Chemical Characterization of Indoor Air Pollutants: Implications to Consumer and Occupational Health

by

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Abstract

Humans living in the contemporary societies find the majority of their time spent indoors, promoting awareness regarding indoor air quality over the past decades. The indoor environment has gained significant complicity due to an increasing variety of inhalable products consumed in our daily lives. Many indoor chemistry processes have not been fully characterized; hence chemical pollutants produced from these processes are under-discovered. In particular, our exposure to air pollutants in residential and occupational settings could be vastly different from the typical indoor environment. This is because chemicals involved in these scenarios are product- and occupation-dependent. One can receive immense exposure to specific chemicals that are uncommon in normal settings. However, very limited research has been done to investigate chemical pollutants involved in consumer and occupational settings. At the same time, it is always challenging to conduct representative studies on this topic due to the high diversity of indoor environments. Hence, fundamental studies on indoor chemistry processes are needed to address this problem.

The goal of this thesis is to provide chemical insight into possible indoor pollutants and to reveal chemical processes behind the scenes. In Chapter 2, I demonstrated the impact on indoor air quality from the use of artificial fog machines. I reported a significant production of chemically rich ultrafine particulate matter generated from artificial fog. In addition, I discovered an accumulation of toxic carbonyl compounds in artificial fog, including formaldehyde and glycolaldehyde, using the 2,4-dinitrophenyl hydrazine derivatization method. I reported that the oxidative degradation of glycols in the fog juice during storage could give rise to carbonyl formation. Finally, I proposed that autoxidation was likely the primary process during the degradation of glycols.

In Chapter 3, I implemented a systematic investigation of the oxidation of glycols according to discoveries made in Chapter 2. I investigated the oxidative degradation of common glycols, including triethylene glycol, diethylene glycol, propylene glycol, glycerol, and commercial e-cigarette juice. All glycols could accumulate carbonyl products during prolonged storage, with triethylene glycol exhibiting the most rapid formation of carbonyls. I further determined time-resolved total peroxide concentrations in different glycols using iodometry, this result is strong evidence to support the autoxidation hypothesis. In addition, I evaluated parameters that could affect the formation rate of glycols, in terms of water mixing ratio, air exposure, and the addition of antioxidants. This project has emphasized that proper storage protocols on glycol-containing consumer products are required to mitigate human exposure to toxic carbonyls.

In Chapter 4, I applied the derivatization with p-toluenesulfonyl chloride to determine oxidation products from nicotine, during the storage of nicotine-containing e-cigarette juice. I discovered numerous amine-containing alkaloid compounds in aged e-cigarette juice, including nornicotine and an amino-peroxide compound. I further confirmed that the formation of these compounds includes radical-initiated oxidation by performing an artificial photooxidation experiment. Finally, I monitored the formation of alkaloid compounds from a set of fresh commercial e-cigarette juices under typical storage conditions and discovered a rapid formation of these alkaloid compounds within a week. Therefore, e-cigarette consumers should be aware of the degradation of their e-cigarette juice to avoid exposure to numerous unknown alkaloids.

In Chapter 5, I performed a field project to reveal the indoor chemistry of a commercial poultry facility. With the aid of the p-toluenesulfonyl chloride derivatization used in Chapter 4, I characterized numerous airborne nitrogenous compounds in the facility and discovered an interesting chemical partition among litter, air, and dust. The detection of these nitrogenous chemicals has addressed the potential source of ammonia pollution, which is a known, persistent environmental problem in animal husbandry industries. In addition, we found a strong correlation among particles, chemicals, and animal activities. An interesting diurnal variation of particles and chemicals in the farm was also discovered. This study have strong implications for animal productivity and the occupational health of farmers.

Overall, this thesis has reported novel observations for the study of chemical processes involved in the indoor environment. Information provided by this thesis can fundamentally explain the formation of indoor air pollutants under certain consumer and occupational settings. Ultimately, further clinical studies can use results from this thesis to address potential adverse health effects due to the consumption of contaminated inhalable products and/or exposure to indoor environments polluted by such products.

Preface

My contributions to each chapters are listed in this section, Chapter 2 and 3 is consist of published work. The materials in Chapter 5 have been submitted to Environmental Sciences: Processes & Impacts, while Chapter 4 and includes unpublished material.

Chapter 1: Introduction

The introduction was written by Xinyang Guo with review and feedback from Dr. Ran Zhao and Shuang Wu.

Chapter 2: Impact of Glycol-based Solvents on Indoor Air Quality – Artificial Fog and Exposure Pathways of Formaldehyde and Various Carbonyls

Guo X., Ehindero T., Lau C., Zhao R. (2022). Impact of glycol-based solvents on indoor air quality—Artificial fog and exposure pathways of formaldehyde and various carbonyls. Indoor Air.; 32:e13100. doi: 10.1111/ina.13100

Contributions: The experiment was designed by Xinyang Guo with critical input from Toluwatise Ehindero, Chester Lau, and Dr. Ran Zhao. Initial analytical method development was conducted by Chester Lau. The single room experiment was performed by Xinyang Guo, Toluwatise Ehindero and Dr. Ran Zhao. Quantification of carbonyl compounds was performed by Xinyang Guo and Toluwatise Ehindero.

Chapter 3: Autoxidation of Glycols Used in Inhalable Daily Products: Implications to the Use of Artificial Fogs and E-cigarettes

Guo, X., Chan, Y. C., Gautam, T., Zhao, R. (2023). Autoxidation of glycols used in inhalable daily products: implications for the use of artificial fogs and e-cigarettes. Environmental Science: Processes and Impacts, 25(10), 1657–1669.

Contributions: The experiment was designed by Xinyang Guo with critical input from Ya-Chun Chan, Tania Gautam, and Dr. Ran Zhao. Quantification of carbonyl compounds was performed by Xinyang Guo and Ya-Chun Chan. Quantification of peroxides was performed primarily by Ya-Chun Chan, with occasional help from Xinyang Guo.

Chapter 4: Chemical Characterization of Nicotine Oxidation Products in E-cigarette using p-Toluenesulfonyl Chloride

Xinyang Guo, Kimberly Wong, and Ran Zhao

Contributions: The experiment was designed by Xinyang Guo with critical input from Kimberly Wong and Dr. Ran Zhao. The chemical characterization was performed by Xinyang Guo. The photooxidation experiment was performed by Xinyang Guo and Kimberly Wong. The iodometry experiment and the absorption spectrum of the e-cigarette juice were collected by Kimberly Wong. Quantification of alkaloid compounds was performed by Xinyang Guo and Kimberly Wong.

Chapter 5: Characterization of Indoor Atmospheric Nitrogenous Chemicals in Poultry Farms

Xinyang Guo, Rowshon Afroz, Shuang Wu, Kimberly Wong, Valerie Carney, Martin Zuidhof, Joey Saharchuk, Hans Osthoff, and Ran Zhao

Contributions: The experiment was designed by Xinyang Guo with critical input from Dr. Ran Zhao. Field deployment of the instrument was done by Xinyang Guo, Rowshon Afroz and Dr. Ran Zhao. The model prediction was performed by Shuang Wu, and calibration curves of amines were obtained by Xinyang Guo and Kimberly Wong. Dr. Martin Zuidhof and Dr. Valerie Carney advised the research team on dust collection and measurement in poultry facilities and proofread the manuscript. Joey

Saharchuk and Dr. Hans' Osthoff were involved in the intercomparison of instrument and proofread the manuscript.

Chapter 6: Conclusions, Recommendations, and Figure Work

Contributions: The conclusion is written by Xinyang Guo with review and feedback by Dr. Ran Zhao.

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I also extend my appreciation to fellow members in Dr. Zhao's group, including former and current researchers: Dr. Max Loebel Roson, Dr. Tania Gautam, Jessica Lima Amorim, Shuang Wu, Mst Rowshon Afroz, Shakiba Talebian, Amanda Hanashiro Moraes, Anastasa Kim, and many more. In particular, I would like to sincerely thank four former undergraduate students who worked with me in the past years: Chester Lau, Toluwatise Ehindero, Ya-Chun Chan, and Kimberly Wong. Your contributions have become the backbone of my thesis and my degree cannot reach the completion without you. In addition, I would like to acknowledge Dr. Max Loebel Roson, Dr. Tania Gautam, Jessica Lima Amorium, and Shuang Wu for maintaining my mental well-being by having coffee breaks and lunch together.

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Table of Contents

List of Tables

List of Figures

Abbreviations

2,4-DNPH 2,4-dinitrophenyl hydrazine.

AFMs Artificial fog machines.

ALA Allantoin.

ANC Airborne nitrogenous chemicals.

BPC Base peak chromatogram.

CAD Cadaverine.

CPC Condensation particle counter.

DEG Diethylene glycol.

DMA Dimethylamine.

EG Ethylene glycol.

EIC Extracted ion chromatogram.

EJ E-cigarette juice.

ESI Electrospray ionization.

EVALI E-cigarette or vaping-associated lung injury.

GC Gas chromatography.

GUA Guanine.

HOM Highly oxidized molecules.

HPLC/UHPLC (Ultra-) high-performance liquid chromatography.

IAQ Indoor air quality.

LC Liquid chromatography.

LOD Limit of detection.

MS Mass spectrometry.

NDIR non-dispersive infrared.

OPC Optical particle counter.

PCHP Personal care and household product.

PG Propylene glycol.

PILS Particle-into-liquid sampler.

PM Particulate matter.

PPE Perosonal protective equipment.

PRC Poultry Research Center.

PUT Putrescine.

SEMS Scanning electrical mobility spectrometer.

SMPS Scanning mobility particle sizer.

SOA Secondary organic aerosols.

SPE Solid phase extraction.

TEG Triethylene glycol.

TPM Total particle mass.

TsCl p-toluenesulfonyl chloride.

UA Uric acid.

UFP Ultrafine particles.

UV-vis Ultraviolet-visible spectroscopy.

VG Vegetable glycerin.

VOC Volatile organic compound.

Chapter 1

Introduction

1.1 What Is Indoor Air Quality (IAQ)

Air quality is the measure of indoor or outdoor air pollution. Air pollution is caused by any chemically, physically, or biologically produced pollutants that modify the natural characteristics of the atmosphere. As many people start to value their wellness, air quality has received growing attention in the past decades. Conventionally, outdoor air pollution has been intensively studied, which includes urban air pollution, wildfire pollution, and biological emissions.[1] On the other hand, indoor air quality (IAQ) has not received as much attention.[2] IAQ refers to air quality within a structure or building. As of 2020, data from the World Health Organization estimated that household air pollution is responsible for approximately 3.2 million deaths, including more than 237 thousand young children.[3] In addition, the mortality rate of IAQ pollution has a rising trend in developing worlds.[3] Despite being an existing issue, only a few governments have established guidelines for IAQ.[4] On the individual level, ordinary people spend most of their time in the indoor environment, including residential homes, workplaces, vehicles, and restaurants (Figure 1.1) .[5] Therefore, in addition to being a global environmental problem, improving IAQ is also meaningful to the health and productivity of individuals. Acute exposure to polluted indoor air may immediately cause discomfort, while chronic exposure to certain air pollutants can lead to severe health consequences.

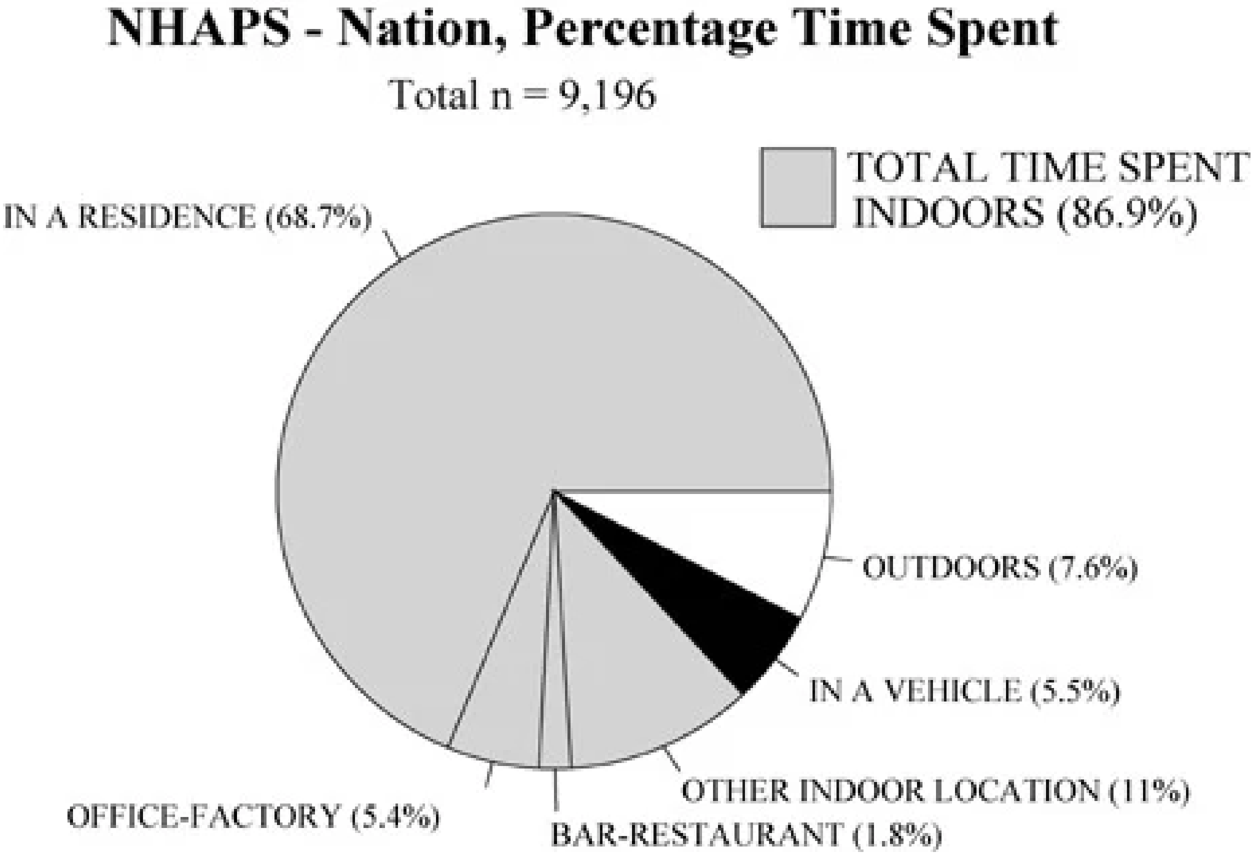

Figure 1.1: The average percentage of a day spent indoors by people. Figure adapted with permission from Klepeis, N. et al. “The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants.” J. Expo. Sci. Environ. Epidemiol. Vol. 11, pp. 231–252, 2001.[5]

1.1.1 Indoor Environments

The indoor atmosphere is very complex, for instance, it is challenging to make long-term monitoring strategies based on short-term measurement sessions.[6] Implications from studies done in different places may not be consistent with each other.[7] Several indoor parameters can affect the severity of air pollution. For example, the lifetime of indoor air pollutants varies with the scale of the room.[8] Temperature and relative humidity dictate the thermal comfort of the indoor space, while also affecting microbial activities and the resuspension of particles. Ventilation is an effective way to remove air pollutants, but the rate of which can vary among indoor places. Building construction, furnishing, and human or animal metabolism are commonly identified emission sources .[9]

Residential Homes

As shown in Figure 1.1, among all indoor places, people spend most of their time in residential homes. Residential IAQ can be affected by indoor activities and building materials (Figure 1.2). For example, the use of biofuels as a source of household energy in developing regions gives rise to high emissions from biomass burning.[10] Although considered as a cleaner fuel, the combustion of natural gas can also pollute urban kitchens.[11] In addition, different cooking techniques can also affect the IAQ. Higher emissions are found from vigorous cooking techniques,[12, 13] along with foods with higher fat contents.[14]

Home furnishings, appliances, and consumer products can result in unintended air pollution. Wall paints, floor finishes, and wood furniture can release organic compounds such as formaldehyde into the air.[15] Marble-based structures can cause the accumulation of radon, especially in a poorly ventilated basement.[16]

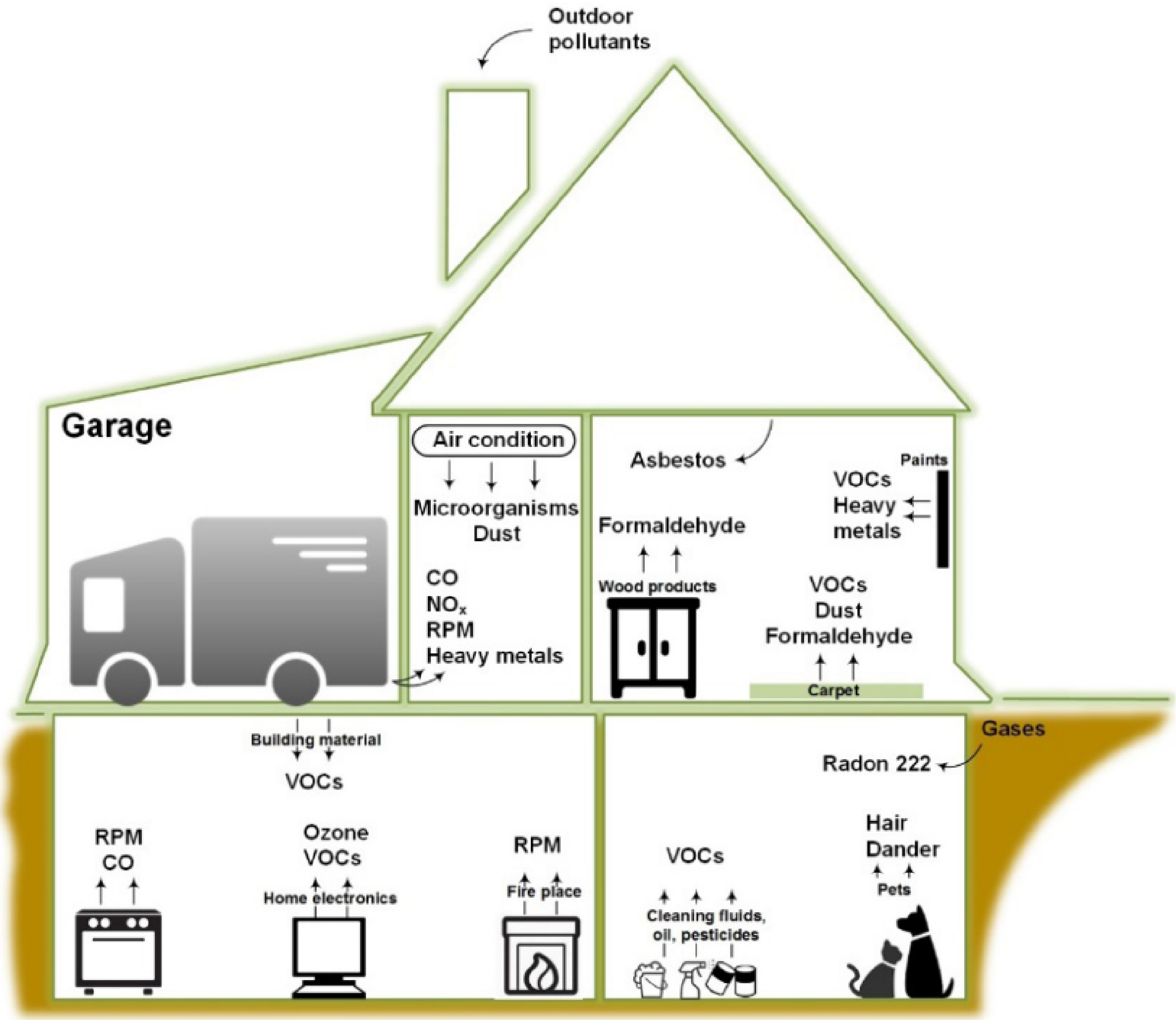

Figure 1.2: Source of residential indoor pollutants . Figure adapted under Creative Commons Attribution (CC BY-NC-ND 3.0 DEED) from Eltzov et al. “Indoor air pollution and the contribution of biosensors”, The EuroBiotec Journal, vol. 3, pp. 19-31, 2019.[17]

Occupational Environments

In addition to residential homes, people stay at their workplaces for extended periods. Many occupations predominantly interact with indoor environments, as shown in Figure 1.3. This figure plots the indoor/outdoor proximity of different occupations in the U.S. from 2014 to 2019. The horizontal axis refers to Standard Occupational Classification codes for jobs assigned by the U.S. Bureau of Labor Statistics, and the vertical axis stands for the number of employees. The color code refers to different proximities to indoor or outdoor work. For instance, occupations like education workers (#25), health care practitioners (#29), and food preparation workers (#35) are mainly working indoors. In comparison, occupations such as building and ground maintenance jobs (#37) are usually outdoors, but these workers can still occasionally work indoors. IAQ in occupational environments is very distinct from residential settings. Firstly, occupational IAQ is job-dependent. Office workers can be exposed to emissions from ubiquitous office equipment, such as computers, laser printers, and personal care products from colleagues.[18–21] Agricultural facilities will have a high indoor concentration of biogenic emissions, in which producers and animals can receive prolonged exposure.[22] Secondly, industrial-level pollutant concentration is significantly higher than levels typically experienced in residential settings, and workers are obligated to work through their work shifts. For example, beauty industry workers are exposed to fragranced styling products much more than a typical individual.[23, 24] Restaurant chefs are exposed to more cooking emissions than household families, as they cook far more foods than typical household dishes.[25] Workers and their employers are often unaware of their exposures, and the negative impact of indoor pollution on workers' health and productivity is rarely investigated. Understanding the concentrations of indoor pollutants and chemical processes behind the scenes can be the initial step to solving the problem.

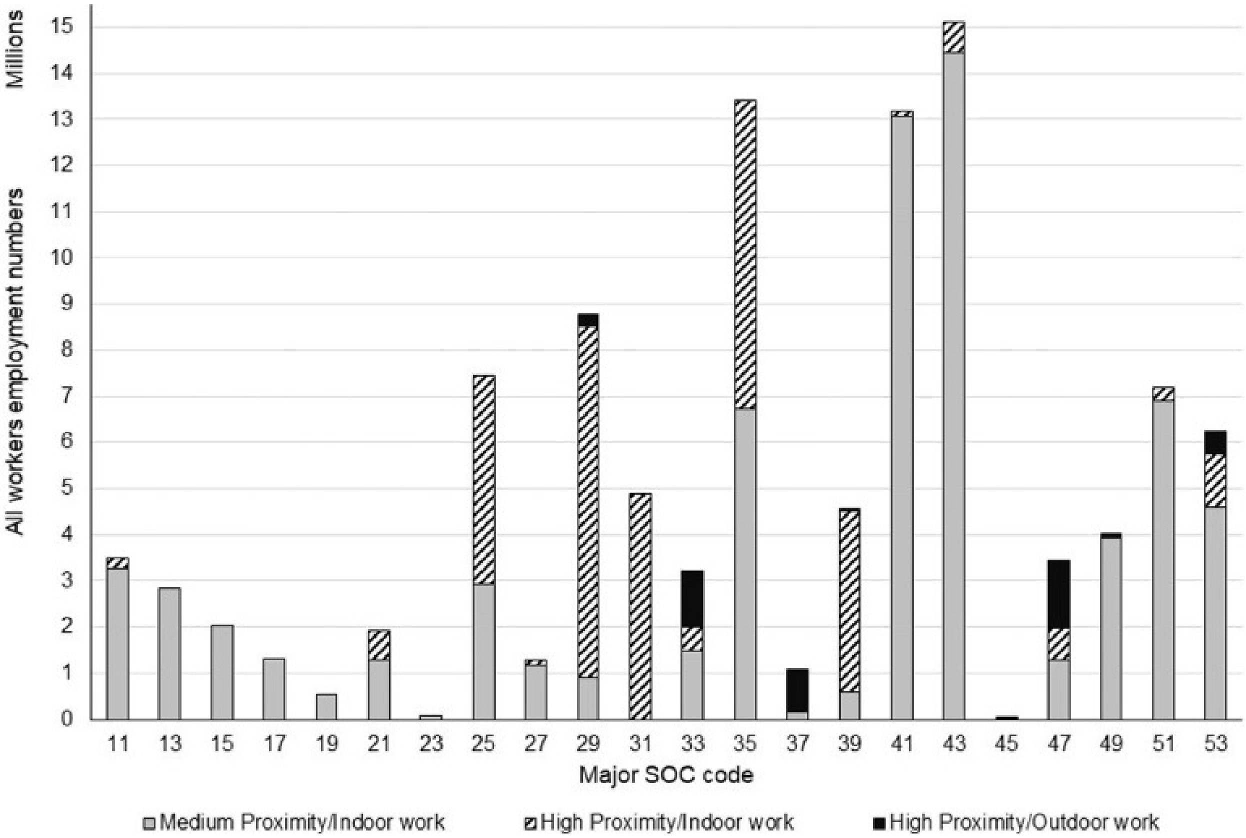

Figure 1.3: Estimated distribution of indoor/outdoor occupations. Figure adapted with permission from: Jean M. et al. "Occupations by Proximity and Indoor/Outdoor Work: Relevance to COVID-19 in All Workers and Black/Hispanic Workers", American Journal of Preventive Medicine, Vol. 60, 5, pp. 621-628, 2021.[26]

Consumer Health

Studies have shown that personal care and household products (PCHP) are part of the main sources of indoor air pollutants.[27] PCHPs are generally formulated with water, organic solvents, active ingredients, additives, and fragrances.[27] Similar to occupational settings, volatile PCHPs, such as fragrances, can cause discomfort if the concentration is too high.[28] Frequent applications of some PCHPs have been found to be associated with lung diseases, such as asthma.[29–31]

Smoking electronic cigarettes (or vaping) has gained a lot of popularity among young consumers. The rampage of vaping is spreading throughout North America and the e-cigarette or vaping-associated lung injury (EVALI) has become a public health epidemic.[32, 33] The cause of EVALI is not fully understood. While vitamin E acetate is the most recognized cause, it is unclear if any other chemicals can contribute to this problem. The e-juice is a mixture of glycols, nicotine, flavoring agents, and additives. Studies have reported many harmful compounds emitted by e-juices, such as carbonyls from flavoring agents, and heating byproducts from glycol-based solvents.[34] Vaping is considered a safer alternative than traditional tobacco smoking, but vaping in indoor spaces could drastically deteriorate IAQ, threatening the health of both smokers and surrounding non-smokers.

1.2 Indoor Air Pollutants and Their Direct Sources

This thesis will cover four major types of IAQ pollutants, they are particulate matter (PM), oxidants, volatile organic compounds (VOCs), and inorganic gases. These pollutants can all be emitted from previously mentioned sources. In addition, their concentrations are highly correlated with each other, i.e., the rise of one pollutant can be caused by its interaction with others. This section provides an overview of existing information about these pollutants in the indoor environment.

1.2.1 Particulate Matter (PM)

PM refers to inhalable solid or liquid particles in the air. They are usually classified based on the diameter of particles. PM10 stands for inhalable coarse particles with a diameter equal to or less than 10 micrometers (μm); Fine particles with a diameter of less than 2.5 μm are noted as PM2.5;[35] ultrafine particles (UFPs) have a diameter of less than 100 nanometers (nm).[36] The size of PMs matters because they can settle at different parts of the human respiratory system. Particles greater than 10 μm will deposit in the upper airways; PM10 and smaller particles can deposit along the trachea; PM2.5 can deposit in the bronchi and branches, while UFPs are small enough to settle in the alveoli.[37]

PMs are primarily transmitted from the outdoors or emitted by indoor sources. Many studies reported an elevated indoor PM during the wildfire season. Liang et al.[38] reported that the average indoor PM2.5 concentration is nearly tripled compared to non-fire days in California; O'Dell et al.[39] reported that the wildfire-driven indoor PM2.5 concentration is 82% higher than normal days in the western USA. Besides transfer from the outdoors, there are a lot of indoor PM sources, but only a handful of them have been fully characterized. For example, recent studies show that air fryers in domestic kitchens can generate much more PM10 than conventional pan frying.[14] The use of an ultrasonic humidifier would also raise the indoor PM concentration equivalent to a heavily polluted urban atmosphere.[40]

Indoor chemistry processes can also generate PM, as will be discussed in later sections. The aging of VOCs can alter their molecular mass and water solubility, aged compounds can then either condense on the fine particle or dissolve in the aqueous content of the particle,[41] generating secondary organic aerosol (SOA).

1.2.2 Atmospheric Oxidants

Atmospheric oxidants determine the lifetime of indoor VOCs.[42] Common oxidants include tropospheric ozone (O_3), hydroxyl radical (OH), hydroperoxyl radical (HO_2), singlet oxygen ($^1O_2$), and nitrate radicals (NO_3).[43] Indoor oxidants come from many sources, such as infiltration from outdoors,[44] the use of disinfection products, cooking, or the use of UV-generating lamps and electronics.[45] The oxidation mechanism of indoor pollutants is a complicated network, and a comprehensive understanding of the mechanism is still developing.

Among the common indoor oxidants, ozone is the most abundant compound, it has a typical indoor-outdoor ratio of 0.2 to 0.7,[46] and a greater indoor-outdoor ratio can be observed in a well-ventilated area.[47] In the outdoors, OH radicals are produced from ozone photolysis to form $O(^1D)$, followed by its reaction with water.[48] However, the indoor UV flux is less intense due to the lack of sunlight, an alternative OH production route is the ozonolysis of VOCs. A typical indoor OH concentration is reported to be on the order of 10^5 molecules per cm^3,[49] which is an order of magnitude smaller than typical outdoor values.

1.2.3 Inorganic Gases

Many inorganic gases are indoor air pollutants.[50, 51] This includes CO_2, carbon monoxide (CO), nitrogen oxides (NOx), and O_3.[52, 53] Emerging studies also reported the detection of ammonia (NH_3), isocyanic acid (HNCO), and inorganic acids.[54–56] CO_2 and NH_3 can be directly emitted by humans and animals[57], especially, CO_2 is emitted by respiration. A high concentration of CO_2 can cause difficulties in breathing and alter our decision-making performance.[58] A high level of NH_3 can cause acute effects, such as irritation of the mucous membrane in the eyes or the respiratory system.[59] In agricultural facilities, a high concentration of NH_3 is also associated with a reduction in body weight and calorie gain of the animals. Therefore, the concentration of these gases is frequently monitored in crowded indoor environments.

In addition to human and animal emissions, inorganic gases such as CO can be emitted by incomplete combustion. It will significantly reduce the oxygen-carrying capacity of red blood cells, which can eventually lead to fatal consequences.[60] In addition to primary emissions, inorganic pollutants can be produced from the decomposition of large VOC molecules. For example, NH_3 is produced by hydrolysis of urea.[61] CO_2 is formed due to the decomposition of organic compounds.[62] Recent studies also reported that HNCO is found from the decomposition of nicotine [63] and can further decompose into CO_2 and NH_3.[64]

1.2.4 Volatile Organic Compounds (VOCs)

VOC represents chemicals that have high vapor pressure. Common sources of residential VOC include building materials, PCHPs, static contents, building occupants, and their activities.[65] These sources can emit VOCs including alcohols, aldehydes, organic acids, alkyl carbons, and aromatic compounds.[66] Some VOCs can cause severe health consequences. For example, formaldehyde is carcinogenic and its concentration is monitored in places such as new homes and art galleries. Therefore, its indoor guidelines are well established by international organizations and governments.[67] Glycols are a class of VOCs used in many daily consumable products, and the inhalation of these compounds has been proposed to cause certain respiratory system irritations and diseases.[68] VOCs can be primary or secondary. Less oxidized VOCs, such as aromatics, alkanes, and alkenes, can be emitted directly from the source.[69] During their stay in the atmosphere, primary VOCs can react with atmospheric oxidants, producing oxidized compounds that have higher molecular masses and polarity, as well as oxidized fragmented products. With these features, VOCs will be more likely to dissolve in aqueous phase or deposit on particles. Therefore, the SOA is an aggregation of VOCs after several generations of oxidation.[70] Oxidized VOCs are generally more harmful than less oxidized species. In addition to formaldehyde previously mentioned, existing studies also reported that organic acids can cause cosmetic damage to furniture and objects;[71] Highly Oxidized Molecules (HOMs) and reactive oxygenated species can cause oxidative stress in the human body.[72]

1.3 Indoor chemistry

As mentioned above, in addition to direct emissions, many pollutants, including SOA, are produced through indoor chemistry processes. This section will include two categories: biological processes and oxidation processes.

1.3.1 Biological Processes

Bioaerosols are generated from biological sources, such as microorganisms, animals, or plants.[73] The size of particles varies according to their emission sources. Microbial activities can also decompose large molecules,[74] leading to the formation of small organic or inorganic products. For example, the biological decomposition of amino acids can form volatile amines.[75] As many biological processes are catalyzed by enzymes, the rate of the reaction is strongly dependent on environmental conditions, such as the building material, temperature, and relative humidity.[76, 77] Therefore, controlling these parameters can eliminate unwanted biological activities.

1.3.2 Oxidation by Atmospheric Oxidants

Oxidation processes have been studied intensively outdoors as UV light from the sun can generate a high level of oxidants. On the other hand, the abundance of oxidants in the indoor environment is relatively lower, hence received less attention in the past. The most important atmospheric oxidant in the indoor environment is OH radical, as this radical is highly reactive, it can initiate the chain reaction of oxidative decomposition of VOCs.[78–80] However, its concentration is relatively low indoors and is very short-lived.[42] Another oxidant is O_3, as mentioned in previous sections, it is the most abundant indoor oxidant. O_3 can react with VOCs through ozonolysis, enhancing the formation of indoor OH radicals.[81] Recently, new oxidants such as chlorine radicals have been found indoors. Existing studies reported the formation of chlorine radicals due to household cleaning and the application of sanitizers.[82] Hence, the indoor atmosphere is also a very oxidative environment. Studying indoor oxidation is very important for predicting potential indoor oxidized pollutants.

As shown in Figure 1.4, indoor oxidation of VOCs includes three major processes: initiation, propagation, and termination. Initiation is predominantly the reaction between atmospheric radicals and alkyl carbons, as shown by the green label in the figure. Here, OH radical can abstract one hydrogen away from the carbon because the unpaired electron in the radical is highly electrophilic. Once the hydrogen has been taken, a carbon-centered radical will form, and the following propagation reactions will take place. Propagation steps are labeled in blue in Figure 1.4. The first propagation step is the attachment of oxygen from the ambient atmosphere to the carbon-centered radical, forming a peroxy-radical. This peroxy-radical has multiple reaction pathways during the propagation, including the reaction with an HO_2 radical or another peroxy-radical in the matrix to form an alkoxy radical.[83] An alternative route of propagation is the intramolecular 1,5 H-shift, which is the formation of a temporary bond with the hydrogen on the beta carbon. This process can convert the peroxy-radical into a hydroperoxide, and initiate the formation of another peroxy-radical on the beta carbon. Eventually, all carbons on the molecule can become hydroperoxides if this process repeats infinitely.[84] Therefore, this process is called autoxidation, and it includes rapid reactions and transformations without losing a radical center on the molecule. Autoxidation is one of the most frequently studied processes in atmospheric chemistry and plays an important role in indoor chemistry. This process can produce highly oxygenated species including peroxides, carbonyls, and organic acids.[84]

The termination of oxidation is the loss of radical intermediates, as shown by orange labels in Figure 1.4. As radicals are very unstable, they can be lost by colliding with another radical, or undergo unimolecular processes including fragmentation and isomerization.[83] Common products from these two termination processes include short-chain carbonyls, organic acids, alkyls, and alcohols. Organic hydroperoxide and peroxide compounds can also form when two radicals collide. However, these products have short lifetimes and can readily decompose,[14], so they can occasionally be classified as intermediates. The research field is still developing an understanding of products generated from indoor oxidation. In the past decade, the oxidation has been introduced as an important indoor chemistry process.[85] Particularly, autoxidation has been found to be responsible for the formation of highly oxygenated indoor air pollutants.[86, 87] For example, edible oil can have a different taste when aged in room air.[88] The oxidation of limonene from citrus fruit peels can produce contact allergens.[89] Recently, consumers may notice a change in the smell or appearance of their PCHP products, including skin creams and e-juice. E-cigarette smokers are aware that e-juice turns brown spontaneously and some consumers assume it is safe. The oxidation process of these consumer products is not well established; thus consumers can potentially be exposed to harmful byproducts during their consumption.

1.4 Approaches to Measure Indoor Air Pollutants

The measurement of gas and particles is particularly important, as they are primary constituents of indoor pollutants.[90] In general, measurements can be made using online or offline techniques. Online techniques are very useful during onsite monitoring, while offline techniques are good for laboratory-based analysis. Each type of technique has its strengths and weaknesses, which will be discussed in the following section.

1.4.1 Online Techniques

Online techniques perform sample collection and data analysis at the same time. Online IAQ measurement can include temperature, relative humidity, and gaseous and particle-phase chemical compositions.[91] Given that concentrations of pollutants can change drastically within minutes, online techniques have tremendous advantages

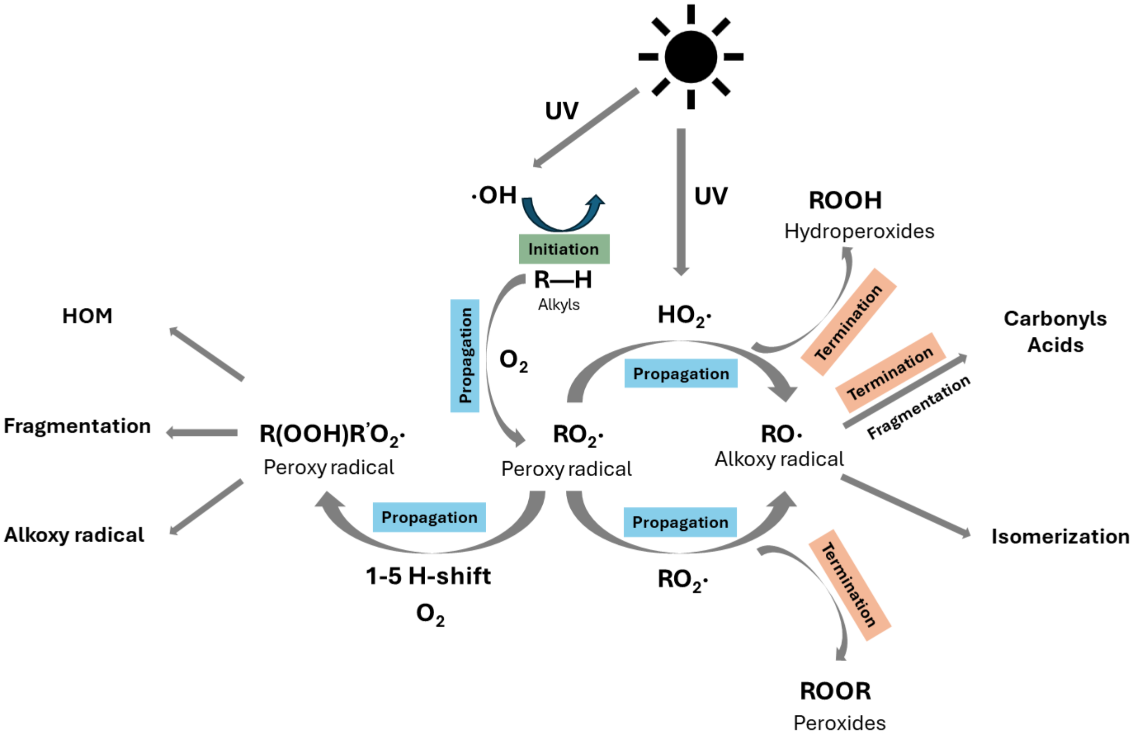

Figure 1.4: Mechanism of autoxidation initiated by OH radicals.

in capturing real-time events that affect IAQ. In addition, online techniques typically require little to no sample preparation and thus can avoid common artifacts related to sample handling required for offline techniques, such as transportation, storage, extraction, and derivatization.

However, online techniques often fail to offer chemical details that are achievable with offline techniques. Given that fast analysis and high time resolution are the priorities, online techniques have very limited compatibility with sample separation and chemical derivatization. As such, the deconvolution of complex environmental matrices and selective analyzes on targeted groups of analytes are significant challenges associated with online techniques. In this section, a couple of online aerosol measurement techniques used in this thesis work are briefly introduced.

Optical Particle Counter (OPC)

The optical particle counter (OPC) is a very portable device; it measures the optical diameter of particles based on Mie scattering (Figure 1.5).[92] When particles pass through an infrared laser, light scattering can occur. The amount of light scattered from the particles changes with their size. Because it utilizes Mie scattering, OPC can be useful with a wide range of particle diameters, from sub-μm up to more than 30 μm.[93] However, Mie scattering is no longer significant when particles are much smaller than the wavelength of the laser used; therefore, the OPC is not compatible with ultrafine particles.

Particle information collected by the OPC is based on several assumptions. First, the aerosol density is assumed to be uniform and consistent at a specific value. Second, it is assumed that the shape of PMs is perfectly spherical.[94, 95] This is because 1) aerosol density must be calculated based on the volume of spheres, and 2) spherical particles give uniform light scattering patterns. However, the actual density of particles can be highly variable and subject to change depending on the mobility diameter of aerosols.[96] The shape is also not necessarily spherical. Therefore, although OPC offers a portable solution for IAQ monitoring, its result could be biased. Multi-instrument cross-comparison is often required for accurate results.

Scanning Mobility Pparticle sizer (SMPS) and Scanning Electrical Mobility Spectrometer (SEMS)

Scanning mobility particle sizer (SMPS) and scanning electrical mobility spectrometer (SEMS) are common aerosol instruments that are based on a similar detection mechanism. The working size range of SMPS and SEMS is typically 1-1000 nm.[98] Both instruments determine the mobility diameter of particles by utilizing a differential mobility analyzer, in which an electrical field is applied, such that particles with different sizes will travel in different trajectories. Although the working principle of these two instruments is the same, there is a slight difference in their designs.[99] Both SMPS and SEMS rely on a condensation particle counter (CPC) to obtain particle counts. Fine particles will grow in the CPC, in which there are supersaturated vapors of water or butanol.[100] These vapors condense on fine particles and facilitate particle growth through a similar principle to cloud formation in the atmosphere.[101] Grown particles are then detected by optical detectors built into the CPC. Therefore, this mechanism allows SMPS and SEMS to determine ultrafine particles that the OPC could not detect.

Online Chemical Analysis

Online chemical analysis techniques can provide instant feedback on chemical concentrations. Routine air monitoring utilizes spectrophotometry techniques.[102] For example, the analyzer for NOx, NH_3, and total nitrogen utilizes a chemiluminescence detector following a molybdenum catalytic converter.[103] Ambient O_3 concentration can be monitored by its absorption of UV light at 254 nm.[104] Recent studies also reported the use of cavity ring-down spectroscopy for monitoring trace gaseous species in the ambient and indoor air.[105–107]

Online mass spectrometry (MS) remains popular in atmospheric chemistry because

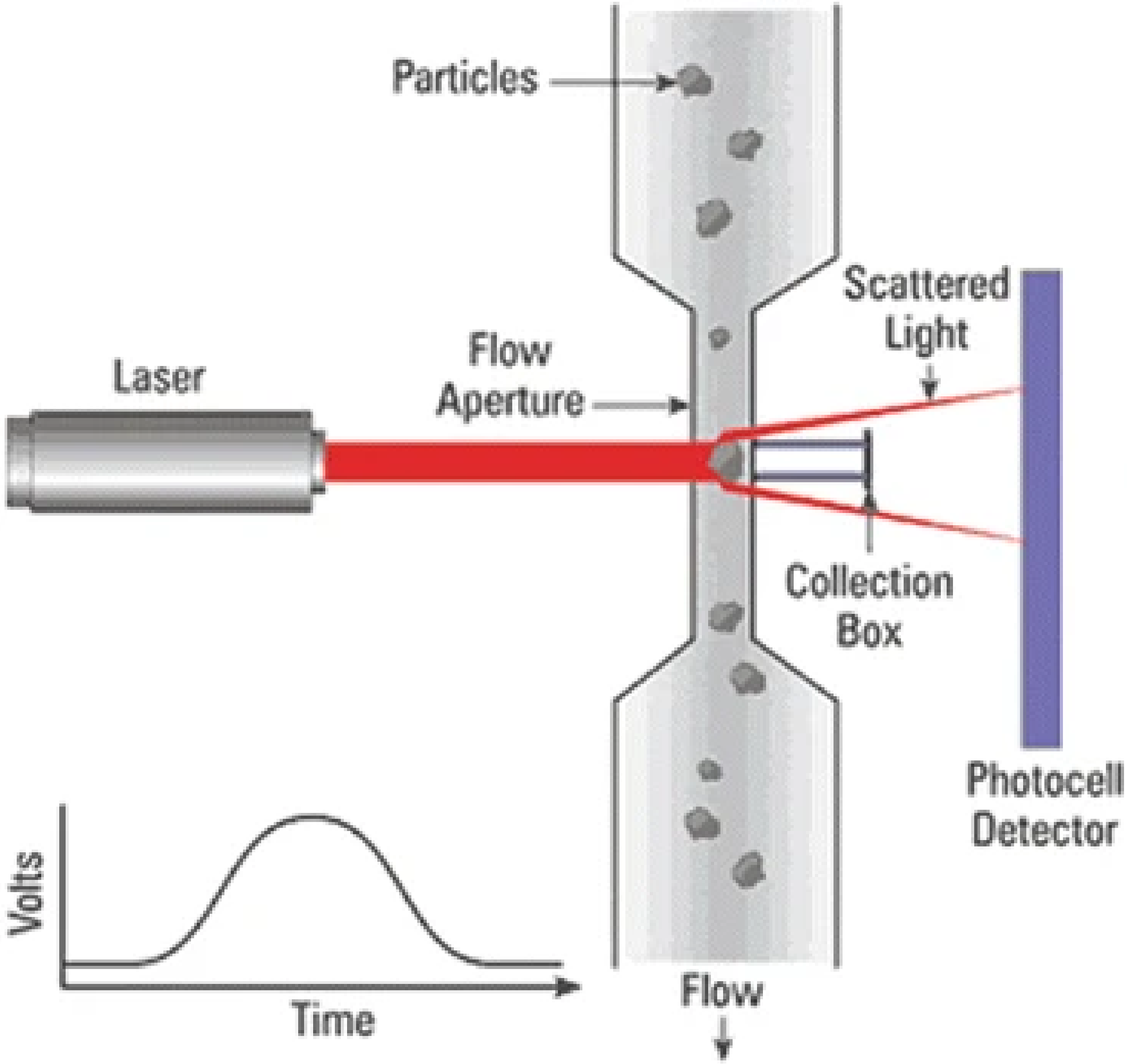

Figure 1.5: Workflow of an optical particle counter (OPC). Figure adapted with permission from: Paolo Rosario Dambruoso et al. “School Air Quality: Pollutants, Monitoring and Toxicity”, Pollutant Diseases, Remediation and Recycling. Environmental Chemistry for a Sustainable World, vol 4. Springer, Chem, 2013.[97]

of its sensitivity and ability to conduct both targeted and non-targeted analyses on gas and aerosol samples. Molecular mass is a determining factor of the volatility of organic compounds and thus the potential for them to form SOA.[108] Online MS can directly measure the mass-to-charge ratios of organic compounds, offer very relevant information for atmospheric research. Several online MS techniques have been widely developed in outdoor atmospheric measurements, including aerosol MS, chemical ionization MS, and proton transfer reaction MS.[109] In recent years, the applications of these techniques to the indoor air have also begun.[91] Despite the versatility of online MS, they also face challenges associated with online measurement techniques, as summarized previously. In addition, online MS cannot distinguish isomers or fragments from electron impact or tandem MS scans, because no separation is involved. As will be outlined below, chemical analyses in this thesis were conducted with offline techniques to provide desired chemical details.

1.4.2 Offline sampling techniques

Offline techniques separate sample collection from analysis. Sample collection is performed on-site, while analysis is performed in the laboratory. As such, offline techniques cannot offer real-time air quality data. However, treated samples can be analyzed with multiple laboratory instruments, so a greater sensitivity, flexibility, and selectivity can be achieved. In addition, offline techniques can offer nontargeted analysis, allowing sample preparation methods to be tailored to target different classes of compounds. Therefore, they are frequently applied to discover unknown contaminants in environmental samples. This thesis includes several offline methods to collect indoor air pollutants, such as gas impingers, filters, and the particle-into-liquid sampler (PILS).

Gas Collection

Numerous gas collection techniques are used in atmospheric chemistry, such as polymer bags, sorbent cartridges, and gas canisters.[110] The impinger is a simple and effective method for collecting water-soluble gases. Occasionally, it is also known as a 'bubbler', where a stream of sample gas passes through a glass chamber that contains the solvent.[111] The equilibrium of gas and water is achieved while the gas is flowing through the device. This equilibrium is governed by Henry's law solubility constant which describes the relationship between the partial pressure of the gas and the aqueous concentration.[112]

$$H_s = c/p \tag{1.1}$$

Where H_s is the Henry's law solubility constant of the compound, c is the chemical concentration in the solution, and p is the partial pressure above the surface of the solution. H_s is subjected to the changes in temperature, pH, and salt concentrations.[113] The temperature dependence is described by the van't hoff equation,[114] whereas the pH dependence arises from the acid dissociation of the compound.

$$H_T = H_0 \text{exp}\left(\frac{-\Delta H_{sol}}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right)\right) \tag{1.2}$$

Where $H(T)$ is the Henry's law constant at a given temperature, H_0 is the Henry's law constant under standard temperature (273.15K), $\delta_{sol}H$ is the enthalpy of dissolution, R is the ideal gas constant, T is the given temperature, and T_0 is the standard temperature.[114]

Particle Collection by Filter Substrate

Particle collection is mostly done with an impactor or a filter substrate. The impactor provides a size-segregated particle collection, where particles with different aerodynamic sizes can be differentiated on multiple layers of substrates. This mechanism allows the mass concentration of each size bin to be known.[115] Our work has utilized one single filter substrate instead of the impactor. This is because of its high portability and the fact that the size distribution is provided by the OPC. During the filter collection, sample air is set to pass through the filter substrate at a controlled flow rate. Particles larger than the pore size of the filter will remain on the substrate, while the gas and fine particles will pass through. Therefore, this method requires a careful selection of the filter substrate. Eventually, the filter will be extracted by a solvent of choice to dissolve collected chemicals. This method also allows a gravimetric measurement of the PM concentration during the sampling period. Gravimetric PM measurement is commonly conducted, as regulations and health impacts are both dependent on mass.[116]

Particle Into Liquid Sampler (PILS)

PILS is a novel particle collection instrument that was developed over the past two decades. This instrument collects a wide range of water-soluble particles, the resulting solution can be used for offline chemical analysis.[117, 118] Before collection, sample air is driven by an external diaphragm pump and will pass through a gas denuder to remove any gaseous chemical interferences. Particles in the sample air will enter a particle growth chamber, in which they are grown to a collectible size in supersaturated water vapor. This step is the same as that mentioned previously in the CPC. Upon collection, a peristaltic pump is used to drive the solvent through an impact window, at which the grown particles will strike and dissolve in the solvent. The PILS workflow is illustrated in Figure 1.6. PILS has several advantages over conventional particle collection methods. Firstly, it collects ultrafine particles due to the particle growth process. The reported collection efficiency is greater than 97%, for particle diameters greater than 30 nm.[119] Secondly, gaseous compounds can be eliminated by the attached denuder, which ensures that the output solution only reflects the chemical composition of particles. However, the accuracy can also

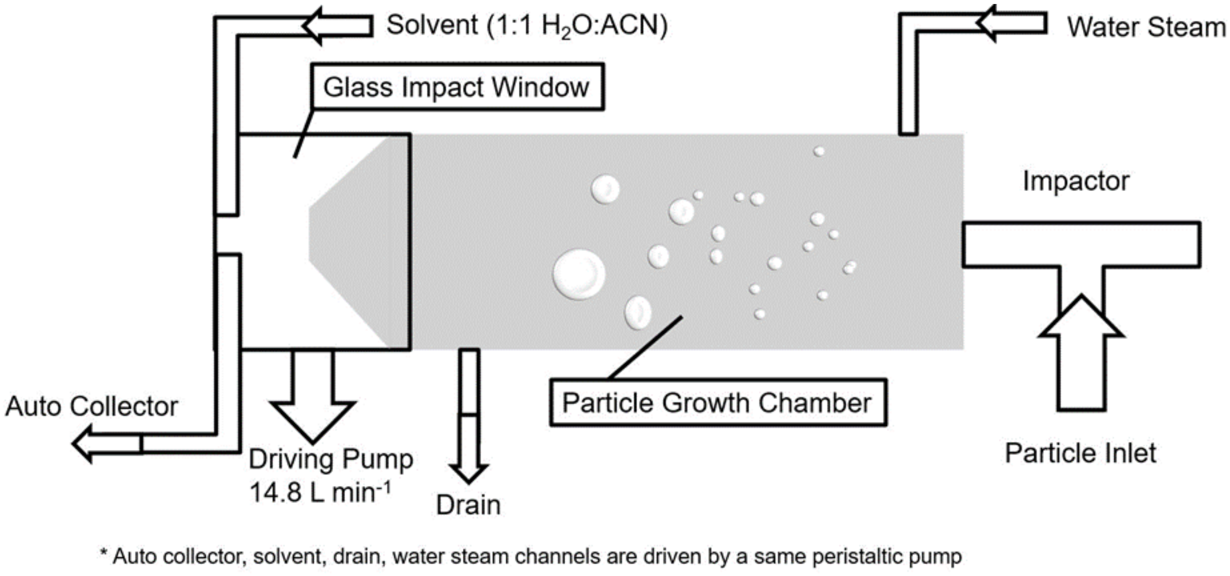

Figure 1.6: Workflow of the PILS Figure adapted under Creative Commons Attribution (CC BY 3.0 DEED) from J. V. Amorim et al. "Photo-oxidation of pinic acid in the aqueous phase: a mechanistic investigation under acidic and basic pH conditions", Environ. Sci.: Atmos., 2021, 1, 276.[120]

be affected by the denuder efficiency, which should be verified with an established gas analyzer. Most importantly, PILS can achieve a time-resolved collection since the solution is continuously driven by a pump. This feature allows PILS to work as a sub-online instrument. Although the result does not appear immediately, analyses with laboratory-based instruments offline can reveal changes in indoor pollutants over time. Therefore, the utilization of PILS takes key advantages of both the online and offline methods.

1.5 Characterization of VOCs

1.5.1 Optical Spectroscopy Methods

Conventionally, optical spectroscopy instruments are used as online detectors or coupled with chromatography for offline analysis. The advantages of these detectors include simple instrumentation, low ownership cost, and good sensitivity and specificity. This section includes two techniques: fluorescence spectroscopy and ultraviolet-visible

(UV-vis) spectroscopy.

Fluorescence Spectroscopy

Fluorescence spectroscopy detects fluorescence light emitted by analytes.[121] During the analysis, the sample receives an incoming radiation from the light source. Analytes can absorb the radiation energy and get excited. As an electron absorbs energy from a photon, it will be promoted to an excited state from the ground state. When excited, molecules will have a higher chance of colliding with each other due to elevated internal energy. The energy contained by the electron will then drop to a metastable state, which refers to the lowest vibrational energy level of the excited state. Eventually, a photon with a longer wavelength will be emitted as the electron relaxes to its ground state.

Fluorescence spectroscopy is a non-destructive method with a very high sensitivity.[121] It can be used to determine biologically based aquatic and airborne pollutants.[122, 123] However, this technique also has several drawbacks. 1) Fluorescence sensitive to environmental factors such as temperature, pH, and solvent matrix. 2) Signals can overlap due to the broad emission spectrum of certain analytes. 3) The excitation of analyte is not tunable, so it is challenging to apply the technique to complex environmental samples.[124]

UV-Vis Spectroscopy

Many chemicals can absorb UV radiation, and UV-Vis spectroscopy makes use of this feature. The spectrometer detects the transmitted light from the sample and outputs the absorption/transmission value, the principle is explained by Beer's law:[125]

$$A = \lambda \times b \times c \tag{1.3}$$

Where A is absorbance, λ is the molar absorptivity of the compound, b is the absorption path length which is usually 1 cm with a standard cuvette, and c is the concentration of the absorbing compound. By applying Beer's law, if the molar absorptivity of the analyte is known, the concentration of analytes can be determined without a calibration curve. For compounds with unknown absorptivity, calibration is required for quantitation.

UV-Vis can be applied in either online or offline mode. As mentioned in the previous section, commercial O_3 monitors utilize a UV-Vis detector. Online UV-Vis is also commonly used to monitor the rate of a reaction. In projects covered by this thesis, UV-Vis works in offline mode. It has been combined with iodometry to determine the concentration of oxidants in the sample.[126, 127] In iodometry, an excess amount of iodide is added to react with oxidants to form iodine. Iodine can react with iodide ions to form triiodide ions (I3-), which have a unique absorbance peaking at 351 nm. Therefore, the concentration of total oxidants can be determined by evaluating the absorbance. This technique is useful for measuring short-lived oxidants in the sample, such as peroxides.

1.5.2 Separation of VOCs

Separation is required for VOC determination due to the complex organic environmental matrix. In addition, signals from trace compounds can be suppressed by concentrated compounds. Separation can differentiate sample signals into different retention times based on their properties. During the separation, analytes are allowed to pass through a packed column that contains the stationary phase. The interaction between different compounds and the stationary phase will be different. Stronger interactions will result in longer retention times, and weaker interactions cause the compound to elute earlier. Common separation techniques involve solid phase extraction (SPE), gas chromatography (GC), and liquid chromatography (LC). The following section will focus on chromatography techniques.

Gas Chromatography (GC)

GC is a versatile separation technique that can separate relatively volatile analytes. The mobile phase of GC is an inert carrier gas, such as nitrogen, helium, or argon.[128] The stationary phase is usually a long silica capillary column which is occasionally up to a few hundred meters long.[129] The long column is coiled inside a temperature-controlled oven. During the GC analysis, a temperature gradient in the oven is applied to obtain the optimized separation, since the temperature affects the vapor pressure of VOCs. Downstream of the GC, detectors such as flame ionization detectors or MS are commonly used. A wide application of GC has been observed in IAQ-related studies. Kaikiti et al.[130] reported the discovery of more than thirty VOCs in indoor hair salons using GC-MS. Sun et al.[131] reported a GC study that humans can exhale up to 98 different VOCs in an indoor environment. Gallagher et al.[132] applied both GC-MS and SPE to characterize VOC emissions from human skin. Wu et al.[133] applied GC with flame ionization detection to evaluate acetal formation in e-juices from the reaction between glycols and aldehydes.

Liquid Chromatography (LC)

While the GC is useful in IAQ studies, one main drawback is that it is not suitable for non-volatile or aqueous analytes.[134] The separation of non-volatile environmental samples requires the use of LC. This instrument has two operational modes: the normal phase and the reverse phase. In the normal phase, the stationary phase is made from polar compounds like silica, whereas the reverse phase uses non-polar hydrocarbons.[135]

LC columns are much shorter than GC. They are also typically packed beds while GC columns are hollow tubes. Improved separation can be achieved with longer columns and smaller silica beads.[136] The resolving power of an LC column can be explained by the plate theory.[137] In this theory, the column is divided into multiple sections of plates, with each plate having a fixed plate height. The height of the plate depends on three analyte diffusion pathways, which are Eddy-diffusion, longitudinal diffusion, and the mass transfer between two phases.[138] With the plate height fixed for each analyte, higher resolution can be achieved in long columns by having higher plate counts. On the other hand, long columns generate a higher back pressure which may exceed the mechanical tolerance of the system. Therefore, instruments with a better pressure tolerance are designed to meet the demand for better separation, such as the (ultra-) high-performance liquid chromatography (HPLC/UHPLC). The flow of the LC mobile phase is driven by a solvent delivery pump, as shown in Figure 1.7. Gradient separation is frequently used, in which the ratio of mobile phase constituents is changed during chromatographic separation. A detector is required after the column separation. Typically, a UV-Vis detector or MS is used, and Figure 1.7 gives an overview of the HPLC-UV setup. These two detectors can also be applied in a series downstream of the LC.

HPLC has a wide application on water-soluble VOCs. Zhu et al.[139] reported a determination of polycyclic aromatic hydrocarbons in kitchen air using HPLC and a fluorescence detector. Zielinska et al.[140] applied HPLC and a UV detector to measure formaldehyde from vehicle emissions in house-attached garages. Došen et al.[141] have determined biomarkers of fungi from contaminated building materials by using UHPLC-MS.

1.5.3 Mass Spectrometry (MS)

MS is a cutting-edge technology that can provide targeted or nontargeted analysis. In an MS instrument, molecules become charged ions at the ionization source. They are then displayed according to their mass-to-charge ratio (m/z). The ionization source on the MS dictates the type of detectable compounds. When MS is coupled with HPLC, common ion sources include (atmospheric pressure) chemical ionization, atmospheric pressure photoionization, and electrospray ionization (ESI).[143] In this present thesis, ESI-MS will be used as the primary technique. ESI sprays the sample

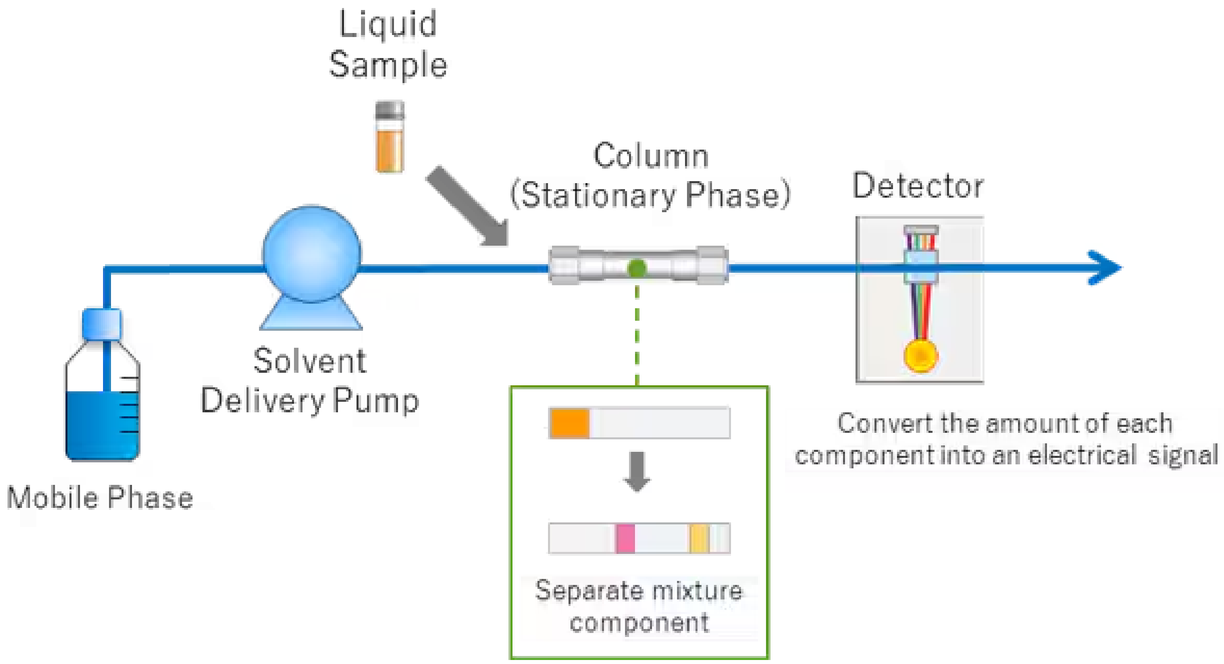

Figure 1.7: Simplified HPLC workflow. Figure adapted with permission from: Courtesy of Shimadzu Corporation, Kyoto, Japan.[142]

solution with a controlled flow of nebulizing gas. The ionization happens at the tip of the ESI probe which carries a few kilovolts of charge (Figure 1.8). It is a relatively simple ionization source that is versatile for polar organic compounds, or aqueous compounds. In addition, the ESI is a soft ionization source. This means ions can retain their molecular structure until they reach the detector, so it does not have significant source fragmentation issues.[144] However, one main drawback of the ESI is that it has an extremely low tolerance for ionic salts in the sample. This is because the ionization efficiency of salt particles is very high, which will inhibit the formation of molecular ions at the spray tip.[144]

Although MS is one of the most advanced analytical tools, it has several limitations. First, the instrumental cost and the cost of ownership is much higher than those of other detectors. Second, MS is relatively less user-friendly, because data processing and method development require intensive training. Third, offline MS is not field deployable, because it requires a lot of consumables, such as high-purity gases. Most importantly, many compounds cannot be detected directly. This is due to 1) lack of retention on chromatography columns, 2) inability to form stable molecular ions at the ion source, and 3) low-mass compounds that are hard to differentiate from the background noise. As a result, derivatization is often required to enable the MS detection of these compounds.

Derivatization for Semi-Targeted Analysis

Derivatization is often applied in environmental samples to improve the method selectivity and sensitivity.[146] It is a method that labels the compound of interest with a known derivatization regent so that the target compound can be isolated from the matrix. The limit of detection (LOD) of the target compound can be significantly improved due to the alternation of the structure, which can increase its ionization efficiency under MS.[147] This technique can be referred to as a semi-targeted technique by detecting a specific group of unknown compounds.[146]

Common derivatization agents include anhydrides, hydrazines, aldehydes, and alcohols.[146] This thesis has utilized two derivatization methods. The first is 2,4-dinitrophenyl hydrazine (2,4-DNPH) for carbonyl species. The second method is the use of p-toluenesulfonyl chloride (TsCl) for nitrogen-containing species.

Derivatization with 2,4-DNPH has been a benchmark technique for carbonyl analyses.[148, 149] The reaction between carbonyls and 2,4-DNPH forms hydrazone. It is very challenging to detect small carbonyls directly in the LC-MS, thus 2,4-DNPH is needed. Conventionally, the total carbonyl concentration can be determined using the UV-Vis detector, as hydrazones usually have a maximum UV absorption of around 450-480 nm.[150] However, it is challenging for UV-Vis to distinguish different carbonyls, making non-targeted analysis not efficient. With the application of LC-MS, we can obtain the elemental composition of derived species. In addition, MS can also distinguish structural isomers of aldehydes and ketones, by performing tandem MS scans.[151]

Conventionally, TsCl is widely used in synthetic chemistry, as it can selectively

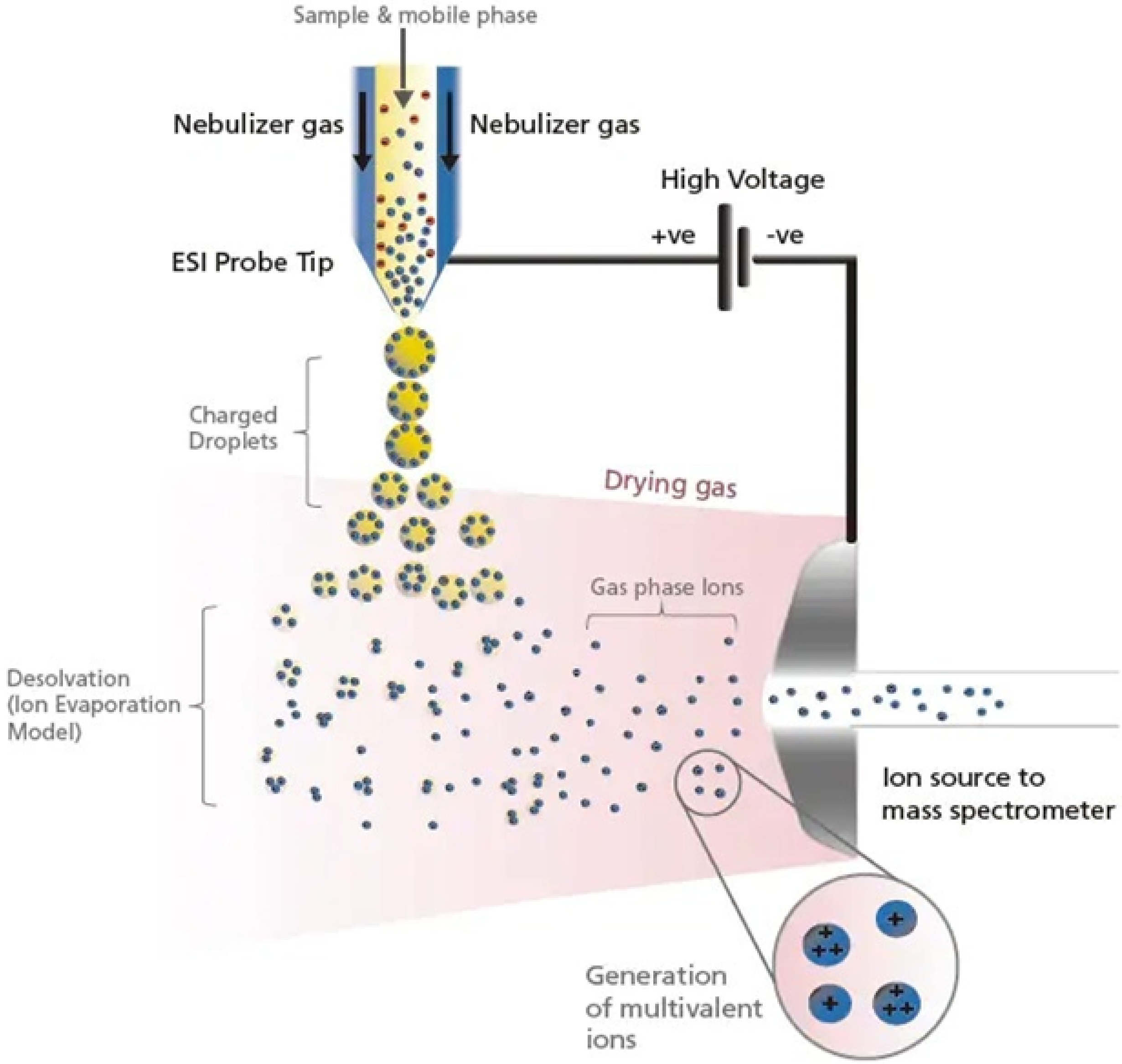

Figure 1.8: ESI-MS Working Principle. Figure adapted with permission from Courtesy of Shimadzu Corporation, Kyoto, Japan.[145]

react with amino groups and hydroxyl groups. The reaction replaces these terminals with a good leaving group for subsequent synthesis.[152] The reaction of TsCl with amines and alcohols forms sulfonamides and sulfonates, respectively, with greater selectivity towards amines due to the higher nucleophilicity of nitrogen. This derivatization technique has been used to quantify amines in foods, beverages,[153] and drugs,[154] but it has rarely been applied in atmospheric samples.

1.6 Motivation

With the development of our lifestyles, the indoor environment has become very complex due to the increasing number of emission sources. IAQ complexity is further enhanced in various occupational and consumer settings. Indoor chemical processes behind these scenes can produce harmful unintended by-products. Although many studies have been performed in the past, we are still lacking a comprehensive understanding of the reactions involved. In addition, many pollutants remained uncharacterized. For example, personal care and entertainment products can generate various indoor VOCs, but corresponding studies remain scarce. These consumables can be oxidized during storage, but many consumers and manufacturers assume that they are safe. Furthermore, several industries are facing persistent issues with indoor pollution. Under such conditions, industrial workers may develop adverse health problems that can reduce their productivity. By systematically studying harmful chemical sources in a few typical indoor settings, this thesis would enhance our knowledge on existing IAQ issues. The discoveries made in this thesis would be a good reference for future clinical studies on occupational and consumer exposure to IAQ pollutants. At the same time, new indoor chemistry processes will be revealed. Our studies will serve as a fundamental analysis that can be applied to different types of indoor environment, which is beneficial for the establishment of guidelines in the future.

1.7 Thesis Objectives

The overall goal of this thesis is to provide chemical insights into possible indoor pollutants in different consumer and occupational scenarios. More specifically, four objectives were formulated:

- To investigate the accumulation of harmful carbonyl contaminants in oxidized artificial fog juice, a glycol-based product that has been widely used in the entertainment industry and home parties.
- To perform a systematic study of autoxidation of any other glycol-containing daily products, and to investigate parameters that will affect the oxidation process.
- To elucidate unrecognized contaminants from the autoxidation of e-juice. In particular, the oxidation of nicotine will be studied.
- To implement a field study in a commercial poultry facility to reveal novel aspects of persistent IAQ concerns of the poultry industry.

1.8 Thesis Outline

This thesis contains 6 chapters. Chapter 1 gives an overview of the background of IAQ, including current challenges, different emission sources, indoor chemistry processes, and current analytical tools to characterize indoor pollutants. This chapter also emphasized that characterizing pollutants in occupational and consumer settings is important to protect workers and consumers. Chapter 2 provides LC-MS characterization of chemical contaminants from the artificial fog juice, a glycol-based product that is widely used in the entertainment industry and house parties. This chapter also formulated preliminary proposal for autoxidation of glycol compounds. Chapter 3 is the extension of Chapter 2, as it reports more solid evidence for the autoxidation of glycols and discovers the parameters that can alter the reaction rate. In addition, this chapter suggests that all glycol-containing products, such as e-juices, will be oxidized once exposed to the air. Chapter 4 reports a selective chemical analysis of contaminants in aged nicotine-containing e-juice using LC-MS. This chapter investigates the radical oxidation mechanism of nicotine in indoor environments, which provides preliminary evidence that nicotine oxidation in e-juices can be a health concern. Chapter 5 summarizes all techniques gained from the previous chapter; it demonstrates a field study of measuring indoor air pollutants in a commercial poultry farm and addressing the root of persisting ammonia pollution issues. Finally, Chapter 6 concludes the overall findings of the thesis, and proposes future research directions.

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Chapter 2

Impact of Glycol-based Solvents on Indoor Air Quality – Artificial Fog and Exposure Pathways of Formaldehyde and Various Carbonyls

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2.1 Introduction

Artificial fog, or synthetic fog, refers to artificially generated liquid aerosol. Artificial fog machines (AFMs) are mostly found and utilized in the theatrical and entertainment industries to produce special visual and photographic effects[155]. Smaller and more affordable AFMs are also available on the market for household use. Many different brands and types of AFMs are available on major online shopping platforms. Most of them are marketed for use on holidays, celebrations, and parties. In both industrial and household settings, AFMs are commonly deployed in indoor settings.

Artificial fogs are classified into inorganic fog, oil-based fog, and glycol-based fog, depending on the source used in AFMs[156]. One of the most common types used is the glycol-based type, also often marketed as water-based fog machine fluids (fog juice) for the absence of mineral oil. This type of fog juice is mainly made with triethylene glycol (TEG), propylene glycol (PG), and demineralized water, with some containing a small fraction of vegetable glycerin (VG). The use of AFM can introduce such chemicals and other impurities to the indoor air.

While people spend approximately 90 percent of their days indoors, air pollutants in the indoor environment are poorly understood.[157–159] Since energy efficiency is achieved indoors by minimizing air ventilation[160], indoor sources can give rise to air pollutants at concentrations much higher than those outdoors.[161] Previous studies have identified a wide spectrum of sources of air pollutants unique to the indoor environment, including cooking,[162, 163] cleaning,[164–166] and the use of ultrasonic humidifiers.[40] While the propagation of particulate matter (PM) and volatile organic compounds (VOCs) produced by many indoor sources has been studied,[167] those generated by AFMs remain unclear.

Only a few previous studies focused on the inhalation risks of artificial fogs, particularly those based on glycols. Varughese *et al.* [168] found that stage actors are more likely to suffer from respiratory complications, likely due to inhalation of glycols. It has been found that many glycol compounds may cause high cell cytotoxicity and will potentially influence the voice of stage performers.[169–172] The physical and chemical properties of suspended fog droplets and aerosols have not been studied in a systematic manner. Additionally, chemical analyses of fog samples were performed solely on freshly manufactured fog juice. Little is known about trace impurities that can arise from the slow degradation of fog juice components and/or from the heating processes in AFMs. In particular, carbonyl compounds are known products of glycols through oxidation[148] and pyrolysis.[173] It is noteworthy that the composition of glycol-based fog juice is similar to e-cigarettes, or e-liquids, which are using PG and/or VG-based solvents.[174] Increasing cases of E-cigarette and Vaping Use Associated Lung Injury (EVALI) were observed, and the vaping crisis in the US before the COVID pandemic has caused more than 2800 cases of EVALI due to vaping.[175–178] Given that Varughese *et al.*[168] have mentioned the risks of glycol inhalation to the voice and health of stage actors, this paper was referred by numerous vaping studies because glycols are employed as the solvent of e-liquids. However, as mentioned earlier, very few studies have investigated the composition and impact of artificial fogs.

Aerosol from AFM is highly volatile, and its size and number distribution change drastically. This has been shown by the evaporation of glycol-based aerosol generated from vaping.[179, 180] A wide spectrum of online aerosol instruments is used by atmospheric scientists to achieve real-time, size-resolved measurements of aerosol. These instruments determine aerosol sizes based on optical, mobility, or aerodynamic techniques and can achieve a time resolution of a few minutes or less.[181, 182] Such time resolution is sufficient to monitor rapidly evolving aerosol generated by AFM. Chemical analysis for rapidly evaporating aerosol can be highly challenging. Aerosol is usually collected with an impactor or filter substrates. Filter collection can be continued for a long period to overcome chemical detection limits, but a disadvantage of filter collection is that it does not provide the time resolution needed to monitor artificial fogs. Further, evaporation after aerosol collection on the filter can be problematic. A particle-into-liquid sampler (PILS) can potentially overcome these challenges because it can collect and extract the water-soluble fraction in real-time, providing time-resolved aerosol chemical composition.[183]

The objective of our study is a fundamental investigation of the impact of artificial fog on the indoor environment. It is the first systematic study for the physico-chemical properties of artificial fogs. Our study also provides new insights into the slow formation of carbonyl compounds due to the degradation of fog juices. The results serve as an important input for artificial fog exposure, including workers and audiences in the theatrical and entertainment industries, as well as household AFM users. Given the use of glycols in a variety of applications, the implications of this work can be extended to other types of glycol-based aerosols, such as those from vaping.

2.2 Methods

2.2.1 Chemicals and Materials

The water used in this study was MilliQ water generated by a Thermo-Fisher Scientific Barnstead^{TM} E-Pure^{TM} Ultrapure Water Purification Systems. Chemicals were purchased from Sigma-Aldrich without further purification, including HPLC-grade acetonitrile (Purity $\geq$99.9%), reagent grade 2,4-dinitrophenyl hydrazine (2,4-DNPH) (Purity 97%), 37% formaldehyde in water solution (with 10-15% methanol), triethylene glycol (TEG, Purity 99%), and 100 μg ml^{-1} formaldehyde-DNPH standard solution in acetonitrile. The fog fluid used in this work was purchased from a popular manufacturer on a major online shopping platform. This brand was one of the best sellers and had thousands of customer reviews. According to the product label of the fog juice, the juice contained 14-30% of TEG, 4-10% of PG, and 60-78% of demineralized water.

2.2.2 Single Room Experiment: Dynamics of Evaporating Artificial fog droplets

Generation of Fog Aerosol in an Experimental Office

A series of experiments were conducted in a single, unoccupied office. Experimental details for these sections can all be found in Appendix A.1. The air exchange rate in the office was maintained by the central ventilation system of the building. We determined the air exchange rate of the room by injecting CO_2 into the room and measuring the decay of the CO_2 mixing ratio using a non-dispersive infrared (NDIR) CO_2 sensor (SCD-30, Adafruit). The air exchange rate coefficient was calculated to be 5.0×10^{-4}s^{-1}, or 1.8 h^{-1}, based on the first-order decay of CO_2. This method is a common way to determine the air exchange rate in indoor spaces.[164, 184]

The fog was generated by a commercially available AFM. It is portable and one of the popular models sold online. It is driven by an internal low-pressure pump, which forces the fog juice through a heated metal capillary. Once the heated vapor is exposed to the cold air, it creates a mist.[185] For each experiment, a 20-second pulse of fog was generated in the office, with the evolution of aerosol continuously monitored. To ensure reproducibility, the experiment was repeated four times, and each experiment was conducted on a separate day to avoid carry-over contamination.

Monitoring and Sample Collection

Aerosol instruments involved are a particle-into-liquid sampler (PILS) (Bretchtel Inc., Model 4001) with an auto-collector, a Scanning Electrical Mobility Spectrometer (SEMS, Bretchtel Inc., Model 2100), and an Optical Particle Counter (OPC, Grimm, Model 11-C). These instruments were placed at the same location inside the office room for aerosol collection and monitoring. Figure 2.1 shows the layout of the experimental room. With the room air rapidly homogenized by a fan, we assumed that all the instruments were sampling the same air composition.

SEMS and OPC were used to monitor the evolution of particle size distribution and number concentration in real-time. SEMS monitors the aerosol from 10 nm to 800 nm in diameter and acquires data every 78 seconds.[186, 187] OPC collects and monitors aerosol from 0.1 μm to 32 μm at a rate of 6 seconds per scan.[188] Having both SEMS and OPC simultaneously was crucial for our experiments since a significant change in particle size is expected.

Offline samples were collected with PILS for detailed chemical analyses. We collected particles into a 1:1 (v/v) water : acetonitrile solution. The sampling rate of PILS was set to be 3 minutes per vial, while the experiment lasted for 93 minutes. Sample vials were mounted on an auto-collector. As will be explained in the next section, analyses of glycols and carbonyls require separate methods, with carbonyls

Figure 2.1: Experimental office layout and instruments involved

requiring derivatization with 2,4-DNPH. To collect samples for both glycol and carbonyl analysis from each single room experiment, the vials on the auto-collector were placed in an alternative manner. The ones for glycol analysis were empty, while those for carbonyl analysis were pre-filled with a 2,4-DNPH working solution (explained below). The operation mechanism of PILS has been described in several previous studies and can be found in Appendix A.1.[183, 189, 190]

Optionally, a gas denuder can be installed at the inlet of PILS to remove gas-phase species. In this work, we have removed this denuder by default to capture both particle- and gas-phase species. We performed a set of experiments to address the effect of gas denuder. In this experiment, we compared the chemical difference and the particle profile difference between samples with and without the denuder. This experiment was repeated once to ensure reproducibility.

2.2.3 Chemical Analysis

Derivatization of Carbonyls by 2,4-DNPH

We performed 2,4-DNPH derivatization to detect carbonyl species in fog samples and the fog juice. 2,4-DNPH reacts selectively with carbonyls and forms stable hydrazones that can be detected by several analytical methods; thus, 2,4-DNPH derivatization has been a canonical method for carbonyl analysis.[191, 192]

A 2,4-DNPH stock solution was prepared by dissolving 2,4-DNPH solids into a 1:1 (v/v) water : acetonitrile solvent at 10 mM concentration. A working solution is created by acidifying the 2,4-DNPH stock solution by adding concentrated HCl into the stock solution, resulting in a pH = 3.0. For sample derivatization, this working solution is mixed with the sample at a volume ratio of 20%, such that the final concentration of 2,4-DNPH would be 2 mM.

As described in the previous section, half of the auto-collector vials were pre-filled with the 2,4-DNPH working solution; thus, the derivatization of fog samples started immediately upon PILS sample collection in pre-filled vials. After sample collection, all the vials were kept at room temperature for 1.5 hours before being injected into the LC-MS. Inevitably, those samples will not have the same derivatization time due to their waiting time on the PILS auto collector and the LC-MS autosampler. To address potential bias, we have tested the effect of waiting time on the concentration of hydrazones by analyzing a derived fog sample at multiple time stamps. We discovered that the hydrazone signal would gradually increase to a plateau between 1 to 1.5 hours, and become stable after 1.5 hours, and no significant decay of signal was observed when left on the tray for at least 24 hours. Therefore, the bias of derivatization time is negligible.

For the derivatization of fog juice, 300 μl of fog juice was mixed with 300 μl of 2,4-DNPH working solution, and the vial was topped up to 1.5 ml by 1:1 water : acetonitrile solution, resulting in a 20% (v/v) final concentration of the fog juice. The rest of the derivatization procedure is the same as the fog samples described previously. To comply with the undetermined efficiency of 2,4-DNPH reaction efficiency, we performed the method standard addition to quantify carbonyl compounds, which will be described later in this section.

Mass Spectrometric Analyses

The main instrument used in this work is a liquid chromatography-mass spectrometer (LC-MS) with an Agilent 1100 series HPLC and a Thermo Fisher Scientific LTQ XL Linear Ion Trap Mass Spectrometer system. Glycol compounds were analyzed by direct flow injection and electrospray ionization, in positive mode (ESI (+)). Carbonyl compounds present in fog aerosol were sampled by collecting PILS aerosol extract directly in DNPH-prefilled autosampler vials. The vials were loaded on the LC autosampler for LC-MS analysis after the experiment in the office was completed. All derived samples were analyzed in negative mode ESI (ESI (-)).[192, 193] The LC separation was conducted with a 150 × 2.1 mm Luna Omega 3 μm Polar C18 column (Phenomenex). Detailed settings for HPLC and ESI-MS can be found in Appendix

A.2.

Identification and Quantification of Carbonyls

Given that the formaldehyde 2,4-DNPH standard is commercially available, formaldehyde is identified by retention time comparison and standard addition. For the identification of the rest of the carbonyl species, we utilized their m/z ratios and fragmentation patterns observed in MS^2. Due to the derivatization, all carbonyls were detected as their 2,4-DNPH hydrazones, such that the m/z of a given carbonyl would be m/z = $M_{RC=O} + M_{DNPH}$ -19, where $M_{RC=O}$ and M_{DNPH} are the molecular masses of the carbonyl and 2,4-DNPH, respectively. The loss of m/z 19 is due to dehydration during the derivatization and deprotonation in ESI (-). Compounds with aldehydic functional groups were confirmed by the presence of a fragment at m/z = 163 in their MS^2 spectra, which is specific to aldehyde-DNPH hydrozones. [151]. Ketones are also derived by 2,4-DNPH, but the fragment at m/z 163 would be absent. Instead, a dominating m/z = 152 fragment would be observed.[191] For quantification, due to the unavailability of commercial standards, only formaldehyde in the fog juice was quantified using standard addition. Formaldehyde standards at variable concentrations were made by serial dilution and were spiked into the fog juice. The signal of formaldehyde-DNPH was normalized against an internal standard with m/z = 308. This compound is an undertermined contaminant in the 2,4-DNPH solid, it has a very consistent signal across different samples, and has a retention time far away from other hydrazones. The concentration of formaldehyde in the fog juice was determined by the x-intercept of the linear regression curve.

2.3 Results and discussion

2.3.1 Dynamics of Evaporating Fog Aerosols

The evolution of fog particles in an example single-room experiment is presented in Figure 2.2. During this experiment, aerosol monitoring with SEMS and OPC, as

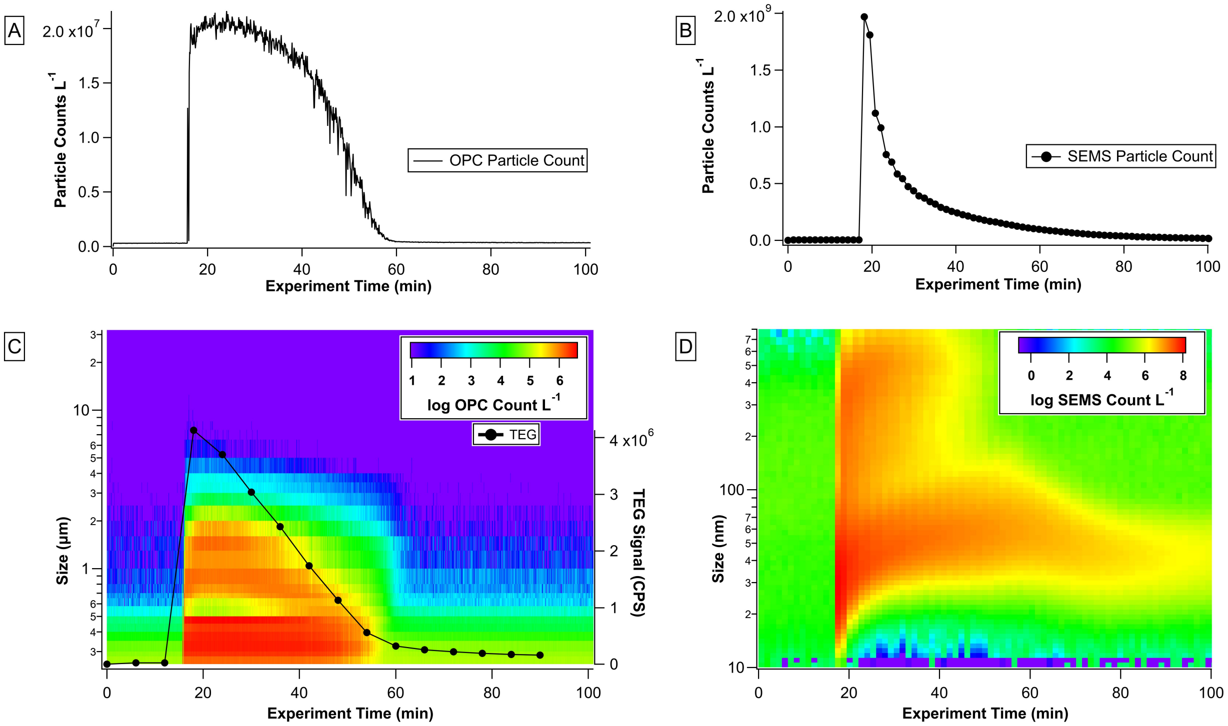

Figure 2.2: Time profile of fog particle evolution collected by the OPC, the SEMS, and TEG measured by PILS followed by MS. Fog was injected into the office at time = 15 min. A) and B): total number concentrations recorded by OPC and SEMS, respectively; C) and D): Size distribution recorded by OPC and SEM, respectively. The time profile of the TEG signal is included in C).

well as offline sample collection with PILS were performed simultaneously. Before the fog injection, the background room air was monitored. Upon the 20-second fog injection, particle numbers exhibited a sharp increase. The number concentration collected by the OPC is shown in Figure 2.2A. The time profile demonstrates that the particle count plateaued for roughly 20 minutes, then diminished at an increasing rate. Eventually, the concentration of particles returned to the baseline. The time profile observed in Figure 2.2A agrees with the visual appearance of fog in the room, with turbid air sustained for more than 20 minutes but completely dissipated by 40 minutes after injection.

The mass concentration of particles was also recorded by the OPC. The average $PM_{2.5}$ and PM_{10} concentrations were 15.1 ± 0.8 and 16.6 ± 3.1 $\mu g/m^3$, respectively. Upon the 20-second fog injection, the mass concentration of particles experienced the

Source/Activity	$PM_{2.5}$ (μg/m^3)	PM_{10} (μg/m^3)	Ref.
Artificial fog[a]	1.07×10^4	1.09×10^4	this work
Cooking [b]	11 - 2.73×10^3	520 - 1.33×10^3	[194, 195]
E-cigarette vaping	4.80×10^3 [c]	9.05×10^3 - 1.32×10^4 [d]	[196, 197]
Ultrasonic humidifier	505 [e]	N.A	[184]

Table 2.1: Peak particular matter mass concentration in different indoor activities

[a] The 5-min average value from the OPC.

[b] Chinese residential cooking style.

[c] $PM_{2.5}$ measured 0.8 meters away from the source.

[d] During an indoor vaping convention.

[e] Steady-state concentration in a house campaign

same increase as the number concentration. At the peak time, we assume that the density of particles is equivalent to that of TEG (i.e., 1.13 g/cm^3). The peak 5-minute average $PM_{2.5}$ and PM_{10} reading recorded by the OPC was 1.07×10^4 μg/m^3 and 1.09×10^4 μg/m^3, respectively. For SEMS, the 5-minute average reading at the peak time was 8.60×10^3 μg/m^3 for particles less than 780 nm in diameter.

Table 2.1 has compared the peak-time mass concentration of PM in different indoor activities. The contribution of each source to indoor PM is highly dependent on specific sources (e.g., cooking style or fuel type) and ventilation conditions. The values provided on Table 2.1 are intended to be a reference for the typical values. The use of the artificial fog will contribute to an indoor PM_{10} concentration as high as E-cigarette vaping during the first few minutes of the fog injection, and about eight-times higher than common cooking techniques. The $PM_{2.5}$ mass concentration generated from the fog spray is slightly lower than its PM_{10} concentration, indicating that the majority of particles in the artificial fog are $PM_{2.5}$.

The total number concentration monitored by the SEMS is shown in Figure 2.2B, which is drastically different from that recorded by OPC (Figure 2.2A). The number concentration initially decreased at a much faster rate up to approximately 40 min. It then exhibited a more gradual decay profile, with a first-order rate coefficient of

$7.7\times10^{-4}\text{s}^{-1}$ ($2.8\ \text{h}^{-1}$) until the end of the experiment. This rate roughly agrees with the air exchange rate of the room, $5.0\times10^{-4}\text{s}^{-1}$ ($1.8\ \text{h}^{-1}$), determined in the method section. This observation indicates that fog droplets evaporate and are left suspended as ultra-fine PM that is detectable with SEMS but not OPC. These ultra-fine particles are likely composed of non-volatile compounds, such as inorganic salts from the water in the fog juice, as their removal from the office is dominated by air exchange. The identity of such compounds is not identified, as they are not retained on the LC column. The decaying shape of the time profile is different in Figures 2.2A and 2.2B. Particle concentration recorded by the OPC tends to remain at a high concentration for a longer time, while the concentration recorded by the SEMS decayed sharply after the spray. This difference is likely due to the evaporation of fog particles in the sheath flow of SEMS. Due to the sheath flow, all particles will have an accelerated decay rate. For large particles which contain a larger volatile portion, the size distribution will be shifted towards a smaller diameter due to the accelerated evaporation. In contrast, for smaller particles, the portion of volatile component is smaller. Therefore, the size distribution shift is less significant. In the later section of the experiment, since the sheath flow is already in equilibrium with the sample air, the bias on size distribution would become less pronounced. As a result, SEMS data in the latter half should be more reliable, either since sheath flow and room air are now better equilibriated, or particles remaining are less volatile and less subject to evaporation in sheath flow. A detailed discussion can be found in Appendix A.3 and Figure A.2.

Figures 2.2C and 2.2D are contour plots illustrating the evolution of particle size distribution recorded by OPC and SEMS, respectively. The removal of large particles was recorded by both instruments. This is expected since large particles can be removed by both the evaporation of volatile compounds and the deposition due to their greater mass. The trends in the two figures are relatively consistent. The OPC data shows that the droplets were up to approximately 5 μm in diameter immediately after the pulse, and evaporation occurs rapidly. In an hour, most of the particles in the office become smaller than the detection range of OPC (> 100 nm). The SEMS data shows that the residuals of evaporating particles reach a final size of approximately 50 nm in diameter and are left suspended for a prolonged period. We propose that those particles that stayed for a prolonged time are likely to be non-volatile species in the fog juice and are only removed by air exchange. This is evidenced by their removal rate being similar to the air exchange rate (see above). There are certain differences between Figures 2.2C and 2.2D, likely due to the issue associated with particle evaporation in SEMS, which we discussed previously.

In Figure 2.2C, we have also added the temporal profile of TEG, which was measured using PILS collection, coupled with flow injection MS. Our PILS-MS technique was very successful in elucidating the real-time evolution of chemical composition in the office. The time profile of TEG matched that of OPC but not with SEMS. This is understandable, given that OPC monitors the larger droplets, where most TEG is present. The signal of TEG decreased rapidly when the large fog particles were evaporating rapidly. The trend of TEG decay became much slower 40 minutes after the fog pulse, following a first-order rate coefficient of $4.1\times10^{-4}\text{s}^{-1}$ (or 1.48 h^{-1}), which roughly matches the air exchange rate (1.8 h^{-1}). This slow decay of the TEG signal is likely because PILS can collect some of the gas-phase TEG. To test this hypothesis, we installed a gas denuder at the sample inlet of the PILS. The corresponding result and discussion can be seen in Figure A.3 in Appendix A.4. The tailing of the TEG signal at the end of the experiment is absent when the gas denuder is mounted, which indicates the tailing is likely due to gas-phase TEG. Although we do not have a direct gas-phase measurement in this work, it is evident that components of the fog droplets can evolve to the gas phase and remain in the office until air ventilation removes them.

2.3.2 Chemical Compositions of Fog Samples and Fog Juice

Figure 2.3 shows the time profile of dominant glycols and carbonyls detected in the fog samples and the corresponding ESI (-) extracted ion chromatogram (EIC). A complete list of detected species can be found in Table A.3 in Appendix A.2. According to the ESI (+) spectrum with flow injection, TEG is the major chemical in ESI (+). Diethylene glycol (DEG) is the second abundant species whose signal is 50 times smaller than that of TEG. While PG comprises 10% of the fog juice, we did not detect its signal, likely because the molecular ion is not efficiently ionized in ESI (+). The major species detected match the fog juice composition mentioned in the method section. As discussed previously, the TEG time profile shown in Figure 2.3A is in agreement with the particle profile. The signals of TEG and DEG did not return to the baseline at the end, which indicates the presence of gas-phase TEG and DEG in the office.

Time profiles of TEG-aldehyde, DEG-aldehyde, and PG-ketone, acquired by ESI (-) with LC-MS, are presented in Figure 2.3B as carbonyl representatives due to high signal intensity. The presence of other carbonyls can be found in the corresponding EICs in Figure 2.3C. The time profile of carbonyls is also in agreement with the particle time profile, which is evidence for their presence in the aerosol. However, a substantial fraction of them likely remains in the gas phase at the end of the experiment, as shown by signals much higher than the initial background, as well as discussions provided in Appendix A.4.

To determine the source of carbonyls, we performed the same analysis for carbonyls on the fog juice. Higher concentrations and a wider spectrum of carbonyls are detected. Figure 2.4A presents the EICs of the old fog juice (purchased eight months before the measurement) we used in the office, and Figure 2.4B presents the EICs of a newly purchased fog juice. All detected compounds are listed in Table A.4 in Appendix A.5. A total of nine carbonyl compounds were detected in the old fog juice,

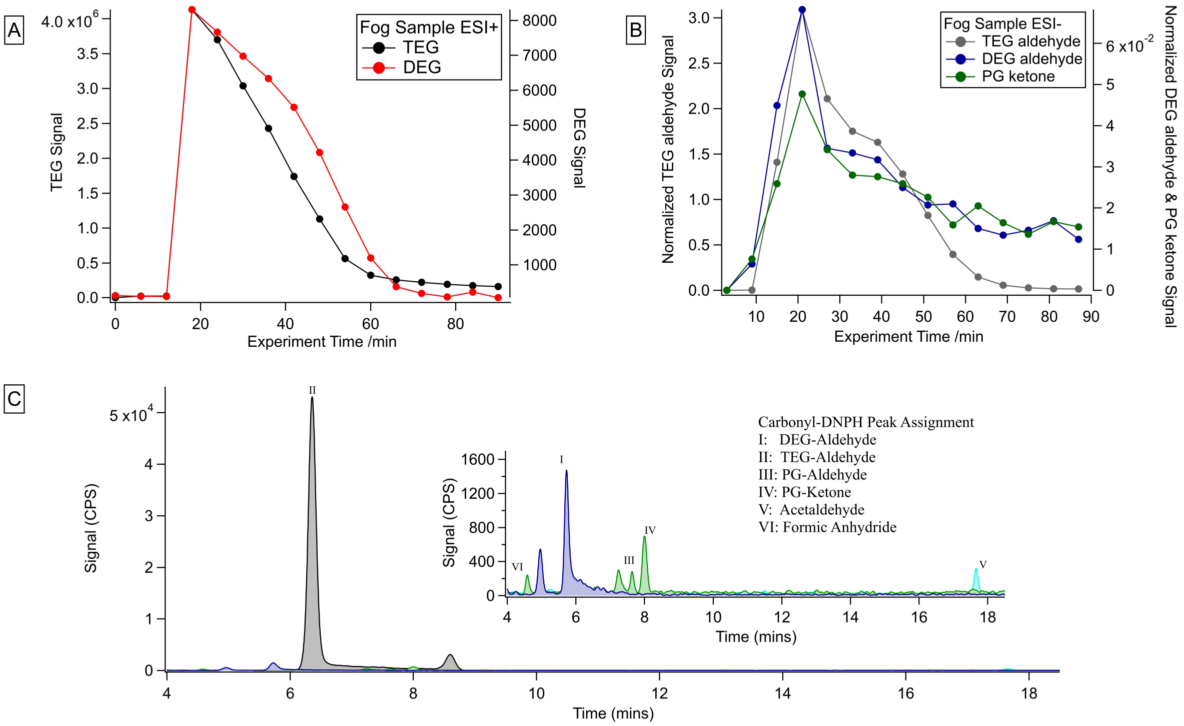

Figure 2.3: Chemical species detected from fog aerosol suspended in the office. A) Time profile of glycols by ESI (+); B) Time profile of major carbonyls by ESI (-); C) Extracted ion chromatogram of 2,4-DNPH derived fog sample at the peak time (18 minutes).

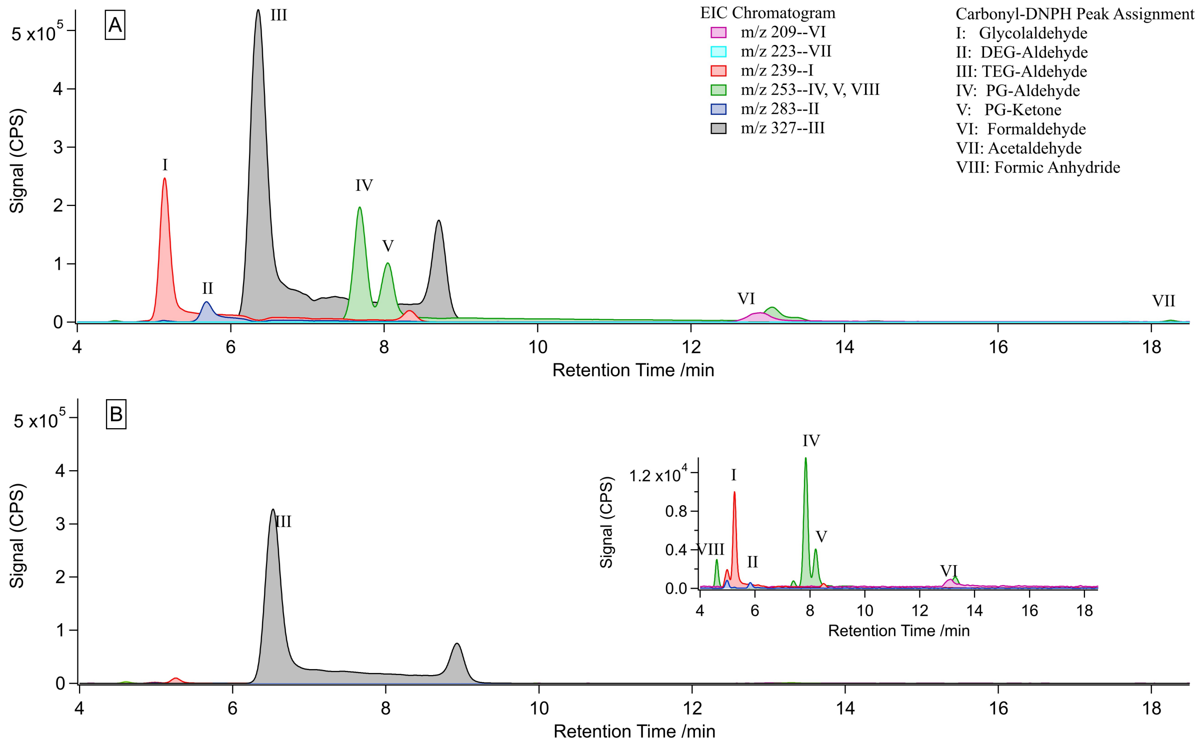

Figure 2.4: Extracted ion chromatogram (EIC) of DNPH-derived fog juice; A) The 8-month-old fog juice; B) The new fog juice.

most of them were aldehydes. Note that a compound is defined as detected when its signal is at least three times higher than the signal-to-noise ratio. As discussed in the method section, the fragment at m/z 163 serves as a signature for the aldehyde-DNPH hydrazone.[151] Corresponding MS^2 fragmentation patterns of hydrazones in the fog juice can be found in Figure A.4.

Among the detected carbonyl species in Figure 2.4A, the dominant peak is attributed to TEG-aldehyde. Other species detected in fog juice include formaldehyde, acetaldehyde, and glycolaldehyde. These aldehydes are toxic and have a negative impact on indoor air quality.[198–201] We employed standard addition to quantify formaldehyde and to confirm the identity of species found in the fog juice; the results of this experiment can be found in Appendix A.6. We obtained a formaldehyde concentration of 9.75 ± 0.01 mM in the fog juice.

The detection of a wide spectrum and high concentration of carbonyl impurities was unexpected, as they were not listed on the safety data sheet provided by the manufacturer. When comparing the EICs of the new fog juice (Figure 2.4B), the chromatogram contains less intense carbonyl signals, with only TEG aldehyde being significant. Although small aldehydes were reported from pyrolysis of PG and VG, [202, 203] we did not observe evidence of fog juice pyrolysis because all the carbonyls in fog aerosols are also found in the fog juice. PG and VG have been shown to undergo pyrolysis at 527 ℃ and 660 ℃ respectively.[202, 204] Using a thermocouple, we found that the heating tip of our fog machine reached 180 °C during operation, which is unlikely to cause pyrolysis. Given the difference in chemical composition between the old juice and the new juice, we conclude that airborne carbonyls detected (Figures 2.4B and C) are likely coming directly from the fog juice, which in turn, could arise from chemical reactions that occurred during the storage.

2.3.3 The Use of AFMs and Indoor Formaldehyde Concentration

By assuming complete evaporation of formaldehyde to the gas phase upon fog injection, its concentration in the office room would be 27.9 ppb at the peak time of one injection. Given that the short-term formaldehyde exposure limit set by the Government of Canada is 10 ppb for most sensitive individuals, the formaldehyde concentration in our office could be in the harmful range. [205] Small carbonyls were detected only from the fog juice but not from fog aerosol, though they are likely presenting in the room air upon fog droplet evaporation. These species are highly volatile, and the PILS likely has a limited capability to collect gas phase compounds.

While only a pulse of fog was injected in our experiment, we generated a single box model to simulate continuous fog generation. We assumed that formaldehyde is only generated via fog machine and only lost through air exchange (no reaction loss or deposition). Under the scenario where the fog was injected 10 times in an hour, the steady-state concentration of formaldehyde would be approaching 155 ppb. Details of the box model calculation can be found in Appendix A.7 and Figure A.7 in the SI.

The application of fog machines in real life would be different between users and places. Under a more realistic scenario, where the room volume is about 10-times bigger than our experimental office, and an air exchange rate of 0.35 h^{-1} according to the minimum ventilation rate suggested by the US EPA. One fog machine would contribute about 79.6 ppb of formaldehyde in the steady-state concentration. The simulated model prediction of this scenario can be found in Figure A.8 in the SI. Additionally, to maintain a foggy environment, more frequent sprays may be used; therefore the concentration of formaldehyde can become even higher than Government of Canada's exposure limit of 10 ppb, which is likely to cause an acute exposure effect (40 ppb for 8-hour minimum exposure, 100 ppb for 1-hour exposure).

2.3.4 Formation of Carbonyl Impurities during Storage of Fog Juice

Comparison between Old and Newly Purchased Fog Juice

We hypothesized that the presence of impurities in the fog juice could be due to the gradual decomposition of fog juice components. By the time experiments and analyses described in the previous section were conducted, the fog juice had been stored for more than eight months on a shelf that was exposed to the room light but avoided direct sunlight. The fog juice was contained in its original plastic container with a standard screw cap. The bottle was temporarily opened only when experiments and analyses were conducted. Over an 8-month storage period, the bottle was opened approximately 40 times. To evaluate the impact of storage, we analyzed a newly purchased fog juice from the same manufacturer. The concentration of formaldehyde in this new bottle, quantified with the same standard addition method, is 13.1 ± 2.4 μM, which is far less than that in the eight-month-old fog juice. The detailed results, including the standard addition curve, can be found in Figure A.5.

Aging of Fog Juice

To confirm our hypothesis that formaldehyde was produced during fog juice storage, we monitored the formaldehyde concentration over nine weeks in the new fog juice. Two conditions were examined in this experiment. One is a portion of fog juice stored in a loosely caped glass vial that is constantly exposed to room air; the other is the fog juice sealed tightly in its original container and was opened only for analyses. For both conditions, the formaldehyde-DNPH signal was recorded using the same LC-MS method, and the results are shown in Figure 2.5. Signal intensities in Figure 2.5A are the peak area of the formaldehyde-DNPH normalized by that of the same internal standard mentioned in the method section. This experiment continued for nine weeks. Quantification of formaldehyde with standard addition was also conducted on weeks 0, 5, and 8.

According to Figure 2.5, the formation rate of formaldehyde in the air-exposed sample is much faster than in bottled samples: 3.04 mM/week, and 0.64 mM/week, respectively, these values were estimated from a linear fit to the data. By using a one-tailed two-sample t-test on MS responses, we confirmed the formaldehyde accumulation in the air-exposed sample is significantly faster than in the bottled sample at 5% significance. By week 9, the air-exposed sample contained 25.2 mM of formaldehyde, which is already far beyond the level we detected in the eight-month-old fog juice. On the other hand, the bottled sample has accumulated roughly 5 mM of formaldehyde. These observations confirm our hypothesis that formaldehyde has been formed during storage. When exposed to the air, the formation rate is about seven times faster. Even for fog juice stored in the bottle, formation seems to start as soon as its contents are exposed to the open air.

Two mechanisms can potentially explain the formation of formaldehyde upon air exposure: 1) partitioning of gas-phase formaldehyde and 2) oxidation of fog juice components. Partitioning of gas-phase formaldehyde cannot give rise to a concen-

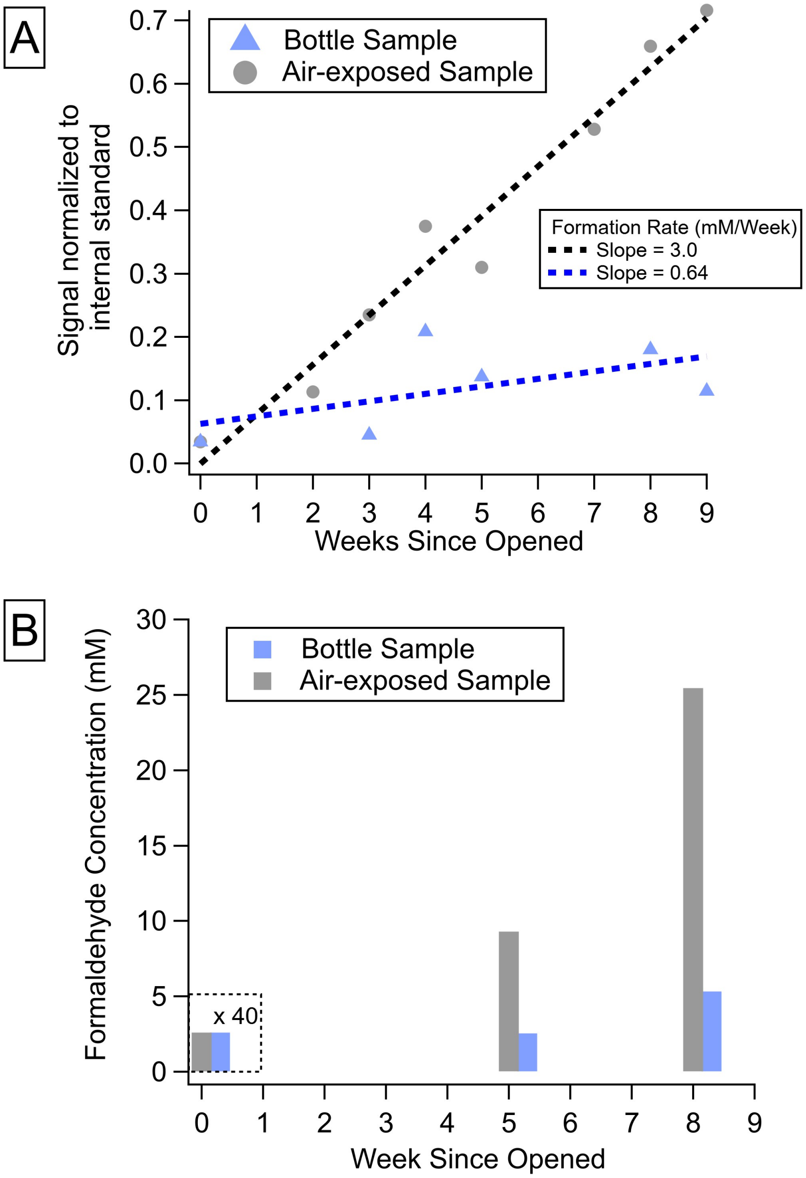

Figure 2.5: Formation of formaldehyde during storage; A) MS signal and fitted line of air-exposed sample (black) and bottle-sealed sample (blue); B) the concentration of formaldehyde in two sets of samples, quantified at three timestamps by standard addition; The initial concentration is magnified by 40-times for better visualization. The LOD of Formaldehyde-DNPH was calculated as 3.63 μM.

tration at the mM level considering formaldehyde's Henry's Law Constant; thus, we consider oxidation of major fog juice components, namely TEG and PG oxidation, as a more feasible explanation.

Two major indoor oxidants are likely to react with glycols: hydroxyl radical (·OH) and singlet oxygen ($^1O_2$).[206–208] Although hydroxyl radical generally has a very low indoor concentration, it is a highly reactive and unselective oxidant that usually initiates a chain of radical reactions via H-abstraction.[209] TEG is very reactive to OH radicals, given that it has many electron-rich sites due to electron-donating hydroxyl and ether groups.[210] Therefore, hydrogens on the carbons adjacent to ether and hydroxyl groups are the most reactive to H-abstraction. OH radical is more abundant outdoors due to active photochemistry, while indoor OH radical is less available but not negligible. Although air exchange would introduce precursors of the OH radical, such as ozone, to the indoor environment, the short-lived radical can only have a steady-state concentration of 10^4 to a few 10^5 molecules cm^{-3}.[211] The fast growth of formaldehyde we observed previously (approximately 3 mM per week) cannot be fully explained by such low concentration of OH radical. Therefore, the oxidative degradation of TEG is likely initiated by the OH radical but sustained by other mechanisms.[212] We propose that the radical chain reaction is propagated via autooxidation, given that autooxidation is responsible for the oxidation of food and cooking oils.[213, 214] Autooxidation does not require a high concentration of radical to propagate, while it only needs an initiation.

Singlet oxygen is a more selective oxidant than the OH radical, as it is known to undergo electrophilic addition towards the double bond on alkenes. [215] However, a recent study has shown that $^1O_2$ would selectively insert to C-H bonds adjacent to ether groups. Due to the C-H bond strength on this carbon being weaker than other bonds, $^1O_2$ would rather undergo direct insertion, forming a peroxide.[216] TEG has two ether groups in one molecule, so the direct insertion of the $^1O_2$ is more likely to occur on the α-carbons, rather than electrophilic addition. Additionally, $^1O_2$

can undergo electrophilic addition towards proximal carbons to OH groups due to the hydroxyl group(s)' electron-donating effect. The peroxide molecule formed can subsequently decompose due to light or heat, producing an alkoxy radical. Therefore, autooxidation is less likely happening when singlet oxygen is the initiator because there are no peroxy radicals involved during the process.

While detailed oxidation mechanisms of TEG and PG are proposed in Figure A.9 and A.10 in Appendix A.8, a brief scheme is also shown in Figure 2.6. Based on these proposed mechanisms, we were able to explain the formation of all the carbonyl species detected from the aged fog juice and fog samples, especially the fast growth of formaldehyde. According to the full mechanism we proposed in Appendix A.8, one TEG molecule would generate multiple formaldehyde molecules through autooxidation and the alkoxy radical routes. Some oxidation products, such as the DEG-Aldehyde, could also be further oxidized to small carbonyls due to the existence of the ether group. In particular, the proposed aldehydic products also agree with those confirmed by fragmentation in MS^2, as discussed previously. Figure 2.6A shows an example reaction mechanism initiated at the most reactive position of the TEG molecule. Formaldehyde and glycolaldehyde are the terminal products of TEG degradation. In Figure 2.6B, we show that PG oxidation can be initiated at the secondary and tertiary carbons. However, since PG is a short-chained molecule, the chance of autooxidation to occur is very limited, while the formation of alkoxy radicals is preferred.

2.3.5 The Implication to Indoor Air Quality

Our study found that the use of an AFM has negative implications on indoor air quality. AFMs generate a huge number of aerosol particles within a short time. While most of these particles evaporate into the gas phase, a significant fraction remains suspended as ultra-fine particles (< 100 nm diameter) for a prolonged period. The detection of major chemical compositions (e.g., glycols and their aldehydes) in the fog

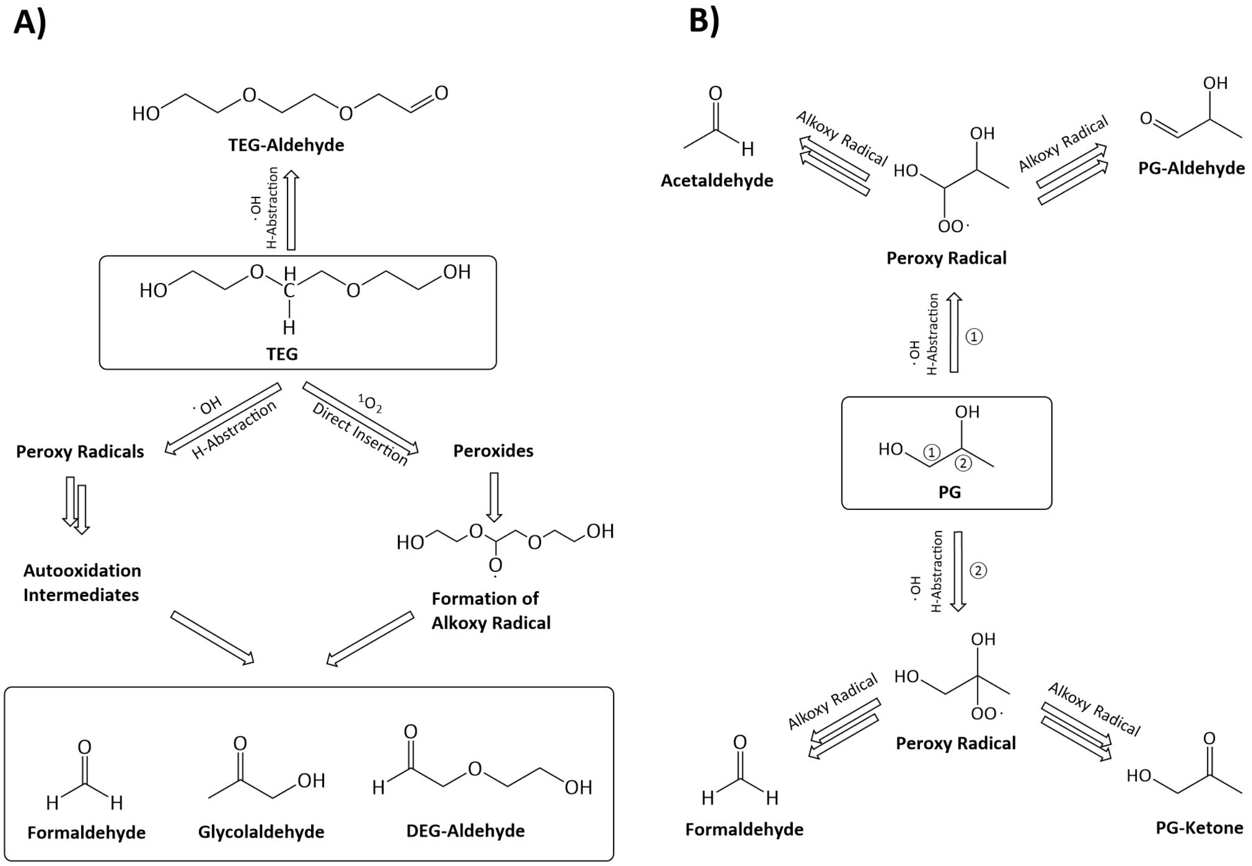

Figure 2.6: A brief scheme for the proposed mechanism of carbonyl formation in the fog juice from the oxidative decomposition of TEG (A) and PG (B). Full Schemes can be found in Schemes S1 and S2 in the SI.

sample was achieved by a novel technique, combining a PILS with MS and LC-MS. The ultra-fine particles left suspended in the air could be composed of non-volatile species, with their rate of removal close to the air exchange rate. This implies that their removal is dominated by the room air exchange.

A significant discovery of the current work is the detection of high concentrations of formaldehyde and other carbonyl compounds in the fog juice, and its growth in concentration over time. Through a series of careful experiments, we propose that the likely source of these carbonyls is the oxidative degradation of glycols via exposures to the OH radical and $^1O_2$ in the air. Carbonyl compounds, especially formaldehyde and other small aldehydes, are toxic to humans. Potential exposure to such high levels, especially that in aged fog juice, may result in severe health implications such as respiratory irritations or cancers. Newly purchased fog juice contained low concentrations of these aldehydes, but the formation initiated immediately after the bottle was opened. The use of aged fog juices, that are more than a few months old, may serve as a previously unrecognized source of these carbonyl compounds. We note that the oxidation of TEG and PG involves other intermediates that we did not target in this work, e.g., peroxides. These intermediates may represent further risks that should be addressed in future studies.

A major weakness of our study is the lack of the gas-phase measurement, We could not directly monitor the evaporation of carbonyl compounds from fog particles to the gas phase. We did, however, present preliminary evidence of TEG and other species remaining in the gas phase. Therefore, those harmful carbonyls will likely remain in the gas phase even after fog dissipates, which presents an inhalation hazard for AFM users, as well as actors and audiences involved in the entertainment industries. Future studies should focus on measuring gas-phase components that we could not achieve in this work.

The findings from this study can be extended beyond artificial fogs and have implications for other practices that involve glycol-based solvents. In terms of chemical composition, fog juice shares many similarities with e-liquids, which are predominantly made from PG and VG. Previous studies have focused on carbonyl compounds in vaping aerosol as added flavoring agents[217, 218] or arising from intense heating. [219, 220] Carbonyl compounds arising from aged PG and VG have never been investigated and can represent an additional adverse health effect of vaping.

2.4 Acknowledgement

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Chapter 3

Autoxidation of Glycols Used in Inhalable Daily Products: Implications to the Use of Artificial Fogs and E-cigarettes

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3.1 Introduction

Glycols, or diols, are families of alcohols that have two hydroxyl groups (-OH) attached to an aliphatic carbon chain. By having different lengths of the carbon chain, every glycol has its unique physical and chemical properties that make them useful in various industries and daily products. Due to the presence of multiple hydroxyl groups, glycol molecules have very strong intermolecular forces, which give rise to their low volatility and high viscosity. Conventionally, glycols are found in liquid or gel-like products, such as engine coolants [221], drug delivery media [222], food additives [223], as well as antifreeze or dehydrators [224]. Recently, growing demand for glycols has been found in volatile organic compound-generating (VOC-generating) or inhalable products[225, 226]. Ethylene glycol (EG), diethylene glycol (DEG), triethylene glycol (TEG), and polyethylene glycol (PEG) are common constituents in products including wall paints [227], artificial fog juice [228], and perfumes. Glycerol (VG) and propylene glycol (PG) are mostly seen in food or drug additives, solvents of personal care products, and E-cigarette juice[196, 229–231]. In particular, as the indoor environment becomes where people spend the majority of their daily life, the aforementioned inhalable products could lead to elevated human exposure to glycols and potentially other harmful compounds, leaving a strong implication for indoor air quality. Especially for occupations under frequent glycol exposure, the adverse health effects and productivity loss due to elevated indoor air pollutants could be significant[232, 233].

With the development of the entertainment and vaping industry in the recent decade[234], individual and public health implications of inhalable glycols have garnered more attention from consumers and researchers. Since the early 2000s, a few studies proposed that stage actors may experience adverse health effects due to the high exposure of glycols in artificial fog [156, 235]. Wieslander *et al.* discovered that exposure to propylene glycol mist during aviation training would cause respiratory system-related symptoms[236]. However, not many studies have addressed the origin of the health impact of glycol exposure in the following decade. In the past years, emerging e-cigarette and vaping-associated lung injuries (EVALI) became a serious health concern among the young population in North America[33, 237]. Many e-cigarette-related studies have proposed that the thermal degradation of glycol in e-cigarette juice will produce various toxic aldehydes, such as formaldehyde[238, 239]. The degradation is found under high-temperature settings of the heating coil [240, 241]. Thermal degradation may not be the only cause of the carbonyls in glycols, as carbonyls were also discovered under milder coil temperatures[242]. Meanwhile, studies also proposed aldehyde formation from autoxidation of poly-glycols[243–245], but no subsequent research has been systematically carried out since then. Consequently, the potential of various glycols forming toxic compounds via autoxidation during storage remains unknown, which may have implications for indoor environmental chemistry, consumer health, and occupational health.

Autoxidation is a spontaneous oxidative process of chemicals when exposed to air initiated by oxidative radicals and propagated via peroxide-involved radical chemistry.[246] Autoxidation is first known in the condensed phase, which is the cause of the deterioration of many daily consumables, such as cooking oil[247, 248], and foods[249, 250]. A decade ago, gas-phase autoxidation of VOCs was discovered by Crounse et al.[251]. Sooner this process has been identified as the critical process to produce highly oxygenated organic molecules, including the production of carbonyls and organic acids from biogenic gaseous monoterpenes[252–254]. While autoxidation was associated with numerous compounds, such chemical processes on glycols did not gather enough attention in the past. Additionally, the oxidation of TEG is one of the major concerns in the natural gas dehydration industry[255], leading to significantly reduced productivity. The aliphatic nature of glycols, i.e., lack of unsaturated bonds, makes them relatively less reactive to oxidative electrophiles (radicals, O_3), which are usually the initiators of autoxidation[256]. However, work described in Chapter 2 was the first to discover the formation of glycolaldehyde and formaldehyde from glycol-based fog machine juices during their storage and proposed evidence of autoxidation[257]. Glycolaldehyde and formaldehyde are two toxic carbonyls found in the indoor air[258]. These aldehydes are often released indoors as the product of organic combustion, bacterial activity, or atmospheric oxidation.[67, 259–261].

Study in Chapter 2 also highlighted the need to find stronger evidence for the occurrence of autoxidation, as well as the conditions under which autoxidation is favored. The presence of peroxides is an indicator of autoxidation, whose concentration reflects the extent and the rate of reaction. It can be quantified via certain mass spectrometric techniques[262–265], but the canonical method for total peroxide quantification has been iodometry [126, 266, 267]. Iodometry is usually based on UV-Vis spectrometry because I^- reacts selectively and quantitatively with organic peroxides in the sample, and the resulting triiodide ion (I_3^-) has a unique absorption, peaking at 351 nm[268]. This feature makes iodometry a sensitive and selective method to quantify the total peroxide concentration[269].

The objective of this work is to systematically investigate the autoxidation of common glycols during storage under room conditions and to discover its implications on indoor air quality, product safety, and occupational health across various industries. Specifically, we aim to quantify the formation of harmful end-products of autoxidation, such as formaldehyde and glycolaldehyde. Moreover, iodometry will be conducted to monitor peroxide intermediates, and thus, the occurrence of autoxidation. Beyond these fundamental chemical analyses, we would also investigate the effect of external factors, such as the water mixing ratio or the presence of antioxidants, to provide suggestions to mitigate such risks of autoxidation in glycol products.

3.2 Material and Methods

3.2.1 Chemicals and Materials

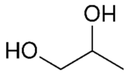
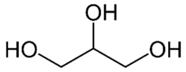
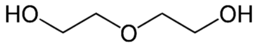
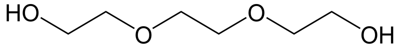
MilliQ water used in this study was generated by a Thermo-Fisher Scientific Barnstead^{TM} E-Pure^{TM} Ultrapure Water Purification Systems. Reagent grade 2,4-dinitrophenyl hydrazine (2,4-DNPH) (Purity 97%) was purchased from Alpha Aesar, and propylene glycol was purchased from Fisher Scientific. Acetonitrile (HPLC-grade, Purity 99.9%), triethylene glycol (TEG, Purity 99%), diethylene glycol (DEG, Purity 99%), glycerol (VG, Purity 99.5%) hydroquinone (Purity 99%), L-ascorbic acid (Vitamin C, Purity 99%), 37% formaldehyde in water solution (with 10-15% methanol), glycolaldehyde dimer (Crystalline), propionaldehyde (Purity 97%) were purchased from Sigma-Aldrich. A commercially available E-cigarette juice (EJ) is acquired from a local vape shop and contains 1:1 PG-VG and 10 mg/ml nicotine. Potassium iodide

(KI) was purchased from Fisher Scientific. Hydrogen peroxide in water (30% w/w), and glacial acetic acid were purchased from Sigma-Aldrich.

3.2.2 Choice of Glycols

All the experimented glycols in the current study are listed in Table 3.1. Triethylene glycol was selected to further investigate the fundamental of glycol autoxidation because it demonstrated a significant formation of carbonyl according to Chapter 2[257]. Additionally, PG and VG were selected for their common use in inhalable products, including EJ. DEG, the smallest poly-glycol commonly used as a food and drug additive, was selected to be compared with TEG, given their chain length difference. Finally, an EJ was also tested in this study to observe autoxidation in an actual product. We note that the EJ was chosen to have no additives besides PG, VG, 10 mg/ml nicotine, and flavorless to minimize unknown side reactions.

Table 3.1: Glycols of interest in this study

Name of Glycol	Common applications	Structure/composition
propylene glycol (PG)	Food & drug additives, E-Juice solvent	
Glycerol (VG)	Food & drug additives, E-Juice solvent	
Diethylene glycol (DEG)	Food & drug additive, Smallest poly-glycol	
Triethylene glycol (TEG)	Small poly-glycol, Solvent of Fog juice, common de-icer	
E-juice (EJ)	Basic version of any commercial E-juice	50% PG, 50% VG, 10 mg/ml Nicotine

3.2.3 Sample preparation

The summary of sample preparation of the following three subsections is illustrated in Figure B.1 in the Appendix. All aging experiments listed below were conducted over 7-8 weeks. All samples were stored under room conditions in a typical chemistry laboratory, with temperature controlled at around 22 ℃. Sampling activity was carried out at least once weekly, with occasionally more frequent sampling. Before sampling, all samples were stirred on magnetic stir plates for at least five minutes to homogenize the glycol mixture.

Aging of Glycols

Two aging experiments were conducted to monitor the autoxidation of different glycols. The first aging experiment (Exp.1) was conducted with two groups of samples, referred to as air-exposed samples or sealed samples. Each group of samples had five glass vials filled with 20 ml of each glycol, as shown in Table 3.1 (TEG, PG, VG, DEG, and EJ) without any dilution or modification. Air-exposed samples were stored without caps, which allowed constant exposure to room air. Sealed samples were kept inside the vial with caps and parafilm. The EJ sample in the sealed group was capped in its original package bottle and sampled by directly squeezing it out. Additionally, sealed samples only had air exposure for roughly 30 seconds during each sampling activity.

We acknowledge that storage conditions are different among households due to environmental factors. Hence to demonstrate the relevance of our experimental design, we have evaluated factors such as room light, room temperature, and pH variations. All glycols were stored in a temperature-controlled lab room, with temperature fluctuation within one degree. Although the rate of autoxidation is temperature sensitive, the rate constant of autoxidation would be maintained within the same order of magnitude.[270] The lab room is equipped with fluorescence lights. Sample vials were stored without direct exposure to any light sources, scattered light was unavoidable as vials has to be air-exposed. We confirmed through UV-Vis absorption that all glycols have no absorption in the visible light region, hence scattered room light won't affect the autoxidation process. In terms of pH, we found that our pH meter can not give reproducible results under high glycol concentrations. In aqueous phase autoxidation, pH is only dependent when acid-base chemistries are involved, such as the oxidation of carboxylic acids due to the formation of carboxylates.[120] However, this project focuses on carbonyls and peroxides, which are known as precursors of organic acids[271]. Therefore, changing pH will be relevant to the removal of carbonyls, but will be independent of peroxide and carbonyl formations.

Effect of Water Mixing Ratios

Exp.2 was designed to understand whether mixing with water would affect the rate of glycol autoxidation. A set of TEG-water mixtures with increasing mixing ratios of water (10%, 30%, 50%, and 70% of water) was prepared. The pure TEG sample mentioned in the previous section also served as 0% water when making the comparison.

As we discovered a variation across different water mixing ratios from Exp.2, we repeated the measurement of 50% TEG in a separate experiment (Exp.3) as a detailed investigation. A triplicate set of air-exposed TEG samples, mixed with 50% (v/v) water was prepared in the same glass vials. This water ratio was selective as we later discovered that the 50% water mixing ratio has the most rapid formation of carbonyls. Also, this mixing ratio represents commercial fog juice, as their water ratio may vary between 40% to 60%. For the negative control group, we prepared the same 50% (v/v) sample and sealed it as described previously. We noted that due to the capacity of our instrument, triplicate sets were only done in air-exposed TEG samples, while other samples were only done in singlets. Error propagation of samples in singlets can be found in the later quality control section.

Effect of Antioxidants

This experiment (Exp.4) was designed based on the hypothesis that antioxidants can suppress the autoxidation process in glycol mixtures. There are many types of antioxidants studied previously[245, 247, 272], Vitamin C (L-ascorbic acid) was selected as the antioxidant used in our experiment, as it is an inexpensive and naturally existing antioxidant that can be found in many consumables and in the human body[273]. Due to its ability to react with a wide range of oxidants, it is considered the total reactive oxygen species scavenger[274, 275]. Although the inhalation risk of Vitamin C aerosols remains unclear, some studies show that the inhalation of Vitamin C is not harmful at proper dosages[276, 277]. Vitamin C was added directly into the air-exposed 50%-TEG water mixture, resulting in a concentration of 60 mM. This concentration is selected to ensure that antioxidant concentration is at least 10 times higher than that of peroxides determined in our sample, such that Vitamin C would not be consumed entirely during the aging experiment.

Derivatization by 2,4-DNPH

The quantification of carbonyl compounds in this study primarily depended on a derivatization reaction with 2,4-DNPH. 2,4-DNPH, or Brady's reagent, is one of the most widely used chemicals to measure small carbonyl compounds[278, 279]. The specific methodology was adapted from Chapter 2[257], and thus is introduced only briefly here. A 2,4-DNPH working stock solution was prepared before any of the analyses. It was a 1:1 (v/v) water-acetonitrile solution containing 10 mM 2,4-DNPH and acidified by concentrated HCl, resulting in a pH of 3.0. Glycols mentioned above were derivatized using the same method. Samples were prepared in autosampler vials directly, each vial consisted of a diluted 2,4-DNPH working solution (20% of the total volume, 2 mM final concentration) and the glycol (2% of the total volume), a propionaldehyde internal standard (380 μM in the sample), and a spiked carbonyl standard (20% of the total volume) for standard addition, as explained below. All samples were derivatized in a 25°C-water bath for 2 hours. According to Chapter 2, the reaction will reach completion in 2 hours[257], and neither a significant growth nor decay of the hydrazone chromatogram peak was observed within 24 hours.

Standard Addition of Carbonyls

The method of standard addition was used to identify and quantify the formaldehyde and glycolaldehyde in all samples, which can correct the fluctuation of derivatization efficiency among samples. Carbonyl standards were prepared at five concentrations, such that their final concentrations in autosampler vials ranged from 0 μM to 50 μM. Standard solutions only contain formaldehyde and glycolaldehyde, it was prepared by dissolving formaldehyde (37% water solution) and glycolaldehyde (crystalline dimer) into a 50% ACN solution. This stock solution was then diluted to the correct concentrations. Standard solutions were refreshed monthly to avoid the decomposition of carbonyls. The limit of detection (LOD) values for formaldehyde and glycolaldehyde are 3.1 μM and 4.1 μM, respectively.

Mass Spectrometric Analysis

Liquid chromatography-mass spectrometry (LC-MS) was used in this study. Separation was done by an Agilent 1100 series LC, and detection was done by a Thermo Fisher Scientific Linear Ion Trap Mass Spectrometer system (Thermo Fisher LTQ-XL). The LC separation was conducted with a Phenomenex Luna Omega 150 × 2.1 mm 3 μm Polar C18 column. All measurements were done by electrospray ionization in negative mode (ESI (-)). Detailed settings for the mass spectrometer and the HPLC can be found in Appendix B.2.

Iodometry UV-Vis Measurement

The solution and sample preparation procedure of iodometry can be found in Appendix B.3, the method is adopted and modified based on the work of Mutzel et al[262]. UV-Vis instrument used in this experiment is Agilent 8453 UV/VIS spectrophotometer. Absorbance at 351 nm was selected to quantify the peroxide concentration in samples.

3.2.4 Safety

This project is associated with the use of 2,4-DNPH, concentrated acid, carcinogenic aldehydes, and a mass spectrometer. 2,4-DNPH is shock-sensitive and explosive when dried, hence it must be stored under damp conditions and away from oxidizer. Concentrated acid is required to make up the 2,4-DNPH derivatization solution, thus must be handled inside the fume hood, and appropriate personal protective equipment (PPE) should be used. Aldehydes involved, such as formaldehyde, are very volatile, therefore handling inside the fume hood with appropriate PPE required. The mass spectrometer is utilizing high voltage and high temperature at the injection housing. Therefore it is crucial to avoid touching the area during instrumental operations.

3.3 Results and Discussion

3.3.1 Carbonyl Production from Aging

Various carbonyls were recognized in all glycol samples. Different chromatograms of TEG and EJ were observed in Figures 3.1A and 3.1B after exposure to the air over weeks. Identities of detected peaks were confirmed via molecular mass, or spiking with pure carbonyl standards. Aldehydes and ketones with the same molecular mass were identified via MS^2 scan since their hydrazones have unique fragmentation profiles. The peak with m/z 163 is the indicator of aldehydes due to the loss of -RNO_2, while this fragment is absent in ketone-derived hydrazones[280].

Aged glycols contain carbonyls of various sizes. Small carbonyls, like formaldehyde or glycolaldehyde, were likely produced due to the decomposition of long-chain glycols; Large carbonyls, such as TEG-aldehyde ([2-(2-Hydroxyethoxy) ethoxy] acetaldehyde), PG-ketone (Lactaldehyde), or VG-ketone (Hydroxyacetone), were formed due to functionalizations which convert hydroxyl groups to the carbonyl groups. These functionalized carbonyls are glycol-specific, as their structures are dependent on the

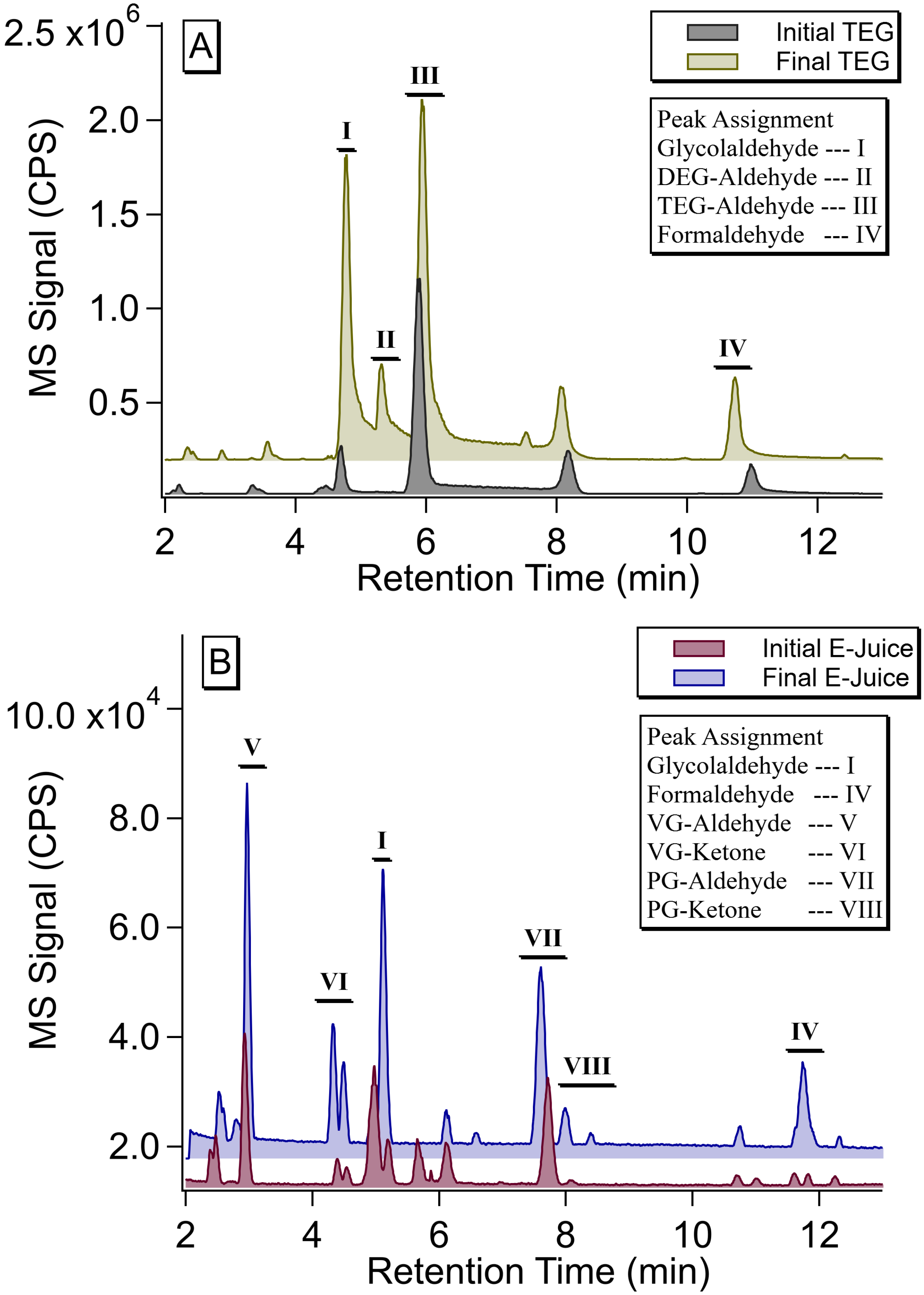


Figure 3.1: Base-peak chromatogram of all carbonyls detected in A) TEG samples and B) EJ samples the initial (week 1) and the final (week 8) stages of the aging experiment.

parent glycol. In the TEG sample shown in Figure 3.1A, we identified the dominant carbonyl as TEG-aldehyde, which comes from the oxidation of one hydroxyl terminal on the glycol. Formaldehyde and glycolaldehyde were identified as the decomposition product of TEG, whose peaks were intensified after 7-8 weeks of storage. This indicates a rapid fragmentation of TEG has happened during its aging. The aged TEG also produced a peak of DEG-aldehyde, suggesting that DEG-aldehyde is one of the fragmentation products of the TEG molecule, this implies the gradual chain reduction of long glycols produces smaller derivatives.

EJ sample is based on a mixture of PG and VG, it contains PG and VG-derived carbonyls after aging, such as VG-aldehyde, PG-aldehyde, and ketones, as shown in Figure 3.1B. The aging of EJ has also intensified peaks of formaldehyde and glycolaldehyde, similar to the TEG sample. This suggests that these two carbonyls are the common products of glycol decomposition despite the structural differences. It is intriguing to note that the majority of identified carbonyl species were already present in samples before we started the experiment. Hence the accumulation of carbonyls was initiated while the product is still with the manufacturer or the vendor.

3.3.2 Carbonyl Accumulation in Pure Glycols

We selectively quantified glycolaldehyde (Figure 3.2A) and formaldehyde (Figure 3.2B) in all glycol samples involved in Experiment 1, due to the limited commercial availability of pure carbonyl standards. Error bars represent the standard deviation of at least three samples within two weeks. Results in both panels confirm that air-exposed glycols likely to have a higher aldehyde concentration than sealed samples after 6-8 weeks of aging. Hence, air exposure is a key factor of carbonyl formation during storage, which is also in agreement with the conditions required for autoxidation. Deposition of carbonyl from the air is unlikely to give rise to such a high concentrations of liquid phase, judging from their air-liquid partitioning coefficients (e.g., Henry's Law constants[281]).

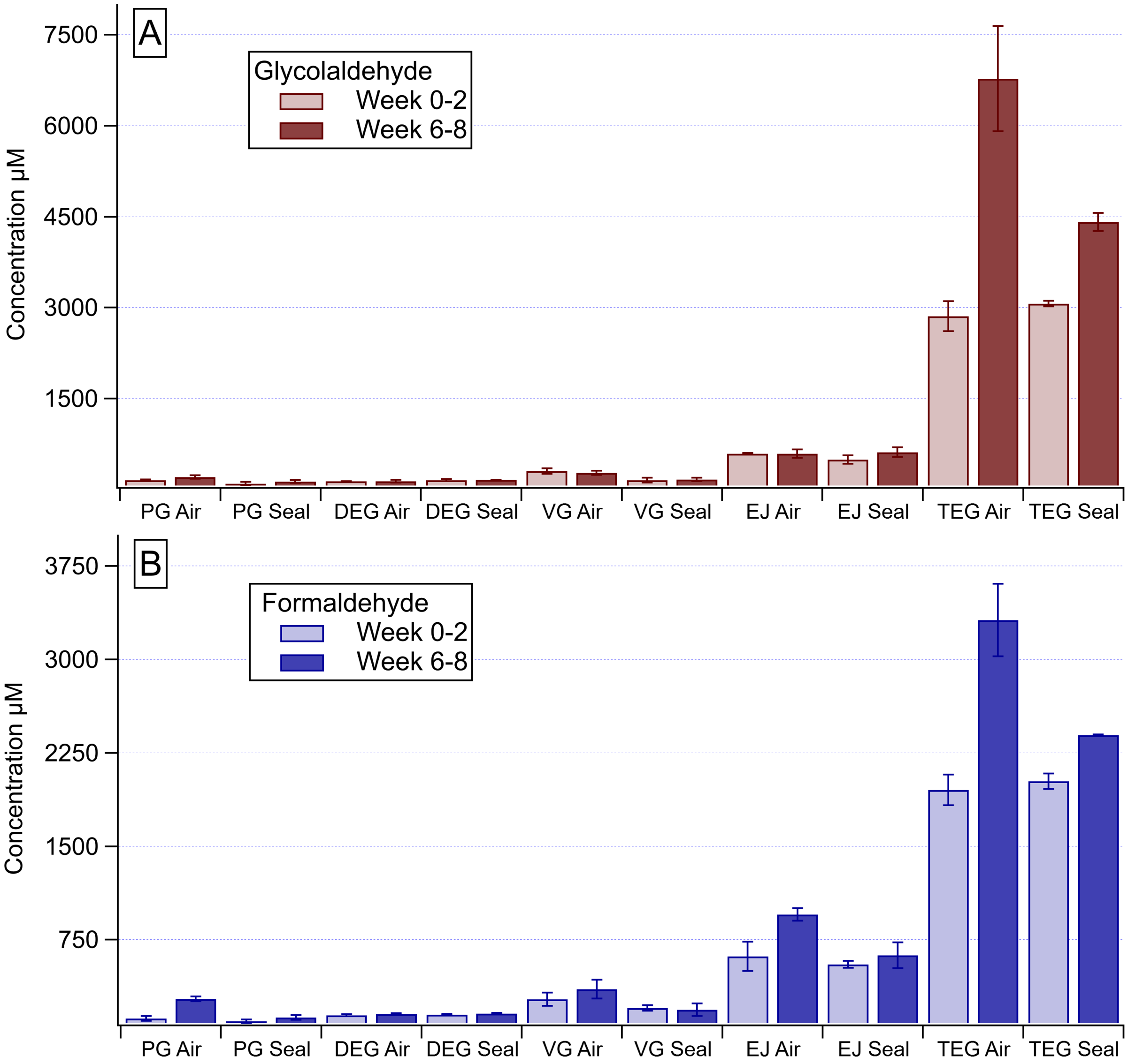


Figure 3.2: 2-Week average concentration of carbonyls in all glycol samples in two experiment periods. A) Glycolaldehyde and B) Formaldehyde; Error bars represent standard deviations of averaged concentrations.

TEG samples under both aging conditions have by far the highest initial concentration of aldehydes, followed by EJ samples, while PG and DEG samples have the lowest. The initial concentration of aldehydes comes from the autoxidation of glycols during manufacturing and transportation, as this process starts as soon as they are contacting with air. Details about carbonyl concentrations are listed in (Figure B.5 in Appendix B.4). Among air-exposed samples, PG has the most rapid percentage increase of formaldehyde, likely due to its low initial concentration. TEG had the most rapid formation of absolute formaldehyde, as well as glycolaldehyde. Among sealed samples, the formation of carbonyls is not as rapid as air-exposed samples. We noted that sealed samples are more representative of real-life storage of glycol-containing products, as they are stored in closed containers during the majority of their shelf life.

Besides TEG, carbonyls in EJ samples also have a higher abundance than other glycols. We have discovered more than 952 μM of formaldehyde in aged EJ. For each mL of EJ consumption, the smoker is exposed to 28.5 μg of formaldehyde. The Government of Canada has established indoor exposure limits for formaldehyde in both 1-hour (123 $\mu g/m^3$) and 8-hour (50 $\mu g/m^3$) exposure conditions[282]. Assuming a typical respiratory rate of 6 L/min, these numbers are translated into exposure limits of 44.4 μg and 140 μg formaldehyde for 1h and 8h, respectively.[283–285] The exposure to each mL of EJ level is 64% of the 1-hour exposure limit and 20% of the 8-hour exposure limit. We note that this calculated exposure amount is only due to unheated EJ, while intensive vaping or other environmental sources can also contribute to the total exposure. In comparison with other vaping studies, our calculated value is between 1% to 28% per puff relative to other reported values, assuming each mL of EJ requires 300 puffs[286, 287]. However, those studies were using heated vaping devices, which are proven to generate extra carbonyls under different power settings.[242, 288, 289] Our calculation shows unheated EJ could contribute to a portion of inhalable carbonyls, that is independent of the power setting of vaping devices. Finally, our result indicates that improperly stored vape juices or active vaping could be a source of indoor carbonyls. The quantification remains challenging, as it can be affected by aging, additives, power settings, and room settings such as size or ventilation.

An significant aldehyde concentration observed in TEG in Figure 3.3 indicates that TEG could undergo autoxidation more rapidly than others. It is likely due to chain lengths and the ether-like structure. The initiation of autoxidation is often carried out via electrophilic H-abstraction, which prefers carbon atoms adjacent to an electron-donating group[290]. While hydroxyl groups are electron-donating, electron density on the ether group is higher[291]. Hence, TEG is susceptible to H-abstraction by having two ether groups within the molecule. Additionally, a longer and less-hindered chain of TEG makes more active sites for H-abstraction. This allows more frequent 1,5-H shift, which is a crucial process of the peroxide formation and autoxidation propagation[251, 292, 293]. Moreover, functionalized products such as TEG-aldehyde or DEG-aldehyde still retain multiple active sites for electrophilic addition. Hence subsequent autoxidation is likely to happen on those products, leading to a high yield of small carbonyls per glycol molecule. On the other hand, the chain length for PG, VG, and DEG are short, therefore fewer proton abstraction sites. Additional branching, although the concept remains preliminary, could affect the propagation in either positive or negative ways.[294, 295]

3.3.3 Aging of TEG in Water Mixtures

Given that carbonyl formation was observed to be the most rapid in TEG, TEG was further used here for an in-depth investigation. To test out the effect of the water mixing ratio on formation rates of formaldehyde and glycolaldehyde from TEG, we have monitored the concentration of the carbonyls in a gradient of water mixing ratio ranging from 0% to 70% water.

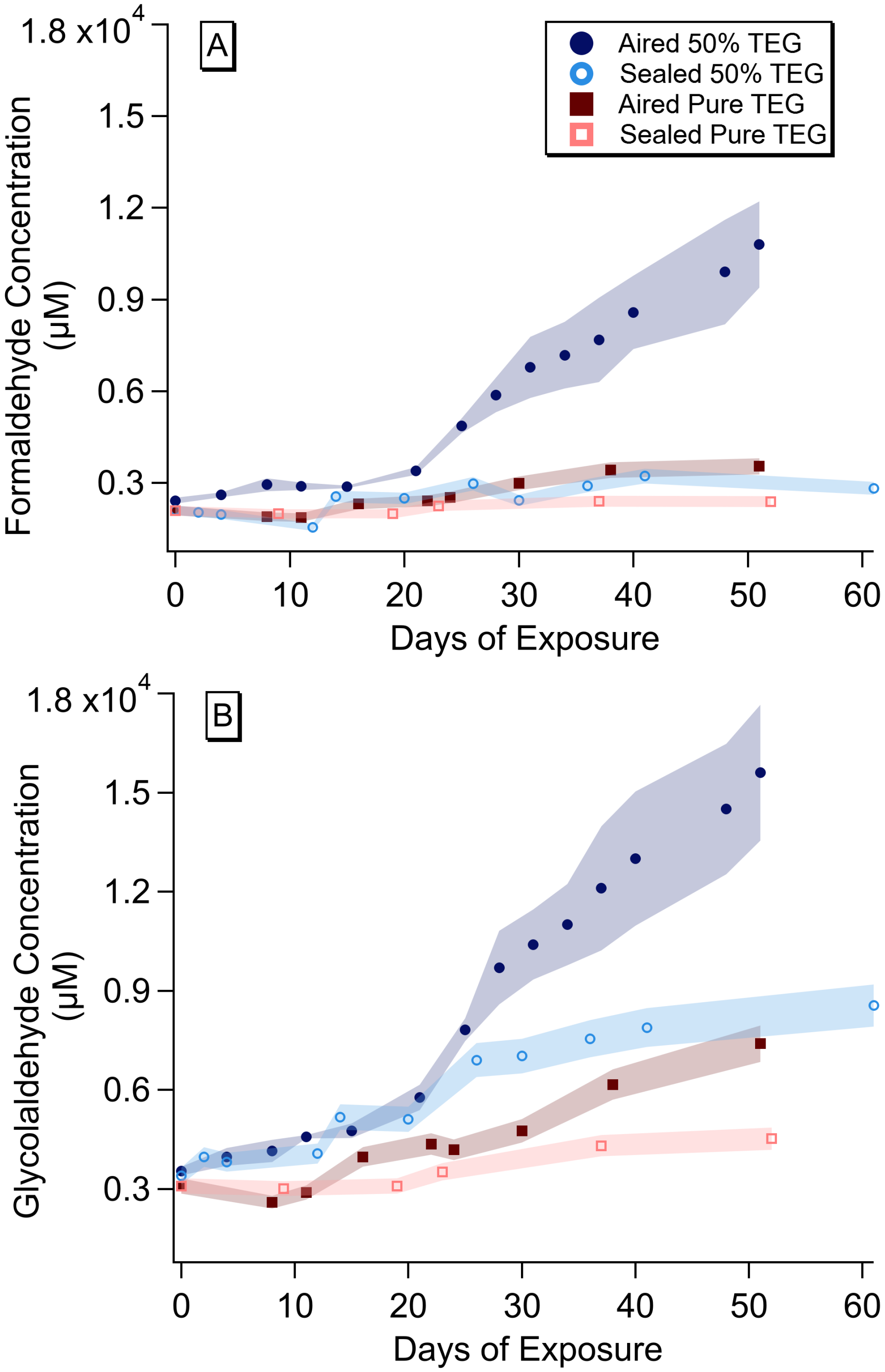


Figure 3.3: Formation of (A) formaldehyde and (B) glycolaldehyde in TEG under different water mixing ratios.

Quality Control

Two aspects in our experimental design that may cause bias to our results and were investigated first. The first aspect is the evaporation of the solution, which concentrates analytes over time. This is due to uncovered air samples experiencing unavoidable solution evaporation constantly. According to the database[296], all glycols in this work have far less vapor pressure (at least three orders of magnitude) than water. Therefore, we assume that loss of water contributed to all observed evaporations. This aspect was addressed by monitoring the mass loss of the solution in glycol-water mixtures over weeks. A first-order fitting of the remaining mass was performed for each of the four glycol-water mixing ratios. Based on this time-dependent trace of evaporation, a correction was applied to all of our observations.

Another aspect is the uneven recovery ratios of carbonyls from different glycol-water mixing ratios, especially when the ratio is affected by water evaporation. Although the method of standard addition was applied, which ideally eliminates all matrix effects, smaller recovery rates in pure glycol samples were observed. This is confirmed via four sets of repeated spike-recovery experiments. On average, we observed a 70.6% (±4.7%) recovery in pure glycol samples and 90.9% (±4.4%) in 50% glycol samples. Thus, we assumed a linear relationship between the recovery rates and glycol mixing ratios and applied the corresponding correction to all of our data. Details of bias correction to our data can be found in Appendix B.5. A total number of 16 sets of standard addition (done on different days) was performed in this recovery experiment. The mean error of standard addition was calculated to be 7.45%, which will be treated as the standard error of all later carbonyl quantitation.

Effect of Water Mixing Ratios

The formation rate of carbonyls varies between different water mixing ratios for both formaldehyde (Figure 3.4A) and glycolaldehyde (Figure 3.4B). All data shown were corrected by the solvent evaporation and recovery artifacts, explained in the previous section. Both aldehydes exhibit a similar trend: the 50% mixing ratio was the fastest, followed by the 30% mixing ratio, and 0%, 10%, and 70% ratios have slower rates. We also noticed that the 50% mixing ratio has a two-stage time profile and that the formation rate was accelerated around day 20 in both aldehydes. This two-stage profile may have implications for the formation of peroxides in the mixture, which is a determining factor of carbonyl formation rates. This will be discussed in the latter section.

Rather, the 70% water sample displayed behavior that was inconsistent with other ratios. In terms of formaldehyde, its formation rate was comparable to pure and 10% water samples, while it started accelerating after day 30. Eventually, the final concentration of formaldehyde in the 70% mixing ratio was about 500% of the initial value, which is lower than the 30% and 50% mixing ratios (about 650% and 800%, respectively). In terms of glycolaldehyde, the time profile is almost overlapping with the pure sample. Overall, our results show that water likely plays a non-linear role in the autoxidation of TEG and the formation of carbonyls. Up to 50% water, the formation rate of carbonyls increased with the water mixing ratio; however, this trend is no longer observed at water ratios above that. The inconsistent behavior of a 70% mixing ratio requires further investigation.

Aging of 50% TEG

As we discussed in the previous section, 50% TEG has the most rapid carbonyl formation. Additionally, Chapter 2 has observed that formaldehyde accumulation in the artificial fog juice (typically around 50% water) was more pronounced than in pure glycol done in this project[257]. As a result, we have conducted a separate experiment to further investigate the aging of 50% TEG in both air-exposed and sealed conditions.

According to Figure 3.4, air-exposed 50% TEG has a more rapid formation of both compounds than the air-exposed pure TEG, confirming that water is promoting

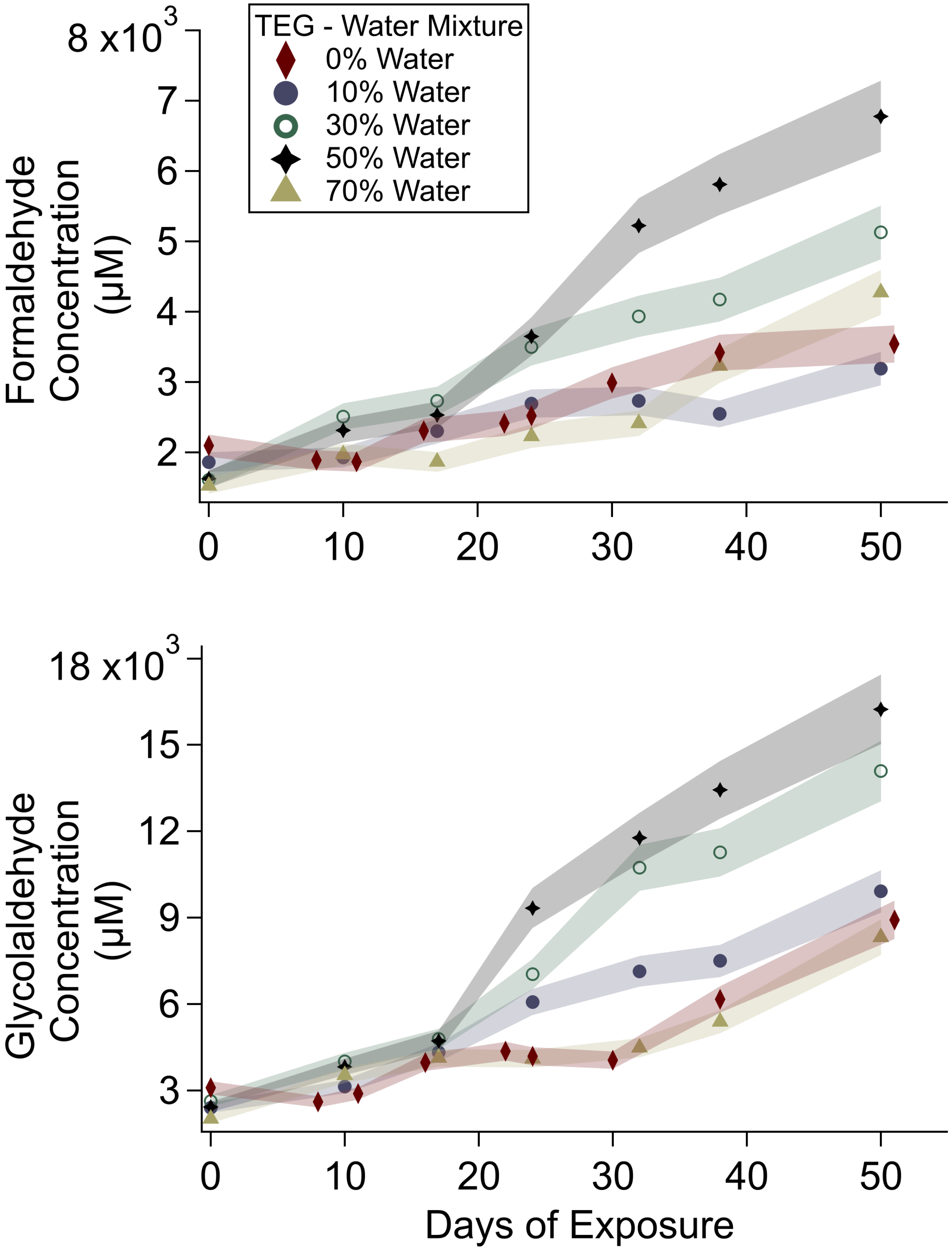


Figure 3.4: Formation of Carbonyls in 50% water-TEG mixture and pure TEG; A) Formation of formaldehyde; B) Formation of glycolaldehyde. The error band of air-exposed 50% represents the standard deviation determined from the triplet group, and the error bands of other samples are the mean error of standard addition (7.45%), determined previously in the quality control section.

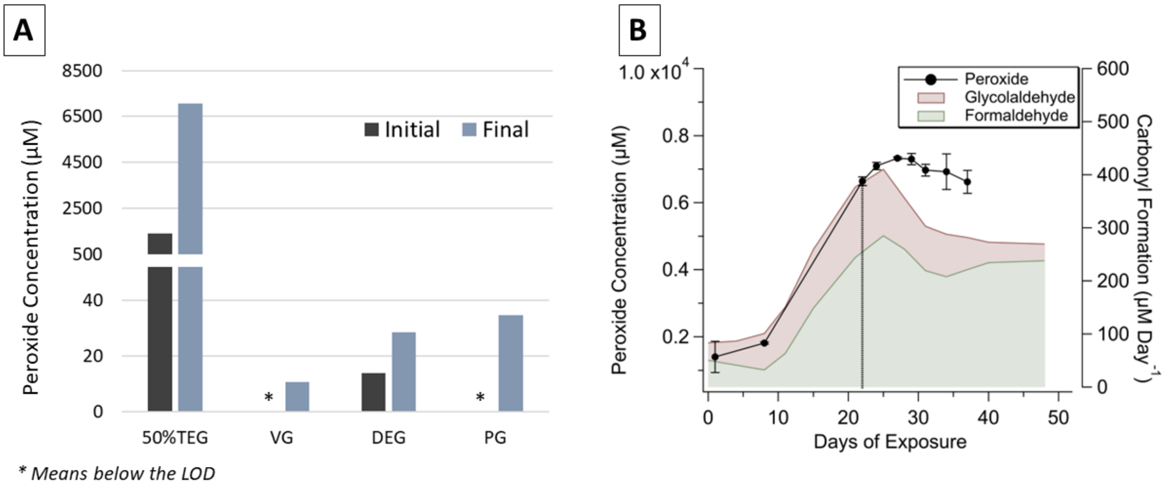
the formation of carbonyls. As also mentioned previously, formaldehyde formation in the air-exposed 50% TEG sample appears to have two distinct stages before and after approximately day 22, where the formation rate of formaldehyde has drastically increased, indicating accelerated autoxidation. The final concentration of formaldehyde in air-exposed 50% TEG was about 400% of that in the pure sample, whereas for glycolaldehyde it was about 300%. The two-stage profile of formaldehyde has coincided with the evaporation of water. As we tracked the first-order rate of water evaporation from 50% TEG, we calculated that water would be mostly evaporated by day 22. Therefore, the presence or absence of water could potentially alter the formation of autoxidation products.

3.3.4 Iodometry and Peroxide Accumulation

Observations from the previous sections highlighted that the formation of aldehydes was not monotonic throughout the aging period. The rate of autoxidation was likely varying over time, and as such, it is crucial to monitor the peroxide concentration in glycol samples so that we can estimate the extent of autoxidation during air exposure.

The concentration of peroxides in air-exposed 50% TEG and other glycols were quantified at two stages of the experiment, as in Figure 3.5A. Overall, we observed all samples had higher peroxide concentrations at the end of the experiment. 50% TEG has the most rapid peroxide formation, which raised from about 1.4 mM to 7 mM. PG and VG have about 10 μM and 35 μM at the end, while their initial concentration was below LOD (3 μM). DEG has an initial concentration of 14 μM, which increased to 29 μM eventually. The formation of peroxides mirrored that of carbonyls, and this was particularly pronounced for 50% TEG.

Figure 3.5B presents the average concentration of peroxides in a set of triplicate air-exposed 50% TEG samples throughout the experiment. Error bars on the peroxide concentration reflect the standard deviation of peroxide concentration in these samples. The two shaded areas are the average formation rates of formaldehyde and



* Means below the LOD

Figure 3.5: Summary of peroxide determination (A) peroxide concentration in air-exposed glycol sample at two different stages (B) time-dependent peroxide concentration and carbonyl formation rate in air-exposed 50% water TEG sample; the dashed line represents the day when more than 99% of water evaporation from the sample.

glycolaldehyde in these samples with a three-point smoothing applied. The formation rate is calculated based on the slope of two consecutive points of their concentration profiles, i.e., the differential.

The peroxide concentration varied significantly as the exposure time got longer. Initially, it was less than 2000 μM in all triplicate samples, while a week later it started rising rapidly. Between day 22 and day 30, peroxide concentration reached a peak beyond 7000 μM. Finally, it starts gradually descending from the peak and is still above 6000 μM before we stopped measuring. The time profile of the carbonyl formation rate has shown a strong correlation with the peroxide concentration with the two reaching their peaks around the same time. This peak time also coincides with the time that water has completely evaporated. After the peak period, the carbonyl formation rate stabilized at around 300 μM per day.

The agreement between the peroxide and the carbonyl formation is a critical observation, indicating that the rapid carbonyl formation is the result of a high peroxide concentration. The involvement of water in autoxidation has never been investigated previously. The role of water could be very complicated and cannot be explicitly explained by our work; however, there are a few potential explanations. Water could increase the OH radical reactivity by changing the solution viscosity. Lower viscosity allows the diffusion of atmospheric OH radical towards the glycol, or diffusion of glycol molecules to the surface of the solution so direct contact with atmospheric oxidants is made[297]. OH radicals can also form a relatively stable solvation complex with a neighboring water molecule, thus the radical becomes more stable in the aqueous environment[298]. According to the literature value[299], the viscosity of pure TEG is about 36 times higher than that of pure water.

Moreover, the presence of water can promote local OH formation in the solution. Indoor concentration of OH radicals are a few orders of magnitude lower than outdoors (about 10-6 ppb) due to the low availability of ultraviolet radiation[42, 300], and their transportation from outdoors is less significant due to their reactive nature[43]. However, the transportation of ozone is more significant, whose indoor concentration is about 5-6 orders of magnitude higher than the OH radical[46, 301]. Ozone, once dissolved in water, can spontaneously react with water to produce OH radicals[302, 303]. This reaction is favored in neutral or basic conditions since it is initiated by ozone and hydroxide ions, while the pH of fresh TEG is approximately 7[255].

3.3.5 Effect of Antioxidants

Compared to samples without antioxidants, Vitamin C has successfully suppressed the formation of both formaldehyde (Figure 3.6A) and glycolaldehyde (Figure 3.6B) in our sample throughout the entire period. For glycolaldehyde, the concentrations in the air-exposed sample were even smaller than those in the sealed sample, indicating that the anti-oxidizing capacity of Vitamin C overcame the enhanced oxidant exposure in the air-exposed sample. The suppression of formaldehyde formation by Vitamin C is likely due to its ability to scavenge a wide variety of reactive oxygen species[304], including organic peroxides[305]. We could not apply iodometry after vitamin C application, as it can react with I_2 spontaneously and no I_3^- will be formed.[306]

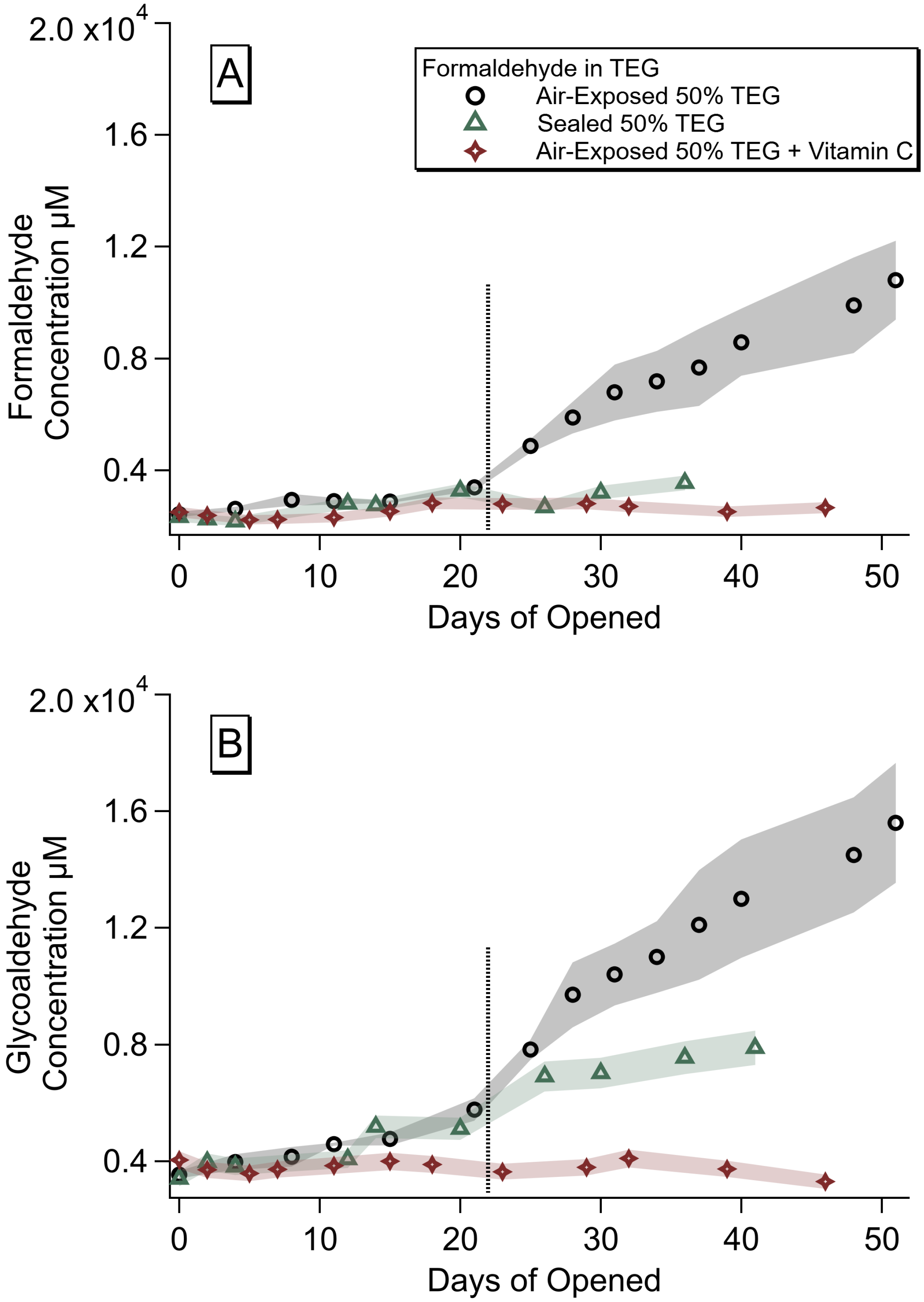


Figure 3.6: Formation of (A) formaldehyde and (B) glycolaldehyde in the air-ex posed group, sealed group, and an antioxidant-added group of TEG samples; dashed lines represent¿99% of water evaporated from the mixture.

3.4 Conclusions

This study represents hitherto the most detailed investigation of autoxidation of common glycol species used in daily inhalable products, intending to understand toxic compound formation during storage. All of the investigated glycols exhibited the formation of harmful carbonyl compounds, including formaldehyde, glycolaldehyde, and many others, when exposed to room air over weeks. Currently, the causes of EVALI and other health issues associated with glycol inhalation - such as voice loss in stage actors[307] - have not been linked to these carbonyl compounds. The detection of these small- and medium-sized carbonyls in glycol mixtures raises the possibility that such negative health impacts can be associated with glycols, as well as previously unrecognized products formed during their storage. Our observations provide strong and novel evidence that autoxidation is responsible for their formation because 1) faster formation rates were observed for air-exposed samples, 2) TEG (with the longest chain) exhibited the most significant carbonyl formation, 3) peroxide formation corresponded with the carbonyl formation, and 4) the addition of an antioxidant (L-ascorbic acid) suppressed carbonyl formation.

The formation of carbonyls in inhalable products can be a significant health concern. Although commercial glycol products are usually sealed in air-tight packaging, in which autoxidation is generally slow, according to our study, this process starts once the package is opened. Autoxidation will propagate whenever there is an air exchange, such as consumers' daily consumption or improper storage, and the accumulation of carbonyls can be very rapid in certain products or under optimal conditions. Formaldehyde and glycolaldehyde are known carcinogens, while peroxides belong to a class of reactive oxygen species and introduce oxidative stress to the human body[308]. Inhaling contaminated products, such as e-cigarettes or artificial fog, can represent an unrecognized exposure pathway to these harmful compounds. The actual exposure risk depends on the type of products used, their shelf age, as well as the indoor environment. For instance, smoking an e-cigarette could lead to high carbonyl exposure despite only glycols and nicotine being involved; Chapter 2 also showed that the frequent use of a fog machine in a poorly ventilated venue might lead to a formaldehyde concentration greater than 150 ppb in the air[257]. It is expected that e-cigarette smokers and people who frequently use such products in an indoor setting, e.g., actors and workers in the entertainment industries, are at a greater risk.

A discovery made by this work is the relationship between the carbonyl formation rate and the TEG-water mixing ratio. We have shown that water likely promoted the autoxidation of TEG. The explicit reason was complicated and could not be identified by this work, but possible explanations were explored. The mixture of glycols and water is variable across consumable products. For example, personal care products and cosmetics are water-dominant; paints and fog juices usually contain around 50% of water; e-cigarettes and surface coatings typically contain minimal water. Additionally, the pure form of glycols is not completely immune from oxidative degradation either, as shown by a slower but consistent carbonyl formation observed in this work, as well as the fact that many purchased glycols contained certain concentrations of carbonyl and peroxides.

Overall, our study raises potential concerns regarding product safety for glycol-based consumables. Proper storage protocols and expiration dates should be mandated and regulated. Based on this work, a few suggestions can be made to mitigate the risk of glycol autoxidation. First, minimizing air exposure is important to prevent rapid autoxidation. Second, avoiding glycol-water mixture during storage can slow down the autoxidation process. For instance, artificial fog juices can be sold as TEG or a mixture of glycols without water, and consumers should mix it with water before use. While this work was limited to TEG-water mixtures, future studies should be extended to the water mixtures of other glycol species. Third, as shown in this work, the addition of antioxidants can suppress autoxidation and the formation of harmful chemicals. However, the inhalation risks of antioxidants themselves should be carefully evaluated before application.

3.5 Acknowledgement

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Chapter 4

Chemical Characterization of Nicotine Oxidation Products in E-cigarette using p-Toluenesulfonyl Chloride

4.1 Introduction

In recent decades, many smokers have shifted their smoking habits away from conventional tobacco smoking, resulting in a rapid increase in worldwide e-cigarette consumption.[309, 310] Vaping involves the use of the e-juice (EJ) in vaping devices. There is no active burning taking place during vaping because the EJ is heated up at the coil within the vaping device,[311] hence it is considered a safer and healthier substitute than conventional tobacco smoking.[312] Therefore, some e-cigarette smokers have neglected potential risks of vaping in indoor environments, including residential homes, vehicles, office buildings, and schools. However, numerous studies have shown that vaping in such kinds of environments can significantly reduce indoor air quality, thus causing unintended exposure to vaping-related chemicals to non-smokers in the building.[313]

In countries with high e-cigarette consumption, vaping and nicotine-associated volatile organic compounds (VOCs) have gathered public attention. To maintain a good public health practice, governments and international organizations have implemented regulations regarding the consumption of vaping-related products.[314–316] However, these regulations could not stop the widespread vaping habit among the young population in North American high schools,[317, 318] which has rapidly become a major public health concern. According to surveys done in Canada and the US in 2019, over 40% of surveyed high school students have vaped at least once in their lifetime, and close to 20% of students are regular smokers.[319] In addition, some heavy smokers can have a rather extreme consumption of EJ within a short period.[320, 321] Existing studies have shown that intensive vaping can cause adverse health effects, including irritations from glycols,[322] nicotine addiction, and e-cigarette or vaping-associated lung injuries (EVALI). Nevertheless, a comprehensive understanding of vaping-borne health issues is still developing, and in particular, negative health effects of chemical components in the EJ remains unclear.

Exposures to vaping-related VOCs can be classified into first-hand, second-hand, or third-hand smoke. These exposure pathways can harm the smoker and their surrounding environment in different ways. It is estimated that 5 million first-hand smokers die annually due to the consumption of tobacco products.[323] Exposure to second-hand smoke is also concerning,[324, 325] as non-smokers can be passively exposed to hazardous chemicals from smokers.[326, 327] Recently, third-hand smoke has been newly recognized as a threat to indoor air quality and public health.[328, 329] Via this mechanism, VOCs and particles will deposit on indoor surfaces and will re-emit into the atmosphere upon changes in environmental conditions. More importantly, in the third-hand smoke route, as VOCs from smoking can interact with the indoor atmosphere for sufficient time, they may undergo indoor chemistry processes, including oxidation, to generate unknown products. EJ is a complicated matrix made of glycol solvents, nicotine, flavoring agents, and additives. Among these chemicals, nicotine is the primary addictive component, because it can efficiently attach to the receptor of acetylcholine, a common neurotransmitter in the human body.[12] The chemical complexity of EJ is further enhanced when producers develop new flavors to attract more smokers. Common flavoring agents include aldehydes, ketones, acetate, organic acids, and alcohols. When heated, all constituents from the EJ will be emitted as VOCs into the atmosphere. Upon inhalation, these chemicals can enter the human body through the lungs and may deposit into different organs and cause malfunctions.[330] In addition, studies also discovered that some inhalable chemicals do not belong to the original constituent of the EJ, which indicates new compound formation before or during the vaping activity. For instance, pyrolysis of vitamin E acetate at the heating compartment can generate carcinogenic alkenes and ketenes.[331] Heating of glycols at high-temperature settings can produce carcinogenic products, including carbonyls.[332]

Besides the vaping process, chemistry processes during the storage of EJ can also alter its chemical component. It is widely known by consumers that the EJ gradually turns brown during prolonged storage. While having no scientific support, there are plenty of online social media posts suggesting that this is due to the oxidation of nicotine and assumed it would be harmless. Although the oxidation process has not been fully investigated, studies have reported the formation of products during storage, including carbonyls[333] and acetals.[133, 334] A reduction of nicotine concentrations in EJ was also reported,[335] indicating potential degradation of nicotine. Very limited studies have investigated the reaction mechanisms and products of nicotine.

Secondary organic aerosols and ultrafine particles can be produced when smoking nicotine products.[336, 337] Isocyanic acid and many heterocyclic peroxides are produced due to the gas phase oxidation of nicotine.[63, 338] Alkaloid compounds, including nornicotine, anabasine, and anatabine, can be produced via enzyme-catalyzed mechanisms.[339] However, the abiotic oxidation of nicotine in the condensed phase in the indoor environment has not been investigated. Chapters 2 and 3 suggested that glycol-based inhalable products can be oxidized during typical indoor storage conditions.[333, 340] This emphasizes the fact that oxidation can apply to all constituents in the glycol solvent, including nicotine. Therefore, understanding the fate of nicotine in EJ during storage can help evaluate the exposure to harmful products by the smoker. More importantly, future clinical studies can develop a improved understanding on the causes of vaping-associated health problems, by referring to these harmful products. However, identification and analyses of nicotine-derived oxidation products comes with noteworthy analytical challenges. Many small amines are not readily retained by liquid chromatography. Detection of nitrogen-containing alkaloids are often difficult when they are present in trace amount in matrices rich in background organic compounds. The application of an analytical method that is selective and sensitive to nitrogen-containing products of nicotine is needed.

The purpose of this study is to conduct a comprehensive chemical analysis of the oxidation of nicotine in EJ. Specifically, a nontargeted analysis of oxidation products will be performed using a selective derivatization method and high-resolution mass spectrometry. Next, the formation mechanism of these products will be confirmed via artificial photooxidation with OH radicals. Finally, the formation of nicotine-derived products will be monitored during the indoor storage of EJ.

4.2 Methods

A brief overview of the experiment workflow is illustrated in Appendix C.1 in the Appendix.

4.2.1 Chemicals and Materials

A Thermo-Fisher Scientific Barnstead^{TM} E-Pure^{TM} Ultrapure Water Purification System was used to generate Milli-Q water in this project. Nicotine (99%), Nornicotine (98%), p-toluenesulfonyl chloride (TsCl, 99%), boric acid (99.5%), hydrogen peroxide (30% in water), HPLC grade acetonitrile, formic acid (98-100%), acetic acid (98%), caffeine (99%) were purchased from Sigma-Aldrich. Sodium hydroxide pallets and potassium iodide (KI) solids were purchased from Fisher Chemical, and flavorless commercial EJ products (0 mg/ml, 3 mg/ml, and 20 mg/ml nicotine) were purchased from local vaping stores in Edmonton, Canada. The 3 mg/ml product is made from free base nicotine, whereas the 20 mg/ml product is made from nicotine salt with the addition of organic acids, such as benzoic acid and lactic acid.[341] The use of nicotine salt allows for a higher solubility of nicotine in the EJ.

The derivatization solution used in this study was made by dissolving 52 mM TsCl in pure acetonitrile. A pH=9 buffer is made by dissolving boric acid and sodium chloride together, resulting in a 0.25 M sodium borate buffer. A 25 mM caffeine solution was added to each sample serving as the internal standard.

4.2.2 Instrumentation

Chemical characterization was conducted by a liquid-chromatography (Agilent 1100 LC system) tandem mass-spectrometry (Thermo-Fisher LTQ-XL mass spectrometer) setup, operated in positive electrospray ionization mode (LC-ESI(+)-MS). LC separation was done by a Phenomex Luna Omega polar C-18 column, dimension 150 mm × 2.1 mm × 3 μm. A high-resolution mass spectrometer (Thermo-Fisher Exactive Orbitrap) was used to determine the identity of compounds. A UV-Vis spectrophotometer (Hewlett Packard Model 8453) was used to track the light absorbance of samples, and a photoreactor (Rayonet, PRP200) was used to carry out the photooxidation reaction.

4.2.3 Derivatization and Chemical Analysis

The derivatization method used in this study was adopted and modified according to Rudnicka et al.[153] TsCl is commonly used in synthetic chemistry, due to its wide availability and selective reactivity. It can serve as the protective agent for reactive alcohols or amines, or act as a leaving group to allow further substitution.[342–344] Existing studies also reported the detection of amines in beverage and drugs using this agent.[153, 345] However, very limited environmental studies have utilized this method.

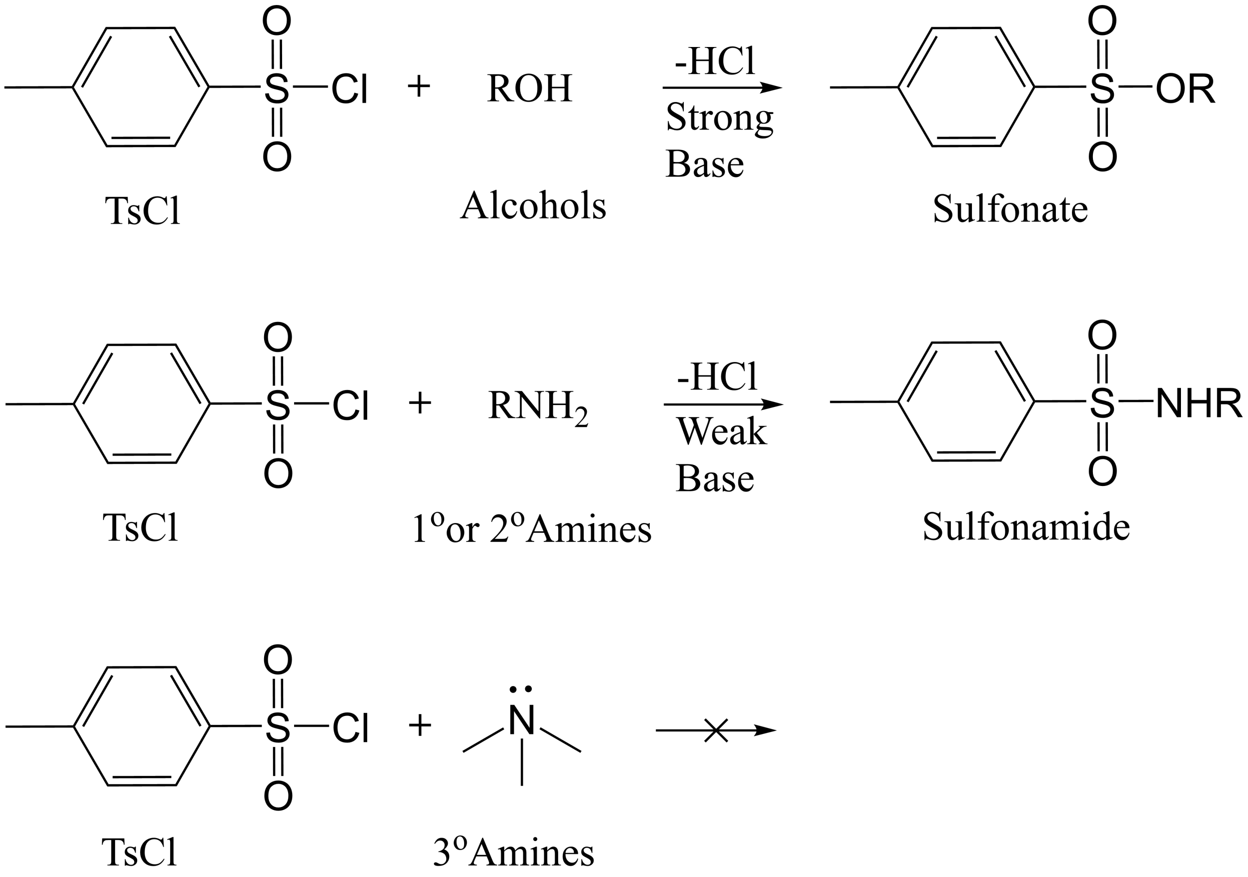
In a standard 2-ml LC glass sampling vial, buffer solution, TsCl solution, internal standard solution, and nicotine-containing samples were mixed, resulting in a sample matrix containing 1-to-25 dilution of nicotine samples, 20.8 mM TsCl, and 20 μM caffeine internal standard. The derivatization was carried out in a 50 ℃ water bath for at least one hour. After derivatization, samples were queued up on an LC autosampler for chemical analysis. Details about LC-MS instrument parameters can be found in Appendix C.2 of the SI.

As shown in Figure 4.1, TsCl is very selective towards alcohols, and primary and secondary amino compounds. It will not react with tertiary amines like nicotine due to the lack of available -NH group. This is beneficial from the analytical point of view, as nicotine is present in excess and may deplete TsCl or overwhelm the mass spectrum. Not reacting with nicotine allows TsCl to react with and detect trace concentrations of nicotine-derived alkaloid compounds.

The derivatization of TsCl is initiated by nucleophilic addition onto the sulfur atom by the alcoholic oxygen or the amino nitrogen. Due to the nucleophilicity of nitrogen being higher than oxygen,[346] amines would have a higher affinity to TsCl than alcohols. In addition, it has been shown that alcohol-initiated nucleophilic addition can be only achieved under highly basic conditions (pH 12.5),[347] thus, our mild basic condition ensures the selectivity of amino compounds.

4.2.4 Identification of Peroxide with Iodometry

Iodometry is known to have a good selectivity and sensitivity on peroxide species (Tania 2023). The reaction of iodide ions can destroy peroxide molecules, causing a significant signal reduction in LC chromatographs.[86] To perform iodometry experiments, a 2 M KI solution was prepared by dissolving the salt into Milli-Q water. Samples were mixed with the KI solution followed by the addition of 1M acetic acid. After an hour, the solution was derived by TsCl and was compared with samples without iodometry treatment.



$$\text{Sulfonamide mass} = M_{\text{TsCl}} + M_{\text{amine}} - M_{\text{HCl}}$$

Figure 4.1: Reaction of TsCl with amines and alcohols.

4.2.5 Aqueous-Phase Photooxidation of Nicotine

This experiment is aimed to confirm whether products in the EJ are due to OH-initiated oxidation. This experiment was done in the photoreactor under UV-B radiation (wavelength 280-315nm). A 2% (w/w%) aqueous nicotine solution was prepared by dissolving pure nicotine in Milli-Q water. This concentration was chosen as it is the highest concentration of EJ available in local stores (equivalent to 20 mg/ml, or 0.12 M). During this experiment, this solution was stirred continuously on a magnetic stir plate inside the photoreactor with 5 mM hydrogen peroxide added. Under UV radiation, hydrogen peroxide is photolyzed into OH, which can oxidize nicotine in the solution. About 0.5 ml of aliquot was taken out by a syringe at each sampling time stamp. This portion of the solution is used to determine the relationship between reaction time and peroxide concentration.

4.2.6 Natural Aging of EJ

The purpose of this experiment was to gauge the formation of potential products within a relatively short period after opening the bottle. EJs containing three different nicotine levels were purchased for this experiment from the local store. They are nicotine-free, 3 mg/ml (free-base), and 20 mg/ml (nicotine salt). Every EJ is divided into three 20-ml glass vials, serving as the triplicate measurement. The chemical composition of these samples was monitored over 9 days of air exposure. At the beginning of the project, one 3 mg/ml sample was prepared to serve as the long-term air exposure sample, which is approximately one year old at the time of sampling. This one-year-old sample is used to gauge eventual products that can be formed after prolonged storage. All samples were stored loosely covered by aluminum foil to block the incandescent light from the lab room and allow for continuous air exchange. This storage strategy represents a storage condition in which the EJ is not properly sealed. It likely serves as an upper limit for the amount of oxidant exposure during storage. The lab room is temperature-controlled (21±1℃) and humidity-controlled (20-30%).

Prior to sampling, the EJ vial was homogenized for 2 minutes on a magnetic stir plate.

4.2.7 Color Monitor of EJ

The purpose of this experiment was to discover the relationship between the color and the chemical composition of the EJ. This experiment was conducted using the same set of samples prepared in the aging experiment. To monitor the color change, the UV-Vis absorption spectrum (200-800 nm) for each sample was collected weekly. For visual reference, pictures of the EJ samples were taken at the same time.

4.3 Results and Discussions

4.3.1 Overview of Nicotine Oxidation Products

Figure 4.2 shows an overview of TsCl derived alkaloid detected from a fresh EJ juice and one-year-old EJ with and without added nicotine. As shown in Figure 4.2A, the nicotine-free EJ does not contain any significant peaks despite its age. This ensures all compounds in the chromatogram originated from nicotine. Although the flavorless EJ is only made of glycols and nicotine, the chromatogram of fresh EJ already contains a few product peaks, this indicates that a portion of our detected products have already formed before its air exposure, likely during the manufacturing process. Through analyzing blank samples, we confirmed these product peaks are TsCl derivatives, which means that they are likely primary or secondary amines. Compared with the fresh EJ, the aged EJ has a more complex chromatogram profile. Impurity peaks are significantly intensified after aging. For example, the peak heights of the two peaks at 8.7 min and 9.2 min had increased by more than 20 times after aging.

Among all product compounds, we have identified and collected the elemental composition of nine compounds. They were selected based on their detection by both low- and high-resolution MS. To further confirm if they are TsCl derivatives, we utilized the high-resolution MS and obtained their isotopic peak pattern. This is because

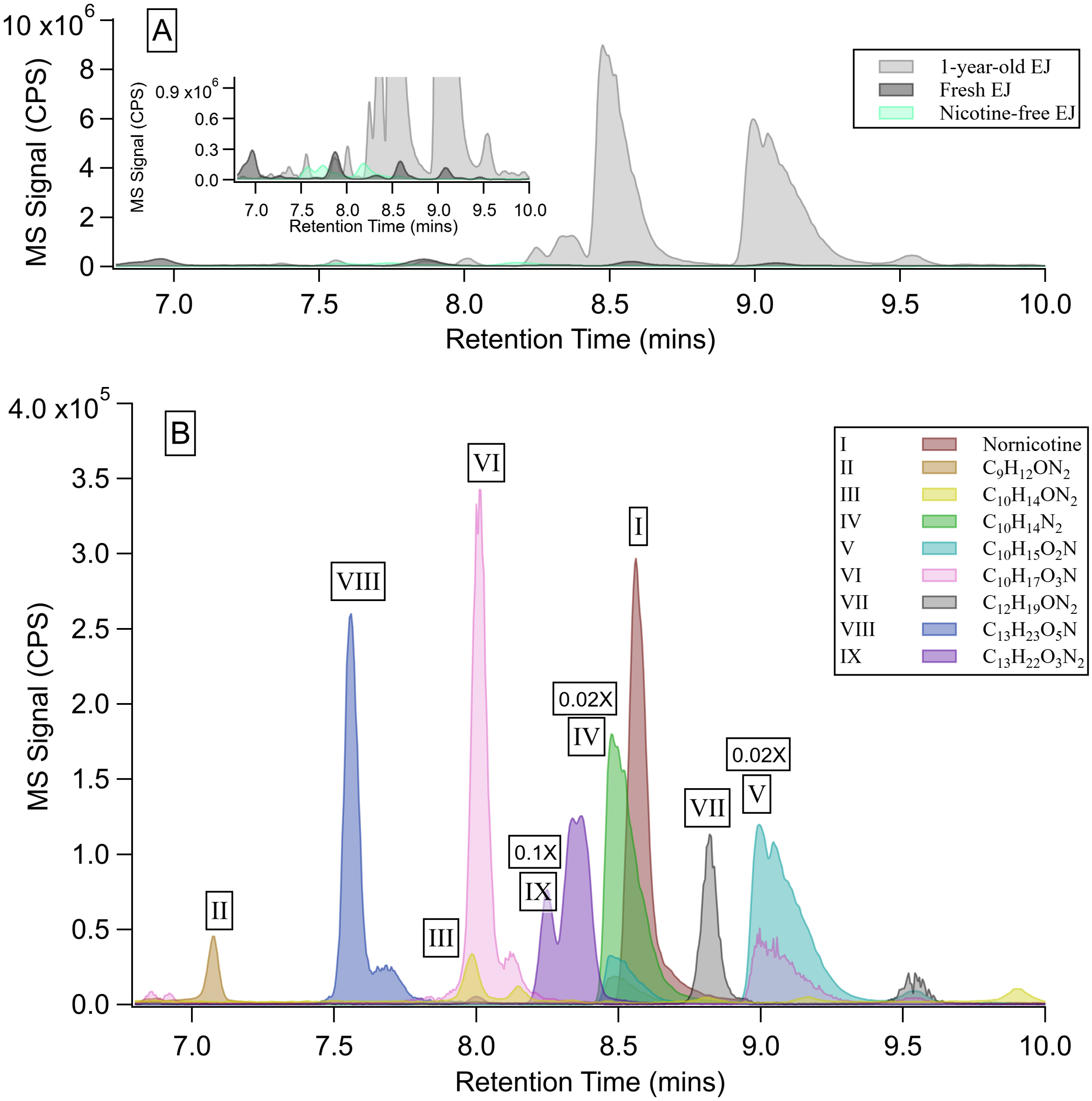


Figure 4.2: Overview of products in aged EJ, A) base peak chromatogram (BPC) of fresh EJ, one-year-old, and one-year-old nicotine-free EJ and B) EIC of identified compounds from aged EJ, some peaks are scaled down (by factors indicated in the figure) to match the intensities of other peaks for visual purposes.

sulfur-containing compounds will have a signature mass spectrum peak pattern at the $[M+2]^+$ position. Assuming the only source of sulfur in our sample is TsCl, any compounds having this peak pattern will be TsCl-derivative. Details about this identification procedure are explained in Appendix C.3 in the SI. Elemental compositions of these compounds were obtained by library matching using ThermoFisher Freestyle^{TM} software. The mass tolerances of these compounds were smaller than 5 ppm, and their matching scores were greater than 90.

In Figure 4.2B, we plotted the extracted ion chromatogram of the nine compounds from the aged EJ and labeled their elemental composition. Due to the limited availability of commercial standards, we have only confirmed the identity of nornicotine (Compound I), whose retention time is about 8.7 min. Although many other compounds remained unidentified, all detected compounds have carbon numbers similar to nicotine, ranging from C9 to C13. Additionally, these compounds could be structurally similar to each other. This hypothesis is supported by the fact that several compounds have retention times overlapping with each other. For example, nornicotine and compounds IV, III and VI.

Furthermore, seven out of nine compounds are oxygenated, with only nornicotine and compound IV being oxygen-free. The prevalence of oxygen elements suggests that most of our detected compounds are oxidation products of nicotine, and oxidation is the primary process of the aging of nicotine. There are a few interesting aspects of compound IV. It is a structural isomer of nicotine but contains at least one primary or secondary amino group to be derivatized by TsCl. Hence, this compound could be produced via a structural rearrangement of nicotine during its reaction.

4.3.2 Identification of Peroxide Products

Iodometry is a versatile technique to identify peroxide species, and details about this reaction are explained in Chapter 3[333]. In iodometry-assisted LC-MS, peroxide peaks will be suppressed due to their reaction with iodide ions, and non-peroxide compounds will remain unchanged. Therefore, a complete depletion of peaks after iodometry indicates peroxide compounds. We identified one peroxide compound in our aged EJ samples - compound III in Figure 4.2B.

The result of iodometry-assisted LC-MS is illustrated in Figure 4.3. We constructed this figure based on a tandem MS scan to improve the selectivity. The fragment ion with m/z = 155 is the TsCl fragment without the chlorine, thus it can only be produced by TsCl derivatives. After the treatment with iodometry, the signal of compound III disappears, suggesting that it is a peroxide. For reference, we have also compared the peak intensity of nornicotine before and after the iodometry and the peak remained the same. Therefore, we proved that iodometry is exclusively applicable to peroxides only, without affecting any other non-peroxide alkaloid compounds. According to the high-resolution MS, the empirical formula of compound III is $C_{10}H_{14}ON_2$. Though the iodometry observation suggests that it is a peroxide, this compound does not contain two oxygen atoms. The one missing oxygen could be due to the decomposition of peroxide groups during the derivatization or sample preparation. Regarding the elemental composition, compound III has the same empirical formula as compound IV ($C_{10}H_{14}N_2$), except that it contains only one extra oxygen atom. Therefore, compounds III and IV can be structurally similar to each other, with compound III having an extra peroxide group attached.

4.3.3 Natural Aging of EJ

To determine the natural aging of EJ during storage, we selected nornicotine as the trace chemical and monitored it for over a week. The primary reason for monitoring nornicotine is that it is the precursor of carcinogenic N-nitrosonornicotine during the processing of tobacco leaves.[348] In addition, the formation of this carcinogen is also reported from the reaction between nornicotine and human saliva.[349] The commercial EJ was divided into three air-exposed vials, and all data points were collected in triplicate. Figure 4.4A shows the change of nornicotine in three commercial EJ

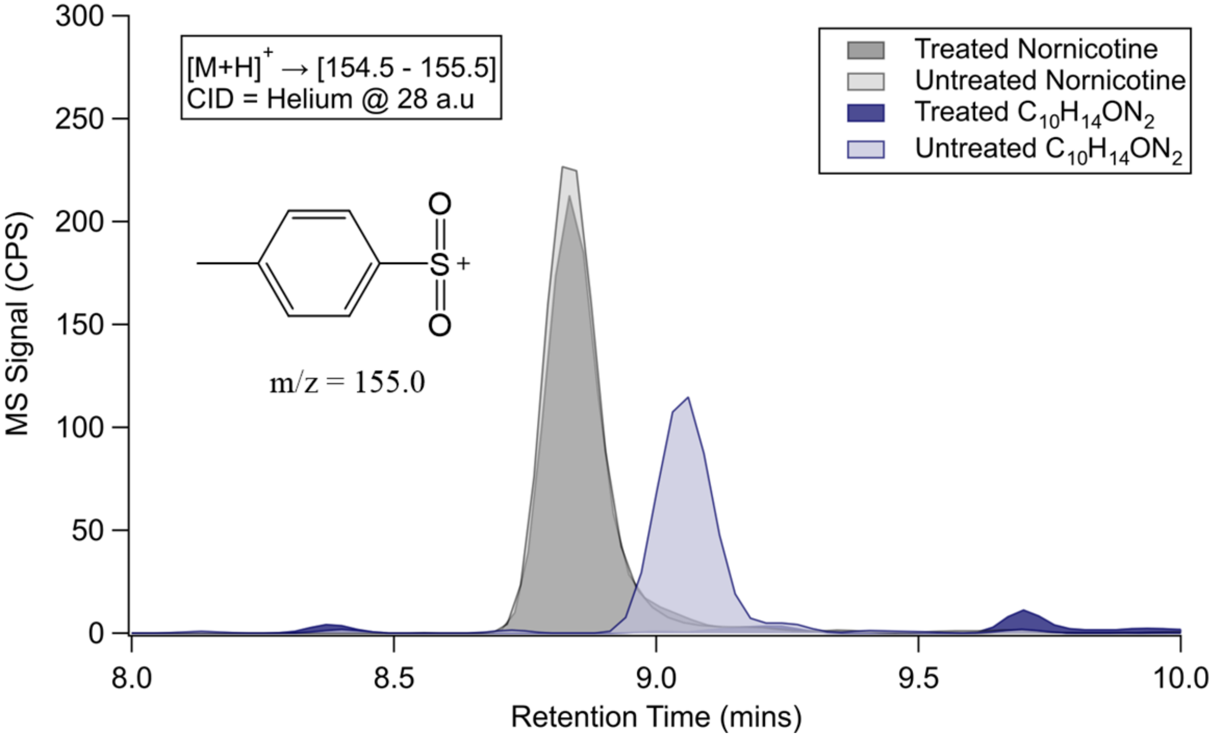


Figure 4.3: MS/MS spectrum of nornicotine and compound III before and after the treatment of iodometry. The sub-window stands for the structure of the fragment ion.

samples under three different nicotine concentrations. These EJs are all flavorless products. The 0 and 3 mg/ml samples contain freebase nicotine, while the 20 mg/ml sample contains nicotine salt. Figure 4.4B illustrates the calibration of nornicotine, while caffeine was added as the internal standard to track the variation of instrument sensitivity.

The trend of nornicotine formation is distinct among the three concentrations of EJ. For the nicotine-free product, nornicotine concentration is consistently below our LOD, which is 3.90 μM . For the other two nicotine-containing EJs, the accumulation of nornicotine was initiated at the onset of the air exposure, then plateaued around day 7. The 3 and 20 mg/ml EJ have a concentration of about 120 μM and 200 μM, respectively, at plateau. For a standard bottle of EJ (30 ml), 200 μM of nornicotine is translated into 0.89 mg of inhalable nornicotine to the consumer, which is 0.15% of the nicotine or 29.6 ug/ml. This result is in good agreement with existing literature. Palazzolo et al.[350] reported a range of 5-21 ug/ml of nornicotine among five 20 mg/ml commercial EJs. Flora et al.[351] reported the nornicotine concentration to be less than 0.2% of the stated nicotine. This reported value is consistent with our observation, indicating that our method could be feasible to characterize a trace amount of nornicotine from EJ samples.

Although the content of nornicotine in one bottle of aged EJ is relatively small, many consumers, especially heavy smokers could consume a higher volume of EJ. Thus, exposure to nornicotine by smokers and surrounding non-smokers is inevitable. Additionally, nornicotine can further undergo oxidation into smaller and highly oxygenated products. As a result, long-term exposure to nornicotine may occur to regular smokers, which may represent an unrecognized contribution to the development of EVALI, but further clinical research is required.

Despite that nornicotine has been reported as a tobacco products by several existing studies, little research was done to further investigate the origin of this compound. A few studies have investigated the N-demethylation of nicotine via catalytic conver-

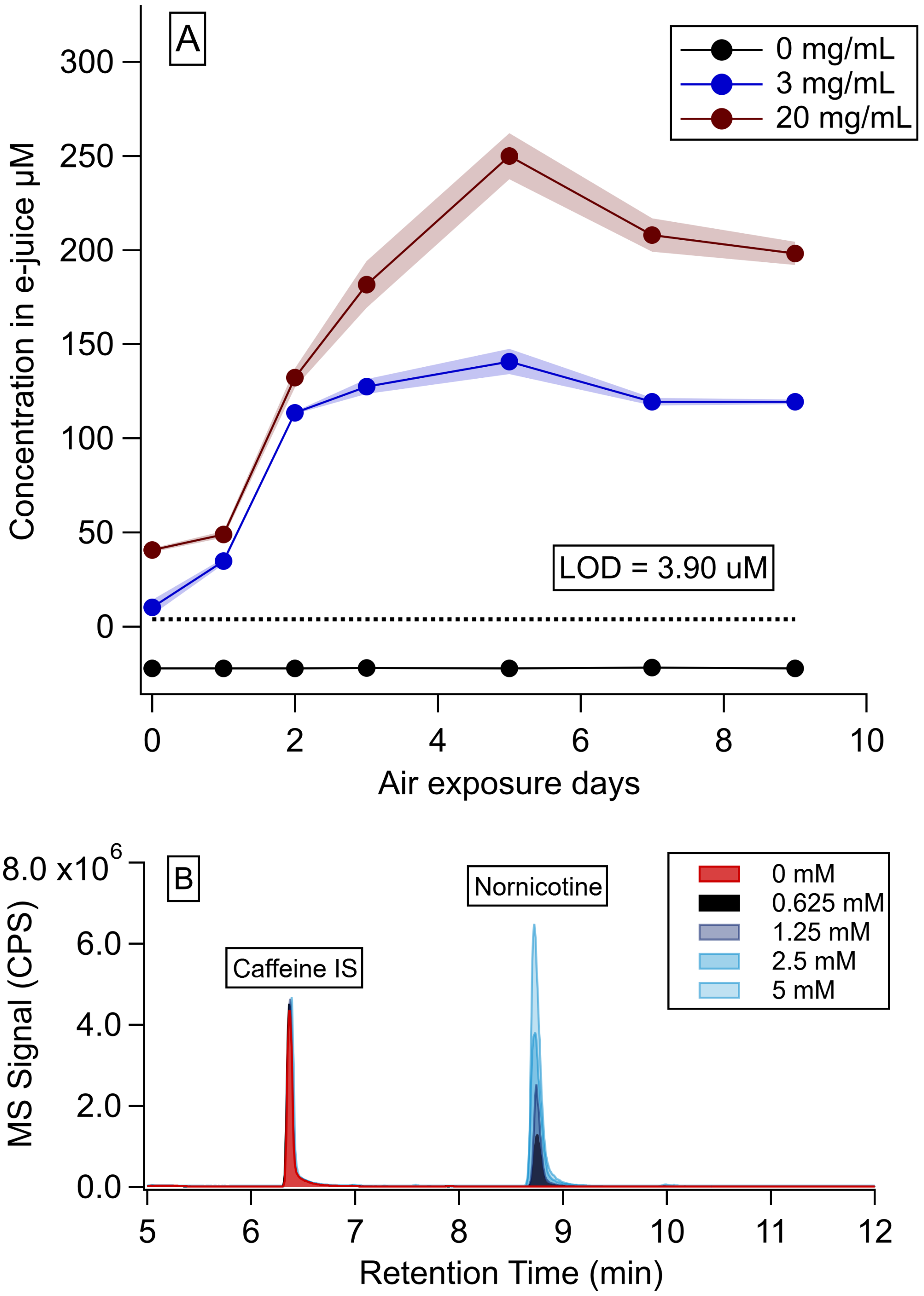


Figure 4.4: Natural aging of nicotine-containing EJ during short-term storage. A) formation of nornicotine during the storage period. The shaded area reflects the standard deviation obtained from triplicated measurements. The dashed line represents the method limit of detection (LOD) = 3.90 μM . B) Chromatogram of the calibration curve of nornicotine.

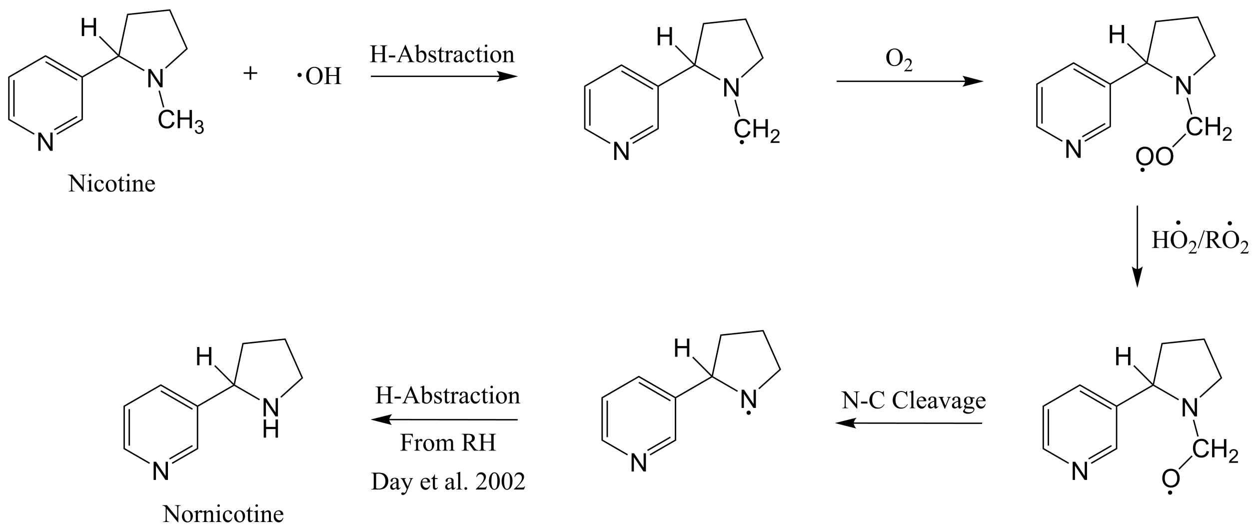


Figure 4.5: Suggested formation mechanism of nornicotine.

sion by nicotine demethylase enzyme,[348, 352, 353] however, the mechanism of this conversion remained unclear in both biotic and abiotic pathways.[354] The consistent production of nornicotine from both natural aging and photooxidation suggests that OH-initiated radical oxidation can be responsible for the formation nornicotine in the ambient environment. In Figure 4.5, we proposed the OH-initiated nornicotine formation mechanism. For a tertiary amine, H-abstraction by OH radicals can take place on its adjacent alkyl groups.[355, 356] The propagation of this mechanism is the same as conventional radical oxidation, which includes the formation of the peroxy radical and the alkoxy radical. The N-C bond will be cleaved due to the alkoxy radical being unstable, producing a nitrogen-centered radical. Unlike the carbon-centered radical, the nitrogen radical can perform H-abstraction on another molecule to form an amine and terminate the reaction.[357] In conclusion, nornicotine can be produced by N-demethylation of nicotine, via the formation of nitrogen-centered radicals.

4.3.4 Aqueous Photooxidation of Nicotine

To further confirm the mechanism of nicotine oxidation, we performed a photooxidation experiment by reacting aqueous-phase nicotine under UVB light with hydrogen peroxide added as the source of OH radicals. The same nine peaks shown in Figure

4.2B) were observed to be major products involved in this experiment, with no other major peaks observed. Peaks exhibited either increase or decrease during this experiment, as illustrated in Figure 4.6. All samples were done in triplicates, and their standard deviations are illustrated as the shaded area. Unlike the EJ, we used water instead of glycols as the solvent for nicotine, as glycols would consume all the OH radicals produced.

As shown in Figure 4.6, seven out of nine compounds were found to change during OH oxidation, while the other two (compounds VIII and IX) remained unchanged throughout the experimental period. According to our observations made from the fresh EJ, nicotine can be easily oxidized when exposed to air. Therefore, one major challenge in this experiment was that our purchased nicotine already contained some oxidation products. Therefore, we could not achieve an absolutely clean baseline for our photooxidation samples. For a better visualization, we plotted the concentration of the seven compounds normalized to their starting concentration (0 min).

We noticed that all compounds had plateaued after 1 minute, and their concentration remained unchanged until the end of the experiment. This is indicating the reaction has stopped, or their concentration has reached a steady state. Two types of trends have been observed in this experiment. Concentrations of nornicotine, compounds II and III have increased by up to 30 times, while concentrations of compounds IV-VII have dropped by nearly half. The reasons leading to such different behaviors between products are currently unclear and requires further experiments. During rapid OH-oxidation, whether a compound increase or decrease in its concentration depends on the balance of its formation and degradation rates. This is, in turn, related to the concentrations of their precursors and their reactivities with OH radicals. Currently, we do not have enough information to fully explain this observation, but it is sufficient to confirm that many products observed during natural aging are also formed during accelerated oxidation.

One of the potential artifacts in this experiment is that chemicals may decompose

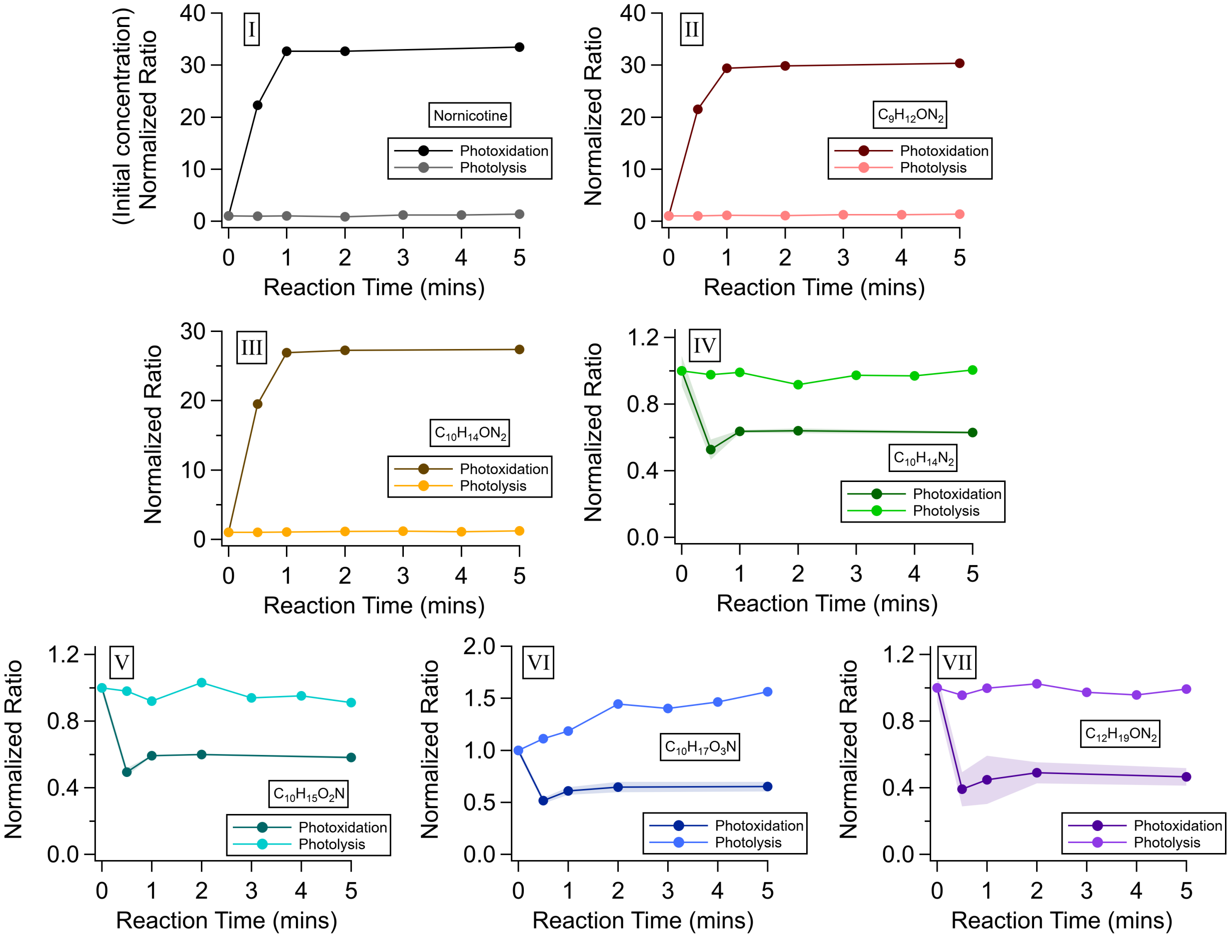


Figure 4.6: The time profiles of nicotine oxidation products during the aqueous-phase photooxidation experiment. Numbers of figures correspond with compound numbers labeled in Figure 4.2 The shaded area represents the standard deviation obtained from triplicated measurements. The normalized ratio refers to the signal of a compound normalized to that at the beginning of the experiment.

under UV without the presence of oxidants, known as photolysis. To eliminate this artifact, we performed a separate set of photolysis experiments. This experiment contains the same UV light intensity as the photooxidation experiment, while no hydrogen peroxide was added to provide OH radicals. For all seven compounds, their concentrations changed in a much lower amplitude compared to the photooxidation, indicating that exposure to UVB light alone led to neither the formation nor the decay of these products. As a result, we confirmed that our observations during the photooxidation experiment are predominantly due to the addition of hydrogen peroxide, hence OH-initiated oxidation.

4.3.5 Color Change of EJ

During the limited natural aging experimental period, we did not witness significant color change of the EJ. Our UV-vis data (Figure D.3 in appendix) of the aged 3 mg/ml freebase EJ shows that it does not have any significant absorbance in the visible light range (380 – 700 nm). Therefore, the brown color of EJ could be due to the tailing from the UV range and is not correlated with our detected alkaloid compounds. We displayed the appearance of our aged EJ samples in Figure 4.7. All nicotine-containing EJs turned brown after prolonged storage, whereas the nicotine-free EJ remained clear. The brown color is visually more intense in the aged 20 mg/ml EJ. However, the intense brown color observed may not be exclusively due to high nicotine. The reason is that the 20 mg/ml EJ is made from nicotine salt which is augmented with organic counter ions, for example, lactic acid and benzoic acid.[341] Therefore, the aging of these organic compounds may contribute to the color change. For the same reason, we did not analyze the nicotine salt sample under UV-Vis for absorption analysis.

It is worth mentioning that many commercial EJ products exhibit color changes, including some nicotine chemicals sold by chemical distributors. This is a sign that nicotine in these products have gone through chemical reactions, likely giving rise

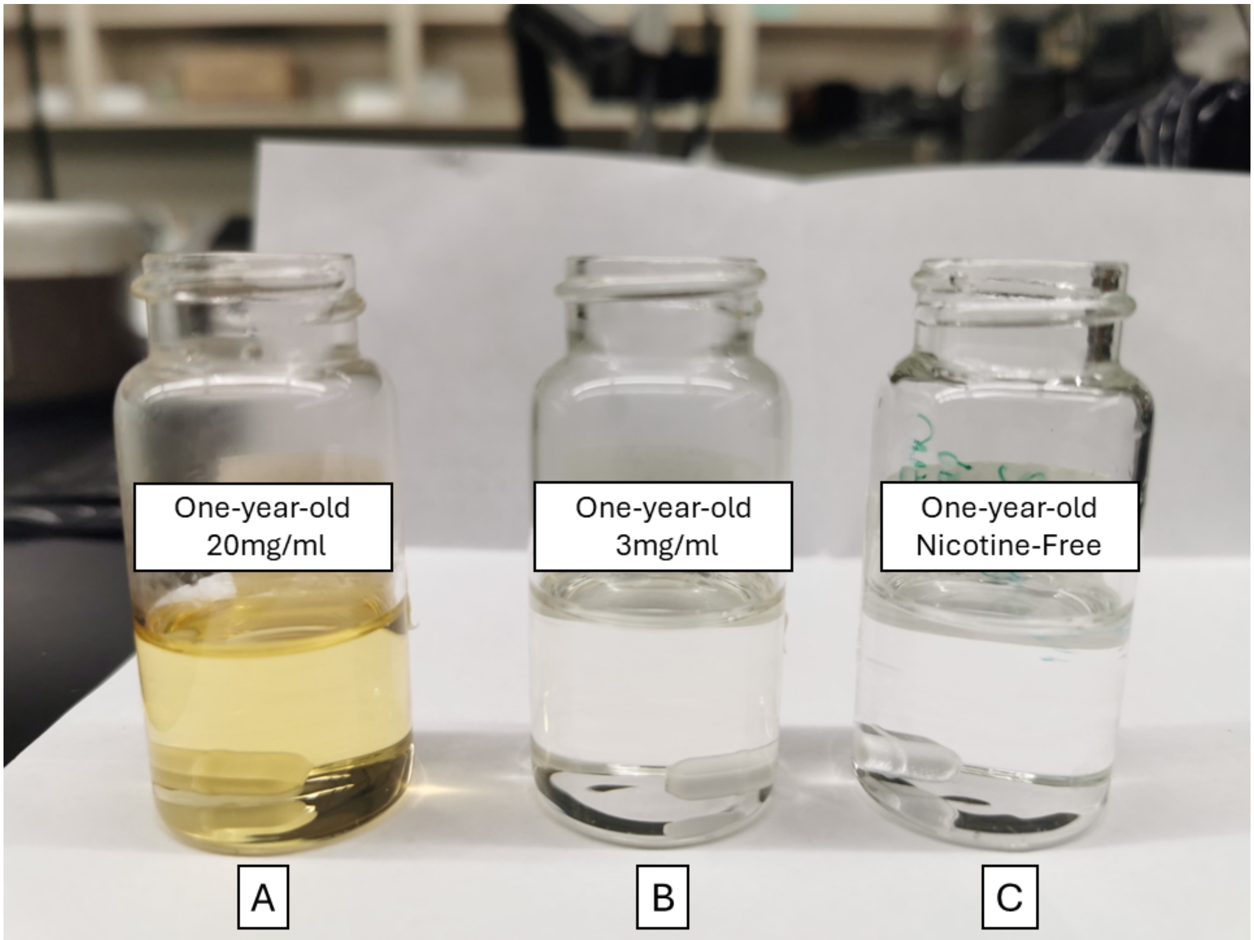


Figure 4.7: Color comparison between EJs, A) aged 20 mg/ml EJ, B) aged 3 mg/ml EJ, and C) aged nicotine-free EJ.

to compounds discovered in our previous sections. Therefore, consumers should be aware of the color change because it can be a rough estimate of the shelf age of the product with respect to the nicotine contents.

4.4 Conclusion

This project has presented a detailed chemical analysis of intermediates and products involved in the condensed phase oxidation of nicotine-containing EJs. Our results highlighted a significant accumulation of alkaloid compounds and suggested their production from oxidation. After prolonged storage, nicotine-containing EJ can be rich in such compounds. Upon frequent consumption of EJ, the exposure to these compounds by smokers can be significant. In addition, releasing these products into the atmosphere can harm indoor air quality and the health of surrounding non-smokers. Discoveries reported by our work can be referred to by future clinical studies to determine the adverse health effects of vaping-associated alkaloid exposure.

While only very few studies have characterized alkaloid compounds in EJ, our research offers mechanistic insights into the source of these compounds. Natural abiotic oxidation of nicotine has rarely been reported and many consumers or manufacturers have assumed it to be safe. We have applied a versatile LC-MS method which is highly selective towards amino compounds in our sample. Including nornicotine, we discovered a total number of nine amino alkaloid species in EJ. Our aqueous phase photooxidation experiment resulted in a mix of products that are in agreement with the natural aging of EJ, exemplifying that radical-initiated oxidation is likely their source.

Although we did not witness any significant color change during our natural aging experiment, we discovered a rapid formation of nornicotine from freshly purchased EJ. The accumulation of nornicotine can plateau over a week, with the final concentration agreeing with existing literature. We have also discovered a variation of nornicotine concentration across different EJs, with a higher nicotine level leading to elevated concentrations of nornicotine. These results imply that 1) the natural oxidation of nicotine is a very rapid process, in which concentrations of oxidation products can reach a high plateau within days; 2) consuming a high nicotine EJ may lead to a higher human exposure to alkaloid compounds. As a result, aged EJs are not necessarily safe to consume, and smokers should be aware of the EJ storage conditions to mitigate exposure to various nicotine oxidation products.

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Chapter 5

Characterization of Indoor Atmospheric Nitrogenous Chemicals in Poultry Farms

5.1 Introduction

Indoor air quality (IAQ) has attracted attention as its relevance to public health and well-being has become clearer in recent years.[358] Current studies reported residential homes contain a complex mixture of human emissions,[359, 360] animal or biological activities, and chemical processes.[310, 361] The IAQ of the workplace is as important as that of residential homes, as many contemporary occupations occur indoors.[362] Government agencies have established IAQ protocols at work to protect workers.[363] However, workers may face air pollutants specific to their occupations; thus, it is challenging to establish customized standards. For industries that are primary emitters of air pollutants, workers can have prolonged exposure to concentrations that exceed exposure thresholds, threatening their productivity and occupational health.[364, 365]

The US Department of Labor has identified common biological, chemical, and particulate pollutants in commercial and institutional indoor buildings. However, only general administrative and control guidance was provided.[366] With a highly diverse indoor environment, managing workplace IAQ remains challenging and general benchmarks are not sufficient to meet the demand for clean air. Studies found that air pollution in office environments not only causes discomfort, but also contributes to cardiovascular or respiratory diseases.[367–370] For industries that usually involve indoor activities, such as exhibitions,[371, 372] entertainment,[68, 340] and beauty industries,[23, 24] the exposure to volatile organic compounds (VOCs) is concerning. Similarly, the poultry industry faces challenging problems of air pollution in indoor poultry facilities. Elevated levels of air pollutants have been observed on farms, including carbon dioxide,[373] ammonia (NH_3), particulates (PM_{10}, $PM_{2.5}$),[374] and VOCs.[375] These pollutants are often associated with low chicken productivity and welfare,[376–378] but systematic studies remain rare. Despite the fact that air ventilation has always been a costly burden for producers,[379] many commercial poultry farms still suffer from heavily polluted air.[380, 381]

The main source of air pollutants in poultry farms is chicken manure. Due to its low density, sand-like texture, the manure can easily be suspended by birds' activities.[382] Airborne nitrogenous chemicals (ANCs) are abundant in livestock facilities and are usually odorous or toxic.[383] Small ANCs, such as aliphatic amines and NH_3, are among the commonly identified species, as they are highly volatile, concentrated, and odorous.[381, 384, 385] NH_3 is a benchmark compound that is used as an indicator of IAQ in poultry facilities and is in the guide to animal care.[386] A high concentration of NH_3 is found to be responsible for the reduction in body weight gain, calorie conversion, and immune system functions in chickens.[387] However, the current literature and the control strategies of NH_3 often neglect the fact that most NH_3 are not directly emitted by birds. Instead, it is chemically produced by enzyme-assisted microbial decomposition of uric acid (UA).[388, 389] Understanding the chemical processes that occur in indoor poultry facilities is needed to manage ongoing NH_3 pollution, as well as to mitigate risks associated with farmer health and animal welfare.

UA is a common biogenic nitrogenous chemical in animal and plant bodies,[390, 391] and is rich in agricultural facilities and waste. While UA is the major source of nitrogens in agricultural facilities,[386, 392, 393] its presence in aerosols and the indoor atmosphere is rarely reported. Although not volatile, UA is available to producers and livestock through the inhalation of dust particles.[394] UA-rich particles can affect the dynamics of nitrogen cycles in the farm.[395] Chronic exposure to such chemicals can cause adverse health effects to both producers and livestock. More importantly, through enzyme-assisted microbial decomposition, UA decomposes to urea through a chain reaction, which eventually leads to CO_2 and NH_3 by hydrolysis of urea.[396, 397] Studying UA in the indoor atmosphere is beneficial in addressing existing ammonia pollution problems in livestock facilities.

There are many organic ANCs present in the poultry facility, and some of them are precursors of small inhalable nitrogenous species.[398] Some studies considered these compounds insignificant[375, 399, 400] due to limitations of analytical techniques.[401] Recent evidence indicates their importance in indoor farms: amines, such as cadaverine (CAD), putrescine (PUT), and guanine (GUA), are associated with the decay of proteins and amino acids.[402, 403] Existing review studies have also discussed them as part of total VOCs in livestock facilities.[404] Analyses of these ANCs in poultry facilities are rarely performed and little is known about their behaviors and distributions.

The objective of this study is to provide information on nitrogen cycles in indoor poultry farms. First, this study will demonstrate a time-resolved collection and quantification of ANCs. Second, the distributions of the ANCs in different phases (air, particles, and litter) will also be evaluated. Third, using UA as an example, the correlation between ANCs and IAQ parameters will be addressed by monitoring the aerosol dynamic. By reporting results obtained from a campaign in local commercial poultry farms, this work provides a comprehensive assessment of the origin of IAQ issues in poultry farms. The discoveries made in this work can contribute to reducing air quality, occupational health, agricultural productivity, and animal welfare issues in livestock facilities.

5.2 Material and Methods

5.2.1 Chemicals and Materials

The deionized water used in this study was made using a Thermo-Fisher Scientific Barnstead^{TM} E-Pure^{TM} Ultrapure Water Purification System. HPLC grade acetonitrile, boric acid (>99.5%), formic acid (98-100%), ammonium hydroxide (NH_4OH) solution (28% NH_3 in water), uric acid (>99%), guanine (98%), allantoin (>98%), urea (99.0-100.5%), p-toluenesulfonyl chloride (TsCl) (>99%) were purchased from Sigma-Aldrich. Sodium hydroxide pallets were purchased from Fisher Chemical.

Two buffers were prepared for sample collection and extraction. A 0.25 M sodium formate buffer was prepared by dissolving boric acid solids in deionized water, with its pH then adjusted to 9.0 by NaOH. A 0.1% formic acid solution (pH = 2.7) was prepared by dissolving formic acid in deionized water. These two solutions are herein referred to as the basic buffer and the acidic buffer to be used in subsequent steps.

5.2.2 Instrumentation

Aerosol samples were collected using a particle-into-liquid sampler (PILS) (Model 4001), and an auto collector manufactured by Brechtel Inc. The aerosol monitoring instrument was an optical particle counter (OPC) (Model 11-C) manufactured by Grimm Inc. The primary chemical analysis instrument was the Thermo-Fisher Accela HPLC system and Thermo-Fisher LTQ-XL mass spectrometer, operated in ESI-positive mode. The column for LC separation was a Phenomex Luna Omega polar C-18 column, dimension 150 mm × 2.1 mm × 3 μm. An Orbitrap high-resolution mass spectrometer (Thermo-Fisher Exactive Orbitrap) was also used for the determination of exact mass. For quality control, Thermo 17i NH_3 analyzer and a scanning mobility particle sizer (SMPS, TSI Inc.) were used. The SMPS includes a diffusion mobility analyzer (Model 3080) and a condensation particle counter (Model 3775)

5.2.3 Sample Collection and Treatment

Figure 5.1 is a schematic of the approaches taken to measure ANCs in indoor poultry facilities. Functionality tests of all instruments involved in Figure 1 were performed preliminarily at the Poultry Research Center (PRC) of the University of Alberta. The farm had floor pen housings for a small flock of 70-75 birds, and the entire barn area had about 1200 birds. Commercial farm samples involved in this study were collected on a farm located near Camrose, Alberta, Canada (Figure D.1). The farm was a completely indoor, organic free-range table egg farm. The barn we sampled was home to 8000 birds at approximately 60 to 70 weeks of age. On the commercial farm, instrument testing and sample collection were performed between November 2022 and March 2023, for a total of four farm visits. The results shown in this study were collected in April 2023. During the winter season, the ventilation of the air in the barn was usually minimized to reduce the heat loss to the outdoor environment. The lighting in the barn is governed by incandescent light bulbs that are covered with red plastic covers. We were advised by farmers that red light can reduce chicken anxiety. The field samples collected were analyzed the same day in the lab. A sketch of the barn can be found in Figure D.2 in the appendix.

Gas samples were collected using a homemade impinger driven by a diaphragm pump, and the gas flow rate was controlled by an Allicat Mass Flow controller at 0.7 L/min. Upstream of the pump, a 0.2 μm Watman filter was installed to remove the incoming particles. The acidic buffer described above was used to maximize the recovery efficiency of the gaseous NH_3.

The OPC collected real-time particle profiles. Time-resolved aerosol samples were collected by PILS and its auto collector in the basic buffer. An activated charcoal gas denuder was installed upstream of the instrument inlet to remove gas phase species. Through preliminary trials, we discovered that a better solubility of most ANCs was achieved using the basic buffer, which can compromise the collection efficiency of

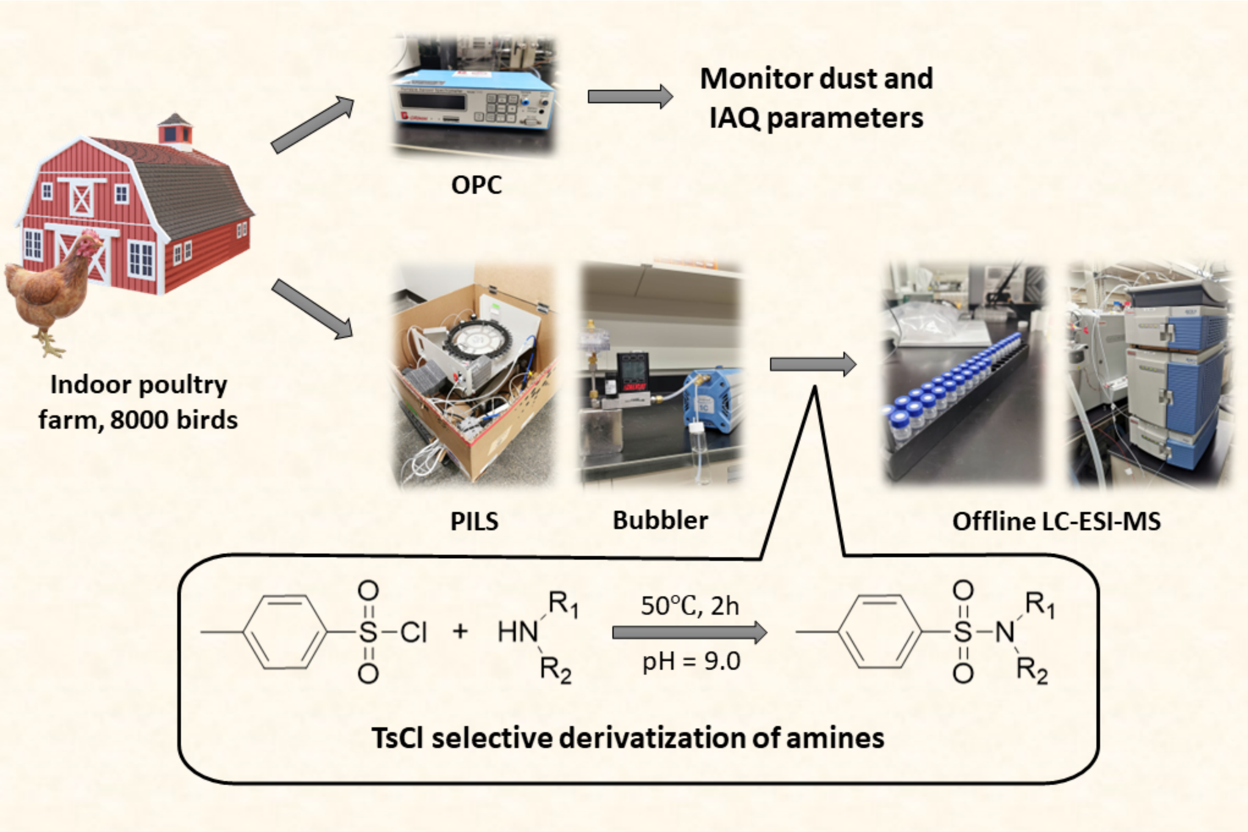

Figure 5.1: Layout of sample collection, derivatization, and analysis. OPC: optical particle counter, IAQ: indoor air quality, PILS: Particle into liquid Sampler, TsCl: p-toluenesulfonyl chloride, LC-ESI-MS: liquid chromatography electrospray ionization mass spectrometry.

NH_4^+. The solvent was driven by a peristaltic pump at a rate of 0.3 mL/min, the resulting solution was then injected directly into a 1.8 mL autosampler vial every 2 min. Due to limited slots on the autosampler, there were also occasions when these samples were collected in a 12 mL vial every 20 minutes for prolonged collections.

Chicken litter samples were collected by handpicking from five random locations within the farm. The five samples were pooled by shaking them in a 20 mL glass vial after collection. A portion of the litter was weighed and extracted using the basic buffer during the treatment of the sample in the lab. We noted that the litter sample was a mixture of bedding materials and chicken manure (Figure D.3 in the appendix). Our process did not exhaustively extract the bedding material, as it is mainly wood pellets. Therefore, we assume that all the chemicals obtained in the extracted solution come from chicken manure.

5.2.4 Derivatization and Chemical Analysis of ANCs

Derivatization was carried out directly inside the autosampler vial. The derivatization method was developed according to Rudnicka et al..[153] All samples were mixed with 0.052 M TsCl solution in acetonitrile and prepared in the basic buffer. The derivatization takes at least two hours in a 50 ℃ water bath. All derived samples were analyzed via LC-ESI-MS, and the details and settings regarding this instrument are listed in Appendix D.2.

TsCl is known to be selective towards R-NH and R-OH functional groups, forming sulfonamides and sulfonates by nucleophilic tosylation.[343, 405] We did not experience interferences from any sulfonates, as our basic condition would favor their detosylation reaction, while sulfonamides remained stable.[406–408] Thus, sulfonates were excluded from our chromatography, which made our method very selective toward sulfonamides. All detected TsCl-derived species were first isolated via background subtraction in high-resolution orbitrap MS, with a proposed molecular formula. The identities of the samples were then further confirmed by comparing them with the derivatives of commercially available standards.

We selectively quantified UA and NH_3 in our sample with external standards. UA calibration was performed in the basic buffer and a five-point calibration ranging from 0 to 400 μM was completed by serial dilution, with the R^2 value greater than 0.9990. NH_3 calibration was done by derivatizing diluted NH_4OH solution and constructing a six-point calibration curve ranging from 0 to 20 mM by serial dilution, with an R^2 value greater than 0.9990. These calibration curves were reviewed monthly by analyzing standard solutions.

5.2.5 Quality Control and Instrument Characterization

Although the PILS is designed to collect particles, some gaseous chemicals can be collected even with a gas denuder installed. To identify the bias of gaseous chemicals that have broken through, we performed a joint calibration between the PILS and the Thermo 17i ammonia analyzer. During this experiment, we measured laboratory-generated ammonia and ammonium bisulfate particles. The gas removal efficiency of the PILS gas denuder and the standard error of the PILS were determined (6.7%). This standard error value will serve as error bars in the following quantitative analysis in this study. Detailed information on this experiment can be found in Appendix D.3.

Without the gas denuder, PILS collected 59.1% of the gas phase NH_3 - related to the NH_3 analyzer. When the denuder was mounted, the NH_3 concentration was below the detection limit (LOD, 20 ppb, equivalent gas phase). Hence, we assumed that the breakthroughs of gaseous ANCs during our particle collection were not significant.

PILS has demonstrated its ability to collect fine particles (30 nm and above). Although the literature has shown that the collection efficiency between 30 nm and 10 μm is greater than 97%,[119] a portion of the salt particles generated in this experiment was less than 30 nm, which was outside the designed range of PILS. We noted that the NH_3 analyzer is also capable of measuring aerosols containing ${NH_4}^+$. Its internal catalyst evaporates NH_3 which is oxidized in the heated stove (approximately

800 °C). NH_3 then inputs NO which can be detected by O_3 chemiluminescence. In this specific intercomparison, the PILS obtained 71.8% of ${NH_4}^+$ particles related to the NH_3 analyzer. Higher efficiency can be achieved when the particle size is larger according to the working fundamentals of the PILS.[117, 119] As will be addressed later, most particles in the commercial poultry facility were larger than 30 nm; therefore, the collection efficiency of ${NH_4}^+$ particles would be higher than in our intercomparison experiment.

A recovery test for UA was performed by injecting a standard UA solution with a known concentration into a bedding material extract. This test was designed to examine the efficiency of derivatization. Two sets of samples were prepared for this test: one had five replicates of nonspiked bedding extract and the other had five replicates of UA-spiked extract. The recovery value obtained was 72.7% ± 11.5%. Additionally, we have also performed a stability test of the derived sample to account for the sequence queueing time on the autosampler. This was done by repetitively analyzing the same derived standard compound over time. The results of this control experiment are shown in Appendix D.3, and the corresponding correction to sample degradation has been applied to our time-resolved data series.

5.3 Results and Discussion

5.3.1 Identification of ANCs in Different Phases

With the aid of high-resolution mass spectrometry (resolution greater than 50,000), our nontargeted analysis has detected 15 ANCs, with 10 of them identified. Appendix D.4 summarizes the proposed identities of these ANCs. TsCl derivatives are identified by signature isotopic profiles (Figure D.7). Sulfur in the TsCl-derivative can cause split peaks at the mass of $[M{+}2]^+$ position. Due to the mass of $[^{34}S-^{32}S]$ being smaller than $2\times[^{13}C-^{12}C]$, the lighter peak refers to $[M(^{34}S)]^+$, and the heavier peak refers to $[M(^{13}C_2)]^+$ or $[M(^{14}C)]^+$. Furthermore, since the natural abundance of ^{34}S is higher than ^{14}C or ^{13}C, the lighter peak will be more intense.[409] Assuming that the only source of sulfur is TsCl, its derivatives are identified. Details about this identification method can be found in Appendix D.4. We further confirmed some ANCs by referring to commercial standards, which are NH_3, dimethylamine (DMA), GUA, UA, PUT and CAD. We have also identified a trace peak of urea and allantoin (ALA), which are proven intermediates in the decomposition mechanism of UA.[396, 397] Although not detected, trimethylamine, a tertiary amine, is abundant in livestock facilities.[383, 384, 410, 411] It is absent in our sample because TsCl cannot react with any tertiary amines as a result of the lack of active amino groups.

The phase distribution of identified ANCs among gas, particle, and litter was evaluated via targeted analysis. The distribution of ANCs shows significant variation. The litter phase had the highest variety of compounds and fewer ANCs were observed in the gas or particle phase. We propose that ANCs in the gas and particle phase are due to the partitioning or suspension of chemicals from the litter. According to Figure 5.2A, only highly volatile ANCs were found in the gas phase. Large ANCs, such as the UA, are restrained by their low volatility, hence their gaseous concentration is below our LOD. To support our proposal, we constructed a model that predicts the fraction of a chemical in the air phase at two different particle concentrations in Figure 5.2B. Details about the model can be found in Appenxid D.5. When tested species reach equilibria between the gas phase and the particle phase, NH_3 and DMA would be found exclusively in the gas phase. A fraction of CAD and PUT may enter the gas phase, but their concentrations in our sample were insignificant. According to our model, the ANC partition would remain consistent between 5 and 20 mg/m^3, which are typical concentration we observed inside the barn.

In the particle phase, the volatile DMA is absent, whereas ANCs with less volatilities are observed. UA has the most intense peak, which has suppressed the responses of others. Four ANCs are detected in the particle sample, suggesting that these compounds are the main forms of nitrogenous compounds in suspended dust and can be

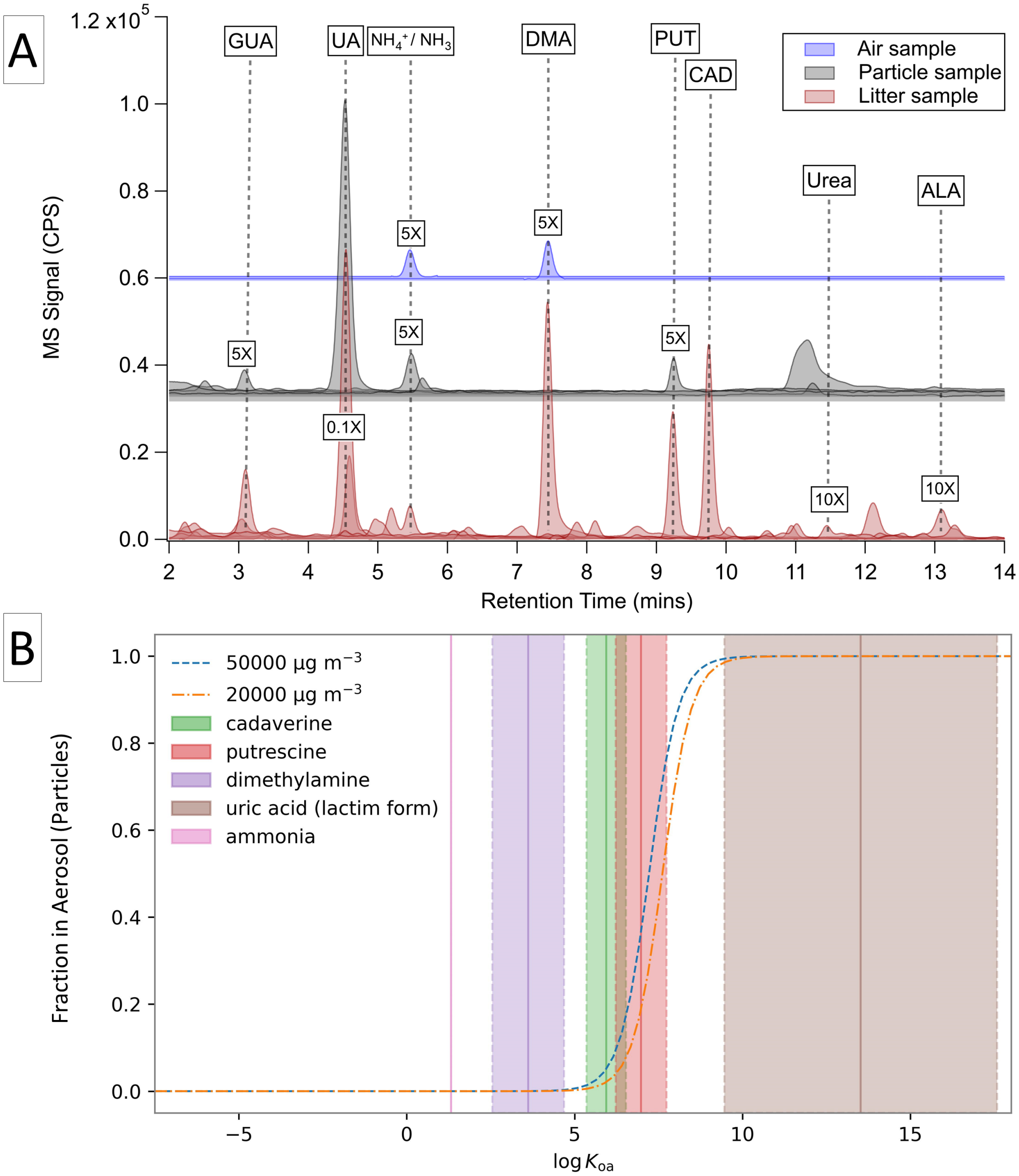

Figure 5.2: Identification of ANCs in air, particle, and litter phases, A) Extracted ion chromatogram of identified ANCs, certain peaks are scaled for better visualization; B) Aerosol-air equilibria of target compounds. The calculated fraction in aerosol under two selected concentrations of aerosol was a function of log K_{oa}. Shaded regions represent the predicted range of log K_{oa} values for the compounds, while the solid lines in the center represent the predicted log K_{oa} values.

exposed to producers and chickens by inhalation. The model result (Figure 5.2B) supported this observation by showing that minimal DMA is expected to be in the particle phase, regardless of the concentrations of particles. The only discrepancy between the model and the observation is NH_3, which the model predicts is predominantly present in the gas phase. However, we note that the K_{oa} (partitioning coefficient of chemicals between air and octanol) values used in the model were simulated based on the neutral forms of the compounds (i.e., NH_3). Acid-base equilibria are known to significantly affect the partitioning of compounds such as NH_3. The particle phase NH_3 signal is probably attributed to ammonium salts in the dust. Compared to gas and dust samples, chicken litter contains the largest variety of ANCs. The MS signal of UA in this phase is very high, exemplifying that the source of UA is the litter. Volatile ANCs are also found in the litter, such as DMA, PUT, and CAD. They are likely dissolved in the water or organic contents of the litter or trapped within the air space within the litter particles. Urea and ALA are only detected in the litter. The detection of these two compounds indicates that the litter is the reaction site of UA decomposition. In other words, the litter serves as a persistent source and reservoir for NH_3 in the barn.

5.3.2 Distribution of Nitrogenous Species in Each Phase

In the previous section, ANCs have shown a distribution profile among three phases. Here, we quantify these ANCs to add more details to the mentioned distribution. ANCs concentrations in the gas phase were calculated based on the total volume of air sampled by the impinger. ANC percentages in the particle phase were calculated based on the amount quantified by LC-MS calibration and then were related to the total particle mass monitored by the OPC. The litter phase was calculated based on the dry mass of the litter. For the litter samples, we used dry mass to calculate the percentage of mass, while the extraction of the litter was performed with fresh litter; this is because the loss of volatile amine during drying is inevitable. Anion molarity percentages were shown in pie charts and their molarity was determined using the US EPA colorimetric method[35] carried out by the Natural Resource Analytical Laboratory at the University of Alberta. We did not perform a cation analysis, as a result of the scope of the study and limited instrument availability. Therefore, we assumed that all the anions were counterions of the ammonium pool. To discover the molarity distribution of different salts, charge ratios between ions are considered. For example, ammonium phosphate has a higher percentage of molarity than its percentage of mass, since the ratio between two ions is 1 to 3.

According to the anion molarity distribution of ammonium salts between the particle and the litter, their distribution has shown some correlations. Note that we have quantified only five anions. Other anions, such as bisulfates or biphosphates, cannot be detected with our method. Therefore, our reported percentages may be overestimated and serve as a preliminary quantification. Regarding the pie chart of Figure 5.3A, phosphate in suspended particles has the largest molarity fraction, followed by chloride, sulfate, and nitrate. Compared to the particle phase, the pie chart in Figure 5.3B describes the anion distribution in the litter. Here, phosphate has a dominant molarity fraction over the other salts, followed by nitrate and sulfate. As a result, chicken litter contains a very high concentration of phosphate, due to direct excretion by chickens via manure,[412] raising the phosphate content in the litter. The high fraction of phosphates in the particles is likely due to the suspension of litter, either due to air circulation or animal movement. Chloride is the second most abundant anion in particles; it does not share a similar fraction in litter, suggesting alternative sources of chlorides other than chicken manure. Analysis of the anions in the particles and litter indicated significant inhalable exposure to elevated phosphate salts by animals and workers, which may cause problems with phosphate toxicity.[413]

According to Figure 5.3A, the gas phase contains a level of ammonia and DMA in ppm, while this concentration can be variable depending on ventilation: weaker ventilation in cold weather may concentrate gaseous ANCs. In the particle phase, we

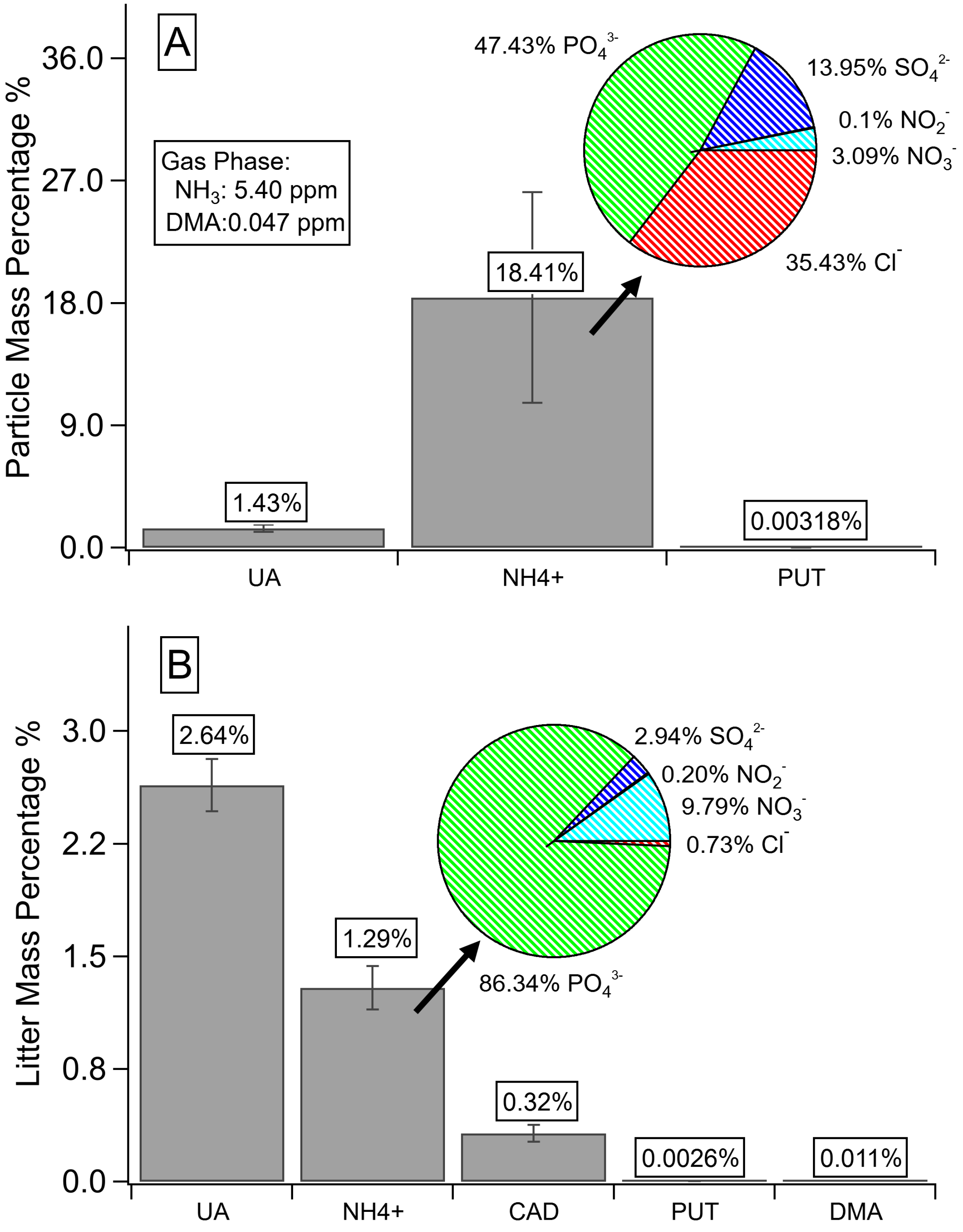

Figure 5.3: Distribution of nitrogenous species in A) particle phase and gas phase (as an insert), B) litter phase (dry mass). Only NH_3 and DMA were detected in the gas phase, and their concentrations are shown as an inset in A). Error bars represent one standard deviation of collection. The y-axis represents mass percentages of ANCs, and pie charts represent the calculated molarity percentage NH_4^+ salts. We note that only two compounds were found in the gas phase, with their concentrations more than 100-times different from each other. Therefore gas phase distribution is only expressed as an insert in the panel A.

obtained the mass fractions of each ANCs based on the total particle mass (TPM), which was obtained by the OPC with an hourly average of 19 mg/m^3. Ammonium salts occupied more than 18% of TPM, followed by 1.43% of UA. However, this concentration was 1.29% in the litter sample (Figure 5.3B), which is more than 10 times less than that in the particles. Therefore, ammonium salts in dust particles did not necessarily come from the litter. We propose that it is due to the high CO_2 concentration (about 2000 ppm according to the farm monitor) in the farm air that increases the acidity of suspended particles,[414] leading to the repartitioning of ammonia gas into particles. However, this proposal needs further research to confirm. Compared to particles, the litter sample had a higher mass concentration of UA (2.64%) than in particles, suggesting that the only source of airborne UA is the resuspension of the litter. Existing studies reported that exposure to high concentrations of ammonium salts can cause airway constriction.[415]

CAD and DMA have higher fractions in the litter than in other phases. 0.32% of the litter is occupied by CAD, making it the third most dominant nitrogenous chemical. DMA has the lowest mass ratio among all ANCs, which is 0.011%. The production of amines is likely due to the microbial metabolism of amino acids excreted by birds.[416]

The comparison of nitrogenous species with other literature is made in Table 5.1. The indoor environment of a commercial poultry farm is very dynamic, and concentrations of pollutants are often governed by the activity of chickens, ventilation, and farm infrastructures. Therefore, it is very challenging to find a representative concentration even for the most commonly measured air pollutants (i.e. NH_3 and PM). As shown in Table 5.1, our gas phase NH_3 is within the range of values reported in the literature and less than the concentration stated in the regulations (10 ppm).[417, 418] In the particle phase, our ammonium measurement is within the same order of magnitude as the reported value, but more than three times higher. It could be due to the different conditions between farms. Furthermore, our measurement included active periods for chickens, which caused a larger amplitude of standard deviation. In addition to NH_3 or ${NH_4}^+$, there is a lack of quantitative analysis of all other ANCs, such as UA, DMA, CAD, and PUT, making our study the first to report their concentrations in an indoor poultry facility.

Table 5.1: Comparison of nitrogenous species with other literature

	Gas		**Particle**		**Litter**	
Chemicals	Literature	This work	Literature	This work	Literature	This work
$NH_3/{NH_4}^+$	6.55 ± 2.2 ppm[373]	5.40ppm	5.45% ± 1.53%[419]	18.41% ± 7.76%	0.78% ± 0.92%[420]	1.29% ± 0.15%
DMA	<0.22 mg/m^3 [384]	0.047ppm	N/A	Below LOD	N/A	0.011%
UA	N/A	Below LOD	N/A	1.43%	2.6%-3.0% [421]	2.64% ± 0.17%
Total Particle	N/A	N/A	0.168-9.61 mg/m^3[381]	7.2-36.8 mg/m^3	N/A	N/A

5.3.3 Dust and Chemical Correlation

To explore the correlations of ANCs with other conditions, including farm lighting and common IAQ parameters, we conducted a case study on April 13, 2023. This date was selected for several reasons. First, the outdoor temperature was mild, so the ventilation rate on the farm was moderate. Second, the producers planned to remove birds from the farm on this date. This was a unique opportunity to observe how human-induced chicken activities would directly affect airborne compounds. Third, this opportunity allowed us to study the diurnal cycle of IAQ on the farm in a relatively short sampling period, as farmers will awaken the chickens in the evening.

The size distribution of particles in the atmosphere has been evaluated, as we consider that PILS has a minimum particle size requirement (30 nm) for optimal collection efficiency. We obtained a 2-D contour plot of OPC particle concentrations in different bin sizes, ranging from 0.25 μm to 32 μm. This plot can be found in Appendix D.6. We confirmed that most of the particles in the farm atmosphere were greater than 0.25 μm. Thus aerosols collected by the PILS fall in its designed working range, which has a collection efficiency greater than 97%.[119]

Figure 5.4A shows the time profile of UA and TPM measured by PILS-LCMS and OPC, and the shading of the background indicates the change in the lighting conditions in the barn. UA and TPM concentrations were plotted against each other to elucidate their correlations (Figure 5.4B). We differentiated our sampling period into three zones: daytime, sunset, and nighttime, each of them representing different light conditions. The farm light had the maximum output during the daytime (white zone) and gradually dimmed during the sunset period (light gray zone). At night, there were no lights inside the farm (dark gray zone). During the daytime, TPM fluctuated around 3×10^4 μg/m^3 while the UA concentration can be as high as 500 μg/m^3. The mass percentage of UA among the TPM is about 1.5%, which agrees with the results presented in Figure 5.3. According to our observations on site, most of the birds were gathering on the ground during the daytime and were in direct contact with the chicken litter. Bird motions will suspend dust from litter bedding. Thus, an elevated concentration of both UA and TPM was observed. Fluctuations in the TPM may be due to local activities of chickens, giving rise to plumes of the TPM that arrive at the instrument. When there was a major event, for example, when the chickens were agitated around 17:05, both the TPM and the UA concentration saw a significant surge.

During the sunset period, the chickens began to relocate to the upper layers, which were made of steel frames and served as the sleeping places of the birds. As the steel frame could not retain many litter particles, the chicken motions cannot resuspend litter particles, leading to a reduction of both PM and UA particles. When the night came, the chickens fell asleep in a short time and could seemingly remain asleep. The concentration of UA and TPM would remain at a low level until the next morning. However, as the producers were in the process of removing the flock from the farm, sleeping birds were awakened. Therefore, an increase in UA and TPM was observed after 19:00. The time profile of the TPM exhibited multiple sharp peaks that were not observed during the daytime. It is likely caused by farmer-induced localized and sporadic bird activities. The UA profile has shown rather a single broad peak than

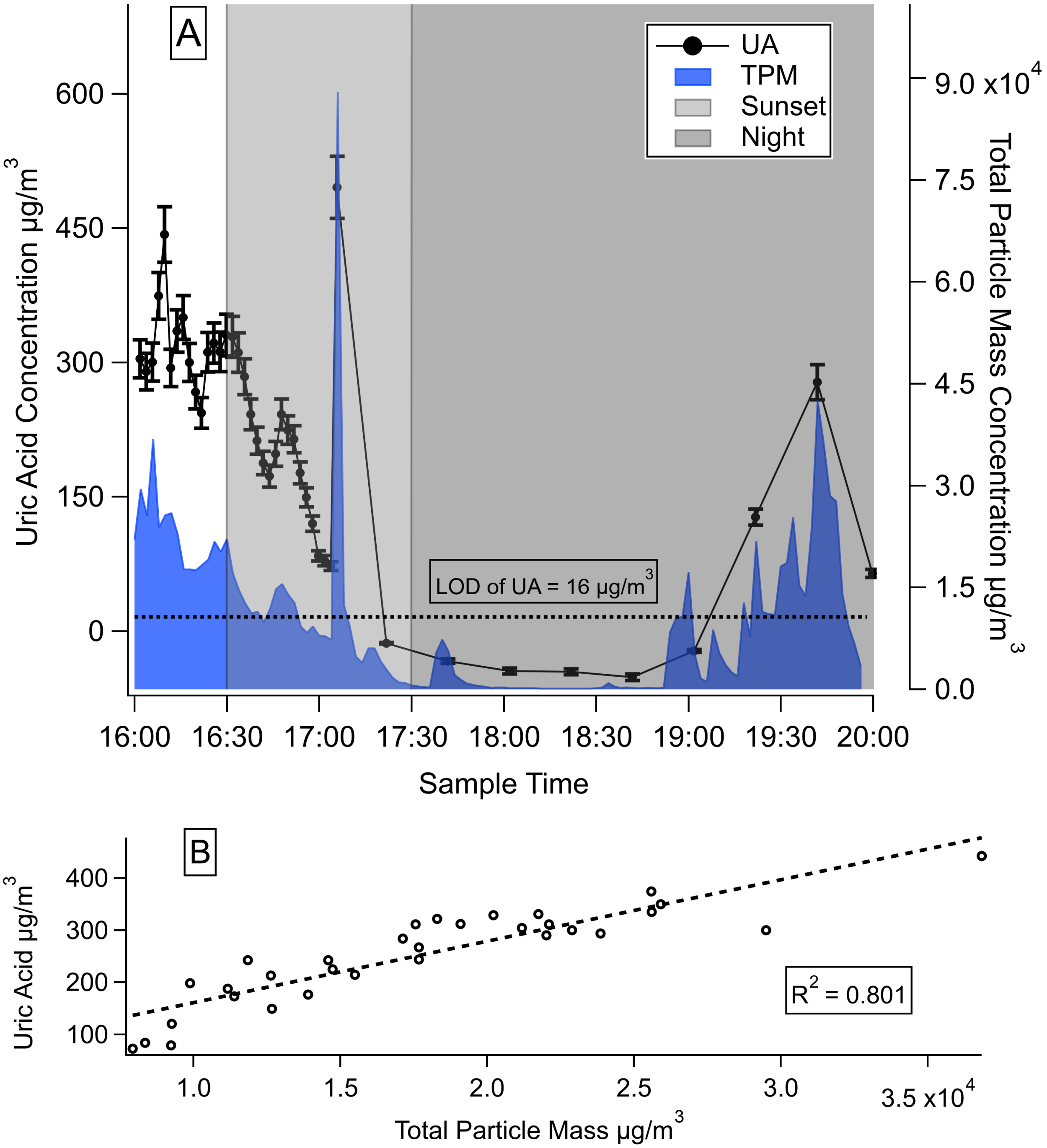

Figure 5.4: Time-resolved measurement of particles in the poultry farm, A) Time series of UA and TPM; B) Correlation plot between two sets of data. Error bars for UA in A) represent the standard deviation of PILS collection (6.7%) obtained from quality control experiments. The LOD of UA in particles is 16 μg/m^3 represented by the dashed line in panel A.

multipeaks, because of the reduced PILS sampling frequency at night.

The correlation between the PILS and the OPC results ($R^2 > 0.8$) is shown in Figure 5.4B. These two instruments were co-located during measurement. The regression analysis indicates that 1) TPM is a major carrier of airborne UA, which is consistent with the discussions in previous sections, and 2) the fluctuating concentration of airborne UA reflects changing chicken activities on the farm. This agreement also confirms that UA shares a relatively stable ratio in airborne particles, which again implies that airborne UA has a consistent source, for example, manure suspension.

5.4 Conclusions

Our project has demonstrated the most detailed exploration of airborne nitrogenous chemicals (ANCs) within a commercial poultry farm. Various organic and inorganic ANCs have been identified and quantified in this study, while most of them have never been evaluated in existing research. Nitrogenous species share a large proportion of chemicals in commercial poultry farms. Elevated concentrations of these chemicals can directly reduce indoor air quality. Therefore, it puts the occupational health of producers at risk. More importantly, the birds' welfare, productivity, and cost-effectiveness of investments made in farm ventilation will also decrease.

Although existing research generally focuses on small volatile compounds,[373, 375] our results demonstrated the presence of a wide variety of ANCs and ammonium salts in farm air. ANCs are key components in the nitrogen cycle in poultry farms and, at the same time, serve as precursors to ammonia. ANCs also demonstrate a variable distribution between three indoor phases. In the gas phase, ammonia and DMA were quantified and concentrations were comparable to those of the existing literature.[373, 384] In the particle phase, the concentration of ammonium was significantly higher than that of litter, implying the result of the repartition of gaseous ammonia into particles. Large organic ANCs, such as UA, were also found in airborne particles. These organic ANCs could be inhaled directly or serve as reservoirs of NH_3, as they can undergo microbial decomposition. Litter bedding is the main reservoir for all ANCs observed in other phases; particularly for NH_3 formation, it is the potential reaction site for microbial decomposition of UA.

Our time-resolved measurements have provided explicit and novel relationships between animal activity, total suspended particles, and individual inhalable chemicals. This observation implies that 1) a significant difference was observed between day and night TPM and ANC concentration, 2) spikes in both TPM and ANCs corresponded to events that caused intense animal activity, and 3) a strong agreement was detected between TPM and ANCs time profiles. Prolonged exposure to airborne ANCs and dust particles by chickens will not only reduce their quality of life, but can also compromise the effectiveness of investments. Events that cause acute increases in airborne ANCs can also put farmers' health at risk when proper personal protective equipment is absent.

In general, our study has provided new information on air pollutants that can be associated with the formation of gaseous NH_3. According to discoveries made in this work, resolving indoor air pollution in poultry housing may benefit from taking a different approach. First, controlling NH_3 formation in poultry facilities requires a better picture of the entire nitrogen cycle. Various types of ANCs are involved in the nitrogen pool, with UA being the most abundant organic ANCs. This high diversity of ANCs will eventually contribute to the production of NH_3. Therefore, the removal of ANCs precursors in the environment would be beneficial, and future studies should explore technologies that can make this possible. Second, our study has demonstrated the importance of chemical partitioning of ANCs within the farm. In other words, pollutants can be unevenly distributed among the gas, particle, and surface phases. A better understanding of this distribution can lead to new waste and ventilation treatment strategies that can remove specific pollutants in a more targeted manner.

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Chapter 6

Conclusions, Recommendations, and Future Work

6.1 Conclusions

This present thesis aimed to provide chemical insight into the possible exposure to indoor air pollutants in different consumer and occupational settings. Specific goals are 1) to investigate harmful chemicals accumulated in the aged artificial fog juice, 2) to investigate the autoxidation of common glycols and to determine external parameters that can affect the process, 3) to study unrecognized oxidation products of nicotine in the e-juice during its degradation, and 4) to present a chemical analysis of the indoor environment of a commercial poultry farm, such that persisting environmental concerns by the poultry industry can be addressed.

To begin with Chapter 2, I described the impact on IAQ by using AFM in an enclosed indoor environment. A huge number of chemically rich particles are generated shortly after the start of the equipment. With the application of LC-MS and the derivatization of 2,4-DNPH, the chemical composition of the particles was investigated and the significant presence of carbonyl species was discovered. These carbonyl species, including formaldehyde and glycolaldehyde, are found to accumulate in fog juice during storage of the product. By monitoring carbonyls in fog juice in a month-long experiment, I proposed that carbonyl accumulation is caused by the autoxidation of glycols. Observations made in this chapter could potentially address occupational health problems faced by workers in the entertainment industry and stage actors.

In Chapter 3, I presented a fundamental study of glycol autoxidation to further support my proposal. In this chapter, I selected a few common glycols as target compounds, including TEG, DEG, PG, and VG. These glycols are widely used as the solvent for fog juice or EJ. After the monitoring experiment, the time-resolved formation of carbonyls and peroxides was quantified in these glycols. In addition, I investigated external parameters that can affect the accumulation rate of products, including the water mixing ratio, air exposure, and the addition of vitamin C as an antioxidant. Observations made in this chapter provide strong evidence that autoxidation is responsible for the formation of carbonyls and peroxides in any glycol-containing product, and hence consumers should be aware of the storage conditions of their glycol products.

In Chapter 4, I further investigated the oxidation of nicotine in the EJ, as it is one of the major components of the EJ other than glycols. Using a novel selective derivatization method with TsCl, I have determined nine nitrogen-containing alkaloid oxidation products from natural aging of nicotine. In addition, I further confirmed their formation by performing an aqueous phase photooxidation experiment, which exemplified that product formation is likely caused by radical-initiated oxidation. Finally, I monitored the formation of these alkaloid compounds and identified the production of nornicotine during nicotine degradation. Therefore, I proposed an abiotic N-demethylation mechanism of nicotine. The determination of nornicotine and many other alkaloid compounds provides a mechanistic insight into the fate of nicotine during storage. At the same time, e-cigarette consumers should be aware of the chemistry process that occurs in their EJ.

Finally, by gathering all the experience and techniques obtained from the laboratory-based project, I implemented a field study in Chapter 5. In this chapter, I presented a dedicated exploration of ANCs within a commercial poultry facility. Various organic and inorganic nitrogenous species, including UA and ammoniacal compounds, are determined among the phases of litter, gas, and dust in the farm. The detection of these nitrogenous species has indicated one major source of ammonia pollution in poultry facilities, and emphasized the importance of maintaining proper waste management protocol. In addition, we have also discovered the correlation between animal activities and indoor air pollution. Elevated concentrations of indoor ANC pollutants could reduce chicken productivity, while threatening the occupational health of farmers.

6.2 Future Work

6.2.1 On Autoxidation of Glycols

Autoxidation involves a spontaneous inter- and intramolecular hydrogen shift and continuous formation of peroxy radicals.[251] The determination of these reaction intermediates is the benchmark for proving the existence of autoxidation.[84] Peroxy radicals are generally highly reactive and have short a lifetime,[422] hence it is always a challenge to determine these species. Although this thesis has provided strong evidence that glycols can undergo autoxidation, the reaction scheme is not fully justified because there was no detection of peroxy radicals. As a result, the application of rapid online MS techniques, including chemical ionization and extractive electrospray ionization MS, would be advantageous to detect these radical intermediates according to exisiting literature. [423, 424]

6.2.2 Systematic Study on TsCl Derivatization

In this prensent thesis, I demonstrated the preliminary application of TsCl onto environmental samples in Chapters 4 and 5. In these studies, TsCl has shown its versatility in recovering trace amounts of amino-containing species from the complex environmental matrix and its wide selectivity toward different types of amines. Nevertheless, this method has not been fully characterized, as there are no studies done to systematically investigate its selectivity and sensititity toward amines. As a result, a crucial future perspective would be to explore this derivatization method in a more quantitative manner. For example, one can examine its sensitivity on various common amines and compare with exisiting derivatization methods, explore reaction parameters that could affect the recovery rate of the derivatization, and investigate the reaction kinetics of TsCl.

6.3 Proposed Research Directions

6.3.1 Investigate the Autoxidation of Polyethylene Glycols in PCHPs

Glycols are common constituent of numerous PCHP products. Polyethylene glyols belong to the class of polymerized ethylene glycol. They can be found in almost any viscous PCHPs, serving as a solvent, surfactant, emulsifier, or viscous-controlling additive. [425] In addition, polyethylene glycols are also the backbone of the manufacture of PCHP additives which are used in various fragrance products.[426] With the increasing use of PCHPs in different indoor scenarios, human exposure to oxidation products from polyethylene glycols is inevitable. Thus, studying polyethylene glycols and their degradation products is crucial to comprehensively understand their impact on IAQ, occupational health, and consumer health.

According to discoveries made in this thesis, I posit that polyethylene glycols may also undergo autoxidation. In addition, since chain lengths of these compounds are highly diverse, their oxidation products could be much more complicated than short glycols mentioned in this thesis.

6.3.2 Determination of Amines in Environmental Samples

Environmental samples consist of a significant portion of amines, in the forms of amino acids, alkyl amines, and aniline. These compounds are widely produced from biological activities and the degradation of large nitrogenous species.[427] The detection of amines requires a highly selective derivatization method, since many environmental amines are in trace concentration. As a result, TsCl derivatization can be applied to environmental samples to quantify trace amount of amines from a complex matrix.

Amines in Animal Husbandry Facilities

Animal husbandry facilities are tremendously rich in biogenic emissions. Chapter 5 of this present thesis has provided a preliminary evaluation of amines in a commercial poultry farm. However, this study has a rather limited representation. Due to restrictions in experimental design, only one poultry farm has been investigated. In addition, additional organic nitrogenous species could exist in the farm in addition to the compounds reported in Chapter 5.

Future studies may utilize the established PILS sample collection workflow explained in Chapters 2 and 5 and adapt the TsCl dervatization strategy with corresponding optimization. Hence, an overview of amino species in multiple poultry farms can be elucidated, such that a more representative implication can be made. In addition, this technique can be applied to other animal husbandry facilities, such as swine and diary facilities, to assess the exposure of nitrogenous pollutants by livestock and farmers.

Amines in Biomass Burning

Along with the climate change, biomass burning has received increasing attention from the research field. Wildfires have become significant during the summer in North America. Highly functionalized nitrogen-containing air pollutants have been reported to be emitted from the combustion of boreal forests.[428] It is important to determine these pollutants, as they can be inhalable when emitted. In addition, their aging in the atmosphere could lead to the formation of reactive nitrogen species[429] and oxygenated amines.

With the help of TsCl derivatization, amino combustion products from biomass burning can be selectively determined. In laboratory-based future studies, one can combust different types of biofuel to obtain an amino footprint for each type of fuels and to discover any potential tracer compounds. For field-based studies, the PILS aerosol collection technique can be applied to collect time-resolved wildfire samples, followed by the in-lab derivatization. As a result, potential wildfire amino tracers can be determined, and thus the emission source is determined.

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Appendix A: Supporting Information For: Impact of artificial fog on indoor air quality – a potential exposure pathway of formaldehyde and other carbonyls

A.1 Office Experimental Details

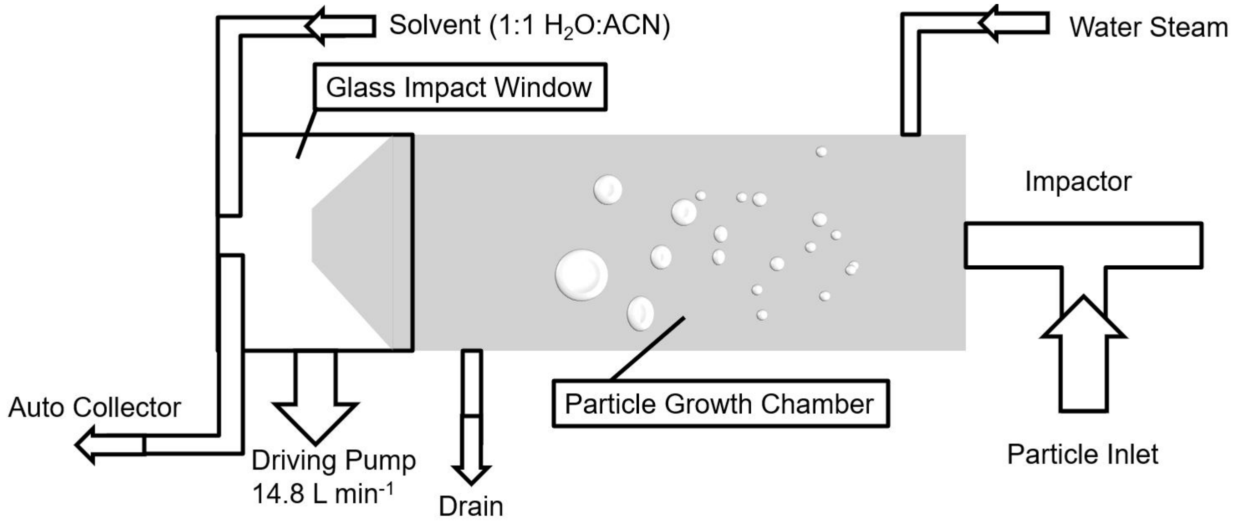
The volume of the office is 38 m^3, it is equipped with standard office furniture. A window in the office (constantly closed) allows ambient light into the office. The office is adjacent to an outer office, but the door was closed during experiments.

A.1.1 Air Exchange Rate Measurement

Injection of CO_2 was used for air exchange rate measurement. The injection of CO_2 was conducted by placing a pile of dry ice in front of a fan for five minutes. Then the dry ice was removed and the concentration of CO_2 in the room was continuously monitored by a CO_2 sensor (SCD30, Adafruit) until it returned to the initial concentration.

A.1.2 Operation of PILS

PILS collection was started 15 minutes before the fog spray for background collection. During the operation, an external pump will drag air samples through the inlet of the PILS at a rate of 14.8 L/min. An optional gas denuder that removes gas-phase species



* Auto collector, solvent, drain, water steam channels are driven by a same peristaltic pump

Figure A.1: Operation principle of PILS, Inspired by R.J. Weber et al. [117]

can be mounted at this point; air samples are then mixed with water steam in the particle growth chamber so that aerosol particles grow to a larger size to be collected on a quartz impactor window. A multi-channel peristaltic pump carries the solvent to the impactor window and transfers the final solution to the auto collector, which injects the solution into HPLC vials at a rate of 3 minutes per vial. The resulting volume of the collected solution is 1.2 mL. Figure A.1 below shows the operation of PILS, reproduced based on R.J Weber et. al.[117]

A.2 MS Operation

Samples collected from the PILS were sent to MS for chemical analysis. Flow-injection-ESI (+) mode was used for non-derived glycol samples; ESI (-) mode was used for derived carbonyl samples. Separation of derived samples was carried out by an Agilent 1100 series LC system. Details of MS operation and LC separation can be found in Table A.1 and Table A.2

Table A.1: Offline flow-injection MS and LC-MS instrument parameters

	Flow-Injection for Glycols	**LC-MS for derived carbonyls**
Liquid Chromatograph		
Injection volume	10μL	2μL
Solvent A	0.1% (v/v) Formic Acid in MQ Water	0.1% (v/v) Formic Acid in MQ Water
Solvent B	0.1% Formic Acid in ACN	0.1% Formic Acid in ACN
Pump Rate	5 μL/min	400 μL/min
Gradient	Isocratic (A: B = 68: 32)	See Table A2
Column	No Column	Luna Omega C18 column 150 mm x 2.1 mm x 3 μm
Mass Spectrometer		
Acquisition Time	7 min	30 min
Scanning Mode	Positive	Negative
Spray Voltage	3.5 kV	-3.5 kV
Sheath Gas Flow Rate	40 a.u.	40 a.u.
Aux Gas Flow Rate	8 a.u.	8 a.u.
Sweep Gas Flow Rate	0 a.u.	0 a.u.
Capillary Temp	150 ℃	150 ℃
Capillary Voltage	35 V	-35 V
Tube Lens	65 V	-51.88 V
Collision Gas (MSMS)	n.a.	Helium
Normalized Collison Energy	n.a.	22 27 a.u.

Table A.2: LC Gradient for derived carbonyls

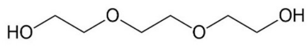
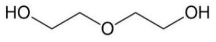
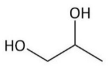
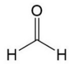
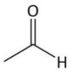
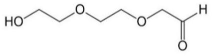
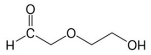
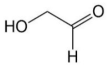
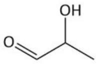
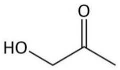
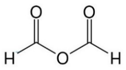
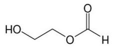
Time /min	**Flowrate μL/min**	**Solvent A**	**Solvent B**
0	400	68	32
10	400	68	32
15	400	54	46
20	400	54	46
25	400	40	60
26	400	40	60

A.3 Accelerated Aerosol Evaporation in SEMS

SEMS relies on a recirculating sheath flow to minimize the temperature rise during its operation. According to the manufacturer's instrument manual, the chemical composition of the sample flow and the sheath flow will eventually become the same. However, the equilibration of sheath flow and sample flow does not occur immediately. Shortly after the fog injection to the office, the vapor pressure of fog juice constituents (e.g., TEG) is expected to be temporarily higher than that in the sheath flow of SEMS. Exposure to the sheath flow, which is "cleaner" than the room air, may accelerate the evaporation of sample aerosol, especially when the sample aerosol is highly volatile, such as fog aerosol.

A bimodal particle size profile was collected by both the SEMS and the OPC after the fog injection (Figure A.2A). The SEMS profile has a similar bimodal distribution to the OPC profile; however, it is shifted to a smaller diameter. To verify our hypothesis that SEMS causes evaporation of fog aerosol, another experiment was carried out with the SEMS and the OPC, but this time an ultrasonic humidifier was used as the source of particles (Figure A.2B). Humidifier particles are considered non-volatile particles because they are mainly made of mineral salts.[40] The large shift of particle diameter between the SEMS and the OPC profile is less significant, with the peaks shifted by roughly 30 nm. This observation supports our hypotheses that

Table A.3: Compounds of Interest

	CAS number	**Molecular Weight**	**Structure**
Triethylene Glycol (TEG)	112-27-6	150.17	
Diethylene Glycol (DEG)	111-46-6	106.12	
Propylene Glycol (PG)	57-55-6	76.09	
Formaldehyde	50-00-0	30.03	
Acetaldehyde	75-07-0	44.05	
[2-(2-Hydroxyethoxy) ethoxy] acetaldehyde (TEG-Aldehyde)	108306-81-6	148.16	
2-(2-Hydroxyethoxy) acetaldehyde (DEG-Aldehyde)	17976-70-4	104.1	
Glycolaldehyde	141-46-8	60.05	
Lactaldehyde (PG-Aldehyde)	598-35-6	74.08	
Hydroxyacetone(PG-Ketone)	116-09-6	74.08	
Formic Anhydride	1558-67-4	74.04	
Glycol Formate	628-35-3	90.08	

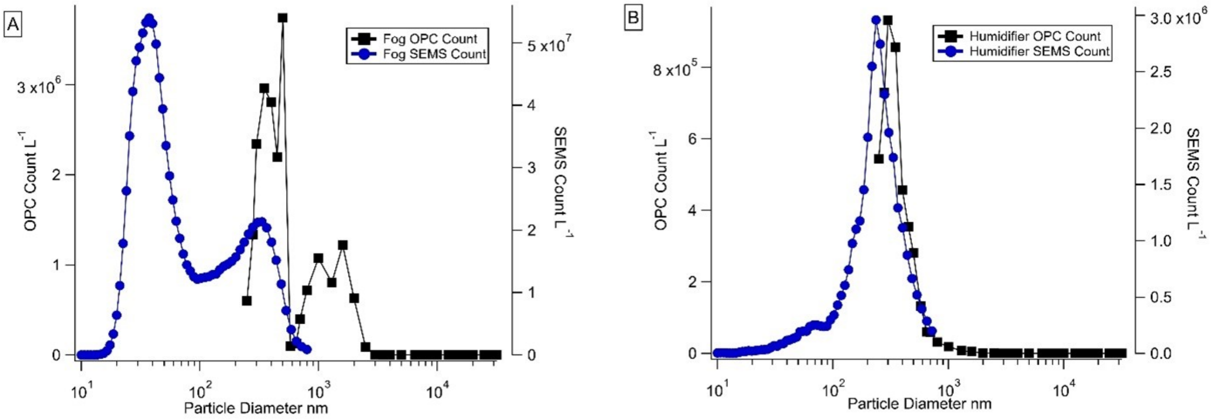


Figure A.2: Particle size distribution at the most concentrated time measured by the SEMS and the OPC; A) Data from fog aerosols; B) Data from humidifier aerosols.

highly volatile fog aerosol has evaporated in the sheath flow of SEMS, giving rise to a difference between the observed number concentrations by OPC and SEMS.

A.4 Gas-Phase Chemical Collection by PILS

A separate experiment was performed with a PILS gas denuder mounted at the inlet. When comparing the EIC of the two experiments, the no-denuder group has DEG aldehyde, PG aldehyde, and PG ketone peaks present, while the denuder group did not detect these compounds. This means most of such compounds are removed by the gas denuder, they are more likely to stay in the gas phase. When comparing the PILS time profile, no denuder group always has a stronger signal at any given time. (Figure A.3) TEG signal of no denuder group even showed a tailing which is significantly higher than the background, implicating the presence of gas-phase TEG.

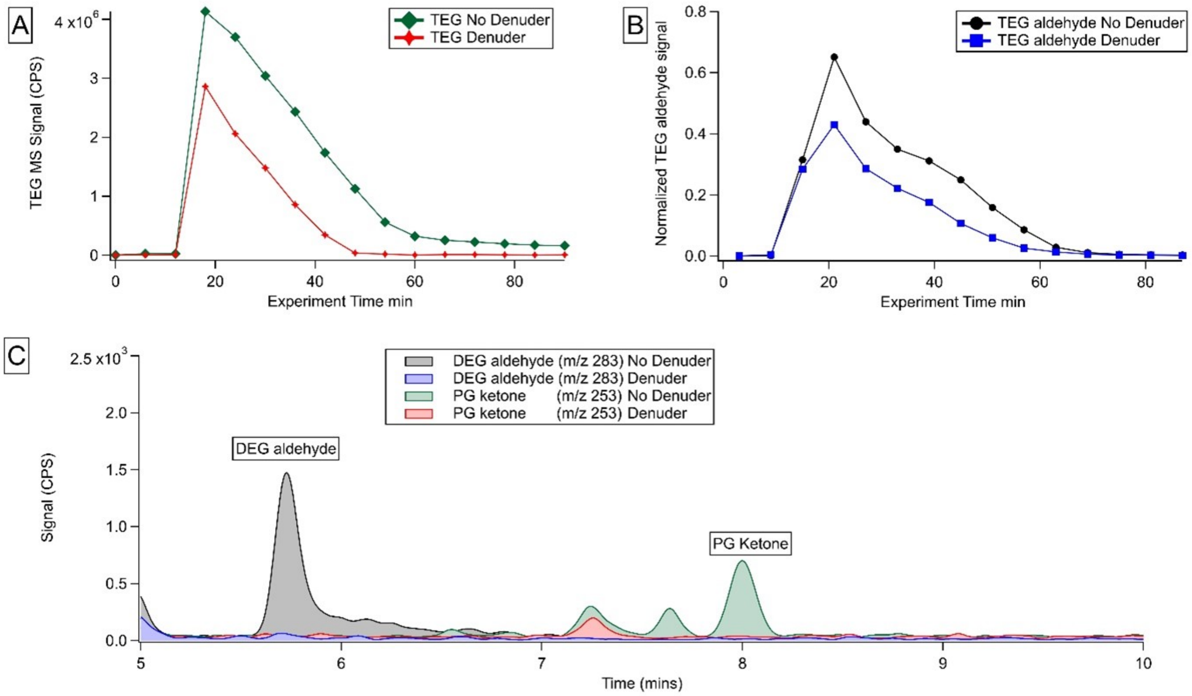


Figure A.3: Comparison of samples collected with and without denuder. A) time profile of TEG; B) Time profile of TEG aldehyde, and C) EICs of detected species.

A.5 Carbonyl Species Detected from Fog Juice and Fog Sample

This section contains the peak assignment in the mass spectrum from different samples (Table A.4) and the MS2 fragmentation of carbonyls, which serves as the proof of identities (Figure A.4).

A.6 Formaldehyde Standard Addition

Formaldehyde is one of the most common indoor air pollutants and is known to be very carcinogenic to humans. Many of the carbonyls, as well as their DNPH-hydrazones, were not commercially available. Our quantification was specifically targeted at formaldehyde, the most concerning compound on the list. We performed the standard addition method to quantify the formaldehyde in the fog juice, as this method does not require external calibration and will overcome any potential ma-

Table A.4: Chemical Detected in Fog Sample and Fog Juice by ESI-MS

#	Compound	Mode	m/z	Fog Sample	Old Fog Juice	New Fog Juice
1	Triethylene Glycol	ESI+	151	√	√	√
2	Diethylene Glycol	ESI+	107	√	√	√
3	Propylene Glycola	ESI+	76	n.a.	n.a.	n.a.
Compounds below are DNPH-Hydrazones, analyzed by the LC-MS						
4	Formaldehyde (Volatile)	ESI-	209	n.a.	√	Below LOD
5	Acetaldehyde (Volatile)	ESI-	223	n.a.	√	√
6	TEG-aldehyde	ESI-	327	√	√	√
7	DEG-aldehyde	ESI-	283	√	√	√
8	Glycolaldehyde	ESI-	239	Below LOD	√	√
9	PG-aldehyde	ESI-	253	√	√	√
10	PG-ketone	ESI-	253	√	√	√
11	Formic Anhydride	ESI-	253	n.a.	√	√
12	Glycol Formate	ESI-	269	√	Below LOD	n.a.

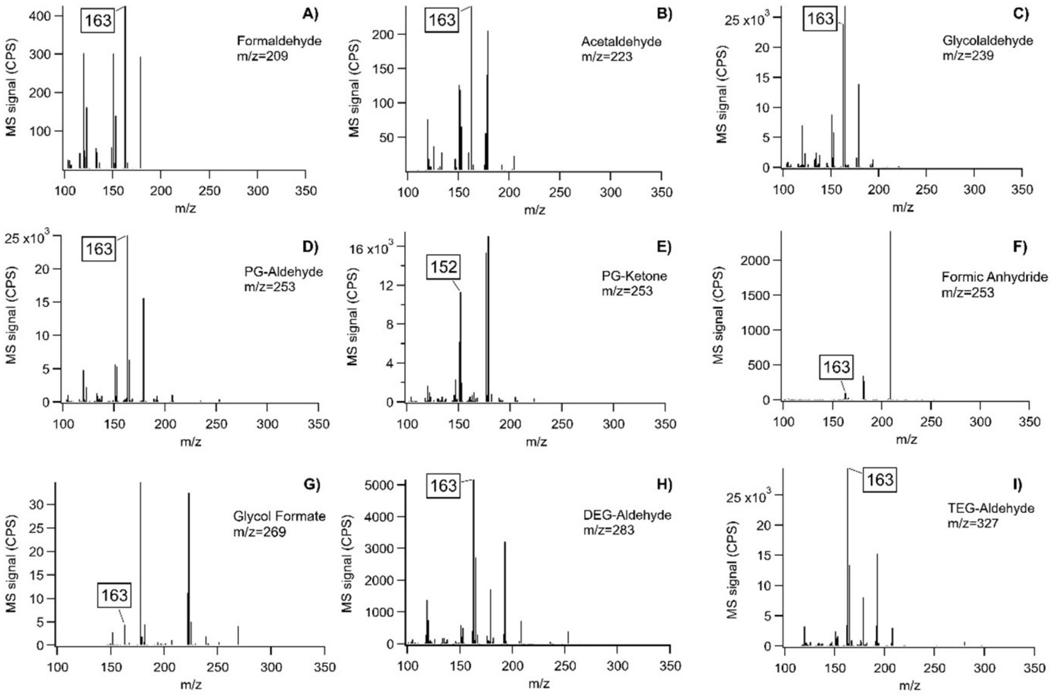


Figure A.4: MS2 fragmentation pattern of carbonyl-DNPH hydrazones detected in fog juice.

trix effects. In brief, we prepared a set of derivatized fog juice with known dilution and spiked it with a gradient of commercial formaldehyde-DNPH standards. The result of formaldehyde standard addition is shown in Figure A.5. The extracted ion chromatogram (EIC) of formaldehyde-DNPH hydrazone grows as the commercial standard is spiked into the solution, which confirms the identity of the species. According to the standard addition curve and chromatogram peak growth displayed in Figure A.5, we calculated 9.75 ± 0.01 mM of formaldehyde in the fog juice.

A.7 Box Model of Formaldehyde

For a simple one-box model illustrated in Figure S6, the mass balance of formaldehyde can be established by:

$$dC_{room}/dt = Q_{in}/V + P_{total}/V - k_{air} \times C_{room} - k_{loss} \times C_{room} \tag{A.1}$$

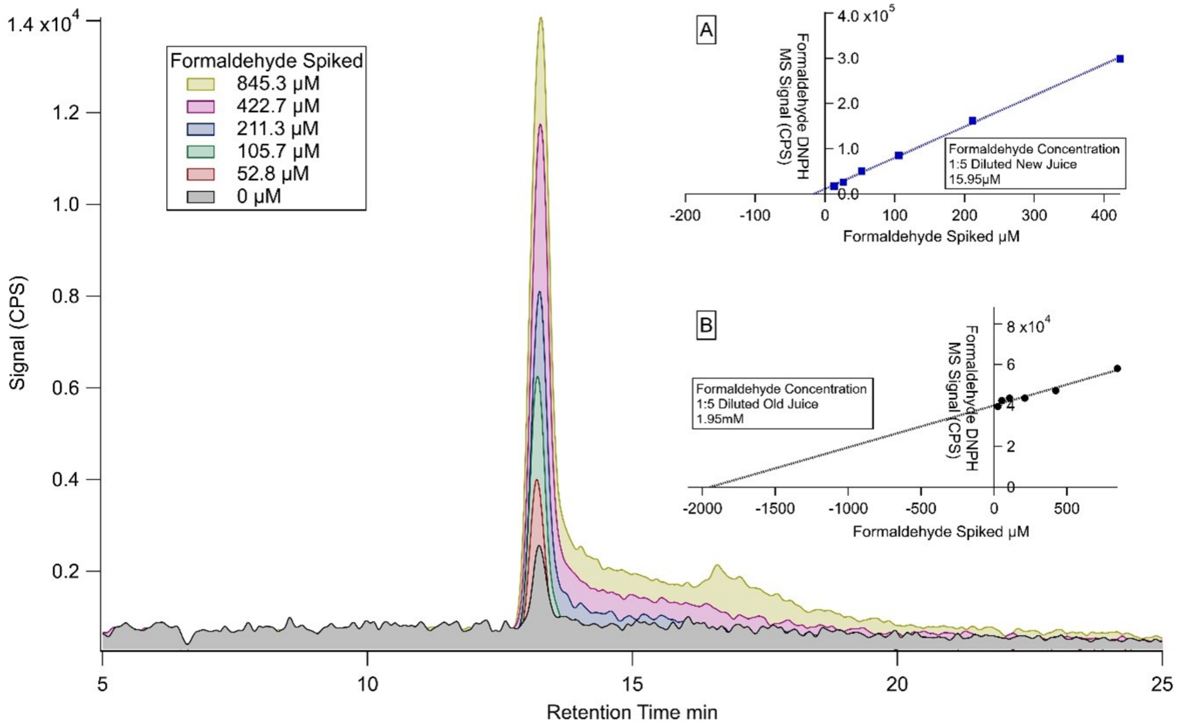


Figure A.5: Growth of formaldehyde peak in the fog juice during the standard addition. The main graph is the EICs of the growing formaldehyde-DNPH peak during a standard addition to the new fog juice; A) New fog juice standard addition curve, $R^2 = 0.999$; B) Old fog juice standard addition curve, $R^2 = 0.96$

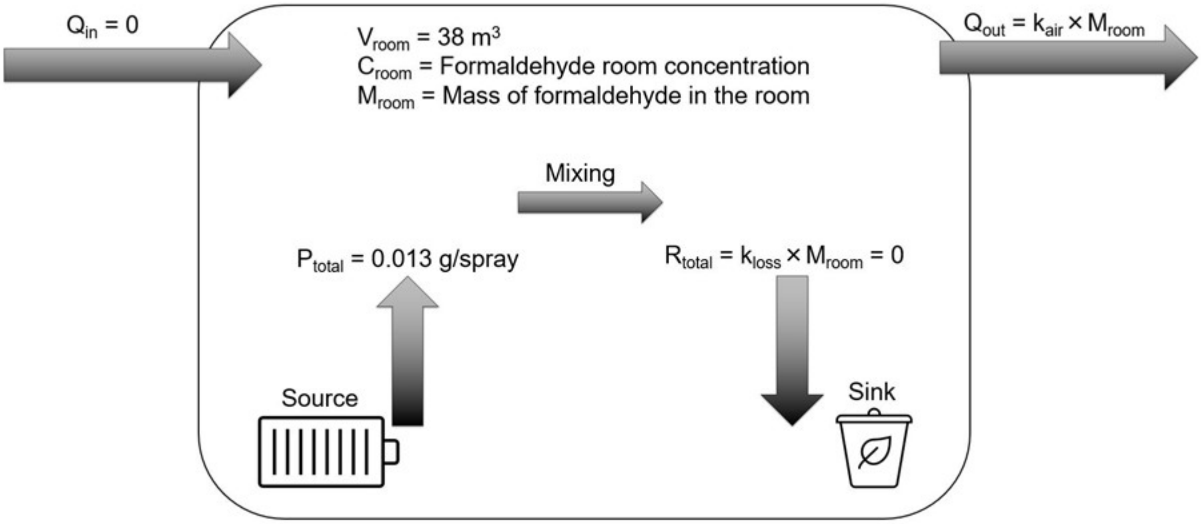


Figure A.6: One-box model of formaldehyde concentration in the experimental office.

Where C_{room} is the concentration of formaldehyde in the room, Q_{in} is the flux of formaldehyde into the room, V is the volume of the room, Ptotal is the production rate (fog spray) of formaldehyde per hour, k_{air} is the air exchange rate, k_{loss} is the loss rate of formaldehyde. Given that there are no external sources of formaldehyde outside of the room, and reactive loss and deposition of formaldehyde are assumed to be negligible, $Q_{in} = 0$, $k_{loss} = 0$.

The scenarios considered in our simulation are summarized in Table A.5, where V_{spray} is the volume of fog juice consumed by each fog spray, $C_{Formaldehyde}$ is the concentration of formaldehyde in the fog juice. We have considered two scenarios. The first scenario, we refer to as the Single Room scenario, considers our experimental office with the continuous use of a fog machine. The second scenario, referred to as the Real-life case, considers a more realistic indoor volume with the minimum ventilation rate recommended by in the household by the US EPA.

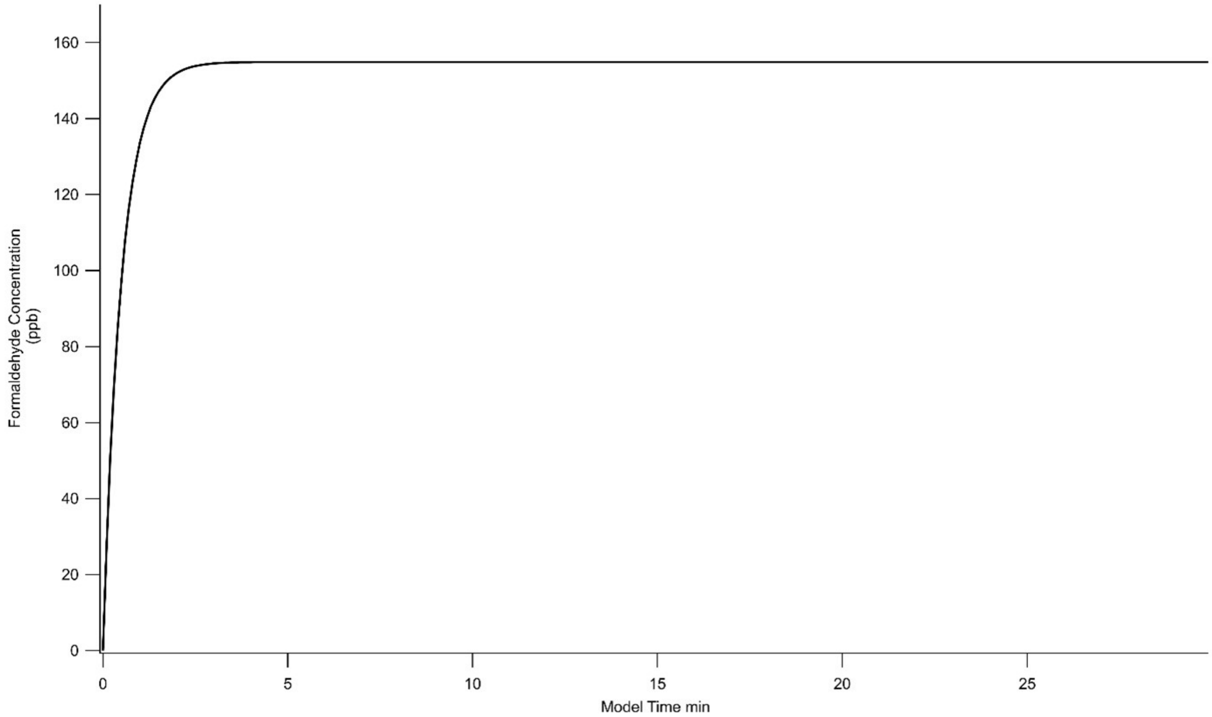


Figure A.7: Simulated formaldehyde concentration in the experimental office by a one-box model.

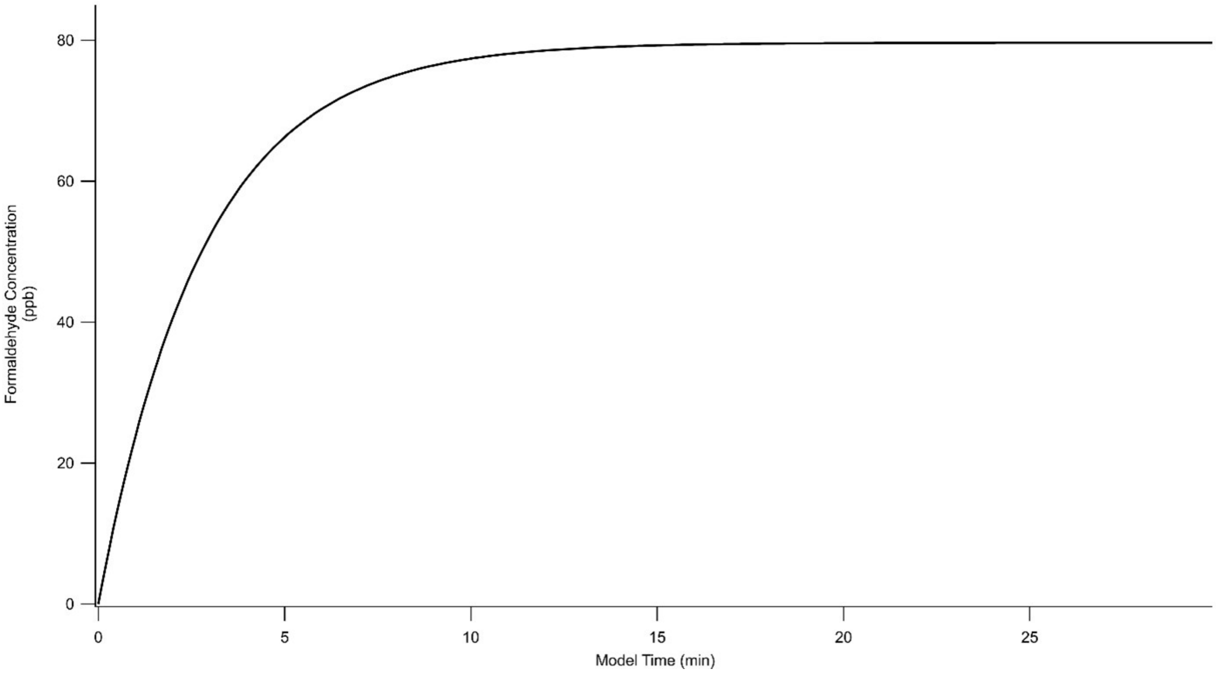


Figure A.8: The concentration of formaldehyde in a real-life application of a fog machine.

Table A.5: Simulated scenarios of artificial fog application

Model Inputs	**Single room**	**Real-life (Simulated)**
${}^{a}Q_{in}$	0	0
Q_{out}	Mass of formaldehyde flows out	Mass of formaldehyde flows out
${}^{b}k_{air}$	1.8 h^{-1}	0.35 h^{-1}
${}^{c}k_{loss}$	0	0
V_{room}	38 m^3	380
M_{room}	Mass of formaldehyde in the room	Mass of formaldehyde in the room
C_{room}	Formaldehyde room concentration	Formaldehyde room concentration
${}^{d}V_{spray}$	4.44 ml	4.44 ml
${}^{e}C_{Formaldehyde}$	9.75 mM	9.75 mM
${}^{f}P_{total}$	0.013g	0.013g
Spray Frequency	10 sprays/hr	10 sprays/hr
Temperature	25℃	25℃
Pressure	1 atm	1 atm

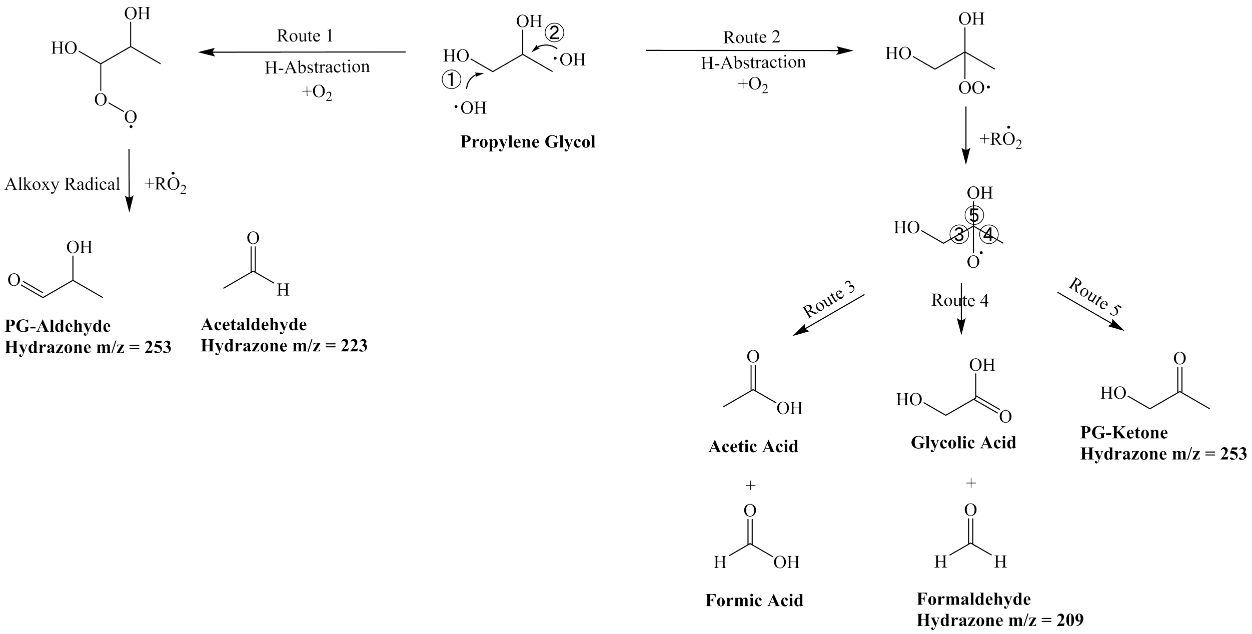


Figure A.9: Proposed oxidative decomposition mechanism of PG.

A.8 Proposed Full Mechanisms

The mechanisms shown on Figures A.9 and A.10 are to best highlight species detected in our study. Other possible products during the oxidation, like organic acids or esters, are not shown here because they are not DNPH-active due to a lack of activated C=O group.

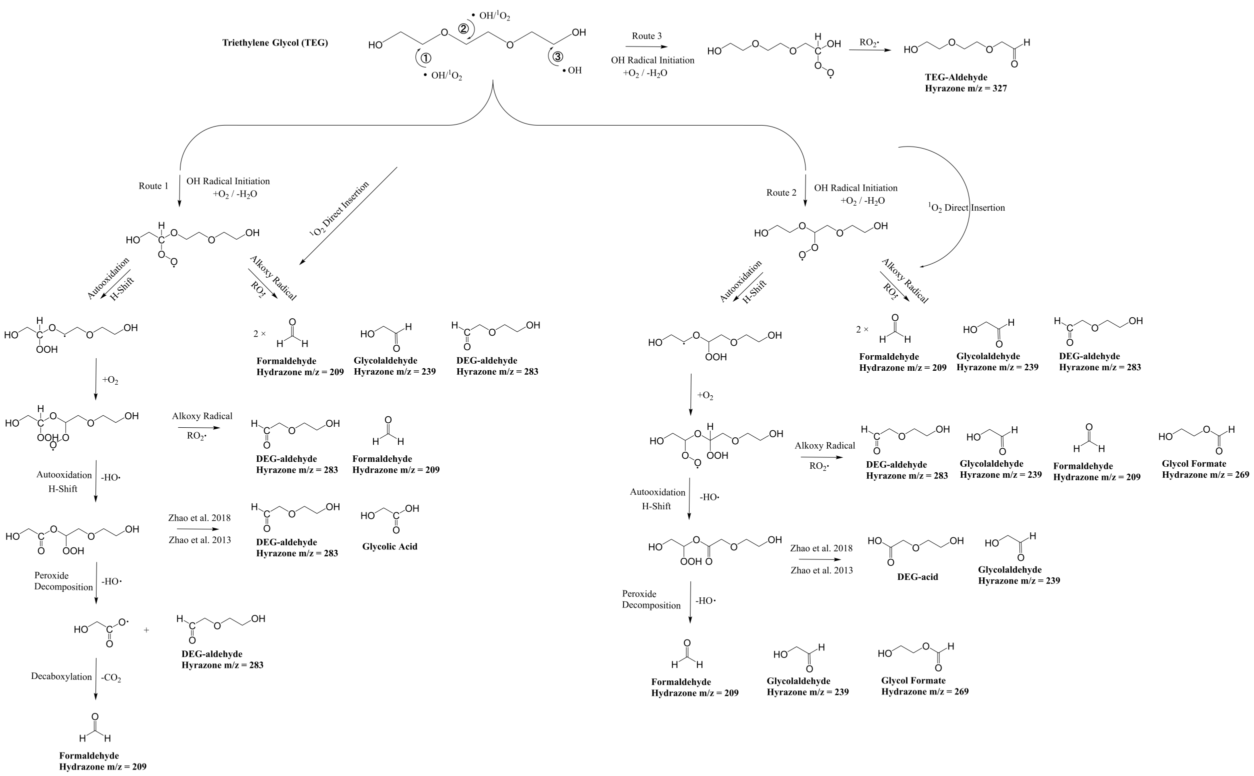


Figure A.10: Proposed Oxidative decomposition mechanism of TEG.[126]

Appendix B: Supporting Information For: Aqueous Autoxidation of Common Glycols in the Indoor Environment

B.1 Experiment Details

B.1.1 Sample Preparation

Experiment 1: Five different pure glycols were separated into two groups. The first group contains air-exposed samples, where 10 ml of the five glycols were added into 20 ml clear glass vials. These samples were exposed to room air all the time without vial caps while avoiding direct sunlight exposure. The second group was the same set of glycols, stored under the same condition as the first group, but with caps closed and sealed with parafilm.

Experiment 2: Three vials containing 10 ml of 50% (v/v) TEG were prepared by mixing 5 ml of water and 5 ml of TEG. The sealed 50% TEG was prepared in the same way. Triplicate 50% TEG samples were stored under room conditions without vial caps, and the sealed 50% TEG samples were capped with parafilm sealing. Masses of 50% TEG triplicate were monitored by an analytical balance, to track the water evaporation from the mixture.

Experiment 3: Four vials containing 10 ml of TEGs with varying water mixing ratios were prepared. Specifically, 1 ml, 3 ml, 5 ml, and 7 ml of water were added to different volumes of TEG to achieve a total volume of 10 ml. These four samples

[262]

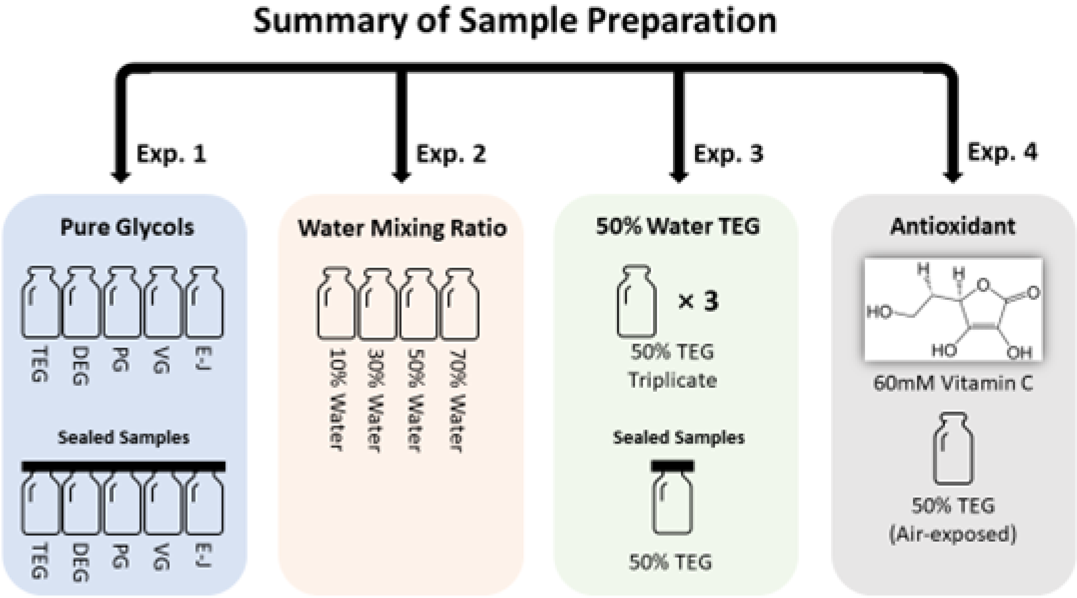


Figure B.1: Summary of samples involved in this study; four sets of experiments were performed.

represent varying volumetric water mixing ratios of 10% to 70%. All samples were stored under room conditions without vial caps, their masses were monitored weekly to track water evaporation.

Experiment 4: 106 mg of L-ascorbic acid (Vitamin C) solid was added into 10 ml of 50% TEG mixture, resulting in a 60 mM final concentration of Vitamin C. This sample was stored under room conditions without the vial cap, and its mass was also recorded weekly.

B.2 Instrumental Settings

Detailed LC-MS settings are shown in Tables B.1 and B.2.

B.3 Iodometry-UV-Vis Peroxide Quantitation

[262]

Table B.1: LC-MS instrument parameters

Table B1. LC-MS instrument parameters	
Injection volume	2 μL
Solvent A	0.1% (v/v) Formic Acid in MQ Water
Solvent B	0.1% Formic Acid in ACN
Flow Rate	400 μL/min
Gradient	See Table B2
Column	Luna Omega C18 column 150 mm x 2.1 mm x 3 μm
Acquisition Time	20 min
Scanning Mode	Negative
Spray Voltage	-3.5 kV
Sheath Gas Flow Rate	40 a.u.
Aux Gas Flow Rate	8 a.u.
Sweep Gas Flow Rate	0 a.u.
Capillary Temp	150℃
Capillary Voltage	-35 V
Tube Lens	-51.88 V
Electron Multiplier 1 Voltage	-783.44 V
Electron Multiplier 2 Voltage	-853.44 V
Collision Gas (MSMS)	Helium
Normalized Collison Energy	22 27 a.u.

Table B.2: LC gradient for derived carbonyls

Table B2. LC gradient for derived carbonyls			
Time /min	Flowrate μL/min	Solvent A	Solvent B
0	400	68	32
5	400	68	32
10	400	55	45
15	400	30	70
18	400	10	90
20	400	10	90

B.3.1 Solutions Involved

1 M CH_3COOH solution: prepared in MilliQ water and kept in the refrigerator for storage. 1.5 M KI solution: prepared in MilliQ water. KI solution is prepared fresh every time before the experiment.

H_2O_2 solution: Served as calibration standards, ranging from 0 to 50 μM. It is prepared from the concentrated 30% H2O2 stock solution and serial dilution. Prepared fresh before use.

Sample for analysis: One UV-Vis sample is consisting of 200 μL KI solution, 150 μL CH_3COOH solution, and corresponding volume glycol solution, and filled up with MQ water to a total volume of 5 ml. The volume of glycol was varying to reach the desired dilution (1:400 for TEG, 1:10 for PG, VG, and DEG). For instance, the TEG sample for UV-Vis contains KI solution, CH_3COOH solution, 11.6 μL of TEG, and 4.6 ml of water. UV-Vis samples were allowed to react under room conditions for one hour before the analysis. Figure B.2 justified the reaction completeness.

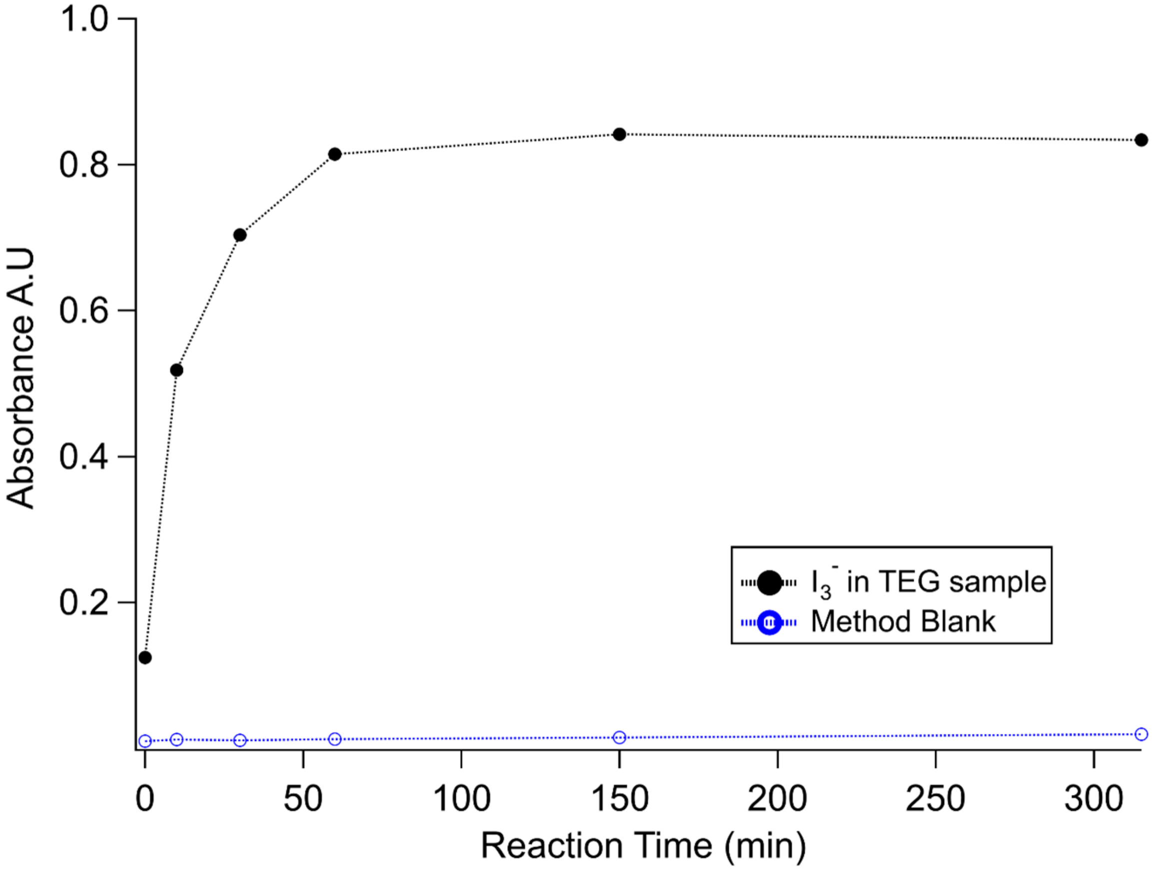


Figure B.2: The absorbance of TEG sample in iodometry over time. We consider 60 min as the reaction completion time, due to the longer reaction time can be biased by the reaction between ambient oxygen and iodide ions.

B.3.2 Instrumentation

The Agilent 8453 UV/VIS spectrophotometer was employed to obtain the absorbance value. The spectrum is collected from λ=200 to 1200 nm in a 1 cm path length semi-micro quartz cuvette from Fischer. A standard solution of 25 mM hydrogen peroxide was measured on every analytical day to prevent any instrumental variation.

B.3.3 Calibration of Peroxide

Two calibration curves were constructed at the beginning and the end of the experiment, shown in Figures B.3 and B.4 below, this is to evaluate the instrumental variation throughout the experiment.

B.4 Quanitfication of Carbonyls

Detailed carbonyl concentrations are illustrated in Figure B.5.

B.5 Quality Control

We identified two major factors that can potentially induce bias in our results. The first one is the loss of water, causing increased concentrations of chemicals. We monitored the loss of water from all water gradients and fitted a first-order decay of the remaining solution, shown in Figure B.6.

We also observed a varying recovery rate of formaldehyde in pure glycol and 50% glycol samples, despite standard addition being applied. Thus, we assumed a linear fitment of recovery rate from 0% to 50% of water, and extrapolated to 70%, shown in Figure B.7:

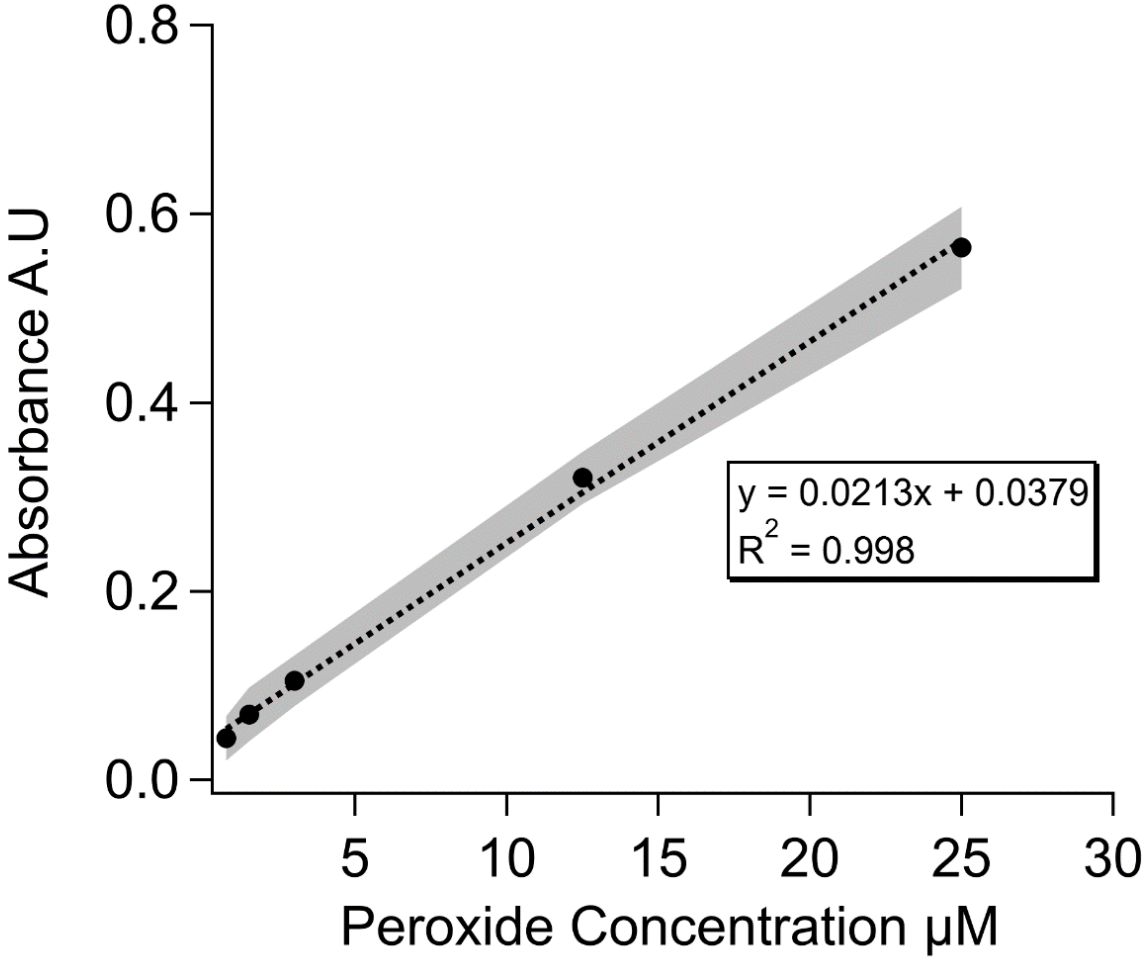


Figure B.3: Iodometry-UV-Vis calibration curve at the beginning of the experiment, done in triplicates. Plotted is the average absorbance of three curves against concentration. The shaded area is the standard deviation of the triplicates.

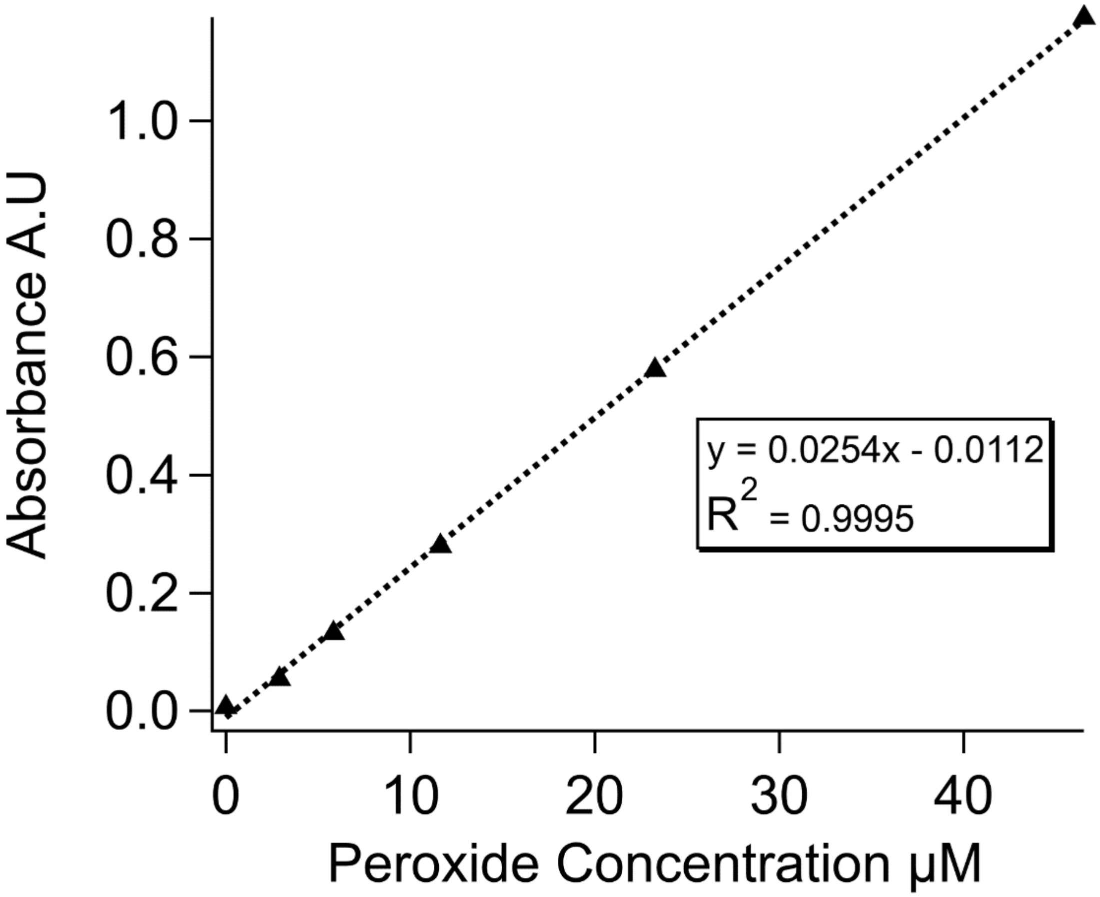


Figure B.4: Iodometry-UV-Vis calibration curve at the end of the experiment. This calibration has only been done once.

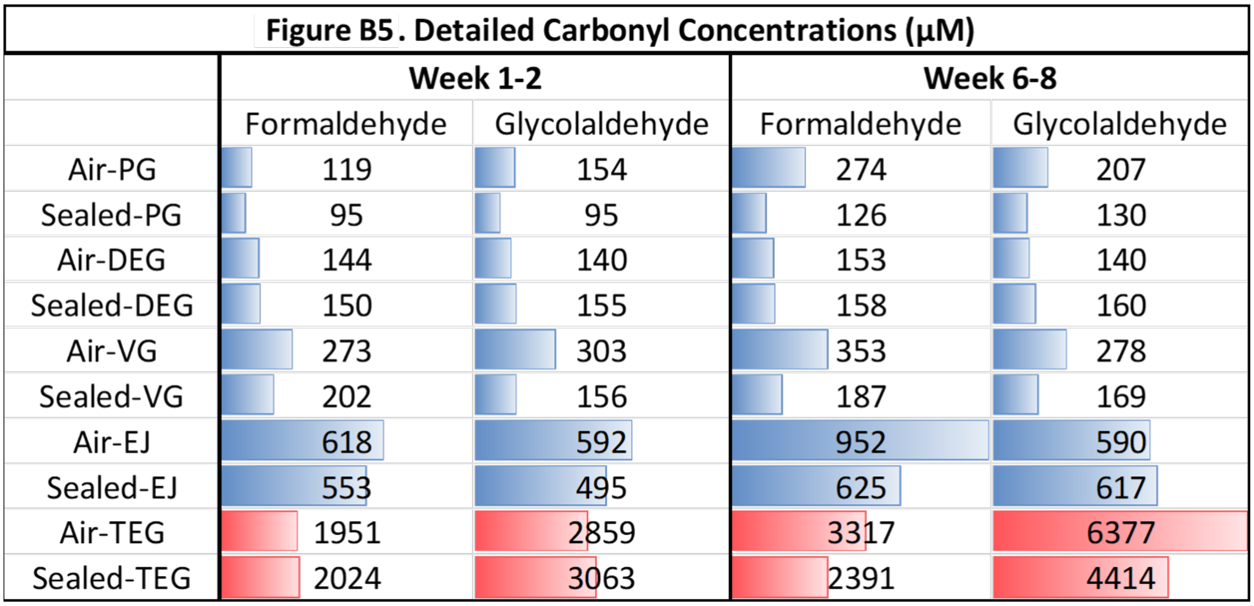


Figure B5. Detailed Carbonyl Concentrations (µM)

	Week 1-2		Week 6-8	
	Formaldehyde	Glycolaldehyde	Formaldehyde	Glycolaldehyde
Air-PG	119	154	274	207
Sealed-PG	95	95	126	130
Air-DEG	144	140	153	140
Sealed-DEG	150	155	158	160
Air-VG	273	303	353	278
Sealed-VG	202	156	187	169
Air-EJ	618	592	952	590
Sealed-EJ	553	495	625	617
Air-TEG	1951	2859	3317	6377
Sealed-TEG	2024	3063	2391	4414

Figure B.5: Detailed carbonyl concentrations.

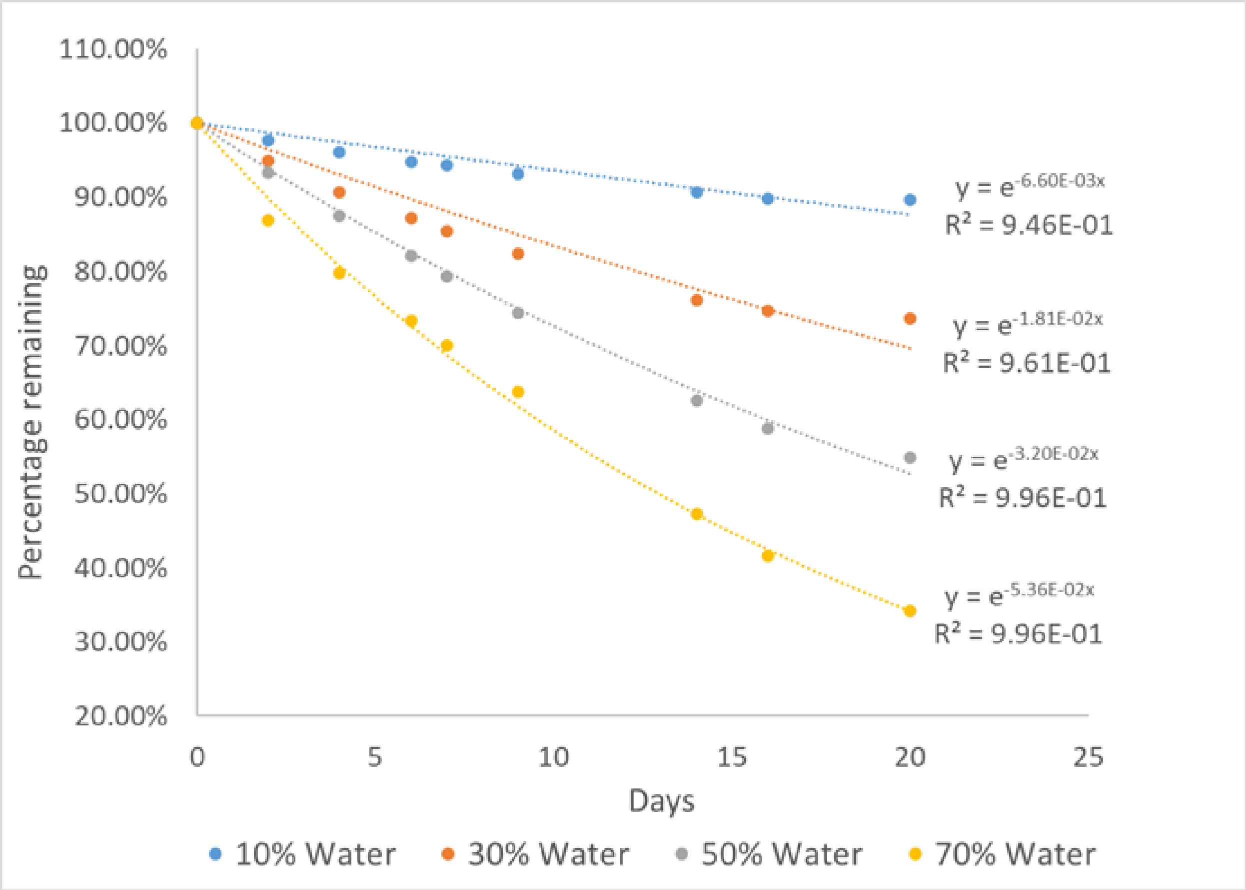


Figure B.6: First-order fitment of remaining glycol solution time during constant water evaporation

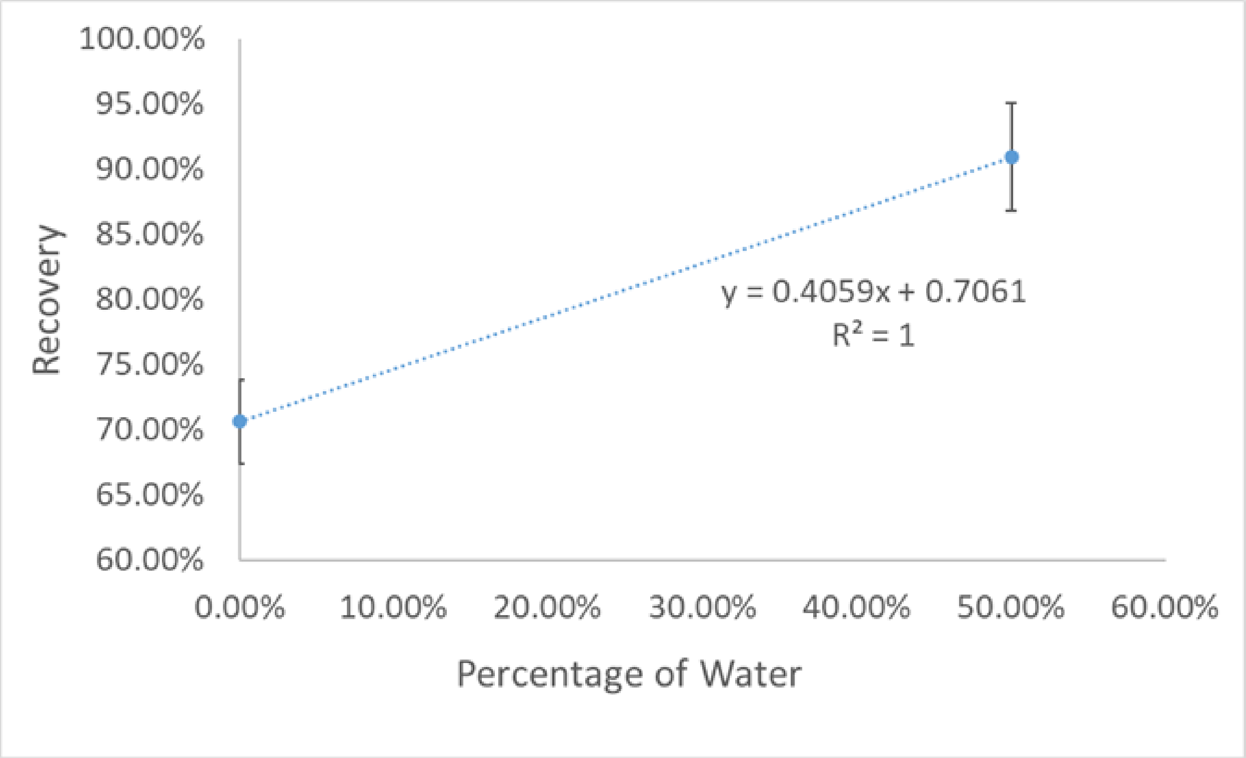


Figure B.7: Assumed linear recovery rate in different mixing ratios of water. The error bar represents the standard deviation of recovery rates obtained from four replicates.

Appendix C: Chemical Characterization of Nicotine Oxidation Byproducts in E-cigarette Juice using p-Toluenesulfonyl Chloride

C.1 Experimental Layout

This section contains a brief overview of the experiment, shown in Figure C.1

C.2 LC-MS Settings

This section contains detailed settings of the LC-MS setup (Table C.1) and the LC gradient (Table C.2).

C.3 Identification of TsCl derivatives

The reaction between amines and TsCl includes a neutral loss of the HCl molecule. The mass-to-charge ratio of protonated TsCl derivatives in ESI-positive mode is determined by the following calculation:

$$[M+H]^+ = M_{molecule} + M_{TsCl} - M_{HCl} + 1 \tag{C.1}$$

As mentioned in the main text, by assuming that the only source of sulfur in the sample is TsCl, the signature isotopic peak profile at $[M+2]^+$ of sulfur-containing

Table C.1: LC-MS instrument parameters

Table C1. LC-MS instrument parameters	
Injection volume	1 μL
Solvent A	0.1% (v/v) Formic Acid in MQ Water
Solvent B	0.1% Formic Acid in ACN
Gradient	See Table C2
Column	Luna Omega C18 column 150 mm x 2.1 mm x 3 μm
Acquisition Time	16 min
Scanning Mode	Positive
Spray Voltage	4.5 kV
Sheath Gas Flow Rate	40 a.u.
Aux Gas Flow Rate	8 a.u.
Sweep Gas Flow Rate	0 a.u.
Capillary Temp	275°C
Capillary Voltage	35 V
Tube Lens	90 V

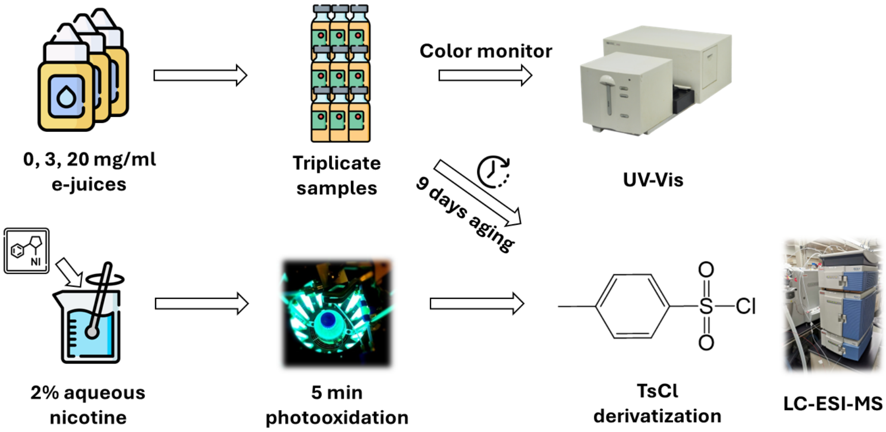


Figure C.1: A brief flowchart of the experimental layout

Table C.2: LC gradient for TsCl derivatives

Table C2. LC gradient for TsCl derivatives

Time /min	Flowrate μL/min	Solvent A	Solvent B
0	380	99	1
2	380	75	25
12	380	75	25
14	380	1	99
16	380	1	99

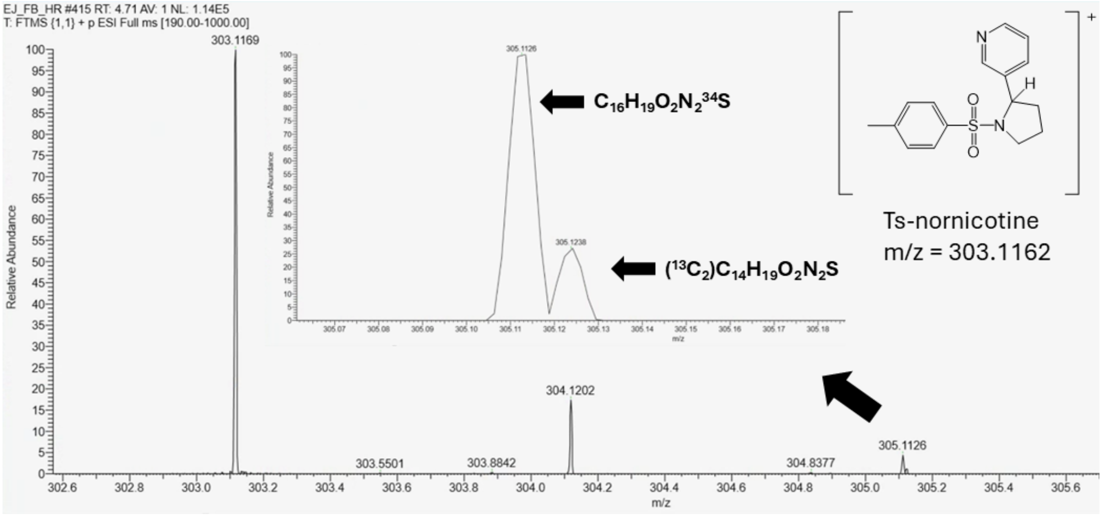


Figure C.2: High-resolution mass spectrum of nornicotine

species can be used to confirm TsCl derivatives. This peak profile is due to the mass difference between ^{34}S and ^{14}C. In detail, the mass of M(^{34}S) is slightly smaller than M(14C) or M($^{13}C_2$), therefore, the $[M+2]^+$ position will have a split peak, with the lighter peak referring to M(^{3}4S). In addition, the peak intensity of the lighter peak is higher because the natural abundance of ^{34}S is higher than ^{14}C. In Figure C.2, we illustrated this identification procedure by showing a TsCl-derived nornicotine under high-resolution MS, with a resolving power greater than 50,000.

C.4 UV-Vis absorption of EJ

This section contains the UV-Vis absorption spectrum of an aged 3 mg/ml freebase EJ.

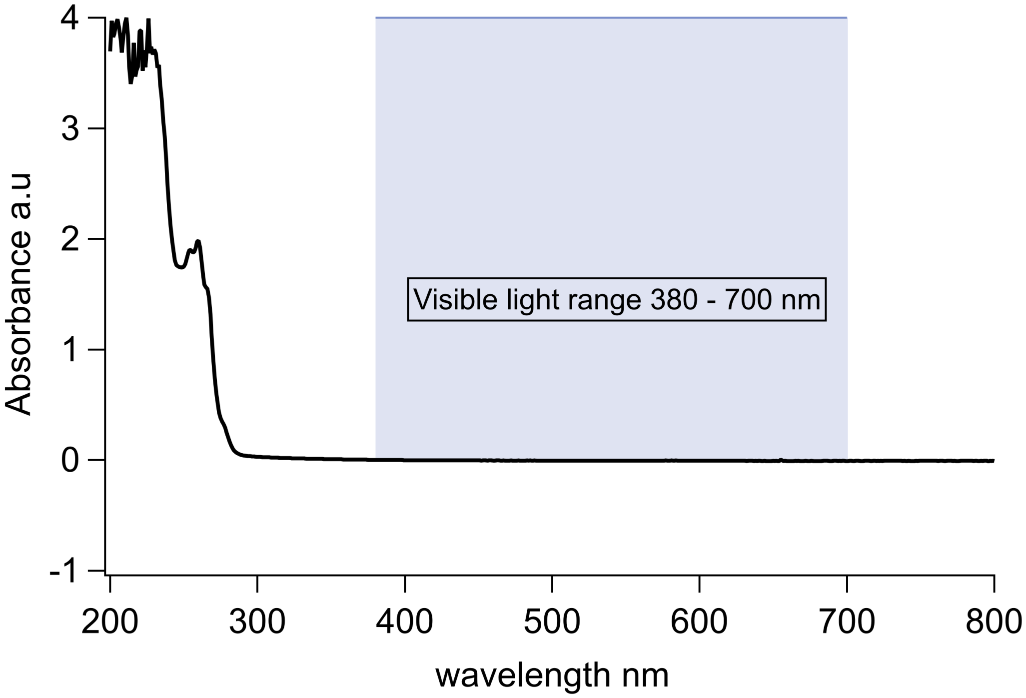


Figure C.3: UV-Vis absorption spectrum of an aged 3 mg/ml freebase EJ

Appendix D: Supplemental Information for Quantification of Nitrogenous Chemicals in Poultry Farms

D.1 Experimental Site

Images of the farm satellite vision (Figure D.1), the farmhouse layout (Figure D.2), and the appearence of a litter bedding sample (Figure D.3) is shown in this section.

D.2 LC-MS Settings

Detailed LC-MS settings and LC gradients are displayed in this section (Tables D.1 and D.2).

D.3 PILS Multi-Instrument Calibration and Quality Control

This calibration was performed in a joint experiment with Dr. Hans Osthoff's group at the University of Calgary. In this experiment, the aim was to compare the collection efficiency of our PILS-LCMS method for NH3 and other ANCs with a dedicated NH_3 analyzer (Model 17i, ThermoFisher). We also discovered the effect of the PILS gas denuder on the collection of chemicals in gas and particle phases. Table D.3 summarizes the results of all calibrations. The standard error of PILS (6.7%) is determined from the relative standard deviation (RSD) of the NH_4HSO_4 measurement,

Figure D.1: Satellite image of the commercial farm.

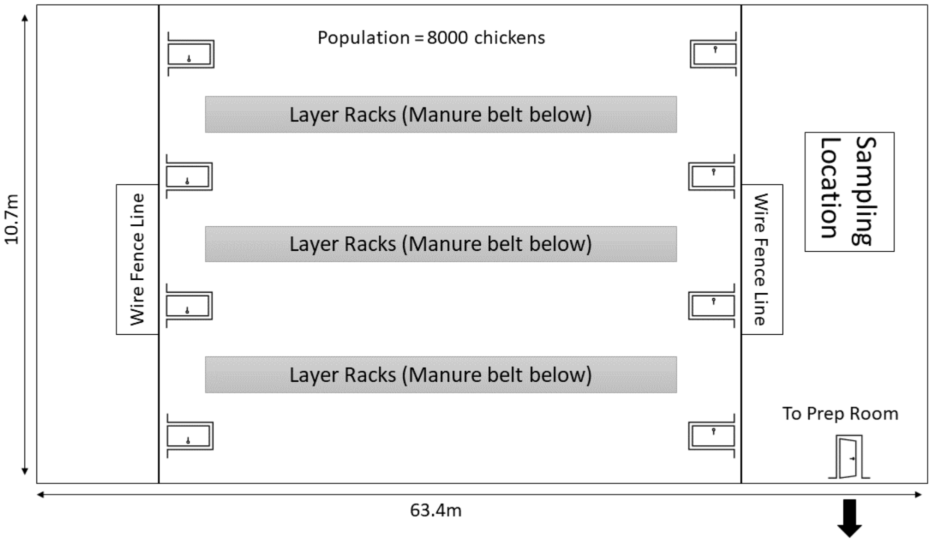


Figure D.2: The sketched layout of the poultry farmhouse.

Figure D.3: Picture of a litter bedding sample.

Table D.1: LC-MS instruments parameters

Table D1. LC-MS instrument parameters	
Injection volume	1 μL
Solvent A	0.1% (v/v) Formic Acid in MQ Water
Solvent B	0.1% Formic Acid in ACN
Gradient	See Table D2
Column	Luna Omega C18 column 150 mm x 2.1 mm x 3 μm
Acquisition Time	16 min
Scanning Mode	Positive
Spray Voltage	3.5 kV
Sheath Gas Flow Rate	40 a.u.
Aux Gas Flow Rate	8 a.u.
Sweep Gas Flow Rate	0 a.u.
Capillary Temp	275°C
Capillary Voltage	35 V
Tube Lens	90 V

Table D.2: LC gradient for TsCl derivatives

Table D2. LC gradient for TsCl derivatives			
Time /min	Flowrate μL/min	Solvent A	Solvent B
0	400	80	20
2	400	80	20
16	400	1	99

with the gas denuder on. This error value serves as the error bar of the chemical quantification in the main text.

Table D.3: Joint calibration results between PILS-LC-MS and ThermoFisher 17i

Table D3. Joint calibration results between PILS-LC-MS and ThermoFisher 17i				
Chemicals	**NH_3 Gas (ppb)**		**NH_4HSO_4 Particles (NH_3 equivalent, ppb)**	
Denuder	**On**	**Off**	**On**	**Off**
PILS	Below LOD	73.0±3.7	59.6±4.2	32.5±8.3
Thermo 17i	118.1±6.2	123.6±1.4	85.8±16.5	28.1±2.3
Efficiency (PILS/17i)	Below LOD	59.10%	71.80%	115.60%

D.3.1 Ammonia Gas

The PILS and the NH_3 analyzer sampled the same NH_3 source in this calibration. NH3 was generated from the photolysis of ammonium carbonate and was diluted with zero air. We separated this calibration into two sessions: one with the PILS gas denuder attached, and another one with the denuder detached. Each session lasted 8 minutes and was equivalent to four LC-MS samples. PILS samples were transferred back to the University of Alberta for TsCl derivatization and MS analysis. We did not obtain any significant NH3 signal when the denuder was attached, while the gas collection efficiency was 59.1% without the denuder (Figure D.4A). Therefore, we confirmed that the gas denuder can effectively remove gaseous species into our particle samples.

Table D.4: List of proposed ANC identities

Table D4. List of proposed ANC identities			
m/z (TsCl Derived)	**Molecular Formula (Without TsCl)**	**Proposed Identity**	**Confirmation with Standard**
200.0739	C_2H_7N	Dimethylamine	√
258.1155	$C_5H_{13}NO$	3-ethoxypropylamine	
306.0653	$C_5H_5N_5O$	Guanine	√
323.0441	$C_5H_4N_4O_3$	Uric Acid	√
325.212	$C_7H_{26}O_2N_2$	Unknown	
341.1349	$C_9H_{18}N_2S$	Cyclohexylethylthiourea	
343.0778	NH_4	*Ammonium	√
344.0196	$C_7H_3O_4N$	Unknown	
397.12503	$C_4H_{12}N_2$	Putrescine	√
411.1402	$C_5H_{14}N_2$	Cadaverine	√
477.0547	$C_{12}H_{10}O_5N_4S$	Unknown	
499.0367	$C_{10}H_4O_3N_{10}S$	Unknown	
631.0639	$C_{11}H_{12}O_{10}N_{10}S$	Unknown	
313.3	$C_4H_6N_4O_3$**	Allantoin	√
316.14	CH_4N_2O **	Urea (unknown cluster)	√

*Double derivatization, with NH_4^+ adduct
**Confirmed by standard resolution MS

D.3.2 Ammonium Particles

A Teflon chamber was used to generate NH_4^+ particles using NH_4HSO_4. This calibration was carried out in the same manner as the gas calibration. A higher PILS-MS response of NH_4^+ (115.6% related to ThermoFisher 17i) was obtained with the gas denuder detached, which is likely caused by existing gaseous NH_3 (Figure D.4B). With the intended PILS setup (with the gas denuder mounted), our measurements show that PILS has collected 71.8% of NH_4^+. According to the onsite scanning mobility particle sizer (SMPS), we note that some particles generated from this experiment are smaller than 30nm. Hence the PILS would have a reduced collection efficiency. Figure D.5 shows the size distribution collected by the SMPS.

D.3.3 Autosampler Queue Time Corrections

Figure D.6 shows the loss of UA peak area over time as the sample queues up on the LC autosampler. The sample used in this experiment is one of the litter extract samples, contains a high concentration of uric acid, and has the same matrix effect as the samples mentioned in the main text.

D.4 Chemical Identification by HR-MS

D.4.1 Derivatization by TsCl

TsCl-derivatization includes a loss of the HCl molecule. Therefore, the mass-to-charge ratio of a derived compound in ESI-positive mode can be calculated by the following equations:

$$[\text{M+H}]^+ = M_{molecule} + M_{TsCl} - M_{HCl} + 1$$

(D.1)

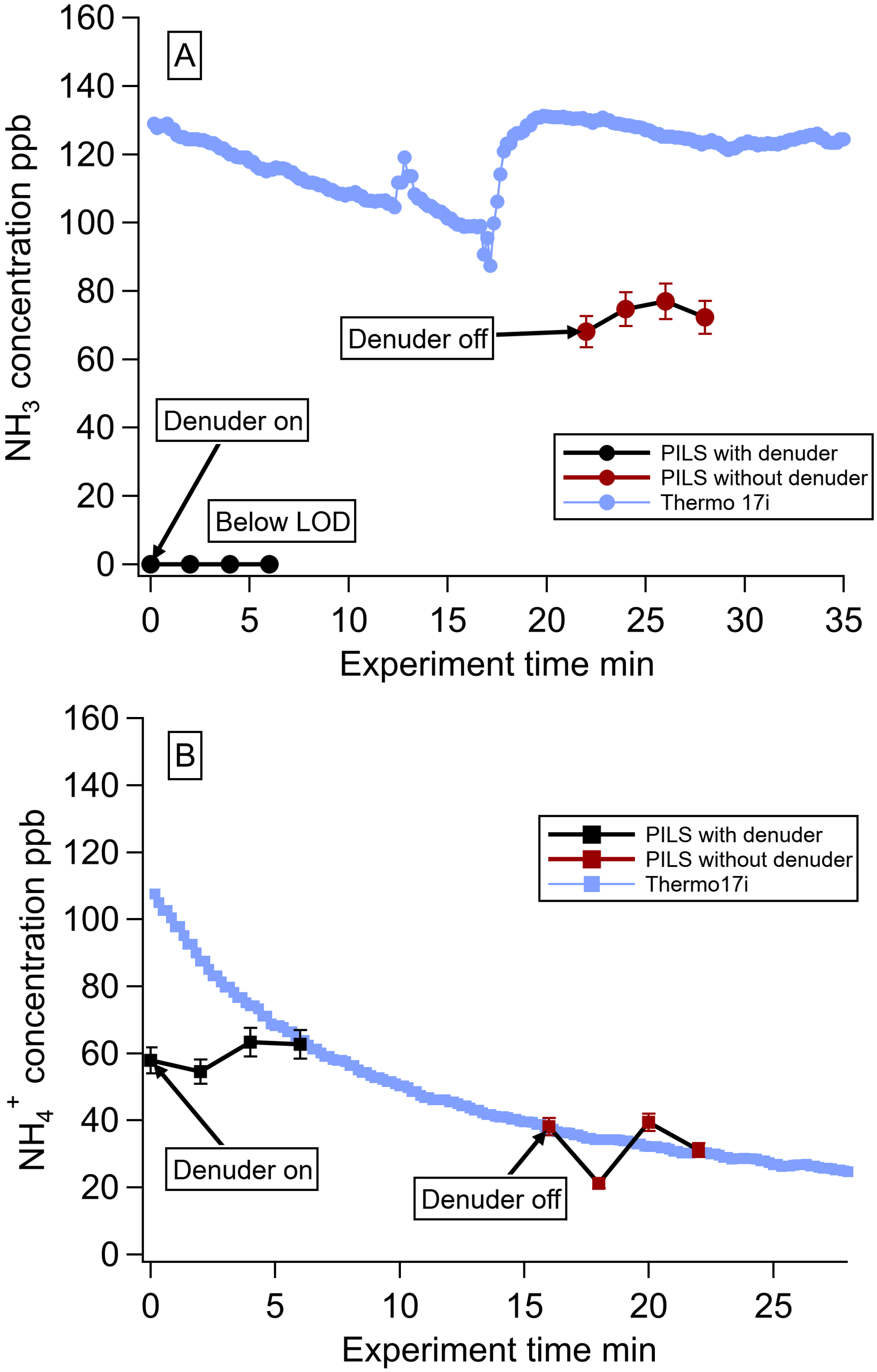


Figure D.4: Time-resolved comparison between PILS and ThermoFisher 17i, A) NH_3 comparison, and B) NH_4^+ comparison.

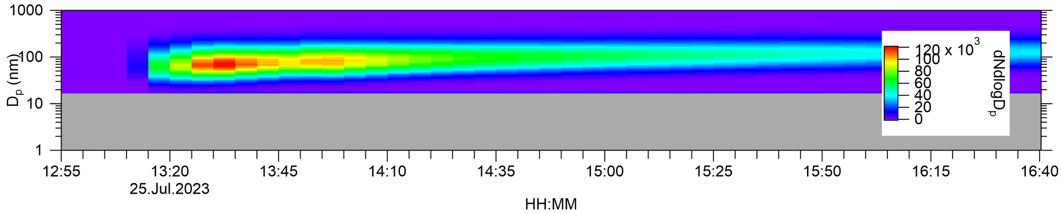


Figure D.5: Particle size distribution of the entire experimental period.

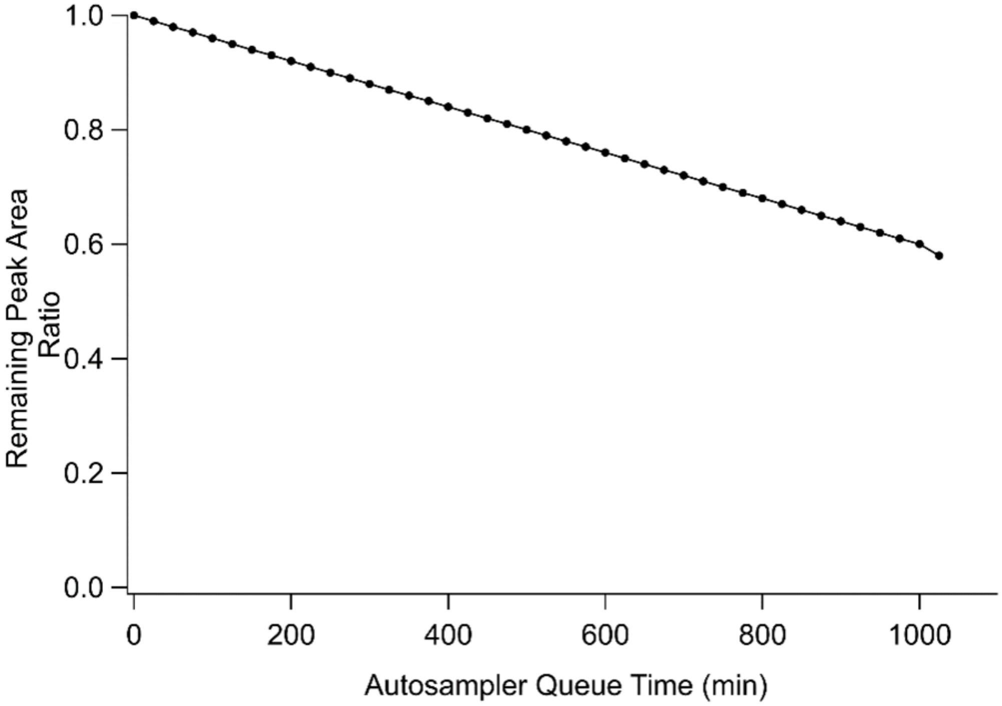


Figure D.6: Repetitive measurement of a single uric acid LC-MS peak over time. The queue time is equivalent to the length of the sequence to obtain the time-resolved data.

$$[M+H]^+_{double-derived} = M_{molecule} + 2 \times M_{TsCl} - 2 \times M_{HCl} + 1 \tag{D.2}$$

There are also chances of double-derivatization, or other adduct ions present in the ESI-positive mode, such as NH4+ or Na+. Figure D.7 shows the high-resolution mass spectrum of selected ANCs in the sample, which also indicates the signature peak profile of sulfur-containing compounds due to the presence of ^{34}S. These peaks are also confirmed by simulated isotopic profiles with a resolution of 100,000 MS in Thermo FreeStyle^{TM}.

D.4.2 Proposed Identities of ANCs

Proposed Identities of ANCs are listed in table D.4

D.5 Model Prediction of Phase Distribution

To better understand the phase distribution of target compounds between air and particles in a chicken farm, it is essential to consider the aerosol phase. This model focused on two primary phases: the aerosol phase and the air phase. 1-octanol was selected as a representative for the aerosol phase since most of the particles on chicken farms are organic matter. 1-Octanol serves as a widely accepted thermodynamic surrogate for the organic phase in atmospheric research, while the octanol–air partition coefficient (K$_{oa}$) is a commonly employed metric for assessing the properties and partitioning behavior of organic pollutantsṪhe composition of PM in poultry facilities is much more complex than 1-octanol, and additionally, acid-base chemistry is involved in the partitioning of acid-base active species. Thus, this model should be considered as a rough estimate for the partitioning and distribution of the target species.

In this study, the K$_{oa}$ values with their respective standard errors for the target compounds were estimated using the EAS-E Suite platform and the UFZ-LSER database[430]. These values are presented in Table D.5 for reference. Note that the estimated values of K$_{oa}$ are those of the neutral forms of these compounds. Chemical

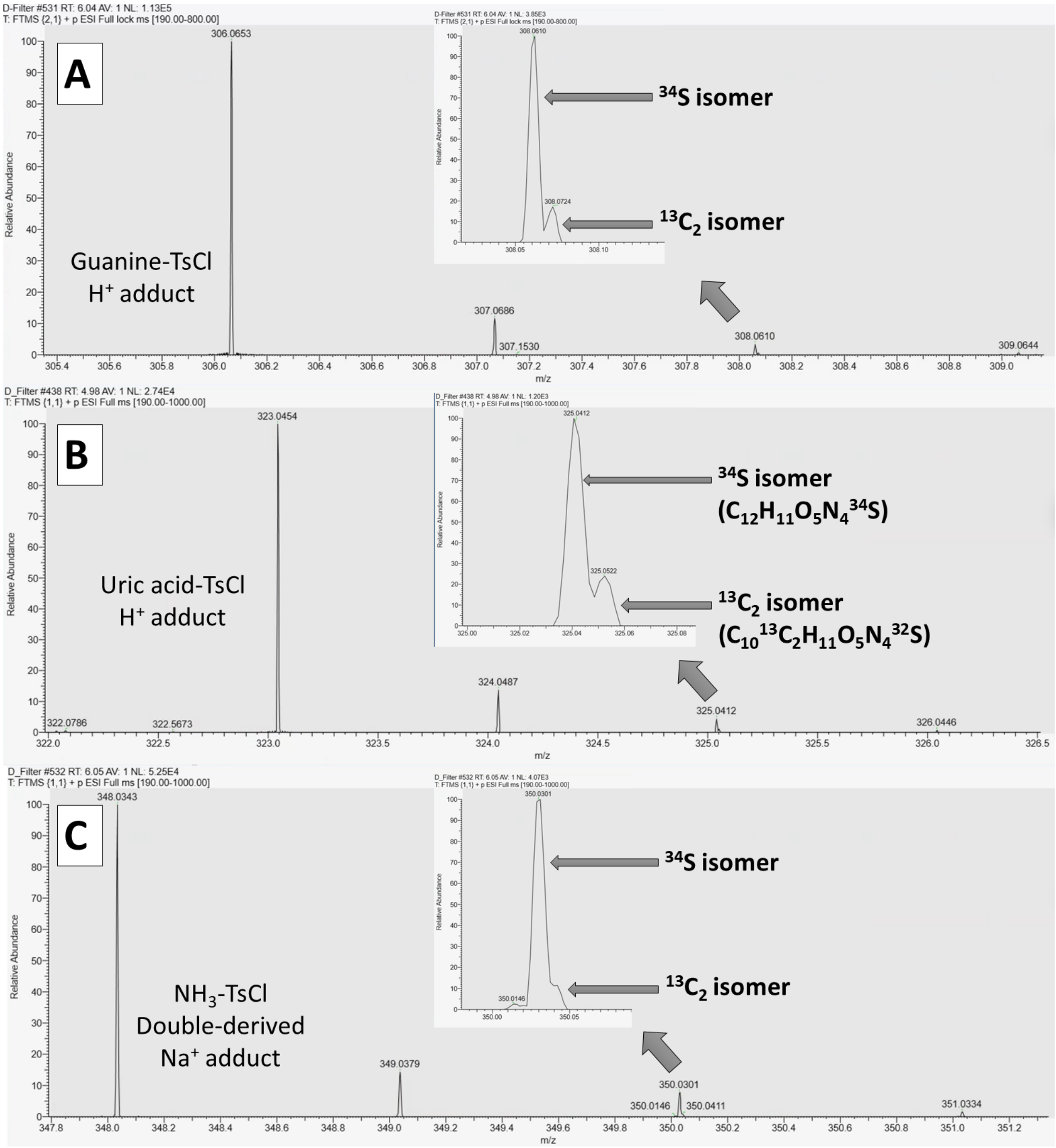


Figure D.7: Mass spectrum of selected ANCs, A) guanine, B) uric acid, and C) ammonia partitioning is known to be sensitive to acid-base equilibria for certain compounds, such as NH_3[431]. Assuming equilibrium has been established between the aerosol and air, the fraction of a species in the aerosol phase can be determined using the following equation:

$$F_p = R_{pa}/(1 + R_{pa}) \tag{D.3}$$

where R_{pa} is the dimensionless ratio of the equilibrium amount of a species in the aerosol and gas phases and can be calculated as follows[432]:

$$R_{pa} = 10^{(-6)} \times K_{oa} \times C_p/D_p \tag{D.4}$$

Here, 10^{-6} serves as a conversion factor, K_{oa} represents the octanol-air partitioning coefficient, C_p is the aerosol concentration in units of g/m^3, and D_p is the aerosol density ($0.824 g/cm^3$). In this study, 20000 ug/m^3 and 50000 ug/m^3 were selected as C_p to cover the range of particle concentrations measured by OPC in this work in the main article.

Table D.5: Predicted log Koa values and respective standard errors for compounds

Table D5. Predicted log Koa values and respective standard errors for compounds

Chemicals	**Log Koa**[a]
Cadaverine	5.94±0.59
Putrescine	5.47±0.59
Dimethylamine	2.54±0.61
Uric acid	11.91±3.77
Ammonia	1.32±0.00[b]

[a] Predicted data from EAS-E Suite, unless otherwise noted

[b] Predicted data from the UFZ-LSER database

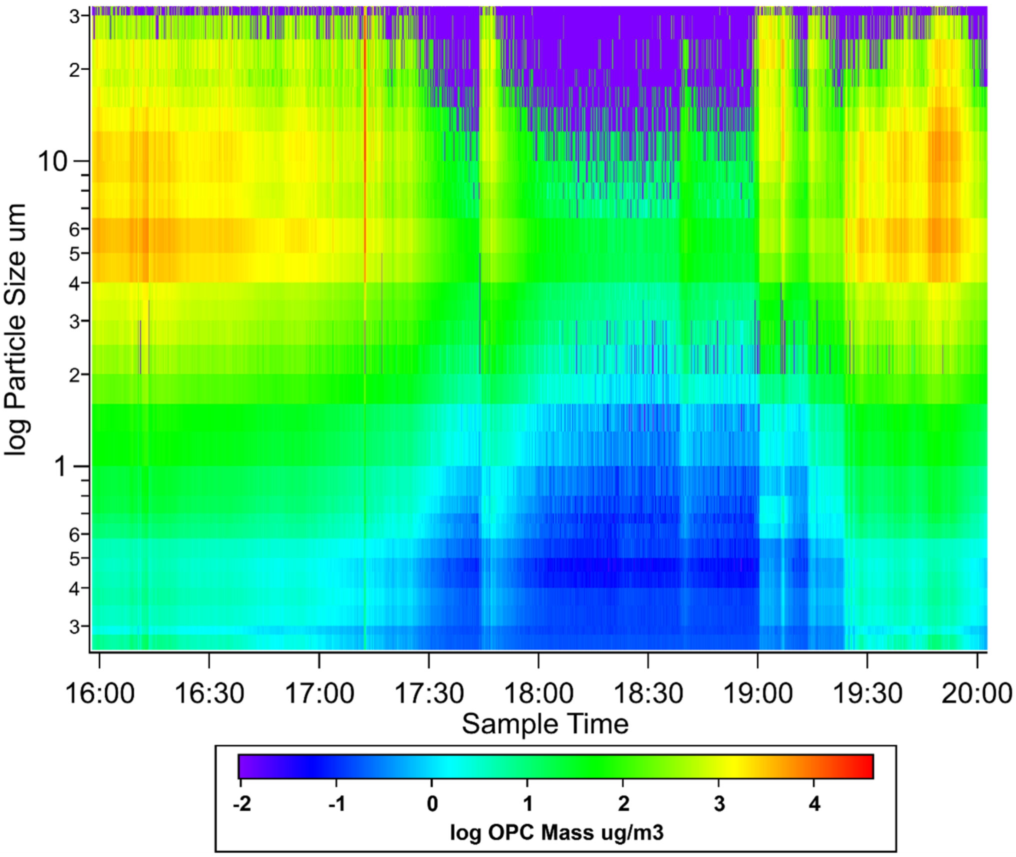


Figure D.8: 2-D plot of the mass concentration distribution of all particle sizes throughout the experimental period.

D.6 Particle Size Distribution

Figure D.8 shows the time resolved particle size distribution data during the experiment period. During the daytime, the concentration of suspended particles within individual size bins reached a level of 1000 ug/m^3, with most of their diameter greater than 4 μm, as visualized in the orange zone of the 2-D profile. When the chickens were asleep at night, the particle concentrations in all bins were reduced by a few orders of magnitude. Large particles were up to 1000 times less compared to the maximum concentration and remained stable.