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DETERMINATION OF VOLATILE ORGANIC COMPOUNDS IN INDOOR AIR WITH GC-MS

Method Development

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ABSTRACT

Tampere University of Applied Sciences
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Method Development

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An average western person spends most of his life indoors, therefore volatile organic compounds may play a significant role in healthiness. Certain VOCs have been classified as carcinogenic or mutagenic, and elevated TVOC concentrations have been statistically linked to adverse health effects. (Klepeis 1996, 15; Apte & Daisey 1999, 1–5.)

This thesis was commissioned by the chemistry laboratory of Tampere University of Applied Sciences. The aim of this bachelor's thesis was to provide a GC-MS-method for reliable determination of indoor air VOCs. The objective was to develop and validate a method based on the ISO 16000–6 to identify and quantitate VOCs between hexane and hexadecane utilizing adsorbent solvent extraction.

In the method to be created, the individual VOC-components of a sample were to be identified in scan-mode and simultaneous scan/SIM-mode was to be used for quantitation. The results of the quantitation were to be expressed as toluene equivalents, for which toluene response factors were to be determined.

To practically approach the determination, a tentative method was created and evaluated. However, the intensity of the tentative method was found lacking, therefore a thorough fine-tuning of the method parameters was performed to meet the extremely high requirements comparing to an air sample.

A method was successfully created. With the finalized method, toluene response factors and a linear range of operations required were determined. The finalized method reached a detection limit of 3 µg/ml in scan mode and 1 ηg/ml in SIM-mode. Validation of the method was not performed due to encountering a recurring contamination and limited time resources.

The aim and objective could be considered partially met. With the finalized method, the quantitation limits comparable of a generic air sample were met in SIM-mode. However, the capability of the method in scan-mode was found insufficient for practical identification. The optimization of the parameters enhanced greatly the chromatographic separation, and the quality and the intensity of the peaks. The obtained results can be considered significant and may provide significant insights leading to enhanced results and more efficient determinations of VOCs in the future.

Key words: indoor air, volatile organic compounds, gas chromatography-mass spectrometry, adsorbent solvent extraction

TIIVISTELMÄ

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RIIHONEN, VESA
Haihtuvien orgaanisten yhdisteiden määritys sisäilmasta GC-MS-laitteistolla
Menetelmän kehitys

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Keskivertoihminen viettää suurimman osan elinajastaan sisätiloissa. (Klepeis 1996, 15) Haihtuvat orgaaniset kemikaalit on todettu yhdeksi merkittävistä tekijöistä sisäilman laadun suhteen, ja tutkimuksissa ollaan yhdistetty tietyt VOC-yhdisteet terveydelle haitallisiksi. (Apte & Daisey 1999, 1–5.)

Opinnäytetyön toimeksiantaja oli TAMKn kemian laboratorio. Opinnäytetyön tavoitteena oli kehittää laboratoriolle menetelmä VOC-yhdisteiden määrittämiseksi GC-MS-tekniikalla. Tarkoituksena oli kehittää sekä validoida menetelmä standardin ISO 16000–6 pohjalta, jolla kyettäisiin tunnistamaan ja kvantitoimaan VOC-yhdisteet heksaanin ja heksadekaanin väliltä liuotinuuttomenetelmällä.

Kehitettävässä menetelmässä yksittäiset komponentit oli tarkoitus tunnistaa scan-moodissa, ja kvantitointi oli tarkoitus suorittaa yhtäaikaisessa scan- / SIM-moodissa. Kvantitointia varten yksittäisille komponenteille muodostettiin tolueenivasteet sekä muodostettiin tolueenin avulla lineaarisuusalue.

Tarkoituksen saavuttamiseksi luotiin alustava menetelmä, jonka perusteella arvioitiin määrityksen toteutettavuutta. Alustavan menetelmän suorituskyky todettiin riittämättömäksi ilmanäytettä vastaaville analyyttimäärille, joten suoritettiin laaja parametrien optimointi kaasukromatografille sekä massaspektrometrille. Menetelmälle ei suoritettu riittävää validointia prosessin loppuvaiheessa tapahtuneen kontaminaation sekä ajan puutteen johdosta.

Viimeistellyllä menetelmällä määritettiin tolueenivasteet sekä määrityksen lineaarisuusalue ilmanäytettä vastaaville pitoisuuksille. Saavutetut toteamisrajat olivat 3 µg/ml scan-moodissa ja 1 ηg/ml SIM-moodissa.

Tavoite ja tarkoitus voitiin todeta vain osittain saavutetuksi. Kehitetyllä menetelmällä ei saavutettu suorituskykyä, jolla pystyttäisiin tunnistamaan yksittäiset komponentit scan-moodissa. SIM-moodissa saavutettiin kvantitoinnille asetetut intensiteettivaatimukset. Luodulla menetelmällä saavutettiin hyviä tuloksia muun muassa kromatografisen erottumisen suhteen, tolueenivasteille ja nesteinjektion määritysrajojen suhteen. Kehitetyn menetelmän tuloksia voidaan pitää merkittävinä, ja prosessin aspekteja voidaan hyödyntää tulevaisuudessa parempien ja tarkempien tuloksien saavuttamisessa sekä VOC-yhdisteisiin liittyvien ilmiöiden tulkitsemisessa.

Asiasanat: VOC-yhdisteet, sisäilma, kaasukromatografi-massaselektiivinen detektori, liuotinuutto

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ABBREVIATIONS AND TERMS

2-EH	2-ethyl-1-hexanol
ALS	automatic liquid sample injector
ATD	adsorbent thermal desorption
ASE	adsorbent solvent extraction
EM	electron multiplier
GC	gas chromatograph
IAQ	indoor air quality
EN	European Standard
ISO	International Organization for Standardization
LOD	limit of detection
LOQ	limit of quantitation
LV	limit value
MSD	mass selective detector
MVOC	microbial volatile organic compound
NIST	National Institute of Standards and Technology
P&T	purge and trap
PEG	polyethylene glycol
RSD	relative standard deviation
SBS	sick building syndrome
SIM	selected ion monitoring
SVOC	semi-volatile organic compounds
TAMK	Tampere University of Applied Sciences
TIC	total ion chromatogram
TVOC	total volatile organic compounds
TXIB	2,2,4-trimethyl-1,3-pentanedioldiisobutyrate
VOC	volatile organic compound(s)
VVOC	very volatile organic compound(s)
WCOT	wall coated open tubular

1 INTRODUCTION

Volatile organic compounds have been associated with diminished indoor air quality since 1980s. Ambient air contains tens of thousands of organic compounds, of which some have been associated with adverse chronic and acute health effects. Specific VOCs are known carcinogens and may cause adverse chronic and acute adverse health effects even in low concentrations (United States Environmental Protection Agency 1991, 1–3).

Significant sources of VOC-emissions to indoor air include building materials, household chemicals and chemicals utilized in anthropogenic activities. According to Brown, Cockram, Crump & Gavin (1994, 111) indoor VOC-concentrations are 5–20 -fold in comparison to outdoor levels.

According to Finnish legislation, official determination of VOCs is performed following directives of the ISO-16000:6:2011, in which VOCs between hexane and hexadecane are determined. According the standard, the sample is collected to Tenax TA® adsorbent, thermally desorbed, and analyzed with a gas chromatograph-mass selective detector. (EN-ISO 16000-6:2011, 2; Valvira 2016, 6).

This bachelor's thesis was conducted for the laboratory of the Tampere University of Applied Sciences. The aim of this bachelor's thesis was to provide a GC-MS-method for reliable determination of indoor air VOCs. However, TAMK lacked the equipment for thermal desorption, therefore the aim of this bachelor's thesis was set to developing and validating a method based on the ISO 16000–6 utilizing adsorbent solvent extraction.

The development of the ASE-method turned out to be challenging. After extraction, the amount of substance injected into the gas chromatograph is approximately 1:1700 of the ATD-methods, which induced elevated performance requirements (appendix 1). Therefore, a significant part of this bachelor's thesis comprises of method development, in which the system parameters of the gas chromatograph-mass selective detector were enhanced.

With the finalized method (SIM-mode), reached limits of detection and quantitation compared to the level of an individual component of an air sample. The finalized method was not validated, nor an indoor air sample was collected and analyzed during the process.

2 VOLATILE ORGANIC COMPOUNDS

Volatile organic compounds are a branch of ubiquitous organic compounds, which can be present or emit from synthetic materials, natural materials and organisms. The most common VOCs include carboxylic acids, esters, aldehydes and ketones, alkanes, aromatic hydrocarbons, alcohols, glycols and glycol ethers, amides, terpenes and chlorinated hydrocarbons. (Järnström 2007, 13; Koppmann 1999, 3.). VOCs are utilized in innumerable ways, inter alia, as fuels, solvents, fragrances, biocides, and in technochemical products. VOCs exist generally in the form of vapors or liquids in the room temperature, but some may exist in solid form, for instance naphthalene and 1,4-dichlorobenzene. (Bloemen & Burn 1993, 1.)

2.1 Definition and Classifications

Due to the broad range of VOCs, different adaptations have been created to define volatile organic compounds. Approaches to classify VOCs include their physicochemical characteristics, chemical moieties and sources of emission (Hodgson, Levin, Wolkoff 1994, 297).

The European Commission defines VOCs in the VOC Solvents Directive (1999/13/EC) and in the amended Paints Directive (2004/42/EC) as “any kind of organic compound, which has a vapour pressure of 0,01 kPa at 293,15K or a has a boiling point of 250 °C in standard pressure of 101,3 kPa”.

A common practice in analytical, research and development or quality control facilities and directive agencies is to classify VOCs according to the classification of World Health Organization (1989), in which VOCs are divided into three subcategories according to their respective volatilities. These categories include very volatile organic compounds (VVOCs), volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs). The classification is further elaborated in the table 1. Additionally, VOCs can be also classified based upon the sources of their corresponding emissions, for instance, VOCs emitted from micro-organisms can be classified as MVOCs. (United States Environmental Protection Agency, 2016.)

TABLE 1. Classification of Organic Pollutants (United States Environmental Protection Agency 2016, adapted from World Health Organization 1989)

Description	Boiling point (°C)
Very volatile (gaseous) organic compounds (VVOC) [1]	<0 to 50–100
Volatile organic compounds (VOC) [2]	50-100 to 240–260
Semi volatile organic compounds (SVOC) [3]	240-260 to 380–400

[1] Propane, butane, methyl chloride, dichloromethane

[2] Formaldehyde, d-Limonene, toluene, acetone, ethanol, 2-propanol, hexanal

[3] Pesticides (DDT, phthalates, fire retardants (PCBs, PBB))

2.2 Sources of Volatile Organic Compounds in Indoor Air

The emission sources for indoor VOCs are diverse. Technically, next to any kind material or natural source may emit VOCs or participate in generation of VOCs, for instance, limolene can be excessively emitted from citrus fruits and perfumes. However, the majority of the indoor air VOC-emissions originate from anthropogenic sources. Construction materials, for example, floor carpeting, wood preservatives, glues, adhesives, tapestries, chipboards, paints, and paint strippers, are advocated as the most significant source. Other significant emission sources include air fresheners, aerosol sprays, cleaning agents, disinfectants, pesticides, stored fuels, office equipment such as copiers and printers, permanent markers, correction fluids and carbonless copy paper. (United States Environmental Protection Agency 2017; Austin, Brimblecombe & Sturges 2002, 79–83.) The emission sources are further elaborated in the table 2.

TABLE 2. Representative selection of indoor VOC emission sources according to Rundt., Backlund & Paakkola (2005)

Functional group	**Emission source**
Aldehydes: pentanal, hexanal, heptanal, octanal, nonanal	Wooden structures, chipboard, tapestries, floor waxes, fragrances, linoleum, dampened mineral wool
Benzaldehyde	Exhaust gases, chipboard and fiberboard
Aliphatic and cyclic hydrocarbons: hexane, heptane, octane, cyclohexane, methylcyclohexane	Glues, gasoline, exhaust gases, solvents, polyurethane
Nonane, decane, un-, do-, tri, tetra-, penta-, and hexadecane	Exhaust gases, fuel oil and diesel oil
C4-C5 hydrocarbons: Butanes, pentanes	Foaming agents, propellants, liquid gas (butane), polyurethane
Alcohols: propanols, butanols, pentanols	Solvents, cleaning agents, paints
Aromatic hydrocarbons: ethylbenzene, xylenes, trimethylbenzenes, toluene	Paints, varnishing, glues & adhesives, exhaust gases, gasoline, wall coatings, polyurethane, cleaning agents
Benzene	Gasoline, exhaust gases, smoking
Styrene	Polyester resins, rubber flooring, smoking
Glycols: 1-methoxy-2-propanol. 1-ethoxy-2-propanol	Water-soluble paints, varnishing
1,2-propanediol, 2-(2-ethoxyethoxy)ethanol	Cork tiling
Chlorinated hydrocarbons: tri- and tetrachloroethane, 1,1,1-trichloroethane	Solvents, dry cleaning agents. glues
Siloxanes: i.a. decamethylcyclopentasiloxane	Caulking agents, waterproofing insulations, textile impurity repellents
Terpenes: α- & β-pinene, 3-carene, limolene	Wood materials, fragrances, cleaning agents, paints, adhesives, solvents

2.3 The Effect of External Circumstances to Indoor Volatile Organic Compound Concentrations

Total volatile organic compounds (TVOC) level indoors depends significantly on external circumstances. Significant factors affecting emission rates include temperature, humidity, ventilation, emissions from materials and anthropogenic activities.

According to Järnström (2007, 19), an automated intake-exhaust ventilation system reduced the TVOC value of new constructions compared to buildings equipped only with automated exhaust ventilation. According to Wolkoff (1998, 2659–2668), the emissions of 2-ethyl-1-hexanol and phenol from polyvinyl chloride (PVC) were directly proportional to the flow speed of ventilation.

Several researches also indicate increased emission rates when relative humidity is risen, for instance, elevated levels of ammonia, formaldehyde and 2-ethyl-1-hexanol have been reported. (Järnström 2007, 15). Indirect linkages to relative humidity have been also established, for instance, according to Ministry of Social Affairs and Health (2009a, 137), absorption of VOCs to decorative and construction materials is greater under dry circumstances. Studies indicate increase in emissions of the compounds bound to materials and in degenerative emissions when the relative humidity is risen. When the humidity is risen, the levels of VOCs may increase significantly, the concentration of TXIB may triple and concentration of 2-EH may double. (Markowicz & Larsson (2015, 5772–5779.)

Elevated temperature increases the emissions from various sources, especially from construction materials. Different seasons result in mild changes in temperature, and there exists variance in temperatures within buildings and apartments. Moreover, elevated surface temperatures induce reactions of VOCs, inter alia, with ozone, and obscure the determinations. (Ministry of Social Affairs and Health, 2009a, 137; Järnström 2007, 27.)

VOC-levels are also dependent on anthropogenic activity. For instance, smoking increases concentrations of of several VOCs, for example, benzene and styrene. Austin et al. (2002, 81) refers to results obtained by Wolkoff et al. (1991), Adkofer et al. (1993), Norbäck (1993) and Hartwell (1987), in which higher VOC concentrations in the living room and lower concentrations in the second bedroom were reported.

2.4 Environmental and Health Effects of Volatile Organic Compounds

According to the Indoor Air Association (2008), the quality of the indoor air has been associated with healthiness, productivity and satisfaction. The adverse health effects VOCs cause depend on the concentration and the time of exposure. In higher concentrations, VOCs can be narcotics and depress the central nervous system, and exposures can lead to irritations of the mucous membranes and cause sensitization reactions in the eyes, skin and lungs.

Symptoms associated with VOCs are diverse, and include throat irritation, headaches, loss of coordination, nausea, damage to liver, kidney and central nervous system, conjunctival irritation, nose and throat discomfort, headache, allergic skin reaction, dyspnea, declines in serum cholinesterase levels, nausea, emesis, epistaxis, fatigue and dizziness (United States Environmental Protection Agency, 2017). Additionally, several VOCs, for example, benzene and 1,4-dichlorobenzene, vinylidene chloride, chloroform, carbon tetrachloride and ethylene dibromide have been classified as carcinogenic or mutagenic agents. At extreme concentrations, VOCs may result in impaired neurobiological functionality, which may result in coma, convulsions or even death. (Austin et al. 2002, 82–83.)

VOCs have also been associated having a causal effect in the building related illnesses (BRI) and "sick building syndrome". SBS is used to describe a situation where occupants of a building experience acute or chronic health effects, for example, mucosal, skin and general symptoms without being able to discern an apparent illness or cause. In SBS, it is common for occupants to report intensification of symptoms directly proportional to the time spent in the building and alleviation or cessation of the symptoms when being absent from the building. (Apte & Daisey 1999, 6; Norbäck, Torgén & Edling 1990, 739–740; Purge 2004, 185; Joshi 2008, 61–64.)

VOCs partake in diverse chemical reactions which take place on the surfaces or in the air of an indoor environment. For instance, certain VOCs possess a higher reduction potential compared ozone and participate in generation of mono-nitrogen oxides (NO_x-compounds). Wolkoff et al. (1997, 92–106) reported that SBS studies linked considerably lower VOC-concentrations to induce symptoms compared to results reported in the stud-

ies of individual compounds. Therefore, Wolkoff hypothesized the exposure to the reaction products to be of more importance. Reiss, Ryan, Koutrakis & Tibbetts (1995, 1906–1912) measured emissions of several polar VOCs, for example, aldehydes and ketones by reacting latex paint and ozone in a tube flow reactor, obtaining results indicating reactions between VOCs and ozone producing irritant substances, for example, acetaldehyde and formaldehyde.

2.5 Legislation Concerning Volatile Organic Compounds in Finland

The European Union set regulations limiting the usage of organic solvents, decorative paints and varnishes with. The Council of the European Union gave a directive 1999 "On the limitation of emission of volatile organic compounds due the use of organic solvents in certain activities and installations" (Directive 1999/13/EC). The directive was amended 2004 with the paints directive: "On the limitations of emissions of volatile organic compounds due the use of organic solvents in certain paints and varnishes and vehicle refinishing products" (Directive 2004/42/EC.)

Healthcare statute (1994/73) and healthcare degree (1280/1994) contain requirements for the safety of residential buildings and defines hazards to occupant health. According to the clause 26 in the Healthcare Statue (1994/73) "residence and communal spaces are to meet the requirements of "not endangering health of the residents or occupants in the apartment or communal space." Clause 27 states that "If noise, tremoring, odors, light, microbes, dust, smoke, excessive heat, cold or similar sources exists in amounts of causing harm or danger to occupants, procedures to determine, remove or to limit the causal effect are to be set out immediately." (Healthcare statute 1994/73; Healthcare decree 1280/1994.)

According to the clause 32 in the healthcare law (1223/2002) additional directives and information can be given out on the physical, chemical and microbiological factors in residential and communal spaces. In the case of indoor air quality, this has been carried out by giving out the "Residential Health Decree Application Directives".

The residential health decree application directive, part III contains regulations concerning chemical impurities, particles and fibers. sampling, personnel and determination. According to the directive, operational limit values for TVOC is 400 µg/m^3 and 50 µg/m^3 for an individual component. Furthermore, specific limit values have been set for certain compounds due to their prevalence and properties as agents of causing adverse effects. (Valvira 2016, 3-5.) The compounds under exceptional monitoring and the corresponding limit values are represented in the table 3.

TABLE 3. VOC-compounds with exceptional monitoring mentioned in the residential health decree application instructions (Adapted from Ministry of Social Affairs and Health 2016, 3)

Compound	**LV**
2,2,4-trimethyl-1,3-pentanedioldiisobutyrate (TXIB)	10 µg/m3
2-ethyl-1-hexanol (2-EH)	10 µg/m^3
Naphthalene	10 µg/m^3, and no odor
Styrene	40 µg/m^3

2.5.1 Indoor Air Qualifications and the General VOC-concentrations

The indoor air quality classification was updated 2018. The classification is directed to be utilized in architecture, construction and planning of housing complexes and to provide aid to construction industry when the aim is to build healthier and cozier buildings. The classification determines the limits for different variables in indoor air, which consist of limit values considering odors, structural damages affecting general indoor air quality, impurities, thermal comfort, draft, visual elements and noise levels. To obtain a specified classification, each subcategory must be met. The respective indoor air quality classifications are represented in the table 4.

TABLE 4. Indoor air classifications (Adapted from Säteri, 2018, 2)

Classification	**TLV**
S1	Individual indoor climate
S2	Good indoor air
S3	Satisfactory indoor climate

Materials used in construction and decoration can emit diverse chemicals to indoor air. The chemicals originate, inter alia, from materials, flaws in the manufacturing process, ageing of the materials or incorrect usage of the materials. The concentrations of impurities can be reduced by increasing ventilation or by reducing emissions. The primary procedure for reduction should be utilizing materials with low emissions. (Järnström 2007, 13.)

Construction materials are classified into three categories, M1-M3 according to their ability to create impurities. To reach indoor air qualification of S1 or S2, the majority of the construction materials should comprise of M1- and M2-classes (Järnström 2007, 16). Class M1 comprises of materials which have tested for emission rates (table 5).

TABLE 5. Limit values for M1-materials (Adapted from Säteri 2018, 17)

Variable	**TLV (µg / m²h)**	**Small / very small surfaces (0,4m²) (µg/m³)**
TVOC	≤ 200	≤20
Individual VOC component	≤ EU-LCI	≤ EU-LCI / 10
Formaldehyde	≤ 50	≤ 10
Ammonia	≤ 30	≤10
Carcinogens	≤ 1	≤ 1
Acceptance of odor	≥ 1	≥ 1

2.6 Volatile Organic compound concentrations in Finnish indoor environments

An approximation of a Finnish residential or communal space contains VOCs within the range of 50-250 µg/m^3. (Ministry of Occupational health 2012, 1). According to Salonen (2009, 239-247) investigations on the sources and preventing exposure is recommended when the TVOC exceeds 250 µg/m^3. Supporting the estimate, Järnström (2007, 46), found an average residence of the age of 12 months having TVOC levels of ~270 µg/m^3.

The age of the buildings plays a significant role. Young buildings exhibited higher VOC-concentrations, and the emissions gradually decrease to reach stabile emissions at the age of 12 months. Järnstrom (2007, 46), measured TVOC concentration of ~800 µg/m^3 in

apartments of zero months of age, and within the age of six months the apartment had significantly stabilized towards common levels of 250 µg / m^3.

VOC-concentrations in indoor industrial facilities are diverse. The ministry of occupational health performed a wide survey on the VOC-emissions in industrial environments, in which TVOC levels ranged from 50-260000 µg/m^3, and the average TVOC-level was found to be ~3600 µg/m^3. (Ministry of occupational health 2012, 6.)

3 INSTRUMENTATION

Applications of gas chromatography can be highly specific and precise. Combining a gas chromatograph with detection units of high selectivity and sensitivity, for example, an MSD, trace levels analytics is performable, and even isomeric compounds can be distinguished with certain applications. The range of gas chromatography applications is limited by only few factors, the most important being the requirement for the substances to possess a sufficient stability and volatility for the thermodynamical processes occurring during the determinations. (Rouessac 2007, 31.)

3.1 Gas chromatograph

Gas chromatography is a form of partition chromatography, in which an immobilized liquid is used as the stationary phase and a high purity gas, most often hydrogen or helium, as the mobile phase. A modern gas chromatograph comprises of thermostatically controllable components: an injector, a column, an oven and a detector. A basic schematic of a gas chromatograph is illustrated in the figure 1. (Hübschmann 2009, 2; Rouessac et al. 2007, 31–32.)

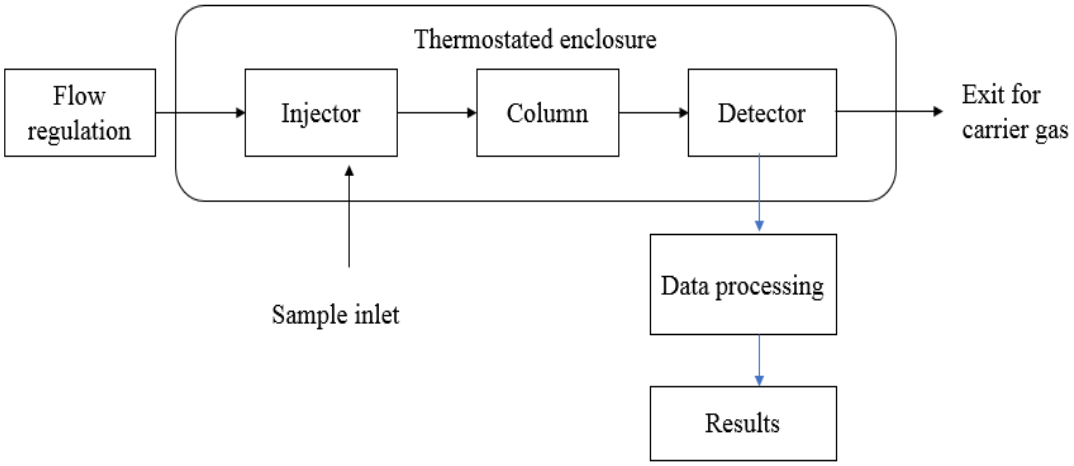


FIGURE 1. Schematic of a gas chromatograph (Rouessac 2007, 32)

A chromatographical assay is initiated by introduction of a liquid or a gaseous sample into the injector. The analytes are carried alongside the carrier gas from the injector

through the column, where the separation occurs. At the end of the column, the mobile phase passes through a detector and the analytes are identified or quantitated. (Rouessac 2007, 31.)

3.1.1 Sample introduction and the injector

The injector functions as the inlet for the sample to the column. The injector (figure 2) is a thermodynamically controllable, metal coated vessel with a replaceable glass liner. The injector has two entrances (one for sample, one for carrier gas) and three exits (two to purge valves and one to column). The most common injection method is liquid injection, where a small volume of the sample is introduced into a microsyringe, and the sample is injected through a gas tight septum into the liner. The introduction-injection process is commonly automatized: most gas chromatograph installations contain an application-controllable automatic liquid sample injector (ALS), which repeats the process washing of the syringe, sample introduction and injection. (Rouessac 2007, 35; McMaster 2008, 7)

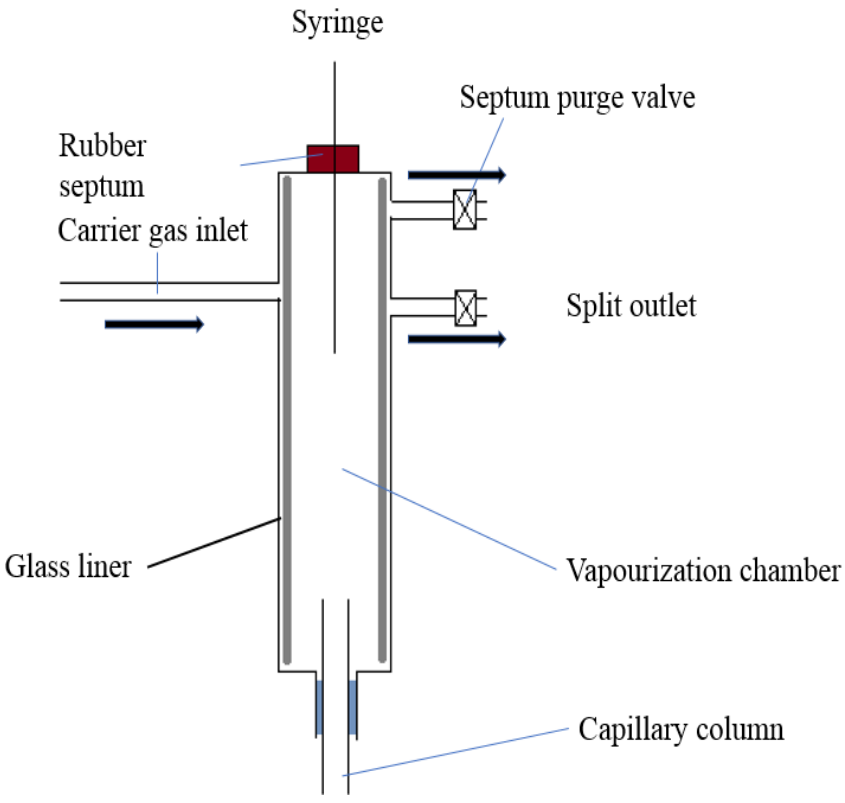


FIGURE 2. The structure of an injector (Adapted from Rouessac 2007, 38)

The interior of the injector consists of a replaceable glass liner. In the liner, the introduced sample is mixed with the carrier gas and ultimately carried to the column alongside with the carrier gas flow. Injectors can be set to function in split or splitless mode; in the former one only a portion of the analyte enters the column. (Rouessac et al. 2007, 34–37; Morgan 2012, 1.)

There exist also other methods to introduce the sample to the injector or column. For instance, sample introduction can be done with a "purge and trap"-technique, where a sample is vaporized with an external adsorbent thermal desorption device and transferred into the injector by utilizing a focusing trap. Another example is direct "on column injection", where the sample is injected directly into the column with a syringe. (Harris 2007, 37; Rouessac et al. 35–39.)

3.1.2 Capillary columns and oven

The functionality of the column is to separate the individual components of a mixture. Individual components retain characteristically in the stationary phase and elute inversely proportional to their corresponding vapour pressures and affinities to the stationary phase. (Rouessac 2007, 42.)

The stationary phase of modern WCOT capillary columns consists of thin layer of a vicious liquid is bound upon polymerized, high-purity silica (SiO_2) or polyethylene glycol (PEG). A variety of functional groups can be bounds upon the surfaces of the stationary phase to alter their properties, for instance, the 5% of the surface area of the stationary phase in HP-5-columns have been bound with methyl-phenyl groups. The outer coating of a column is manufactured from polyimide, aluminum, nickel or steel. (Rouessac et al. 2007, 31–35; Harris 2010, 566.) The inner diameter of a column varies within a range of 0,05-0,5 µm and the length of a column within 12–100 m. (Rouessac 2007 et al., 41). Thinner columns provide a higher resolution but require higher operating pressures and have a lower sample capacity. (Harris 2010, 567.)

In gas chromatographical installations, the column is placed in the oven, which is used to thermodynamically control the vapor pressure of the analytes. In isothermal or temperature programmed modes, the temperature of the oven must meet the limit of 0,1 °C deviation to obtain reproducible separations. (Rouessac 2007, 39.)

3.2 Mass Spectrometry and a Mass Selective Detector

Mass spectrometry is an analytical method of characterizing the masses of atoms or their corresponding fragmentation molecules. Mass spectrometry is a versatile and sensitive method used extensively in trace analytics. (Rouessac et al. 2007, 369.). According to Harris (2010, 502), a mass spectrometer is even capable of differentiating ions with the same retention time.

A mass spectrometer comprises of three major components: an ionization source, a mass selective analyzer and a detector. The sample is processed in subsequent steps of ionization, acceleration, separation and detection (figure 3). The result is converted into a mass spectrum. (Rouessac 2007, 369–371; McMaster 2008, 9)

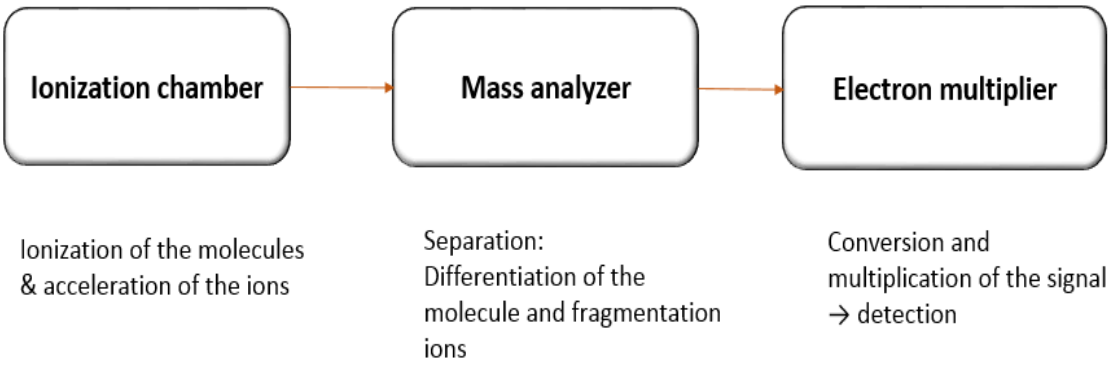


FIGURE 3. A simple schematic of the processing of a sample in the MSD (Rouessac 2007, 369–402)

A mass spectrum for an individual compound comprises of the specific breakdown ion m/z-distributions against their abundance (intensity). The ion with largest abundancy is defined as the base peak and receives a value of 100. Other ions are classified as percentages of the abundancies against the base beak. The characteristic distribution can be used

for identification, and quantitation is performable by combining the characteristic distribution and the measured intensity. (Rouessac 2007, 370.) The figure 4 illustrates the mass spectrum of methanol.

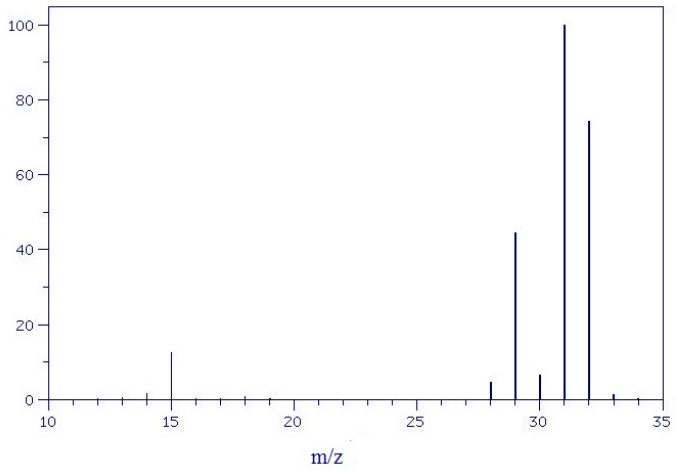


FIGURE 4. Mass spectrum of methanol (Adapted from Spectral Database for Organic Compounds)

3.2.1 Ionization Technique: Electron Ionization (EI)

In mass spectrometry, ionization of the target molecules is a prerequisite for the separation and differentiation. Electron ionization (EI) is a common method used to ionize the neutral compounds (McMaster 2008, 41).

The compounds emerging from the column are lead through a transfer line to a vacuumed ionization chamber, where the molecules or their vicinity is bombarded with electrons emerging from a hot filament. The electrons are accelerated to a level of 70eV, and when they make a close passage to neutral compounds, a fluctuation occurs in the local electric field, causing the electrons in the HOMO to gain enough kinetic energy to break free. As a result, a radical cation of $M^{+\bullet}$ is created (figure 5). The $M^{+\bullet}$ usually has enough internal energy to break into species-characteristic fragments. (Taylor 2012, 358; Harris 2010, 503.)

$$M + e^- \rightarrow M^{+\bullet} + e^- + e^-$$

FIGURE 5. Creation of the radical cation in EI (Harris 201, 503)

3.2.2 Mass Separation: Transmission Quadrupole Mass Analyzer

The purpose of the mass analyzer is differentiation of molecular ions and fragmentation ions. A variety of applications have been created for the purpose, for example, quadrupole mass, quadrupole ion trap, ion cyclotron and time of flight analyzers. A transmission quadrupole mass separator is a common choice due to its low cost and the small space the installation requires. (Harris 2010, 513-514; Rouessac et al. 2007, 381.)

A transmission quadrupole mass analyzer is a vacuumed chamber with four parallel metal placed within. A constant voltage is applied to the positive rods and an oscillating radiofrequency voltage is applied to the negative rods, which results in the creation of an electric field with a focusing effect (positive rods) and a defocusing effect (negative rods). Forces exerted upon the ions emerging from ionization chamber causes them to resonate in complex helical or corkscrew trajectories. Colliding with the rods culls the non-resonant ions, and only ions with a particular m/z-ratio reach the detector. The process is illustrated in figure 6. (Harris 2010, 513–514, Rouessac 2007, 383–384.)

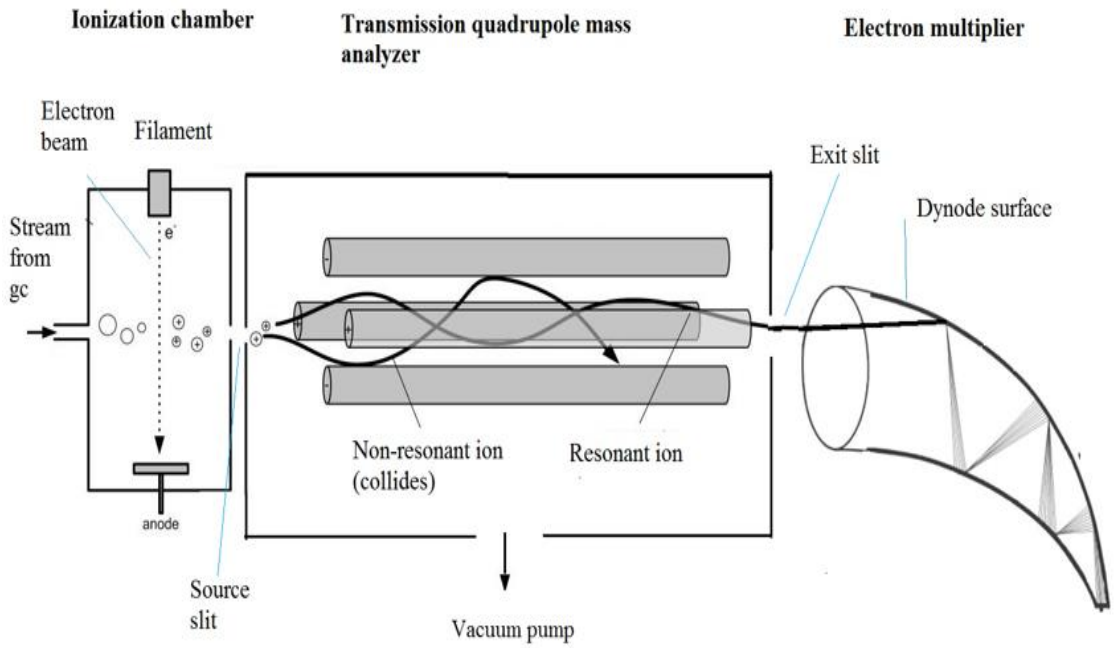


FIGURE 6. Simple schematic of a MSD-installation (Adapted from Wittmann (2007) and Burinsky (2011)

3.2.3 Detection: electron multiplier

An electron multiplier is a device used in mass spectrometry to convert the signal into an interpretable form and to amplify the signal. The lead doped glass walls of the electron multiplier function as a positively charged conversion electrode, dynode. The ions emerging from mass analyzer collide with the walls, which releases cascade of electrons upon impact. The secondary electrons can be accelerated and made to collide with dynode several times, each collision yielding in an exponential gain, up to 10^8. (Rouessac 2007 et al., 402; McMaster 123–124 .)

Modern applications can amplify the interpretable signal by applying a voltage across the EM, which amplifies the small ion current arriving from mass analyzer, intensifying both the response of the analytes and the background noise. In modern applications, the applied amount of voltage is expressed as a gain factor, where the factor is directly multiplicative to the present tuning. (Prest, Foote, Kernan & Peterson 2007, 1; Prest & Horn 2013, 1)

3.2.4 Scan and Selective Ion Monitoring Modes

The MSD can be operated in two different modes. In scan-mode, a specified, wide range of m/z-ions is detected and monitored; for instance, each ion within a range of 50–350. However, more time in a data acquisition cycle is required to differentiate the ions, and the background noise is also monitored. (Harris 2010, 522–523; Sparkman 140–141.)

In selected ion monitoring (SIM), the MSD is configured to analyze only few m/z-ions during specific time intervals, therefore eliminating the noise and interferences almost completely. Operating in SIM-mode requires less time in a data acquisition cycle for the measuring of the ion current of the specified ions. As a result, the signal-to-noise-ratio (SNR) is increased and the limits of detection and quantitation are lowered. (Harris 2010, 522–523; Sparkman 140–141.)

4 ANALYTICAL METHOD DEVELOPMENT AND VALIDATION

According to Riley (1996, 3) in laboratory environment, method development and validation are processes of creation, enhancement, affirmation or implementation of analytical or productive procedures. Method development and validation are essential tools to affirm credibility of the assays the laboratories provide.

4.1 Analytical Method Development

Analytical method development is a scientific process comprising of selecting, developing and ascertaining an assay to provide adequately accurate quantitative or qualitative results. In method development, an analytical procedure is developed to evaluate a characteristic of an analyte(s) to meet the established criteria of acceptance. (Chauhan, Mittu & Chauhan 2015, 1.)

The method development usually follows a protocol with subsequent steps (table 6). Method development for pre-existing methods is performed by tuning the method parameters and validation of the method. (Chauhan, et al. 2015, 1.)

TABLE 6. Method development tasks (Chauhan et al. 2015).

Process task
1. Standard analyte characterization
2. Evaluation of the method requirement
3. Literature survey
4. Selection of the method
5. Evaluating the instrument
6. Optimization of the parameters
7. Validation procedures

4.2 Selectivity, Limit of Detection and Limit of Quantitation

Selectivity is defined as a parameter to evaluate the capability of the method to detect accurately and specifically the analyte under defined circumstances, when the sample matrix contains several components. Specificity is defined as the capability of the method to detect only the defined analyte. (Ehder 2005, 27.)

Limit of detection is the lowest analyte concentration likely to be reliably distinguished from the blank. LOD is determined by measuring blanks and test replicates of a sample known to contain a low concentration of the analyte. LOD is the lowest concentration at which the analyte can be reliably detected and includes certain predefined goals for bias and precision. The real limit of quantitation (LOQ) may be equivalent to the limit of detection (Armbruster & Bry 2008, 1)

There are occasions when limits of blank cannot be measured. In these cases, the LOD and LOQ can be estimated utilizing regression analysis. The statistical estimates The LOD and LOQ can be calculated respectively to the equations 1 & 2. (Eurachem 2014, 17–19; Ehder 2005, 29–30.)

$$c_{\mathrm{LOD}} = \frac{3\, s_0}{b_1} \tag{1}$$

Where c_{LOD} is limit of detection, is s_0 is the standard deviation and b_1 is the slope of the calibration curve.

$$c_{\mathrm{LOQ}} = \frac{10\, s_0}{b_1} \tag{2}$$

Where c_{LOQ} is limit of detection, c_{LOQ} is s_0 is the standard deviation and b_1 is the slope of the calibration curve. (Ehder 2005, 30.)

5 PRINCIPLE OF THE ADSORPTION SOLVENT EXTRACTION METHOD

The principle to determine VOC-compounds can be considered complex. The process contains multiple phases, and the expression of the results as toluene equivalents further adds to the complexity. To elucidate the process of method development, this section covers the principle of the ASE-GC-MS-method which was to be developed.

The process of determining indoor air VOC-compounds between the range of hexane-hexadecane with "gas chromatograph - mass selective detector, adsorbent solvent-liquid injection"-method contains three entities: Formation of the retention time windows and toluene response factors, formation of linear range of operations and analyzation of a concentrated air sample. A schematic of the process (figure 7) elaborates on the relations and dependencies of the process.

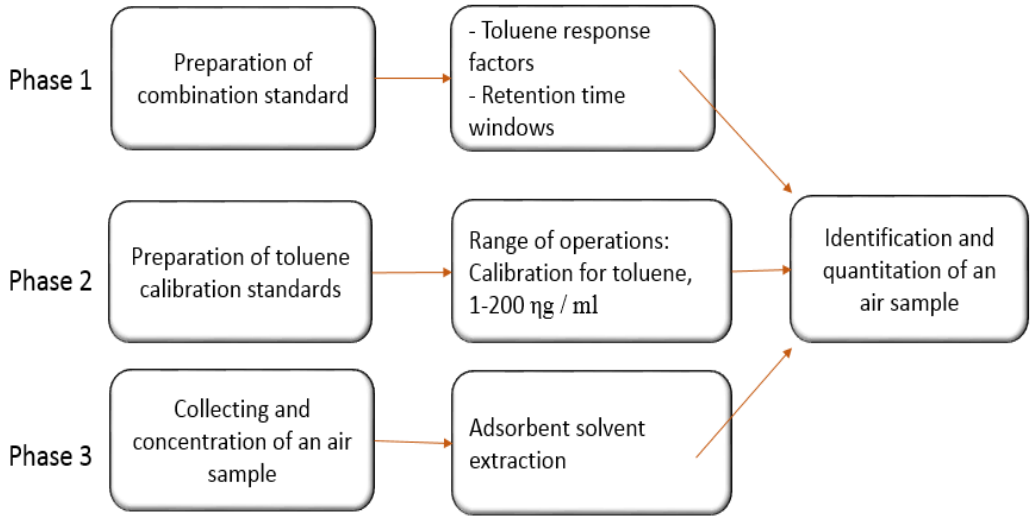


FIGURE 7. Schematic of the process in the ASE-GC-MS-method

The analysis of the calibration standards and samples is done with gas chromatograph-mass selective detector. Automatic liquid sample injector is used as the injection method.

A combination standard is prepared by injecting a defined volume of surrogate standards with a precision syringe into a headspace vial to prevent diffusion of the analytes through the septum. Appropriate further dilutions can be prepared from the stock solution.

To determine the toluene response factors and retention time windows for individual VOC-components, aliquots of the combination standard dilutions are analyzed. The MSD should operate in scan-mode. The toluene response factors are determined by dividing the area of an individual component by the area of toluene. Additionally, the method parameters should be adjusted in this phase to obtain adequate chromatographic separation.

The purpose of the second phase is to determine a range of operations. The toluene response factors of VOC-compounds range from 0,5–1,2. Therefore, other VOCs can be assumed to provide responses of a similar magnitude compared to toluene. To establish a linear range of operation, calibration standards containing toluene within the range of 1-200 ηg/ml are to be analyzed. The MSD should operate in simultaneous SIM / scan-mode.

In the third phase, an air sample is to be collected and concentrated. 10 dm^3 of indoor air is pulled through a metal tube containing Tenax TA®-adsorbent (poly(p-2,6-diphenylphenyleneoxide)-polymer). After collection, the adsorbent is transferred into a headspace vial, sealed, and 5 ml of methanol is added through the septum. The vial is vigorously shaken to desorb the analytes. An aliquot of the extracted sample is to be analyzed. The analytes are to be identified in scan-mode and quantitated in SIM-mode.

The results of the quantitation are to be expressed as toluene equivalents. The conversion should be done by adjusting the response of an individual component with the respective toluene response factor. TVOC calculated as the sum of the individual toluene equivalents. Analytes without pre-determined toluene response factors are to be calculated with a factor of 1.

The target level for identification and quantitation is 12 ηg/ml, which compares to an estimate of an individual component of an air sample introduced to the column. The requirement is further elaborated in the appendix 1.

If the sample is considered too dilute for the detection of individual components in scan-mode, SIM-mode can be utilized for identification. Comprehensive formation of toluene response factors and retention time windows covering each possible analyte is to be done prior to analyzing a sample. Chromatographic separation is to be sufficient; while operating in SIM-mode, overlapping compounds cannot be determined in a single run.

6 METHOD DEVELOPEMENT

A tentative method was created by obtaining information from literature, legislation and VOC-assays. Considerable sources in addition to the ISO 16000–6:2011 were, inter alia, assays performed by Hollis & Prest (2012) and Karine, David & Sandra (2008). The figure 8 illustrates the process scheme of the method development in this process.

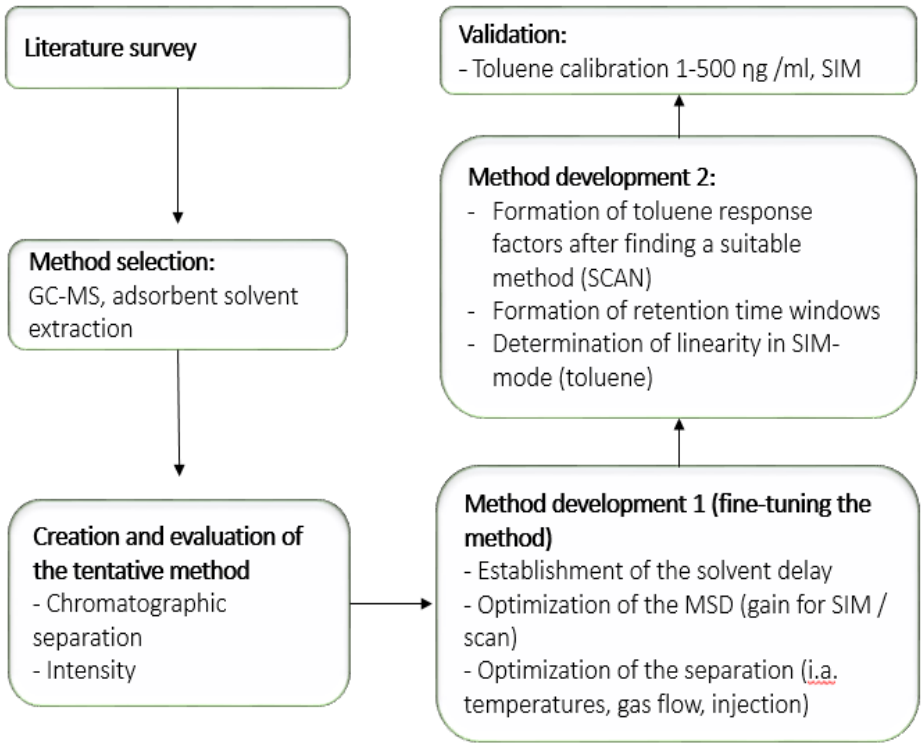


FIGURE 8. Roadmap of the whole process.

A combination standard stock solution containing either specific VOC-compounds or specific moieties prevalent in an indoor air sample was prepared from the chemicals in possession of TAMK. The combination standard or its dilutions were injected into the GC-MS to assess the performance of the specific methods.

A practical approach was chosen for the identification, in which individual components of a sample were to be identified in scan-mode. To reach the set goal, a wide-scale method development was performed to optimize the method parameters to reach sufficient intensity and chromatographic separation. Toluene response factors and retention time windows for individual components were determined with the finalized method.

Due to the dilution of the sample during ASE-ALS-process, a more reliable and precise quantitation in SIM-mode was considered necessary to ensure obtaining reliable results from samples containing trace level amounts of analytes. A representative linear range of operations was created by injecting calibration standards of toluene.

The obtained data from measurements was processed with MassHunter Qualitative client. The quantitation was performed by integrating the peaks utilizing “Integrate MS”-function. Different settings were used to select peaks to be integrated within a range of 1–8% of the largest peak. Identification was performed utilizing NIST library, and a visual evaluation of the total ion chromatogram (TIC) was used to determine the selectivity.

6.1 Instrumentation

The Intuvo 9000-series gas chromatograph installation was used to perform the assays. The assembly was altered during the assay by changing the column from HP-5 to HP-1. Figure 9 illustrates the Agilent Intuvo 9000-series gas chromatograph installation paired with the Agilent 5977b MSD.

FIGURE 9. The MSD and GC are to the left, installation to the right is the headspace-installation simultaneously connected to the gas chromatograph

The performance of two different columns, HP-1 and HP-5 was evaluated. The detailed setup for the instrumentation is presented in the table 7.

TABLE 7. Instrumentation for the assay

Technology	Specification
GC	Agilent Intuvo 9000 series
Autosampler	G4567A
Columns	HP-1 (60 m / 0,32 mm / 0,25 µm /
Column 2	HP-5 (30 m, 0,25 mm, 0,25 µm)
Carrier gas	Helium, 99,9995 %
MSD	Agilent 5977b
Applications	Agilent MassHunter Qualitative

6.2 Reagents and Equipment

The reagents used in the assay were pre-existent in the chemistry laboratory of TAMK. The respective chemicals and their providers are presented in the table 8, in which the chemicals are listed in the ascending order of elution.

TABLE 8. Chemicals used in the process.

Chemical	Provider	Purity (%)	Boiling point (°C)
Methanol	J.T. Baker	Ultra HPLC grade	64,7
2-butanone	J.T. Baker	>99	80
Hexane	Merck	ACS	69
2-butanol	Merck	p.a. >99	98-101
1,1,1-trichloroethane	J.T. Baker	>95%, 4% stabilizer	74
2,2,4-trimethylpentane	Fisher Scientific		98
Toluene	Merck	ACS	111
Hexanal	Sigma-Aldrich	98 (GC)	131
M-xylene	Fluka	p.a. >99	138
Nonane	Fluka	99%	150
1,4-butanediol	Sigma-Aldrich	ReagentPlus®, >99%	229
Benzaldehyde	Merck	For synthesis, >95	178
β-pinene	Merck	For synthesis, >95	164
Hexadecane	Fluka	Purum, >98%	287

Reliable determination required specific equipment to prepare the calibration standards (table 9). The caps of the vessels were made of PTFE to prevent dissolutive contamination and headspace vials were used to prevent diffusion of the analytes.

TABLE 9. Equipment used to prepare the calibration standards.

Piece of equipment	Etc.	Manufacturer
Headspace vial	22 ml	Agilent
Headspace septum material	PTFE / S	Agilent
GC vials	2 µl	Agilent
GC vial septum material	PTFE / RS	Agilent
Finnpipettes	250, 1000, 5000 µl	Thermo Labsystems
Tip	Polypropene	
Precision syringes	10-500 µl	Hamilton

6.3 Preparation of the Calibration Standards

A stock solution containing approximately 1000 µg/ml each surrogate standard was prepared by injecting the surrogates through the septum with a precision syringe to a pre-sealed headspace vial containing methanol. To avoid cross contamination, the precision syringe was rinsed between each addition with methanol at least five times, and a new batch of methanol was added to clean graduated cylinder between the injections. The amounts of different chemicals used to prepare the stock solution are presented in the table 10.

TABLE 10. The volume required to prepare the combination standard stock solution of 1000 µg/ml

Chemical	Volume (µl)
Methanol	14815
2-butanone	14,75
Hexane	18,00
2-butanol	14,65
1,1,1-trichloroethane	8,10
2,2,4-trimethylpentane	17,15
Toluene	13,70
Hexanal	14,55
M-xylene	13,80
Nonane	11,00
1,4-butanediol	11,70
Benzaldehyde	11,35
β-pinene	13,80
Hexadecane	15,35

A working solution of 1 µg/ml was diluted to headspace vial from the stock solution. Calibration standards of 1 ηg/ml–1000 µg/ml were prepared by injecting appropriate aliquots of stock or working solution to sealed GC-vials containing appropriate amount of methanol prior to injection.

For the calibration of toluene, a 1000 µg/ml stock solution was prepared by injecting 13,7 µl of toluene to a headspace vial containing 14987 µl of methanol. A working solution of 1000 ηg/ml was prepared by injecting 15 µl of the stock solution to a headspace vial containing 14985 µl methanol. Calibration standards of 1-500 ηg/ml were prepared by injecting appropriate aliquots to pre-sealed GC-vials containing methanol.

6.4 Preliminary Tests

Preliminary tests were performed to evaluate the adaptability of the tentative method. Chromatographic separation, intensity and quality of the peaks, column material were evaluated to discern possible shortcomings. Several samples of the combination standards within the range of 1–1000 µg/ml were analyzed. Respective standards are presented in the appendix 3.

The instrumental parameters of the tentative method are presented in the table 11. To reduce the time required for the assays, the small initial ramp of 5 °C ramp was considered unnecessary for the compounds eluting after toluene, and was increased to 15 °C/min.

TABLE 11. Significant parameters for the tentative method used in the preliminary tests

Parameter	**Specification**
Injection volume	3 µl
Guard chip	70 °C
Split	1:10, 1:5, 1:2
Column	HP-1 (60 m, 0,32 mm, 0,25 µm) / HP-5 (30 m, 0,25 mm, 0,25 µm)
Column flow	1,7 ml/min
Oven	40 °C, 5 °C/min → 130 °C 15 °C/min → 280 °C
MSD transfer line	280 °C
MSD mode	Scan
Gain factor	1
Trace ion	Off

6.5 Optimization of the System Parameters

The optimization of system parameters may have a huge impact to the outcomes of gas chromatographical assays. Optimizing the parameters of the gas chromatograph can enhance the chromatographical separation and the quality of the peaks, whereas optimization of the MSD parameters may increase the intensity tremendously.

According to the results obtained from preliminary tests (chapter 7.1.), a high-level optimization was considered imperative. Modifications were made to guard chip parameters, injection volumes, and to parameters of the inlet, the column and the MSD. The effect of the optimization procedures was evaluated by performing several determinations to combination standard dilutions within the range of 1 ηg/ml–1000 µg/ml

6.5.1 Optimization of the Guard Chip Parameters

To prevent contamination of the column, the Intuvo 9000-series is equipped with a guard chip in between the inlet liner and the column. A guard chip is a microfluidic which traps the sample residues into a 1 m inert flow path. (Intuvo Guard Chips and Jumper Chips.)

The temperature programme of the guard chip was altered to "follows oven temperature" from the original isothermal 70°C. The effects of the change are illustrated in the figure 10. The first picture (a) illustrates guard chip at constant temperature, and the latter one, (b) temperature follows oven, in which the forms of the peaks are sharper, and intensity increased approximately 15%

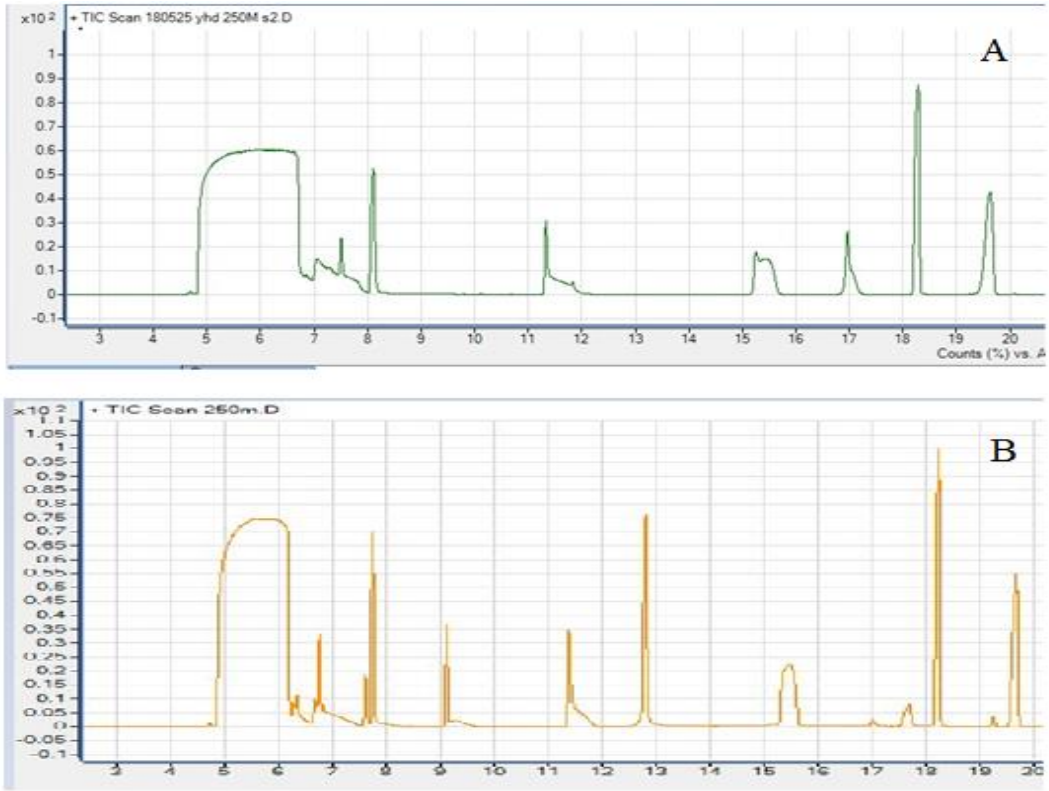


FIGURE 10. Results of the injections of 250 µg/ml, with different guard chip programmes

6.5.2 Optimization of the Column Parameters

Modifying the temperature ramp can be considered a two-faceted. Increasing the ramp reduces the duration of the assays and improves the quality of the peaks. However, higher temperature ramps may induce overlapping of the peaks, and extreme ramps induce bleeding of the column which may interfere with the assays.

The temperature ramp of 5 °C/min was considered inadequate for chromatographic separation of the early eluting compounds, thus the remediating measures were targeted at the temperature range of 40–70°C. The temperature programme of the oven was altered by reducing the temperature ramp between 40–73 °C from 5 → 2 °C/min. The 5 °C/min ramp between 73–130 °C of was maintained. Preliminary tests also indicated no necessity to alter the last ramp of 15 °C/min → 280 °C. In addition to the ramp changes, an isothermal holdup temperature of 5 minutes was added to the end of the assay at 300 °C as a measure to prevent contamination.

There are multiple facets to the gas flow. The chromatographic separation may be enhanced by lowering the gas flow of the column in the cost of increased run times. The Intuvo 9000-series utilizes thinner 0,32 mm columns (compared to more common 1 mm), which require less gas flow. If the split ratio is to be maintained, reduction of the column flow simultaneously reduces the inlet purge flow. Reduced column flow may expose the column to contamination, and reduced purge flow may expose the inlet to contamination.

Considering these aspects, the gas flow of the column was changed from 1,7 → 1 ml/min. Lower values were not tried out.

6.5.3 Split Ratio and the Injection Volume

Introduction of greater amounts of analytes to the column increases the response, however, it may induce adverse effects, for instance, saturation of the column or overloading the transfer line to the MSD. According to Rouessac (2007, 35) capillary columns can only handle a small amount of sample and are very susceptible to saturation even with an injection of 0,1 µl. Estimates of the safe injection masses and concentrations for Agilent 0,25 mm columns are included in the appendix 2.

Splits of 1:10, 1:5 and 1:2 were evaluated during the parameter optimization phase. After increasing the gain factor and considering an adequate purge flow, a conclusion of utilizing a split of 1:5 for the finalized method was reached.

6.5.4 MSD: Establishing Solvent Delay Parameter

The most significant factor to maintain the performance of the MSD is reduction of the strain to the filament. Besides the strain from an activated state, when sample matrix and analytes reach the ionization chamber, an additional strain is directed at the filament from the increased pressure. As a preventative measure, modern applications include a parameter of "solvent delay", which enables turning off the filament for a specified time, which can be used to eliminate the effect of the sample matrix. (Taylor 2016, 74.)

The peaks of methanol, 2-butanone, hexane, 2-butanol and 1,1,1-trichloroethane were in the vicinity of each other, and formation of the solvent delay required high precision. The respective retention time windows for the early eluting compounds are presented in the table 12.

TABLE 12. The retention time windows for the run performed 13.06.2018

Compound	**Start (min)**	**End (min)**
1: 2-butanone	6,624	6,941
2: n-hexane	6,941	7,09
3: 2-butanol	7,09	7,294
4: 1,1,1-trichloroethane	7,84	8,061

Several samples with different concentrations were analyzed to determine a compromised solvent delay of 6,5 minutes. The complete elimination of methanol was found impossible; residues of methanol eluted with the early eluting peaks. Graphical illustrations of the enhancement to the chromatographical separation and solvent delay are provided further in the section 7.2 and 7.3.

6.5.5 MSD: Optimization of the Electron Multiplier and Trace Ion Detection mode

One of the significant factors was the gain factor (chapter 3.2.3). In the tentative method, a gain factor of 1 was used according to the obtained instructions. However, the low gain factor resulted in significantly lower intensities which did not compare even close to the set target levels. As a reference value for trace analytics, Prest et al. (2007, 5), reported a common gain factor of 15 for EI ionization techniques. These factors invoked a necessity to alter the gain factor. After performing several assays, a conclusion of utilizing a gain factor of 10 for the finalized method was reached.

The Intuvo software provides an option of "Trace ion detection", which is a complex algorithm functioning as a filter. Enabling trace ion detection reduces peak intensity, increases peak width and reduces background noise. (Roushall & Prest 2007, 1–2.) The trace ion-mode was turned on.

6.5.6 Summary of the Parameters and the Finalized Method

The finalized method was used in determination of the toluene response factors (scan-mode, in evaluation of the identification (scan-mode) and in creating a calibration for toluene (SIM-mode). The finalized parameters for the gas chromatograph-mass selective detector are listed in the table 13.

TABLE 13. Equipment and parameters of the GC-MS

Instrument / parameter	Value
ALS (G4567A)	
Solvent wash	6x, 300 µl
Injection volume	3 µl
Guard chip (G4587-60565)	
Temperature	Temperature follows oven
Inlet	
Total flow	5 ml/min
Septum purge flow	3 ml/min
Split mode	1:5
Column (HP-1)	(60 m / 0,32 mm / 0,25 µm)
Column flow	1,0 ml/min
Avg velocity	22,035 cm^3/sec
Holdup	4,53 min
Oven	40 °C, hold 5 min 2 °C/min → 73 °C 5 °C/min → 130 °C 15 °C/min → 300 °C 300 °C, hold 5
MSD (Agilent 5977B)	
Transfer line temperature	280 °C
Thermal aux	On, 100 °C
MSD mode	Scan / SIM
Gain factor	10
Trace ion	On

6.6 Determination of Toluene Response Factors

To determine the individual toluene response factors, several assays were performed with the finalized method. The responses of the surrogate standards within the range of 1–1000 µl/ml were measured and compared to the response of toluene. Measurements with a wide range were performed to ensure the reliability.

According to Dietz (1988,2), within linear range, an individual response factor can be calculated by dividing the response of the analyte with the response of the internal standard. However, this applies only to analytes with the same concentration. The equation 3 represents a derivation from Dietz's formula, containing option for distinct concentrations. The toluene response factors were determined with equation 3.

$$RF_{\text{Analyte}} = \frac{A_{\text{Analyte}} \bullet c_{\text{ISTD}}}{c_{\text{Analyte}} \bullet A_{\text{ISTD}}} \quad (3)$$

Where *RF* is the response factor, A_{Analyte} is the measured area of the peak of the analyte, A_{ISTD} the measured area of the internal standard, c_{ISTD} the concentration of the internal standard, and c_{Analyte} the concentration of the analyte.

6.7 Target Level

To compare the obtained results to a realistic scenario, a target level was established by calculating concentration of an estimated concentration of an individual component in a generic indoor air sample after extraction and injection (equation 4).

$$RDC = \frac{m_{\text{TVOC}} \times V_{\text{air sample}} \times V_{\text{inj}} \times ratio_{\text{IC}} \times ratio_{\text{split}}}{1000\ dm^3 \times V_{\text{solvent}}} \quad (4)$$

Where, *RDC* is the required detection capability, m_{TVOC} is the total mass of the VOC-compounds in 1 m^3 air, $V_{\text{air sample}}$ is the volume of the collected sample, V_{inj} is the amount of injection, $ratio_{\text{IC}}$ the estimated ratio of an individual component in an air sample, $ratio_{\text{split}}$ is the split ratio and V_{solvent} the volume of the solvent used for the extraction.

Typical Finnish indoor air has approximately a TVOC of 250-300 µg/m^3 (Ministry of Occupational health 2012, 1), and a rough estimate of an individual component amounts to 1/30 of the TVOC. According to equation 4, a required detection capability for the ASE-method was estimated to

$$RDC \approx \frac{300000\ \text{ηg} \times 10\ \text{l} \times \frac{1}{30} \times 3\ \mu\text{l} \times \frac{1}{5}}{1000\ \text{l} \times 5000\ \mu\text{l}}$$

$$\text{RDC} \approx 0{,}012\ \text{ng}/\mu\text{l} = 12\ \ \text{ng}/\text{ml}$$

The estimated requirement is expressed in the same magnitude of injection volumes (microliters) and as the concentration of the calibration standards (milliliter-scale). The picogram-scale introduction to the column was considered extremely low.

6.8 Determination of the Linear Range of Operations

To determine the linear range of operations, calibration standards containing only toluene within the range of 1–500 ηg/ml were analyzed with the finalized method in SIM-mode. The MSD was configured to detect only ions characteristic for toluene (table 14).

TABLE 14. Significant breakdown ions of toluene (National Institute of Standards and Technology Chemistry WebBook, toluene (2017)

Breakdown ion	Primary	Abundance
91	Molecular ion	100
92	Molecular ion	78
65	Fragmentation ion	16

The obtained data was further exported to Microsoft® Excel and analyzed with data analysis toolpack. Regression, linearity and residuals of the calibration were evaluated.

7 RESULTS

This section covers the results of the preliminary tests, evaluation of the selectivity, determination of the toluene response factors, evaluation of the performance of the scan-mode for the identification and evaluation of the linear range of operations. The results of the preliminary tests were obtained using parameters of the tentative method (table 11), and the results of selectivity, identification, toluene response factors and the linear range of operations was determined with the finalized method (table 13).

7.1 Results of the Preliminary Tests

The results of the preliminary tests indicated that HP-1 was far superior for this assay compared to HP-5. With the tentative method, an overlapping of the analyte peaks occurred, especially hexane, 1,1,1-trichloroethane, 2-butanone and 2-butanol. Moreover, the overlap intensified in lower concentrations. The quality of the peaks was considered obscure: In lower concentrations, certain peaks became deformed or tailed significantly. The figure 11 represents the total ion chromatogram (TIC) of a 50 µg/ml where 2-butanone, 2-butanol, hexane, 1,1,1-trichloroethane and residues of methanol overlapped in the wide peak between 7–8 minutes.

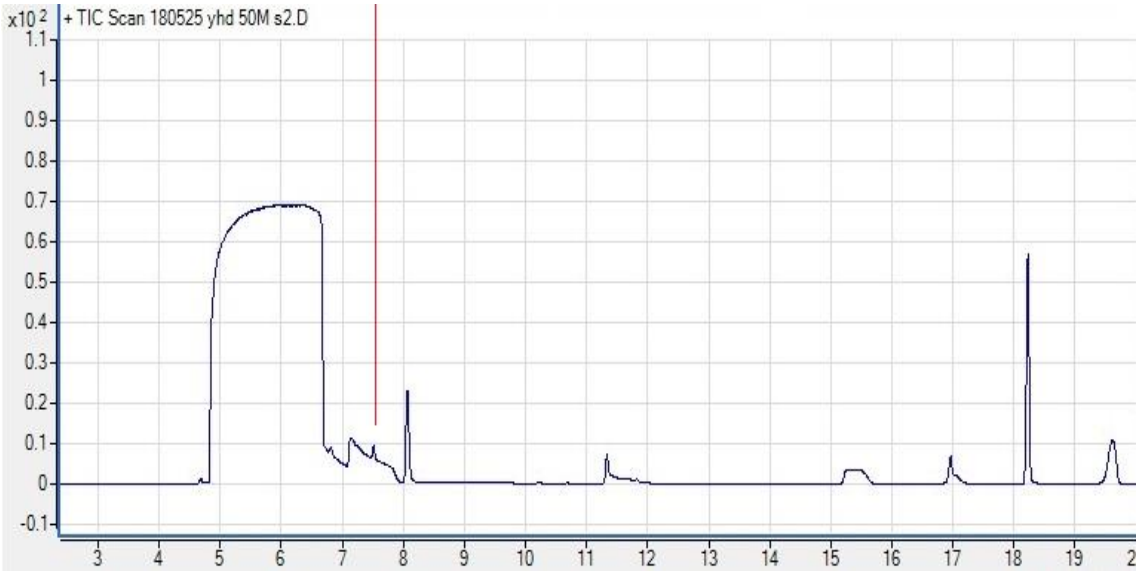


FIGURE 11. A TIC of 50 µg/ml (all surrogates) with the tentative method

Intensity was considered very low. The figure 12 represents the TIC of an assay where surrogates at 10 ηg/ml were analyzed. On the target level, none of the surrogate standards could be distinguished, the only distinguishable peak was the solvent, methanol.

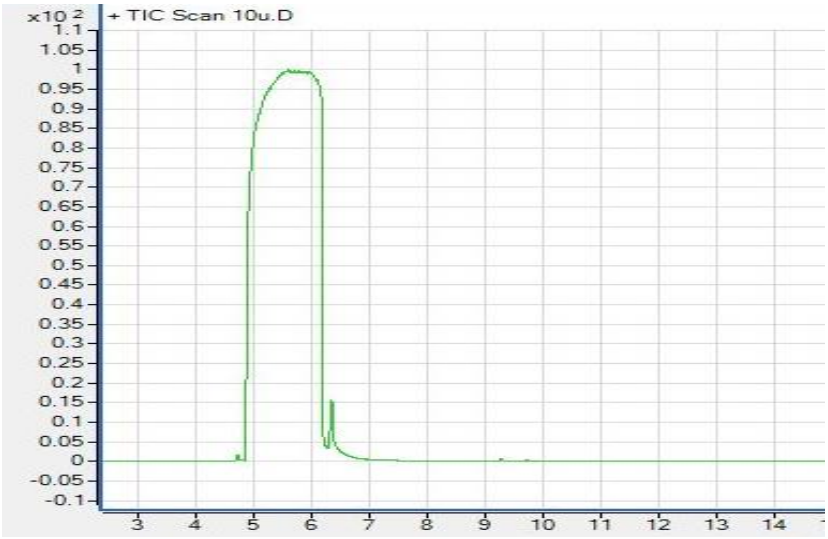
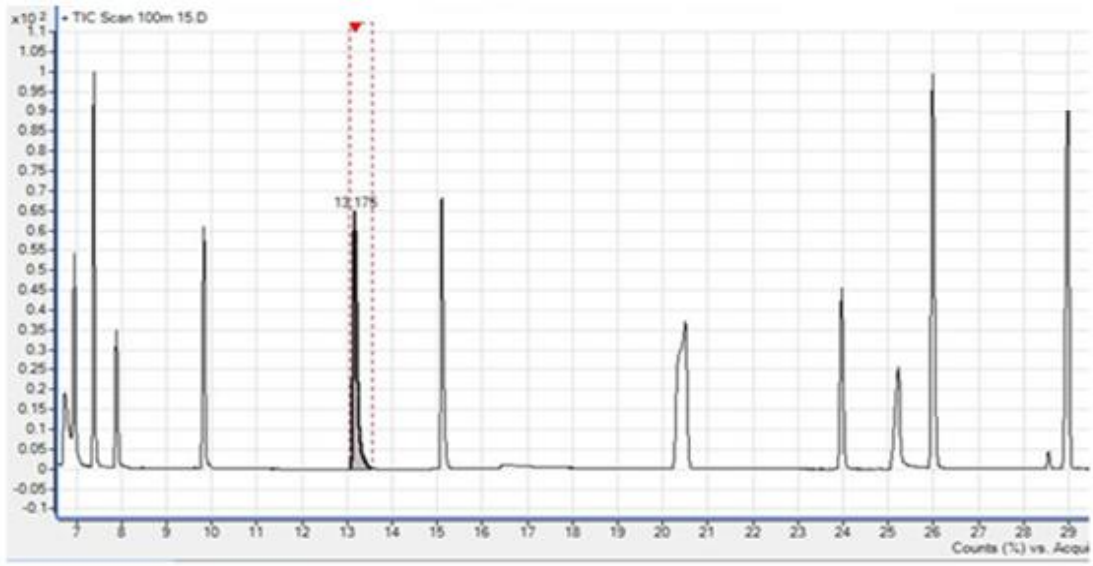


FIGURE 12. Obtained total ion chromatogram from an assay of 10 ηg/ml with the tentative method

7.2 Selectivity, Finalized Method

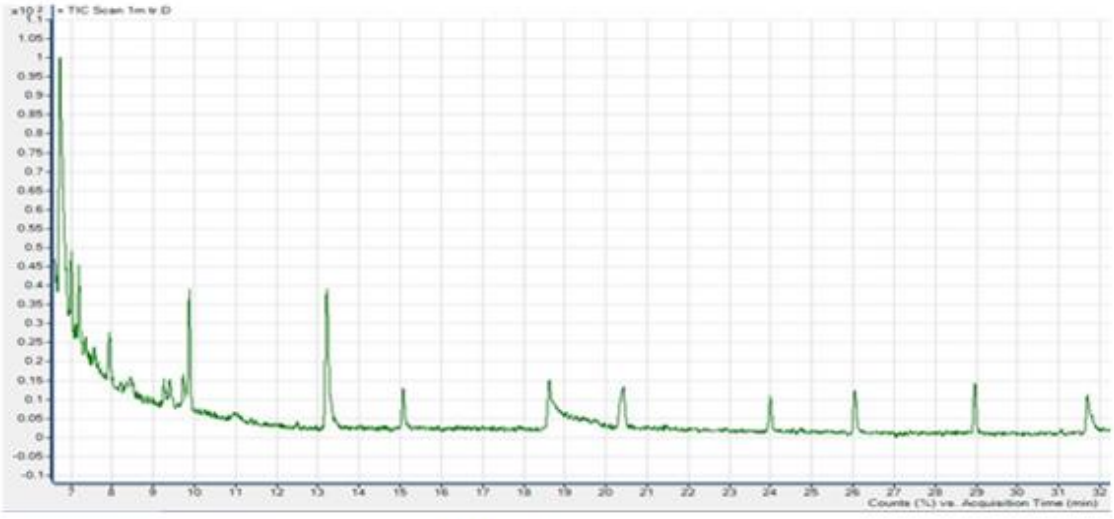
The adjustment of 35 → 73 °C, 2 °C/min to the temperature programme resolved the separation of the early eluting compounds with respect to each other. However, residues of methanol tailed extensively from six to nine minutes and overlapped with the early eluting compounds. The overlap effect more significant with assays performed in lower concentrations.

With the alterations, the data processed with MassHunter could efficiently distinguish the individual VOCs in adequate concentrations. The overlap of methanol was considered irredeemable; however, the chromatographic separation could be found sufficient to be utilized in SIM-mode to quantitate the early eluting compounds by excluding the breakdown ions of methanol. The chromatographic separation is illustrated in the figure 13a for a higher concentration sample and a lower concentration sample in the figure 13b, where an elevation of the baseline with the early eluting can be observed.



2-butanone	6,7 min	Hexanal	14,9 min
Hexane	7,0 min	M-xylene	20,4 min
2-butanol	7,2 min	Nonane	23,9 min
1,1,1-trichloroethane	7,9 min	1,4-butanediol	25,9 min
2,2,4-trimethylpentane	9,8 min	Benzaldehyde	25,9 min
Toluene	13,2 min	B-pinene	28,9 min

(a)



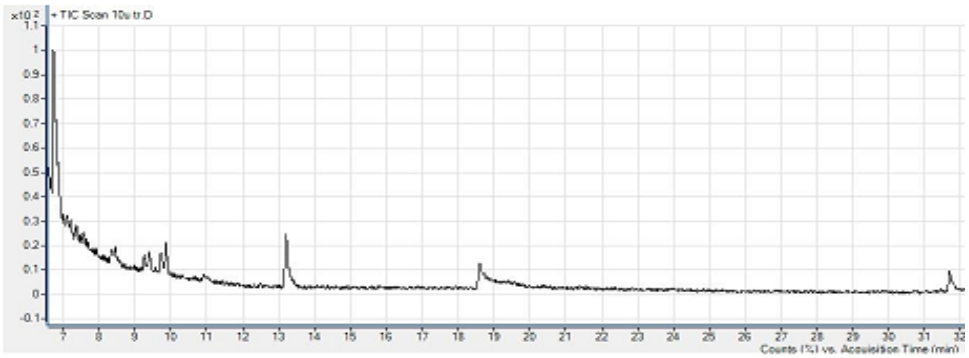
(b)

FIGURE 13. (a) The TIC of a sample containing surrogates at 100 µg/ml; (b) The TIC of A sample of a sample containing surrogates at 1 µg/ml

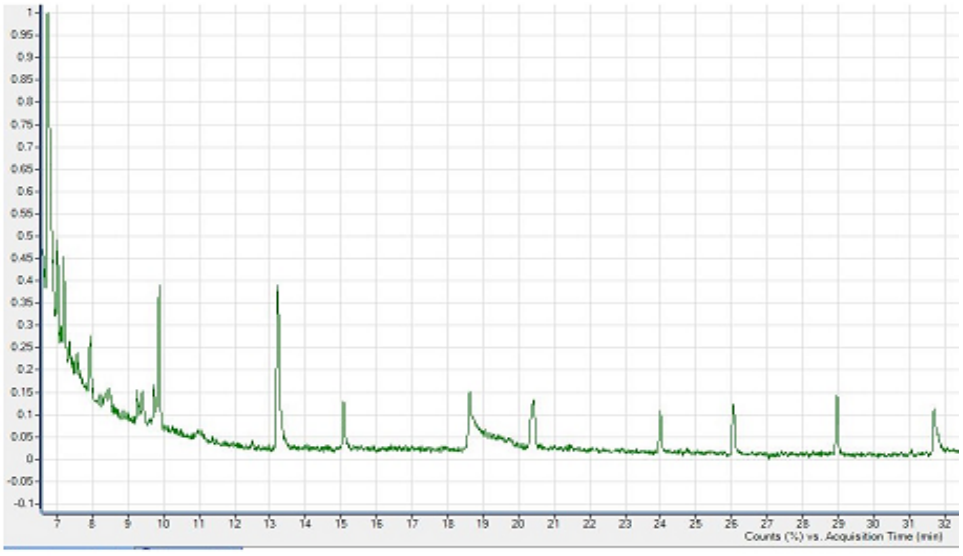
7.3 Identification of the Individual Components in SCAN-mode

The evaluation of identification in scan-mode was performed by analyzing combination standards with the finalized method within the range of 10–10 000 ηg/ml. The lowest calibration standard compared to the approximated to the target level.

The intensity for the identification in scan-mode was found insufficient. The figure 14a, represents TIC of 10 ηg/ml, in which MassHunter could identify none of the VOC-components. The figure 14b represents a scenario of sample of 1000 ηg/ml with an acceptable identification rate of 90 %, which compared to injections eighty times of the target level (12 ηg/ml). The results demonstrated the unviability of the scan-mode for identification comparing to the level of an indoor air sample.



(a)



(b)

FIGURE 14. (a) TIC containing surrogates at 10 ηg/ml, where no identification could be performed by MassHunter; (b) TIC containing surrogates at 1000 ηg/ml, in which most of the compounds could be identified

7.4 Toluene Response Factors

The toluene response factor for a specific component was calculated using equation 3. The results were calculated as the average of the responses obtained from the combination standards of 50, 100 and 250 µg/ml. The individual response factors are presented in the table 15, and raw data for the determination is included in the appendix 4.

TABLE 15. The toluene response factors and corresponding relative standard deviations

Compound	Response factor	RSD (%)
2-butanone	0,471	0,1
Hexane	0,496	0,7
2-butanol	0,664	0,9
1,1,1-trichloroethane	0,347	1,3
2,2,4-trimethylpentane	0,640	0,3
Toluene	1,000	0,0
Hexanal	0,679	2,4
M-xylene	1,152	4,0
Nonane	0,550	2,4
1,4-butanediol	0,509	17,8
Benzaldehyde	1,203	7,5
β-pinene	1,131	5,7
Average deviation		3,8

The toluene responses indicated only minor deviations. However, some compounds, like 1,4-butanediol, benzaldehyde and β-pinene had deviating responses due to obscure retention, and the deviation intensified inversely proportional to the concentration.

7.5 Linear Range of Operations

Three different range calibration curves for toluene, 1–200 ηg/ml, 10–200 ηg/ml and 10–500 ηg/ml were evaluated to determine the linear range of operations. The selected ranges covered widely the range around the target level. The calibration was created by measuring the response of the toluene calibration standards at 13,3 minutes. Table 16 contains the concentrations of the calibration standards, areas and width of the peaks. The standard

of 1 ηg/ml did not correlate according to the regression and the width of the peak deviated from the average.

TABLE 16. Results of the toluene calibration

Concentration (ηg / ml)	Area	Width	Retention window (min)
Blank	0	0	~13.3
1	847	0,181	13,308
10	5232	0,262	13,292
20	8619	0,25	13,292
50	17551	0,279	13,297
100	33762	0,263	13,297
200	64994	0,28	13,292
500	169020	0,284	13,297

Calibration for the range 1–200 ηg/ml (figure 15) was created to evaluate the linearity in realistic setting, where lowest standard compared to 8% of the estimate of an individual component. However, range between 1–10 ηg/ml could be considered non-linear. Even with the early inclination, the coefficient of variation (R^2-value) could be still considered satisfactory.

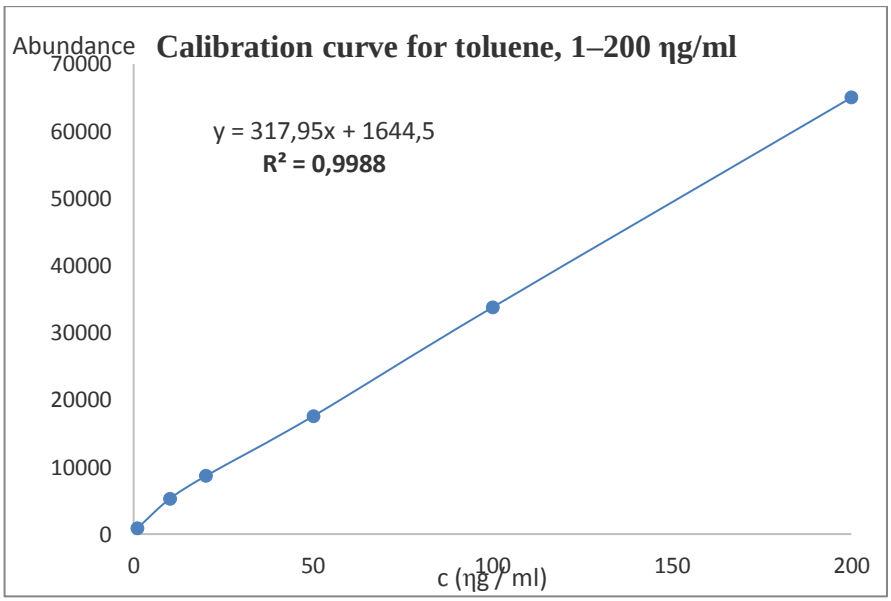


FIGURE 15. Graphical illustration for the calibration of 1–200 ηg/ml.

Due to the non-linearity of the initial point, a calibration for the range of 10-200 ηg/ml (figure 16) was evaluated according to the obtained results. The coefficient of variation was considered excellent.

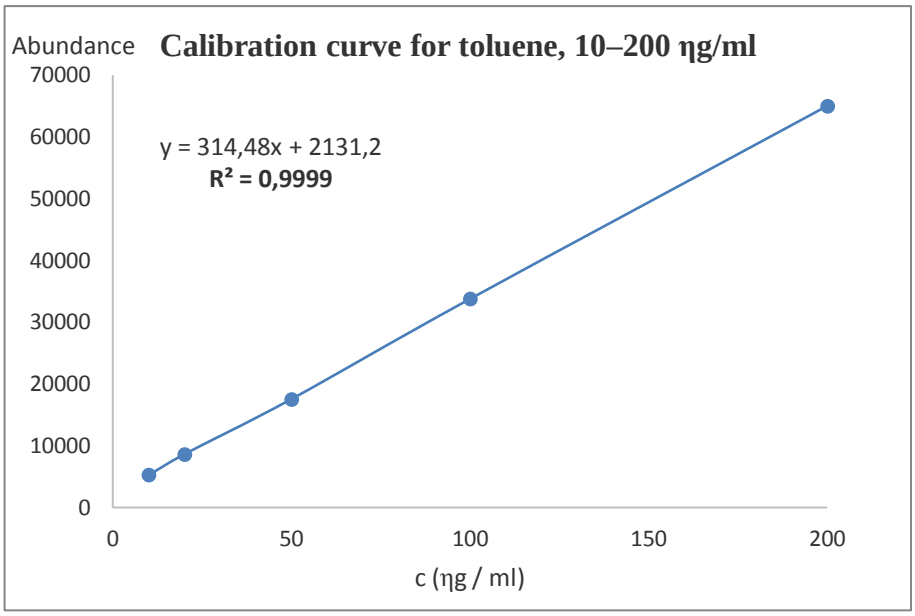


FIGURE 16. Graphical illustration for the calibration of 10–200 ηg/ml

To extend the operational range, a calibration of 1-500 ηg/ml (figure 17) was evaluated. The highest point of the calibration approximated to 42 times the estimate of an individual component. A significant incline from 200→500 could be detected from graphical illustration. The coefficient of variation was considered satisfactory.

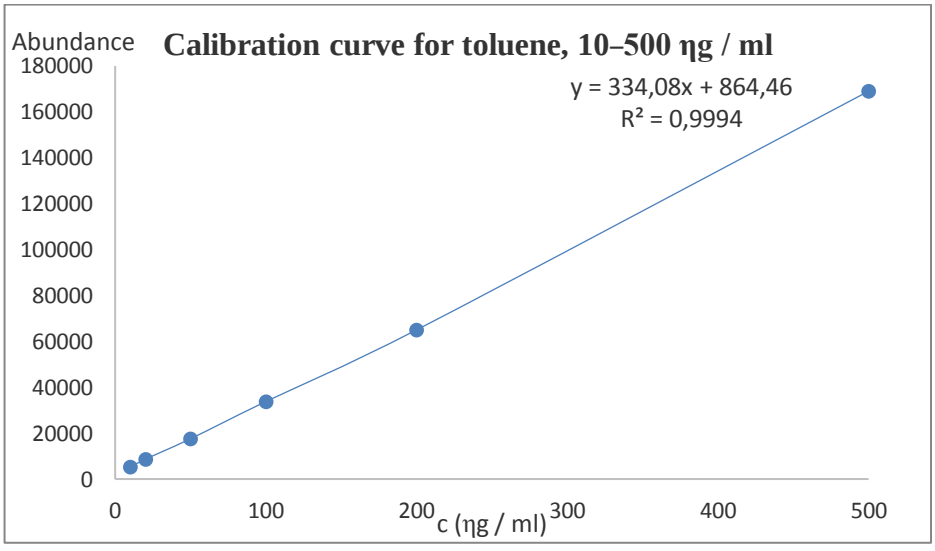


FIGURE 17. Calibration of 10–500 ηg/ml.

The linearity of the calibration standards was excellent above ranges of 10 ηg/ml, and residuals for each calibration (appendix 5) adhered to normal distribution. However, the responses of the calibration curve of 10–200 ηg/ml adhered significantly better to the real responses compared to the calibration of 10–500 ηg/ml (Appendix 6). Therefore, the linear range of operations was determined as 10–200 ηg/ml.

A contamination was detected in the system during the calibration of the toluene. However, the contamination did not interfere with the 13,3-minute timeframe during the successful calibration of toluene.

7.6 Limit of Quantitation and Limit of Detection

To establish the empirical limit for SIM-mode, the values, linearity and quality of the toluene calibration standard responses were evaluated. For scan-mode, the limits were calculated using the responses of toluene from the combination standards.

The statistical estimates were calculated from the regression analysis utilizing equations 1 and 2. Empirical limits were concluded more accurate for SIM-mode ones and the statistical estimates were considered more credible for scan-mode. The LOD and LOQ for both modes are presented in the table 17.

TABLE 17. Limits of detection and limits of quantitation for scan and SIM-modes; the most credible limits are underlined

Method and parameter	**Limit, empiric (ng/ml)**	**Limit, statistical estimate (ηg/ml)**
Target level	12	12
LOD (scan)	1000	<u>2920</u>
LOQ (scan)	5000-10000	<u>9747</u>
LOD (SIM)	<u>1</u>	3,65
LOQ (SIM)	<u>10</u>	12,16

8 DISCUSSION

The aim of the bachelor's thesis was to provide the laboratory with a GC-MS-method for reliable determination of indoor air VOCs. The objective was set to developing and validating an adequate method based upon the ISO 16000–6 to identify and quantitate VOCs between hexane and hexadecane utilizing adsorbent solvent extraction. The approach for the method development was to utilize scan-mode for the identification and SIM-mode for precise quantitation of the individual VOC-components.

As the outcome of the process, a GC-MS-method was successfully developed and fine-tuned, and the finalized method in SIM-mode met the demanding intensity target level Chromatographic separation was concluded sufficient for compounds between hexane and hexadecane. The aim can be considered partially reached due to the prowess of the method in SIM-mode.

The objective was partially reached: A method was developed and fine-tuned, but the method in scan-mode was conclusively found insufficient for reliable identification on the levels comparing to air sample. Additionally, adequate validation was not performed due to occurring contamination and limited time resources.

There exists a possibility for utilizing the SIM-mode for identification: A comprehensive categorization of the VOC-compounds would provide the required retention time windows and toluene response factors. A prerequisite for identification is adequate chromatographic separation, which was achieved with the finalized method.

As a significant shortcoming, a real sample was not collected or analyzed during the process. Therefore, the performed assays did not represent a real sample-scenario, but rather functioned as a credible simulation to one, in which the performance of the method was evaluated using representative analytes comparing to concentrations of an air sample. Due to the high cost of the materials and equipment, the collection and analysis of an air sample was to be considered after development and affirmation of an adequate method. Additionally, without acquisition of the Tenax® TA-adsorbent, the efficiency of the adsorbent solvent extraction was not evaluated.

The chromatographic separation was intentionally enhanced for the early eluting compounds. Traditionally, VOC assays use temperature ramps a lot higher than 5 °C. However, the higher ramps could not separate several of the early eluting compounds with the Intuvo 9000 and HP-1, and many of the early eluting compounds, inter alia, chloroform and chloroethanes are likely to exist in Finnish indoor air.

The toluene responses obtained with the finalized method were considered reliable. The toluene responses measured in different concentrations (50-250 µg/ml) yielded similar responses, the average relative standard error (RSD) being 3,8%. Ahn, Pandei & Kim (2011, 22) reported similar RSDs for a direct injection-method, Hollis (2012, 16–17) over 10% for P&T-method, and Karine et al. (2008, 12–13) reported RSDs over 12% for a headspace-assay.

The linear range for operations was initially considered narrow. However, Zabiegala, Partyka, Zygmunt & Namiesnik (2009, 498) reported highest individual component concentration for heptanol, 750 µg/m^3, which would compare 140 ng/ml after the extraction in this method. The linear range of operations for the finalized method was concluded as 10-200 µg, therefore it was concluded to cover the legislative range in Finnish indoor environment. The wider calibration of 10-500 ηg/ml induced a small deviation to the regression and the coefficients of variation were considered decent, but comparison of the real obtained values to the values obtained with the trendline equation deviated 5%. However, the deviation was still within generally accepted limits.

The LOD for scan-mode was established as the worst-case scenario, where the MassHunter Qualitative software was unable to identify the individual components sufficiently. In scan-mode, the LOD (2920 ηg/ml) and the LOQ (9747 ηg/ml) were far off from the target level of 12 ηg/ml. However, in SIM-mode, an LOD of 1 ηg/ml and LOQ of 10 ηg/ml were established, which met the target level. According to Hollis (2012, 18) a common LOD with P&T-methods is 0,5 ηg/ml, and Karine et al. (2008, 12–13) reported LOD of 4,2 ηg/ml.

There were several fundamental aspects relating to the assay, of which intensity was the most significant. The premonition of scan-mode being insufficient for wide-scale, practical identification was conclusively confirmed during the process. Results obtained with the finalized method were significantly better compared to tentative method. Further fine-

tuning of the method parameters to elevate the performance was considered unavailing; the scenario of reaching target levels was unlikely. Further optimization would have also been challenging, and elevated gain values would have induced heavy strain to the electron multiplier.

Passing larger volumes of air through the adsorbent to further concentrate an air sample is not recommendable. According to the ISO 16000–6, at least 200 mg of Tenax® TA should be used for the concentration. However, increasing the volume of air, for instance to 50 dm^3, would exceed the breakthrough volumes for specific compounds. Moreover, according to the breakthrough volume data presented Scientific Instruments Service Inc. (2017), even recommended amounts of adsorbent may experience losses of analytes with 10dm^3 sampling volumes, especially with haloalkanes.

The combination standard prepared from the chemicals pre-existing in TAMK was not thoroughly representing VOCs prevalent in Finnish indoor air. The prepared combination standard contained thirteen specifically selected chemicals; in comparison the commercial standards contain over fifty analytes. However, the selected chemicals were representative, and covered a wide range of similar structures, moieties or chemical reactivity. As a significant shortcoming in chemical selection, the compounds under special monitoring 2-EH, TXIB, naphthalene and styrene were not acquired. Utilization of a comprehensive standard and categorizing the compounds under exceptional monitoring would enable the utilization of the SIM-mode for the identification.

An unorthodox method was used to prepare the stock and working solutions of the calibration standards. The choice to use headspace vials as vessels was considered the most optimal available in terms of analyte preservation, cost-efficiency and waste. The composition of a headspace is designed to withstand pressure alterations and the material and thickness of the septum is greater compared to alternatives. This prevented diffusion of the most volatile analytes and conserved solvent. Additionally, when introducing the calibration standards to GC-vials, the container could be maintained sealed, and the application of aliquots to the GC-vials was simple due to the easy introduction of the stock solution to the precision syringe from the headspace vial.

During the determination of linear range of operations, a recurring contamination was detected in the system, where residues of toluene could be detected. The fluxing of toluene was considered low, therefore it affected only sensitive SIM-mode assays. However, reliable reproduction of the toluene calibration was not performable. A plausible reason for the contamination was utilization of low initial point - low ramp temperature programme, which may have caused condensation of the analytes in the early parts of the column. Additionally, there exists an affinity-interaction with toluene and silica (Jin, Wang, Wang, Jin, Lu, & Luo 2011, 405–411). When toluene is mixed with silica, it converts the structure of the light grey silica to transparent entity, which is an indication for a strong interaction. Pressure-dependent thermal desorption of toluene bound to silica requires more intense conditions compared to other solvents, for instance, chloroform. The same affinity-interaction most likely occurred with the stationary phase of the HP-1 capillary column, and subsequent exposures to hundreds of samples may have promoted contamination even in low concentrations.

To resolve the issue of toluene-silica interaction, for instance, methyl pivalate (appendix 7) could be a considered as an ITSD due to its boiling point of 101 °C (Merck, 4). Moreover, a tertiary ester is expected to exhibit thermodynamical and chemical stability. Unfortunately, determinations according to present legislation offer no alternatives to replace toluene.

As one measure to avoid the contamination, utilizing a higher initial temperature of 40 °C and a higher temperature ramp of 5-10°C for the early eluting compounds is to be recommended. The higher ramp would additionally enhance the quality of the peaks, especially with problematic compounds like toluene, conjugated diols and aldehydes. In retrospect, the flow speed of the column should have been prioritized in spite of alterations to the temperatures.

The ASE-method could provide an alternative for the P&T-methods. However, there were several issues with the assay which require further investigation. For the utilization of SIM-mode in identification, a wide-scale categorization of the individual components utilizing commercial VOC-standards and specific individual chemicals should be performed. The cause for the contamination should be thoroughly investigated; it is highly likely for similar contamination to occur widely in assays containing toluene. For reliable

quantitation and reporting, uncertainty of the measurement should be investigated by performing repetitions of analyzes for a specific concentration of the combination standard in SIM-mode. Additionally, the efficiency of the adsorbent solvent extraction is to be evaluated and the acquisition of a tube conditioning equipment to recycle the Tenax® TA-adsorbent is to be considered. Considering the intensity, it is recommendable for the service provider to utilize P&T-methods.

A reliable determination of (indoor) VOCs is multi-levelly challenging. Several concepts, inter alia, diversity of the sample, sample collection, materials, behavior and reactivity of the chemicals, column properties, calibration standard preparation, safe sampling volumes, instrumental parameters and instrumental efficiency are to be considered simultaneously. Cost-efficient and accurate results are obtainable only with a combination of adequate instrumentation, chemicals, materials, methods and proficient personnel.

Lastly, recent surveys indicate that the quality of indoor air and especially the concentrations of VOCs is of great significance to residential and occupational health. Further research in the subject is of great importance both nationally and globally; there exists a necessity to obtain more credible, updated information and for a deeper understanding of the phenomena to which VOCs participate in.

REFERENCES

Agilent. Intuvo Guard Chips and Jumper Chips. Viewed 3.7.2018. Retrieved from https://www.agilent.com/en/products/gas-chromatography/gc-supplies/intuvo-supplies/intuvo-guard-chips

Ahn, J., Pandey. S., Kim, K. 2011. Comparison of GC-MS Calibration Properties of Volatile Organic Compounds and Relative Quantification Without Calibration Standards. Journal of Chromatographic Science, vol 49. pp 19-28

Armbruster, D., Pry, T. 2008. Limit of Blank, Limit of Detection and Limit of Quantitation. The Clinical Biochemist Reviews.

Apte, M., Daisey, J. 1999. VOCs and "Sick Building Syndrome": Application of a New Statistical Approach for SBS Research to U.S. EPA BASE Study Data. Indoor Environment Department, Lawrence Berkeley National Laboratory. Berkeley, CA, USA

Austin, J., Brimblecombe, P., Sturges, W. 2002. Air Pollution Science for the 21st Century. 1st edition. Kidlington: ELSEVIER SCIENCE Ltd. ISBN: 0 08 044119 X

Bloemen, H., Burn, J. 1993. Chemistry and Analysis of Volatile Organic Compounds in the Environment. New Delhi, India: Springer Science+Business Media Dordrecht. ISBN 978-94-010-4953-5

Brown V., Cockram A., Crump D., Gavin M. Indoor Air assessments in the U.K. carried out by the building research establishment advisory service. In: Saarela K, Kalliokoski P, Seppänen O, editors. Proceedings of Indoor Air '93, Helsinki, vol. 2. 1993. p. 111–6.

Burinsky, D. 2006. Comprehensive Analytical Chemistry. Volume 47. Pp. 319-396.

Chauhan A, Mittu B, Chauhan P. 2015 Analytical Method Development and Validation: A Concise Review. J Anal Bioanal Tech 6. 233. DOI: 10.4172/2155-9872.1000233

Dietz, W. 1988. Response Factors for Gas Chromatographic Analyses. Journal of chromatographic science, vol. 5(2). pp.68-71. DOI: 10.1093/chromsci/5.2.68

Directive 1999/13/EC. 1999. On the Limitation of Emissions of Volatile Organic Compounds Due to the use of Organic solvents in Certain Activities and Installations. Council Directive. Official Journal of the European Communities. Retrieved from https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31999L0013&from=EN

Directive 2004/42/EC. 2004. The European Parliament and the Council of the European union. 2004. On the Limitation of Emissions of Volatile Organic Compounds due to the Use of Organic Solvents in Certain Paints and Varnishes and Vehicle Refinishing Products and Amending. Council Directive. Official Journal of the European Union. Retrieved from https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52011DC0297&from=EN

Edher, T. 2005. MIKES: Kemian metrologian opas. Helsinki: Advisory board for the metrology in chemistry. Retrieved from https://www.vtt.fi/inf/pdf/MIKES/2005-J6.pdf

EN-ISO 16000-6. Determination of volatile organic compounds in indoor and test chamber air by active sampling on Tenax TA® sorbent, thermal desorption and gas chromatography using MS or MS-FID. 12.1.2011. SFS Online. https://sales.sfs.fi/fi/index/tuotteet/ISO/ISO/ID9998/1/177312.html.stx

Eurachem. 2014. The Fitness for Purpose of Analytical Methods: A Laboratory Guide to Method Validation and Related Topics. Retrieved from https://www.eurachem.org/images/stories/Guides/pdf/valid.pdf

Harris, D.C. 2010. Quantitative Chemical Analysis. Eight Edition. New York: W. H. Freeman and Company

Healthcare Statute 19.8.1994/763. Effective 01.01.1995. Retrieved from https://www.finlex.fi/fi/laki/ajantasa/1994/19940763

Healthcare Decree 1280/763. Effective since 01.01.1995. Retrieved from https://www.finlex.fi/fi/laki/ajantasa/1994/19941280#a23.3.2006-207

Hollis, J., Prest, P. 2012. Volatile Organic Compounds in Analysis Using Purge & Trap, Agilent Technologies Inc.

Hodgson, M., Levin, H., Wolkoff, P. 1994. Volatile Compounds in Indoor Air. Journal of Allergy and Clinical Immunology.

Hübschmann, H-J. 2009. Handbook of GC/MS. Fundamentals and Applications. Second Edition. KGaA, Weinheim: Wiley-VCH Verlag CmbH & Co.

Indoor Air Association. 2008. Sisäilman vaikutukset. Viewed 23.08.2018. Retrieved from http://www.sisailmayhdistys.fi/Terveelliset-tilat/Sisailmasto/Sisailman-vaikutukset

Indoor Air Association. 2018. Sisäilmastoluokitus 2008.

Jin,W., Wang, Y., Wang, X., Jin, L., Lu, J., Luo, M. 2011. Sorption Properties of Ordered Mesoporous Silica for Toluene and Ethyl Acetate. Adsorption Science and Technology 29(4). pp 405-412. DOI: 10.1260/0263-6174.29.4.405. Retrieved from https://journals.sagepub.com/doi/pdf/10.1260/0263-6174.29.4.405

Joshi, M. 2004. The Sick Building Syndrome. IJOEM. DOI: 10.4103/0019-5278.43262.

Järnström, H. 2007. Reference values for building material emissions and indoor air quality in residential buildings. VTT Publications 672. Espoo: VTT

Karine, J., David, F. Sandra, P. 2008. Analysis of Volatile Organic Compounds in Water Using Static Headspace-GC/MS. Agilent Technologies, Inc.

Klepeis, N. 1996. The National Human Activity Pattern Survey (NHAPS) A Resource for Assessing Exposure to Environmental Pollutants. Retrieved from https://indoor.lbl.gov/sites/all/files/lbnl-47713.pdf

Koppmann, R. 1999. Volatile Organic Compounds in the Atmosphere. Oxford: Blackwell Publishing Ltd. 978-1-4051-3115-5.

McMaster, M. 2008. GC/MS: a practical user's guide. 2nd edition. Hoboken: John Wiley& Sons. ISBN 978-0-470-10163-6.

Markowicz P., Larsson, L. 2015. Influence of relative humidity on VOC concentrations in indoor air. Environmental Science and Pollution Research April 2015, Volume 22, Issue 8, pp 5772–5779.

Merck. 2019. MSDS of Methyl Pivalate.

Ministry of Occupational Health. 2012. Haihtuvien Orgaanisten Yhdisteiden Kokonaispitoisuuden (TVOC) Tavoitetasot Teollisten Työympäristöjen Yleisilmassa. Retrieved from https://www.ttl.fi/wp-content/uploads/2016/12/TVOC-tavoitetasot.pdf

Ministry of Social Affairs and Health. 2009. Asumisterveysohjeen soveltamisopas 2009a. Ympäristö ja Terveys-lehti. Vaasa: Ykkös-Offeset Oy.

Morgan, P. 2012. Gas Chromatography Liner Selection Guide. Thermo Fishcher Scientific. Read 10.6.2018. Retrieved from http://www.separatedbyexperience.com/documents/Liner_Selection_Guide.pdf

National Institute of Standards and Technology. 2014. NIST Chemistry Webbook, SRD 69. Toluene. Retrieved from https://webbook.nist.gov/cgi/cbook.cgi?ID=108-88-3

Norbäck D., Torgén, M., Edling C. 1990. Volatile organic compounds, respirable dust, and personal factors related to prevalence and incidence of sick building syndrome in primary schools. British Journal of Industrial Medicine, p. 733-741.

Prest, H, Foote. J, Kernan.J, Peterson, D. Enhancements to Gain Normalized Instrument tuning: Understanding the Benefits and Features. Agilent. Brochure. Read 3.7.2018. Retrieved from http://www.academia.edu/8963488/Enhancements_to_Gain_Normalized_Instrument_Tuning_Understanding_the_Benefits_and_Features_Technical_Overview

Prest, H., Horn, B. 2013. A Quick Start Guide to Optimizing Detector Gain for GC/MSD. Agilent instruction brochure. Retrieved from https://www.agilent.com/cs/library/technicaloverviews/public/5991-2105EN.pdf

Purge, B. 2004. Sick Building Syndrome. Occupational and Environmental Medicine 2004;61:185–190. DOI: 10.1136/oem.2003.008813. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1740708/pdf/v061p00185.pdf

Reiss, R., Ryan,B., Koutrakis, P., Tibbetts, S. 1995. Ozone Reactive Chemistry on Interior Latex Paint. Environmental Science and Technology 29(8):1906-12.

Riley, M. 1996. Development and Validation of Analytical Methods. Kidlington: Elsevier Science Ltd. ISBN 0 08 042792 8.

Rouessac, F., Rouessac A. 2007. Chemical Analysis. 2nd edition. Chichester, England: John Wiley & Sons Ltd. ISBN 978-0-470-85902-5.

Roushall, R., Prest, H. 2007. The 5975C Series MSDs: Method Optimization and Trace Ion Detection, Technical Overview. Agilent Brochure. Retrieved from https://www.agilent.com/cs/library/technicaloverviews/public/5989-6425EN.pdf

Rundt, A-R., Backlund, P. & Paakkola, K. 2005. Sisäilman hajut ja orgaaniset epäpuhtaudet. Työterveyslääkäri 2/2005 (vol 23), p. 156−163. Retrieved from https://www.ebm-guidelines.com/dtk/shk/avaa?p_artikkeli=ttl00208

Salonen, H. 2009. Volatile Organic Compounds and Formaldehyde as Explaining Factors for Sensory Irritation in Office Environments. Journal of Environmental Health. p.239-247.

Scientific Instrument Services Inc. 2017. Tenax® TA Breakthrough Volume Data. Viewed 20.1.2019. Retrieved from https://www.sisweb.com/index/referenc/tenaxta.htm

Sparkman, O., Zelda, P., Kitson, F. 2011. Gas Chromatography and Mass Spectrometry: A Practical Guide. 2nd edition. Oxford: Elsevier Inc. ISBN ISBN–13: 978-0-12-373628-4

Spectral Database for Organic Compounds. Mass spectrum of methanol. Viewed 15.12.2018. Retrieved from https://sdbs.db.aist.go.jp/sdbs/cgi-bin/img_disp.cgi?disptype=disp1&img-dir=ms&fname=MSNW0072&sdbsno=3302

Säteri, J. 2018. Sisäilmastoluokitus 2018. Powerpoint-presentation in the release of the indoor air quality 2018 classification. Retrieved from http://glt.rts.fi/wp-content/uploads/2018/05/Sisäilmastoluokitus2018-14052018_Jorma-Säteri.pdf

Taylor, T. 2012. Electron Ionization for GC-MS. LCGC North America, Volume 30, Issue 4. p. 358 http://www.chromatographyonline.com/introduction-electron-impact-ionization-gc-ms

Taylor, Tony. 2016. What GC-MS-Operators Need to Know. LCGC North America Volume 34, Issue 1, pp. 74. Retrieved from http://www.chromatographyonline.com/what-quadrupole-gc-ms-operators-need-know

The Council of the European Union. 1999. COUNCIL DIRECTIVE 1999/13/EC of 11

United States Environmental Protection Agency. 1991. Indoor Air Facts No. 4 (revised) Sick Building Syndrome. Viewed 13.8.2018. Retrieved from https://www.epa.gov/sites/production/files/2014─08/documents/sick_building_factsheet.pdf

United States Environmental Protection Agency. 2016. Technical Overview of Volatile Organic Compounds. Viewed 14.8.2018. Retrieved from https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-compounds

United States Environmental Protection Agency. 2017. Volatile Organic Compounds' Impact on Indoor Air Quality. Viewed 13.8.2018. Retrieved from https://www.epa.gov/indoor-air-quality-iaq/volatile-organic-compounds-impact-indoor-air-quality

Valvira. 2016. Residential Health Decree Application Directives. Part III. Office of authorization for Social and Health services.

Wittmann, C. 2007. Fluxome analysis using GC-MS. Published 7.2.2007. Viewed 07.07.2018. Retrieved from http://www.microbialcellfactories.com/content/6/1/6/

World Health Organization, 1989. Indoor air quality: organic pollutant. Report on a WHO Meeting, Berlin, 23-27 August 1987. EURO Reports and Studies 111. Copenhagen: World Health Organization Regional Office for Europe.

Wolkoff, P. 1998. Impact of air velocity, temperature, humidity, and air on longterm VOC emissions from building products. Atmospheric Environment 14/15, 2659-2668.

Wolkoff, P., Clausen, P., Jensen B., Nielsen, G,. Wilkins C. 1997. Are We Measuring the Relevant Indoor Pollutants? International Journal of Indoor Environment and Health. Vol 7, Issue 2. p.92-106.

Zabiegala, B., Partyka, M., Zygmunt, B., Namiesnik, J. 2009. Determination of Organic Compound in Indoor Air in the Gdansk Area Using Permeation Passive Samplers. Indoor and Built Environment, volume 18, issue 6. pp. 492-504.

APPDENDICES

Appendix 1. Estimate of the mass of an individual component in generic indoor air

TABLE 18. Estimate of the mass of an individual component collected from an air sample. The amount of an individual component is estimated as 1/30 of the TVOC-value

Phase of assay	**Mass / concentration**	**Other**
[1]General indoor TVOC, 1 m^3	300 µg	
TVOC, 10 dm^3	3000 ηg	
Individual component 10 dm^3 (1/30)	100 ηg	
[2]Individual component after extraction (5ml)	0,02 ηg/µl	
IC Mass after 3ml injection	0,06 ηg	
IC Mass after split (1:5)	0,012 ηg	
Required concentration for 1:5 split	12 ηg/ml = 0,012 ηg/µl	

[1]Ministry of Social Affairs and Health, 2009

[2]ATD can transfer the whole sample → individual component 1666x compared to ASE. However, the split ratios are quite different (1:5 of ASE vs 1:150 of ATD). Nonetheless, the amount of sample entering the column with P&T is at least 55 times greater.

The estimated introduction for an individual component of an air sample to column after extraction, injection and split is 0,012 ηg. This was set as the target level.

Appendix 2. Safe masses of injection for a 0,25 mm column

TABLE 19. Reference safe injection masses per analyte. The approximation of a safe sampling mass used here is 50–100 ng. Bolded figures exceed the limits

Concentration (µg / ml)	**Split, mass below (ng)**				
	1:1	1:2	1:5	1:10	1:36
1000	**4000**	**2000**	**800**	**400**	111,11
200	**800**	**400**	**160**	**80**	22,22
100	400	200	**80**	40	11,11
10	40	20	8	4	1,11
1	4	2	0,8	0,4	0,11
0,5	2	1	0,40	0,2	0,06
0,2	0,8	0,4	0,16	0,08	0,02
0,1	0,4	0,2	0,08	0,04	0,01
0,05	0,2	0,1	0,04	0,02	0,01
0,02	0,08	0,04	0,02	0,008	0,00
0,01	0,04	0,02	0,01	0,004	0,00
0,001	0,004	0,002	0,00	0,0004	0,00

Appendix 3. Standard concentrations for scan-mode

TABLE 20. The calibration standards utilized in the preliminary tests, in determination of toluene response factors and in method development

Standard	Concentration	Analytes
Std 1, stock	1000 µg / ml	All surrogates
Std 2	250 µg / ml	All surrogates
Std 3	100 µg / ml	All surrogates
Std 4	50 µg / ml	All surrogates
Std 5	10 µg / ml	All surrogates
Std 6	1 µg / ml	All surrogates
Std 7	500 ηg / ml	All surrogates
Std 8	100 ηg / ml	All surrogates
Std 9	10 ηg / ml	All surrogates
Std 10	1 ηg / ml	All surrogates

Appendix 4. Raw data for the toluene responses

TABLE 21.Raw data to determine toluene response factors. Gain 5, trace ion on

Compound	Height	Area	Width	File
Cpd 1: 2-Butanone	470259	3366104	0,272	10m tr.D
Cpd 2: n-Hexane	826981	2519608	0,127	10m tr.D
Cpd 3: 2-Butanol, (R)-	914146	2686807	0,189	10m tr.D
Cpd 4: Ethane, 1,1,1-trichloro-	443325	1672235	0,198	10m tr.D
Cpd 5: 2,2,4 TMP	890277	3269513	0,23	10m tr.D
Cpd 6: Toluene	811006	4698493	0,403	10m tr.D
Cpd 7: Hexanal	591847	2657878	0,316	10m tr.D
Cpd 8: Benzene, 1,3-dimethyl-	519269	4096858	0,44	10m tr.D
Cpd 9: Nonane	428484	2005030	0,318	10m tr.D
Cpd 10: Benzaldehyde	677817	3615601	0,372	10m tr.D
Cpd 11: β-pinene	740389	3259262	0,328	10m tr.D
Cpd 1: 2-Butanone	4310860	29508664	0,316	100m tr.D
Cpd 2: n-Hexane	10165960	30566151	0,149	100m tr.D
Cpd 3: 2-Butanol, (R)-	15469818	42120705	0,198	100m tr.D
Cpd 4: Ethane, 1,1,1-trichloro-	5862705	20845350	0,219	100m tr.D
Cpd 5: 2,2,4-trimethylepentane	11303151	40202504	0,229	100m tr.D
Cpd 6: Toluene	11590721	62537605	0,366	100m tr.D
Cpd 7: Hexanal	9815445	40938860	0,335	100m tr.D
Cpd 8: o-Xylene	8557629	69543104	0,387	100m tr.D
Cpd 9: Nonane	7228879	32847587	0,341	100m tr.D
Cpd 10: 1,4-Butanediol	2968321	20738357	0,415	100m tr.D
Cpd 11: Benzaldehyde	14502222	70569427	0,341	100m tr.D
Cpd 12: β-pinene	15479155	67163106	0,329	100m tr.D
Cpd 1: 2-Butanone	10045718	73636339	0,323	250m tr.D
Cpd 2: n-Hexane	25246578	78916234	0,155	250m tr.D
Cpd 3: 2-Butanol, (R)-	35384073	102665053	0,236	250m tr.D
Cpd 4: Ethane, 1,1,1-trichloro-	15209368	56470030	0,245	250m tr.D

Cpd 5: 2,2,4-trimethylepentane	26303242	99799024	0,289	250m tr.D
Cpd 6: Toluene	26713232	156768723	0,447	250m tr.D
Cpd 7: Hexanal	27004853	110231361	0,31	250m tr.D
Cpd 9: o-Xylene	21529965	186923582	0,395	250m tr.D
Cpd 10: Nonane	19389416	90000067	0,335	250m tr.D
Cpd 11: 1,4-Butanediol	8248880	107701986	0,585	250m tr.D
Cpd 12: Benzaldehyde	38938406	200341344	0,371	250m tr.D
Cpd 13: β-pinene	40385142	186370431	0,285	250m tr.D

Appendix 5. Residuals of the toluene calibration curves

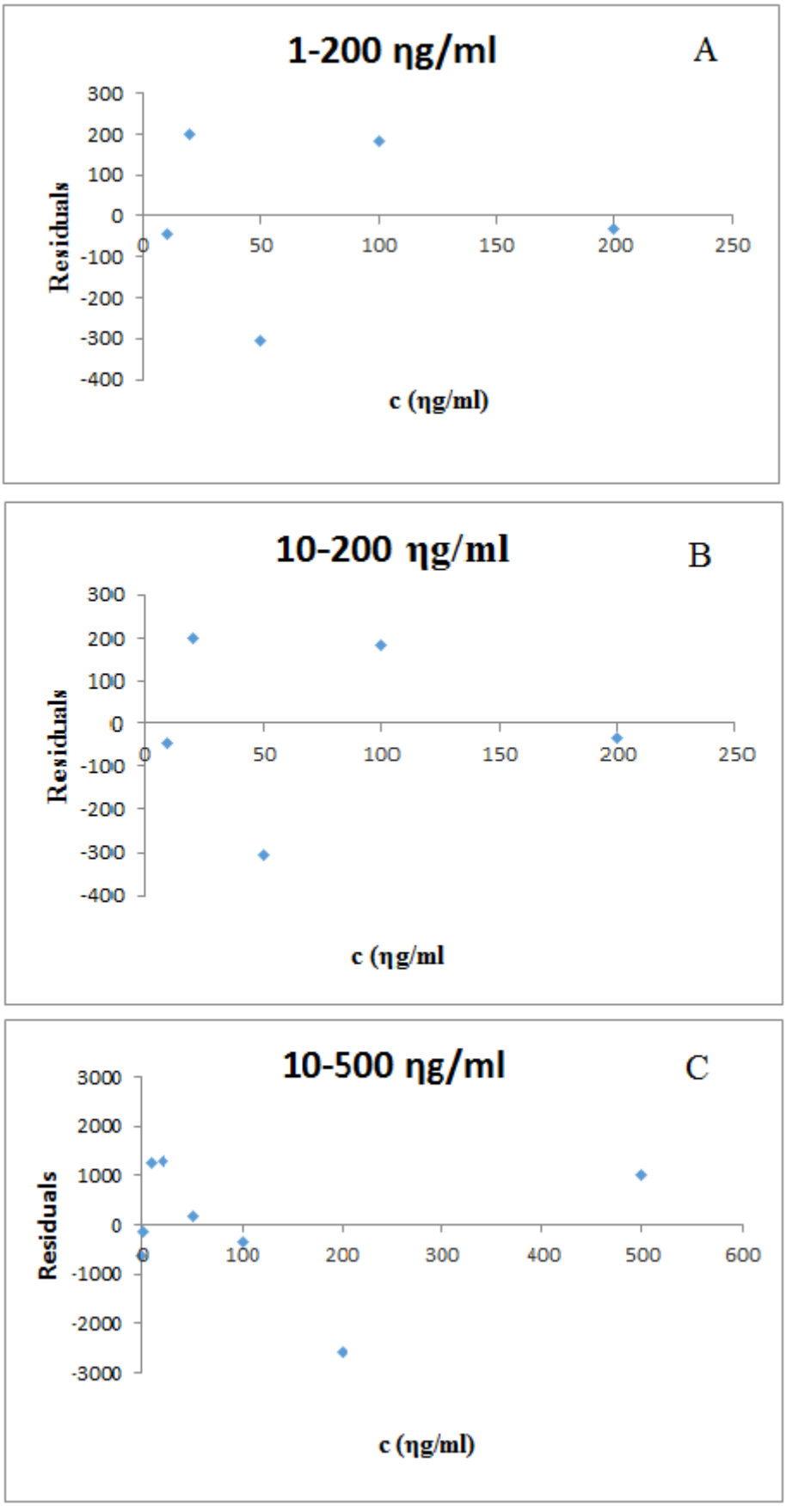


FIGURE 18. Residuals of the calibration curves. The residuals are normally distributed.

Appendix 6. Evaluation of the regression curves

The equation for the regression trendline for the calibration curve of 10-200 was y=334.08x + 864,46, and for the 10-500 y=314.48x+ 2131,2. The linearity could be estimated from the deviations by substituting values of 20 and 200 for the x and comparing the calculated results to the measured ones.

TABLE 22. Obtained values and estimated values created utilizing trendline equation

Standard / value	**10-200 ηg/ml**	**10-500 ng**	**Real value**
20 ng/ml	5276	4205	5232
200 ng/ml	65027,2	67680	64994

The respective deviations compared to the real values for 10–200 ηg/ml were 0,8% and 0,05%, and for the 10–500 ηg/ml were 19,6% and 4,1%. Therefore, the representative linear range of operations was determined as 10–200 ηg/ml.

Appendix 7. Methyl pivalate, CAS 598-98-1

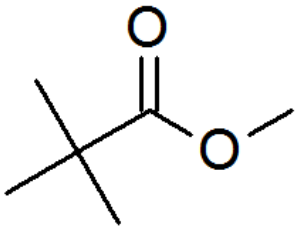


FIGURE 19. Methyl Pivalate (Drawn in Chemsketch)