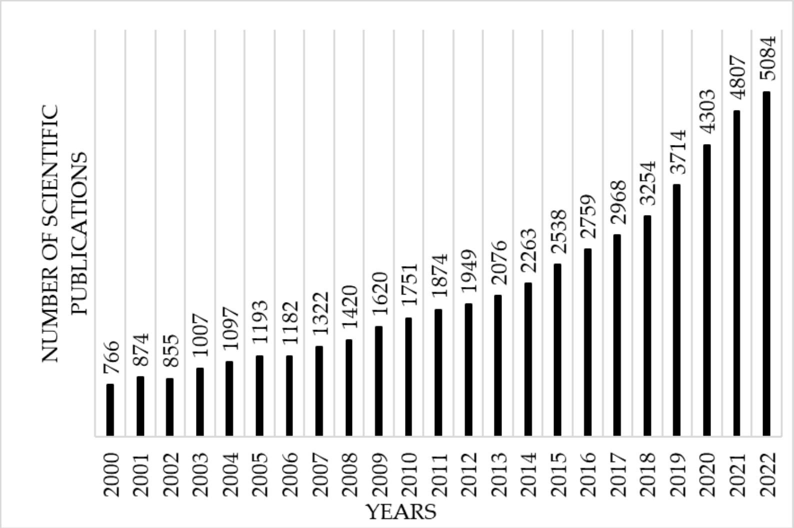

Figure 1 - Number of scientific articles published per year since the year 2000 under the scope "Volatile Organic Compounds".

The European Union directive on the limitations of emissions of volatile organic compounds defines VOCs as *"... any organic compound ..., having at 293.15 K a vapour pressure of 0.01 kPa or more, or having a corresponding volatility under the particular conditions of use.*", i.e., as the name states, VOCs are compounds that present two major characteristics; they are simultaneously organic and volatile [42, 43, 44]. The organic nature of these compounds comes from their main molecular structure which is composed of atoms of carbon covalently bonded to atoms of hydrogen. In addition, the molecules can still bond to functional groups composed of several distinct atoms, leading to the inclusion of the compounds in different groups such as hydrocarbons (e.g. methane and ethane), halogenated compounds (e.g. chloromethane and dichloromethane), amines (e.g. methylamine and ethylamine), ketones (e.g. acetone and propanone), alcohols (e.g. methanol and ethanol), or aldehydes (e.g. formaldehyde and acetaldehyde), among others [45, 46]. Regarding their volatile nature, VOCS are compounds that present a volatile or gaseous state at around room temperature (20 - 25 °C) [47].

Despite their characteristics, it is worth stating that VOCs can be emitted by all kinds of sources. In fact, VOC-emitting sources can be arranged into two distinct categories: natural sources and anthropogenic sources. Natural sources include fauna and flora emissions. Examples of flora emissions are the isoprene abundantly emitted by many plants [48, 49], or the VOCs emitted by edible seaweeds often studied regarding their suitability for culinary purposes [50, 51]. The emission of methane by cattle, or the emissions of formaldehyde from the urine of a vast range of mammals are among the main examples of animal-emitted volatile organic compounds [52, 53].

Regarding anthropogenic sources, a considerably high number of daily-use objects and common activities are directly related to the emission of VOCs into the air. Among daily-use objects, VOCs are often emitted by clothes [54], personal care products like perfumes and creams [55], furniture and decoration [56], building and renovations materials [57], coating solutions like paints and varnish [58], fuels [59], cleaning and disinfectant products like detergents and pesticides [60], glues [61], or writing and printing/copying materials [62], and others. Activities like smoking [63], cooking [64], driving [65], or cleaning [66], are equally important and common sources of emissions of volatile compounds. In this way, VOCs can easily spread throughout the environmental air and are present in all types of indoor and outdoor sites, leading to, not only, scenarios of environmental pollution, but also, to potentially hazardous situations for human beings [67, 68].

Due to their organic and volatile natures, VOCs can traverse biological matrices like alveolar, cutaneous, or ocular tissues, and interact with the human organism [69, 70]. Both short- and long-term exposure to VOCs, even at trace levels of concentrations, can lead to processes of mutation by oxidative stress in the human cells and, consequently, to a vast spectrum of health conditions and pathologies [4, 71, 30]. Allergies, cutaneous and ocular irritation or pruritus, headaches, dizziness, nausea, visual disorders, memory impairment, emesis, epistaxis, and fatigue are among the simpler and less dangerous conditions [72, 73, 3].

Diseases like asthma, chronic obstructive pulmonary disease, and some other inflammatory conditions of the respiratory tract are equally known for their direct dependence on volatile organic compounds [74, 75, 3]. Finally, on the opposite extremity of the spectrum, severe forms of cancers have been studied regarding their relation to chronic exposure to VOCs [76, 77, 78]. In fact, benzene, toluene, ethylbenzene, xylenes, and formaldehyde, for example, are well-known carcinogenic VOCs whose exposure consequences have been linked to lung, oral, breast, and gastric cancers [79, 80, 81].

Considering all the addressed facts, the idiosyncrasies of VOCs, their easiness in spreading throughout the air, and their hazardousness to human health, it is mandatory to study, develop and implement analytical tools that enable an accurate and rapid detection, identification and quantification of organic compounds, especially at locations where their presence can be of special toxicity to the population. Work locations and industrial facilities are perfect examples of those scenarios.

2.2 Industrial Context

At an industrial level, VOCs are elements often found in the composition of the indoor air of the facilities. The activities that are usually undertaken in such locations are conducive to the emission of this kind of compound. For instance, in coating industries and facilities where painting, printing, or similar activities are developed, it is rather usual the detection of relevant amounts of alcohol-based VOCs in the atmosphere due to the frequent use of solvents, paints, and other coating solutions [82, 83, 84]. The environment in automotive, electronics, and comparable assemble lines is equally replete with numerous sources of VOCs, namely, the chemicals, solvents, or rubbers, and the welding, drying, heating, and coating processes often employed during the steps of production [85, 86, 87]. The manufacturing facilities of personal care and cleaning products, due to the intense utilisation of VOCs-based chemicals in the formulas of these products, are often filled with toxic compounds that degrade the air quality and contribute to the lack of work conditions [88, 89, 90]. In summary, independently of the undertaken activities, industrial facilities are frequently crowded with sources of all kinds of VOCs. A car factory painting line is no exception [91, 92, 38].

2.2.1 Car Factory

The process of manufacturing a car is intricate and involves numerous phases. Additionally, most of those phases require the use of products or involve processes that are potential VOCs-emitting sources [93, 94]. In fact, a scientific study estimated that the total emission of VOCs by a car factory ranges from 1.18 to 4.30 kg per produced vehicle, an enormous and very dangerous quantity [95]. These values show how mandatory is to characterise the main sources of VOCs and identify the main compounds emitted in order to study the work conditions and potential hazardousness to the employees of the factories [82, 96].

2.2.1.1 Painting Line

From the total amount of VOCs emitted during the manufacturing of a vehicle, a considerable portion of them is released in the painting line of the factory during the process of coating the car body. This is due to the substantial number of VOCs-based solutions, like the primers, basecoats, and clearcoats, used during all the steps of coating the metallic surface of a car [97].

A generic coating process is initiated by the immersion of the chassis in two contiguous chemical baths, the phosphatising bath and the cataphoresis bath. The solution used in the first bath is composed of phosphoric acid saturated with metallic phosphate. Its main purpose is to protect the metal and prevent future corrosion. The cataphoresis bath, in turn, covers the entire surface of the metal with a thin electrically charged epoxy layer that enables a uniform and consistent application of the coatings throughout the chassis. Once immersed in both baths, the car body is dried in the interior of industrial ovens and then transported to the following section of the line, the coating area [93, 98].

All primers and basecoats are maintained in large reservoirs located in a temperature- and humidity-controlled warehouse, where they are kept under constant blending to prevent eventual substrate deposition and consequent degradation. Between the painting line and the warehouse, a complex and exclusive piping system is utilised for the transportation of each type of coating to prevent contaminations or undesired mixings [98, 93]. In the interior of the painting chambers, robotic arms are used for the application of the coatings. The fingers of the arms create an electrically charged coating cloud that is sprayed onto the metallic surface. The electrically charged particles existent in the cloud interact with the electrically charged epoxy layer previously applied during the cataphoresis bath, enabling a uniform and consistent coating of the entire chassis [93, 97].

Industrial ovens are used once again to dry the coating solutions and then, the coloured chassis is transported to the following stage. Here, a clearcoat, commonly identified as varnish, is applied to the dried surface through a process known as the flooding process [91]. Then, a group of employees uses rotatory machines and tissues to polish the metal. Finally, each chassis is visually inspected in the interior of well-illuminated rooms. If any imperfection is detected, the chassis is recycled and undergoes the coating process for a second time; otherwise, it is transferred to the subsequent assembly stages [93, 94]. The main steps of the coating process are illustrated in Figure 2 for summary purposes.

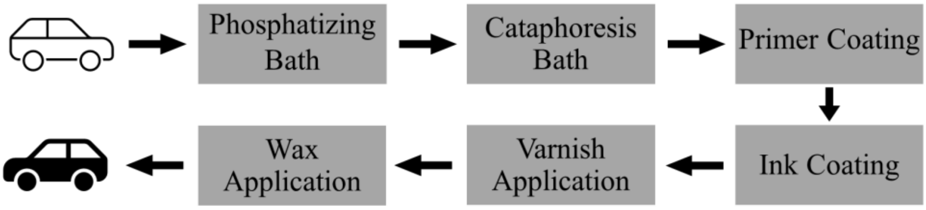

Figure 2 - Main steps of the coating process in a car factory painting line [9].

As addressed, several VOCs-based solutions are used during the entire process, namely the primers, basecoats and clearcoats. These solutions are, in this way, the main VOCs-emitting sources not only in the painting line but from the entire process of manufacturing a vehicle, which represents a heightened risk to the environment and the employees' health [91, 96, 71].

2.2.1.2 Coatings

The majority of coatings are divided into two categories: oil- and water-based. Oil-based coatings contain several organic compounds in their composition whose purpose is to act as solvents [99, 100]. They are toluene, xylene, benzene, ethylbenzene, 1,2,4-trimethyl benzene, naphthalene, acetone, methyl butyl ketone, methyl isobutyl ketone, methyl amyl ketone, di-isobutyl ketone, ethyl acetate, butyl acetate, ethyl propionate, methanol, ethanol, propanol, and butanol, among many others [101, 99]. All the solvents ease the application, drying and durability of the paint; however, their volatilization and consequent presence in the indoor air of the line represent a serious hazard for the exposed employees and the environment [91, 102, 103].

Due to the growing concerns about the toxicological and environmental impacts, restrictive laws have been implemented aiming to limit the application of solvent-based coatings and boost the use of water-based coatings.

Water-based coatings have a considerably lower ratio of organic solvents in their composition which leads, consequently, to lower emissions of VOCs during the coating process [104, 105]. The most common compounds existent in water-based coatings are toluene, xylenes, ethyl acetate, butyl acetate, benzene, ethylbenzene, or methyl ethyl ketone, among others [106, 107]. Besides the advantage of being less hazardous to both the employees' health and the environment, water-based coatings present some disadvantages if compared with solvent-based versions [82, 108, 84]. Due to the lower amount of solvent compounds in their composition, they are considerably more viscous and require the utilisation of higher temperatures during longer periods to dry completely. In this way, when compared to the performance of solvent-based coatings, larger amounts of water-based coatings are required to coat the same area and larger amounts of energy are equally required during the drying process [106, 109, 110].

Independently of their composition and the number of scenarios in which each one is employed, both types of coating are responsible for the emission of VOCs in the painting line [103, 111]. In fact, it was even estimated that the concentration of VOCs in the composition of generic automotive solvent-based coatings ranges between 650 and 800 grams per litre and, in the case of generic automotive water-based coatings, the concentration reaches up to 420 grams per litre [95]. A significant portion of these quantities is emitted into the indoor air during the application and drying of the coatings, in this way, it is relevant to fully address these emissions for further considerations regarding their eventual impacts.

2.2.1.3 Employees Exposure

As mentioned, in an industrial context VOCs are emitted by a very diverse range of sources, namely paints, varnishes, waxes, solvents, plastics, rubbers, and many other chemical-based products [91, 92]. Due to their characteristics, VOCs interact with the human organism through several vias such as the pulmonary, ocular, and cutaneous tissues. This interaction leads to processes of inflammation and causes mutations by oxidative stress in the human cells so, they are directly responsible for a vast range of health conditions and pathologies [69].

Eye allergies and skin irritation are common reactions to the presence of VOCs. Methyl ethyl ketone, also known as 2-butanone, for example, has been studied as a cause of skin and eye irritation, in scenarios of short-term exposure, and for neurological, liver and kidney effects, in cases of chronic exposure [112]. Considering the threshold limit value (TLV) index, an index defined by the United States National Institute for Occupational Safety and Health (NIOSH) to characterise the maximum concentration level to which an employee can be repeatedly exposed throughout his/her professional life without experiencing any relevant health impacts, 2-butanone represents a direct risk for life if a person is exposed to 200 ppm_v or more [113]. In more extreme scenarios, exposure to hazardous VOCs like benzene (TLV: 10 ppm_v), trichloroethylene (TLV: 50 ppm_v), chloroform (TLV: 10 ppm_v) and formaldehyde (TLV: 0.3 ppm_v), all common and very well-known VOCs, has been linked to the development of carcinogenic conditions like lung, breast and some other severe forms of cancer [113, 19, 79, 76, 71].

All the mentioned compounds, and many more, are often present in the indoor air of industrial facilities and, specifically, in car factory painting lines, due to the emissions of all the coating solutions. Nonetheless, the employees are not completely exposed to the VOCs emitted by the coatings. In fact, several types of protective gear are available to be used by the employees during the work shifts.

Activated charcoal masks, glasses and jumpsuits are the main protective gear used by the employees of the painting line. This type of equipment aims to protect them from, not only the exposure to potentially toxic compounds, but also from eventual accidents, spilling of coatings, loose parts, and many other dangerous scenarios often common at industrial working locations and production lines [114]. In addition, car factory painting lines usually have several systems to purify the air and eliminate toxic compounds. One example is the extraction units assembled at the factory ceilings that work constantly to expel the contaminated air from the indoor environment to the exterior. Inside the painting chamber, the factories usually install ventilation systems that use jets of air to drag the pollutant compounds emitted during the formation of the coating clouds, into a water reservoir located directly under the chamber. Here, the compounds are theoretically mixed with the water, which is later eliminated, preventing them from staying in the indoor environment [115, 116].

Independently of the protective gear available or the systems implemented by the factory, the employees are still exposed to potentially toxic conditions. In fact, during the work shifts of eight hours, the employees have often to enter the painting chamber to fix eventual issues and small problems. In addition, the indoor air of the factory is fully connected, i.e., the painting boots are not fully isolated or hermetic, which means that the emitted analytes can easily spread throughout the entire ambient. Finally, none of the systems used for air renovation and elimination of compounds is fully safe and has perfect performance so, at least a portion of the emitted VOCs stays in the indoor air of the car factory painting line and, consequently, represents a threat to the employees' health in both short-term and chronic exposure [117, 118, 119]. Due to all these facts, the identification and quantification of volatile organic compounds is a mandatory task.

2.2.1.4 Legislation

In terms of legislation, the car factory painting line involved in this doctoral project is obliged to comply with a considerably high number of technical considerations, norms, and laws of both national and international provenience.

In terms of national legislation, the car factory painting line is obliged to comply with the following legislation:

- Decreto-Lei n.º 243/86, de 6 de fevereiro – Aprova o Regulamento Geral de Higiene e Segurança do Trabalho nos Estabelecimentos Comerciais, de Escritório e

Serviços. (Decree-Law no. 243/86, of February 6th - Approves the General Regulations on Hygiene and Safety at Work in Commercial Office and Service Establishments).

- Decreto-Lei n.º 24/2012, de 6 de fevereiro – Prescrições mínimas em matéria de proteção contra os riscos derivados da exposição a agentes químicos no trabalho. (Decree-Law no. 24/2012, of February 6th - Minimum requirements for protection against the risks arising from exposure to chemical agents at work).
- Portaria n.º 138-G/2021 de 1 de julho – Estabelece os requisitos para a avaliação da qualidade do ar interior nos edifícios de comércio e serviços, incluindo os limiares de proteção, condições de referência e critérios de conformidade, e a respetiva metodologia para a medição dos poluentes e para a fiscalização do cumprimento das normas aprovadas. (Ministerial Order no. 138-G/2021, of July 1st - Establishes the requirements for assessing indoor air quality in commercial and service buildings, including protection thresholds, reference conditions and compliance criteria, and the respective methodology for measuring pollutants and monitoring compliance with the approved standards).
- Nota Técnica NT-SCE-02 – Metodologia para auditorias periódicas de qualidade do ar interior em edifícios de serviços existentes no âmbito do regulamento dos sistemas energéticos de climatização em edifícios. (Technical Note NT-SC-02 - Methodology for periodic indoor air quality audits in existing service buildings withing the scope of the regulation on energy systems for air conditioning in buildings).
- NP 1796:2014 – Segurança e Saúde do Trabalho - Valores limite e índices biológicos de exposição profissional a agentes químicos. (NP 1796:2014 - Occupational Safety and Health - Limit values and biological indices of occupational exposure to chemical agents.)
- NP EN 482:2008 – Atmosferas dos locais de trabalho. Requisitos gerais do desempenho dos procedimentos de medição de agentes químicos. (NP EN 482:2008 - Workplace atmospheres. General requirements for the performance of chemical agent measurement procedures.)
- NP EN 689:2008 – Atmosferas dos locais de trabalho. Guia para a apreciação da exposição por inalação a agentes químicos por comparação com valores limite e estratégia de medição. (NP EN 689:2008 - Workplace atmospheres. Guide to the

assessment of inhalation exposure to chemical agents by comparison with limit values and measurement strategy.)

In terms of international norms, the car factory painting line is obliged to comply with the following legislation:

- ANSI/ASHRAE 62.1-2010 – Ventilation for Acceptable Indoor Air Quality.
- 2011 ASHRAE Handbook - HVAC Applications – Heating, Ventilating and Air-Conditioning Applications.
- ISO 7730:2005 – Ergonomics of the Thermal Environment - Analytical determination and interpretation of thermal comfort using calculation of the PMV and PPD indices and local thermal comfort criteria.
- ISO 7726:1998 – Ergonomics of the Thermal Environment - Instruments for measuring physical quantities.

Both lists mentioned above were disclosed by the car factory itself. They are a part of the internal specifications on occupational safety for the employees.

By consulting all the aforementioned norms, some information can be extracted. The ministerial order no. 138-G/2021, of July 1st, defines a generic protection threshold of total VOCs in industrial scenarios of 600 $\mu g/m^3$. The technical vote NT-SC-02, in its turn, defines that this value must be evaluated every two years. The international norm ANSI/ASHRAE 62.1-2010 also provides the reference exposure levels (REL) for some of the most well-known VOCs. Further information on the indoor air quality assessment and exposure levels are addressed throughout all the mentioned norms, nonetheless, some limitations and omissions can be seen. Not all relevant VOCs are addressed in the current norms and, since this type of compounds has such a remarkable presence in indoor sites, legislation on all compounds is required. In addition, the levels provided for total VOCs are not accurate enough since some compounds can be extremely toxic even at trace levels of concentration. Finally, the obligation of controlling indoor air quality every two years can equally be inappropriate since the quantities of VOCs can be considerably affected by unexpected emitting sources. Considering all these facts, further considerations must be made in regard to the monitoring and control of VOCS at industrial levels.

2.3 Health Assessment

As aforementioned, both short-term and chronic exposure to potentially toxic compounds and dangerous scenarios can lead to a vast range of health conditions and pathologies that vary from simpler situations to life-threatening diseases. Independently of their harmfulness, the rapidness and accuracy of the diagnosis are often crucial to prevent more dangerous comorbidities. It is known that the success in the treatment of most pathologies depends on several factors; the stage in which the disease is detected is one of those very important factors to achieve a successful cure since pathologies detected in later stages often lead to more dangerous consequences and, in some cases, lethal outcomes. So, the sooner the health condition is detected and accurately diagnosed, the higher the chance of cure and survival [120, 121, 122].

It is known that, despite their relevancy, most of the conventional diagnostic procedures are often time-consuming and tend to delay the beginning of the clinical treatment. These contemporary interventions, which range from simple blood analyses to complex biopsies, are often invasive, painful, and unsafe for the patients, not to mention the several limitations like the cost, the usability, and the repeatability of the results [122, 123]. With this in mind, modern medicine is focused on developing and applying improved methodologies that help to accurately and rapidly diagnose all kinds of pathological conditions. The identification of specific human-borne compounds as biomarkers for the diagnosis of health conditions has gained relevance during the past years due to their non-invasive, low cost and painless nature [12, 120, 124]. In fact, this growing interest can be easily seen in Figure 3, where the number of scientific papers published under the scope "Biomarkers" since 2000 is represented, in accordance with the Web of Science.

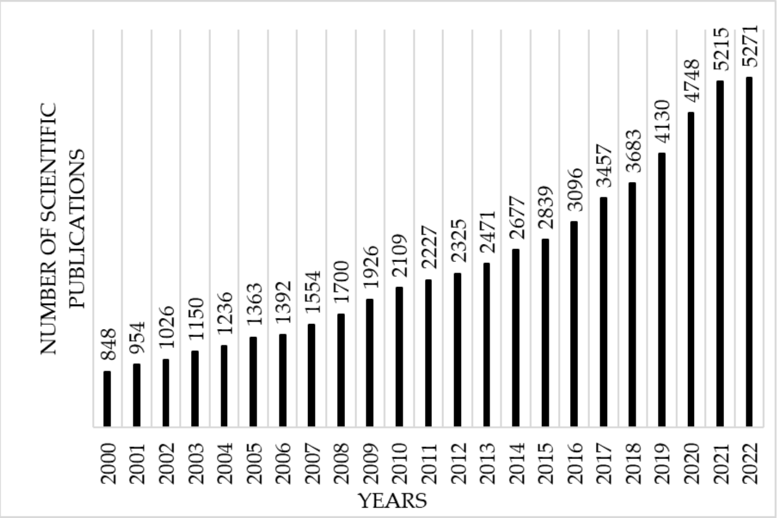

Figure 3 - Number of scientific articles published per year since the year 2000 under the scope "Biomarkers".

2.3.1 Biomarkers

The current definition states that a biomarker is *"… a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention…"* [125, 126]. A biomarker can, indeed, be a biological signal of several natures, that can be accurately measured, whose results are reproducible over time, and that is always associated with a specific normal or abnormal event of the human organism [127, 128].

Among all the different types of biomarkers, the analytes produced by the organism and VOCs, specifically, are among the biomarkers with higher potentialities and that denote an auspicious future. The endogenously-produced VOCs of the body can traverse the human tissues and be detected in the exterior through exhaled breath [129], saliva [130], perspiration [131], faeces [132], or even urine [133], among other ways [134, 131]. Considering the scope of the present doctoral project, the focus is given to the exhaled air VOCs.

These VOCs identified in breath may arise from metabolic activity in lung tissue and airways or have a systemic origin (produced in any part of the body, including other organs and tissues). However, when produced systemically, these VOCs are captured and distributed in the bloodstream. Thus, the gas exchange of compounds between alveoli and capillaries allows the excretion of exhaled compounds in the form of gas, which is exhaled together with respiratory droplets and atmospheric gases. It is important to highlight that VOCs related to certain diseases may result from metabolic processes that occur, for example, inside a tumour cell and in the surrounding tissues that "react" to the presence of cancer. Lipid peroxidation of polyunsaturated fatty acids, for example, is a biological mechanism that leads to the production of saturated hydrocarbons. Known to be formed in different proportions through chain reactions, ethane and pentane are expelled in greater quantities in situations of mental and/or physical stress during lipid peroxidation. Some methylated hydrocarbons were also identified from breath, although their metabolic pathways are not elucidative enough to confirm their complete diagnostic potential [135].

Once collected and analysed, the VOCs emitted in exhaled air represent a useful window for the interior of the body and can represent a valuable source of information about health conditions, about the response of the organism to medical treatments, and to the diagnosis of both carcinogenic and non-carcinogenic pathologies [136, 137].

2.3.1.1 Non-Carcinogenic Diseases

A vast range of carcinogenic and non-carcinogenic pathologies can be potentially diagnosed through specific compounds present in the breath. Asthma is, perhaps, the most studied disease concerning breath biomarkers [138]. An example of that is the work of Montuschi et al. (2010). The authors assessed the potentiality of differentiating healthy individuals from asthmatic patients through the VOCs patterns of the exhaled breath on a cohort of 51 volunteers (24 healthy individuals and 27 intermittent and persistent mild asthma patients), with an electronic nose and a mass spectrometer. This cross-sectional study for asthma diagnostic enabled the authors to prove that the accuracy (87.5%) of the methodology involving VOCs patterns supplanted the typical methods of fractional exhaled nitric oxide (FENO) (79.2%) and lung function tests (70.8%), proving the large potential of VOCs as asthma biomarkers [139]. Among all the studied VOCs, some specific compounds have shown a higher relationship with asthma, namely, acetone [140], nonanal [141], propanol [141], p-xylene [142], ethylbenzene [143], and some others [12, 5].

Chronic obstructive pulmonary disease (COPD) [144] has equally been studied regarding the potentialities of VOCS in breath for its diagnosis. To evaluate the suitability of VOCs as differentiation tools between healthy individuals and COPD patients, Cristescu et al. (2011) performed a breath test with a proton-transfer-reaction mass spectrometry (PTR-MS) device. The 204 volunteers were previously tested by computed tomography (CT) for COPD diagnosis. The exhaled breath profiles, once compared with the CT test results, enabled the diagnosis of COPD with an accuracy of around 95%. These results prove the suitability and potentiality of VOCs as chronic obstructive pulmonary disease biomarkers [145]. Many VOCs have been related to the diagnosis of COPD, among them are acetaldehyde [146], benzaldehyde [147], isopropanol [148], toluene [147], and many others [12, 5].

Cystic fibrosis is another example of a disease deeply studied regarding its diagnosis through breath biomarkers [149]. To develop a breath test for cystic fibrosis diagnosis, Kramer et al. (2015) analysed the headspace emitted by epithelial lung cells previously infected with human pathogens. In addition, 100 mL of exhaled breath from nine cystic fibrosis patients were collected using solid-phase microextraction (SPME) and analysed by GC-MS. Authors claimed that, through the detected analytes, it was possible to successfully identify 100% of the cases proving the suitability of VOCs in the diagnosis of cystic fibrosis [150]. The majority of work developed around the diagnosis of cystic fibrosis focuses on analytes like acetaldehyde [151], butanol [152], ethanol [153], 2-nonanone [152], and isoprene [152], among others [12, 5].

Asthma, COPD, and cystic fibrosis are just a few examples of all the non-carcinogenic pathologies whose diagnosis have been addressed regarding the suitability of biomarkers in exhaled air. Other examples are tuberculosis [154], covid-19 [155], chronic kidney diseases (CKD) [156], chronic liver diseases (CLD) like hepatic encephalopathy [157], non-alcoholic fatty liver disease [158], and liver cirrhosis [159], diabetes [160], malaria [161], and sleep apnoea [162]. All the mentioned pathologies have been deeply studied and already exhibit a vast list of potential breath biomarkers, nonetheless, some other non-carcinogenic conditions also known for their impact on the human metabolism, present a currently unexplored potential that deserves to be addressed. These pathologies are Alzheimer's disease [163], Crohn's disease [164], epilepsy [165], multiple sclerosis [166], obesity [167], and sepsis [168]. Figure 4 represents the main diseases for which potential breath biomarkers have been deeply studied and identified. Further information regarding the biomarkers in exhaled air for the diagnosis of non-carcinogenic conditions can be consulted elsewhere [12, 5].

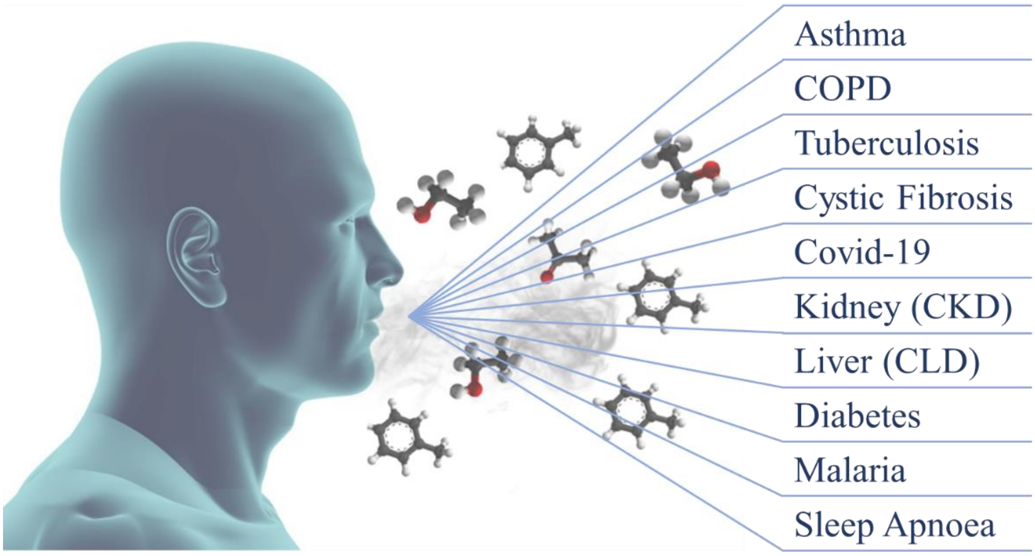

Figure 4 - Non-carcinogenic diseases deeply studied regarding their potential diagnosis by breath biomarkers [5].

2.3.1.2 Carcinogenic Diseases

Under the scope of carcinogenic diseases diagnosis, one should mention lung cancer [169]. This highly mortal pathology is among the most studied conditions regarding the suitability of breath biomarkers. An example of that is the work of Hou et al. (2013). An array of colorimetric sensors was developed and applied by the authors to identify and quantify hexanal, isoprene, p-xylene, and styrene; analytes known for their suitability for the role of lung cancer biomarkers. The device and protocol developed in the study enabled the authors to quantify the mentioned analytes with limits of detection ranging from 50 ppb_v to 500 ppb_v [51]. Many more analytes have been studied with this same purpose. They are acetone [170], benzene [171], butanal [172], isoprene [173], and others [12, 8].

Contemporary unhealthy lifestyles and changes in reproductive behaviour are some of the main risk factors for the rise of breast cancer incidence [174]. Besides de origin, the current methods for breast cancer screening and diagnosis are often aggressive and painful due to the necessity of invasive procedures. This fact leads to a later diagnosis of the pathology and, consequently, to more dangerous comorbidities [175, 176]. Several studies have been developed aiming at the identification of possible biomarkers emitted mainly in the breath, but also in the urine, of the patients, that allow fast, non-invasive, and painless screening of breast cancer [177]. Aiming to differentiate between sub-types of breast cancer tumours, Barash et al. (2015) analysed the breath of 276 women with different types of lesions. As in some of the previously addressed papers, a gas chromatography-mass spectrometry (GC-MS) device was the analytical technique selected to perform the analyses. A total of 23 analytes of interest were detected and 13 were accurately identified [178]. Among these analytes, one can list ethanol [178], benzaldehyde [179], ethyl acetate [180], phenol [181], or α-pinene [178].

Most of the techniques currently used to diagnose gastric cancer involve invasive painful procedures. For example, a digestive endoscopy with biopsy for later diagnosis through histopathological analysis requires the introduction of medical devices for the collection of tissue samples. The development of non-invasive but accurate techniques for gastric cancer diagnosis would enable a faster reaction and treatment of the disease [182, 183]. Having this in mind, Schuermans et al. (2018) used an electronic nose to study the exhaled breath of a cohort of 44 individuals (28 healthy volunteers and 16 gastric cancer patients). The authors were able to use analytes like acetic acid [184], acetone [185], 2-butanone [186], and ethylene [184], to differentiate both groups with accuracy, sensitivity and selectivity levels of 75%, 81% and 71%, respectively [187].

Colorectal cancer (CRC) is one of the cancers with higher incidence and mortality. In fact, around 110000 new cases and 46000 deaths per year are expected just in the United States of America; values extrapolatable to the rest of the world [188]. Since it can be a very silent pathology, CRC is usually detected only in the late stages of development, leading to very low rates of cure [189, 190]. New, precise and, more importantly, rapid diagnostic tools are mandatory. The application of VOCs as an option for an accurate diagnosis of CRC has been deeply studied and already provided substantial results [191]. Considering this necessity, Wang et al.

(2014) detected and identified nine VOCs as potential biomarkers for the diagnosis of colorectal cancer diagnosis. To do so, the exhaled breath of 40 individuals (20 healthy subjects and 20 CRC patients) was collected and analysed with an SPME-GC-MS apparatus [192]. Among these analytes, one can mention benzaldehyde [193], dodecane [194], cyclohexane [195], tridecane [194], and some more [12, 8].

Lung, breast, and colorectal cancers are just a few examples of all the carcinogenic pathologies whose diagnosis have been addressed regarding the suitability of biomarkers in exhaled air. Other examples are gastric cancer [196], prostate cancer [197], and squamous cell cancer [198] like laryngeal cancer [199] and oesophageal cancer [200]. All the mentioned pathologies have been deeply studied and already exhibit a vast list of potential breath biomarkers, nonetheless, some other carcinogenic conditions also known for their impact on the human metabolism, present a currently unexplored potential that deserves to be addressed. These pathologies are bladder cancer [201], liver cancer [202], ovarian cancer [203], pancreatic cancer [204], and thyroid cancer [205]. Figure 5 represents the oncological diseases for which potential breath biomarkers have already been identified (in black) and the ones with unexplored but interesting potential (in blue). Further information regarding the biomarkers in exhaled air for the diagnosis of carcinogenic conditions can be consulted elsewhere [12, 8].

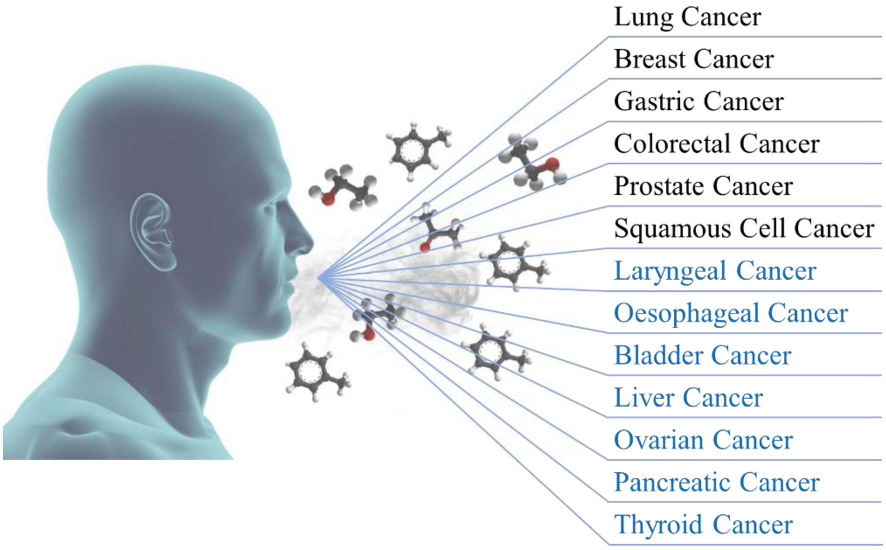

Figure 5 - Carcinogenic diseases deeply studied regarding their potential diagnosis by breath biomarkers (in black) and future trends (in blue) [8].

As visible, several VOCs can act as markers for numerous diseases simultaneously while others are pathology-specific, i.e., their presence and/or concentration levels in body fluids can be related to a single health condition or pathology. Acetone, for example, is among the most useful compounds as its behaviour can be directly related to at least 11 pathologies; they are asthma [140], chronic kidney disease [206], chronic liver disease [207], colorectal cancer [208], covid-19 [209], cystic fibrosis [153], diabetes [210], gastric cancer [211], lung cancer [170], malaria [212], and sleep apnoea [213]. A total of seven diseases can all be studied through a specific compound in breath, 2-butanone, namely chronic kidney diseases [214], chronic liver diseases [207], COVID-19 [155], cystic fibrosis [153], gastric cancer [215], lung cancer [171], and squamous cell cancer [199]. Ethanol, in its turn, is often used as a biomarker for a total of eight pathologies, namely breast cancer [178], chronic kidney disease [216], chronic liver disease [217], colorectal cancer [208], diabetes [153], gastric cancer [218], malaria [219], and squamous cell cancer [220]. Finally, behavioural changes of isoprene have been related to a total of 11 diseases; breast cancer [221], chronic kidney disease [222], chronic liver disease [223], chronic obstructive pulmonary disease [147], COVID-19 [155], cystic fibrosis [152], diabetes [224], gastric cancer [185], lung cancer [225], malaria [212], and sleep apnoea [213].

On the other hand, some compounds are only relatable to single conditions. Ammonia, for example, can act as a biomarker for the diagnosis of chronic kidney disease but no other relationship has been proven yet [156]. Other examples are benzothiazole, relatable to cystic fibrosis [226], 1,4-butanediol, relatable to gastric cancer [186], butanoic acid, relatable to colorectal cancer [193], butanol, relatable to cystic fibrosis [152], cymol, relatable with tuberculosis [227], ethyl vinyl ketone, relatable with prostate cancer [197], 1-isopropyl-3-methylbenzene, relatable with asthma [143], and many other volatile organic compounds.

It is important to mention that, up to date, only a few VOCs have been officially approved as disease biomarkers. For breath tests, the Food and Drug Administration (FDA) has only approved the following compounds: ethanol (for assessment of blood alcohol content), hydrogen (carbohydrate metabolism), nitric oxide (biomarker of asthma), carbon monoxide (biomarker of neonatal jaundice), carbon dioxide (biomarker of H. pylori infection) and branched hydrocarbons (biomarkers of organ transplant rejection) [228]. For exemplification purposes, ethanol is often used by authorities and police figures to assess the alcoholic levels of drivers [229], and nitric oxide, in turn, is deeply used in clinical scenarios for the diagnosis of asthma, as mentioned [230].

Appendix A and, specifically, Table 22 summarizes the majority of VOCs detected in breath and related to all the carcinogenic and non-carcinogenic diseases mentioned above. An updated database of health conditions and their respective biomarkers can be consulted at an online open-source platform exclusively developed under the scope of this doctoral project [12]: https://neomeditec.com/VOCdatabase/ [231].

2.3.1.3 Collection and Analysis Procedures

In order to explore all the potential of breath biomarkers, their proper collection and analysis are very relevant topics that one must briefly mention for informative purposes. The collection, transportation, and storage of breath samples for later analysis are often a challenge. Depending on the type of material used to manufacture the transfer lines and the storage containers, and due to the high affinity of VOCs to solid surfaces, the analytes can adsorb to the inner walls leading to a reduction of the concentration levels and even a complete loss of specific compounds. This adsorption process is dependent on the composition and length of the transfer line material, and the physicochemical properties of the compounds themselves. Furthermore, the sample can also be contaminated and, consequently, degraded due to the reactivity existent between the walls coating and the analytes, i.e., chemical reactions between the walls of the transfer line materials and of the storage containers can result in the formation of new compounds, leading to the alteration of the sample [232, 233].

Considering the aforementioned facts, four types of containers are often used for the purposes of collecting, transporting, and storing the analytes collected from breath. They are Tedlar bags, sorbent tubes, needle trap devices, and syringes [234, 235]. Evidently, all these options have advantages and disadvantages that one shall mention summarily. Tedlar bags are often used for collecting larger volumes (in the range of litres) of a sample. Nonetheless, their larger surface area maximizes the chances of occurring reactions between the material and the collected breath, potentially leading to the formation of exogenous compounds that degrade the original content and adulterate the results. Sorbent tubes and needle trap devices are often used in the research context; however, they are considerably more complex ways of collecting and storing exhaled air samples, not to mention the higher costs of both options. Due to these facts, sorbent tubes and needle trap devices are less adequate for clinical implementation and in-loco analyses. Finally, syringe-based containers are commonly interpreted as being the best option to collect and store breath samples. Their practicality, smaller inner surface area, complete isolation of the sample, and compatibility with a vast range of analytical techniques are important advantages of syringes regarding breath sampling [236, 237, 238].

Regarding the analytical methods most commonly used to analyse breath samples, and despite not being the scope of this project, one can mention that the vast majority of the work in the field of breath biomarkers is developed around two main categories of systems: sensors array-based electronic noses and chromatographic/spectrometry-based techniques [239]. In the field of gas sensors, specific systems often based on quartz crystal microbalance sensors (QCMS), photoionization detector sensors (PIDS), surface acoustic wave sensors (SAWS), solid-state electrochemical sensors (SSES), or metal oxide sensors (MOS), are assembled and exposed to the volatile samples. These systems are highly responsive, have good selectivity, provide stable results, and are low-priced [240, 241, 7]. On the other hand, techniques like gas chromatography (GC), mass spectrometry (MS), ion mobility spectrometry (IMS), and combinations between them, are among the most used analytical procedures for breath analysis [242, 243]. All these techniques provide accurate and repeatable results concerning the content of breath samples and provide not only the identification of the VOCs but also the assessment of concentration levels. In addition, their capability of detecting analytes even at trace levels of concentration, say ppb_v, makes them suitable for biomarkers exploration. Despite the advantages, their complexity and lack of portability are often limitations for *in-loco* studies at clinical locations [14, 244, 245]. Further details on the analytical techniques are addressed in due time.

2.4 Analytical Techniques

Several procedures have been developed and employed for the analysis and assessment of volatile organic compounds in fields like environmental and health research. These technologies are often grouped into two main categories: gas sensors array-based electronic noses (E-noses) and analytical techniques.

2.4.1 Sensors Array-Based Electronic Noses

The development of electronic prototypes and devices based on arrays of gas sensors is a common practice in the fields of VOCs detection, identification, and quantification. Gas sensor is a vulgar definition for a sensor specifically developed to detect one or a limited number of analytes [15], and they can be of several types, namely QCMS, PIDS, SAWS, SSES, and MOS sensors, as previously addressed [246, 247].

Graphene-based sensors, for example, have been largely explored regarding their vast range of applications, their adaptability to distinct scenarios, and their proven results in the identification and quantification of specific molecules. Nonetheless, this exploration is only possible due to the characteristics of graphene whose excitability and sensitivity allow its application in the development of molecular electronic devices for sensing purposes. In fact, graphene can be chemically altered through π–π interactions or via electron transfer processes, for example, when exposed to scenarios rich in organic compounds whose functional groups are effortlessly attachable to graphene [248, 247].

Independently of the type, all of them are highly responsive, selective, stable, simple, and low-priced, as mentioned [239]. Despite their advantages, sensor array-based systems present some characteristics that might act as disadvantages, depending on the scope of the study. Since they are usually capable of detecting a single or a restricted group of compounds, these systems are a poor choice for matrices rich in VOCs and more complex scenarios [249, 250, 251]. Furthermore, due to the necessity of assembling complex and often challenging circuits or devices, sensors-based array systems cannot be used for *in-situ* or *in-loco* analysis. Finally, it is worth stating that these sensors often have poor limits of detection, failing to detect volatile compounds at concentration levels lower than dozens of ppm$_v$ [252, 253, 254].

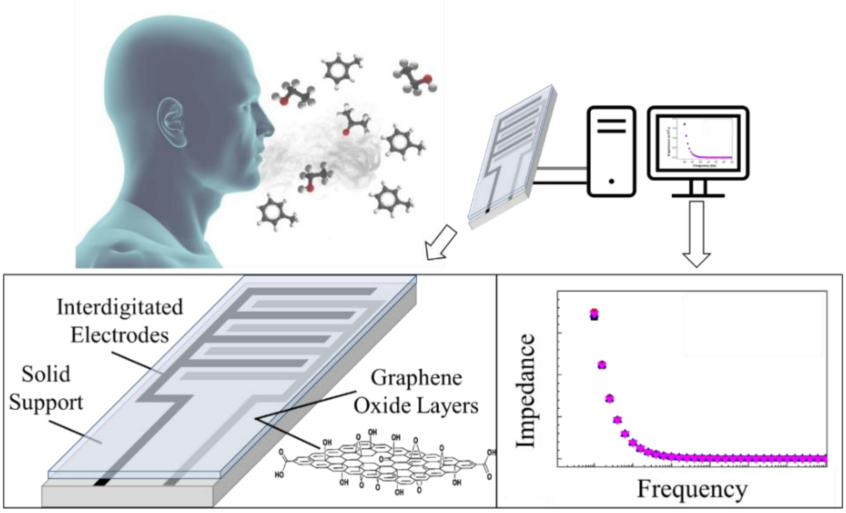

Figure 6 - Schematic of a generic system based on graphene oxide sensors for analysis of volatile samples [7].

These arrays-based systems can be assembled in a vast range of ways that include procedures based on the deposition of thin film layers, and the montage of electronic circuits or even prototypes around the sensors that, once connected to a computer, allow the collection of qualitative and quantitative data regarding the detected analytes [15]. To access that data, the array of sensors is exposed to the volatile sample and, if the sample contains the analytes that the sensors are prepared to detect, they will respond to the presence of those compounds. This response is different for the several types of sensors. In the case of the MOS, for example, these sensors change the conductivity of their sensing element in response to being exposed to the gases. [255]. The response of the sensors is, then, registered and converted to a spectrum or numerical data for posterior processing [256, 257]. Figure 6 describes a generic analysis through a sensor array-based system, where a graphene oxide-based sensor is exposed to a generic sample of exhaled air, and the variance of the sensors' impedance is registered for later analysis.

2.4.2 Analytical Techniques

Considering the main analytical techniques that can be adequate for VOCs assessment in a volatile sample, one will certainly be led to elect chromatographic and spectrometric methods as the most relevant due to their intrinsic specificity and sensitivity to molecular species. Each one of these techniques can even be improved by means of dedicated procedures for specific situations or be enhanced by combining them into a new technique. Ultraviolet (UV), visible, and infrared (IR) spectroscopy, for instance, are three possible specialisations of spectrometric methods. The same applies to mass spectrometry (MS) and ion mobility spectrometry (IMS), which are also spectrometry-based techniques. On the other hand, combined techniques such as gas chromatography - mass spectrometry (GC-MS), and gas chromatography - ion mobility spectrometry (GC-IMS) exemplify enhanced methodologies that provide the best characteristics of several techniques by coupling them into a single device [258, 259, 260, 261]. Gas chromatography, infrared spectroscopy, mass spectrometry, and ion mobility spectrometry are among the techniques more utilized for the assessment of VOCs.

2.4.2.1 Infrared Spectroscopy

Infrared (IR) spectroscopy is a widely used analytical technique that started as the first structural spectroscopic technique available for the assessment of organic compounds. As a specific technique of vibrational spectroscopy, infrared spectroscopy has gained relevance for both qualitative and quantitative analyses of different types of samples, such as gases, liquids, solutions, powders, and even surfaces [259, 262, 263]. IR spectroscopy allows the classification and quantification of samples through its infrared bands in the electromagnetic spectrum region, between 700 nm and 1 mm of wavelength, or 430 THz and 300 GHz of frequency, the region where most of the vibrational resonances of chemical bonds occur [264, 265, 266].

From a simplified perspective, the application and, specifically, the absorption of infrared radiation by the molecules of a sample is associated with the vibration of molecular bonds. Absorption takes place, for different molecular bonds, at specific values of energy; and the infrared spectrum represents the fraction of the incident radiation that is absorbed at a specific energy value. Energy values correspond to certain frequencies of vibration and, complementarily, to particular wavelengths or wavenumbers [267, 268]. The majority of organic compounds, like alcohols, ketones, ethers, and VOCs in specific, absorb radiation in the infrared region of the electromagnetic spectrum. Consequently, infrared spectroscopy is one of the most effective analytical techniques to identify and quantify volatile organic compounds [259, 269]. The group of all the absorption bands observed in a spectrum can be used as a pattern or fingerprint of a molecule or sample. The intensity can be represented in the form of absorbance, transmittance, or reflectance as a function of the wavenumber, which is proportional to the energy change between the initial and final vibrational states of the molecular species [258, 259, 264, 265].

A practical application of the previously described procedure and, generally, of IR spectroscopy is the open-path Fourier Transform Infrared (FTIR) spectroscopy. As mentioned, there are several options for IR radiation sources. Once emitted, this radiation undergoes a division process into two beams of equal intensity, by the Michelson interferometer, due to a set of mirrors used to reflect and refract the light. Thereafter, the radiation beams are expanded in order to enable the analysis of a large volume of interest. The radiation passes, then, through the target volume, and returns to the spectrometer along an optical path, after suffering reflection on a retroreflector placed on the other extremity of the volume of interest. Once reaching the spectrometer, the beams undergo the inverse procedure by being contracted by the same beam expander and by being added to a single radiation beam, generating constructive and destructive interferences among them. Finally, the radiation is captured by the detector and an IR spectrum including information on the analysed analytes is created [258, 264, 267]. Figure 7 illustrates the main steps of a complete analysis with an open-path FTIR spectrometer, where one can see the emission of the IR radiation, the division, reflection, refraction and expansion of the beam, the interaction with the target analytes and the detection of radiation for the spectrum creation [13].

Despite its advantages, IR spectroscopy presents some disadvantages for analytical studies specifically involving volatile organic compounds, namely the detection limits that are often poorer than the limits achieved by other analytical techniques, the necessity of trained personnel, the lack of portability and inadequacy to be employed for *in-situ* studies, and the requirement for additional techniques and pre-analysis procedures [270, 271, 272].

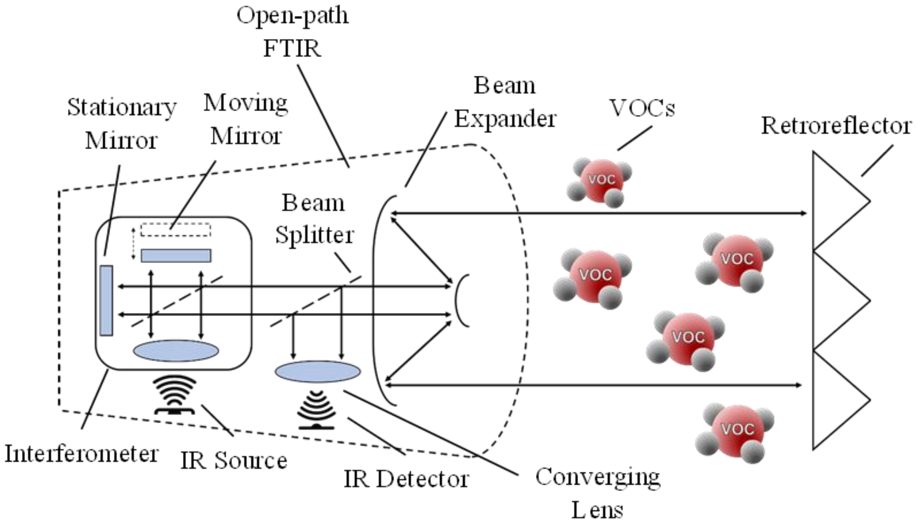

Figure 7 - Schematic of a generic open-path FTIR spectrometer [13].

2.4.2.2 Mass Spectrometry

Mass spectrometry (MS) is, perhaps, the most used detection technique among all the addressed ones. It enables to selectively identify and quantify a vast range of analytes, as well as, to study their molecular structure and composition [273]. MS is the analytical technique that generates more data from the measurements of the analytes and even enables the analysis of any element that can be ionized, independently of their organic or non-organic nature. To assess all this data, MS bases its working principle on the experimental measurement of the mass of gas-phase ions produced from the molecules of an analyte [274, 275].

Very briefly, a measurement via MS starts with the injection of the sample into the spectrometer. By bombarding it with a beam of energetic electrons, the molecules are ionized and disintegrate into multiple fragments. Some of these fragments are positive gas-phase ions. Once formed, the product ions are accelerated by an electric field and deflected by a magnetic field. Since the ions are separated according to their mass-to-charge ratio, only the desired ions are detected at the end of the process. The detection occurs, in this way, in proportion to their abundance. Finally, a mass spectrum of the molecule is produced. The spectrum provides the relation of ion abundance versus mass-to-charge ratio. Usually, the most intense peak is assigned with the relative abundance of 100% and the abundances of all the other peaks are given their proportional values, as percentages of the base peak. To avoid interferences from any other forms of matter, the ions must be analysed in a vacuum atmosphere [276, 277, 278].

Figure 8 schematizes the working principle of a mass spectrometer. Here, a sample composed of three distinct analytes is injected and, once accelerated by an electric field, the analytes suffer different deflections when exposed to a magnetic field, allowing their detection and characterization, as addressed [12].

The detection limits of mass spectrometry can go, for some cases, as low as ppb_v and, as mentioned, it can be employed in the study of a wide spectrum of samples, however, it has some limitations regarding the analysis of VOCs in laboratory settings. Due to the elevated temperatures used during the analysis, the samples can often degrade leading to a consequent loss of some analytes. Additionally, MS requires the use of vacuum systems and pre-sampling procedures before the analysis itself, increasing the complexity of the entire process [275, 278, 279].

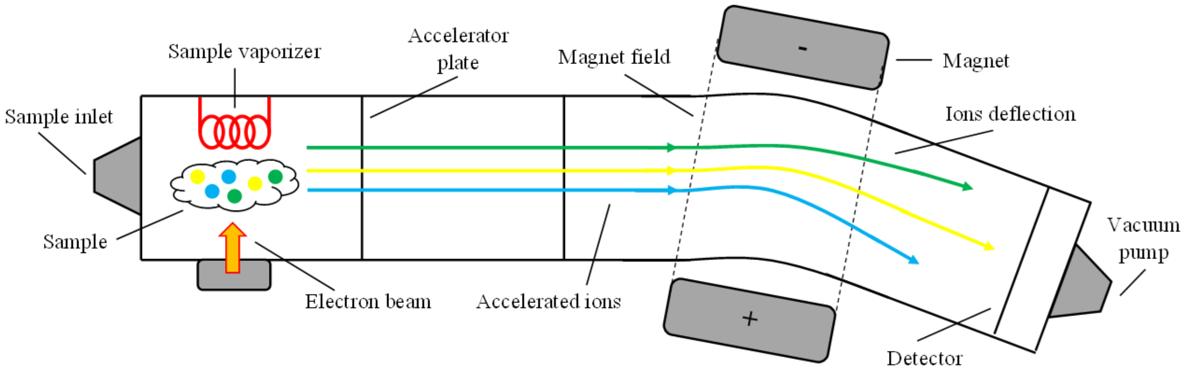

Figure 8 - Schematic of a generic measurement via Mass Spectrometry [12].

2.4.2.3 Gas Chromatography

Gas chromatography (GC) is an analytical technique often applied as a pre-separation method prior to further analyses with other analytical devices like mass spectrometers or ion mobility spectrometers. These devices enable the separation of a sample into its constituting analytes and provide information about their molecular composition and concentration. The GC section, specifically, can separate volatile analytes based on their solubility, i.e., based on their capacity of adsorbing to the walls of the chromatographic column, and whose boiling point ranges from near 0 to over 700 K. The temperature is an important factor for the column performance and, as said, the GC works at a wide range of temperatures so, proper temperature control is crucial for a correct chromatographic analysis [280, 281, 282].

During a GC measurement, the sample is introduced into the system and the analytes are distributed between two phases, the stationary phase, and the mobile phase. The mobile phase moves in a specific direction and is responsible for transporting the compounds through the entire column. This transportation can occur due to gravitational, capillary or pressure forces. In opposition, the stationary phase, usually a solid or an immobilized liquid, counteracts the transport rate of the mobile phase. Since the different analytes have different capacities to adsorb to the walls and different solubility, they will elute from the column at distinct moments. The detector, at the end of the system, registers the time that each compound requires to cross the entire circuit, often called retention time. This time enables the identification of all the analytes present in the initial sample [283, 284, 285].

Figure 9 schematizes a GC measurement. As mentioned, the sample is introduced into the chromatographic column where the analytes are separated considering their intrinsic capacity of adsorbing to the coating of the inner wall of the columns. Once the analytes elude from the column, they are detected, and a final spectrum is produced. This detection is achieved at exact times that are analyte-specific and correspond to the time required by each analyte to elude from the chromatographic column [12].

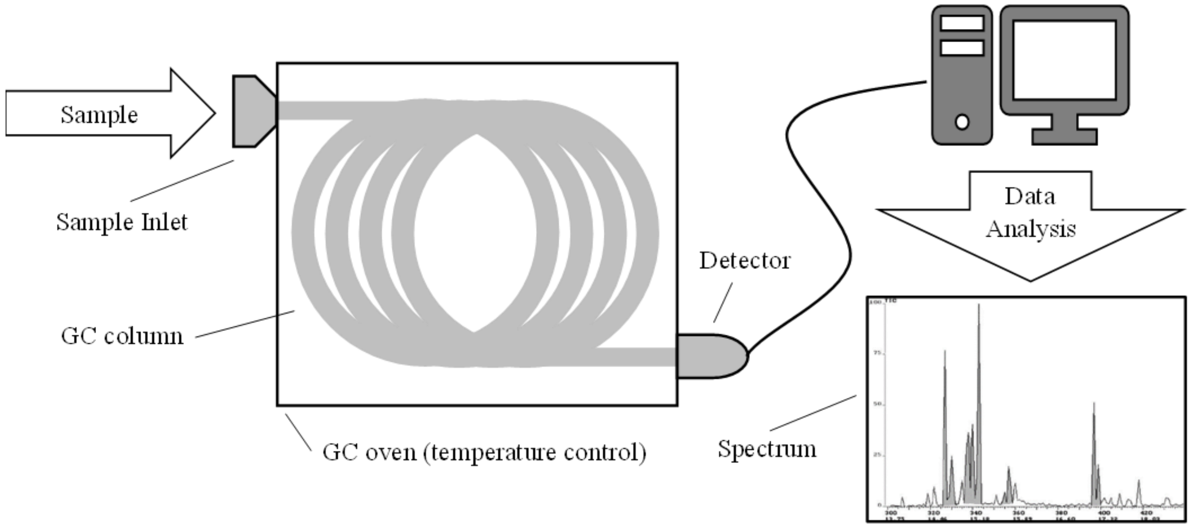

Figure 9 -Schematic of a generic measurement via Gas Chromatography [12].

As addressed, the sensors array-based systems and all the main analytical techniques vulgarly employed for the detection, identification and quantification of volatile organic compounds present some type of disadvantages or less positive points. These limitations can be summarily listed as low levels of sensibility and selectivity, low reproducibility of the data, the necessity of additional procedures, pre-processing methodologies and auxiliary chemicals, the duration of the analysis, the challenge to analyse complex and VOCs-rich matrices, and the lack of portability, among some others. In this way, a recent technology has been gaining space in the field of VOCs assessment.

2.4.2.4 Ion Mobility Spectrometry

Initially developed for military purposes, ion mobility spectrometry (IMS) has recently gathered interest for a large range of civil applications [286]. Ion mobility spectrometers have a set of specificities that enable the detection of VOCs, and VOCs only, in terms that no other analytical techniques allow. Their almost real-time monitoring capacity, analytical flexibility, instrumental simplicity, outstanding sensitivity, high selectivity, and portability make IMS one of the most widespread techniques nowadays whose range of applications extends from simpler topics like food quality/spoilage evaluation, products categorisation, and fraud detection [287, 288, 289], to more complex ones, such as security purposes, health pathologies detection, and air quality assessment [18, 260, 290].

In addition to its main features, IMS can be used in distinct versions such as differential IMS (DIMS) and field asymmetric IMS (FAIMS) or be coupled with additional techniques like mass spectrometry (MS) or gas chromatography (GC). In those cases, the coupling gathers in a single device the advantages of each technique and creates an extremely sensitive and selective new technique. These devices have the remarkable capacity to identify and quantify VOCs in concentration ranges down to ppb_v and ppt_v, based on the compounds' size, weight, and shape [291, 285, 261].

2.4.2.4.1 Applications

The main fields of IMS applications can be divided into three main categories: environmental and safety research, health research, and food research [14].

Considered its primordial field of applications, IMS has been applied for a variety of scenarios under the scope of environmental and safety research since its development. Due to their adequacy to analyse volatile samples, IMS has been largely employed to evaluate air quality and, in specific, for the detection, identification and quantification of all types of volatile organic compounds whose presence in the air and respective concentration levels can represent a threat to both the environment and the human health [16, 18]. Arnanthigo et al., for example, used an IMS-based device to detect possible environmental contaminants inside new buildings under construction. The authors were able to successfully detect and identify several relevant VOCs like limonene, butyl acetate, formaldehyde, and 2-ethyl-1-hexanol, among others [292].

Besides the identification of generic VOCs, IMS has equally been employed in the assessment of particularly hazardous compounds like benzene, toluene, xylenes, and formaldehyde. Szczurek et al. focused their research exactly on these compounds. The authors used an IMS device in its differential IMS version (DIMS) to analyse pure volatile samples of benzene, toluene, and xylenes. Regarding the achieved results in their work, the authors state a 100% success rate for the identification of VOCs [19].

Industrial contaminants and pesticides are well-known hazardous products whose monitoring is crucial to ensure the maintenance of public health. IMS has given some help in this task. An example of that is the work of Bauer et al. who, by using an IMS-based device, were able to identify 280 different compounds, which later led to the creation of a pesticide database with a standard deviation of solely 2%. The pesticide assessment was performed in concentration ranges of 0.100 to 0.001 mg/kg proving, once again, the suitability of ion mobility spectrometry for such topics [293].

Besides the mentioned applications, IMS has equally been employed in several other areas under the environmental and safety research scope. They are the detection of explosives [294], chemical warfare agents [295], drugs [296], and even in catastrophic scenarios and search for lost people [297].

Under the scope of health research, IMS has been mainly applied for the assessment of organic-borne metabolites [14]. The metabolites exhaled in the breath and other fluids of the human body can often be a tool for the Identification of biomarkers and, consequently, the diagnosis of specific pathologies and health conditions. An example of the suitability of IMS to perform this task is the work of Westhoff et al., which used IMS to differentiate two common pulmonary pathologies, chronic obstructive pulmonary disease (COPD) and lung carcinoma, solely based on the exhaled air. A cohort of 132 volunteers, including 35 COPD patients without lung cancer, 62 COPD patients with lung cancer and 35 healthy people, was used for the analysis of 10 mL of exhaled breath with an MCC-ion mobility spectrometer. The authors detected 104 peaks and, due to the IMS capabilities, they were able to differentiate between lung cancer patients and healthy individuals with a sensitivity of 60%, specificity of 91% and a positive predictive value of 95%. Furthermore, the authors identified cyclohexanone as a marker to distinguish healthy volunteers from COPD patients [298].

Not only pulmonary diseases have been studied with IMS; renal diseases are equally known for their impact on the metabolism of the patients, in this way, they can often be linked to endogenously borne biomarkers. For instance, renal failure-related VOCs were studied in the work of Pagonas et al. Having the goal of discovering a fingerprint of volatile organic compounds characteristic of people with any stage of renal failure, the authors analysed breath samples from healthy volunteers and patients undergoing haemodialysis sessions. The IMS data showed a total of 13 relevant compounds. Furthermore, the authors noticed a decreasing in the concentration of hydroxy-acetone, 3-hydroxy-2-butanone and ammonia in the later stages of renal failure. Both the presence and the behaviour of the mentioned analytes enabled the authors to successfully describe several biomarkers for renal diseases [299].

As mentioned, the endogenously borne biomarkers can be emitted to the exterior of the organism in several ways besides the breath. Perspiration is one of those options. Having this in mind, Vautz et al., successfully used a GC-IMS device to analyse volatile samples collected from seven volunteers. The authors claim to have detected 179 metabolites from the skin samples and proved that 13 of those analytes are common to all the volunteers. In this way, the authors state that the VOCs 2-ethyl-hexanol, 3-methyl-butyric acid, 3-octanol, 6-methylhept-5-en-2-one, benzaldehyde, decanal, hydroxy acetone, nonanal, propionic acid, acetophenone, acetic acid, 2-pentanone and 2-octanone, are skin-characteristic analytes [300].

Finally, IMS has been deeply used for several purposes under the scope of food research [14]. Among the food applications, IMS has been applied in the identification of fraud in products like wine. Typically, wine is a valuable and expensive drink, characteristics that often lead to the adulteration and falsification of this type of drink. IMS has allowed to profile the original organoleptic profiles of wine samples and, consequently, identify the adulterated ones [301]. A similar approach has been employed for the quality assessment of olive and other kinds of oils. These alimentary products are often adulterated with less valuable oils for profit reasons, frauds that an analysis through IMS can easily identify [302].

In a different approach, IMS has been employed for long-term evaluation of several processes like the fermentation of alcoholic beverages [303], the roasting of coffee grains [304], or the quality of milk during its utilisation in the manufacturing of milk derivates products [305]. Several studies regarding the profiling of the organoleptic profile of food products like cheese [306], tea [307], chocolate [308], honey [309], or edible seaweeds [50], have equally been developed aiming to fully characterize the emissions of these products and, consequently, assess their flavour or even culinary appropriateness. The freshness and spoilage of easily perishable products like fruits and vegetables have equally been evaluated through IMS due to its portability and easy adaptation to in-situ scenarios [310]. Finally, the capacity of IMS to address the spoilage and contamination of fish and meat-based products by bacterial organisms and consequent emission of potentially toxic compounds has been studied in several scientific studies [311].

2.4.2.4.2 Working Principle

A complete procedure sequence using an IMS device starts with the injection of a volatile sample into the apparatus; a procedure that does not require the employment of vacuum systems. Once prepared and introduced into the IMS device, the sample will suffer ionisation by a radioactive (Tritium or Nickel) or by a photonic ionisation source (X-ray ionisation, for example). One of the most common radioactive ionisation sources is Tritium (^3_1H) ($300\ MBq$). Tritium spontaneously emits a high-energy particle, β^-, as described in Equation 1 [312]:

$$^3_1H \rightarrow\ ^3_2He + \beta^- \tag{1}$$

The emitted β^- particles react with nitrogen, the inert gas present inside the ionisation chamber, to create background ions from nitrogen. Background ions are equally known as primary ions. The reaction occurs as follows:

$$N_2 +\ \beta^- \rightarrow\ N_2^+ + \beta'^- + e^- \tag{2}$$

The emission of both β^- particle and primary ions occur through multiple and continuous reactions. Nitrogen primary ions will then react with molecules of H_2O, NH_3 or NO present inside the ion mobility tube and create new ions. These new ions, $(H_2O)_nH^+$, $(H_2O)_nNH_4^+$ or $(H_2O)_nNO^+$, are called reactant ions and, unlike primary ions, they are visible in the final spectrum. Reactant ions form an intense peak visible along the entire spectrum and named reactant ion peak (RIP) [291, 313, 314]. In the next step, all VOCs of a sample react with the reactant ions. Considering a scenario in which the sample is composed of a single volatile analyte, *M*, the reaction between this generic compound and the reactant ions occurs according to the reaction:

$$M +\ (H_2O)_nH^+ \leftrightarrow M(H_2O)_{n-x}H^+ + xH_2O \tag{3}$$

, in which the x value is dependent on humidity levels. It is worth remembering that this humidity is seen as protonated water clusters that lead to the production of reactant ions [315].

Since one is talking about a chemical bounding between protons and molecules, the product ions of this reaction correspond to protonated monomers of the compound *M* [316, 317]. If the concentration of the analyte is sufficiently high, the monomer can continue to react with the remaining molecules of *M*, giving rise to the formation of protonated dimers, as illustrated in Equation 4. Larger clusters can equally be formed [291, 313, 318]:

$$M +\ M(H_2O)_{n-x}H^+ \leftrightarrow M_2(H_2O)_{n-(x+i)}H^+ + iH_2O \tag{4}$$

IMS is able to work in two different modes, positive and negative. The previous reactions exemplify the positive mode procedure. For the negative mode, the reactant ions are formed due to the reaction of the primary ions with O_2 molecules instead of H_2O, NH_3 or NO molecules. Having *MX* as a generic compound, the respective product ions can be created, in negative mode, by associative or dissociative electron attachments. Those reactions are represented in equations 5 and 6, respectively [291].

$$MX + (H_2O)_nO_2^- \leftrightarrow M + X^- + nH_2O + O_2 \tag{5}$$

$$MX + (H_2O)_nO_2^- \leftrightarrow (MX)O_2^- + nH_2O \tag{6}$$

Once created, the product ions are exposed to a homogeneous and weak electric field ($500\ V/cm$) that accelerates the ions through the IMS tube. The electric field acts along the tube and is created by equally spaced guard rings spread through the drift tube and connected through a chain of resistors. Figure 10 represents the action of this field in the interior of the IMS tube during a complete analysis [13]. Here, a generic sample composed of three VOCs is represented in the interior of the ionisation chamber, and the ionised compounds are then exposed to the electric field and separated across the drift tube.

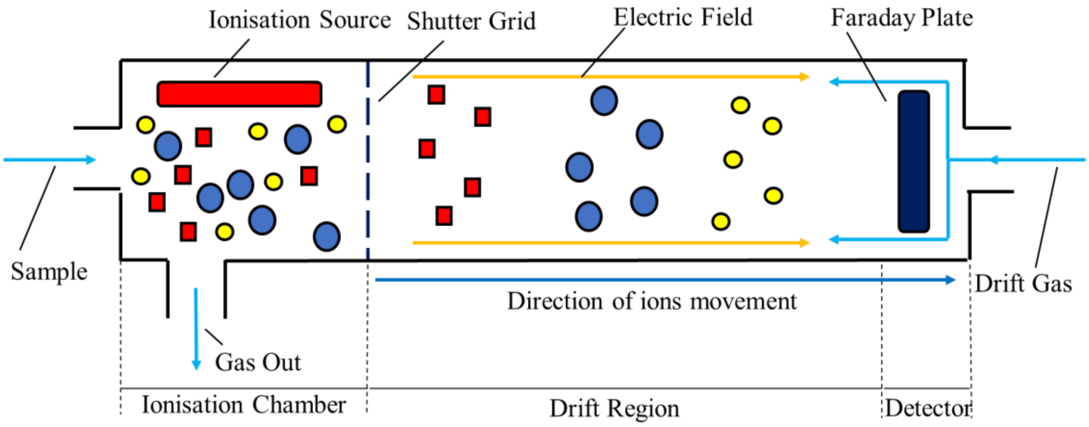

Figure 10 - Schematic of a generic measurement via IMS [12].

Eventually, ions collide with the inert neutral gas molecules (purified air or nitrogen) existent in the interior of the tube causing them to decelerate. Still under the electric field effect, product ions tend to gain velocity until suffering a new collision [291, 314]. This sequence of accelerations/collisions will make the ion velocity tend to an ion-specific value, denominated drift velocity, v_d. Drift velocity, as mentioned, is different for distinct compounds and it can be related to the electric field magnitude, *E*, through the ion mobility constant of the analyte, *K*, [291, 319]:

$$K = \frac{v_d}{E} \tag{7}$$

Additionally, drift velocity can be calculated by the ratio between the IMS tube length, L (around 98 mm), and the time that the product ions take to cross that same length.

$$v_d = \frac{L}{t_d} \tag{8}$$

The drift time, t_d, corresponds to the time each ion takes to go through the entire IMS tube, and it enables a new formulation for the ion mobility constant, K, [313, 320]:

$$K = \frac{L}{Et_d} \tag{9}$$

The ion mobility constant, however, may depend on pressure, P, and temperature, T, conditions. To circumvent this effect, it is common to normalize K to standard environmental pressure, $P_0 = 760\,Torr$, and temperature, $T_0 = 273.15\,Kelvin$. With this calculation, the so-called normalised ion mobility constant, K_0, arises [314, 321]:

$$K_0 = K\left(\frac{P}{P_0}\right)\left(\frac{T_0}{T}\right) \tag{10}$$

As mentioned, both ion mobility constant and drift time are constant and sample-specific values, in this way, the ratio between K and t_d is also a parameter that can be used for VOCs' differentiation. It is worth reinforcing that the entire described procedure occurs at both atmospheric pressure and room temperature and does not require the utilisation of vacuum systems to operate.

When the product ions reach the IMS tube's final extremity, they are detected through a Faraday plate at their specific drift times. In this way, two coordinates are registered during the IMS measurement, the drift time (ms) and the ions' intensity level (V). Figure 11 illustrates two IMS spectra that represent a) the outcome for a VOCs-free sample of air and b) the detection of both monomer and dimer of 3-pentanol [6].

Considering the distinct techniques that can be coupled to the IMS, the final spectrum of each variation presents differences. For the scenario where the IMS is coupled to a gas chromatography column, for example, a third coordinate is also represented in the plotted spectrum, defined as retention time, r_t (s). This temporal value corresponds to the time each compound needs to go through the entire chromatographic column and is directly related to the compounds' capability of adsorbing to the column walls [285, 261, 322]. Here, the analytes of the volatile samples undergo a pre-separation by their capacity of eluting from the inner coating of the chromatographic column, as previously addressed. Figure 12 schematizes a complete GC-IMS analysis. The yellow, blue, and green circles represent the compounds of an arbitrary volatile sample injected into the spectrometer.

A GC-IMS three-dimensional spectrum is, thus, generated as follows: the *x* and *y*-axis represent drift (ms) and retention (s) times, respectively; a third coordinate, typically represented by a colour scale in a two-dimensional view, corresponds to the ions' intensity (V). The intensity can be directly related to the concentration that each compound presented in the analysed sample. Aiming to quantify all the analytes, a calibration protocol must be applied to obtain a calibration curve which, in turn, is used to convert intensity values to concentration values [291, 323]. Figure 13 represents an ion mobility spectrometry spectrum, from a room air sample, in its two- and three-dimensional views, in which some of the represented VOCs are identified (1 – monomer of ethanol, 2 – monomer of isopropanol, 3 – dimer of ethanol, 4 – monomer of acetone and 5 – dimer of isopropanol, among many others) [16].

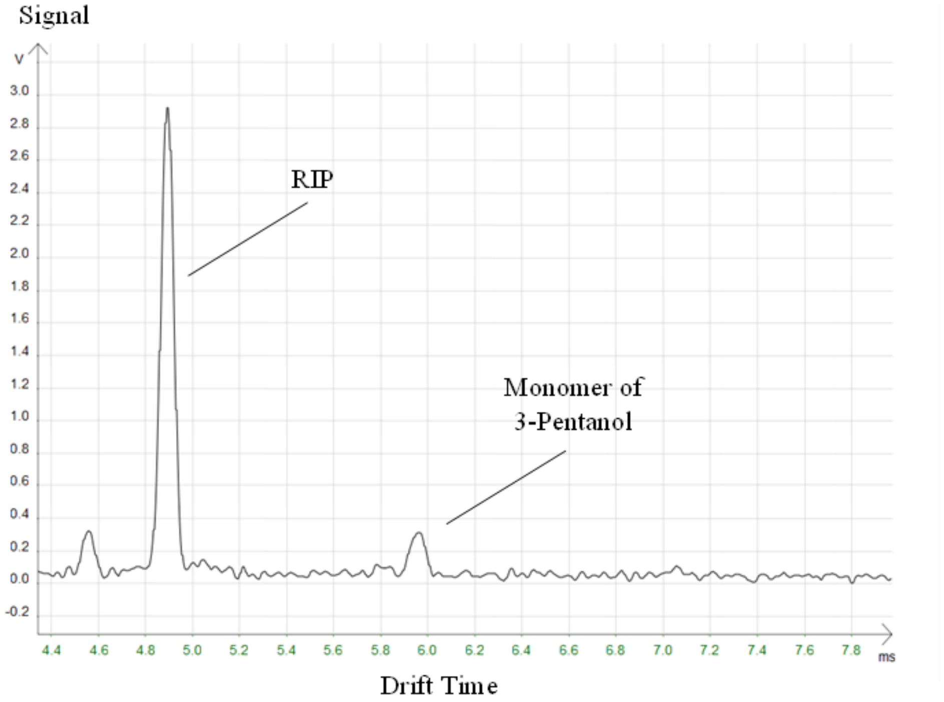

Figure 11 - IMS spectrum produced from a measurement of a generic sample of the volatile organic compound 3-pentanol [6].

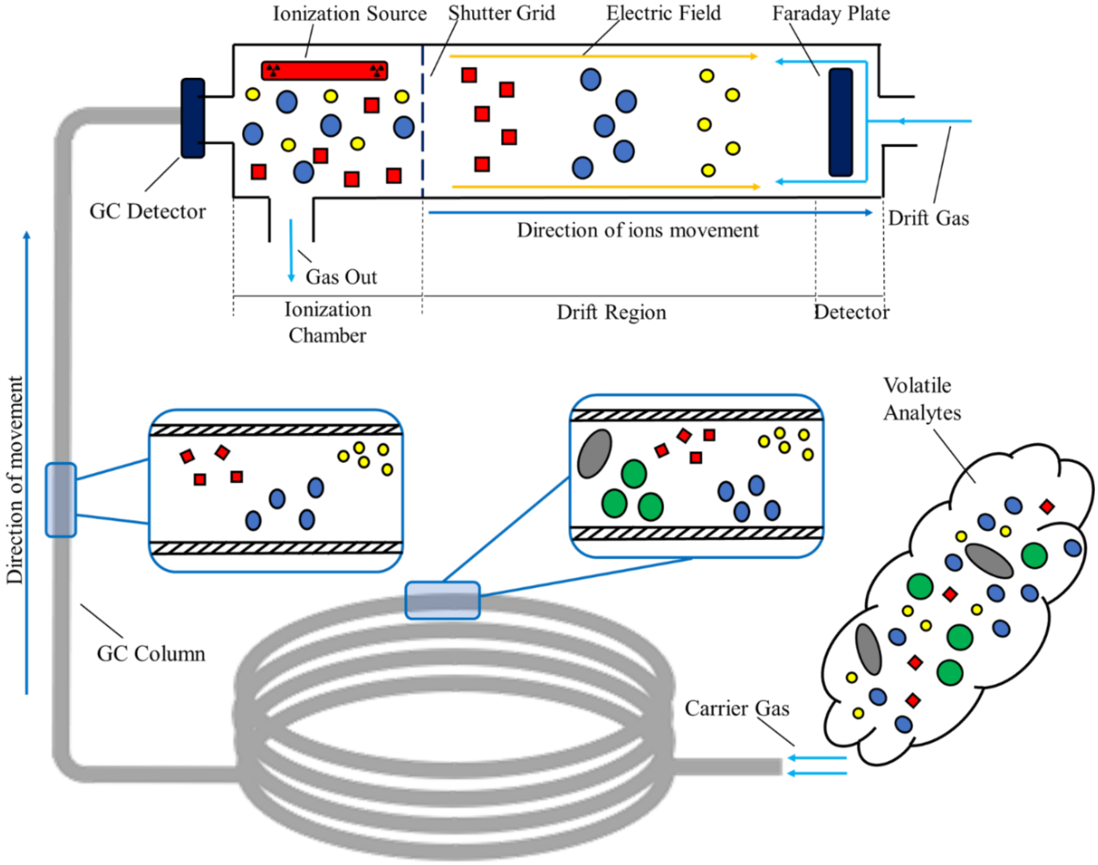

Figure 12 - Schematic of a complete measurement of a generic volatile sample with a Gas Chromatography - Ion Mobility Spectrometry device [16].

Moving from the sampling procedures and VOCs identification to their quantification, some scientific work has been done regarding the issue of establishing calibration protocols for IMS. Unfortunately, the relation between the VOCs concentration and the signal measured at the Faraday plate is a rather complex topic, which involves kinetics and thermodynamics. At this point, it should be considered that, as mentioned, one of the main limitations for the quantification through IMS is the humidity present in the drift tube, which can affect the IMS sensitivity [324]. Another issue that should be considered is that IMS presents some limitations regarding the analysis of high-concentration compounds due to the saturation of the ionisation source and the depletion of reactant ions. IMS devices that use radioactive ionisation sources, like tritium or nickel sources, present a linear behaviour for concentration versus intensity but solely for very low concentration levels. However, when the concentration is seen to increase, the calibration curve exhibits a plateau, limiting the concentration range of analysis. In this way, a typical calibration curve for this type of IMS has a logarithmic behaviour [325]. For IMS devices that do not use radioactive ionisation sources, like the Ultraviolet (UV) – IMS, the calibration models for the concentration/intensity relationship have been reported as linear [326].

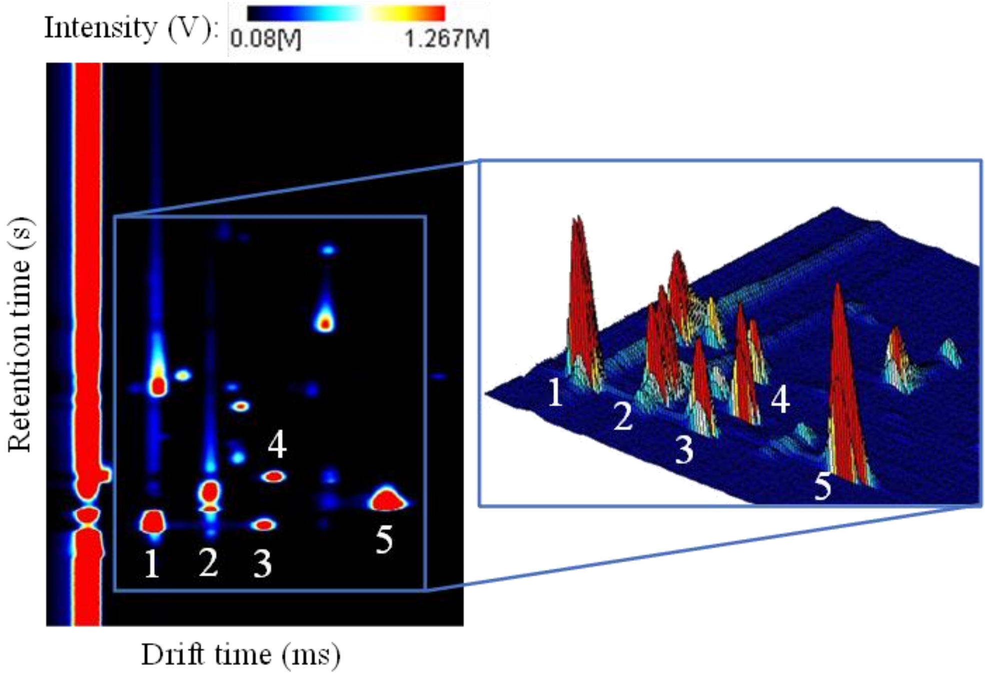

Figure 13 - Typical GC-IMS spectrum with an enlarged section for better visualization of the three-dimensional peaks (1 - monomer of ethanol, 2 - monomer of isopropanol, 3 - dimer of ethanol, 4 - monomer of acetone, 5 - dimer of isopropanol) [16].

As mentioned, the quantification of VOCs through IMS is a rather complex process with several variables to be considered, nonetheless, Puton et al. described pretty well the theory behind the relationship between the concentration of a volatile compound and the intensity of the detected signal. The authors provided detailed information for the scenario of a spectrum presenting contributions from the RIP (*r*) signal and stable monomer (*m*) and dimer (*m2*) signals, without any analyte decomposition during both periods of ionisation and drift [327].

Considering v_i the drift velocity of a given kind *i* of ions, and *t* the time, the ion concentration n_i in the reaction region is obtained by the following equation:

$$\frac{\partial n_i}{\partial t} = div(n_i v_i) + D_i \Delta n_i + P_i - L_i = 0 \qquad (11)$$

In Equation 11, D_i represents the diffusion coefficient, P_i is the component representing the resulting ions from the ionisation, and L_i corresponds to the rate of ions loss due to recombination between them.

Considering k_{rM} and k_{mM} the constant rates of monomer and dimer formation, respectively represented by Equations 3 and 4, and since the signals in consideration are just the RIP (*r*), the monomer (*m*) and the dimer (*m2*) of a single analyte *M*, Equation 11 can be solved for each of these ions, as follows:

$$\frac{\partial n_r}{\partial x} = -\frac{k_{rM} n_M}{K_r E} + \frac{N_0}{K_r E};\ n_r(0) = 0 \tag{12}$$

$$\frac{\partial n_m}{\partial x} = \left(\frac{k_{rM} n_M}{K_r E}\right) n_r - \left(\frac{k_{mM} n_M}{K_m E}\right) n_m;\ n_m(0) = 0 \tag{13}$$

$$\frac{\partial n_{m2}}{\partial x} = \left(\frac{k_{mM} n_M}{K_{m2} E}\right) n_m;\ n_{m2}(0) = 0 \tag{14}$$

In this set of equations, *x* is the drift tube length, the electric field is represented by *E*, K_i is the ion mobility constant of the type *i* of ions, and N_0 corresponds to the rate of reactant ions production. By solving this set of equations, it is possible to obtain the expression for the concentration of RIP (n_r), monomer (n_m) and dimer (n_{m2}), as follows:

$$n_r = \frac{N_0}{k_{rM} n_M}\left(1 - exp(-a_r n_M x)\right) \tag{15}$$

$$n_m = \frac{N_0}{k_{nM} n_M}\left(1 - \frac{a_m exp(-a_r x n_m) - a_r exp(-a_m x n_m)}{a_m - a_r}\right) \tag{16}$$

$$n_{m2} = \frac{N_0 a_{m2}}{k_{mM} n_M}\left(x n_M - \frac{a_r + a_m}{a_r a_m} + \frac{a_m^2 exp(-a_r x n_M) - a_r^2 exp(-a_m x n_M)}{a_r a_m (a_m - a_r)}\right) \tag{17}$$

Where a_r, a_m and a_{m2} are constant values respectively given by:

$$a_r = \frac{k_{rM}}{K_r E} \tag{18}$$

$$a_m = \frac{k_{mM}}{K_m E} \tag{19}$$

$$a_{m2} = \frac{k_{mM}}{K_{m2} E} \tag{20}$$

Once theoretically defined the concentration values, their relationship with the signal detected at the Faraday plate is then given by:

$$S_i = \gamma K_i n_i(x_{RR}) \tag{21}$$

Where γ is a proportionality constant and x_{RR} is the length of the reaction section inside the ionisation chamber. Equations 12 to 17, and Equation 21 show that a calibration curve relating the concentration and the signal intensity is rather complex and not straightforward to deal with.

By analysing each contribution individually, it is expected that the intensity of the detected signal from RIP decreases with concentration since the reactant ions are being used to form monomers and dimers. Regarding the monomer and dimer behaviours, it is expected the monomer intensity to increase with the increase of concentration but, due to the increase of dimer intensity, the monomer intensity starts decreasing after a certain limit. Figure 14 sketches the characteristic behaviour of RIP (blue line), monomer (red line) and dimer (black line) for the relationship between their respective concentration and intensity, for a generic scenario with arbitrary units [327].

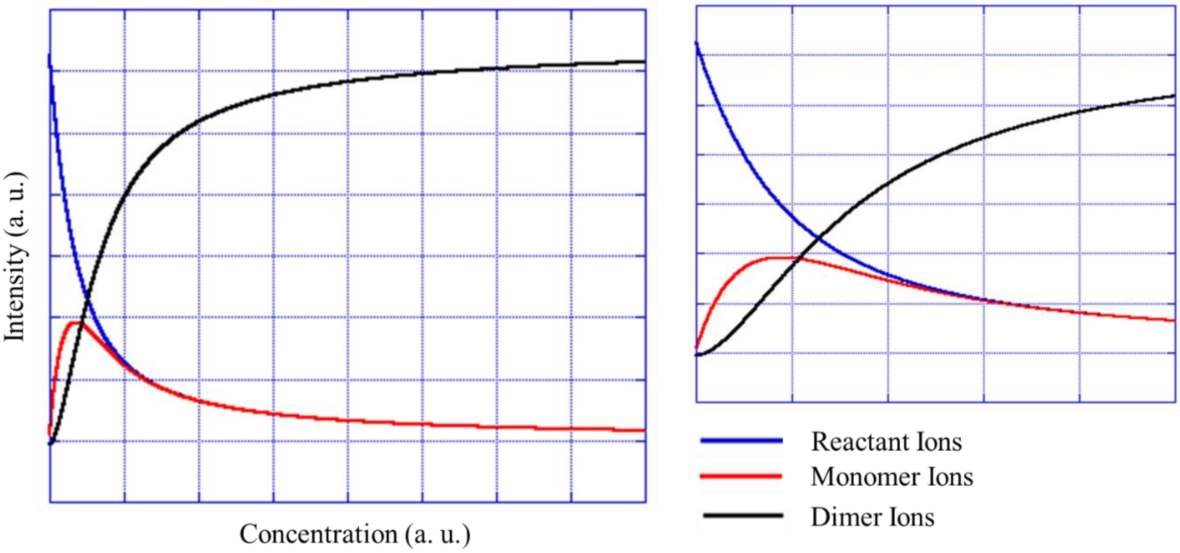

Figure 14 - Curves of the relationship between concentration and intensity, in arbitrary units, for the RIP, monomer and dimer signals of a generic ion [13].

The dimer behaviour is the more complex one. Considering equations 17 and 21, the relationship between the concentration and the dimer relative intensity can be expressed by the equation:

$$S_{m2} = \gamma K_{m2} n_{m2}(x_{RR}) = \gamma K_{m2}(x_{RR}) \left(\frac{N_0 a_{m2}}{k_{mM} n_M} \left(x n_M - \frac{a_r + a_m}{a_r a_m} + \frac{a_m^2 exp(-a_r x n_M) - a_r^2 exp(-a_m x n_M)}{a_r a_m (a_m - a_r)} \right) \right) \tag{22}$$

For better analysis, equation 22 can be further simplified and represented by:

$$S_{m2} = A1 - \frac{A2}{n_M} + \frac{A3}{n_M} exp(-A4 * n_M) - \frac{A5}{n_M} exp(-A6 * n_M) \tag{23}$$

Where:

$$A1 = \frac{\gamma K_{m2}(x_{RR}) N_0 a_{m2} x}{k_{mM}} \tag{24}$$

$$A2 = \frac{\gamma K_{m2}(x_{RR}) N_0 a_{m2}(a_r + a_m)}{k_{mM} a_r a_m} \tag{25}$$

$$A3 = \frac{\gamma K_{m2}(x_{RR}) N_0 a_{m2} a_m^2}{k_{mM}(a_r a_m(a_m - a_r))} \tag{26}$$

$$A4 = a_r x \tag{27}$$

$$A5 = \frac{\gamma K_{m2}(x_{RR}) N_0 a_{m2} a_r^2}{k_{mM}(a_r a_m(a_m - a_r))} \tag{28}$$

$$A6 = a_m x \tag{29}$$

In this way, it is clear that the dimer behaviour is composed of three main parcels which have been plotted in the graph included in Figure 15. Essentially, it represents the three parcels, a hyperbola (red line), and two exponential-like functions (blue and green lines) of Equation 23, as well as the complete dimer curve (black line).

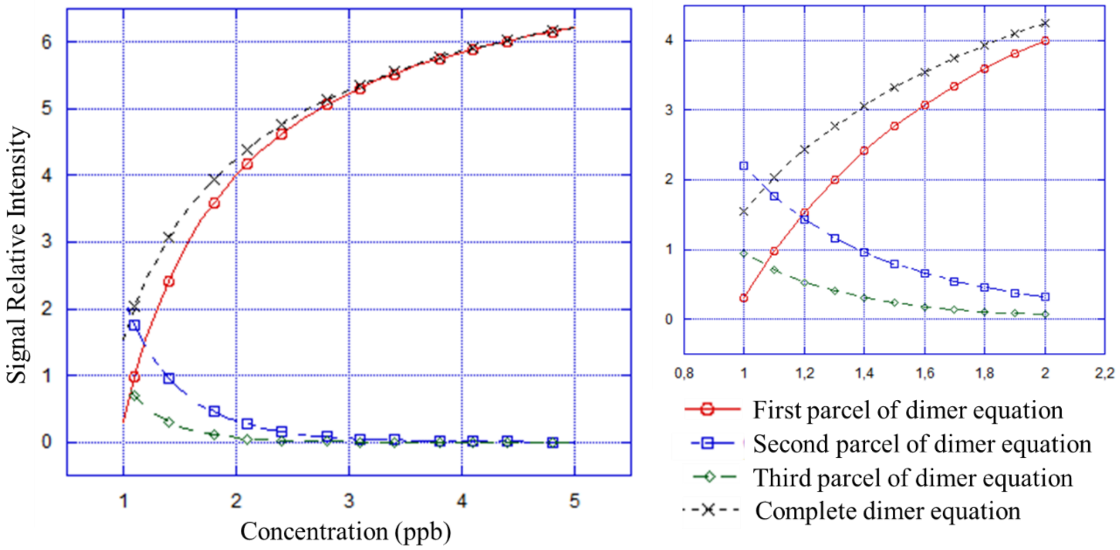

Figure 15 - Representation of the three main parcels, i.e., the hyperbola (red line) and two exponential-like functions (blue and green lines), that comprise the dimer equation (black line) for concentration vs. relative intensity [13].

As seen, calibration procedures for VOCs quantification by IMS are still a very demanding research topic, however, some work is being done about it. This might not be a major drawback as IMS is suited to detect traces (say ppt_v to ppb_v) of VOCs rather than moderate or high concentration levels, for which the device must be adjusted. Nonetheless, the calibration procedures for IMS still require a much deeper study before being completely established and understood.

Taking into consideration all the independent studies and respective results included here, as well as the working principle here detailed, ion mobility spectrometry seems to have several advantages and disadvantages that deserve to be summarized. To do so, a SWOT analysis was carried out and it is featured in Table 1. The SWOT analysis is an expeditious strategic technique that enables the assessment of strengths (S), weaknesses (W), opportunities (O) and threats (T) of the subject under analysis. When applied to characterize an analytical technique, it allows portraying its main advantages (strengths), disadvantages (weaknesses), issues requiring development (opportunities) and topics that may negatively influence or affect both the measurements/results and the device itself (threats).

Table 1 - Ion Mobility Spectrometry SWOT table [13].

<table>
<tr><th colspan="2">Ion Mobility Spectrometry SWOT table</th></tr>
<tr><td>Strengths
• Detection limits;
• Concentration range;
• Almost real-time analyses;
• <i>In-situ</i> measurements;
• Adaptability to distinct scenarios;
• Portability;
• System's simplicity.</td><td>Weaknesses
• Sample type;
• Lack of a library of analytes;
• Lack of calibration procedures;
• Price.</td></tr>
<tr><td>Opportunities
• Possible coupling with additional techniques;
• Calibration protocol development;
• Machine learning algorithm implementation;
• New and distinct applications.</td><td>Threats
• Exposure to hazardous environments leading to the adulteration of the sample;
• Possibility of device damages during in-loco measurements;
• Costs of maintenance.</td></tr>
</table>

3

MATERIALS AND METHODS

This chapter includes all the information on the materials and methods utilised during the entire doctoral project. Specifically, it includes Information on the used analytical techniques and procedures, their manufacturer, and the parameters used for all the measurements done during the project. Information on the characteristics and features of all the samples studied during each one of the developed studies can equally be found in this chapter. Then, all the developed procedures of sample preparation, collection, storing, transportation, and analysis are equally included in this section of the dissertation. Finally, schematics exclusively developed for this dissertation are included for illustrative purposes.

3.1 Instrumentation: GC-IMS

A GC-IMS device manufactured by G.A.S. (Dortmund, Germany) was used to perform most of the measurements included in this work. As previously mentioned, this apparatus couples two distinct techniques, namely, Gas Chromatography (GC) and Ion Mobility Spectrometry (IMS), creating a device with outstanding levels of sensitivity and selectivity, and improved capacity to detect, identify and quantify volatile organic compounds. A photography of the used device was included in Figure 16 for illustration purposes.

An analysis via GC-IMS starts with the injection of the volatile samples into the chromatographic column where the analytes are separated based on their capacity of adsorbing to the inner coating of the column. The column assembled in the used device was an MXT-200 model with 30 m of length and 0.53 mm of internal diameter, coated with stainless steel with a mid-polar stationary phase of trifluoropropylmethyl polysiloxane of a 1 µm thickness.

Figure 16 - Gas Chromatography - Ion Mobility Spectrometry device
used under the scope of this doctoral project.

Once eluted from the chromatographic column, the pre-separated analytes pass to the IMS section of the device. Here, they are ionised and separated based on their drift times when exposed to a homogeneous electric field. The apparatus was equipped with a radioactive ionisation source of tritium (H_3) responsible for the spontaneous emission of β radiation, with an activity of 300 MBq. A drift tube with a length of 98 mm and a 5kV switchable polarity was also assembled in the device. The intensity of the electric field used to make the ions drift through the IMS tube was 500 V/cm. Table 2 lists all the parameters and features of the GC-IMS device used during this work.

Table 2 - Parameters and features of the GC-IMS device.

Parameters	**Values**	**Units**
Sample Loop Volume	1	mL
GC Column Model	MXT-200	–
GC Column Length	30	m
GC Column Diameter	0.53	mm
Ionisation Source	Tritium – β Radiation	–
Ionisation Intensity	300	MBq
Ionisation Polarity	Positive	–
Drift Region Length	9.8	cm
Drift Potential Difference	5	KV
Electric Field Intensity	500	V/cm
Resolving Power Range	65 – 70	–

It is worth stating that a temperature of 343.15 K (70 ºC) was maintained in the interior of the column during the entire duration of each analysis. The temperature in the interior of the drift tube, in its turn, varied between 297.15 K (24 ºC) and 301.15 K (28 ºC). The CG-IMS equipment was connected to a Circular Gas Flow Unite (CGFU) also produced by G.A.S., as visible in Figure 16. The use of a CGFU offers portability to the equipment, which is of particular interest for the present study due to the necessity of using this analytical instrument outside of the laboratory for *in-situ* measurements. This complementary device was responsible for supplying purified air as carrier and drift gases, at flows of 10 to 150 mL/min and 150 mL/min, respectively. All the analyses had a duration ranging from 180 seconds (3 minutes) to 900 seconds (15 minutes). Table 3 summarizes the analysis conditions used throughout the entire project.

Table 3 - Conditions of analysis used during the measurements performed with the GC-IMS device.

Parameters	**Values**	**Units**
Carrier Gas	Purified Air	–
Carrier Gas Flow	10 – 150	mL/min
Drift Gas	Purified Air	–
Drift Gas Flow	150	mL/min
GC Temperature	343.15	K
IMS Temperature Range	297.15 – 301.15	K
IMS Pressure Range	757 – 760	Torr
Analysis Duration	180 – 900	s

Disclaimer: The information included in this chapter was originally published in several scientific papers developed and published throughout the entire doctoral project [16, 9, 18, 10, 11].

3.2 Other Analytical Approaches

Under the scope and all the goals of this doctoral project, some other analytical techniques had to be used in studies parallel to the main one. In specific, a procedure around gas sensors and impedance spectroscopy was developed to achieve one of the goals of the project: assess the suitability of graphene oxide-based sensors to detect and identify VOCs, as well as to develop quantification procedures. On the other hand, the use of a thermogravimetric device was needed in order to develop the calibration procedure for the GC-IMS presented in due time.

3.2.1 Sensors Array-Based Measurements

3.2.1.1 Graphene-Oxide Sensors

The polyethyleneimine (PEI) and graphene oxide (GO) utilised for the preparation of thin films were purchased from Sigma-Aldrich. The ceramic-based sensor supports with deposited gold interdigitated electrodes (IDE) were acquired from Metrohm DropSens (length: 22.8 mm; width: 7.6 mm; thickness: 1 mm; electrodes width: 200 µm; distance between electrodes: 200 µm). A schematic of the ceramic base with the graphene layers on top of it can be consulted in Figure 6.

Thin films of PEI and GO polyelectrolytes were adsorbed through layer-by-layer (LbL) technique on ceramic-based sensor supports with deposited gold IDE. This technique basically settles down on electrostatic forces of the polyelectrolytes that enable the application of alternated electrically charged polyelectrolytes [328]. To do so, the supports were alternately immersed in the PEI and GO aqueous solutions, positively and negatively charged polyelectrolyte solutions with concentrations of 2.5×10^{-1} and 3.2×10^{-1} mg/mL, respectively. Between each immersion, a wash procedure, consisting of the immersion of the support in ultrapure water to remove eventual excesses of polyelectrolyte, was undertaken. Once completing each immersion sequence, the support was dried with a gentle nitrogen air blasting. The described procedure corresponds to the deposition of a bilayer and was repeated 15 times, leading to the deposition of the multilayer thin films of polyelectrolyte in the surface of the ceramic-based support, and forming the sensors denominated as $(PEI/GO)_{15}$. Figure 17 schematises the procedure employed for the deposition of the thin layers on the ceramic base.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, T. P. Pivetta, V. Vassilenko, P. A. Ribeiro, M. Raposo. Graphene Oxide Thin Films for Detection and Quantification of Industrially Relevant Alcohols and Acetic Acid. *Sensors*, 23, 462, 2023. https://doi.org/10.3390/s23010462 [15].

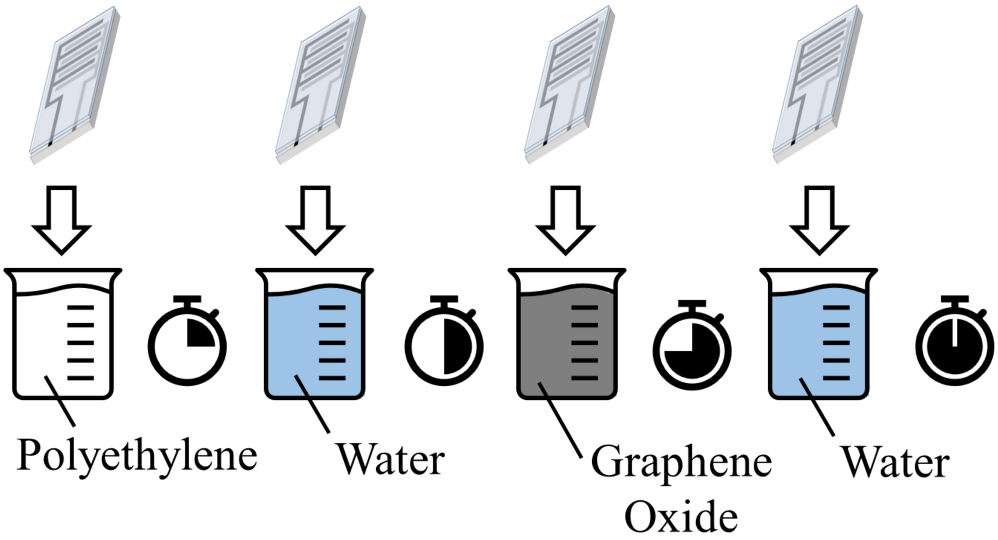

Figure 17 - Schematic of the procedure used to lay the thin layers of polyethylene and graphene oxide on the ceramic base.

3.2.1.2 Impedance Spectroscopy Measurements

Impedance spectroscopy was the analytical technique selected for the characterisation of sensor units' response to the target analytes, as addressed in due time. Detailed information on experimental setup has been described by Magro et al. [329], nonetheless, it is important to mention that a custom-made chamber with a volume of 58 L was employed to create a controlled atmosphere and assess the electrical impedance response of the thin films. Initially, the chamber was evacuated to the pressure of 10^{-3} mbar and the previously calibrated sample of the target VOCs was introduced into a round-bottom glass flask. The VOCs sample was then volatilized and purged through compressed synthetic air (ALPHAGAZ^{TM} 1 AR, Air Liquide). The sensor units were previously placed in the respective sample holder in the chamber and, as next step, their electrical response to the VOCs was measured with an impedance analyser (Solartron 1260 Impedance/Gain-Phase Analyzer coupled with a 1296A Dielectric Interface, AMETEK Scientific Instruments) and assessed with a dedicated software (SMaRT Impedance Measurement Software, version 3.3.1, AMETEK Scientific Instruments). A frequency range of 1 to 10^6 Hz and an AC voltage of 25 mV were applied during the impedance assessment. To ensure that the signal was representative of the sensor's response, these measurements were performed in triplicate. Figure 18 schematises the methodology adopted to analyse samples of VOCs using the previously developed graphene oxide-based sensors with impedance spectroscopy.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, T. P. Pivetta, V. Vassilenko, P. A. Ribeiro, M. Raposo. Graphene Oxide Thin Films for Detection and Quantification of Industrially Relevant Alcohols and Acetic Acid. *Sensors*, 23, 462, 2023. https://doi.org/10.3390/s23010462 [15].

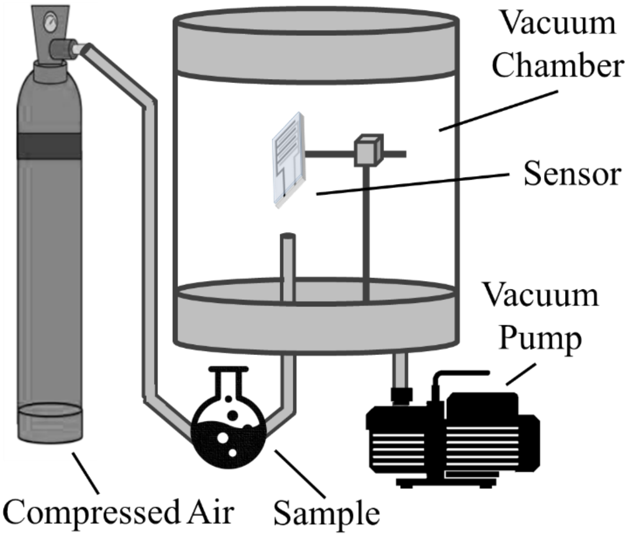

Figure 18 - Schematic of the procedure used to analyse samples of VOCs using impedance spectroscopy and graphene oxide-based sensors [15].

3.2.2 Instrumentation for Quantification Purposes

In order to fully characterise the indoor air quality, it is necessary to identify and quantify the detected analytes, nonetheless, one of the main limitations of GC-IMS, as mentioned, is the lack of standardised procedures and calibration libraries to quantify the detected VOCs. In this way, it was vital to develop a protocol of calibration for later use during the *in-situ* analyses.

Due to the complexity of calibration a GC-IMS device, already addressed previously, a thermogravimetric (TGA) device was used as an auxiliary tool. In specific, a LABSYS evo TGA 1150® device from Setaram Solutions was employed for thermogravimetric analysis of the samples. This device enables to control the temperature to which the samples are exposed in an interval that ranges from room temperature to 100ºC with a precision of ±0.04%. In addition, TGA has a weighing precision of ±0.01% in the milligrams range of weight [17].

All the studied samples were previously prepared in permeation tubes, as addressed in due time, and placed in the interior of the TGA oven. The GC-IMS coupled with the CGFU unit were connected to the TGA device through a Teflon tube with a length of 40. Then, the TGA was responsible for accurately controlling the mass loss ratio of the permeation tubes in accordance with the temperature established in the oven. Temperatures of 40, 60 and 85 ºC were used to test the samples. The emissions from the permeation tubes were later carried into the spectrometer with a flow of purified air created by the CGFU unit. Flows of 25, 50, 100, 150 and 200 mL/min were tested during the study. Measurements were taken every 15 min after a stable mass loss ratio was achieved. Finally, the concentrations emitted by the permeation tubes, assessed by the TGA device, were plotted against the intensity levels detected by the GC-IMS. Figure 19 illustrates the GC-IMS and TGA devices working parallelly (left) and the TGA device by itself (right) [17].

Disclaimer: The information included in this chapter was originally published in the paper: J. M. Fernandes, V. Vassilenko, P. C. Moura, V. Fetter. Gas Chromatography-Ion Mobility Spectrometry Instrument for Medical Applications: A Calibration Protocol for ppb and ppt Concentration Range. In: 12th Advanced Doctoral Conference on Computing, Electrical and Industrial Systems, DoCEIS 2021. Costa da Caparica, Portugal: Springer, 349-357, 2021. https://doi.org/10.1007/978-3-030-78288-7_34 [17].

Figure 19 - GC-IMS coupled with a GCFU unit working in parallel with the TGA device (left), and the TGA device by itself (right).

3.3 Studied Samples

During the entire duration of the doctoral project, several different types of samples were studied in order to comply with the previously defined goals of the project. One can divide into two main sections the type of samples analysed. The first group includes all the volatile samples whose nature prevents their analysis at a laboratory facility. Air analyses at the locations of interest are examples of those cases. The second group focuses on the samples that, by their nature, could or had to be analysed at a laboratory, namely, pure samples of VOCs and samples of VOCs-emitting sources.

3.3.1 *In-Situ* Samples Analyses

As previously mentioned, this doctoral project is composed of several studies. Some of them required the analysis of air samples at locations of interest. In this way, three main studies required the installation of the GC-IMS device at the target locations. They are the study developed to assess the suitability of GC-IMS for *in-situ* measurements, for long-term measurements, and the study of the air quality at the main locations of the car factory painting line.

3.3.1.1 Local Campus

Two main studies were developed at the local university campus to assess the suitability of GC-IMS, in a practical manner, for both *in-situ* and long-term analyses. In this way, two main groups of samples were considered, as addressed below.

3.3.1.1.1 Suitability for *In-Situ* Analyses

Aiming to assess the suitability of GC-IMS for *in-loco* analyses, a total of 465 air samples from 16 different locations across a university campus[1] were tested. The locations were:

- Administration building;
- Mechanical engineering building;
- Electronic engineering building
- Laboratory of atomic and molecular physics;
- Laboratory of biomedical engineering;
- Laboratory of chemistry;
- Laboratory of analytical instrumentation (GC-IMS);
- Laboratory of electronics;
- Laboratory of materials engineering;
- Laboratory of conservation and restoration department;
- Fabrication laboratory (FABLAB);
- Canteen;
- Bathroom;
- Workshop for scientific equipment;

---

[1] For reasons of confidentiality, the name of the chosen campus is not indicated.

- Storeroom for cleaning products;
- Outdoor air (reference air).

Since the campus is located in an ecologically clean area, near the coast of the Atlantic Ocean and far away from industrial areas, the outdoor air is significantly free from toxic and exogenous contaminations. In addition, the ambient air around the campus (30 hectares) is very homogeneous and, normally, its endogenous VOCs are considerably more diluted than they are at any indoor location, i.e., they have lower concentration levels so, they can be utilised as a baseline or reference spectrum for assessing the VOCs in the studied locations. In this way, 31 air samples were collected and analysed from 15 indoor locations and also from the outdoor environment to be used as a baseline, as detailed in due course.

The sampling sites were selected taking into consideration several topics, namely, their characteristics, specific activities developed at the location, particular smells, the use of specific chemical compounds, and people's affluence, among others. For instance, the analysed buildings, like the administration, mechanical engineering and electronic engineering buildings, were considered for the study due to the elevated affluence of people. Heavily populated locations must always be assessed regarding the air quality, as already mentioned. Regarding the studied laboratories, the activities developed at this type of location, usually involving chemical compounds and many other potential sources of VOCs, and the long periods of exposure that the employees have to deal with were the decisive factors in selecting them for analysis. The canteen was selected due to the affluence of people and the activities developed, namely, cooking. The presence of a large number of chemical products and solutions was the reason to select the storeroom.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, V. Vassilenko. Gas Chromatography – Ion Mobility Spectrometry as a Tool for Quick Detection of Hazardous Volatile Organic Compounds in Indoor and Ambient Air: A University Campus Case Study. *European Journal of Mass Spectrometry*, 28, 113-126, 2023. https://doi.org/10.1177/14690667221130170 [16].

3.3.1.1.2 Suitability for Long-Term Analyses

Aiming to assess the suitability of GC-IMS for *in-situ* long-term measurements of VOCs and consequent control of indoor air quality in closed spaces, a year-long study was developed aiming to obtain the GC-IMS spectra of volatile organic compounds, identify the detected analytes and perform the evaluation of the daily variation of the total VOCs (tVOCs) intensity across the period of analysis. It was expected that the achieved results enable to assess the suitability of GC-IMS for the aforementioned tasks, to have a deeper understanding of the main analytes continuously present in the considered closed space and of their overall behaviour throughout an extended period, and test the developed procedure for future detection of potentially hazardous VOCs relevant for the public health.

The GC-IMS device was assembled in a specific room whose main purpose was to simulate a generic closed-space environment. The air samples were automatically collected from the room air by the device's pump without requiring the operator's intervention. Daily air measurements were meticulously performed at the same time across the study period. The temperature and humidity conditions of the room were not artificially controlled during the entire study, that is, no heating, cooling, humidifier or dehumidifier devices were used. The environmental humidity in the room varied between 40% and 60%, mainly depending on the month of the year. The affluence consisted of five people working in the interior of the room for 8 hours per day, 5 days per week. In this way, all the potential sources of VOCs, affluence of people, social interactions and work regime were kept unaltered.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, V. Vassilenko. Long-Term *In Situ* Air Quality Assessment in Closed Environments: A Gas Chromatography – Ion Mobility Spectrometry Applicability Study. *European Journal of Mass Spectrometry*, 29, 231-239, 2023. https://doi.org/10.1177/14690667231187502 [11].

3.3.1.2 Car Factory Painting Line

One of the main goals of this doctoral project was to identify the main critical locations of the painting line and evaluate the indoor air quality at those places. To do so, an exhaustive *in-loco* evaluation of all the steps of the painting line was mandatory. As previously mentioned, the paint of a car involves a lot of intricate steps and the utilisation of a vast amount of potentially toxic solutions. To identify the critical locations, regular visits were made to the painting line and, having per base the map illustrated in Figure 20 (provided by Volkswagen AutoEuropa), and discussing the matter with the employees, one could identify and select the locations to be considered for this doctoral project.

Then, with the aforementioned approach, one could select a total of eight indoor locations of the car factory painting line for posterior analyses regarding the quality of the air. In parallel, an outdoor location was equally evaluated for purposes of reference, as addressed in due time. The studied locations were:

- Phosphatising bath;
- Cataphoresis bath;

- Primer application;
- Basecoat application;
- Clearcoat application;
- Wax application;
- Ceiling of the factory;
- Office of the painting line head;
- Outdoor air (reference air).

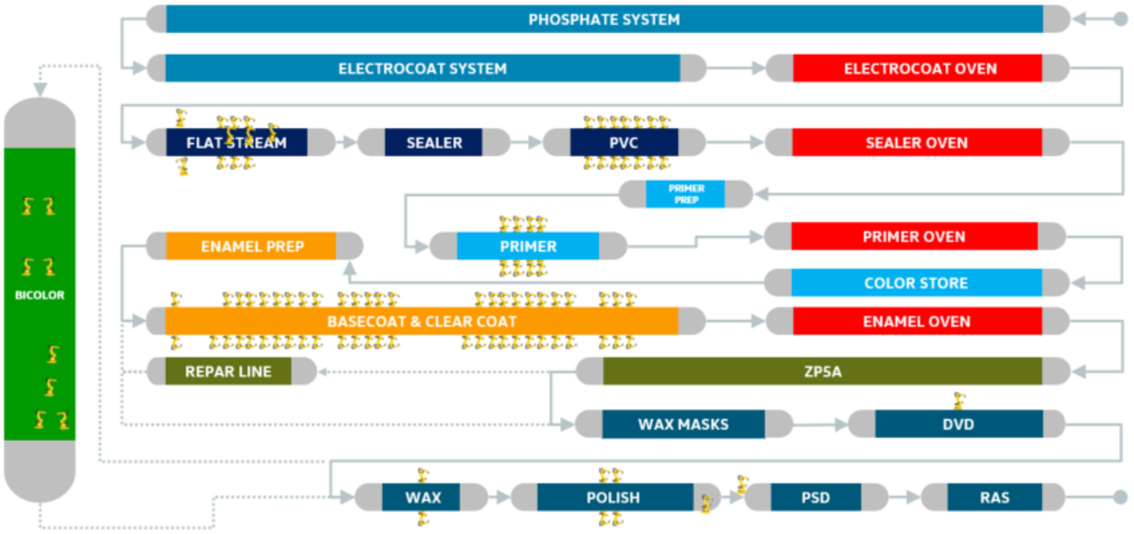

Figure 20 - Map of all the steps of the painting line used to fully coat a car (map provided by Volkswagen AutoEuropa).

Concerning the reasons behind the selection, one can state that, even without access to the exact composition of the bath solutions, the large amount and diversity of chemicals used in both phosphatising and cataphoresis baths make these locations considerably interesting for air analyses. The primer, basecoat (ink), clearcoat (varnish), and wax, in their turn, are applied to the chassis by automated robotic arms, however, the presence of employees inside these locations is extremely common. In this way, due to this continuous exposure, all these four locations were also considered of special interest for air analyses. The extractors and air purification systems are assembled in the factory ceiling so, it is important to assess the presence of VOCs near these systems. The air from the office of the painting line manager was also analysed due to being a room isolated from the painting line but, usually, very crowded. Finally, since they are free of interference from the painting line emissions, samples of the outdoor air were collected and analysed to act as reference air.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, F. Santos, C. Fujão, V. Vassilenko. In Situ Indoor Air Volatile Organic Compounds

Assessment in a Car Factory Painting Line. *Processes*, 11, 2259, 2023. https://doi.org/10.3390/pr11082259 [9].

3.3.2 Laboratory Samples Analyses

In order to study the potential sources of emission of VOCs into the atmosphere, as well as to identify those same compounds, several laboratory works had to be developed. Some studies were conducted under these aims: a first study focused on the evaluation of pure samples of volatile organic compounds for purposes of identification and quantification, and a second study focused on the emissions of the main sources of VOCs emission, i.e., the coatings used in the painting line.

3.3.2.1 Pure Samples

3.3.2.1.1 GC-IMS Analyses

As already mentioned, one of the main limitations of GC-IMS is the lack of certified libraries that enable to accurately identify and quantify the detected VOCs. Due to this fact, and besides all the advantages of the technique, the compounds detected at all locations of interest and during laboratory studies would be unidentifiable and unquantifiable.

To remedy this issue, a database of compounds was developed. To do so, pure samples of the most relevant volatile organic compounds were analysed with the GC-IMS in order to register their exclusive drift and retention times in the mentioned database. This tool was mandatory and was later used for the purpose of identifying all the detected analytes throughout the entire doctoral project. The list of the 158 VOCs analysed and included in the database can be consulted in Table 4, below.

Table 4 - Volatile organic compounds analysed to create a database of compounds for the GC-IMS.

Volatile Organic Compounds			
Acetaldehyde	1,3-Dichloropropene	3-Hexanol	1-Octanol
Acetic Acid	Diethylamine	2-Hexanone	2-Octanone
Acetone	1,2-Diethylbenzene	3-Hexanone	2-Octenal
Acetonitrile	1,3-Diethylbenzene	2-Hexenal	1,3-Octenone
Acetophenone	1,4-Diethylbenzene	1-Hexene	Octylacetate
Acetylacetone	Diethylether	1,3-Hexenone	Pentachloroethane
Aniline	Dihexylether	Histamine	Pentanal

Anisole	Dimethylamine	β-Homocyclocitral	Pentanedial
Benzaldehyde	3,3-Dimethyl-2-butanone	Isoamyl Acetate	Pentanoic acid
Benzene	n,n-Dimethylformamide	Isobutylamine	1-Pentanol
Benzonitrile	2,4-Dimethylpentane	Isobutylbenzene	2-Pentanol
Benzyl Chloride	1,4-Dioxane	Isooctane	3-Pentanol
3-Bromoaniline	Dipropylether	Isopropanol	2-Pentanone
Butanal	1-Dodecanol	Isopropylbenzene	3-Pentanone
Butanoic Acid	1,2-Ethanediol	Isopropylmethylketone	2-Pentenal
1-Butanol	Ethanoic Acid	Limonene	2-Pentylfuran
2-Butanol	Ethanol	Linalool	2-Phenoxyethanol
2-Butanone	Ethanolamine	2,4-Lutidine	Phenylacetaldehyde
2-Butenal	Ethenylbenzene	2,6-Lutidine	2-Picoline
Butyl Acetate	Ethoxyethane	Menthol	3-Picoline
Butylamine	Ethyl Acetate	Mesitylene	4-Picoline
sec-Butylamine	Ethylbenzene	Methanol	Pimelic Ketone
Butylbenzene	Ethylbutyrate	Methylacetate	α-Pinene
sec-Butylbenzene	Ethylenediamine	Methylacrylate	Propanal
tert-Butylbenzene	2-Ethylfuran	Methylbenzene	1-Propanol
2-Butylfuran	2-Ethyltoluene	2,2-Methylbutanol	2-Propenal
3-butylfuran	3-Ethyltoluene	3,1-Methylbutanol	Propionic Acid
tert-Butylmethylether	4-Ethyltoluene	3,2-Methylbutanol	Propoxypropane
Butyric Acid	2-Fluoroaniline	3,3-Methylbutenol	Propylacetate
Cadaverine	4-Fluoroaniline	3-Methylbutyl Acetate	Propylamine
Chlorobenzene	Fluorobenzene	Methyl Cinnamate	2-Propylfuran
Cinnamaldehyde	Formaldehyde	Methylcyclopentane	Pyridine
Citral	Formic Acid	2-Methylfuran	Styrene
Citronelool	2,4-Heptadienal	Methylisobutyrate	Terpineol
β-Cyclocitral	Heptanal	2,3-Methylpentanone	Tetrachloroethylene
Cycloheptane	1-Heptanol	3,2-Methylpentanone	Tetrahydrofuran
Cyclohexanone	2-Heptanol	4,2-Methylpentanone	Toluene

Cyclooctane	3-Heptanol	2-Methylpropenoate	2,4,6-Trichloroanisole
β-Damascone	2-Heptanone	Nitrobenzene	1,1,2-Trichloroethane
Decanal	3-Heptanone	2,6-Nonadienal	Triethylamine
1-Decanol	4-Heptanone	Nonanal	1,2,3-Trimethylbenzene
2-Decanone	2-Heptenal	Nonane	Tripropylamine
2-Decenal	4-Heptenal	Nonanol	2-Undecanone
1,3-Diaminopropane	Hexanal	2-Nonanone	6-Undecanone
1,2-Dichlorobenzene	Hexane	2-Nonenal	Valeric Acid
1,3-Dichlorobenzene	Hexanoic acid	2,4-Octadienal	m-Xylene
1,1-Dichloroethane	1-Hexanol	Octanal	o-Xylene
Dichloromethane	2-Hexanol	2-Octenal	p-Xylene

All these standards were purchased from certified manufacturers and properly stored at the laboratory. The procedure of analysis is addressed in due time.

Aiming to develop a protocol of calibration to convert the intensity levels registered by the GC-IMS during each analysis to the respective concentration levels, a dedicated study was developed, as already mentioned. To do so, a specific compound was selected and used for calibration purposes. The selected compound, 2-hexanone (+99% purity), was purchased from Sigma-Aldrich and used to prepare the permeation tubes that were later analysed with the TGA device. Further details concerning the procedure of analysis can be consulted in due time.

Disclaimer: The information included in this chapter was originally published in the papers: J. M. Fernandes, V. Vassilenko, P. C. Moura, V. Fetter. Gas Chromatography-Ion Mobility Spectrometry Instrument for Medical Applications: A Calibration Protocol for ppb and ppt Concentration Range. In: 12th Advanced Doctoral Conference on Computing, Electrical and Industrial Systems, DoCEIS 2021. Costa da Caparica, Portugal: Springer, 349-357, 2021. https://doi.org/10.1007/978-3-030-78288-7_34 [17], and P. C. Moura, V. Vassilenko, P. A. Ribeiro. Ion Mobility Spectrometry Towards Environmental Volatile Organic Compounds Identification and Quantification: A Comparative Overview Over Infrared Spectroscopy. *Emission Control Science and Technology*, 9, 25-46, 2023. https://doi.org/10.1007/s40825-022-00220-x [13].

3.3.2.1.2 Graphene Oxide-Based Sensors Analyses

Aiming to assess the suitability of graphene oxide-based sensors and impedance spectroscopy for the assessment, i.e., identification and quantification of industrially relevant VOCs, a total of four compounds often found in the indoor air of industrial facilities were studied. The sensors were exposed to those compounds, namely acetone, acetic acid, isopropanol, ethanol, and methanol, and the variation of impedance was registered. The standards of acetone (C_3H_6O; 58.08 gmol^{-1}; 99.0%) and isopropanol (C_3H_8O; 60.10 gmol^{-1}; 98.0%) were purchased from Laborspirit-Labchem. The standards of ethanol (C_2H_6O; 46.07 gmol^{-1}; 99.8%) and methanol (CH_4O; 32.04 gmol^{-1}; 99.8%) were obtained from Honeywell. The standard of acetic acid ($C_2H_4O_2$; 60.05 gmol^{-1}; 99.8%) was purchased from Fisher Scientific.

Principal component analysis (PCA) was used to reduce the data size and to obtain a new space of orthogonal components aiming to distinguish the different samples and respective concentrations. For this analysis, the electrical impedance and impedance angle spectra were considered. It is relevant to emphasize that these values were both collected in a frequency range of 1 Hz to 1 MHz for each sample at different concentrations. Since three replicas were registered, the spectra used in this analysis correspond to the average of those three measurements. Further details are discussed in due time.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, T. P. Pivetta, V. Vassilenko, P. A. Ribeiro, M. Raposo. Graphene Oxide Thin Films for Detection and Quantification of Industrially Relevant Alcohols and Acetic Acid. *Sensors*, 23, 462, 2023. https://doi.org/10.3390/s23010462 [15].

3.3.2.2 Coatings

In order to identify and study the main potential sources of VOCs existent in the interior of the painting line, one listed all the potential VOC-emitting solutions. Among them were the solutions used in both the phosphatising and cataphoresis baths, the smoke emitted by all the heating and drying processes occurring in industrial-size ovens, and all the primers, paints and varnish used to coat the car body.

As mentioned, the phosphatising bath consists of a solution of phosphoric acid saturated with metallic phosphate whose purpose is to protect the metallic surface from eventual corrosion. This solution does not contain any kind of organic compounds in its constitution, in this way, the chance of contributing to the overall emission of VOCs tends to zero. The same logic applies to the solution used in the cataphoresis bath. This solution is merely an epoxy-based mixture whose purpose is to electrically charge the metallic surface of the car. So, its contribution to the overall emission of VOCs is close to none.

Regarding the smoke and all kinds of gaseous pollution, they cannot be exactly studied as an emitting source since they are not a solution or mixture used during the painting processed, but rather a consequence or result of some of the processes. In this way, their impact on the overall indoor air quality was assessed during the *in-situ* measurements.

Finally, all the coating solutions used to paint the car are, in fact, the real concern among all the potential sources of VOCs. Since their composition contains a significant portion of organic solvents, as already addressed, they are the main responsible for most of the emissions of VOCs into the atmosphere.

Once identified as the main sources of VOCs existent in the interior of the painting line, a dedicated laboratory study was developed aiming to identify all the compounds present in the composition of the coatings. A total of 22 distinct samples, among primers, basecoats and clearcoat, were considered for this work and their emissions were evaluated with the same device, a GC-IMS, and the same procedure previously used for the *in-loco* measurements.

The primer applied to a car body is selected accordingly with the colour of the paint to be later applied. Four different water-based primers commercially named after their colour are regularly used in the painting line of the car factory under study. All four were considered for the present work. They are:

- Anthracite;
- Light grey;
- Light red;
- Mid grey.

The factory has access to a pallet of 17 colours of basecoats, ordinarily called paints or inks. Like the primers, all these 17 water-based coatings were analysed during this work:

- Ascot grey;
- Atlantic blue;
- Beech grey;
- Black oak;
- Deep black;
- Indium grey;
- Kings red;
- Lapiz blue;
- Moonstone silver;
- Petroleum blue;

- Pure white;
- Pyrite silver;
- Ravenna blue;
- Reflex silver;
- Romance red;
- Urano grey;
- White silver.

Finally, a twenty-second coating, commercially known as Lumeera, is used by the employees to varnish the already-painted metal surface. The clearcoat Lumeera corresponds to the only solvent-based coating used regularly in the factory and, evidently, was considered for this study.

Table 5 summarizes the analysed samples. The information here contained was fully provided by the car factory involved in the study. Regarding the samples, the names and respective colours of both primers and basecoats are included as provided by the factory and following the information publicly available on the commercial website of the automobile brand. Information regarding the solid or metallic nature of the coating and the primer colour to be used for each basecoat is also provided. Finally, the ratio of VOCs in the composition of each coating is included in the form of a percentage, as provided by the producer. It is noticeable that it ranges from 11.5% to 18.2%. No additional information regarding the composition of the samples was provided by the factory or by the producer.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, F. Santos, C. Fujão, V. Vassilenko. Towards the Characterization of the Coatings Used in a Car Factory Painting Line. *Journal of Coatings Technology and Research*, 2023. https://doi.org/10.1007/s11998-023-00847-7 [6].

Table 5 - Samples of primers (water-based coatings), basecoats (water-based coatings) and clearcoat (solvent-based coatings) analysed during the study, including information regarding the colour, type, and ratio of VOCs [6].

Primer			
Anthracite	Light Grey	Light Red	Mid Grey
Basecoat			
Colour	**Type**	**Primer Colour**	**Ratio of VOCs (%)**
Ascot Grey	Solid	Light Grey	12.1
Atlantic Blue	Metallic	Anthracite	13.0
Beech Grey	Metallic	Anthracite	11.5

Black Oak	Metallic	Anthracite	15.2
Deep Black	Metallic	Anthracite	11.5
Indium Grey	Metallic	Anthracite	15.0
Kings Red	Metallic	Anthracite	18.2
Lapiz Blue	Metallic	Anthracite	13.4
Moonstone Silver	Metallic	Mid Grey	16.7
Petroleum Blue	Metallic	Anthracite	13.3
Pure White	Solid	Light Grey	12.0
Pyrite Silver	Metallic	Mid Grey	15.8
Ravenna Blue	Metallic	Anthracite	13.0
Reflex Silver	Metallic	Mid Grey	15.2
Romance Red	Metallic	Light Red	13.0
Urano Grey	Solid	Anthracite	11.9
White Silver	Metallic	Mid Grey	15.1
Clearcoat			
Lumeera			

3.4 Sampling Procedures

Due to the idiosyncrasies of each study developed throughout the entire doctoral project, different sampling procedures had to be developed and implemented. Following the requirements of each study, all the sampling procedures developed throughout the doctoral project can be grouped into three distinct categories: *in-situ* analyses, *quasi-in-situ* analyses, and laboratory analyses.

The first sampling procedure consists of a direct collection and analysis using the GC-IMS device, and it was solely used for the studies in which the aim was to perform *in-situ* air analyses of indoor and outdoor air samples. The second procedure was similar to the first, but an additional element was added. This element, a Teflon pump or syringe-based container, was used to collect the air samples and transport them to the spectrometer. This procedure was mostly used for scenarios in which the GC-IMS device could not be assembled in the target location. Finally, a third sampling procedure was used to analyse the volatile portion of non-volatile samples that, due to their liquid state, required a previous preparation to foment the volatilization of the VOCs. In this way, glass vials and permeation tubes were specifically used in all the studies whose targets were non-volatile samples, like the coatings.

3.4.1 *In-Situ* Analyses

The first sampling procedure developed during the doctoral project was mainly applied for *in-loco* analyses of air samples. An example of that application was the study developed to assess the suitability of GC-IMS for long-term analysis in closed environments. In these situations, and due to its portability, the spectrometer was assembled in the interior of the room or location whose air content was intended to be analysed. Then, the air samples were automatically collected from the room air by the device's pump without requiring the operator's intervention or any type of sample preparation or additional chemicals. Once collected into the device, a typical analysis procedure was performed as already described.

It is worth stating that, during this kind of *in-loco* analysis, the overall conditions of the room under study were carefully controlled and adjusted in accordance with the undergoing study. The controlled parameters consisted of temperature and humidity levels, operating status of heating or cooling devices, inlets and outlets of air, affluence of people in the room, work regime, cleaning procedures, and eventual untypical presence of VOCs in the indoor air.

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3.4.2 *Quasi-In-Situ* Analyses

In some of the studies, the aim was equally given to *in-situ* analyses, nonetheless, some scenarios prevented the placement of the GC-IMS at the target locations to perform those analyses. This was mostly instigated by the conditions of the location, namely, the activities developed at the site, the presence of heavy machinery, or the large affluence of people. These represent potentially dangerous factors that could lead to the damage of the device.

An obvious example of a potentially dangerous scenario for the GC-IMS apparatus was the painting line itself. Due to the utilisation of a vast range of chemical products, the large affluence of people, and the constant movement of robotic arms, the device could easily be damaged unnecessarily. For cases like this, a dedicated sampling procedure was developed and implemented.

For all the required situations, the GC-IMS device was placed at a nearby and safe location, and all the air samples were collected and transported with a specific container. The containers consisted of a 1-litre volume chemically inert Teflon cylinder equipped with a pump and an accoupled T-valve, or a syringe-based container equally prepared with a T-valve. The samples were always collected within the same temperature range (19-21 ºC) and the transfer time of the cylinders from the collection site to the analytical equipment was as short as possible (in any case, not superior to 5 minutes). To do so, the T-valve was opened, and the piston of the Teflon container was manually pulled until the container was filled with air from the target location. The collection of the sample is represented in Figure 21.

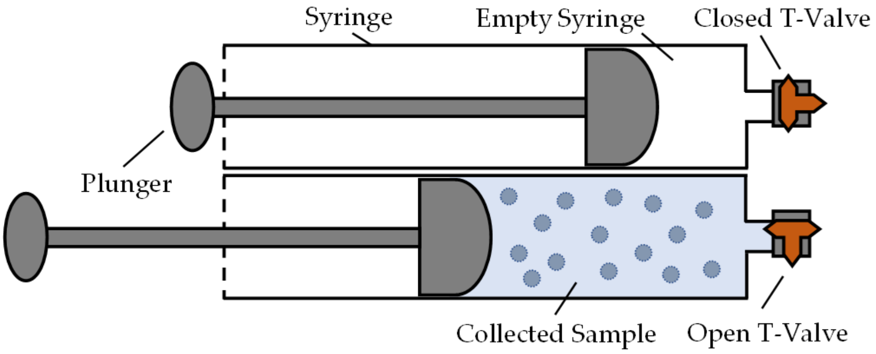

Figure 21 - Teflon pump with an accoupled T-valve used to collect air samples from the target locations.

Then, the T-valve was closed to prevent additional ex-changes between the sample and exogenous contaminants, and the container was transported to the room of the GC-IMS device. Here, the T-valve was connected to the spectrometer and the sample was manually injected into the spectrometer. Figure 22 illustrates the injection of the sample into the spectrometer.

This procedure was drawn aiming to preserve the original quality of air samples, avoid any alterations in the temperature and humidity of the sample, and prevent any kind of interaction with exogenous compounds. The transfer time of the samples was always inferior to three minutes, a procedure that ensured the preservation of the original specificities of the sample by avoiding temperature and humidity variations and as mentioned, interactions with exogenous compounds. It is important to emphasize that, like in the previous sampling procedure, no pre-preparation of the samples nor additional chemicals were necessary to perform the analyses.

Disclaimer: The information included in this chapter was originally published in the papers: P. C. Moura, V. Vassilenko. Gas Chromatography – Ion Mobility Spectrometry as a Tool for Quick Detection of Hazardous Volatile Organic Compounds in Indoor and Ambient Air: A University Campus Case Study. *European Journal of Mass Spectrometry*, 28, 113-126, 2023. https://doi.org/10.1177/14690667221130170 [16], P. C. Moura, F. Santos, C. Fujão, V. Vassilenko. In Situ Indoor Air Volatile Organic Compounds Assessment in a Car Factory Painting Line. *Processes*, 11, 2259, 2023. https://doi.org/10.3390/pr11082259 [9], and P. H. C. Santos, P. C. Moura, V. Vassilenko. Suitability of Short- and Long-Term Storage of Volatile Organic Compounds Samples in Syringe-Based Containers: A Comparison Study. *Metabolites*, 13, 903, 2023. https://doi.org/10.3390/metabo13080903 [10].

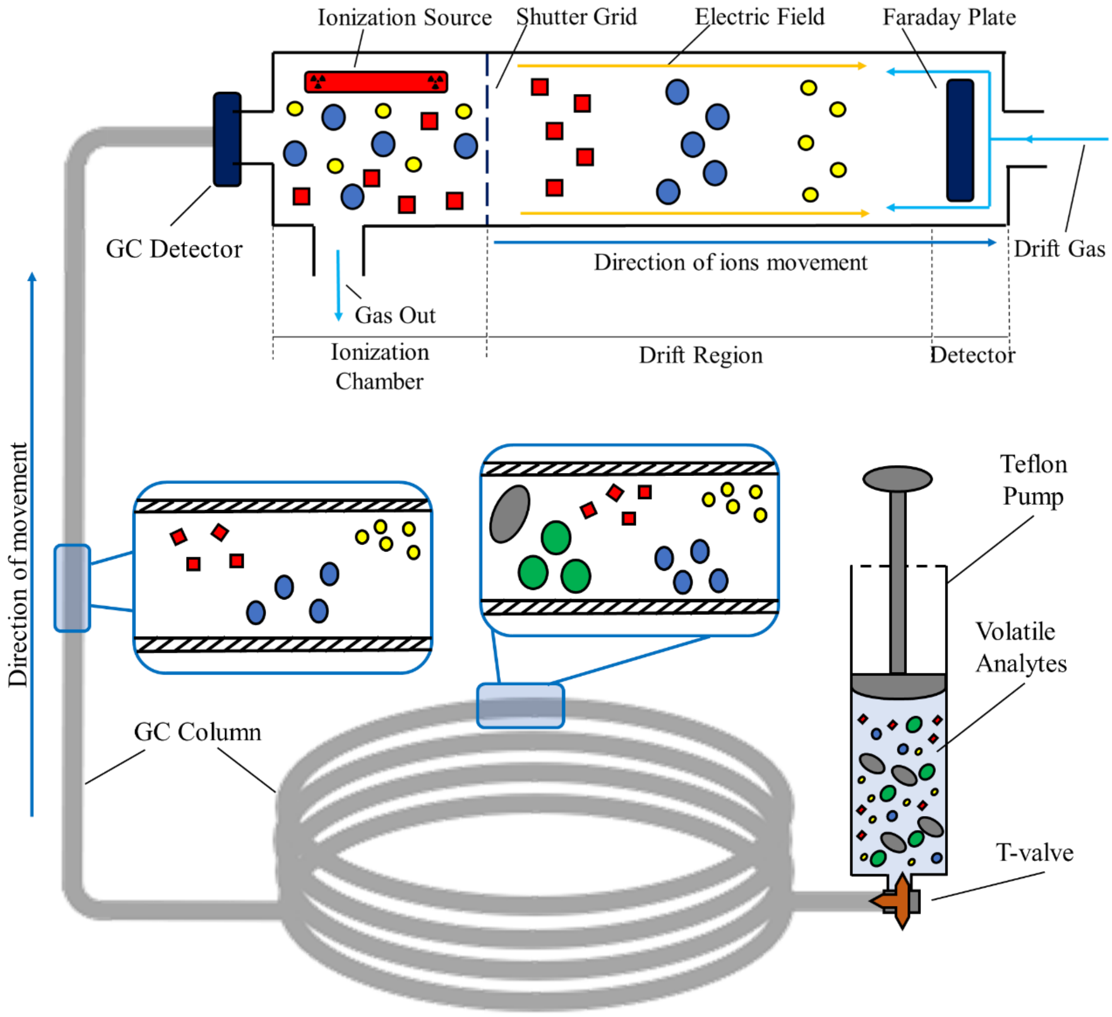

Figure 22 - Injection of the volatile sample previously collected and transported with a Teflon pump into the GC-IMS device [10].

3.4.2.1 Suitability of Syringe-based Containers

As previously addressed, the collection, transport and storage of air samples is an intricate process that, if not properly conducted, can completely ruin the analyses. One of the challenges concerns the containers used for the collection. All the currently used containers for sample collection and storage have their own advantages and disadvantages. Syringe-based containers seem to be the most used containers in the literature, so these kinds of containers were equally considered for the collection of air samples of the factory, as described above.

Three types of syringe-based containers with different compositions (glass and plastic with and without rubbered plungers) were selected and evaluated for their suitability to store air samples [10]. Sterile 10 mL volume containers were used in every case. The glass syringes (AC1) were manufactured by Poulten & Graf®, the plastic syringes with plastic plungers were produced by BD® (AC2), and the plastic syringes with rubbered plungers (AC3) were manufactured by PIC Solution®. The sterile condition of each container was ensured by the manufacturers. All the containers were acquired via officially recognized distributors. Figure 23 displays the three types of air containers used throughout the study.

Figure 23 - Syringe-based air containers (AC) used In this study, namely, full glass (AC1, left), plastic with plastic plunger (AC2, middle), and plastic with rubbered plunger (AC3, right) [10].

Environmental air samples from a controlled closed space (i.e., a laboratory facility) were considered for this study. One single operator collected and analysed the samples to minimize experimental variability among the rounds of sampling. Air samples of 5 mL were collected into sterile containers by applying negative pressure as a result of the forced movement of the plunger and were then constrained using three-way valves. Subsequently, syringes were left exposed to the same conditions of temperature, pressure, humidity, and radiation until the moment of analysis.

Three air sample replicates per container type were collected and analysed over 24 h in several instances, i.e., 0 min, 10 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h after their collection and isolation. Therefore, a total of 99 air samples were included in this evaluation (specifically, 11 measurements were performed for each container, totalling 33 spectra for 3 container types). The data was then processed using LAV software (version 2.2.1. - G. A. S. Dortmund, Germany), and some other statistical tools like partial least square regression and principal component analysis using IBM SPSS Statistics (version 23 - IBM Corporation, USA) [10].

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3.4.3 Laboratory Analyses

The present doctoral program did not focus entirely on analysing air samples for indoor and outdoor locations, as mentioned. It was also necessary to assess the VOCs existent in those samples, and to investigate the main VOCs-emitting sources. To do so, one had to develop several sampling procedures for purposes of laboratory analyses.

One example of these procedures was the development of the database of analytes later used for purposes of identification. Another example was the procedure to calibrate some of the VOCs with the TGA and GC-IMS devices. Finally, the evaluation of the composition of the coatings used in the painting line also required the development of a proper sampling procedure. These procedures often involve the creation of headspace, which can be grouped into two main categories: static headspace and dynamic headspace.

3.4.3.1 Static Headspace

For the static headspace, the sample is usually prepared in the interior of a virgin glass vial, isolated from exogenous contaminations, and left separated for a predefined amount of time. During this period, the liquid and gaseous portions of the sample interact, the analytes volatilise, and a thermodynamic equilibrium is reached. Once attained the equilibrium in the interior of the container, a portion of the headspace is collected and transferred to the device, usually with the help of a syringe and two needles, or with an equivalent system.

Figure 24 exemplifies the headspace formation procedure. On the left, the glass vial containing the compound is closed with an aluminium cap with a septum and sealed with parafilm to avoid eventual contaminations. On the right, two needles are used to collect a portion of the headspace with a syringe or into the spectrometer, for analysis.

This procedure is commonly employed when the study aims to qualify or quantify a large number of discrete samples, at a specific temperature, instead of evaluating continuously their evolution or alteration over time, as for dynamic headspace. Under the scope of this doctoral project, this procedure was employed to analyse the VOCs emitted by pure samples of compounds for the purpose of creating a database of volatile organic compounds. Then, it was used to analyse the emissions of all the coatings used in the car factory painting line [6]. It was equally used during the study developed to assess the suitability of a system based on graphene oxide sensors for the goals of this project [15, 13].

Disclaimer: The information included in this chapter was originally published in the papers: P. C. Moura, F. Santos, C. Fujão, V. Vassilenko. Towards the Characterization of the Coatings Used in a Car Factory Painting Line. *Journal of Coatings Technology and Research*, 2023. https://doi.org/10.1007/s11998-023-00847-7 [6], P. C. Moura, V. Vassilenko, P. A. Ribeiro. Ion Mobility Spectrometry Towards Environmental Volatile Organic Compounds Identification and Quantification: A Comparative Overview Over Infrared Spectroscopy. *Emission Control Science and Technology*, 9, 25-46, 2023. https://doi.org/10.1007/s40825-022-00220-x [13], and P. C. Moura, T. P. Pivetta, V. Vassilenko, P. A. Ribeiro, M. Raposo. Graphene Oxide Thin Films for Detection and Quantification of Industrially Relevant Alcohols and Acetic Acid. *Sensors*, 23, 462, 2023. https://doi.org/10.3390/s23010462 [15].

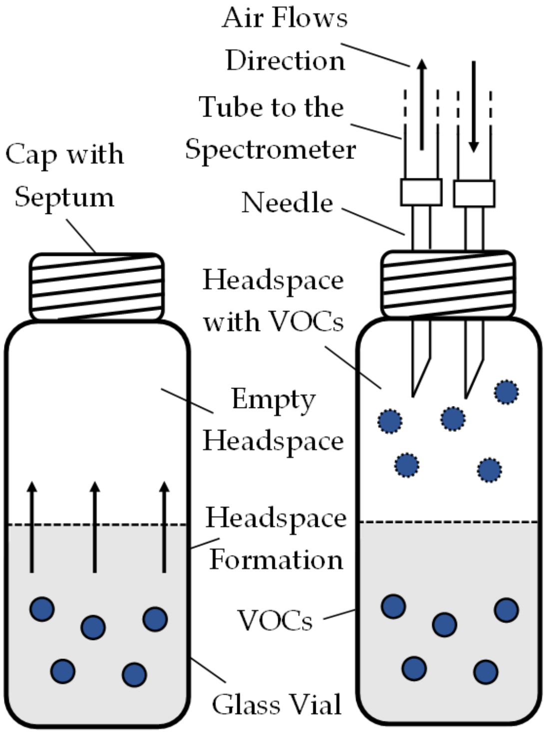

Figure 24 - Illustration of the headspace formation with the volatilisation of the VOCs (left) and later collection with two needles (right) [13].

3.4.3.2 Dynamic Headspace

The dynamic approach is often employed when the study aims to include the temporal variable in the study. Whenever the alterations of the presence of VOCS or the variation of their concentration levels through time is a relevant issue, the dynamic headspace is the procedure commonly selected for sampling preparation. In summary, dynamic headspace allows a continuous analysis rather than a discrete one as it occurs with the static headspace technique.

For the dynamic headspace procedure, in opposition to the static headspace, a continuous carrier gas flow passes through the container holding the VOCs-emitting sample and then, is directed into the spectrometer. The most common containers used in dynamic headspace-based procedures are glass vials and permeation tubes.

A permeation tube consists of a PTFE or other inert but permeable material that is filled with the compound or sample under analysis. The compound is, then, set to permeate through the tube's wall, and a carrier gas with a pre-defined flow is used to drag the VOCs into the spectrometer. This system enables to easily control the temperature and the VOCs permeation rate through the walls, facilitating the assessment of the concentration levels. An exemplificative schematic of a permeation tube is included in Figure 25.

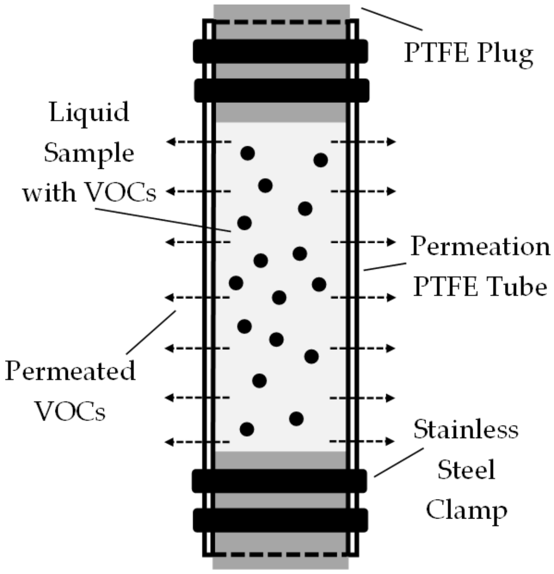

Figure 25 - Illustration of a permeation tube containing a liquid sample whose VOCs permeate through the walls of the tube [13].

Under the scope of this doctoral project, the permeation tubes were used exactly for calibration purposes, i.e., to develop a calibration procedure that led to the quantification of a specific compound. A total of four 1/4" PTFE permeation tubes with a length of 2 cm were prepared with 0.2 mL of 2-hexanone. The extremities of each tube were sealed with 5mm PTFE end caps of 0.5 cm length, which were locked in place with 0.5 cm length steel rings. The length of the effective permeation zone was approximately 1 cm. All the used materials were purchased from Owlstone Medical.

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4

RESULTS AND DISCUSSION

This chapter addresses and discusses all the results achieved in all the studies developed throughout the entire doctoral project. In specific, this chapter includes the results achieved and published during the studies developed to assess the suitability of GC-IMS for both *in-situ* and long-term analysis, the suitability of a graphene sensors-based system for the goals of the project, the results on the indoor air quality of the factory and the emissions from the main emitting sources, and a few more results.

4.1 Graphene Oxide-Based Sensors:

Several techniques have been scientifically addressed regarding their suitability for the assessment of VOCs at an industrial level. These techniques include both multi-sensor array-based procedures and analytical techniques such as chromatographic and spectrometric approaches. Independently of the designation or the nature of the system, their core purpose is the detection of specific and potentially dangerous analytes in the indoor air of the target location.

Considering the auspicious results of graphene oxide-based sensors assembled in an array for the detection, identification and quantification of VOCs, this type of system was studied in practical terms regarding its suitability to accomplish the goals of this doctoral project. In this way, this work proposed the development of a graphene oxide thin-film-based sensor using the layer-by-layer technique, towards the detection, identification, and quantification of industrially relevant VOCs, namely acetic acid, ethanol, isopropanol, and methanol. Impedance spectroscopy was used as a probe of the sensor response in terms of the analyte's presence and concentration. The data was processed through principal component analysis (PCA).

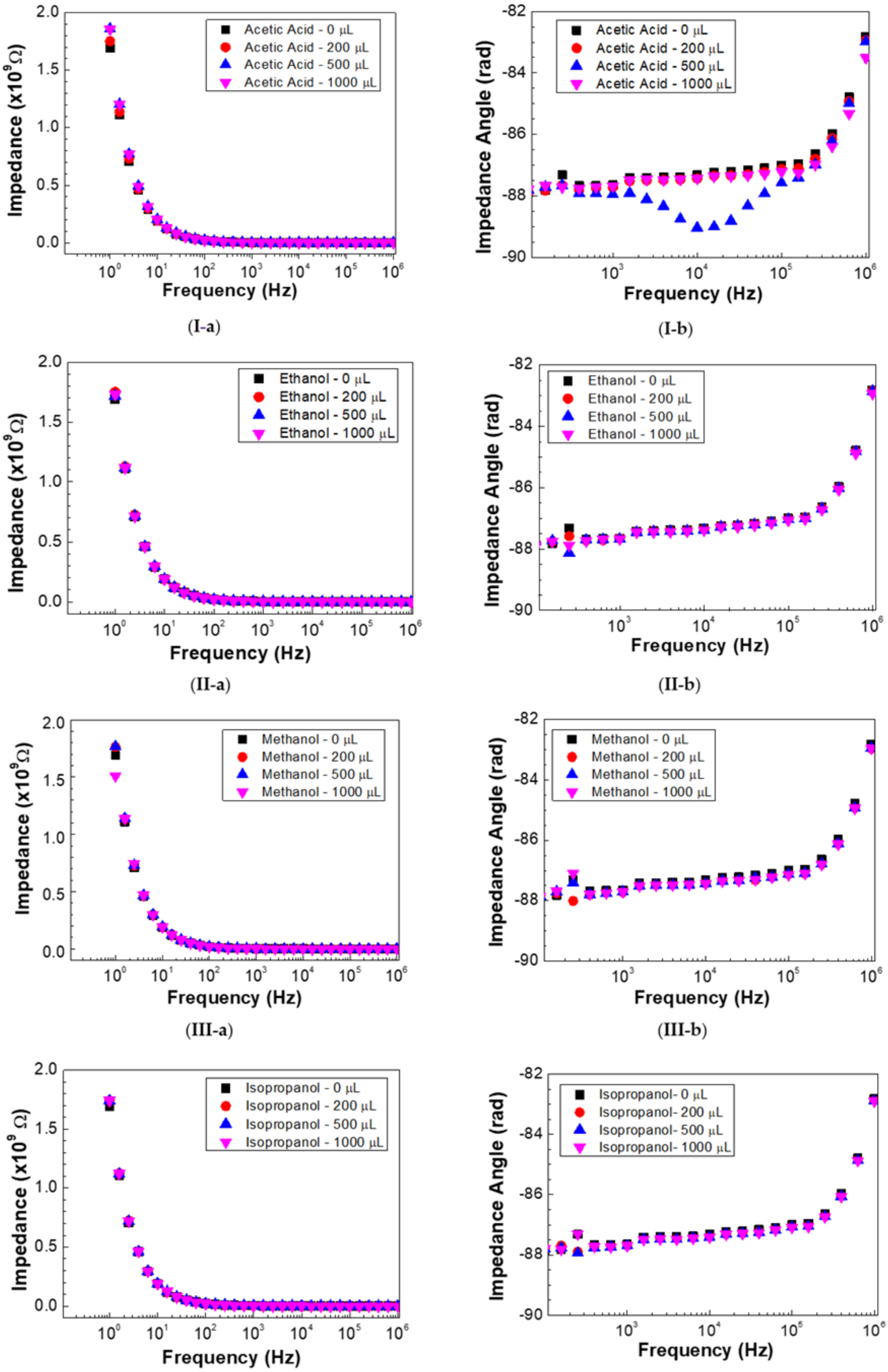
4.1.1 Impedance Results

Figure 26 illustrates the impedance (a) and impedance angle (b) spectra of $(PEI/GO)_{15}$ films deposited on the surface of gold IDEs when submitted to an atmosphere of different concentrations of acetic acid (I), ethanol (II), methanol (III), and isopropanol (IV), represented by the VOCs' evaporated volume. It should be mentioned that, for better clarity and interpretation of the plots present in the figure, the error bars measured for these spectra were not included. Nonetheless, it is relevant to state that both these frequency-dependent measurements presented error values lower than 1% among the three replicas.

To verify if the PEI/GO thin films can distinguish the different concentrations of the measured VOCs, the impedance magnitude and impedance angle at fixed frequencies were analysed for the different VOCs' concentrations. The evaporated volume can be directly related to the concentration levels through the ratio between the mass of the analyte and the mass of the air in the chamber. The mass of each analyte was calculated for each volume through their density. The same approach was employed to calculate the mass of the air existent in the interior of the 58 L volume chamber. Once both the analyte mass for each volume and the total mass in the interior of the chamber were calculated, the corresponding concentrations were estimated by the mentioned ratio. Table 6 summarizes the evaporated volumes and respective concentration levels for the four analysed analytes. The concentration levels were converted to ppm_v scale for easier comprehension.

Table 6 - Evaporated volumes (µL) and respective concentration levels (ppm_v) for the four considered VOCs; acetic acid, ethanol, methanol, and isopropanol [15].

Volume (µL)	**Concentration (ppm_v)**			
	Acetic Acid	**Ethanol**	**Methanol**	**Isopropanol**
200	24	18	18	18
500	60	45	45	45
1000	120	90	90	90



(I-a) (I-b)

(II-a) (II-b)

(III-a) (III-b)

Figure 26 - Impedance (a) and impedance angle (b) spectra of the sensor devices when exposed to atmospheres with different concentrations of acetic acid (I), ethanol (II), methanol (III), and isopropanol (IV) [15].

Figure 27 indicates both the impedance magnitude and impedance angle at 10^4 Hz, plotted as a function of the evaporated volume and, consequently, the concentration of acetic acid, ethanol, methanol, and isopropanol, respectively. These graphs clearly demonstrate that the electrical measurements can distinguish between the different concentrations since both the magnitude and angle vary with the concentration if only a VOC type is considered. However, when analysing the measured values of magnitude and angle at this chosen frequency, one cannot distinguish between the different alcohol VOCs, meaning that is necessary to analyse the data achieved for all the frequencies with mathematical methods such as the PCA method. This analysis allows conclusions to be made as to whether the impedance magnitude and impedance angle spectra depend on the different samples and allows discrimination between the VOCs and their respective concentrations using a single sensor.

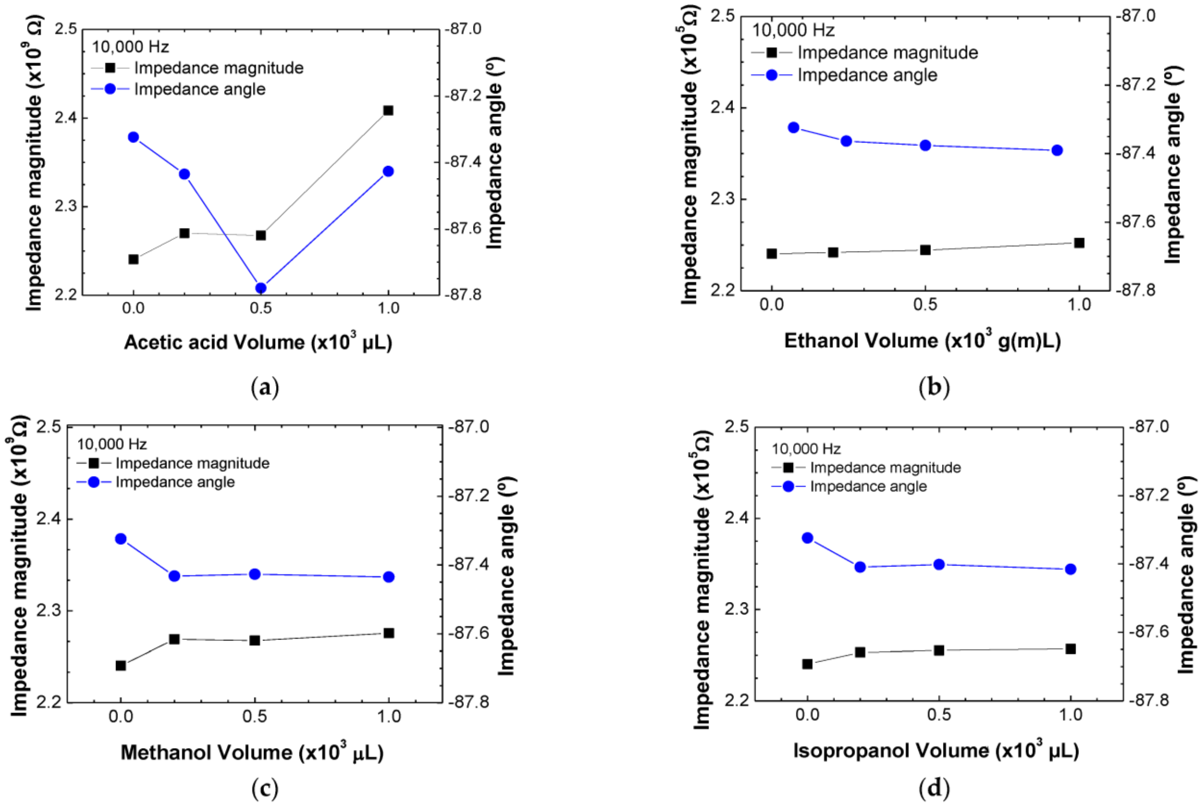
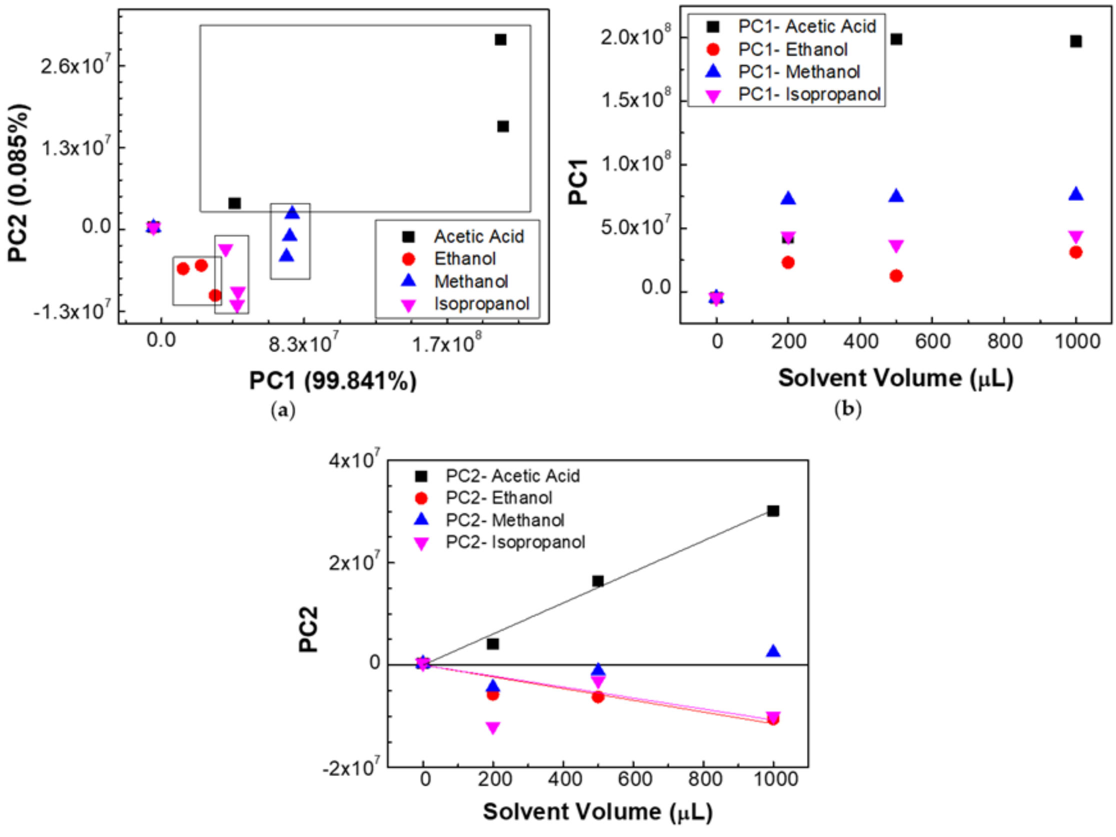


Figure 27 - Impedance magnitude and impedance angle at a fixed frequency of 104 Hz for different concentrations of acetic acid (a), ethanol (b), methanol (c), and isopropanol (d) in air. The lines between the experimental points are guidelines [15].

4.1.2 PCA Results

As one intends to distinguish between different VOCs using a single sensor, the PCA method was applied to both the impedance magnitude and impedance angle spectra data measured for the different concentrations of acetic acid, ethanol, methanol, and isopropanol. The PCA score plots of all the measured data for all four target analytes in air at different concentrations are shown in Figure 28 a). By analysing this figure, one can observe that well-defined PCA score regions can be defined for each type of measured VOC, allowing discrimination between the samples in the concentrations measured using a single sensor.



(a)

(b)

(c)

Figure 28 - Results of a) PCA score plot after analyzing all the measured data for the detection of acetic acid, ethanol, methanol, and isopropanol in air at different concentrations, b) evolution of PC1 components as a function of solvent volume, and c) evolution of PC2 components as a function of solvent volume [15].

To consider if the calculated principal components PC1 and PC2 are concentration-dependent, the achieved values of PC1 and PC2 were plotted as a function of the VOC´s volume in Figure 28 b) and c), respectively. Interestingly, the evolution of PC1 with the solvent volume shows that, except for the PC1 value associated with samples without VOCs and for the acetic acid sample with a volume of 200 μL, one can calculate a PC1 average value for each type of sample.

The calculated values and respective error bars are present in Table 7. Therefore, it is possible to state that the PC1 value can distinguish the ethanol, methanol, and isopropanol in air samples and the acid acetic for higher concentrations. On the other hand, Figure 28 c) clearly demonstrates that the PC2 components can discriminate the VOCs' concentrations, with methanol being the exception. The sensitivity of the sensor when submitted to the different VOCs was estimated by fitting the PC2 data versus concentration with a straight line. The fitting parameters are listed in Table 7, where the sensitivity values correspond to the slope of the PC2 parameters versus the concentration. Sensitivity values of $(30 \pm 1\ ) \times 10^3$, $(11 \pm 2) \times 10^3$, and $(11 \pm 5\ ) \times 10^3$ were calculated for acetic acid, ethanol, and isopropanol, respectively. Since the slope calculated for the case of methanol PC2 data is very low, one decided to calculate the PC2 average. All these values are displayed in Table 7. From these results, one can conclude that this unique sensor can distinguish the different target VOCs and, except for methanol, the VOCs' concentration in the analysed range.

Table 7 - Summarization of the values achieved from Figure 28. The columns PC1 Average and PC2 Average represent the mean value calculated from the data represented in the figure, for the case of methanol, not considering the null concentration data. The sensitivity corresponds to the slope of the straight lines fitting PC2 data displayed in Figure 28 c) [15].

VOC	PC1 Average	Sensitivity (mL^{-1})	PC2 Average
Acetic acid	$(1.98 \pm 0.01) \times 10^8$	$(3.0 \pm 0.1) \times 10^4$	−
Ethanol	$(2.2 \pm 0.5) \times 10^7$	$(1.2 \pm 0.2) \times 10^4$	−
Methanol	$(7.4 \pm 0.1) \times 10^7$	−	$(-0.066 \pm 3) \times 10^6$
Isopropanol	$(4.2 \pm 0.2) \times 10^7$	$(1.1 \pm 0.5) \times 10^4$	−

To compare the achieved data with the results of other sensors existent in the literature, one presents Table 8 where the values of the resolution and range values of the developed sensor are compared with the values of different sensors. To calculate the sensor resolution for this work, the minimum measurable values were considered, as described elsewhere [330]. As in the present results, the PC2 values are linearly dependent on the concentration in ppm$_v$ (C). The sensitivity (S) was calculated by the slope of the straight line, $\Delta PC2/\Delta C$, used to fit the data. Therefore, $\Delta PC2/\Delta C = S \pm u(S)$, with $u(S)$ being the uncertainty of sensitivity given also by the fitting. The resolution corresponds to the calculated value of ΔC in which $\Delta C = u(S)/S$. This procedure enabled the estimation of the resolution values of 0.005, 0.015, and 0.04 ppm$_v$ for acetic acid, ethanol, and isopropanol, respectively. As aforementioned, due to the very low slope calculated for methanol, one opted to not estimate the sensitivity and, consequently, the resolution values of this case. From the comparison included in Table 8, one can conclude that the methodology described in this work leads to limited resolution even though the studied range is of an intermediate level. The achieved values of resolution indicate that this sensor can be used in the development of an electronic nose for the detection of VOCs.

Table 8 - Comparison of the achieved sensors with others available in the literature [15].

Sensor	**Resolution (ppm_v)**	**Range (ppm_v)**
Acetic acid [331]	1.2	1 – 13
Acetic acid [332]	1	10 – 100
Acetic acid [333]	0.5	0.5 – 2000
Acetic acid [334]	0.73	1 – 15
Acetic acid (this work)	0.005	24 – 240
Ethanol [335]	0.05	1 – 200
Ethanol [336]	3	30 – 145
Ethanol [337]	1	1 – 200
Ethanol [338]	0.15	0.15 – 5
Ethanol (this work)	0.015	18 – 180
Methanol [339]	0.015	1.14 – 11.36
Methanol [340]	10	100 – 300
Methanol [341]	0.5	0.5 – 700
Methanol [342]	10	100 – 500
Methanol (this work)	–	18 – 180
Isopropanol [343]	2	2 – 100
Isopropanol [344]	1	1 – 100
Isopropanol [345]	1	1 – 1000
Isopropanol [346]	1	5 – 1000
Isopropanol (this work)	0.04	18 – 180

In summary, a unique sensor based on graphene oxide thin films was used to simultaneously detect four industrially relevant VOCs, acetic acid, ethanol, methanol, and isopropanol, by measuring the impedance magnitude and impedance angle spectra responses in terms of concentrations and processing the data through PCA. The results lead to the conclusion that the impedance data allow both the different VOCs samples and their concentrations to be distinguished in the range of hundreds of ppm_v. From the PCA results, one can conclude that the principal component PC1 values can distinguish the ethanol, methanol, and isopropanol in air samples and also the acid acetic for higher concentrations, while from principal component PC2, one can discriminate the VOCs' concentrations with the exception of methanol. The resolution values for this sensor are lower than 0.04 ppm_v, which proves the relevancy of using this sensor in the sensor array of an electronic nose for the qualification and quantification of VOCs in an industrial context.

Besides all the advantages of this system, it has some major disadvantages that prevent its utilisation for most of the goals of this doctoral project. Among them, one can mention the complexity of the system. The current state of these graphene oxide sensors-based systems prevents their implementation at target locations to perform *in-loco* analyses of, for example, air samples. In addition, all the different elements required for the assemble of the study, namely, the vacuum pump, the vacuum chamber, and the devices to register the variance of the sensors' variation make this system a particularly complex system for purposes of in-situ analyses. Then, graphene-based sensors are still poorly explored regarding their suitability for the analysis of biological samples and, specifically, of exhaled air. In this way, it would be a challenge to evaluate the eventual impacts of the pollutants on the employees' health in practical terms with this system. Considering all these strong limitations, graphene oxide sensors were disregarded as analytical procedure for the purposes of this doctoral project.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, T. P. Pivetta, V. Vassilenko, P. A. Ribeiro, M. Raposo. Graphene Oxide Thin Films for Detection and Quantification of Industrially Relevant Alcohols and Acetic Acid. *Sensors*, 23, 462, 2023. https://doi.org/10.3390/s23010462 [15].

4.2 VOCs Assessment

Several analytical techniques and experimental procedures were considered both in theoretical and practical terms, as mentioned. Among these, one can list spectrometric techniques like mass spectrometry, infrared spectroscopy and ion mobility spectrometry, or sensors array-based systems, like the one addressed in the previous chapter.

After a careful evaluation of all the possibilities and the respective advantages and disadvantages, a device coupling gas chromatography with ion mobility spectrometry was selected as the technique with more potential to comply with the goals defined for this doctoral project. Like any other technique, GC-IMS has some limitations. The lack of databases for purposes of identification of VOCs, and of calibration curves for purposes of quantification are the most relevant ones.

Aiming to overcome the mentioned limitations, two other topics of work were developed, in specific, the development of a library of compounds for later use in the identification of the detected VOCs, and the development of a protocol for the calibration of this type of compounds with GC-IMS for later use in the assessment of concentration levels.

4.2.1 VOCs Identification

In order to create a tool for purposes of identifying the analytes detected with the GC-IMS during all the developed studies, pure samples of the most relevant volatile organic compounds were analysed with the device in order to register their exclusive drift and retention times in the mentioned database. This database is an under-construction tool which contains, at the moment of this thesis writing, 158 VOCs.

The sampling procedure used to analyse the pure samples was described in the Materials and Methods section, however, it is relevant to emphasize that the samples were prepared in virgin glass vials that were, in their turn, sealed and stored. Once reached the thermodynamic equilibrium between both liquid and gaseous portions of the sample, a part of the headspace was collected and inserted into the GC-IMS. Once concluded the measurements, the data registered in the three-dimensional spectrum was processed with a dedicated software. The retention (r_t) and drift times (d_t) of the compound were registered in the database and, after their calculation with Equations 9 and 10, the ion mobility constant (K) and the normalised K (K_0), were equally included in the database. The overall information regarding the VOCs database can be consulted in Table 23, Appendix C.

4.2.2 VOCs Quantification

Another limitation of GC-IMS is the lack of certified calibration curves to assess the concentration levels of the detected compounds. To do so, the GC-IMS was accoupled to a TGA device, and permeation tubes containing pure samples of specific compounds were prepared, as already described in the Materials and Methods section.

A specific compound was selected as the target for this calibration study: 2-hexanone. This volatile compound is known for the formation of a monomer and a dimer in the three-dimensional spectrum produced by the GC-IMS device. In this way, the generic compound M represented in Equations 3 (monomer) and 4 (dimer) can be replaced as follows:

$$C_6H_{12}O + (H_2O)_nH^+ \leftrightarrow C_6H_{12}O(H_2O)_{n-x}H^+ + xH_2O \tag{30}$$

$$C_6H_{12}O + C_6H_{12}O(H_2O)_{n-x}H^+ \leftrightarrow (C_6H_{12}O)_2(H_2O)_{n-(x+i)}H^+ + iH_2O \qquad (31)$$

Once prepared, the tubes were left to stabilise for 24 hours and then placed in the interior of the TGA device, where they were continuously monitored in regard to the levels of temperature, weight and flow. Since the permeated amount of the sample, the permeation rate of the walls and the mass of the tube, the constant control of temperature in the interior of the oven and weight of the tube, enabled to accurately assess the concentration of the emitted portion. Finally, the volatile headspace was carried by a known flow into the spectrometer and the calculated concentrations were related to the intensity levels registered by the GC-IMS [13, 17].

A total of four tubes and 19 measurements were used to plot the calibration curve of 2-hexanone. Table 9 summarises the registered values of concentration (ppm$_v$) and the respective intensity (V) levels detected by the GC-IMS [17].

Table 9 - Concentration (ppm$_v$) levels calculated from the emissions of the permeation tubes and respective intensity (V) levels detected by the GC-IMS device [17].

Concentration (ppb$_v$)	Intensity (V)
46	2888.47
60	3473.57
91	4424.19
181	6428.60
220	6458.79
288	7168.54
362	8607.41
432	8611.60
630	10557.16
702	11394.99
840	11598.73
864	10837.40
918	12403.41
1260	12832.12
1376	13840.21
1727	13241.45
2101	14727.63

2521	15247.31
2753	16309.60

Considering the calculated concentrations and the detected intensities, a calibration curve was successfully plotted using Equations 11 to 29. Figure 29 illustrates the calibration curve plotted using the values included in Table 9, and the respective equation and R^2 value [13, 17].

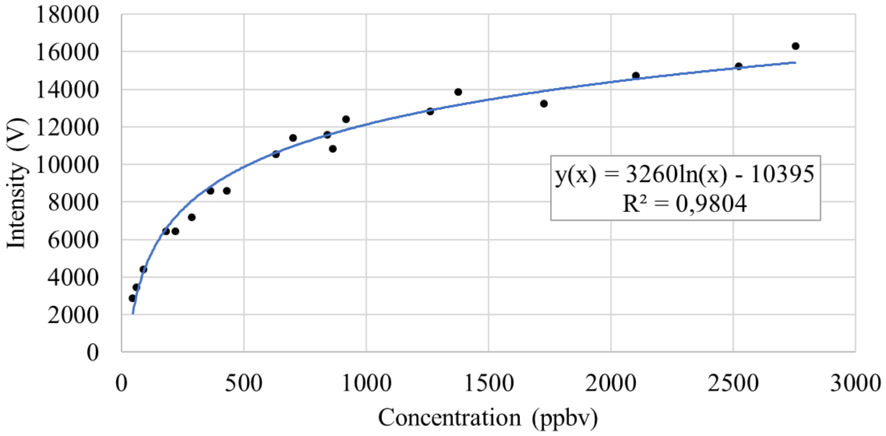


Figure 29 - Calibration curve of 2-hexanone for GC-IMS [13, 17].

As visible in the graph of Figure 29, the calibration curve adjusted to the points exhibits a coefficient of determination of 0.98. Equation 32, in which x is the concentration in ppb_v and y is the intensity in V, corresponds to the calibration curve calculated from the data:

$$y(x) = 3260 \ln(x) - 10395 \tag{32}$$

In summary, the protocol developed for purposes of calibration VOCs analysed with GC-IMS consisted of three main phases: the assemble of permeation tubes containing the target compound, the utilization of a thermogravimetric device to control the concentration of the permeated samples based on the weight, temperature, and flow, and the plotting of calibration curves to relate the intensity levels detected by the GC-IMS with the concentration levels. This protocol proved to be adequate for quantification purposes, nonetheless, all the parameters and features used and employed must be accurately controlled in order to achieve correct results, namely, the dimensions of the permeation tube, the temperature and flows used, the connection between both devices, and the isolation of the sample from exogenous contaminants [13, 17].

It is important to mention that all these procedures, both practical and theoretical, are extremely complex and can easily be perturbed by a vast range of factors. This is, in fact, why the quantification of VOCs keeps being a challenge for GC-IMS analyses. Due to the complexity of the procedure, it was not possible to calibrate any other compound besides 2-hexanone during the entire doctoral project. Nonetheless, the quantification of 2-hexanone allows to interpret the results achieved for the remaining compounds detected at the target locations, as addressed in due time.

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4.3 Study on Containers Suitability

In order to accurately analyse the samples of air and achieve pertinent and useful results, the samples must be carefully collected and stored. Nonetheless, the contemporary procedures have some serious limitations that often contribute to the degradation of the sample and the adulteration of the results, as already discussed. Aiming to assess the suitability of three syringe-based containers for the storage, transportation and preservation of air samples, an additional study was conducted. Summarily, this study involves assessing how the composition of air samples changes over time when stored in various syringe-based containers. By evaluating the temporal stability of samples, this study aims to provide insights into the optimal storage duration and syringe type for preserving sample integrity [10].

Three types of syringes, AC1 - glass syringes, AC2 - plastic syringes with plastic plungers, and AC3 - plastic syringes with rubbered plungers, were studied by measuring the sample of air previously collected and stored for a maximum of 24 hours. A total of 99 air samples were included in this evaluation, specifically, 11 measurements were performed for each container, totalling 33 spectra for three container types [10].

All the analyses were performed with a GC–IMS device. In total, 82 analytes were detected for all observed peaks, thus extracting the values of the drift and retention times, and the normalised intensity variation. As a data pretreatment step, the exported intensity variation was normalised before the PCA by performing a background subtraction (i.e., removing intensity values from the room air measurements directly measured using the GC–IMS device without collection or storage in air containers). Afterward, normalised intensity variations were statistically processed using partial least squares (PLS) regression and principal component analysis (PCA) to quantify the differences between the samples stored in each type of container at different storage times. VOCs identification was not performed for all GC–IMS intensity maxima, as the aim of the study was to compare the suitability of three distinct containers for the long-term storage and preservation of gas samples. Instead, only four VOCs were identified for sample reproducibility evaluation.

4.3.1 Repeatability

A total of 99 spectra were collected from measurements conducted using 11 different storage times. The repeatability of the measurements performed for each type of container and storage time was assessed via a comparison of three replicates. The precision and analytical performance of the method were evaluated by statistically analysing the repeatability of the GC–IMS data, including the normalised intensity for all analytes, and the retention time and relative drift time for four randomly selected VOCs (i.e., ethanol, isopropanol, acetone and propanal).

The VOC patterns detected from the analysis of the samples with the same storage for each container type were similar between the three replicates. The mean value and the standard deviation of the total intensity of the analytes detected in the samples immediately analysed were 4.5 ± 0.1, 4.1 ± 0.3 and 4.1 ± 0.3 V for the plastic syringe with AC1, AC2 and AC3, respectively. This indicates a mean relative error of 5.61% for the normalised intensities of all analytes. Table 10 presents the mean retention and drift times and corresponding standard deviation (SD) values, for the four randomly selected analytes.

Table 10 - Average retention and drift times, and corresponding standard deviation (SD) values, for the four randomly selected analytes [10].

Compound	Retention Time (s)	SD Retention Time (s)	Drift Time (RIP Relative)	SD Drift Time (RIP Relative)
Ethanol	24.2	0.1	1.0617	0.0005
Isopropanol	25.6	0.1	1.1083	0.0006
Acetone	27.5	0.0	1.1650	0.0008
Propanal	33.2	0.2	1.0626	0.0006

The overall relative error was found to be up to 0.46% for the retention time, 0.06% for the relative drift time, and 5.61% for the normalised intensity, which indicates the high precision of the data collected using the GC-IMS. These overall values were calculated using the mean relative error values for the four VOCs selected. Of note, the standard deviation of the retention time for acetone was found to be 0.0 s due to no variations occurring in the acetone retention time for all nine replicates. This careful adherence to the specified conditions confirms that the collection procedure is effective in preserving air samples. Without such observance, the standard deviation for the average values of normalised intensity would be significantly higher, rendering the data statistically invalid and non-repeatable.

Regarding the third value registered in the three-dimensional GC-IMS spectrum, Figure 30 illustrates the total intensity registered for ethanol, acetone, isopropanol and propanal after each one of the considered storage times. Here, the intensity levels are represented in red, blue and green, respectively, for the full glass syringe (AC1), full plastic syringe (AC2), and plastic syringe with a rubbered plunger (AC3).

Further considerations are discussed below; nonetheless, the proposed method demonstrates excellent performance for VOCS analysis using GC–IMS. In fact, the low standard deviation observed between consecutive measurements further confirms the precision and, therefore, repeatability of the method, and highlights the suitability of this technology for analysing air samples. In summary, the variability between replicates indicates that both sampling and analysis procedures applied in this study are reliable and consistent, denoting the stability of measurements per condition evaluated.

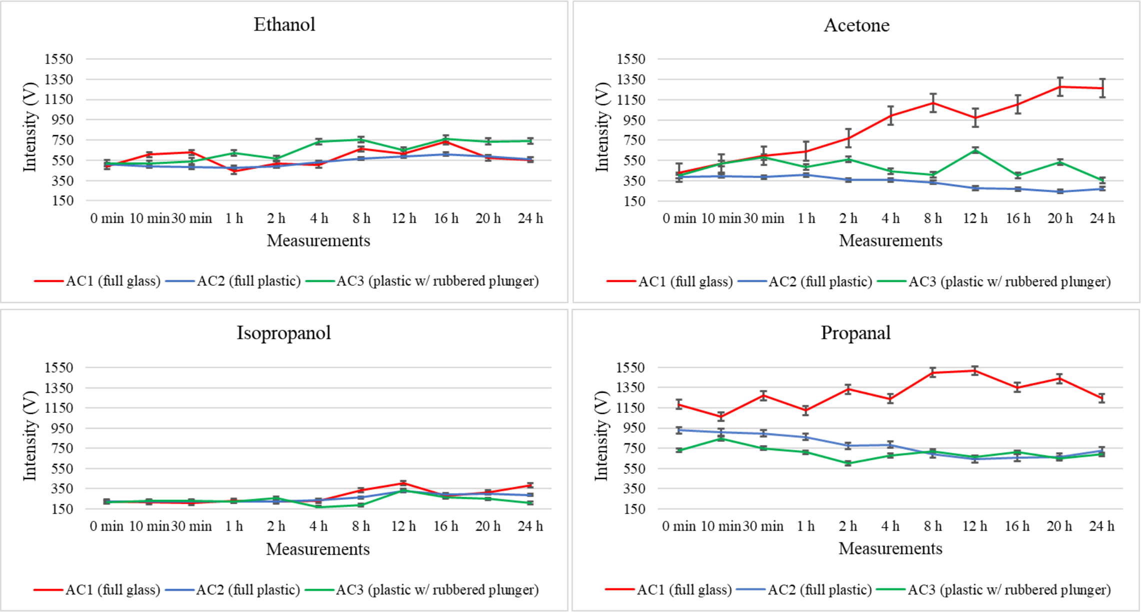


Figure 30 - Variations in the total intensity levels registered for ethanol, acetone, isopropanol and propanal, throughout the 24 h study for the three types of storage containers [10].

4.3.2 Sample Degradation and Compositional Variation

Although a comparison of the visual spectra provides a qualitative assessment of the most concentrated compounds, proper statistical data analysis allows to perceive hidden (or not so visible) evidence and differentiate patterns in the air samples stored for different times using the three container types. The application of PCA, in this case, highlights the differences between the profile of air stored in glass syringes (AC1, circles), fully plastic syringes (AC2, squares) and plastic syringes with a rubbered plunger (AC3, triangles). Figure 31 exhibits the PCA results.

Principal Components (PC) exhibited 76.94% [PC1], 11.63% [PC2] and 5.041% [PC3] of total explained variance in the data set for all measurements of each air sample, resulting in a total explained variance of 93.61%. Besides the high repeatability between replicas (i.e., samples with the same storing conditions: container type and storage time), Figure 31 also evidences a cluster containing measurements of the three container types for short storage times ($t < 4$ h), i.e., a stability group. Such results indicate that all three container types are suitable to use within this timeframe without significant changes in the VOCs profile of environmental air samples, establishing a stability group in the PCA plot.

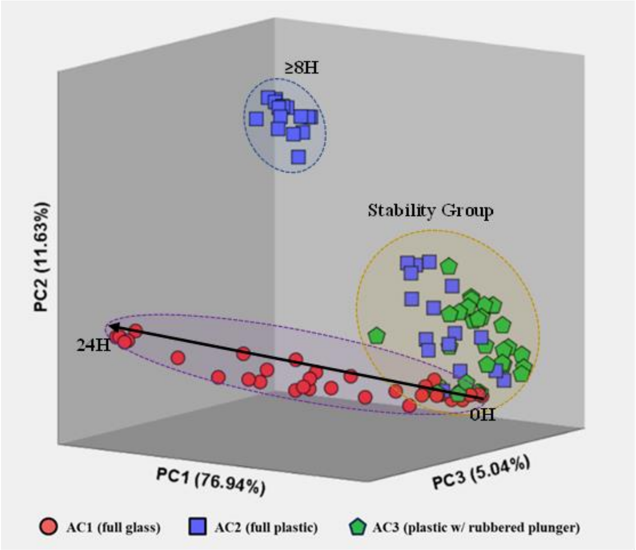


Figure 31 - Representation of AC1 (circles), AC2 (squares) and AC3 (triangles) measurements for all storage times after PCA, including the three most relevant principal components. The total variance is also included for each principal component [10].

Additionally, the VOC emissions for the AC1 air samples follow a horizontal evolution along the PC1. Such behaviour suggests a progressive change in the VOCs emitted from the air samples stored in these glass containers with an increasing storage time. This directly contrasts with the results obtained for AC2 (fully plastic syringes), where an abrupt change in VOC emissions occurs for storage times > 8 h. Contrarily, measurements for air samples stored in plastic syringes with rubbered plungers were all constrained within the stability group.

The overall separation of VOC emissions, within the stability group, is caused mainly by usual compositional fluctuations in the air samples and by equipment uncertainty. Meanwhile, air measurements located outside the stability group may be caused by sample degradation after a certain storage time. Specifically, AC1 appears to have a higher and progressive degree of degradation over time, AC2 has an abrupt change in VOC emissions after 8 h of storage and AC3 indicates that the samples are preserved independently of the storage time (within the 24 h included in the study).

Moreover, the behaviour of the samples stored in each type of container seems to have a common location of origin in the graph (within the stability region). To further understand the behaviour of the air samples stored in the three container types over the storage time considered, new score plots were constructed for each type of container.

4.3.2.1 Air Storage in Glass with Glass Plunger (AC1)

Significant changes in the VOCs emission profile are observed when comparing spectra from three storage times: 0 h (short-term), 8 h (intermediate), and 24 h (long-term). The samples analysed without storage (0 h) exhibit the lowest number of VOCs compared to the other timeframes. In particular, at 8 h of storage, there are significant changes in the VOC emission profiles, characterized by the presence of new intensity peaks in the spectra, indicating the detection of new analytes. From 8 h to 24 h of storage, the VOC emission spectra show an increase in intensity for the newly detected peaks after 8 h, as well as the identification of a novel set of peaks/VOCs. This observation is further supported by PCA, which accounts for 97.59% of the total explained variance for the three most relevant principal components. The PCA analysis demonstrates a progressive linear distribution over time, as depicted in Figure 31 and confirmed in Figure 32. This figure includes three spectra for air samples analysed without storage (0 h), after 8 h, and after 24 h of storage, as well as a PCA score plot representing all measurements across all storage containers.

Since glass is an inert material, it would be expected to have an increased capacity to maintain stable VOC profile emissions throughout the 24 hours in the air container. While the results initially support this expectation, especially for no storage (0 h), where the spectra are most similar to blank measurements, the same conclusion cannot be drawn for longer storage times (>1 h). This discrepancy may be attributed to two possible factors: (a) potential coating treatments applied to glass surfaces that reduce friction during the actuation of the plunger, and/or (b) higher reactivity of VOCs in glass due to their weaker ability to prevent light effects. Both hypotheses suggest the generation of new peaks/VOCs via chemical interactions between the container material and the analytes in the air sample.

4.3.2.2 Air Storage in Plastic Syringe with Plastic Plunger (AC2)

When comparing the spectra for the three different storage times (0 h, 8 h, and 24 h), significant changes are observed in the emission profile of VOCs. The spectra of samples analysed without storage (0 h) exhibit the lowest number of VOCs compared to the other timeframes. At 8 h of storage, there are noticeable alterations in the VOC emission profile with the emergence of new intensity peaks in the spectra, indicating the detection of new analytes. However, no significant changes in the VOC emissions (i.e., same peaks detected) occur between 8 h and 24 h of storage time, only an increase in the intensity or concentration of the VOCs. The application of PCA solely for the air samples stored in AC2, with 98.73% of the total explained variance for the three most relevant principal components, clearly demonstrates the abrupt difference in the VOC emission profiles after 8 h, as depicted in Figure 31 and confirmed in Figure 32.

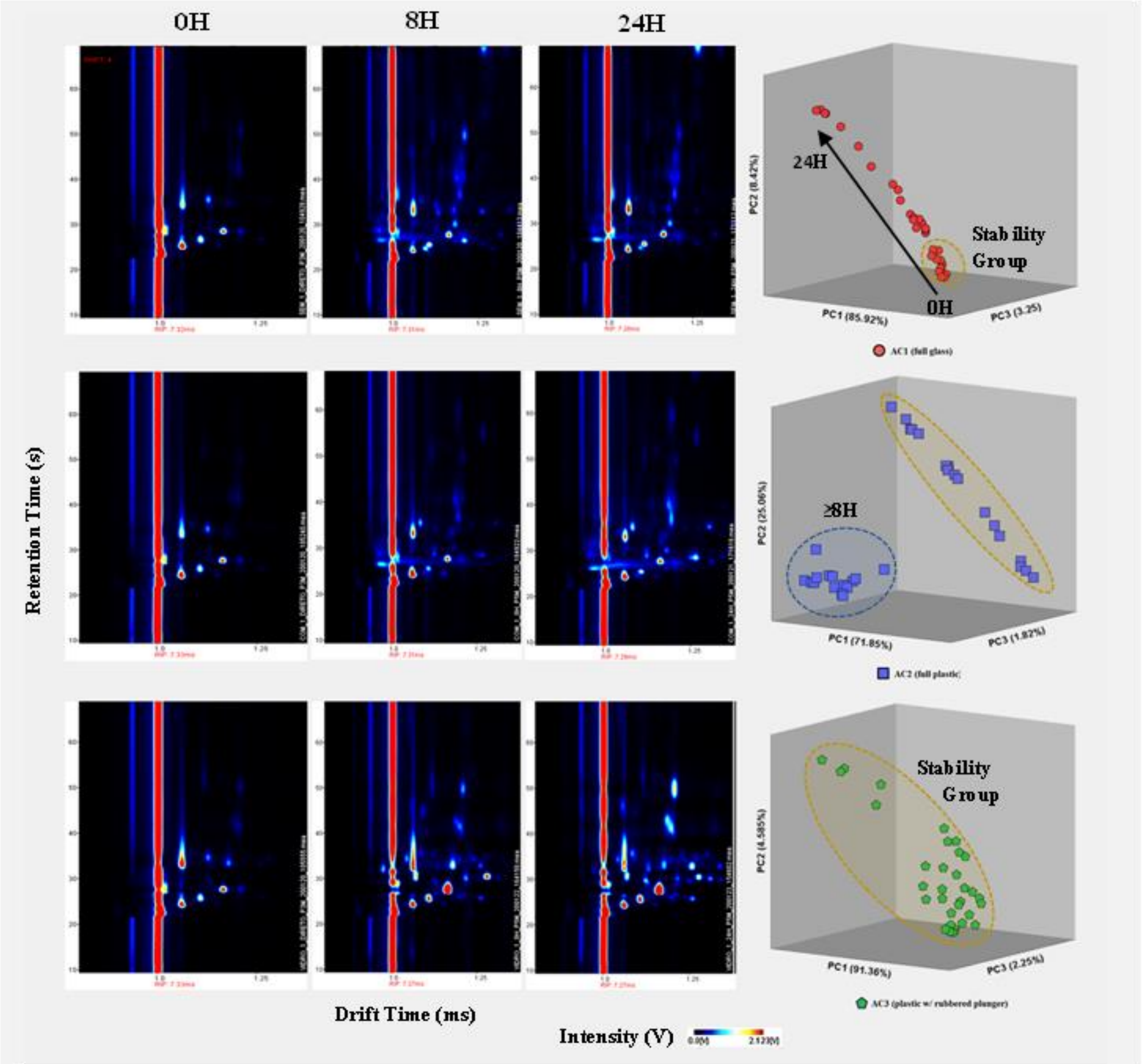


Figure 32 - Temporal comparison of air measurements stored using AC1 (top), AC2 (middle) and AC3 (bottom) for a total storage time of 24 h; (left) three representative GC–IMS spectra for air samples analysed (a) directly after the collection, (b) after 8 h of storage, and (c) after 24 h of storage; (right) PCA plot score demonstrating two distinct VOC profiles for air samples stored over 8 h, for the three replicates (1st blue, 2nd red and 3rd green) [10].

The appearance of new VOCs in the spectra of samples stored for more than 8 hours might be explained by, over time, the initial compounds stored in AC2 being degraded, forming secondary VOCs. Contamination by external VOCs, exogenous or emitted from the plastic, can also explain the increase in VOCs detected, thus indicating the inability to store air samples for more than 8 hours. This might also be linked to the poor isolation of the plastic plunger after this period.

4.3.2.3 Air Storage in Plastic Syringe with Rubber Plunger (AC3)

In contrast to AC1 and AC2, the pattern of the analytes detected in the air samples stored in AC3 remains relatively consistent over the 24 hours. The analytes detected in the samples without storage (blanks and 0 h) exhibit similar intensity levels to those detected in the air samples stored for different timeframes up to 24 h, with only minor intensity increases observed over consecutive 8 h periods. This phenomenon is mainly attributed to the inevitable slow degradation of these compounds.

Furthermore, this observation is supported by the PCA results, with 98.19% of the total explained variance accounted for by the three most relevant principal components (as shown in the bottom images of Figure 32), displaying a distinct cluster within the stability group (as depicted in Figure 32). This indicates that regardless of the storage time in the studied container, the samples maintain their main features without significant degradation or contamination by external analytes. In the case of the PCA for the AC3-stored air samples, the points are closely clustered together, except for five measurements (out of 33) that fall outside this group. However, these five measurements have irregular storage times of 30 min, 2 h, 12 h, and 20 h. The randomness in the storage times for these samples suggests irregularities specific to these samples, unrelated to the storage capabilities of AC3.

Therefore, AC3 has proven to be significantly better at preserving the characteristics of the original sample and avoiding influences from external factors (both environmental and those related to AC3 materials) over extended storage periods, even when considering potential contaminations from the VOC emission profile of the rubbered plunger.

The storage of gaseous samples plays a crucial role in preserving the integrity and stability of volatile organic compounds (VOCs) for various applications, such as disease biomarker research, metabolite detection, and air quality control. This study evaluated the suitability of three commercially available syringes (AC1, AC2, and AC3) commonly used as air containers for sample collection, storage, isolation, and transportation.

The application of GC–IMS as the analytical technique has proven to be highly suitable for evaluating air samples stored over both short and long periods, thus assessing the preservation capabilities of air containers. GC–IMS stands out for its exceptional selectivity, sensitivity, and analytical flexibility, combined with its portability and ability to perform longitudinal studies of volatile samples.

This study demonstrated the good repeatability of the measurements made and identified differences in the VOC profiles based on the storage time and container type. The analysis of the data using unsupervised PCA provided deeper insights into the overall VOC emission profile of air samples stored for different times using the three container types. Samples stored in glass syringes (AC1), fully plastic syringes (AC2), and plastic syringes with rubbered plungers (AC3) exhibited different behaviours over time.

Although all air containers can be used in short-term analysis (up to 1 h), glass syringes have the clearest measurements. Therefore, glass syringes proved to be suitable for direct analyses, but inappropriate for medium- and long-term storage scenarios. For long-term storage, AC3 proved to be the most appropriate for sample preservation.

Despite lacking the confirmation of these findings in real scenarios of breath collection and storage, this study provided crucial insights into the selection of appropriate syringe-based containers for the collection and preservation of the air samples collected from the car factory painting line [10].

Disclaimer: The information included in this chapter was originally published in the paper: P. H. C. Santos, P. C. Moura, V. Vassilenko. Suitability of Short- and Long-Term Storage of Volatile Organic Compounds Samples in Syringe-Based Containers: A Comparison Study. *Metabolites*, 13, 903, 2023. https://doi.org/10.3390/metabo13080903 [10].

4.4 GC-IMS Suitability for *In-Situ* Analyses

Considering all the theoretical evaluation of both advantages and disadvantages of all the techniques available for the study of VOCs in an industrial context, GC-IMS as selected to be used throughout the entire doctoral project. The majority of the remaining techniques often require additional procedures for sample preparation before the analysis, limiting their suitability for *in-situ* air assessment. Others aren't always suitable for the identification of organic molecules, like the MS, since its usual 70 eV radiofrequency ionisation potential frequently breaks the atomic bonds in organic compounds, inhibiting their detection. The lack of portability and complexity of the systems are equally excluding factors for the techniques.

Once selected the GC-IMS as the technique to be used for all the measurements required during the doctoral project, it was mandatory to assess its suitability for *in-situ* analyses in a practical manner. To do so, a study was exclusively dedicated to assessing this topic. The results are discussed below.

A total of 496 spectra were obtained from 16 different locations (including outdoor air). In order to guarantee statistically relevant results, 31 samples were collected, for two consecutive days, from each location. Then, all the spectra registered from the measurements were processed and the values of drift and retention times, and intensity were exported using LAV

(GAS Dortmund) software for further analysis. In specific, the drift and retention times were used for purposes of identification, and the intensity for purposes of quantification.

4.4.1 VOCs Identification for *In-Situ* Analyses

As mentioned, all 31 spectra collected from each location were processed and the drift and retention times were exported. Among monomers, dimers and trimers, a total of 31 peaks were found for all the locations. From these 31 detected analytes, it was possible to identify 23 peaks that correspond to 13 distinct volatile organic compounds. The identified VOCs were ethanol, 2-propanol, propanal, acetone, propanol, butanal, acetic acid, ethyl acetate, 2-butanone, butanol, pentanal, propanoic acid, and 2-hexanone. The identification was achieved, as addressed, by cross-checking the drift and retention times of each analyte with the developed database.

Table 11 includes the drift and retention times for all 31 detected VOCs, as well as the name and CAS number for the identified ones. Unidentified compounds are marked with N.I. (an acronym for not identified). The table is sorted by retention time.

Table 11 - Volatile organic compounds detected during the assessment of GC-IMS suitable for *in-situ* measurements [16].

#	VOCs	Retention Time (s)	Drift Time (ms)	Note	CAS Number
1	Ethanol	73	1.056	Monomer	64-17-5
			1.150	Dimer	
2	2-Propanol	82	1.104	Monomer	67-63-0
			1.203	Dimer	
			1.254	Trimer	
3	Propanal	84	1.058	Monomer	123-38-6
4	Acetone	90	1.012	Monomer	67-64-1
			1.159	Dimer	
			1.205	Trimer	
5	N.I.	93	1.060	–	–
			1.207	–	–
6	Propanol	96	1.123	Monomer	71-23-8
			1.286	Dimer	

7	Butanal	113	1.131	Monomer	123-72-8
			1.333	Dimer	
8	Acetic Acid	118	1.061	Monomer	64-19-7
			1.177	Dimer	
9	N. I.	119	1.049	–	–
10	N.I.	119	1.183	–	–
11	Ethyl Acetate	120	1.121	Monomer	141-78-6
12	N. I.	123	1.227	–	–
13	2-Butanone	124	1.081	Monomer	78-93-3
			1.299	Dimer	
14	N. I.	125	1.061	–	–
15	Butanol	141	1.202	Monomer	71-36-3
16	N. I.	145	1.141	–	–
17	Pentanal	166	1.206	Monomer	110-62-3
18	Propanoic Acid	170	1.118	Monomer	123-38-6
			1.130	Dimer	
19	N. I.	242	1.197	–	–
20	2-Hexanone	262	1.219	Monomer	107-87-9

As stressed, some of the detected compounds may be harmful to human health when their concentrations are elevated or when the exposure time is prolonged. Irritation and pruritus, allergic reactions, pulmonary diseases and carcinogenic pathologies are among the main consequences of exposure to VOCs. According to the literature, all the identified compounds provoke eye, nose, throat, and skin irritation, as well as pulmonary problems. The compounds 2-butanone, propanol, 2-propanol, butanol and acetone, for example, may cause headaches and dizziness. These compounds and 2-pentanone, ethanol and ethyl acetate are the cause of several nervous system disturbances. Some compounds lead to reproductive and genetic problems, specifically, 2-butanone, 2-pentanone, 2-propanol, butanal and ethyl acetate. Finally, two of the identified compounds are proved to be carcinogenic. Ethanol and 2-butanone can be the cause of cancer development in human beings, in cases of continuous exposure, as already mentioned. Overall, all the detected analytes deserve proper attention and their intensities in indoor air must be assessed and controlled [347, 348].

4.4.2 VOCs Quantification for *In-Situ* Analyses

Once identified the VOCs, the next step consisted of plotting the location-specific profiles for the relative intensity values. As stated, these profiles can be extremely useful tools for directly comparing the composition of distinct locations and having a perception of the hazardousness and toxicity of the analytes.

The VOCs profiles of each location were represented in the form of a radar chart where the vertical axis corresponds to the relative intensity level, and the circular axis represents the compounds numeration (from 1 to 20 as represented in Table 11). To clarify, if a compound presents an intensity value of, for example, 4, it means that, with this approach, its intensity is 4 times higher in the studied location than it is in outdoor samples. Similarly, if this compound intensity is -4, then its intensity in the studied location is 4 times lower than its intensity in outdoor samples. Radar charts were arranged in four different groups.

Figure 33 illustrates the profiles plotted for the a) bathroom, b) canteen and c) FABLAB. All these three locations have profiles without considerably elevated values of relative intensity meaning that the intensities and, consequently, the concentrations of the analytes in the indoor locations are very close to the outdoor levels. Notwithstanding, some specific VOCs deserve proper attention.

Butanal (compound 7), for instance, seems to be the analyte with higher relative intensity (two times higher than in the outdoor air) in the bathroom profile and it is the second most intense in the FABLAB profile. Coincidently, compound 5 (N.I.) exhibits the highest relative intensity level in the FABLAB profile and is also one of the most evident VOCs in the bathroom profile. These facts prove that, besides the different activities developed there, there are similar sources of VOCs in both locations. some VOCs are simultaneously worth attention in the FABLAB and the bathroom facilities.

Butanol (compound 15) and 2-hexanone (compound 20) seem to have higher relative intensity, in the bathroom air, than the remaining analytes. Butanol is a common alcohol usually used in cleaning products; a fact that justifies its presence in the bathroom air. A large number of paints, solvents and oils have 2-hexanone in their constitution so, the building materials are the most plausible sources of this analyte in the bathroom. Both of them can cause severe cutaneous and ocular irritation, in this way, their intensity levels must be monitored.

The canteen profile reveals that the intensity values of all its compounds are considerably similar to the outdoor levels, meaning that this location seems to be properly ventilated or to possess good air renovation systems. Overall, all three profiles are very simple and do not exhibit any specific compound with considerably high levels of intensity. None of the analytes constitutes, for now, a potential risk for human health nor can be considered hazardous.

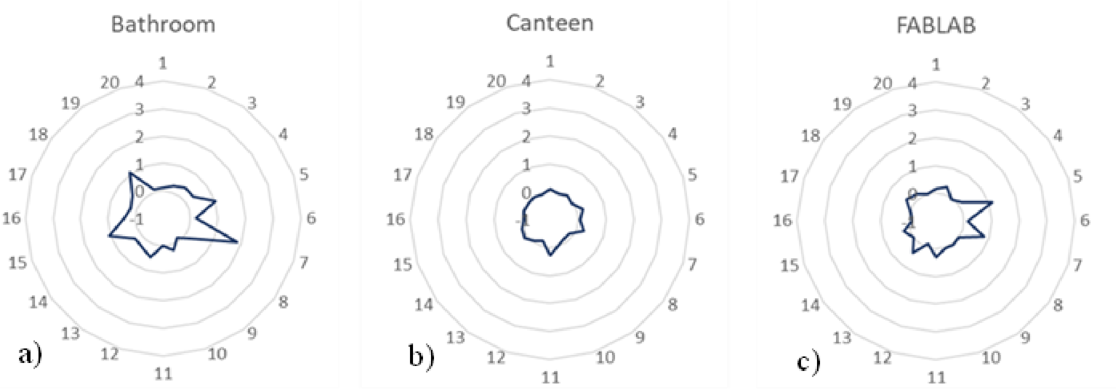


Figure 33 - Relative intensity profiles for a) bathroom, b) canteen and c) FABLAB [16].

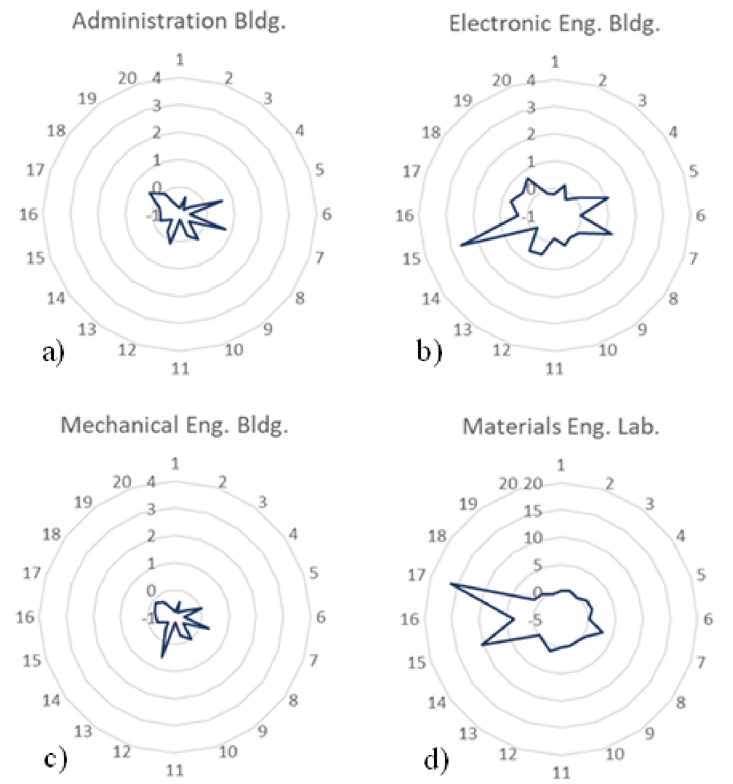
Figure 34 exhibits four profiles: a) administration building, b) electronic engineering building, c) mechanical engineering building, and d) materials engineering laboratory. As in the previous profiles, most of the analytes have relative intensity levels around the outdoor levels, however, the number of VOCs that require proper attention is higher than in the aforementioned group.

Regarding the administration building, butanal (compound 7) and pentanal (compound 17) are the analytes with higher relative intensity. Both these analytes are known for causing severe cutaneous and ocular irritation and, besides that, butanal can be responsible for headaches, nausea and loss of consciousness. These aldehydes are commonly released into the air by activities that require any type of burning and smoke production, like cooking, smoking and fossil fuels or wood burning.

The analyte 12 (N.I.) is the most intense compound detected in the air of the mechanical engineering building. Unfortunately, it was not possible to accurately identify it, however, due to its obvious relevance to the air quality of the location, it is mandatory to use additional procedures and techniques to successfully identify the analyte and assess its eventual hazardousness. The relative intensity levels of the remaining VOCs are similar to the outdoor levels so, for now, they do not represent a risk to human health.

In the case of the electronic engineering building, a specific analyte has a more emphatic behaviour than the remaining. Butanol (compound 15) presents the highest relative intensity and is almost three times more intense in this indoor location than it is in the outdoor samples. The compounds 5 (N.I.), 7 (butanal), 13 (2-butanone) and 20 (2-hexanone) also present relative intensities higher than the outdoor levels. All these compounds are emitted by cleaning and disinfection products, smoking, industrial activities and construction materials like paints and oils, and must be carefully controlled in order to verify if their intensity levels do not increase even further.

Finally, the materials engineering laboratory profile presents the greatest concerns in this group of profiles. The results show that butanal (compound 7), pentanal (compound 17) and butanol (compound 15) are around 5, 10 and 15 times more intense in this location than they are in the outdoor environment. These extremely elevated intensities may represent a serious health risk and corroborate the necessity of developing a calibration protocol to assess the real concentration values for verifying the real hazardousness of the presence of these three analytes in the indoor air.


Administration Bldg.

Electronic Eng. Bldg.

Mechanical Eng. Bldg.

Materials Eng. Lab.

Figure 34 - Relative intensity profiles for the a) administration building, b) electrotechnical engineering building, c) mechanical engineering building, and d) materials engineering laboratory [16].

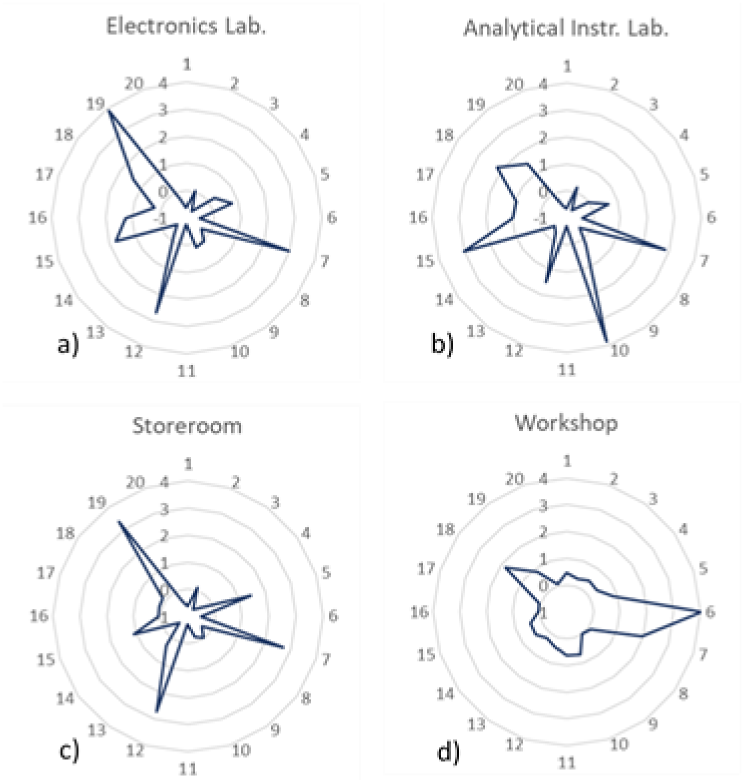


Figure 35 - Relative intensity profiles for the a) electronics laboratory, b) analytical instrumentation laboratory, c) storeroom, and d) workshop [16].

The third group of profiles is illustrated in Figure 35 a) electronics laboratory, b) analytical instrumentation laboratory, c) storeroom and d) workshop.

As happened in previous profiles, butanal (compound 7) has a major role in all profiles. The relative intensity of this analyte in all four locations is around three times higher than it is outdoors. Due to the known consequences caused by long periods of exposure to butanal, namely, headaches, nausea and loss of conscience, this analyte must be carefully controlled.

Both, the electronics laboratory and storeroom have very similar relative intensity profiles. Of all the compounds, the analytes 5 (N.I.), 7 (butanal), 12 (N.I.), 15 (butanol) and 19 (N.I.) stand out from all the 20 VOCs. Unfortunately, it was not possible to identify or quantify these VOCs during the data analysis, but the elevated intensities prove their special status in the air quality assessment. Compounds 12 and 19, for example, are three and four times more intense in both the electronics laboratory and storeroom than they are in the outdoor environment so, their characterization and control are essential topics.

The analytes 7 (butanal), 10 (N.I.), 12 (N.I.), 15 (butanol) and 18 (propanoic acid) present the higher relative intensities in the analytical instrumentation laboratory. Besides the already mentioned health risks of both butanal and butanol, propanoic acid is a corrosive compound that can cause severe forms of irritation in the skin, eyes, nose, throat and pulmonary tissues. Alongside propanol (compound 6) and butanal (compound 7), propanoic acid is also one of the most intense analytes in the workshop air. Coincidently, several activities that involve the use of machinery, solvents, oils and many other chemical products, are developed in both these locations; a fact that can explain the presence of similar levels of intensity for the enumerated analytes.

The fourth and final group of profiles, namely the profiles of a) biomedical engineering laboratory, b) atomic and molecular physics laboratory, c) conservation and restoration laboratory, and d) chemistry laboratory, is represented in Figure 36.

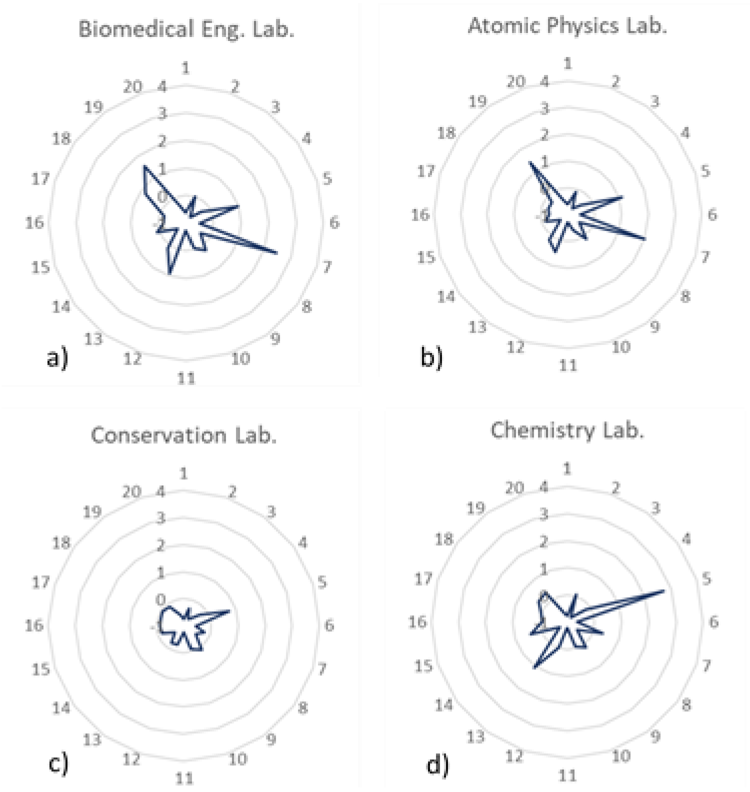


Figure 36 - Relative intensity profiles for the a) biomedical engineering laboratory, b) atomic and molecular physics laboratory, c) conservation and restoration laboratory, and d) chemistry laboratory [16].

The profiles a) and b) are very similar. The analytes with a more emphatic behaviour are the VOCs 5 (N.I.), 7 (butanal), 12 (N.I.), 13 (2-butanone), and 20 (2-hexanone). The remaining analytes present intensity levels comparable to the outdoor values, meaning that they don’t represent a direct risk to human health. Coincidently, these two locations belong to the same building and are very close to each other so, their profiles' behaviour may be related to the similarity of construction materials, furniture and activities developed in both laboratories.

In opposition to what would be expected, the relative intensities of the VOCs existent in the air of both the chemistry laboratory and conservation and restoration laboratory are very close to outdoor levels. Considering that the laboratories of these kinds are, usually, filled with all kinds of chemicals, it would be expected to find some analytes with considerably elevated levels of intensity, however, that was not the case. Except for compound 5 (N.I.), everything else presents very low intensities so, the use of proper ventilation systems and correct use of the chemicals and devices of the laboratory may be the probable cause of such low-intensity levels.

Aiming to quantify the concentration levels of the detected analyte, the calibration curve of 2-hexanone, whose plotting was previously addressed, was applied to the intensity levels detected by the GC-IMS. Table 12 includes all the concentration levels calculated using Equation 32.

Table 12 - Concentration levels and respective standard deviation for all the studied locations [16].

Location	**Average Concentration (ppb_v)**	**Standard Deviation (ppb_v)**
Bathroom	25.7	0.2
Canteen	25.4	0.2
FABLAB	25.5	0.1
Administration building	25.2	0.1
Electrotechnical engineering building	25.6	0.1
Mechanical engineering building	25.1	0.1
Materials engineering laboratory	25.6	0.1
Electronics laboratory	25.6	0.1
Analytical instrumentation laboratory	30.6	2.4
Storeroom	25.2	0.1
Workshop	26.2	0.2
Biomedical engineering laboratory	25.4	0.1
Atomic and molecular physics laboratory	24.9	0.1
Conservation and restoration laboratory	25.3	0.2
Chemistry laboratory	25.4	0.2

Outdoor Air	25.4	0.1

NIOSH defines the TLV of 2-hexanone at 5 ppm_v [113], so, considering the values above, it is safe to say that the indoor levels of this compound are considerably under the recommended level for most of the locations. These values are, therefore, inoffensive to the people chronically exposed to 2-hexanone at the studied locations. Besides this conclusion, it is important to state that some of the detected analytes exhibited levels of intensity several dozens of times higher than the intensity of 2-hexanone. Even though the relationship between the concentration levels of different analytes cannot be directly correlated, one can infer that considerably higher concentrations would be calculated if the calibration curves were available for the remaining compounds.

The present study introduced a simple but very precise methodology for direct determination of VOCs profile in both indoor and environmental air, in a large-scale scenario, with high levels of sensibility and specificity, and capable of providing *in-situ* results in almost real-time. Summarily, it is possible to conclude that the proposed method around GC-IMS proved to be quite suitable, efficient, accurate and rapid for *in-situ* direct analysis and profiling of volatile organic compounds even at trace concentration levels. The proposed methodology exhibited promising results and it can be very useful for indoor air quality monitoring and closed habitats controlling even at complex locations like a car factory painting line.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, V. Vassilenko. Gas Chromatography – Ion Mobility Spectrometry as a Tool for Quick Detection of Hazardous Volatile Organic Compounds in Indoor and Ambient Air: A University Campus Case Study. *European Journal of Mass Spectrometry*, 28, 113-126, 2023. https://doi.org/10.1177/14690667221130170 [16].

4.5 GC-IMS Suitability for Long-Term Analyses

The present study intended to assess the suitability of GC-IMS for *in-situ* long-term measurements of VOCs and consequent control of indoor air quality in closed spaces. For this purpose, a year-long study was developed aiming to obtain the GC-IMS spectra of volatile organic compounds, identify the detected analytes and perform the evaluation of the daily variation of the total VOCs (tVOCs) intensity across the period of measurements.

A total of 167 spectra from the room air analyses were considered during this study. The days in which an analysis was conducted can be consulted elsewhere [11]. These spectra were used for purposes of identification and quantification of the VOCs present at the target location and for purposes of analysing the evolution of the VOCs concentration throughout the entire year.

4.5.1 VOCs Identification for Long-Term Analyses

As previously described, the identification of the detected analytes was achieved by crosschecking their drift and retention times with the times registered in a predeveloped database of VOCs. For purposes of identification, only the long-lasting compounds were considered, therefore, all the analytes that were not present during all the 11 months were disregarded.

A total of 16 analytes were accurately identified with the library and, considering monomers, dimers, and even trimers of the same compound, the 16 analytes totalize 10 VOCs. Among these 10, five belong to the organic family of alcohols (ethanol, isopropanol, propanol, isobutanol, and butanol), two are carboxylic acids (acetic acid and propanoic acid), commonly known as fatty acids, one ether (tert-butyl methyl ether), one ketone (acetone), and one aromatic hydrocarbon (benzene). Table 13 includes all the identified VOCs, their respective retention and drift times, normalised ion mobility constants, and CAS numbers.

Table 13 - Identified VOCs and respective retention and drift times, normalised ion mobility constants, and CAS numbers [11].

#	VOCs	CAS Number	Retention Time (*s*)	Drift Time (*RIP Relative*)	Note
1	Ethanol	64-17-5	73	1.06	Monomer
2				1.15	Dimer
3	Isopropanol	67-63-0	82	1.10	Monomer
4				1.21	Dimer
5				1.25	Trimer
6	Tert-Butyl Methyl Ether	1634-04-4	90	1.16	Monomer
7				1.30	Dimer
8				1.41	Trimer
9	Acetone	67-64-1	91	1.21	Monomer
10	Propanol	71-23-8	96	1.13	Monomer

11	Isobutanol	78-83-1	118	1.19	Monomer
12				1.40	Dimer
13	Acetic Acid	64-19-7	118	1.06	Monomer
14	Benzene	71-43-2	120	1.12	Monomer
15	Butanol	71-36-3	141	1.20	Monomer
16	Propanoic Acid	79-09-4	168	1.12	Monomer

Alcohol-based VOCs are known for their hazardousness not only to the environment but mainly to the human organism, being eyes, skin, and throat irritation the most common reactions. Nonetheless, more complex reactions to alcohol-based compounds exposure have been reported, namely, narcosis and central nervous system depression. Due to these facts, most alcohol-based solutions, like coatings, inks, or personal care products, have even been replaced by considerably safer water-based versions [349, 106].

Severe eyes and skin irritation are equally common reactions of the human organism if exposed to fatty acids like acetic and propanoic acid, ketones, or ethers. Dizziness, nausea, suffocation, vomiting, and hyperaemia have been reported in scenarios of long-term exposure to all these analytes [349, 350, 351].

Finally, the aromatic hydrocarbon detected in the indoor air samples of the closed space analysed is known for its particular hazardousness. Vulgarly known as BTEX compounds, benzene, toluene, ethylbenzene, and xylenes have been largely studied and the risks to human health in both short- and long-term exposures are well-known [352, 353].

Considering all the mentioned facts about the dangerousness of VOCs to the human organism and since these 10 compounds are always present throughout the entire year, all of them deserve special attention and must be of special interest for the maintenance of air quality in a closed environment and for the assessment of exposure conditions of the workers who frequently use the space. Further studies are required to assess the original sources responsible for the emission of the analytes. Regarding the GC-IMS behaviour, there are no doubts about the suitability of GC-IMS to identify analytes *in-loco* [11].

4.5.2 Repeatability

In order to assess the repeatability and, consequently, the precision of measurements and quality of the proposed method, the statistical relevancy of the data collected with the GC-IMS device and the variability of the intensity of the analytes were analysed. For this purpose, the normalised tVOCs intensity registered for 10 subsequent analyses was represented in a line graph. Figure 37 illustrates the repeatability achieved with the GC-IMS technology. The average value of the normalised intensity and the respective average deviation achieved during the processing of this dataset were 0.80 ± 0.05. These values prove that not only the GC-IMS ensures outstanding repeatability of the collected data but also, that this technology is more than suitable for *in-situ* long-term air quality control in closed environments.

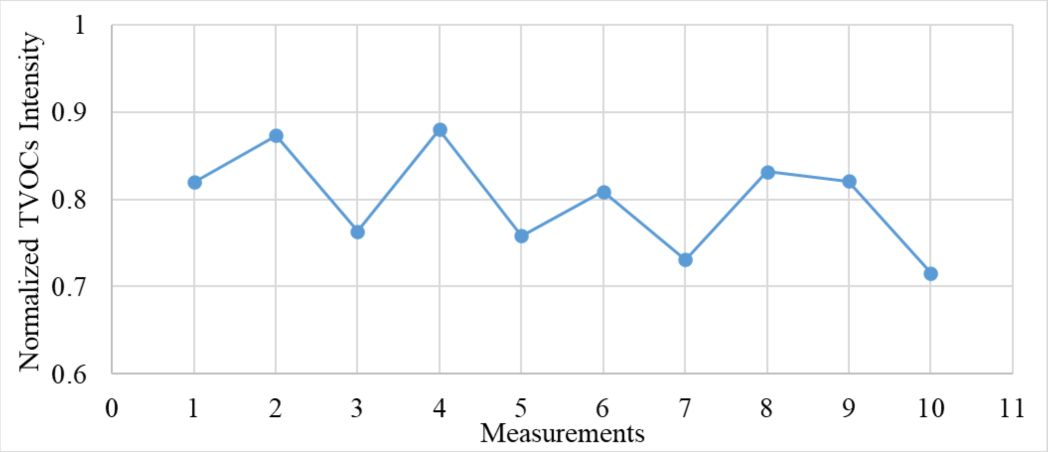


Figure 37 - Variability line chart for the GC-IMS measurements. The average value for the normalised intensity and the respective average deviation are (0.80 ± 0.05) [11].

4.5.3 tVOCs Variation

As described, the total VOCs intensity was determined and normalised for all 11 months. Aiming to understand the evolution of the tVOCs value throughout the entire study, the relative variation between consecutive months was equally calculated. To do so, the percentual variation of tVOCs, for each month, was calculated relatively to the previous month. Table 14 summarizes the normalised tVOCs intensity and the relative variation in percentage form. Information elucidating if the variation corresponds to an increase or decrease in the tVOCs intensity is also included.

Table 14 - Normalised tVOCs intensity and respective variation (%) between consecutive months [11].

Year	Month	Normalised tVOCs Intensity	Relative Variation (%)	Increase or Decrease (↑ or ↓)
2019	September	0.93	–	–
	October	0.87	6.43	↓
	November	0.76	13.61	↓

	December	0.70	7.21	↓
2020	January	0.55	22.08	↓
	February	0.71	30.19	↑
	March	0.82	15.25	↑
	May	0.88	7.23	↑
	June	0.92	4.37	↑
	July	0.99	7.44	↑

Considering the results represented in the previous table, it is possible to remark on the evident decrease in the tVOCs intensity between September 2019 and January 2020. From February to July, 2020, data reports a successive increase in the total average intensity. Coincidently, this behaviour is similar to the variation of the average air temperature of the country where the analysed closed spaced is located. The air temperature tends to decrease between September and January and tends to increase from January onwards. Not being the only impacting factor, air temperature plays a truly relevant role in the volatilization of VOCs, as addressed previously.

To easily qualify the variation of the average intensity along the considered months, a graph was plotted. The graph is represented in Figure 38, where the months are denoted on the x-axis and the left y-axis corresponds to the normalised tVOCs intensity. The average air temperature per month, as recorded by the national institute of meteorology [354], is denoted on the right y-axis.

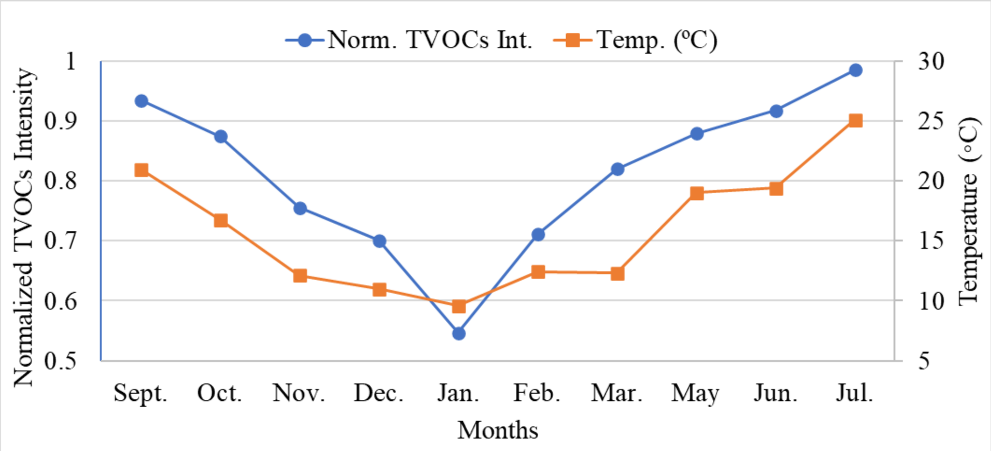


Figure 38 - Variation of the total average Intensity of VOCs between September of 2019 and July of 2020 (April was disregarded) versus the temperature variation [11].

As mentioned, the graph of Figure 38 mimics the behaviour of the tVOCs intensity throughout the 11 analysed months. As included in Table 14, the normalised tVOCs intensity experiences a decrease between September and January. Coincidently, these months typically see a decrease in the overall weather temperature, hindering the volatilization of the VOCs. On the other side, between January and July, the total intensity of VOCs continuously increases. This can be justified by the coincident increase in air temperature during these months, easing the volatilization of the analytes. This correlation can be speculated since no other alterations, affluence variation or replacement of potential sources of VOCs were made in the closed spaced studied throughout the year.

In order to assess if the behaviour of the intensity variation for individual VOCs throughout the studied months also mimics the temperature variation, the absolute intensity (V) per month of each analyte was plotted against the temperature graph. Three of these graphs are illustrated in Figure 39, namely, the graph of intensity variation for ethanol, isopropanol, and tert-butyl methyl ether.

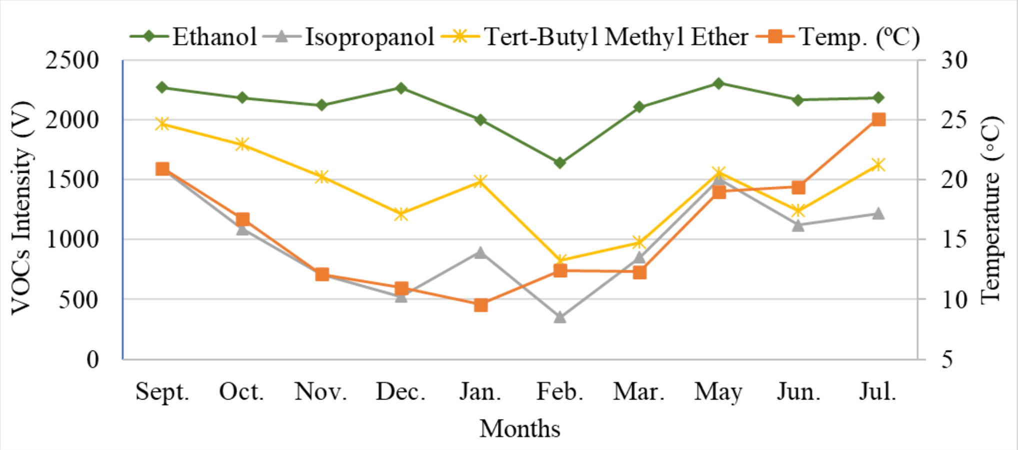


Figure 39 - Variation of the intensity of ethanol, isopropanol, and tert-butyl methyl ether between September of 2019 and July of 2020 (April was disregarded) versus the temperature variation [11].

It is evident that all these three VOCs exhibit behaviours that mimic the variation of the air temperature throughout the entire year. Similar results were attained for all the remaining VOCs, i.e., all the 10 considered analytes seemed to exhibit intensity variations comparable with the temperature variation. A decrease in the tVOCs intensity was registered between the months and September and January, matching the behaviour of the overall air temperature. From February forward, the tVOCs intensity registered a constant increase, again, mimicking the air temperature provided by the national weather institute. Since the VOCs are volatile at room temperature, their volatilization is especially affected by the variation in air temperature.

This direct relationship was evident in the results achieved during the study, i.e., months with higher air temperature led to higher con-centration levels of VOCs and, consequently, to increased exposure risks to human health.

Overall, this one-year-long case study confirmed the necessity of air quality control in indoor, closed, and highly populated environments. It was established that, due to its characteristics, namely, its outstanding sensitivity, very low concentration range, good precision, instrumental simplicity, almost-real-time measuring capacity, and portability, GC-IMS is completely suitable for *in-situ* long-term VOCs detection and air quality control in closed environments. Further studies must be carried on to accurately assess the VOCs concentration, identify the main sources of emission, and evaluate the direct consequences to human health in both short- and long-term scenarios.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, V. Vassilenko. Long-Term *In Situ* Air Quality Assessment in Closed Environments: A Gas Chromatography – Ion Mobility Spectrometry Applicability Study. *European Journal of Mass Spectrometry*, 29, 231-239, 2023. https://doi.org/10.1177/14690667231187502 [11].

4.6 Car Factory Painting Line Air Assessment

The overall suitability of GC-IMS for the purposes defined by the goals of this doctoral project was fully assessed during the previously addressed studies. In this way, one could start to implement the protocols defined for collecting and analysing air samples in the car factory painting line.

Aiming to evaluate the air composition and overall air quality at the main locations of the car factory painting line, the entire line was studied, and the most relevant locations were selected. As already mentioned, eight indoor locations and one outdoor location were considered during this doctoral project.

Ten consecutive air samples were collected from each location and analysed by GC-IMS within a 15-minute interval. For each measurement, a three-dimensional spectrum was created and saved. All the obtained spectra were processed with the LAV software (version 2.2.1., GAS - Dortmund). The values of intensity, drift time, and retention time of each compound were exported and statistically processed for the assessment of the VOCs found in all samples.

As mentioned before, both the drift and retention times and the ion mobility constant are compound-specific values, i.e., they can be used to accurately distinguish between any analyte, even between structurally similar compounds. Thus, the VOCs detected in the air samples were identified by comparing both these parameters with the corresponding values registered in a pre-developed database. Regarding the intensity, the third value of the three-dimensional spectrum was used to plot a profile of relative intensity level for the VOCs existent in each one of the analysed locations. Such profiles enabled a direct comparison between the air composition of distinct sites and to have a perception of the concentration levels of each analyte in the original sample. Finally, aiming to assess the level of concentrations existent in the analysed air samples, the calibration procedure previously developed was applied to 2-hexanone [9].

4.6.1 Data Repeatability

A total of 90 spectra were obtained from all the measurements performed at the nine locations. Aiming to assess the precision and analytical performance of the method, the repeatability for each value of GC-IMS spectra (retention time, relative drift time, and intensity) for every analyte was statistically analysed. The overall precision is up to 1.2% for the retention time, 0.1% for the relative drift time, and 4.1% for the normalised intensity.

For representation purposes, Figure 40 illustrates the variability graphs for a randomly selected analyte (dimer of acetone) analysed in a location randomly selected (phosphatising bath). It is important to state that the mean value for ten replicates (n=10) and respective standard deviation of the retention time, relative drift time, and normalised intensity for these representative analytes were 89.7 ± 0.1, 1.159 ± 0.001, and 0.176 ± 0.007, respectively. Similar repeatability results were achieved for all the remaining analytes detected in all nine locations.

It is worth saying that all ten consecutive sample measurements from each location were always collected and transported with the mentioned Teflon pump. Since these conditions were accurately kept, one can state that the collection procedure is suitable for the preservation and transportation of the air samples, otherwise, the standard deviation for the average values of normalised intensity would be considerably higher and, consequently, the data would have no statistical validity nor would be repeatable.

From the achieved data analysis, it is possible to state that the proposed method demonstrates a good performance for *in-situ* VOCs analysis by GC-IMS showing a full capability of ensuring the repeatability and, consequently, the statistical validity of the collected data. Furthermore, the small standard deviation achieved between 10 consecutive measurements reinforces a good method precision and the suitability of this technology for the analysis of air samples in industrial scenarios.

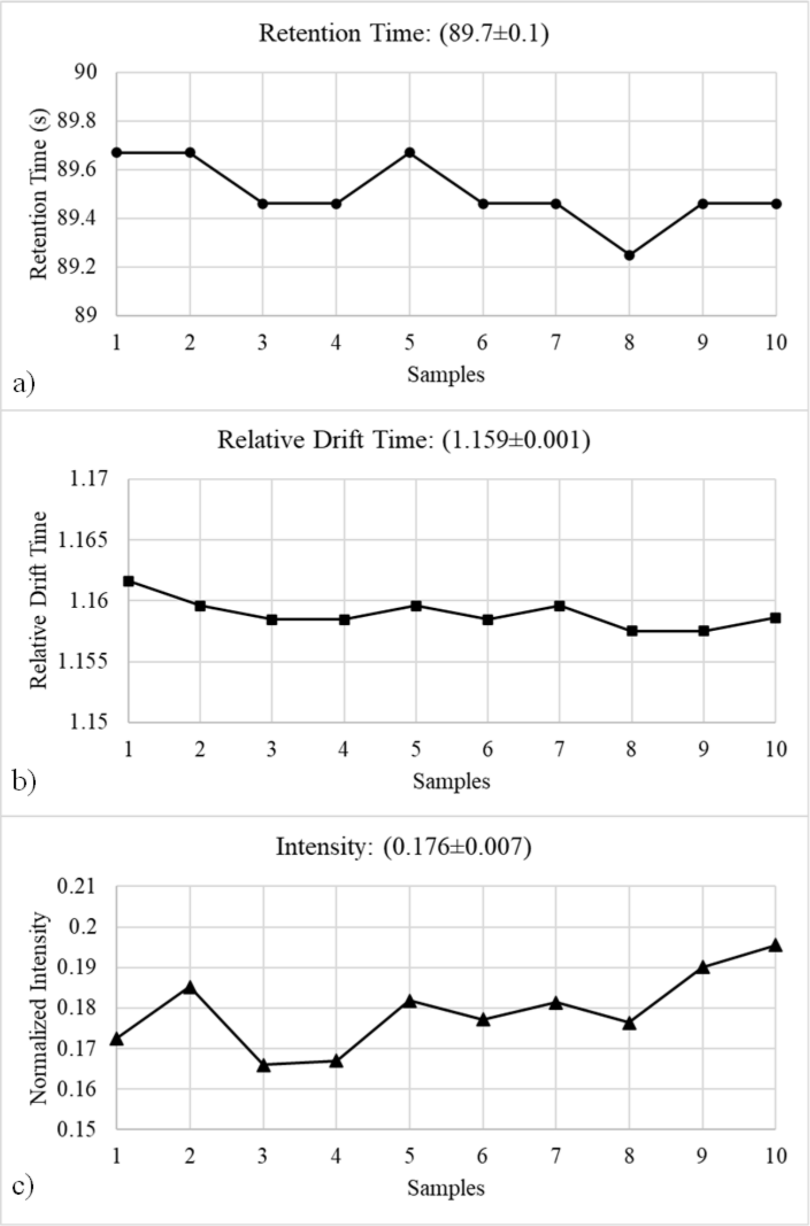


Figure 40 - Repeatability graph for the retention time (a), the relative drift time (b), and the normalised intensity (c) for ten samples of a randomly selected analyte (dimer of acetone) analysed with the GC-IMS.

4.6.2 VOCs Identification for the Painting Line Monitoring

The values of drift time (s), retention (ms) time, and intensity (V) of each analyte were exported from all the spectra. Among monomers, dimers, and even some trimers, 33 peaks were detected. Their identification consisted of crosschecking the exported drift and retention times with the values of the developed database of VOCs. It was possible to successfully identify 22 peaks among the 33 detected. These 22 peaks correspond to 15 VOCs. Table 15 summarizes the information regarding the VOCs detected from nine locations. It contains the retention time (s), RIP relative drift time and the normalised ion mobility constant (K_0) with the indication of monomer, a dimer, or a trimer, as well as the CAS number for all identified compounds. The unidentified peaks are marked with the acronym N.I. (not identified).

Table 15 - Detected in the indoor air samples GC-IMS peaks and identified VOCs. Results for each peak are expressed as a mean value of its retention time (in seconds), and RIP relative drift time based on ten replicate measurements (n=10) [9].

#	VOCs	CAS Number	Retention Time (s)	Drift Time (RIP Relative)	Note
1	Ethanol	64-17-5	73.7	1.055	Monomer
			74.4	1.150	Dimer
2	2-Propanol	67-63-0	84.3	1.104	Monomer
			81.3	1.206	Dimer
			80.9	1.256	Trimer
3	Propanal	123-38-6	84.4	1.058	Monomer
4	Acetone	67-64-1	89.7	1.159	Dimer
			88.7	1.207	Trimer
5	1-Propanol	71-23-8	95.8	1.128	Monomer
6	Butanal	123-72-8	113.2	1.130	Monomer
			113.3	1.334	Dimer
7	Isobutanol	78-83-1	118.6	1.184	Monomer
8	Acetic Acid	64-19-7	119.3	1.060	Monomer
9	Benzene	71-43-2	119.4	1.120	Monomer
10	2-Butanone	78-93-3	123.5	1.081	Monomer
			123.2	1.299	Dimer
11	1-Butanol	71-36-3	143.2	1.203	Monomer
			140.4	1.425	Dimer
12	Pentanal	110-62-3	165.6	1.206	Monomer
13	Propanoic Acid	123-38-6	170.6	1.116	Monomer
14	Hexanal	66-25-1	252.0	1.285	Monomer
15	2-Hexanone	107-87-9	261.3	1.215	Monomer

16	N.I.	-	74.0	1.106	-
17	N.I.	-	96.6	1.056	-
18	N.I.	-	103.1	1.059	-
19	N.I.	-	119.3	1.043	-
20	N.I.	-	123.0	1.227	-
21	N.I.	-	125.9	1.277	-
22	N.I.	-	135.0	1.197	-
23	N.I.	-	139.9	1.340	-
24	N.I.	-	144.9	1.140	-
25	N.I.	-	169.9	1.132	-
26	N.I.	-	261.6	1.706	-

Considering the main reviewed VOCs emitted by both water-based and solvent-based coatings, it was possible to find some matchings among the expected and the identified VOCs, in specific, the compounds 1 (ethanol), 4 (acetone), 5 (propanol), 9 (benzene) and 10 (2-butanone).

Regarding eventual health conditions provoked by exposure to these analytes, ethanol, propanol, acetone and 2-butanone, for instance, are known for causing extreme irritation and burns in the skin, eyes, nose and throat. Several other VOCs can also cause reactions of irritation in diverse tissues, namely 2-propanol, propanal, isobutanol or acetic acid. Compounds like propanol, 2-butanone, butanal, acetic acid or isobutanol can be responsible for dizziness, weakness, headaches, breathlessness, chest constriction and loss of consciousness. Acetone, 2-propanol and butanol can even induce an anaesthetized state, in cases of long-term exposure. Benzene, in its turn, can lead to dizziness, weakness, headaches, breathlessness, nausea, vomiting and, in extreme cases, coma and possible death. Concisely, all the identified VOCs can have serious impacts on employees' health. Deeper studies are already being prepared in order to increase the list of identified compounds and evaluate eventual pathologies promoted by those VOCs [349, 350, 351].

4.6.3 VOCs Quantification for the Painting Line Monitoring

The third value of the GC-IMS spectra i.e., the intensity, was used for plotting intensity profiles for each location. The intensities of each compound's monomer, dimer and trimer were summed, and its average intensity was calculated for all 10 replicates. This procedure was repeated for all 26 detected analytes. Subsequently, the intensity levels of each location were normalised against the outdoor air intensity levels. To do so, the ratio between the average intensity of each VOC, for each location, and the respective intensity value in outdoor air samples was calculated. Thus, the intensity of each compound in outdoor air samples is taken as the zero of reference meaning that if a compound has a relative intensity value above the reference zero, its intensity is higher in that location than it is outdoors. On the other hand, if that compound has an intensity value under zero, for a specific location, its intensity is lower in this location than it is outdoors. As an example, if ethanol has a relative intensity of 2 in some random location, this means that its intensity and, consequently, its concentration is two times higher in this location than it is outdoors. The relative intensity profiles were plotted and arranged in five groups considering the characteristics and the proximity between each location.

The intensity levels against the outdoor intensity, for the 26 VOCs existing in the phosphatising bath and cataphoresis bath stages are represented in Figure 41 a) and b), respectively. As mentioned, both these contiguous stages consist of immersing the car bodies in large reservoirs of chemicals for purposes of metal and surface preparation so, the presence and intensity of VOCs in these locations are relevant topics.

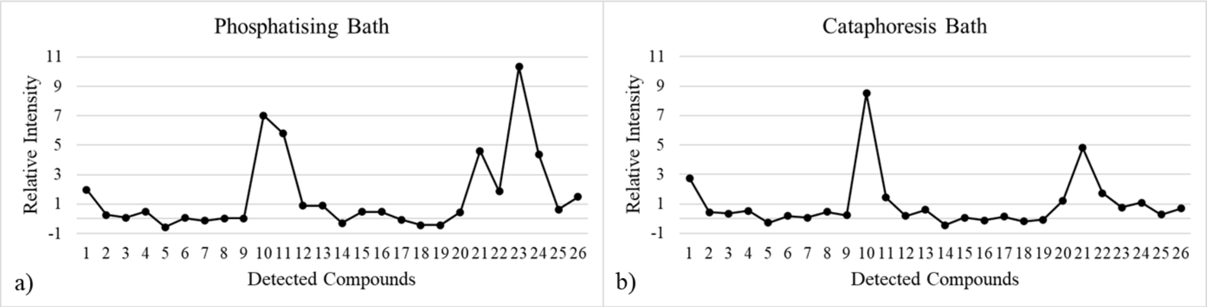


Figure 41 - Relative intensity profiles achieved for a) phosphatising bath and b) cataphoresis bath locations [9].

It is possible to discern several similarities and some differences between the profiles. Regarding the similarities, the VOCs 2 (2-propanol) to 9 (benzene) and 12 (pentanal) to 20 (not identified) present, for both profiles, intensity levels that are very close to the outdoor levels since they barely diverge from the zero of reference, meaning that they do not constitute a threat to the employees' health. Besides that, there are some analytes whose intensities make them of special interest. Compound 10 (2-butanone), for example, is seven and nine times more intense in a) and b), respectively, than it is in the outdoor air. Compound 21 (not identified) also presents similar behaviour in both locations. It is five times more intense in the indoor air samples than it is in the outdoor samples. These elevated intensities prove that not only there is a very efficient VOCs-emitting source in both phosphatising and cataphoresis baths, but also, that the two analytes must be carefully monitored and controlled.

There are some analytes whose elevated intensities are only visible in the profile of the phosphatising bath, namely compounds 11 (butanol), 23 (not identified) and 24 (not identified). These analytes are eleven, five and three times more intense in the phosphatising bath location than they are outside. For this reason, they have to be identified and their concentration levels must be assessed in order to evaluate the eventual impacts on the employees' health. If proven necessary, the extraction systems have to be modified and improved.

The processes of primer and ink application to the metal surface of the car body are also contiguous and the central stages of the entire painting line. Both of them are performed by robotic arms that eject a coating cloud against the metal surface. Figure 42 represents the relative intensity profiles for a) primer and b) ink application.

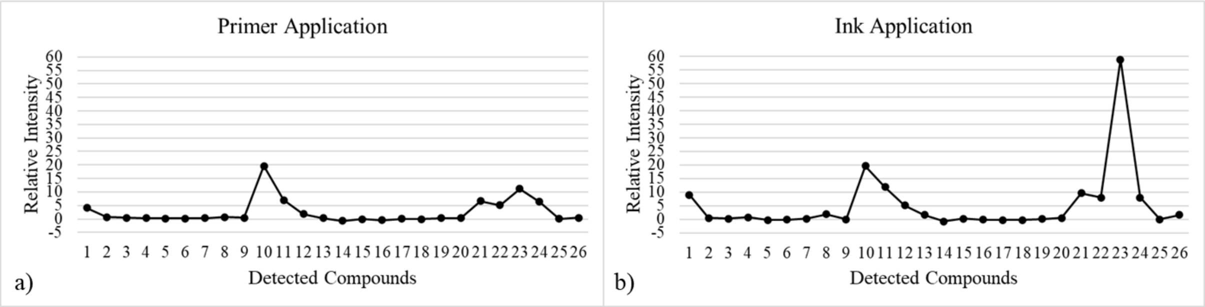


Figure 42 - Relative intensity profiles achieved for a) primer application and b) ink application locations [9].

Differently from the previous group of profiles, here, the differences are less evident. It is clear that most volatile organic compounds have relative intensities of around zero, which means that the intensities of these VOCs inside the primer and ink application chambers are very similar to the intensities of the same VOCs in outdoor air samples. This fact can mean that the extraction systems have some positive effects on maintaining the air quality inside the chamber. Despite the controlled VOCs, both profiles have some compounds whose intensity is significantly elevated.

Compound 10 (2-butanone) is twenty times more intense in both primer and ink application locations than it is in the outdoor environment. Similarly, VOC 11 (1-butanol) also has a considerably elevated intensity, specifically, seven and eleven times higher for a) and b), respectively, than for the outdoor air. Compounds 21 (not identified), 22 (not identified) and 24 (not identified) present the same relative intensities in both a) and b) locations; they are five times more intense in both primer and ink application than they are in the outdoor air. All these analytes must be carefully controlled, and their real concentration levels have to be assessed to preserve the integrity of the employees' health.

A final analyte, compound 23 (not identified), presents a relative intensity close to sixty, meaning that this compound is sixty times more intense in the interior of the ink application chamber than it is in the outdoor air samples. Unfortunately, its identification was not achieved during the development of this work, nonetheless, since its concentration in the air is, potentially, very elevated, it is a mandatory topic to qualitatively and quantitatively assess further details about the analyte and understand what risks and consequences the compound may represent to the workers of the car factory painting line.

Figure 43 represents the relative intensity profiles for the stages of a) varnish application and b) wax application of the painting line. As in the previous two groups of profiles, these two locations are also adjacent so, their comparison is relevant.

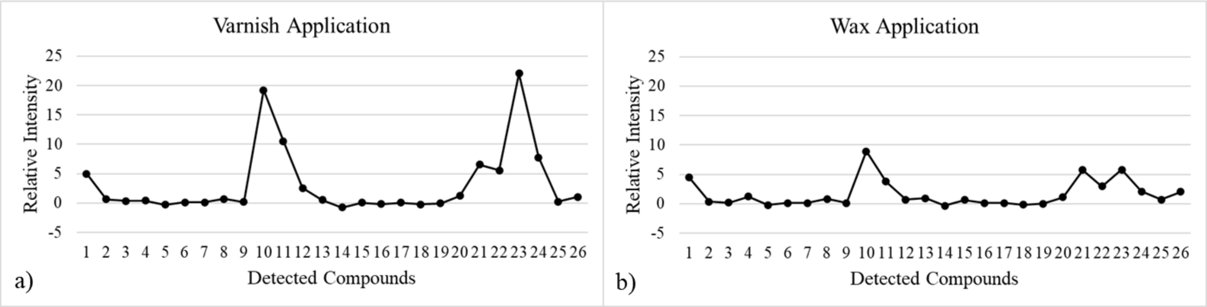


Figure 43 - Relative intensity profiles achieved for a) varnish application and b) wax application locations [9].

As seen in previous scenarios, most of the volatile organic compounds have a relative intensity of around zero. For example, compounds 5 (1-propanol), 6 (butanal), 7 (isobutanol), 8 (acetic acid), and 9 (benzene) have intensities levels close to their intensities in outdoor environments. These are positive results since the compounds do not characterize a significant risk to the health of the workers.

The analytes 1 (ethanol), 21 (not identified), and 22 (not identified) have relative intensity levels of five. Similarly, compound 24 (not identified) presents a relative intensity of seven in the varnish application location, meaning that it is seven times more intense in this indoor location than it is in the outdoor air and, depending on its real concentration, may be potentially hazardous to the employees' health.

Regarding the most intense analytes, three VOCs must be highlighted. Compound 11 (1-butanol) reaches levels of the relative intensity of five and ten times for the locations of wax application and varnish application, respectively. Compound 10 (2-butanone) behaves similarly. Its relative intensity reaches up to ten and twenty for wax and varnish applications, respectively. Finally, the most intense analyte is compound 23 (not identified). Despite having a lower relative intensity in the location of wax application, it is twenty-two times more intense in the indoor air of the varnish application location than it is outside.

All the aforementioned values are worthy of attention so, the identification of the unidentified compounds and the quantification of all 26 analytes are mandatory tasks that must be done immediately.

The factory ceiling is the location where the main air extraction systems and pipelines are installed, in this way, it was expected to find some diversity of volatile organic compounds in this area. Figure 44 represents the relative intensity profile for the measurements performed near the mentioned systems.

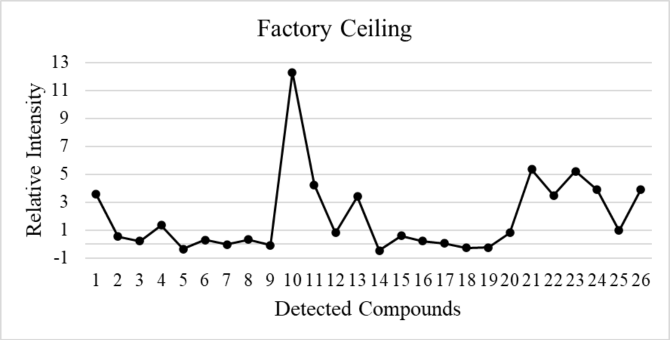


Figure 44 - Relative intensity profiles achieved for factory ceiling location [9].

Curiously, the relative intensity levels were not as elevated as expected. Notwithstanding, some analytes still deserve proper and careful attention. Compound 10 (2-butanone), for instance, is the analyte with higher relative intensity; it is almost thirteen times more elevated in air samples collected near the ceiling than it is in outdoor air samples.

The analytes 11 (1-butanone), 21 (not identified) and 23 (not identified) have relative intensities of 5. Ethanol (compound 1), propanoic acid (compound 13), and the VOCs 22 (not identified), 24 (not identified), and 26 (not identified), in their turn, have relative intensities of around 3. All the mentioned analytes present considerably elevated relative intensity levels, in this way, their eventual impacts on public health must be deeply studied.

Finally, the last analysed location was the office of the painting line manager. As mentioned, this room is independent and isolated from the painting line so, it was expected to find a distinct behaviour of the VOCs' relative intensity. Figure 45 represents the mentioned profile.

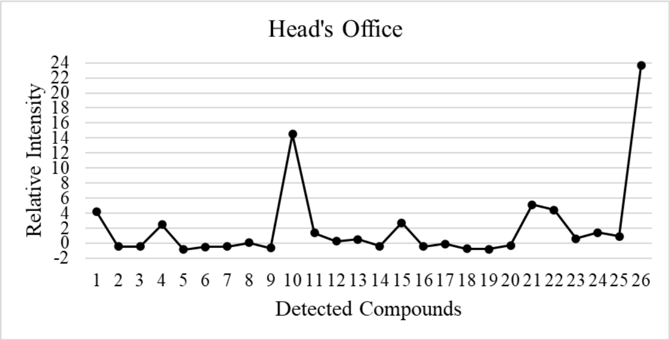


Figure 45 - Relative intensity profiles achieved for head office location [9].

The more relevant volatile organic compounds in this profile are compounds 10 (2-butanone) and 26 (not identified), which are around 14 and 24 times more intense in the interior of the office than they are in the outdoor samples. Compounds 1 (ethanol), 21 and 22 (not identified) have relative intensities between 4 and 6, and compounds 4 (acetone) and 15 (2-hexanone) are 2 times more intense in the indoor air than outside. These values cannot be ignored so, the addressed VOCs must be deeply assessed in order to evaluate eventual risks for workers in both scenarios of short- and long-term exposure.

To understand the real hazardousness of the detected analytes and, consequently, assess the real impact on the health of the employees, it is important to know the levels of concentration existent in the analysed air samples. To do so, the calibration protocol previously developed was applied to the data, in specific, to 2-hexanone. Once applied Equation 32 to the intensity levels detected by GC-IMS, it was possible to quantify the levels of 2-hexanone existent in the indoor air throughout all the studied locations. Table 16 summarizes the concentration levels of this analyte in parts per billion (ppb_v).

Table 16 - Average levels of concentration and respective standard deviation of 2-hexanone throughout the locations studied at the car factory painting line [9].

Locations	**Concentration (ppb_v)**	**Standard Deviation (ppb_v)**
Phosphatising Bath	24.9	0.2
Cataphoresis Bath	24.6	0.1
Primer Application	24.7	0.1
Ink Application	25.6	0.2
Varnish Application	24.7	0.1
Wax Application	24.9	0.1
Factory Ceiling	25.2	0.1

Head’s Office	25.1	0.2

NIOSH defines the TLV of 2-hexanone at 5 ppm_v [113], so, considering the values above, it is safe to say that the indoor levels of this compound are below the recommended level for most of locations. These values lead to the conclusion that 2-hexanone does not represent a risk to the employees of the painting line who are chronically exposed to it. Interestingly, all the studied locations exhibit similar levels of 2-hexanone. This fact was already verified previously, in the graphs of the intensity levels, and proves that the presence of 2-hexanone in the composition of the indoor air of the painting line is not directly related to the type of work developed at the location or, on the other hand, it is present due to a VOCs-emitting source present throughout the entire painting line.

Besides the apparent harmlessness of 2-hexanone, it is important to state that 2-hexanone presented levels of intensity in indoor environments not higher than 2 or 3 times its levels outdoors, but other analytes presented relative intensity levels as high as 10, 20, and even 60 times higher than their levels in the outdoor air samples. This fact might mean that the concentrations of these analytes can equally be considerably higher than the 2-hexanone concentrations, which proves the necessity of calibrating all the remaining detected analytes to fully characterize their hazardousness to human health.

In summary, this work focused on studying the indoor air quality of eight locations of a car factory painting line in regard to the composition in VOCs. A total of 80 three-dimensional spectra from the eight main stages of the painting line were analysed. Among the 33 detected peaks corresponding to 26 analytes, 15 volatile organic compounds were successfully identified. Considering the information gathered about the expected VOCs to be emitted from primer, ink, varnish, and other chemical-based solutions used during the work shifts, it was possible to conclude that five of the 15 identified VOCs belong to the list of anticipated VOCs, namely, ethanol, acetone, propanol, benzene, and 2-butanone. Some of these compounds have been described in the literature as directly responsible for several health conditions and pathologies like eye allergies, skin irritation, liver and kidney conditions, and even lung and other types of cancers. In addition, the remaining identified analytes are equally known for causing several health conditions in both short- and long-term exposure scenarios.

Relative intensity profiles were plotted for all eight analysed locations. For this, the intensity of a compound’s monomer, dimer, and trimer were summed and then the intensity values relative to the outdoor air samples were estimated, i.e., the intensity values were normalised in relation to the outdoor levels. This approach enabled the authors to realize that some VOCs were 5, 10, 25, and even 60 times more intense in the indoor air of the studied environments, specifically, inside the painting line stages, than they were in the outdoor air samples.

Concentration levels were calculated for one of the detected analytes, 2-hexanone, by applying a previously developed logarithmic model developed for calibrating the relationship between the levels of intensity detected by the GC-IMS and the concentration of the analyte in the original sample. The quantification of 2-hexanone was accomplished in the range of tens of part-per-billions, which demonstrates that at least this analyte does not represent a direct threat to the health of the employees.

GC-IMS and the overall sampling procedure, which were used for the first time ever in a car factory painting line, proved to be suitable for indoor air analysis and on-line VOCs detection in real industrial scenarios. Its high selectivity, sensitivity, and analytical flexibility allied with its portability, and *in-loco* measurement capacity characterize GC-IMS as the most adequate technique for the scope and goals of this project.

Disclaimer: The information included in this chapter was originally published in the paper: P. C. Moura, F. Santos, C. Fujão, V. Vassilenko. In Situ Indoor Air Volatile Organic Compounds Assessment in a Car Factory Painting Line. *Processes*, 11, 2259, 2023. https://doi.org/10.3390/pr11082259 [9].

4.7 Analysis of the Coatings

Once concluded the assessment of the indoor air quality and the identification of most compounds existent in the composition of the air, it was relevant to evaluate all the potential emitting sources and analyse the most prominent ones in regard to their composition. In this way, all the solutions and materials existent at the painting line were considered and studied regarding their potential contribution to the emissions of VOCs. Finally, it was defined that the most relevant VOCs-emitting sources correspond to the coating solutions used during the coating process [6].

Considering all the information addressed, this study aimed to fully characterize the emissions of all the coatings used in the painting line of the factory, specifically, their content in VOCs, in order to cross-check the results with the VOCs previously detected in the air of the factory. The overall goal was to deepen the knowledge on the coatings-borne VOCs that might be present in the indoor air and for the development of further studies for later assessment of their real impact on the employees' health. The focus of the study was given to the emissions of the coating and not to their original composition since some of the compounds used in the manufacturing of the coatings are not emitted to the atmosphere, i.e., they are not a direct threat to the employees.

A GC-IMS device was employed, allowing the authors to accurately detect and identify all the volatile organic compounds in the headspace emitted by the coatings. A total of 22 distinct samples, among primers, basecoats and clearcoat, were considered for this work, namely, four primers, 17 basecoats and one clearcoat. The detected compounds were, then, identified with the previously developed database of VOCs. They were not quantified since the concentration emitted by the solutions does not exactly correspond to the concentration present in the indoor air which can, in fact, affect the employees' health.

4.7.1 GC-IMS Spectra

Since a dual polarity GC-IMS was employed during the study, a total of 440 spectra, 220 positive polarity spectra and 220 negative polarity spectra, were collected during the measurements. The negative polarity spectra, however, did not include any relevant data regarding the existence of analytes, in this way, they were disregarded from the study. Nonetheless, this fact leads to an evident conclusion; none of the coatings employed in the car factory painting line emits or has in its constitution analytes that originate negative ions once ionised. Figure 47 illustrates three-dimensional positive polarity spectra for three arbitrarily selected samples, in specific, a spectrum of a a) primer, a b) basecoat, and a c) clearcoat. Figure 46 illustrates a magnified version of Figure 47.

Just by visually analysing the three spectra above, it is possible to see the evident differences in the content of the three types of coating solutions in terms of VOCs. All spectra are considerably populated with compounds, which denotes the complexity of the matrices under study. In addition, also proves that the coatings are VOCs-rich solutions and, consequently, responsible for their emissions into the indoor air of the car factory painting line [6].

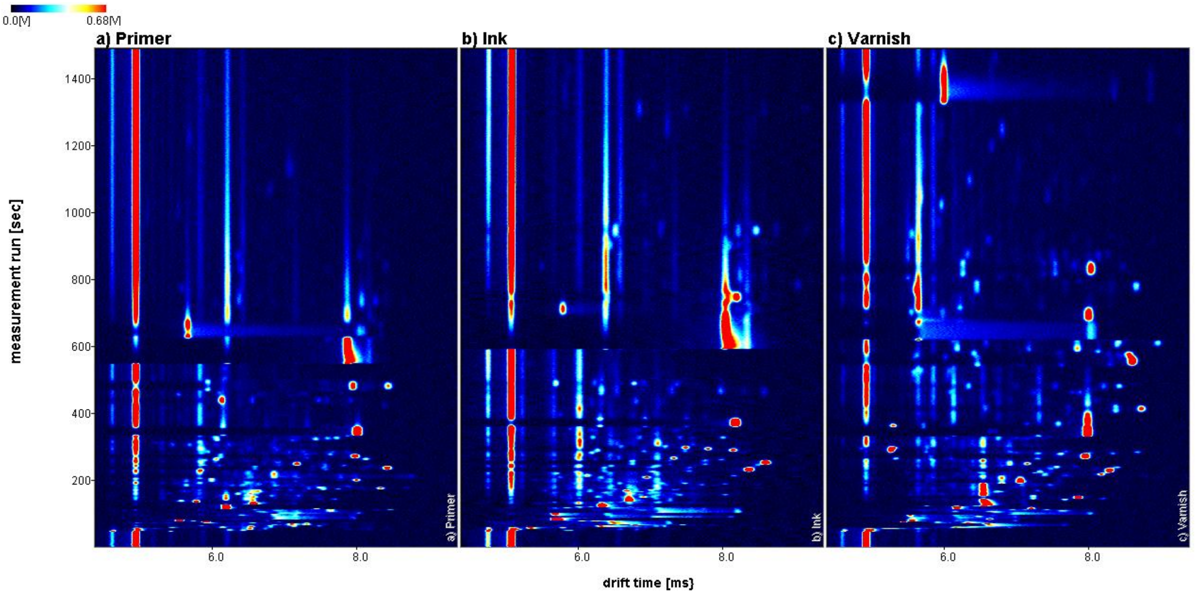


Figure 47 - Three-dimensional positive polarity spectra registered for arbitrary samples of a) primer, b) basecoat and c) clearcoat [6].

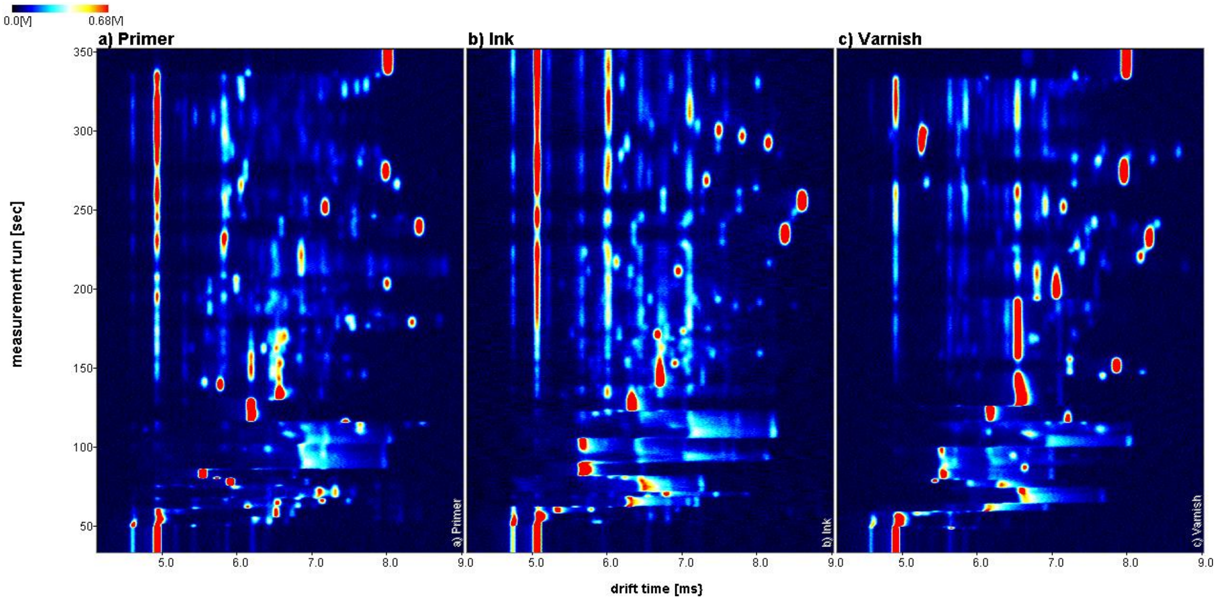


Figure 46 - Magnified view of the three-dimensional positive polarity spectra registered for arbitrary samples of a) primer, b) basecoat and c) clearcoat [6].

4.7.2 Repeatability

Aiming to assess the lack of variability of the data collected with the GC-IMS device, repeatability graphs were plotted. To do so, the intensity of all the detected analytes was summed for each one of the 10 repetitions, resulting in the total intensity of each spectrum.

These values were, then, normalised and plotted in a line chart for further analyses. Figure 48 illustrates the repeatability of the data throughout the 10 spectra of an arbitrarily selected coating. The average value for the normalised intensity and the respective average variation for this dataset are (0.87 ± 0.01), which proves the repeatability of the data and, consequently, the suitability of GC-IMS for such studies. The repeatability graphs of the remaining 21 coatings were not included for logistic reasons but similar variability results were attained for all of them.

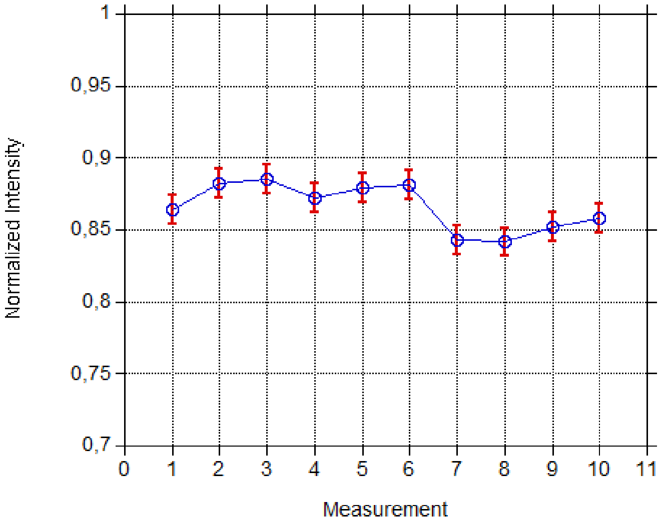


Figure 48 - Variability line chart for an arbitrarily selected coating. The average value for the normalised Intensity and the respective average variation for the data set here included are (0.87 ± 0.01) [6].

4.7.3 Identification of VOCs from the Coatings

It is relevant to reinforce that, for all the data processing included in this chapter, 10 replicas were performed per type of coating. It is equally important to mention that only the analytes common to all those 10 spectra were considered for the study, the remaining peaks were interpreted as sporadic contaminations and disregarded. The identification of the detected analytes was accomplished, as addressed, through the database of compounds exclusively developed for this study.

4.7.3.1 Primers

As previously mentioned, four different primers are used during the coating process of the car factory painting line. From the 10 repetitions performed with the GC-IMS for each type of primer, a total of 84, 99, 95 and 86 analytes were detected respectively for the primers Light Red, Light Grey, Mid Grey and Anthracite. Among monomers, dimers and even trimers, it was possible to use the exclusively developed database to respectively identify 29, 38, 28 and 29 analytes. These analytes correspond to a total of 26 volatile organic compounds. Table 17 summarises all the VOCs identified among the analytes emitted by each kind of primer. Further information regarding the identification data is given in due time but it is relevant to state that the VOCs are listed in ascending order of retention time.

Table 17 - Volatile organic compounds identified per type of primer, listed by ascending order of retention time [6].

Volatile Organic Compounds	**Primers**			
	Light Red	**Light Grey**	**Mid Grey**	**Anthracite**
4-Fluoroaniline		X	X	X
Ethanol	X	X	X	X
Isopropanol	X	X	X	X
Tert-Butyl Methyl Ether		X		
Methyl Acetate	X	X	X	X
1-Propanol	X			X
2-Butanol	X	X	X	X
Acetone	X	X	X	X
Sec-Butylamine		X		
Tetrahydrofuran				X
1-Butanol	X	X	X	
Ethyl Acetate	X	X	X	X
3-Methyl-2-Butanol		X		
2-Butanone	X	X	X	X
3-Methyl-1-Butanol			X	
1,4-Dioxane	X	X	X	
1-Pentanol		X		X
Hexane		X		
Butylamine	X		X	
2-Hexanol		X	X	X
Butyric Acid	X	X	X	
2,4-Dimethylpentane	X	X		X
3-Methyl-2-Pentanone	X	X		
Butyl Acetate	X	X	X	X

1-Octanol	X	X	X	X
3-Heptanone	X			X

By consulting the previous table, several facts can be noticed. The four primers contain a total of nine common volatile organic compounds, namely ethanol, isopropanol, methyl acetate, 2-butanol, acetone, ethyl acetate, 2-butanone, butyl acetate and 1-octanol. On the other hand, six VOCs are present in the composition of just one of the primers, namely *tert*-butyl methyl ether, *sec*-butylamine, 3-methyl-2-butanol and hexane for the primer light grey, tetrahydrofuran for anthracite, and 3-methyl-1-butanol for mid grey. Due to their scarcity, they can be seen as sporadic contaminations rather than constituent compounds. As expected, alcohol-based compounds, with a total of 10 identified analytes, represent the largest group of VOCs. Further considerations regarding the identified VOCs are addressed in due time.

4.7.3.2 Basecoats

Since the negative mode spectra did not contain relevant information regarding the emission of the coatings, a total of 170 positive mode spectra were considered during the analysis of this dataset. A significantly elevated number of analytes were detected throughout all the samples. Table 18 summarizes the number of analytes detected throughout the 17 colours of coatings, the number of identified analytes among the detected ones, and the corresponding number of identified VOCs considering monomers, dimers and even some trimers.

Table 18 - Number of analytes detected throughout the 17 colours of coatings, number of identified analytes among the detected ones, and the corresponding number of identified VOCs considering monomers, dimers and even some trimers [6].

Basecoat	Nº of Detected Analytes	Nº of Identified Analytes	Nº of Identified VOCs
Ascot Grey	77	19	11
Atlantic Blue	88	24	13
Beech Grey	57	21	12
Black Oak	68	19	11
Deep Black	63	21	12
Indium Grey	76	27	15
Kings Red	86	34	18

Lapiz Blue	68	22	11
Moonstone Silver	63	25	13
Petroleum Blue	87	26	16
Pure White	78	23	11
Pyrite Silver	61	22	12
Ravenna Blue	92	28	15
Reflex Silver	75	35	19
Romance Red	73	32	16
Urano Grey	84	30	15
White Silver	97	30	15

Considering all 17 types of coatings, 37 volatile organic compounds were identified overall. Table 19 summarizes all the VOCs identified among the analytes detected from the emissions of each coating. For aesthetical reasons, the names of the coatings were replaced by numbers, nonetheless, the correspondence between the names and numbers is provided in the caption of the table.

Table 19 - Identified volatile organic compounds per type of coating, listed by ascending order of retention time (1: Ascot Grey, 2: Atlantic Blue, 3: Beech Grey, 4: Black Oak, 5: Deep Black, 6: Indium Grey, 7: Kings Red, 8: Lapiz Blue, 9: Moonstone Silver, 10: Petroleum Blue, 11: Pure White, 12: Pyrite Silver, 13: Ravenna Blue, 14: Reflex Silver, 15: Romance Red, 16: Urano Grey, 17: White Silver) [6].

Volatile Organic Compounds	**Basecoat**																
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
4-Fluoroaniline	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ethanol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Isopropanol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Triethylamine	X		X	X	X	X		X	X	X		X	X	X			
Tert-Butyl Methyl Ether						X	X	X	X	X	X	X		X		X	
Methyl Acetate	X	X	X	X	X	X	X				X		X	X	X		
1-Propanol		X											X	X	X		
2-Butanol		X								X			X	X	X	X	

Acetone	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tetrahydrofuran					X	X	X		X		X	X					
1-Butanol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ethyl acetate	X					X	X			X	X		X	X			X
3-Methyl-2-Butanol															X		
2-Pentanol														X		X	
3-Pentanol		X															
2-Butanone	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Propionic Acid										X				X			
Methylisobutyrate									X	X							
Toluene																X	
1,4-Dioxane		X					X		X								X
Propyl Acetate			X														
1-Pentanol							X						X	X	X		X
3-Pentanone			X	X			X	X									
2-Pentanone									X	X		X				X	
Hexane		X	X	X	X	X	X			X			X				X
Butylamine															X		
2-Hexanol														X		X	
2,4-Dimethylpentane													X	X		X	X
4-Methyl-2-pentanone															X		X
Octyl Acetate		X															X
Butyl Acetate	X				X	X	X	X		X	X	X	X	X	X	X	X
1-Hexanol			X				X										
2-Hexanone			X			X	X					X			X		
1-Octanol				X		X		X							X	X	
2-Phenoxyethanol	X						X			X				X			
3-Ethyltoluene					X												X
2-Heptanone									X								

Further considerations regarding the identified analytes are addressed below, nonetheless, some evident conclusions can be drawn by analysing Table 19. Six volatile organic compounds are present in the constitution of all the 17 types of coatings, namely 4-fluoroaniline, ethanol, isopropanol, acetone, 1-butanol and 2-butanone meaning that they belong to the base mixture used for manufacturing all inks. Another six are solely present in the samples of one coating, namely, 2-heptanone for moonstone silver, butylamine and 3-methyl-2-butanol for romance red, propyl acetate for beech grey, toluene for urano grey and 3-pentanol for atlantic blue. As for the results attained during the identification of VOCs in the samples of primers, alcohol-based VOCs are the most common analytes (12 VOCs). Additional remarks will be promptly approached.

4.7.3.3 Clearcoat

Among monomers, dimers and even some trimers of each compound, 87 analytes were detected throughout the 10 analyses performed with varnish samples. From these, 30 analytes were accurately identified with the developed database, totalizing 16 volatile organic compounds. The VOCs identified in the varnish samples are condensed in Table 20.

Table 20 - Volatile organic compounds identified among the analytes emitted by the clearcoat [6].

Volatile Organic Compounds - Clearcoat			
4-Fluoroaniline	2-Butanol	2-Butanone	Butyl Acetate
Ethanol	Acetone	Hexane	o-Xylene
Isopropanol	1-Butanol	Ethylbenzene	2-Phenoxyethanol
Methyl Acetate	Ethyl Acetate	p-Xylene	2-Heptanone

Most of the analytes identified during the analyses of varnish samples are common to both primers and basecoats, nonetheless, three VOCs seem to be varnish-exclusive. They are ethylbenzene, p-xylene and o-xylene. Considering the 16 compounds, five belong to the family of alcohols, three to the esters family, and two to the ketones family. Additional considerations are addressed promptly.

4.7.3.4 Identification Data

As addressed throughout this chapter, 26, 37 and 16 volatile organic compounds were respectively identified during the analyses of primers, basecoats and clearcoat. Since some of these are common to several samples, a total of 45 compounds were accurately identified throughout the entire study using the exclusively developed database. Table 21 condenses the identification data for all VOCs, namely their retention time, drift time, ion mobility constant (*K*) and normalised ion mobility constant (K_0). The VOCs are listed in ascending order of retention time.

Table 21 - Identification data of every volatile organic compound identified during the entire study, namely their retention time, relative drift time, ion mobility constant (*K*) and normalised ion mobility constant (K_0) [6].

Analyte	**CAS Number**	**Retention Time (*s*)**	**Drift Time (RIP Relative)**	**Note**
4-Fluoroaniline	371-40-4	53	0.937	Monomer
			1.047	Dimer
Ethanol	64-17-5	58	1.047	Monomer
			1.143	Dimer
Isopropanol	67-63-0	62	1.099	Monomer
			1.247	Dimer
Triethylamine	121-44-8	64	1.109	Monomer
			1.244	Dimer
Tert-Butyl-Methyl Ether	1634-04-4	70	1.130	Monomer
			1.360	Dimer
Methyl Acetate	79-20-9	83	1.046	Monomer
			1.198	Dimer
1-Propanol	71-23-8	83	1.118	Monomer
			1.276	Dimer
2-Butanol	78-92-2	84	1.161	Monomer
			1.351	Dimer
Acetone	67-64-1	87	1.022	Monomer
			1.124	Dimer
Sec-Butylamine	13952-84-6	101	1.335	Monomer
Tetrahydrofuran	109-99-9	102	1.077	Monomer
			1.236	Dimer
1-Butanol	71-36-3	109	1.190	Monomer
			1.408	Dimer
Ethyl Acetate	141-78-6	110	1.107	Monomer

			1.348	Dimer
3-Methyl-2-Butanol	598-75-4	115	1.219	Monomer
			1.451	Dimer
2-Pentanol	6032-29-7	125	1.230	Monomer
			1.473	Dimer
3-Pentanol	584-02-1	126	1.220	Monomer
			1.443	Dimer
2-Butanone	78-93-3	127	1.076	Monomer
			1.255	Dimer
Propionic Acid	79-09-4	133	1.121	Monomer
			1.302	Dimer
Methylisobutyrate	547-63-7	147	1.160	Monomer
			1.445	Dimer
3-Methyl-1-Butanol	123-51-3	158	1.259	Monomer
			1.527	Dimer
Toluene	108-88-3	166	1.025	Monomer
			1.107	Dimer
1,4-Dioxane	123-91-1	171	1.152	Monomer
			1.332	Dimer
Propyl Acetate	109-60-4	185	1.175	Monomer
			1.485	Dimer
1-Pentanol	71-41-0	188	1.265	Monomer
			1.543	Dimer
3-Pentanone	96-22-0	198	1.127	Monomer
			1.366	Dimer
2-Pentanone	107-87-9	205	1.135	Monomer
			1.378	Dimer
Hexane	110-54-3	210	1.135	Monomer
			1.381	Dimer
Butylamine	109-73-9	226	1.385	Monomer
2-Hexanol	626-93-7	232	1.300	Monomer
			1.595	Dimer
Butyric Acid	107-92-6	238	1.184	Monomer

			1.417	Dimer
Ethylbenzene	100-41-4	284	1.087	Monomer
2,4-Dimethylpentane	108-08-7	290	1.190	Monomer
			1.489	Dimer
4-Methyl-2-Pentanone	108-10-1	291	1.191	Monomer
			1.489	Dimer
Octyl Acetate	112-14-1	294	1.220	Monomer
			1.567	Dimer
3-Methyl-2-Pentanone	565-61-7	308	1.185	Monomer
			1.491	Dimer
p-Xylene	106-42-3	309	1.073	Monomer
			1.169	Dimer
Butyl Acetate	123-86-4	357	1.248	Monomer
			1.624	Dimer
1-Hexanol	111-27-3	374	1.341	Monomer
			1.673	Dimer
o-Xylene	95-47-6	387	1.079	Monomer
			1.163	Dimer
2-Hexanone	591-78-6	407	1.205	Monomer
			1.513	Dimer
1-Octanol	111-87-5	606	1.259	Monomer
			1.603	Dimer
2-Phenoxyethanol	122-99-6	622	1.261	Monomer
			1.602	Dimer
3-Ethyltoluene	620-14-4	645	1.262	Monomer
			1.603	Dimer
3-Heptanone	106-35-4	707	1.253	Monomer
			1.605	Dimer
2-Heptanone	110-43-0	849	1.276	Monomer
			1.639	Dimer

Considering all the compounds detected in the emissions analysed from the samples of coatings, a total of 45 volatile organic compounds were accurately identified with the database exclusively developed for this doctoral project. The identified analytes include 14 alcohol-based analytes, nine ketones, six esters, five aromatic hydrocarbons, four amines, three ethers, two alkanes and two fatty acids.

As addressed in the introductory section of this dissertation, analytes from the family of alcohols have been largely used in the composition of all types of coatings, inks and paints, primers, and varnish, as solvents of the mixture. It was equally mentioned that solvent-based and water-based are still used in a comparable number of applications, despite the efforts to replace the first with the second type. The composition of water-based coatings is considerably less threatening to the environment and the human organism, nonetheless, they are still considerably rich in alcohols and other organic compounds [99, 91]. In fact, even in reduced quantities, the utilisation of alcohols in the composition of the coatings is essential for reducing the coatings' viscosity and time of drying [106], in this way, the existence of a significantly high number of alcoholic analytes in the composition of the coatings is justified.

Ketones and aromatic hydrocarbons are among the predominant compounds in the overall results, which may be justifiable by the fact that both these families of analytes have played a relevant role in the manufacturing of coatings [108]. Ketones like acetone, butanone, or 4-methyl-2-pentanone, and aromatic hydrocarbons like benzene, toluene, ethylbenzene and xylenes, commonly known as BTEX compounds, have been largely used as oxygenated solvents in the manufacturing of coatings for metal surfaces in detriment of the alcohol-based solvents. This substitution aims to reduce the hazardousness to the human organism and the environmental impacts of alcoholic VOCs [106, 84]. In addition, the employment of BTEX VOCs, specifically xylenes, contributes to the decrease of the coating's viscosity [355]. Besides that, it is relevant to reinforce that these analytes, and BTEX compounds in particular, are also considerably dangerous to human health [356]. All the aforementioned VOCs were detected and identified during this study, meaning that these results corroborate the information available in the literature.

Due to their relevant role in the properties of the coatings, ester-based analytes have been largely employed in their manufacturing for many years. The inclusion of these compounds in the composition of coatings enables the improvement of their performance, in specific, their evaporation rate, blush resistance, levelling properties, and viscosity [99, 84]. All these factors are of extreme relevance for the protection of the metal surface and for the durability of the coatings and ester-based VOCs have ensured such factors. Some of these VOCs, namely methyl, ethyl, butyl, propyl, and octyl acetate, were successfully detected and accurately identified during this study, which agrees with the results anticipated by the literature [357].

The identification of several amine-based VOCs among the analytes emitted by the coatings was expected. Due to its large applicability, mechanical properties and low cost, the car body is mostly made of metal, however, metal is susceptible to corrosion if exposed to natural conditions. Aiming to prevent or delay the corrosion process, amines like triethylamine and 4-fluoroaniline have been included as corrosion inhibitors in the composition of modern coatings specifically used for metal-made surfaces. Several scientific studies have been developed concerning the suitability of amines for the development of corrosion-resistant coatings so, the detection of these analytes in the coatings used in the car factory painting line was anticipated [358, 359, 360].

Three ethers were identified during the study here described. They are tert-butyl methyl ether, tetrahydrofuran and 1,4-dioxane. Ether-based compounds are commonly employed in the preparation of coatings due to their contribution to minimizing the drying time and to the solubility properties of the dyes [361, 362]. As with many other VOCs, their emission and consequent presence in the environment represent a potential hazard so, several studies have been developed aiming to eliminate or, at least, reduce the impact of such compounds in nature [363, 364].

Alkane-base analytes like hexane and 2,4-dimethylpentane [365, 101], and fatty acids like butyric and propionic acids [366], have been reported in a few studies regarding the emissions of automotive coatings and overall dyes, nonetheless, their role in the composition of these mixtures is not as deeply addressed as for the previously referred compounds.

By comparing the list of compounds detected during the *in-situ* analyses of the indoor air of the painting line with the compounds emitted by the coatings, one can easily find common compounds. They are, ethanol, isopropanol, 1-propanol, acetone, 1-butanol, 2-butanone, propionic acid, and 2-hexanone [6, 9]. As expected, a significative portion of them are alcohol-based compounds. At least 2 ketones were simultaneously detected in both the indoor air of the factory and the emissions of the coatings. These two groups of compounds are often used in the composition of coating solutions, as already mentioned. In addition, they are known for their direct contribution to the development of a vast range of pathologies that include simple conditions, like allergic reactions or pruritus, and health-threatening pathologies, like some forms of cancer, as previously addressed [367].

The results achieved during this study enabled to expand the knowledge regarding the emissions of the coatings employed in the painting line of the car factory and, since these products represent the largest and most relevant VOCs-emitting sources, define the compounds that must be targeted during further studies on the indoor air content and, later, on the potential risks to the employees. Further studies are mandatory to evaluate the overall consequences of long-term exposure to the employees' health, if any, aiming to comply with the goals of the overall project developed by the car manufacturer.

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4.8 Health Impacts

In order to understand and evaluate the potential impacts of a chronic exposure to the identified compounds on the health of the employees, a deep bibliographic search was conducted. The outcomes of this research were addressed and discussed throughout the entire chapter of Results and Discussion, nonetheless, it is important to address them in a dedicated section for purposes of clarity.

The VOCs identified in the air of the car factory painting line were, as already listed, ethanol, 2-propanol, propanal, acetone, 1-propanol, butanal, isobutanol, acetic acid, benzene, 2-butanone, 1-butanol, pentanal, propanoic acid, hexanal, and 2-hexanone. All these compounds are addressed in regard to their consequences to the human organism.

Ethanol is one of the most common compounds. It was detected and identified in every conducted study, including the GC-IMS suitability studies, and the car factory studies. Since it was detected in samples of the indoor air of the factory line, its consequences to human health deserve to be acknowledged. Nonetheless, it is important to state that its existence in a specific environment does not directly mean that it can be toxic to the exposed beings. In fact, ethanol even was detected at outdoor locations so its presence can be considered almost endogenous. In this way, the detection of ethanol during the analysis of the coatings can be related to the mixing of the VOCs of the indoor air with the compound emitted by the coatings.

According to NIOSH, ethanol has a TLV is 1000 ppm_v. This value is considerably elevated if compared with the same index of other VOCs, meaning that much higher concentration levels are required before real consequences to human health are registered. If these levels are achieved, ethanol is known to cause cutaneous and ocular irritation, as well as inflammatory processes in the airways. In addition, when inhaled, ethanol can provoke dizziness and even asphyxiation. No relationship was found between carcinogenic pathologies and ethanol exposure in human beings, so far, but such a cause-consequences relationship was visualised in animals [368, 369].

Also known as isopropanol, 2-propanol was detected in the composition of the indoor air of the car factory painting line so, it deserves to be properly addressed in terms of health impacts. Nonetheless, it is important to note that its presence can be simultaneously justified by two facts. Isopropanol was detected in the emissions of most of the coatings used in the painting line so, its presence in the air can be caused by these emissions, but it was equally detected in the analyses of other air samples, meaning that isopropanol can also be an endogenous compound of air. In terms of health impacts, it exhibits consequences similar to the ones from ethanol. It can be responsible for irritation and inflammatory processes, as well as, for dizziness and asphyxiation. These consequences, however, occur at a much lower TLV, i.e., 200 ppm_v [370, 371].

Other detected alcohol was 1-propanol (TLV of 100 ppm_v). This compound has been studied regarding its relationship with consequences to the human organism like lethargy, headaches, dizziness, and nausea. In addition, they can equally cause extremely intense inflammatory reactions in the airways. Cellular mutations have been reported too [372, 373]. Like the previous VOCs, 1-propanol was simultaneously detected In Indoor air and coatings analysis, meaning that is origin can be both justified by the coatings' emissions or by the natural composition of air.

Very similar health impacts have been reported to the next alcohol on the list, isobutanol (TLV of 50 ppm_v). These consequences include lethargy, headaches, dizziness, and nausea. In addition, it can equally cause extremely intense inflammatory reactions in the airways and cellular mutations [374, 375]. Coincidently, isobutanol was neither detected in the outdoor air analyses nor the coating analyses. This fact leads to the conclusion that the presence of isobutanol in the indoor air of the car factory painting line is due to some unidentified source of VOCs. Further studies are required to fully identify the VOCs-emitting sources and accurately address their impacts on employees' health and safety.

The last alcohol detected in the indoor air of the factory was 1-butanol. This VOC was simultaneously detected in outdoor air samples and in the emissions of the coatings so, its presence in the indoor air of the factory can represent a risk to the health of the chronically exposed employees. This volatile compound is known for being toxic when inhaled and responsible for dizziness and asphyxiation. Lethargic states, nausea, and headaches have been reported in exposure cases, as well as irritation of the respiratory passages. The TLV of 1-

butanol is 20 ppm$_v$, meaning that very low concentrations are required to cause impacts on the human organism [376, 377].

As already mentioned, ketones are often used in the manufacturing of coating solutions. Coincidently, acetone, 2-butanone and 2-hexanone were detected in the composition of the indoor air and in the emissions of most of the studied coating solutions. Since they are present in the coating solutions and also in the indoor air, the employees are chronically exposed to these compounds, in this way, it is important to be aware of the potential health Impacts.

Acetone (TLV of 250 ppm$_v$) and 2-butanone (TLV of 75 ppm$_v$), when inhaled, are responsible for irritation processed in the eyes and mucous membranes. They can equally lead to lethargic and anesthetic states. Neurological impacts have been reported in scenarios of chronic exposure [378, 379, 380]. The inhalation of 2-hexanone (TLV of 5 ppm$_v$), in its turn, has been related to narcosis, peripheral neuropathy and systems injuries. Dermatitis and ocular irritation have equally been reported by the literature [374]. It is important to note that the TLV index od acetone and 2-butanone are considerably high if compared with the one form 2-hexanone, meaning that lower concentrations in the air are required to cause the mentioned impacts on the human organism.

Benzene (TLV of 0.5 ppm$_v$) is among the most toxic VOCs. Being a part of the BTEX compounds, it has been strongly linked to carcinogenic conditions. In addition, depending on the concentration levels and the duration of exposure, it can cause nausea, vomiting, chest constriction, breathlessness, weakness, dizziness and even coma [19, 381]. Interestingly, benzene was not detected during the study targeting the emissions of the coating solutions. This fact leads to the conclusion that the origin of this compound, having in mind that it does not correspond to an endogenous compound of the air, is an unidentified source. Further studies ae mandatory to fully characterise these VOCs-emitting sources or to identify eventual compounds not detected during the studies targeting the coatings.

Nose and throat irritation, as well as nausea and vomiting have been directly linked to exposure to propanal (TLV of 20 ppm$_v$) [382]. Interestingly, the TLV of this compound is considerably low when compared to others, meaning that low concentration levels in the indoor air are enough to trigger the mentioned consequences in the human organism. Like the benzene, propanal was not detected in the emissions of the coatings, however, not all the VOCs emitted by these solutions were successfully identified so, propanal can indeed be emitted by the coatings, or it can be present due to an unidentified source.

Butanal (TLV of 20 ppm$_v$) was also undetected during the study of the VOCs emitted by the main VOCs-emitting sources, nonetheless, it was present in the composition of the indoor air of the car factory painting line. In addition, it was equally detected during the study of air samples for purposes of evaluating the *in-situ* capacity of GC-IMS. These facts can lead one to conclude that butanal can be an endogenous element of air. Besides its origin, the consequences to the employees' health must be considered. This compound exhibits the same health impacts of propanal and can additionally cause loss of consciousness [383].

Another compound detected simultaneously in the indoor air of the factory and in the air of other locations was pentanal (TLV of 50 ppm_v). Since the employees of the painting line are chronically exposed to this compound, its Impacts on the human organism are worth of attention. Ocular and cutaneous irritation, dizziness and asphyxiation have been reported as the main consequences to health [384, 385].

Hexanal (TLV of 50 ppm_v) was equally among the VOCs detected in the indoor air of the car factory painting line. Interestingly, it was not detected during the studies targeting the emissions of the coatings nor the air content of samples from other non-industrial locations. This may lead to the conclusion that further work must be developed aiming to identify all the detected analytes, or that the origin of hexanal was not addressed during this doctoral project. In spite of the possibilities, the employees exposed to hexanal on a daily basis can experience ocular and cutaneous irritation, dizziness and asphyxiation [384, 385].

Finally, acetic acid (TLV of 10 ppm_v) and propanoic acid (TLV of 10 ppm_v) have been linked to mild reactions in the airways, nose, eyes, and skin. Nonetheless, no systemic illnesses were reported or directly linked to chronic exposures to these two compounds [386, 382]. Both these compounds were identified in the indoor air of the car factory painting line, as well as, in the indoor air of other non-industrial locations. Interestingly, they were not detected in the composition of the studied coatings. This leads to the conclusion that both acetic and propanoic acid can be considered endogenous elements of the air, or that their source was not assessed during this doctoral project.

Unfortunately, and besides the efforts made and the preparatory work developed, it was not possible to assess the real impacts of the exposure on the employees' health in practical terms. In spite of the limitations, and as addressed throughout this chapter and the entire dissertation, chronic exposure to the VOCs detected in the composition of the car factory represents a threat to the health of the employees so, proper monitoring procedures like the ones described and developed during this doctoral work are mandatory. Further work to asses biological samples collected near the employees and quantify the real health impacts is also required.

5

CONCLUSIONS AND FUTURE WORK

This chapter addresses the primordial issues that led to the creation and development of the doctoral project here explored. In specific, this chapter includes the overall conclusions drawn from all the theoretical data reviewed and studies developed during the entire doctoral project. Considerations on the positive and negative points of the work done were equally included. Finally, some information on unaddressed topics and future work is equally included.

5.1 Conclusions

This doctoral project was developed under a partnership between NOVA School of Science and Technology - NOVA University of Lisbon and Volkswagen AutoEuropa. It aimed to address a very relevant and contemporary issue; the work conditions offered to the employees of industrial sites in regard to the quality of the indoor air. In this way, this doctoral project intended to develop a complete methodology that enables to assess the indoor air quality of the car factory painting line considering three overall goals: identify the main pollutants, isolate the main emitting sources, and evaluate the impacts on the health of the employees.

In order to comply with all the goals defined for the project, extensive research was conducted aiming to understand the current state of the art in the field of indoor air quality, define the main challenges, review the contemporary work developed to tackle the challenges and investigate the topic of work. Then, numerous protocols were developed aiming to characterise the quality of the air existent in the painting line, define the main locations to be analysed, assess the major pollutants, and identify and quantify those compounds. Finally, additional information was extensively gathered to address the impacts of the detected compounds on the health of the employees.

Aiming to define the most suitable analytical technique for the analysis of the target samples, the most relevant techniques among the ones capable of measuring VOCs were theoretically compared in regard to their advantages and disadvantages. Due to all its characteristics, namely, its high selectivity and sensitivity, portability, instrumental simplicity, almost real-time monitoring capacity, and others, GC-IMS was defined as the most suitable technique to achieve the goals defined in this project.

An initial study to assess the suitability of a different procedure based on graphene oxide to comply with the goals of the doctoral project was also developed. The results achieved during the study proved that this system was fully capable of detecting and quantifying industrially relevant VOCs, however, some challenges prevented its implementation throughout the entire project. The complexity of hardware, the necessity of using a vacuum chamber and a vacuum pump, and the fact that graphene-based sensors are still poorly explored regarding their suitability for the analysis of biological samples, prevented the utilisation of this system for *in-situ* measurements, a crucial topic for this project.

Once defined GC-IMS as the main analytical technique to be used throughout this doctoral project, it was necessary to develop procedures to utilise it, namely, create a database of VOCs for purposes of identification, and a calibration protocol for purposes of quantification.

Regarding the database of VIOCs, pure samples of nearly two hundred of compounds were measured with the spectrometer and their characteristic features, i.e., their drift and retention times, their ion mobility constant and their normalised ion mobility constant, were successfully registered in the library. This tool proved to be an accurate and effective way of identifying all the VOCs detected during the subsequent studies.

The quantification of VOCs with GC-IMS is one of the major challenges of this technology, nonetheless, it was possible to successfully develop a protocol for the calibration of one specific compound. By utilising specific methodologies, a calibration curve was plotted for 2-hexanone, enabling to accurately assess the concentration levels of this compound and, in addition, drawing some conclusions on the overall VOCs concentration levels existent in the interior of the car factory painting line.

In order to assess the suitability of GC-IMS for both in-situ and long-term measurements, two specific studies were developed. The study based on *in-situ* measurements of a specific set of locations enabled to introduce a simple but very precise methodology for direct determination of VOCs profile in both indoor and environmental air, in a large-scale scenario, with high levels of sensibility and specificity. It proved that the GC-IMS technology is suitable, efficient, accurate and rapid for *in-situ* direct analysis and profiling of volatile organic compounds even at trace concentration levels.

In parallel, the study focused on long-term analysis proved the fitness of GC-IMS for long-term VOCs detection and air quality control in closed environments. This was achieved due to the outstanding sensitivity, very low concentration range, good precision, instrumental simplicity, almost-real-time measuring capacity, and portability of the technology.

Besides all the measurements performed, procedures and protocols for sample collection, transportation, preparation, and analysis were carefully developed. These protocols addressed all the main procedures available for VOCs sampling and studied them in regard to their advantages and disadvantages. With this in mind, it was possible to conclude that for air analyses, the most proper procedure consists of *in-situ* measurements by placing the spectrometer at the target location. In addition, procedures based on the collection of the sample with Teflon containers and syringes proved to be equally suitable for air analyses. In terms of laboratory studies, procedures based on both static and dynamic headspace proved to be the most accurate for pure samples or non-volatile solutions testing.

By performing a careful evaluation of all the steps of the painting line, it was possible to identify the critical locations whose air deserved to be tested. Then, in-situ measurements were performed at all the selected sites. By applying all the previously developed protocols, it was possible to detect and identify the major VOCs existent in the air composition of the painting line. In addition, was possible to successfully address the relative intensities of all the compounds and the concentration levels of 2-hexanone. All the results were of extreme importance since they enabled to deepen the knowledge in regard to the air quality of the painting line and assess the compounds that represent a threat to the health of the employees.

Once identified the compounds of interest, it was crucial to study the main sources responsible for their presence in the indoor air. To do so, a careful evaluation of the solutions and material used during the coating process was performed, and the coating solutions were identified as the main responsible for the VOCs emission. By developing a dedicated protocol and applying it to analyse all the coatings, it was possible to successfully identify most of the emitted VOCs and to prove that there is an evident relationship between the compounds emitted by the coating solutions and the ones detected in the indoor air of the painting line.

In regard to the health impacts of the detected compounds, an exhaustive bibliographic search was conducted. It allowed to understand the potential impacts in terms of diseases on the health of the employees chronically exposed to the VOCs. In addition, enabled to understand that further studied are mandatory in order to test biological samples and *de facto* characterise the impacts.

In summary, all the developed protocols, measurements performed, and results achieved enabled to create accurate and suitable procedures to continuously monitor and control the indoor air quality at the car factory painting line and, in specific, at any industrial site. These methodologies and tools can be used and applied by employers as a proper way of ensuring good work conditions for their employees while they monitor the overall state in regard to the air of the factory. Finally, all the work developed throughout this doctoral project allows to understand the putative impacts that the employees may face on their organism and to implement further systems of pollutant extraction, air purification and body protection.

It is relevant to reinforce that, besides all the mentioned goals achieved, this doctoral project intended to give a step forward in the increment of the knowledge in regard to the impacts of VOCs existent at industrial locations aiming the definition of new and improved norms and legislation. As addressed throughout this dissertation, the current laws are poorly adamant and do not impose the requirements that the hazardousness of VOCs deserves. The results achieved in this study are expected to be a contribution to the definition of newer and improved legislation less flexible with the levels of exposure to VOCs, more restrictive in regard to the work conditions offered to the staff, and more demanding in terms of the quality monitoring and control procedures.

5.2 Future Work

Besides all the work done throughout the duration of this doctoral project, some topics deserved more attention and detailed addressing.

One of the main topics deserving further attention is the database of VOCs. In order to increase the level of knowledge in regard to indoor air quality, all the detected analytes must be identified. To do so, the number of compounds in the library must be increased for later cross-checking with the detected compounds. So, additional pure samples of VOCs must be measured and their respective drift time, retention time, ion mobility constant and normalised ion mobility constant must be registered in the database.

To fully understand the real hazardousness of the identified VOCs, it is mandatory to quantify the concentration levels in which they are present in the air composition. To do so, the developed protocol of calibration requires further improvements that allow to overcome the main challenges of the quantification of VOCs measured with GC-IMS. In addition, this protocol must be applied to all the detected analytes to fully characterise their concentration levels and, consequently, accurately assess their real impacts on the health of the employees.

Further measurements at the target locations and at other locations for longer periods of time can equally be made in order to increase the knowledge regarding all the potentially toxic compounds existent in the air composition. The identification of all the VOCs present in the indoor air, as well as, their study throughout long periods of time are mandatory topics to monitoring the work conditions of the car factory.

The same logic can be applied to the VOCs-emitting sources. Additional measurements can be made with the already identified sources, i.e., the coating solutions, as well as, with other potential sources of VOCs, in order to completely describe the compounds potentially present in the car factory atmospheric air.

Finally, one of the most important topics that must be addressed in the future is the impact on the employees' health to the VOCs exposure. In order to accurately understand the real health conditions and pathologies that might be caused by the VOCs existent in the air of the painting line, a protocol for the study of biological samples must be developed. This protocol must be capable of assessing potential diseases accurately, rapidly, non-invasively and, more importantly, without disturbing the correct functioning of the painting line. The detection and identification of biomarkers in exhaled air seems to be the most suitable methodology for such a complex task.

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B

BIOMARKERS IN BREATH

Table 22 - Summary of the majority of breath biomarkers for the diagnosis of both carcinogenic and non-carcinogenic diseases [12, 5, 231, 8].

VOCs	**Pathologies**															
	Asthma	**Breast Cancer**	**CKD**	**CLD**	**COPD**	**Colorectal Cancer**	**Covid-19**	**Cystic Fibrosis**	**Diabetes**	**Gastric Cancer**	**Lung Cancer**	**Malaria**	**Prostate Cancer**	**Sleep Apnoea**	**Squamous Cell Cancer**	**Tuberculosis**
A																
Acetaldehyde				X	X		X	X					X			

Acetic Acid		X					X			X						
Aceticamide										X						
Acetone	X		X	X		X	X	X	X	X	X	X		X		
Acetophenone		X		X											X	
Acetyl acetate													X			
2-Acetylpyridine					X											
Allylmethylsulphide												X				
Ammonia			X													
Ammonium acetate															X	
Aniline			X													
(+)-Aromadendrene		X														
B																
Benzaldehyde		X			X	X									X	
Benzene					X						X	X				
Benzoic acid						X										
Benzonitrile					X											
Benzothiazole								X								
Bicyclo[4.1.0]hepta-1,3,5-triene			X													
Biphenyl	X															
2,5-Bis-1,1-dimethylethylphenol															X	

Bis-(3,5,5-trimethylhexyl) phthalate																X
Butanal					X						X					
Butane					X						X					
1,4-Butanediol										X						
2,3-Butanediol															X	
2,3-Butanedione								X							X	
Butanoic acid						X										
Butanol								X								
2-Butanone			X	X			X	X		X	X				X	
2-Butenol								X								
4-Butoxybutanol										X						
2-Butoxyethanol										X						
Butyl Acetate								X								
Butylatedhydroxytoluene					X	X										
2-Butyloctanol		X			X											X
6-t-Butyl-2,2,9,9-tetramethyl-3,5-decadien-7-yne						X										
Butyric Acid								X							X	
C																
Camphene																X
Carbon disulphide											X					

3-Carene												X				
Caryophyllene		X		X												
[E]-Cinnamaldehyde					X											
2-Chloroethylester-carbono-chloridic acid			X													
Chloroform											X					
3-Chloropropanoylchloride			X													
Cyclohexane						X					X					
Cyclohexanol		X														
Cyclohexanone		X			X	X						X				
Cyclooctylmethanol						X										
Cyclopentane		X														
Cyclopentanone		X														
o-Cymene			X													
Cymol																X
D																
Decanal						X									X	
Decane	X				X						X			X		
1,2-Decanediol															X	
Decene		X		X												
E-3-Decen-2-ol															X	
1,4-Dichlorobenzene	X														X	

Dichloronitromethane			X					X								
Dihydro-2(3H)-furanone															X	
2,4-Dimethylbenzaldehyde		X														
1,3-Dimethylbenzene		X				X										
1,4-Dimethylbenzene						X										
2,2-Dimethylbutane		X													X	
2,3-Dimethylbutane															X	
Dimethyl Carbonate								X								
1,4-Dimethylcyclohexane		X														
2,2-Dimethyldecane						X						X			X	
3,6-Dimethyldecane	X											X				
3,7-Dimethyldecane												X				X
Dimethyl disulphide					X											
4,6-Dimethyl-dodecane															X	
2,4-Dimethylheptane	X		X								X				X	
2,6-Dimethylheptane					X											
2,3-Dimethylhexane		X														
3,3-Dimethylhexane								X								
1,7-Dimethylnaphtalene	X															
4,5-Dimethylnonane															X	
2,6-Dimethyloctane		X														
2,3-Dimethylpentane										X						

2,4-Dimethylpentane	X	X														
2,2-Dimethylpropanoic acid															X	
Dimethyl Selenide				X												
2,6-Dimethylstyrene																X
Dimethyl sulphide			X	X				X	X		X					
3,7-Dimethylundecane															X	
4,7-Dimethylundecane					X											
6,10-Dimethyl-5,9-undecadien-2-one						X								X		
1,4-Dioxane								X								
1,3-Dioxolan-2-one										X						
1,3-Di-ter-butylbenzene		X														
2,5-Ditert-butylcyclohexa-2,5-diene-1,4-dione		X														
2,6-Ditert-butylcyclohexa-2,5-diene-1,4-dione		X														
Δ-Dodecalactone					X											
Dodecane	X	X				X				X					X	
Dodecanoic acid						X										
2-Dodecanone		X														
E																
Ethanal							X									

Ethanol		X	X	X		X		X	X		X				X	
Ethenesulfonyl chloride			X													
2-Ethenylnaphtalene	X															
2-Ethoxyethyl acetate								X								
Ethyl acetate		X				X		X								
Ethyl acrylate								X								
Ethylaniline						X										
Ethylbenzene	X					X					X	X		X		
Ethyl butyrate								X					X			
Ethylcyclohexane												X				
1-Ethyl-3,5-dimethylbenzene		X														
Ethylene										X						
Ethylene Carbonate		X														
Ethylidenecyclopropane		X														
2-Ethylhexanol		X										X				
M-Ethylmethylbenzene			X													
6,2-Ethylmethyldecane					X											
5-Ethyl-2-methylheptane																X
3,4-Ethylmethylhexane					X											
2-Ethyl-4-methylpentanol	X															
4-Ethyl-1-octyn-3-ol						X										
2-Ethylpentane			X													

3-Ethylpentane			X													
Ethylphenol															X	
Ethyl propanoate		X														
2-Ethyltoluene															X	
3-Ethyltoluene															X	
4-Ethyltoluene															X	
Ethyl-Tris(Trimethylsilyl)-Silicate		X														
Ethyl vinyl ketone													X			
F																
Formic acid propylester										X						
Furan											X					
Furfural										X						
H																
Heptanal		X	X		X		X				X					
Heptane		X			X									X		
Heptanoic Acid															X	
2-Heptanone		X														
4-Heptanone					X											
Heptene				X												
Hexadecane					X										X	
Hexamethyldisilane		X														

Hexanal			X		X			X			X	X				
Hexane	X									X				X		
Hexanoic Acid															X	
Hexanol										X						
2-Hexanone	X															
3-Hexanone					X											
Hexene											X					
Hexylcyclohexane																X
Hexylethylphosphonofluoridate					X											
2-Hexyloctanol		X														
Hydrogen cyanide								X							X	
2-Hydroxy acetaldehyde											X					
3-Hydroxy-2-butanone								X			X					
4-Hydroxyhexenal											X					
4-Hydroxy-4-methylpentan-2-one												X				
3-Hydroxy-2,4,4-trimethylpentyl 2-methylpropanoate						X										
I																
Indole				X	X	X										
Iodide cycloheptatrienylium			X													
β-Ionone														X		

Isobutyl acetate								X								
Isobutyric acid		X														
Isoprene		X	X	X	X		X	X	X	X	X	X		X		
Isopropanol		X		X	X				X		X					
Isopropylacetate								X								X
Isopropylmyristate		X														
4-Isopropoxylbutanol										X						
1-Isopropyl-3-methylbenzene	X															
Isopropyl myristate								X								
L																
Limonene		X	X	X	X										X	
(+)-Longifolene		X														
M																
Menthol		X								X						X
Methane								X								
Methane sulfonyl chloride			X													
Methanethiol			X					X								
Methanol		X		X			X	X	X		X					
3-Methoxy-1,2-propanediol		X														
1-(3-Methoxypropoxy)propanol								X								
Methyl Acetate								X								

9-Methylacridine														X		
Methylacrylic acid		X														
Methylamine			X													
Methylbenzene						X										X
2-Methyl-1,2-bis(trimethylsiloxy)-propane		X														
2-Methylbutanal															X	
3-Methylbutanal															X	
2-Methylbutane						X					X					
2-Methylbutanoic acid		X			X											
3-Methyl-2-butanone															X	
3-Methylbutanonitrile				X												
3-Methyl-3-butenol		X														
Methyl butyrate													X			
Methylcyclohexane						X										
Methylcyclopentane						X										
3-Methylcyclopentanone					X											
4-Methyldodecane																X
3-(1-Methylethyl)oxetane																X
Methylene Chloride			X													
4-Methyl-2-heptanone		X														
6-Methyl-5-hepten-2-one		X			X					X						

2-Methylhexane	X		X	X						X						
3-Methylhexane		X		X						X					X	
5-Methyl-3-hexanone															X	
4-Methylhexene-1,4-diol																X
Methylisobutylketone										X						
Methylisobutyrate					X											
1-Methyl-4-(1-methylethenyl)cyclohexene	X															
(R)-1-Methyl-5-(1-methyl)cyclohexene		X														
N-Methyl-2-methylpropylamine								X								
2-Methylnaphthalene								X								
3-Methylnonane															X	
4-Methyloctane					X	X				X	X				X	
2-Methylpentane	X					X				X					X	
3-Methylpentane	X		X			X				X					X	
4-methyl-2-pentanone						X										
Methylphenol															X	
2-Methylpropene				X												
Methylpropylsulphide					X											
3-Methylpyridine		X														

α-Methylstyrene										X						
1-(Methylsulphonyl)propane	X															
2-Methyltetrahydrofuran															X	
Methylthiocyanate								X								
1-(Methylthio)propane				X								X				
Methylthiopropene												X				
Methylundecane												X				
4-Methylundecane						X										
N																
Naphthalene		X														
6-Nitro-2-picoline			X													
Nonadecane					X											
4,6,9-Nonadecatriene	X															
Nonanal	X		X		X	X	X				X	X				
Nonane	X			X										X		
Nonanoic Acid					X											
Nonanol										X						
2-Nonanone		X						X								
(E)-2-Nonene				X												
O																
Octadecane					X											
Octadecyne	X															

Octamethylcyclotetrasiloxane		X														
Octanal							X				X					
Octane	X			X	X									X		
Octanoic acid						X										
3-Octanone										X						
2-Octenal	X															
Octene				X											X	
2-Octene								X								
3-Octene								X								
P																
Pentadecane		X														
1,2-Pentadiene						X										
1,4-Pentadiene		X						X								
2,2,4,6,6-Pentamethylheptane	X															
Pentanal			X								X				X	
Pentane				X							X					
Pentanoic acid						X									X	
Pentanol								X								
3-Pentanol																X
2-Pentanone		X		X	X						X				X	
3-Pentanone				X												
2-Pentylfuran				X												

Phenyl acetate										X						
Phenylacetic acid														X		
Phenylbutene	X															
2-Phenyl-2-propanol		X														
4-(1-Phenyl-2-propenyloxy)-benzaldehyde			X													
Phenol		X		X		X		X		X					X	
α-Pinene		X		X	X							X				
β-Pinene				X										X		X
Pivalic acid										X						
Propanal					X		X	X		X	X					
Propane											X					
1,2-Propanediol		X														
1,3-Propanediol										X						
Propanoic Acid					X											
Propanol	X			X			X				X					
2-Propenal											X					
Propene											X					
2-Propenenitrile										X					X	
2-Propenoic acid		X														
Propylcyclohexane												X				
Propyl propionate													X			

1H-Pyrazole-4-carbonitrile			X													
2-Pyridinecarbonitrile			X													
1H-Pyrrole-3-carbonitrile			X													
Pyrrolidine		X														
S																
Silicon tetrafluoride			X													
Styrene			X	X							X					
T																
α-Terpinene				X												
γ-Terpinene				X												
Terpineol					X											
Tetrachloroethene														X		
Tetradecane	X	X		X	X	X				X				X		
9-Tetradecenol															X	
1,2,3,5-Tetramethylbenzene		X														
1,2,4,5-Tetramethylbenzene		X														
Tetramethylsilicane		X														
1,1,3,3-Tetramethylurea		X														
Tolualdehyde								X								
Toluene		X			X											
Trans-2-dodecenol						X										
4H-1,2,4-Triazol-4-amine			X													

Trichlorethylene		X														
Trichloromethane			X													
Tridecane		X		X		X						X				X
Trifluoroacetic acid		X														
Triglyceride															X	
Trimethylamine			X	X											X	
1,2,3-Trimethylbenzene										X					X	
1,2,4-Trimethylbenzene											X				X	
1,3,5-Trimethylbenzene										X				X	X	X
Trimethyldecane						X										
2,4,6-Trimethyldecane					X											
2,6,10-Trimethyldodecane	X															
2,6,11-Trimethyldodecane		X								X						
2,7,10-Trimethyldodecane		X														
2,2,4-Trimethylheptane	X															
2,2,3-Trimethylhexane			X									X				
2,3,5-Trimethylhexane												X		X		
4,6,8-Trimethylnonene																X
2,2,6-Trimethyloctane			X													
2,6,6-Trimethyloctane															X	
2,3,6-Trimethyloctane	X															
2,4,4-Trimethylpentene					X											

1,3,5-Tri-tert-butylbenzene					X											
Tolualdehyde										X						
Toluene			X								X	X		X	X	
U																
2-Undecanal	X															
Undecane		X			X			X							X	
V																
Vinylpyrazine					X											
X																
m-Xylene										X						
o-Xylene											X					X
p-Xylene	X	X									X			X	X	

C

DATABASE OF VOCS

Table 23 - Database of VOCs that includes the respective CAS numbers, retention times, drift times, ion mobility constant and normalised ion mobility constant.

Volatile Organic Compounds	CAS Number	Retention Time (s)	Drift Time (RIP Relative)	K ($cm^2/V.s$)	K_0 ($cm^2/V.s$)	Note
Acetic Acid*	64-19-7	119.91	1.062	2.512	1.976	Monomer
			1.123	2.374	1.867	Dimer
Acetone	67-64-1	87.3	1.022	2.260	2.039	Monomer
			1.124	2.056	1.854	Dimer
Acetonitrile	75-05-8	91.9	1.061	2.142	1.941	Monomer
			1.135	2.000	1.813	Dimer
Acetophenone*	98-86-2	982.8	1.106	2.223	1.748	Monomer
			1.106	1.627	1.280	Dimer

Acetylacetone	123-54-6	319.8	1.12	2.069	1.860	Monomer
			1.418	1.634	1.469	Dimer
Aniline	62-53-3	1178.6	1.18	1.917	1.745	Monomer
			1.434	1.578	1.436	Dimer
Anisole	100-66-3	536.3	1.066	2.175	1.980	Monomer
Benzaldehyde*	100-52-7	535.5	1.183	2.275	1.789	Monomer
			1.544	1.743	1.371	Dimer
Benzene*	71-43-2	118.23	1.112	2.395	1.883	Monomer
Benzonitrile*	100-47-0	663.6	1.211	2.213	1.740	Monomer
			1.562	1.715	1.348	Dimer
Benzyl Chloride	100-44-7	274.1	1.024	2.224	2.020	Monomer
			1.259	1.810	1.644	Dimer
3-Bromoaniline	591-19-5	1106.3	1.182	1.949	1.746	Monomer
			1.438	1.602	1.436	Dimer
Butanal*	123-72-8	111.72	1.130	2.361	1.856	Monomer
			1.335	1.998	1.571	Dimer
1-Butanol	71-36-3	108.6	1.19	1.930	1.742	Monomer
			1.408	1.632	1.472	Dimer
			1.633	1.407	1.269	Trimer
2-Butanol	78-92-2	84	1.161	1.995	1.796	Monomer
			1.351	1.714	1.543	Dimer
2-Butanone	78-93-3	127.1	1.076	2.118	1.935	Monomer

			1.255	1.815	1.658	Dimer
Butyl Acetate	123-86-4	357.3	1.248	1.813	1.650	Monomer
			1.624	1.393	1.267	Dimer
Butylamine	109-73-9	226.1	1.385	1.653	1.487	Monomer
sec-Butylamine	13952-84-6	101.1	1.335	1.708	1.544	Monomer
Butylbenzene	104-51-8	1047.9	1.217	1.875	1.710	Monomer
			1.319	1.731	1.579	Dimer
sec-Butylbenzene	135-98-8	711	1.199	1.906	1.736	Monomer
			1.296	1.763	1.606	Dimer
tert-Butylbenzene	98-06-6	681.3	1.203	1.898	1.730	Monomer
			1.3	1.761	1.605	Dimer
tert-Butylmethylether	1634-04-4	69.9	1.13	2.009	1.842	Monomer
			1.36	1.670	1.531	Dimer
Butyric Acid	107-92-6	238.1	1.184	1.937	1.743	Monomer
			1.417	1.618	1.456	Dimer
Cadaverine	462-94-2	51.7	0.936	2.408	2.201	Monomer
Chlorobenzene	108-90-7	289.4	1.054	2.173	1.976	Monomer
Cinnamaldehyde	14371-10-9	1333.4	1.159	1.962	1.777	Monomer
			1.475	1.542	1.397	Dimer
Citral	5392-40-5	526.5	1.098	2.071	1.874	Monomer
			1.367	1.663	1.505	Dimer
Citronelool	7540-51-4	613.9	1.085	2.094	1.897	Monomer

			1.344	1.690	1.531	Dimer
Cycloheptane	291-64-5	1349.9	1.165	1.959	1.790	Monomer
			1.484	1.539	1.406	Dimer
Cyclohexanone	108-94-1	1069.1	1.162	1.974	1.784	Monomer
			1.46	1.572	1.421	Dimer
Cyclooctane	292-64-8	283.3	1.138	2.006	1.827	Monomer
Decanal*	112-31-2	2388.54	1.594	1.691	1.330	Monomer
			2.183	1.235	0.971	Dimer
2-Decanone	693-54-9	863	1.166	1.985	1.787	Monomer
			1.538	1.505	1.355	Dimer
1,3-Diaminopropane	109-76-2	47.7	1.048	2.152	1.971	Monomer
			1.279	1.763	1.615	Dimer
1,2-Dichlorobenzene	95-50-1	1180.7	1.126	2.011	1.844	Monomer
			1.216	1.863	1.708	Dimer
1,3-Dichlorobenzene	541-73-1	835.3	1.133	2.022	1.836	Monomer
			1.245	1.842	1.672	Dimer
1,1-Dichloroethane	75-34-3	82.2	1.059	2.164	1.968	Monomer
			1.182	1.940	1.765	Dimer
Dichloromethane	75-09-2	628.4	1.261	1.820	1.653	Monomer
cis-1,3-Dichloropropene	10061-01-5	424.9	1.273	1.792	1.631	Monomer
			1.53	1.491	1.357	Dimer
Diethylamine	109-89-7	185.5	1.104	2.054	1.870	Monomer

			1.281	1.769	1.611	Dimer
1,2-Diethylbenzene	135-01-3	1188.9	1.19	1.910	1.744	Monomer
			1.269	1.792	1.635	Dimer
1,3-Diethylbenzene	141-93-5	1005.5	1.214	1.871	1.707	Monomer
			1.287	1.765	1.611	Dimer
1,4-Diethylbenzene	105-05-5	966	1.2	1.910	1.730	Monomer
			1.286	1.782	1.613	Dimer
Diethylether*	60-29-7	74.13	1.089	2.438	1.917	Monomer
			1.198	2.217	1.743	Dimer
			1.284	2.069	1.626	Trimer
Dihexylether	112-58-3	379.2	1.338	1.701	1.552	Monomer
			1.671	1.362	1.244	Dimer
			1.994	1.141	1.042	Trimer
Dimethylamine	124-40-3	82.9	0.934	2.434	2.209	Monomer
			1.064	2.138	1.940	Dimer
3,3-Dimethyl-2-butanone	75-97-8	226.4	1.196	1.901	1.743	Monomer
			1.521	1.495	1.371	Dimer
n,n-Dimethylformamide	68-12-2	937.6	1.034	2.201	1.994	Monomer
			1.25	1.820	1.650	Dimer
2,4-Dimethylpentane	108-08-7	290.6	1.19	1.912	1.751	Monomer
			1.489	1.529	1.401	Dimer
1,4-Dioxane	123-91-1	170.5	1.152	1.992	1.807	Monomer

			1.332	1.723	1.563	Dimer
Ethanol	64-17-5	58.3	1.047	2.218	1.994	Monomer
			1.143	2.033	1.828	Dimer
Ethanolamine	141-43-5	59.8	0.934	2.437	2.207	Monomer
			1.047	2.173	1.959	Dimer
Ethyl Acetate	141-78-6	109.9	1.107	2.084	1.878	Monomer
			1.348	1.713	1.543	Dimer
Ethylbenzene	100-41-4	284.2	1.087	2.098	1.914	Monomer
Ethylbutyrate	105-54-4	297.3	1.22	1.866	1.691	Monomer
			1.567	1.452	1.316	Dimer
2-Ethylfuran*	3208-16-0	133.35	1.081	2.495	1.962	Monomer
2-Ethyltoluene	611-14-3	918.6	1.036	2.235	2.011	Monomer
			1.254	1.848	1.662	Dimer
3-Ethyltoluene	122-99-6	644.9	1.262	1.831	1.648	Monomer
			1.603	1.442	1.298	Dimer
4-Ethyltoluene	622-96-8	371.6	1.151	2.009	1.807	Monomer
			1.527	1.515	1.362	Dimer
2-Fluoroaniline	348-54-9	972.9	1.214	1.840	1.692	Monomer
			1.47	1.519	1.397	Dimer
4-Fluoroaniline	371-40-4	53.2	0.937	2.398	2.189	Monomer
			1.047	2.146	1.959	Dimer
Fluorobenzene	462-06-6	957	1.116	2.056	1.865	Monomer

Heptanal*	111-71-7	405.09	1.365	1.970	1.549	Monomer
			1.787	1.505	1.183	Dimer
1-Heptanol	111-70-6	759.5	1.412	1.622	1.476	Monomer
			1.794	1.276	1.161	Dimer
			2.158	1.061	0.965	Trimer
2-Heptanol	543-49-7	458.6	1.373	1.674	1.520	Monomer
			1.719	1.336	1.214	Dimer
			2.085	1.102	1.001	Trimer
3-Heptanol	589-82-2	415.4	1.354	1.698	1.540	Monomer
			1.678	1.371	1.243	Dimer
			2.034	1.131	1.025	Trimer
2-Heptanone	110-43-0	848.6	1.276	1.787	1.634	Monomer
			1.639	1.391	1.272	Dimer
3-Heptanone	106-35-4	707.3	1.253	1.843	1.664	Monomer
			1.605	1.438	1.299	Dimer
4-Heptanone	123-19-3	634.9	1.246	1.855	1.672	Monomer
			1.602	1.443	1.301	Dimer
2-Heptenal*	2463-63-0	621.600	1.295	2.076	1.632	Monomer
			1.759	1.528	1.202	Dimer
4-Heptenal*	62238-34-0	392.07	1.190	2.232	1.755	Monomer
			1.603	1.656	1.302	Dimer
			1.704	1.558	1.225	Trimer

Hexanal*	66-25-1	250.53	1.286	2.091	1.644	Monomer
			1.641	1.638	1.288	Dimer
Hexane	110-54-3	67.2	1.098	2.090	1.877	Monomer
			1.246	1.842	1.654	Dimer
Hexanoic acid	142-62-1	1083.7	1.359	1.667	1.516	Monomer
			1.644	1.378	1.253	Dimer
1-Hexanol	111-27-3	374.5	1.341	1.710	1.556	Monomer
			1.673	1.371	1.247	Dimer
			1.996	1.149	1.045	Trimer
2-Hexanol	626-93-7	231.5	1.3	1.771	1.601	Monomer
			1.595	1.443	1.304	Dimer
			1.915	1.201	1.086	Trimer
3-Hexanol	623-37-0	212.9	1.285	1.786	1.621	Monomer
			1.561	1.470	1.335	Dimer
			1.875	1.224	1.111	Trimer
2-Hexanone	107-87-9	406.6	1.205	1.919	1.730	Monomer
			1.513	1.527	1.377	Dimer
3-Hexanone	589-38-8	363	1.186	1.949	1.750	Monomer
			1.481	1.561	1.402	Dimer
2-Hexenal*	505-57-7	364.980	1.210	2.212	1.739	Monomer
			1.590	1.683	1.324	Dimer
1-Hexene	592-41-6	763.2	1.189	1.920	1.746	Monomer

			1.522	1.500	1.364	Dimer
β-Homocyclocitral*	472-66-2	3025.26	1.367	1.965	1.545	Monomer
Isobutanol*	78-83-1	118.65	1.191	2.254	1.772	Monomer
			1.410	1.904	1.497	Dimer
Isobutylamine	78-81-9	84	1.029	2.201	2.004	Monomer
			1.123	2.017	1.837	Dimer
			1.277	1.773	1.615	Trimer
Isobutylbenzene	538-93-2	771.8	1.203	1.915	1.724	Monomer
			1.309	1.761	1.585	Dimer
Isooctane	540-84-1	183.63	1.177	1.955	1.683	Monomer
			1.488	1.547	1.332	Dimer
Isopropanol	67-63-0	61.7	1.099	2.09	1.896	Monomer
			1.247	1.842	1.671	Dimer
Isopropylbenzene*	98-82-8	328.23	1.162	2.295	1.804	Monomer
			1.202	2.218	1.744	Dimer
Isopropylmethylketone	563-80-4	179.3	1.131	1.986	1.831	Monomer
			1.377	1.632	1.504	Dimer
Limonene*	138-86-3	478.8	1.261	2.113	1.661	Monomer
			1.338	1.991	1.566	Dimer
			1.738	1.533	1.2059	Trimer
Linalool*	78-70-6	892.5	1.270	2.118	1.665	Monomer
			1.802	1.492	1.173	Dimer

2,4-Lutidine	108-47-4	712.7	1.488	1.539	1.400	Monomer
2,6-Lutidine	108-48-5	379.4	1.097	2.069	1.886	Monomer
			1.454	1.561	1.423	Dimer
Menthol*	89-78-1	554.19	1.348	1.986	1.562	Monomer
Mesitylene	108-67-8	585.7	1.142	2.026	1.844	Monomer
Methanol*	67-56-1	64.47	1.004	2.613	2.055	Monomer
Methylacetate	79-20-9	82.6	1.046	2.152	1.969	Monomer
			1.198	1.878	1.719	Dimer
Methylacrylate*	96-33-3	116.13	1.086	2.456	1.931	Monomer
			1.333	2.000	1.572	Dimer
2,2-Methylbutanol*	594-60-5	123.9	1.037	2.594	2.040	Monomer
			1.072	2.508	1.972	Dimer
			1.316	2.043	1.606	Trimer
3,1-Methylbutanol	123-51-3	158.5	1.259	1.813	1.651	Monomer
			1.527	1.495	1.361	Dimer
			1.802	1.267	1.154	Trimer
3,2-Methylbutanol	598-75-4	114.8	1.219	1.885	1.712	Monomer
			1.451	1.583	1.438	Dimer
			1.727	1.330	1.208	Trimer
3,3-Methylbutenol	56539-66-3	165.8	1.182	1.949	1.759	Monomer
			1.45	1.589	1.434	Dimer
Methylcyclopentane	96-37-7	170.6	1.152	1.992	1.806	Monomer

			1.332	1.723	1.562	Dimer
Methylisobutyrate	547-63-7	147.3	1.16	1.951	1.775	Monomer
			1.445	1.565	1.424	Dimer
2,3-Methylpentanone	565-69-5	279.6	1.178	1.959	1.759	Monomer
			1.472	1.567	1.407	Dimer
3,2-Methylpentanone	565-61-7	307.8	1.185	1.950	1.759	Monomer
			1.491	1.550	1.399	Dimer
4,2-Methylpentanone	108-10-1	290.9	1.191	1.943	1.745	Monomer
			1.489	1.554	1.395	Dimer
Nitrobenzene	98-95-3	925.3	1.339	1.731	1.557	Monomer
2,6-Nonadienal*	557-48-2	1965.6	1.422	1.889	1.485	Monomer
			2.007	1.338	1.052	Dimer
Nonanal*	124-19-6	1193.01	1.523	1.768	1.390	Monomer
			2.063	1.306	1.027	Dimer
Nonane	111-84-2	223.7	1.233	1.863	1.691	Monomer
Nonanol	143-08-8	636.6	1.255	1.831	1.655	Monomer
			1.595	1.440	1.301	Dimer
2-Nonenal*	2463-53-8	2173.5	1.460	1.846	1.452	Monomer
			2.083	1.294	1.017	Dimer
2,4-Octadienal*	30361-28-5	1577.31	1.305	2.064	1.623	Monomer
			1.895	1.422	1.118	Dimer
Octanal*	124-13-0	673.89	1.445	1.863	1.464	Monomer

			1.928	1.396	1.098	Dimer
2-Octenal*	2363-89-5	1076.985	1.379	1.953	1.536	Monomer
			1.925	1.400	1.100	Dimer
1-Octanol	111-87-5	606	1.259	1.842	1.659	Monomer
			1.603	1.447	1.303	Dimer
2-Octanone	111-13-7	304.3	1.349	1.714	1.544	Monomer
			1.764	1.311	1.181	Dimer
1-Octenol*	3391-86-4	504.63	1.205	2.227	1.751	Monomer
			1.689	1.597	1.255	Dimer
2-Octenol*	22104-78-5	867.93	1.206	2.234	1.756	Monomer
			1.691	1.593	1.252	Dimer
1,3-Octenone*	106-68-3	617.82	1.299	2.051	1.613	Monomer
			1.778	1.499	1.178	Dimer
Octyl Acetate	112-14-1	294	1.220	1.888	1.706	Monomer
			1.567	1.470	1.329	Dimer
Pentachloroethane	76-01-7	401.1	1.053	2.168	1.967	Monomer
			1.36	1.679	1.523	Dimer
Pentanal	110-62-3	166	1.206	1.980	1.557	Monomer
Pentanedial*	111-30-8	584.22	1.107	2.412	1.896	Monomer
			1.467	1.819	1.430	Dimer
1-Pentanol	71-41-0	188.1	1.265	1.822	1.647	Monomer
			1.543	1.494	1.350	Dimer

			1.822	1.265	1.143	Trimer
2-Pentanol	6032-29-7	124.6	1.23	1.885	1.695	Monomer
			1.473	1.574	1.416	Dimer
			1.748	1.326	1.193	Trimer
3-Pentanol	584-02-1	126.5	1.22	1.893	1.707	Monomer
			1.443	1.600	1.443	Dimer
			1.715	1.346	1.214	Trimer
2-Pentanone	107-87-9	204.9	1.135	2.006	1.833	Monomer
			1.378	1.652	1.510	Dimer
3-Pentanone	96-22-0	197.6	1.127	2.031	1.851	Monomer
			1.366	1.067	1.528	Dimer
2-Pentylfuran*	3777-69-3	455.49	1.288	2.066	1.624	Monomer
2-Phenoxyethanol	122-99-6	622	1.261	1.822	1.655	Monomer
			1.602	1.434	1.302	Dimer
Phenylacetaldehyde*	122-78-1	537.18	1.183	2.275	1.789	Monomer
			1.545	1.742	1.370	Dimer
2-Picoline	109-06-8	296.9	1.052	2.190	1.968	Monomer
			1.358	1.697	1.525	Dimer
3-Picoline	108-99-6	529.9	1.072	2.162	1.942	Monomer
			1.399	1.657	1.488	Dimer
4-Picoline	108-89-4	555.6	1.069	2.166	1.948	Monomer
			1.382	1.675	1.507	Dimer

α-Pinene*	80-56-8	306.6	1.272	2.122	1.669	Monomer
			1.350	2.000	1.572	Dimer
			1.755	1.538	1.209	Trimer
Propanal*	123-38-6	86.1	1.058	2.523	1.984	Monomer
			1.184	2.254	1.772	Dimer
1-Propanol	71-23-8	82.9	1.118	2.028	1.858	Monomer
			1.276	1.776	1.627	Dimer
Propionic Acid	123-38-6	132.6	1.121	2.041	1.839	Monomer
			1.302	1.756	1.583	Dimer
Propylacetate	109-60-4	184.9	1.175	1.933	1.750	Monomer
			1.485	1.529	1.385	Dimer
Propylamine	107-10-8	65.3	1.099	2.046	1.882	Monomer
			1.247	1.803	1.658	Dimer
Pyridine	110-86-1	260.3	1.022	2.267	2.036	Monomer
			1.258	1.842	1.654	Dimer
Terpineol	8006-39-1	769.7	1.34	1.696	1.536	Monomer
			1.735	1.309	1.186	Dimer
Tetrachloroethylene	127-18-4	257.3	1.024	2.229	2.036	Monomer
			1.26	1.812	1.655	Dimer
Tetrahydrofuran	109-99-9	102.1	1.077	2.112	1.934	Monomer
			1.236	1.840	1.686	Dimer
Toluene	108-88-3	166.2	1.0246	2.260	2.035	Monomer

			1.107	2.092	1.883	Dimer
			1.45	1.597	1.437	Trimer
1,1,2-Trichloroethane	79-00-5	602.2	1.218	1.883	1.711	Monomer
			1.404	1.635	1.486	Dimer
Triethylamine	121-44-8	64.2	1.109	2.044	1.859	Monomer
			1.244	1.822	1.657	Dimer
1,2,3-Trimethylbenzene	526-73-8	970.4	1.147	2.015	1.814	Monomer
Tripropylamine	102-69-2	344.6	1.272	1.765	1.618	Monomer
2-Undecanone	112-12-9	866.8	1.275	1.806	1.631	Monomer
			1.635	1.408	1.271	Dimer
6-Undecanone	927-49-1	832.5	1.277	1.785	1.631	Monomer
			1.639	1.390	1.271	Dimer
Valeric Acid	109-52-4	537.8	1.252	1.807	1.645	Monomer
			1.542	1.467	1.336	Dimer
m-Xylene	108-38-3	310.9	1.079	2.146	1.930	Monomer
			1.173	1.974	1.775	Dimer
o-Xylene	95-47-6	387.5	1.079	2.148	1.929	Monomer
			1.163	1.993	1.790	Dimer
p-Xylene	106-42-3	308.9	1.073	2.160	1.942	Monomer
			1.169	1.983	1.782	Dimer

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DEVELOPMENT OF METHODOLOGY FOR AUTOMATIC ON-LINE MONITORING OF VOCS IN AN AUTOMOTIVE PLANT AND DIRECT EVALUATION OF ITS IMPACT ON EMPLOYEES

PEDRO RAFAEL CATALÃO MOURA

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