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# Ubiquitous atmospheric contamination by tobacco smoke: Nicotine and a new marker for tobacco smoke-derived particulate matter, nicotelline

Noel J. Aquilina<sup>a,b,\*</sup>, Christopher M. Havel<sup>b</sup>, Polly Cheung<sup>b</sup>, Roy M. Harrison<sup>c,1</sup>, Kin-Fai Ho<sup>d</sup>, Neal L. Benowitz<sup>b</sup>, Peyton Jacob III<sup>b</sup>

<sup>a</sup> Department of Chemistry, University of Malta, Msida MSD 2080, Malta

<sup>b</sup> Division of Cardiology, Clinical Pharmacology Program, Department of Medicine, University of California, San Francisco, CA 94143, United States

<sup>c</sup> Division of Environmental Health and Risk Management, School of Geography, Earth and Environmental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom

<sup>d</sup> The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, China

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## ABSTRACT

Second Hand Smoke (SHS) has always been primarily linked with indoor pollution. To date nicotine was the favoured marker for SHS alongside measurements of particulate matter (PM) levels. As nicotine is mainly found in the gas-phase and reactive in the outdoor environment it is not ideal as a marker for the SHS-driven particulate component in PM. Nicotelline, a minor tobacco alkaloid that is stable, found almost exclusively in the particle phase and easy to quantify even at low concentrations, is being proposed as a better marker. It is the first study using bisulfate-treated quartz fiber filters to show that airborne nicotine (gas+particle phase) is directly proportional to airborne nicotelline in countries that have different climates. The analytical method developed has been validated to show that the use of untreated filters is suitable for the quantification of nicotelline even at low concentrations. Although nicotelline exhibits a seasonal and geographical variation, this is the first comprehensive study which demonstrates the ubiquitous presence of nicotelline in PM from outdoor air samples collected in the USA (0.1–285.6  $\text{pgm}^{-3}$ ), UK (2.3–9.1  $\text{pgm}^{-3}$ ), Hong Kong (3.8–109.3  $\text{pgm}^{-3}$ ) and Malta (4.2–280.8  $\text{pgm}^{-3}$ ). From the nicotelline apportionment factor of 1589 ng/mg of tobacco smoke PM we estimate the fraction of outdoor airborne PM derived from SHS to be in the range of 0.03–0.08%. While it is unlikely for tobacco smoke-related toxics in outdoor PM to be considered a major health hazard, in heavily polluted microenvironments this marker would be useful in tracing the presence of SHS and emerging Third Hand Smoke components that form or are found in airborne and settled PM that could induce serious health effects.

## 1. Introduction

Although the global prevalence of daily smoking has decreased (Ng et al., 2014), the absolute number of smokers has increased to almost one billion people in 2012 (Beaglehole et al., 2015). About 6 trillion cigarettes were smoked worldwide in 2016 (World-Lung-Foundation, 2015). Secondhand Smoke (SHS) alone releases 10.5–34.4 mg of particulate matter (PM) and 1.9–5.3 mg of nicotine per cigarette into the air (WHO, 2004). Considering a conservative value, cigarette smoking

worldwide, releases about 22 million kilograms of nicotine and about 135 million kilograms of PM into the atmosphere each year (Jacob et al., 2013). In 2004, about 1.0% of the global mortality was attributed to SHS exposure whilst lower respiratory infections in children younger than 5 years, ischaemic heart disease in adults, and asthma in adults and children (Öberg et al., 2011) indicate there is no risk-free level of exposure to SHS (U.S. Department of Health and Human Services, 2014).

SHS has been well characterized in both chamber and field studies and has always been an important and significant contributor to indoor

**Abbreviations:** SHS, Second Hand Smoke; PM, Particulate matter; TSP, Total Suspended Particulate; DCM, Dichloromethane; EtOAc, Ethyl acetate; IPA, Isopropyl alcohol; SRM, Standard Reference Material; CARB, California Air Resources Board; The seasons are defined as: DJF, December, January, February; MAM, March, April, May; JJA, June, July, August; SON, September, October, November.

\* Corresponding author at: Department of Chemistry, Faculty of Science, University of Malta, Msida MSD 2080, Malta.

E-mail address: [noel.aquilina@um.edu.mt](mailto:noel.aquilina@um.edu.mt) (N.J. Aquilina).

<sup>1</sup> Also at: Department of Environmental Sciences/Center of Excellence in Environmental Studies, King Abdulaziz University, PO Box 80203, Jeddah 21589, Saudi Arabia.

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PM (Benner et al., 1989; Carrington et al., 2001; Charles et al., 2008; Douce et al., 2001; Eatough et al., 1989; Guerin et al., 1992; Hoffmann et al., 1991; Kleeman et al., 1999; Morawska et al., 1997; Ogden and Maiolo, 1992; Rogge et al., 1994; Schauer, 1998; Streibel et al., 2013).

Historically, several markers of SHS were proposed and Table S1 (of the Supplementary Material) outlines their main limitations. The typical criteria for an ideal marker are that the marker is expected to behave similarly to the material for which it is a marker under a range of environmental conditions and a variety of products, in this case tobacco cigarette smoke (Guerin et al., 1992; LaKind et al., 1999; National Research Council, 1986). The fact that the primary, specific component of SHS is nicotine, it would be expected that an increase in tobacco smoke prevalence should result in higher airborne nicotine concentration. Given that nicotine is found almost exclusively in the gas phase of SHS (Alonso et al., 2010; Daisey, 1999) the implication is that it would be unsuitable as a marker of tobacco smoke in PM. From specific experiments using commercial cigarettes in a chamber study, nicotine, was proposed as a potentially suitable marker given that it is found primarily in the particle phase (Jacob et al., 2013).

Exposure to SHS in indoor microenvironments was usually studied by measuring PM and nicotine concentrations, the latter being the preferred marker associated with SHS (eg. (Arku et al., 2015; Butz et al., 2011; Chan et al., 1995; Martínez-Sánchez et al., 2014; Okoli et al., 2007)). When smoking bans were enforced in public places in several countries, the majority of studies looked into changes in SHS levels in indoor spaces and their immediate outdoor spaces where smoking was permitted (eg. (Agbenyikey et al., 2011; Barnoya et al., 2010; Cains et al., 2004; Lopez et al., 2012; Martínez-Sánchez et al., 2014; Navasacien et al., 2004; Satran et al., 2014)). Very few studies were conducted to investigate the SHS contribution to airborne PM away from direct cigarette smoke emissions (eg. (Alier et al., 2013; Cecinato et al., 2012; Ladji et al., 2009; Moussaoui et al., 2010; Rogge et al., 1994; Romagnoli et al., 2016; Sureda et al., 2012; van Drooge et al., 2018; Van Drooge and Grimalt, 2015)).

This paper aims to test the validity and utility of nicotine as an airborne marker of SHS by: 1) testing its atmospheric stability on filters during sampling of PM; 2) comparing it to airborne nicotine in the field; 3) testing if it exhibits a ubiquitous presence by analysing outdoor PM samples collected in different places of different climates and population densities and 4) evaluate the load of tobacco smoke particulate in airborne PM. It also documents the presence of both nicotine and nicotine in a range of geographic locations, from urban to rural to remote desert, in three continents.

The rest of the paper will be divided as follows: first the methods used in this study will be described in Section 2 comprising the sampling sites and equipment used for nicotine and nicotine, followed by the analytical method used and its validation. Results and discussion in Section 3 and ending with conclusions in Section 4.

**Table 1a**  
Sampling sites' characteristics in California (USA).

Country	USA (California)					
City	Canebrake (CB)	Yosemite Village (YTD)	Shasta Lake (SLM)	Bakersfield (BCA)	Sacramento (STS)	San Francisco (SF)
Sampler type	High volume					
Year of Sampling	2010					
Model make	Tisch 1200	Sierra Andersen 1200	Sierra Andersen 1200	Sierra Andersen 1200	Sierra Andersen 1200	2016 Thermofisher
Filter type	8 × 10 in. -Quartz					
Sampling head	PM <sub>10</sub>					
Average flow rate (m <sup>3</sup> min <sup>-1</sup> )				1.22		
Area	Rural	Suburban	Urban			
Population	27,554	1,035 <sup>(c)</sup>	10,146	349,322	467,382	876,103

## 2. Materials and methods

### 2.1. Description of sampling sites and equipment

Note: Several samples were either available or collected from various places of distinctly different climates, at different times and using different sampling heads on the samplers as outlined in Tables 1a and 1b. The scope of this study was not to discuss and quantify nicotine in the different PM size fractions and although the variety of datasets appears a random choice, this approach is justified to test the claim of the ubiquitous nature of nicotine in airborne PM. The sites are described in date order as samples were collected.

The California Air Resources Board (CARB) operates an air quality monitoring network within the state of California. In this network, 24-hour samples are collected every week for gravimetric PM<sub>10</sub> monitoring and stored according to USEPA protocols. 8 × 10 in. high volume (hivol) filters from five locations, namely, Bakersfield (BCA), Sacramento (STS), Shasta Lake (SLM), Yosemite Village (YTD) and Canebrake (CB) (Fig. S1), collected in 2010, were made available to this study for analysis. These filters were not bisulfate treated (as described later in Section 2.2) and thus could not be analysed for nicotine but provide insight about the spatial and temporal variability of nicotine. The daily PM<sub>10</sub> gravimetric information recorded was valuable to evaluate the load of nicotine in PM<sub>10</sub> (in ng/g).

Outdoor 24-hour samples using untreated quartz fiber filters were

**Table 1b**  
Sampling sites' characteristics in Birmingham (UK), Msida (Malta) and Hong Kong (China).

Country	UK	Malta	China, Hong Kong		
	City	Msida	Tseung Kwan O	Tseung Kwan O	Tin Shui
	Birmingham (BHAM)	(MSD)	Industrial Estate (MA)	(TKO)	(TSW)
Sampler type	Low volume	Low volume	Medium Volume		
Year of Sampling	2016	2016/2018	2014/2015	2014/2015	2015
Model make	Dichotomous Partisol 2025	Leckel SEQ47/50	URG-3000ABC		
Filter type	47 mm QM-A <sup>(b)</sup>	47 mm QM-A <sup>(b)</sup>	47 mm QM-A <sup>(b)</sup>		
Sampling head	PM <sub>2.5</sub> and PM <sub>10</sub>	PM <sub>2.5</sub> or PM <sub>10</sub>	PM <sub>2.5</sub>		
Average flow rate (m <sup>3</sup> min <sup>-1</sup> )	0.017	0.038	0.008		
Area	Urban Background	Urban	Industrial/Urban	Urban	Urban
Population	1,124,600	8,545 <sup>(d)</sup>	396,000	368,000	292,000

<sup>(a)</sup> EMP2000 – Whatman filters chosen by the USEPA to be the standard filters used in the High-volume air samplers. <sup>(b)</sup> QM-A – Whatman quartz filters (2 μm pore size). <sup>(c)</sup> Visitors to Yosemite National Park were 3,901,408 in 2010. <sup>(d)</sup> Town is within the urban area of Malta having 413,040 inhabitants.

collected during short campaigns in three locations in Hong Kong, China namely, Tseung Kwan O (TKO), Tseung Kwan O Industrial Estate (MA) and Tin Shui Wai (TSW) in 2014/5, in San Francisco, USA (SF), Birmingham, UK (BHAM) and Msida, Malta (MSD) in 2016 and 2018.

Details of the sampling locations and equipment used are presented in Table 1a and 1b. All samplers were calibrated and operated according to standard atmospheric sampling protocols. Further details on the choice of these specific sites and their characteristics in terms of population, location and expected smoking patterns and the calibration of the instruments are given in the Supplementary Material.

## 2.2. Nicotine sampling

To sample nicotine, quartz fiber filters were pre-treated according to the method developed by Hammond and colleagues (Leaderer and Hammond, 1991). Briefly, a well-mixed solution of HPLC grade water, glycerol, sodium bisulfate and tetrasodium EDTA are placed in a DCM cleaned glass trough. Filters are placed in the solution and left to soak for 30 min and then left standing on a clean metal stand, with the least possible area touching the sides to remove the excess solution. Once the treated filters dry completely in a fume-hood where tobacco-related compounds are not handled, these are stored in aluminium foil and in an airtight plastic container prior to sampling.

Treated filters prepared as described above were used to have a subset of data representative of airborne nicotine and nicotelline sampled concurrently under the same atmospheric conditions. Sampling with treated filters was carried out in Msida, Birmingham and San Francisco in order to verify the nicotelline levels in PM over a range of nicotine concentrations given that nicotine concentration in outdoor air exhibits a high variability.

## 2.3. Collection efficiency of sampling filters and atmospheric stability of nicotelline

As nicotine has to be sampled on a treated filter as described in the previous section, to test the collection efficiency of the different treatments of filters for nicotelline, two calibrated PM<sub>2.5</sub> samplers running concurrently for 24 h were used, one fitted with a pre-treated 47 mm quartz fiber filter (T), and the other with an identical but untreated filter (U).

In order to test if nicotelline suffers any significant atmospheric degradation, the same samplers were run concurrently at the same location. One sampler was used to collect 24-hour samples and the other collected 48-hour samples, both equipped with untreated filters.

These two experiments were carried out in autumn in Msida, Malta and real-time meteorological information, ozone (O<sub>3</sub>), nitrogen dioxide (NO<sub>2</sub>), PM<sub>2.5</sub> and PM<sub>10</sub> concentrations were recorded alongside nicotine and nicotelline to better elucidate the fate of airborne nicotine and nicotelline under normal atmospheric conditions.

## 2.4. Sample preparation and analysis

### 2.4.1. Reagents and standards

Water, methanol, dichloromethane (DCM), pentane, isopropyl alcohol (IPA), ethyl acetate (EtOAc), toluene and butanol (all HPLC grade) and sulfuric acid, hydrochloric acid, potassium carbonate, tetrasodium EDTA, acetone and ammonium formate (all reagent grade) were purchased from (Fisher Scientific, USA). Nicotelline and the internal standard for LC-MS/MS analysis, nicotelline-d<sub>8</sub> were synthesised as previously reported (Jacob et al., 2013). Nicotine-d<sub>4</sub> used as an internal standard was synthesised and converted to the tartrate salt as described by Jacob et al. (Jacob et al., 1988). Nicotine-d<sub>0</sub> base was purchased from Sigma Aldrich, USA, and converted to the tartrate salt based as previously described (Jacob et al., 1988). The Standard Reference Material (SRM) 1649b (Urban Dust) was purchased from the National Institute of Standards and Technology, USA.

### 2.4.2. Instrumentation and analytical parameters

The LC-MS/MS analyses were carried out using a Thermo Instruments Quantiva Triple Quadrupole LC-MS/MS system. A Phenomenex Kintex Phenyl Hexyl 3 × 150 mm column, 2.6 μ particle size, was used for the LC separations. The instrument parameters are described in the work by Whitehead et al. (Whitehead et al., 2015). Nicotine concentrations were determined by GC-MS/MS (Jacob et al., 1991) modified for tandem mass spectrometry for improved sensitivity. GC-MS/MS analyses were carried out using a Thermo Trace 1310 GC interfaced with a TSQ Evo 8000 triple quadrupole mass spectrometer. Parameters for selected reaction monitoring (SRM) were as follows: *m/z* 162 to *m/z* 84 for nicotine and *m/z* 166 to *m/z* 88 for nicotine-d<sub>4</sub> at a collision energy of 9 eV.

### 2.4.3. Working standards and controls

The concentrations of the standards, which span the expected range were typically 0.025–100 ng mL<sup>-1</sup> for nicotelline and 4–1200 ng mL<sup>-1</sup> for nicotine. For quality assurance purposes, 1, 2, 5, 10 and 20 ng mL<sup>-1</sup> nicotelline-d<sub>0</sub> spiked filters and 5, 10, 125, 370 and 1111 ng mL<sup>-1</sup> nicotine-d<sub>0</sub> spiked filters were included with every 10 samples. Field and analytical blank filters were run every five samples.

### 2.4.4. Storage and extraction of filters

The 47 mm sampled filters used with low volume samplers were stored in aluminium foil at -20 °C before extraction. Although the CARB filters were not collected for this study but in 2010, they were transferred to the laboratory and stored at the same above-mentioned conditions as that it is a standard protocol in air quality monitoring.

An 8 × 10 in. filter used with the high-volume sampler had the non-sampled border removed. The remaining sampled filter was weighed and then cut in twelve equal 3.5 × 1.5 in. sections and all were individually weighed. The pieces were extracted and analysed separately as described below. The amount of nicotelline in each strip indicated that the distribution of the PM and nicotelline on the whole filter was uniform (see Table 2) hence justifying the procedure to use a 3.5 × 1.5 in. section of the filter as a representative percentage of the whole filter. In the analysis involving hivol filters, two strips from each filter were cut and always analysed individually, and then an average value of these two strips was reported. The amount of pollutant on the whole filter was then worked out proportionally to calculate the atmospheric concentration. The 3.5 × 1.5 in. filters pieces were stored in a similar manner as the 47 mm filters.

Before extraction, every filter was left to reach room temperature, it was cut in thin strips and placed in a 16 × 150 mm glass culture tube using a DCM cleaned tweezers. The internal standards, nicotine-d<sub>4</sub> and nicotelline-d<sub>8</sub>, both at 1000 ng/mL in 2 mL of 0.1 M sulfuric acid, were added to the filter followed by 5 mL of DCM/Pentane/EtOAc/IPA (40:40:15:5). The tubes were vortexed for 30 s, sonicated for 30 min at room temperature, vortexed for 2 min and centrifuged for 10 min at 3000 rpm. The tubes were placed in a dry ice/acetone bath to freeze the aqueous phase, and the upper organic phase were poured into 13 × 100 glass tubes and stored in a freezer at -20 °C for future analysis of other organic pollutants. The aqueous phase was kept for the extraction of nicotelline and nicotine. 1 mL of 45% potassium carbonate containing 5% tetrasodium EDTA and 8 mL of DCM/Pentane/EtOAc/IPA (40:40:15:5) were added and the tube was vortexed for 2 min, centrifuged for 10 min and placed in a dry ice/acetone bath. The organic phase was split for analysis by GC-MS/MS and LC-MS/MS. In a 13 × 100 mm tube, 3 mL of the organic phase was added for nicotine analysis by GC-MS/MS. The remaining 5 mL of the organic phase were poured in a 13 × 100 mm tube and spiked with 100 μL of 1% hydrochloric acid in methanol to retard evaporation of the analyte. The organic phase was dried at 60 °C under a gentle nitrogen flow. The extract was reconstituted with 200 μL of 0.1 M ammonium formate in 20% methanol. 30 μL were injected in the LC-MS/MS for the analysis of nicotelline.

### 2.4.5. Data analysis

The Thermo XCalibur software was used to generate calibration curves and calculate concentrations using peak area ratios of analyte/internal standard. Linear regression with 1/X weighting was used and not forcing the line through the origin. Blanks were included in the standard curves and “ignore origin” was used to correct for the small amounts of nicotine present in solvents and reagents. Standard curves were linear from 0.025 to 100 ngmL<sup>-1</sup> for nicotelline and from 4 to 1200 ngmL<sup>-1</sup> for nicotine. Concentrations of standards are specified in Section 2.4.3.

The sampling time and volume, the gravimetric amount of PM collected on the filter and the load of the analytes in the extracts were used to compute the data described below.

## 3. Results and discussion

### 3.1. Extraction of filters and analytical method validation

The analytical methods are based on our previously reported methods for nicotelline, nicotine, and other tobacco-derived compounds in house dust (Whitehead et al., 2015; Jacob et al., 2013), with the sample preparation and extraction procedure modified for analysis of filters used to collect airborne PM.

Performance of the method including precision and accuracy, Limits of Quantitation (LOQs), analysis of blanks that verify lack of interfering substances, and verification of uniformity in deposition of PM on filters is summarized in Table 2A.

Precision and accuracy of the method were determined from the results of analysis of the spiked filters described in Section 2.4.3 above. LOQs were determined as the minimum quantity on the calibration curve that does not exceed an RSD of 15% for blank filters or blank filters spiked with analytes. These were 0.025 ngmL<sup>-1</sup> for nicotelline and 4 ngmL<sup>-1</sup> for nicotine. As part of the analytical quality control protocol to document the precision of the analytical method, the amount of nicotine and nicotelline found in the SRM 1649b analysed during this study are reported. These compounds are not listed in the NIST certificate of this SRM and therefore the results for precision only are reported.

During the method development for the analysis of alkaloids in house dust, from a very limited number of samples (N = 2), the mean nicotelline level in the same SRM used in this study was 418 ng/g and for nicotine it was 66,000 ng/g (Whitehead et al., 2015). Table 2B reports

**Table 2A**

Precision and accuracy for determination of nicotelline and nicotine in analyte spiked filters used as QC samples.

Analyte	Added Amount (ngmL <sup>-1</sup> )	Measured Mean (ngmL <sup>-1</sup> )	Accuracy (% of Expected)	Precision (%RSD)
Nicotelline LOQ = 0.025, N = 44, 16 Analytical Runs	0 <sup>a</sup>	BLOQ	NA	NA
	0 <sup>b</sup>	BLOQ	NA	NA
	0 <sup>c</sup>	BLOQ	NA	NA
	1	1.15	115	6.3
	2	2.10	105	5.3
	5	5.71	114	12.2
	10	11.1	111	10.7
Nicotine LOQ = 4, N = 10, 4 Analytical Runs	0 <sup>a</sup>	BLOQ	NA	NA
	0 <sup>b</sup>	BLOQ	NA	NA
	0 <sup>c</sup>	BLOQ	NA	NA
	5	5.1	101	1.3
	10	10.2	102	1.0
	125	129.2	103	2.8
	370	377.7	102	9.3
	1111	1158	104	1.2

a. Analytical blanks; b. Travel blanks; c. Field blanks; N: Number of replicate samples; LOQ: Limit of Quantitation; BLOQ: Below Limit of Quantitation; RSD: Relative Standard Deviation; NA: Not Applicable.

**Table 2B**

Precision for determination of nicotelline and nicotine in NIST SRM 1649b-Urban Dust and in Hivol filter sections. The NIST SRM served as a QC sample in analytical runs. The analysis of filter sections was performed to verify the uniformity of deposition of the analytes on the filter.

Analyte	Measured Mean	Precision (%RSD)
Nicotelline, SRM 1649b (N = 9) (in ng/g)	451	5.6
Nicotelline, Hivol Filter Sections (N = 12) (in ngmL <sup>-1</sup> )	189	15
Nicotine, SRM 1649b (N = 9) (in ng/g)	52,800	8.4
Nicotine, Hivol Filter Sections (N = 12) (in ngmL <sup>-1</sup> )	3,990	12.0

N: Number of samples; RSD: Relative Standard Deviation.

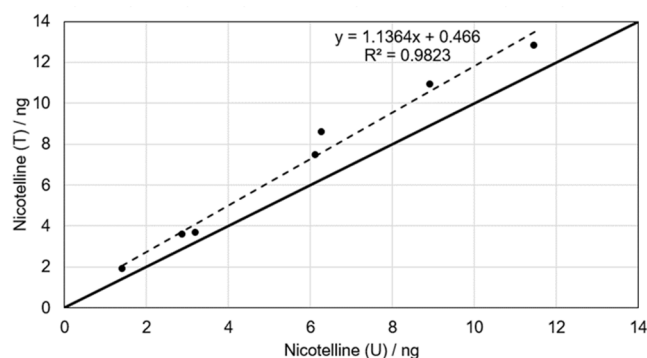
similar results for more samples (N = 9) and with higher confidence. The validation data for the proposed method is considered suitable and is comparable to the previously reported method (Jacob et al., 2013).

To verify the uniform distribution of analytes on filters and to justify analysis of partial sections, hivol filters were cut into twelve equal 3.5 × 1.5 in. sections as described above in Section 2.4.4, individually weighed, and analysed. The %RSD in the results tabulated in Table 2B, for both nicotine and nicotelline indicate the suitability of this approach.

### 3.2. Effect of filter treatment on collection of nicotine and nicotelline

From the co-located sampling experiment (N = 6) described in Section 2.3 to compare the collection efficiency of a bisulfate-treated filter (T) to an untreated filter (U), the average nicotelline mass obtained on a T filter was 7.0 ± 4.1 (in ng ± SD) as compared to the average nicotelline mass on a U filter (U) which was 5.7 ± 3.6. The ratio of nicotelline mass collected on untreated filters to that collected on treated filters (U/T) is 0.81 ± 0.06. The regression of the treated to untreated filters data indicates a slope of 1.136 (p < 0.00014) (with 95% lower bound CI equal to 0.961 and upper bound CI equal to 1.312) (see Fig. 1). For nicotine, the average nicotine mass obtained on a T filter was 1719 ± 1108 (in ng ± SD) as compared to that on a U filter which was 291 ± 426 ng. The U/T ratio is 0.17 ± 0.14, as expected due to, primarily, the volatility of nicotine base or, secondarily, its reactivity with ozone and/or nitrous acid (Petrick et al., 2011; Sleiman et al., 2010) (Refer also to Fig. 3). Treatment of the filters with sodium bisulfate serves to retain nicotine as the salt which has low volatility.

Given the small datasets, a Mann-Whitney U non-parametric test was run for nicotelline and nicotine mass on T and U filters. The T filters have the highest nicotelline and nicotine mass from the highest mean ranks and the test statistics indicate that for nicotine, there is a statistically significant difference between the treatments (p = 0.016) whilst for nicotelline there is no statistical difference between the U and the T filters (p = 0.482), as summarised in Table S6.



**Fig. 1.** Nicotelline (in ng) on bisulfate-treated (T) and untreated (U) filters. (Solid line represents Y = X).

### 3.3. Atmospheric stability of nicotine

In this experiment described in Section 2.3, when untreated filters (N = 7) were exposed to the same atmospheric conditions, the average nicotine mass on the filter after 48 h was  $10.4 \pm 8.3$  (in ng  $\pm$  SD) and the average of the sum of two 24-hour consecutively sampled filters was  $11.2 \pm 9.0$  ng. A paired samples test indicated the 95% CI in the difference ranges from 0.055 and 1.55 which is statistically significant ( $p < 0.039$ , 2-tailed), indicating that losses of nicotine from the filter due to evaporation, partitioning or further chemical reactions do occur. It should be pointed out that that the reported losses are somewhat higher than those observed in a controlled chamber environment (Jacob et al., 2013) with higher levels of aerosol coming from freshly generated tobacco smoke (two orders of magnitude higher) that was aged for up to 30 min as compared to longer-aged ambient aerosol.

### 3.4. Nicotelline in airborne samples

#### 3.4.1. Airborne nicotine vs nicotelline

When pubs, restaurants, nightclubs, discos and other hospitality venues permitted indoor tobacco smoking, the preferred marker to SHS has always been nicotine. In indoor settings, nicotine concentrations ranged from 10,000 to 6,010,000  $\text{pgm}^{-3}$  (Agbenyikey et al., 2011; Arku et al., 2015; Barnoya et al., 2010; Butz et al., 2011; Kim et al., 2010; Martínez-Sánchez et al., 2014; Navas-acien et al., 2004; Okoli et al., 2007; Satran et al., 2014). When smoking bans were enforced, as expected, indoor concentrations decreased by an order of magnitude whilst outdoor concentrations increased by a similar magnitude as smoking shifted to the immediate outdoor space of the venues (Lopez et al., 2012). Limited studies focussed on airborne nicotine away from direct cigarette smoking. Studies in Los Angeles, Barcelona, Madrid, Rome, Palermo, Messina and Algeria have shown that nicotine concentrations are typically higher in the following order: roadside > urban > urban-background > rural ranging from 58,000  $\text{pgm}^{-3}$  to 600  $\text{pgm}^{-3}$  (Alier et al., 2013; Cecinato et al., 2012; Ladjji et al., 2009; Moussaoui et al., 2010; Rogge et al., 1994; Romagnoli et al., 2016; Sureda et al., 2012; van Drooge et al., 2018; Van Drooge and Grimalt, 2015). This high variability in nicotine concentration, although partially associated with smoking prevalence and population densities it was associated also with the different modes of sampling nicotine.

As nicotine in SHS is almost entirely in the gas phase, this poses a challenge to sample both the gaseous and particle phases of airborne nicotine. A pre-treatment of quartz fiber filters as described in Section 2.2 efficiently traps nicotine in the gaseous phase alongside the particle-phase.

To investigate the relationship between airborne nicotine and nicotelline, 24-h samples were collected on treated filters (T) from three sites in three countries that have climates which are intrinsically different, between 2016 and 2018.

From Fig. 2, the measured nicotine concentration ranges in this study were 412–7,628  $\text{pgm}^{-3}$  for San Francisco, 541–5,489  $\text{pgm}^{-3}$  for Birmingham and 6,761–81,537  $\text{pgm}^{-3}$  for Msida, all within the same order of magnitude and variability noticed in previous studies. In a study by van Drooge et al. (van Drooge et al., 2018) it was observed that there is a nicotine concentrations gradient between roof and street level, with the roof concentrations were lower than roadside levels, independent of city or season. A similar observation could be made from the measurements in San Francisco that were carried out at a higher level compared to the locations.

The range of concentrations on treated filters (T) (Table S3) varied considerably but nicotelline was easily detected even at low nicotine concentrations such as in San Francisco on a 5 storey building and in Birmingham away from proximity to smokers. In a similar fashion nicotine and nicotelline were easily detected in PM of different size fractions such as in San Francisco (Total Suspended Particulate, TSP), in Birmingham (PM<sub>10</sub>) and in Msida in PM<sub>2.5</sub> and in PM<sub>10</sub>.

With reference to Fig. 3, in Msida, for both campaigns, carried out between October and December, real-time PM<sub>2.5</sub> and PM<sub>2.5-10</sub> (coarse) fractions were recorded alongside O<sub>3</sub> and NO<sub>2</sub>. Unfortunately, no OH radical measurements were available for this study. Both the mean fine fraction PM<sub>2.5</sub> ( $15.6 \pm 2.9 \mu\text{gm}^{-3}$ ) and the mean coarse fraction PM<sub>2.5-10</sub> ( $29.0 \pm 5.6 \mu\text{gm}^{-3}$ ) were higher in 2016 than in 2018 where in the second campaign the mean concentrations of PM<sub>2.5</sub> and PM<sub>2.5-10</sub> were ( $8.0 \pm 2.9 \mu\text{gm}^{-3}$ ) and ( $11.3 \pm 4.1 \mu\text{gm}^{-3}$ ) respectively. It appears that the variability in the corresponding levels of nicotelline in PM<sub>2.5</sub> (mean,  $52.4 \pm 19.5 \text{pgm}^{-3}$  in 2016 to  $14.3 \pm 9.6 \text{pgm}^{-3}$  in 2018) is more closely related to the airborne PM levels than that of nicotine, indicating the stability of the proposed marker in variable atmospheric conditions is promising.

The median wind speeds during the campaigns were  $3.9 \pm 1.4 \text{ms}^{-1}$

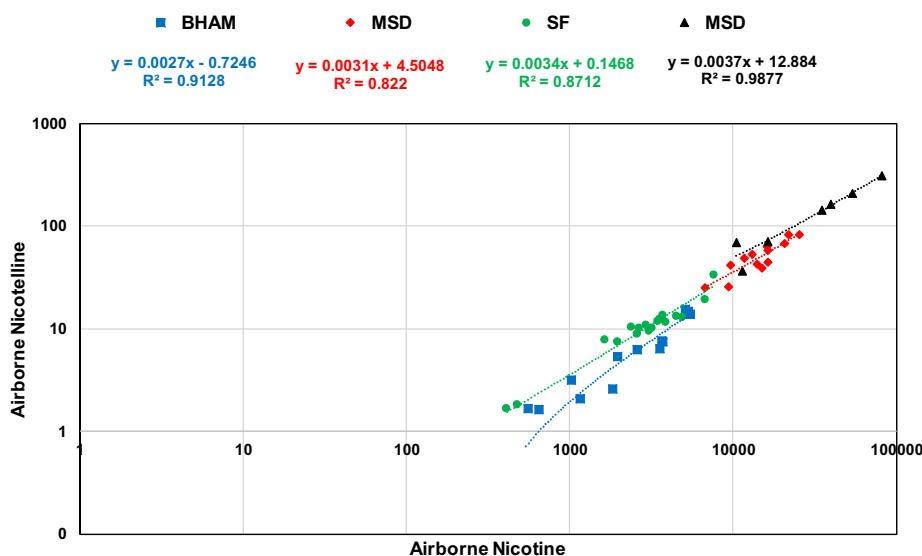
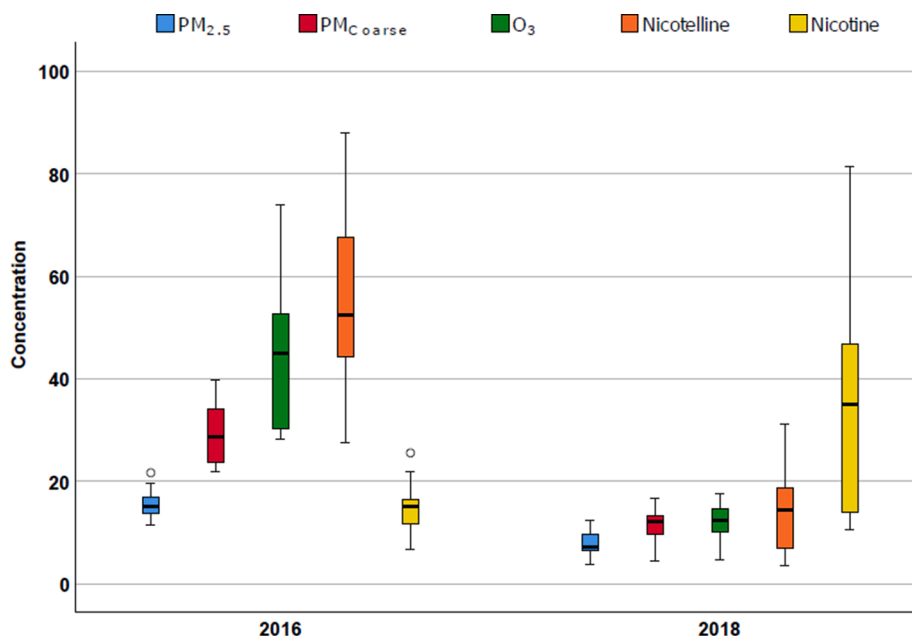


Fig. 2. Airborne nicotelline (in  $\text{pgm}^{-3}$ ) vs airborne nicotine (in  $\text{pgm}^{-3}$ ) in Birmingham (BHAM-PM<sub>10</sub>■), Msida (MSD-PM<sub>10</sub>◆) and San Francisco (SF-TSP●) in 2016 and Msida (MSD-PM<sub>2.5</sub>▲) in 2018.



**Fig. 3.** Comparison of variability in airborne concentration of  $PM_{2.5}$ ,  $PM_{2.5-10}$  (coarse) and  $O_3$  (in  $\mu g m^{-3}$ ), nicotelline ( $\times 10$ ) and nicotine ( $\times 1000$ ) (in  $pgm^{-3}$ ) in Msida 2016 and 2018.

and  $0.8 \pm 0.5 \text{ ms}^{-1}$  in 2016 and 2018 respectively. Given the difference in wind speeds, in 2016 it is expected that air from the neighbouring urban areas was transported and well mixed while in 2018, wind speeds were very low, hence indicating that the levels are primarily associated with local sources. In 2016,  $O_3$  varied from 28 to  $74 \mu g m^{-3}$  (mean,  $43.6 \pm 14.4 \mu g m^{-3}$ ) and airborne nicotine varied from 7 to  $26 \text{ ngm}^{-3}$  (mean,  $15.0 \pm 5.3 \text{ ngm}^{-3}$ ). In 2018, the  $O_3$  levels were much less, ranging from 5 to  $18 \mu g m^{-3}$  (mean,  $12.1 \pm 4.2 \mu g m^{-3}$ ) possibly leading to less reactive loss of nicotine by reaction with  $O_3$ , 11 to  $82 \text{ ngm}^{-3}$  (mean,  $35.5 \pm 26.0 \text{ ngm}^{-3}$ ). As sampling was done close to a traffic site, the  $NO_2$  values were typical of such a site and traffic emissions may explain the levels and variability of PM and  $O_3$ . During these campaigns the mean  $NO_2$  in 2016 was  $45.6 \pm 14.0 \mu g m^{-3}$  as compared to  $10.9 \pm 8.9 \mu g m^{-3}$  in 2018, suggesting that the most probable source of PM at this site was traffic exhaust. The reactivity (oxidation) of nicotine is driven more by the concentration of OH radicals rather than  $O_3$  (Destailats et al., 2006; Kosno et al., 2014). Borduas et al. measured the second order rate coefficient between OH and nicotine to be  $(8.38 \pm 0.28) \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$  at  $298 \pm 3 \text{ K}$  (Borduas et al., 2016). Typically, in an indoor environment the OH radical concentration is up to  $5 \times 10^5 \text{ molecules cm}^{-3}$  (Gómez Alvarez et al., 2013) and nicotine would have a lifetime of 6.6 h. (Weschler and Shields, 1996) Outdoors, during daytime, the OH radical concentrations are typically of the order of  $2 \times 10^6 \text{ molecules cm}^{-3}$  hence shortening the lifetime of nicotine to 1–2 h (Borduas et al., 2016).

Given that nicotine ( $pK_a$  is 8.0) is much more basic than nicotelline (estimated  $pK_a$  is 3.69) (Jacob et al., 2013), under ordinary atmospheric conditions, indoors or outdoors, essentially all nicotelline will be unprotonated, but this is not necessarily the case for nicotine. Variability in pH that is expected under ordinary conditions could very easily change the partitioning of nicotine between the gas and particle phases (Pankow, 2001). Based on inference from the chamber study by Jacob et al. (Jacob et al., 2013), nicotelline collected in the particle phase for different sampling and aging times showed less variability (RSD of 15%) in comparison to nicotine that was highly variable (RSD of 60%), the latter indicating that the partitioning of nicotine would be more susceptible to changes in atmospheric conditions than nicotelline. Fig. 2 implies a linear relationship between nicotine and nicotelline, apparently contradicting the abovementioned explanation; however, with

treated filters both nicotine and nicotelline concentrations represent their gas+particle phases and hence may explain the obtained relationship.

#### 3.4.2. Seasonal and spatial variability of nicotelline

Fig. S2 in the Supplementary Material illustrates the concentrations and seasonal variability in airborne  $PM_{10}$  (in  $\mu g m^{-3}$ ) for each site by the air basin. Across the seasons, the highest variability in the median concentration ( $29\text{--}54 \mu g m^{-3}$ ) was observed in Bakersfield. In the other basins/sites, the  $PM_{10}$  concentration variability across the seasons is less pronounced and the highest median concentration tends to occur in fall varying between 11 and  $25 \mu g m^{-3}$ .

Fig. 4 shows the seasonal distribution of nicotelline found in  $PM_{10}$  (ng/g) for each site by the air basin. All sites show a higher content and higher variability of nicotelline in PM in the colder seasons (fall and winter, September through February). Referring to Fig. S2, the  $PM_{10}$  concentration in Canebrake does not seem to be different from the other air basins, however the content of nicotelline in the  $PM_{10}$  at this site is about 30 times less than the other sites. From Table 1, Canebrake is a rural site in the Mojave Desert with a very low population density and possibly the local air has limited emission of tobacco PM. Furthermore, south of Canebrake is very windy (Fig. S1(b)) and most probably this leads to less of an accumulation of nicotelline, but the concentration of  $PM_{10}$  in Canebrake remains quite stable due to the continuous transport of PM from the surrounding desert. This argument is corroborated in Fig. 4 where the amount of tobacco smoke in  $PM_{10}$ , in Canebrake, indicated by nicotelline, is much lower than the other sites.

Statistical details are presented in Table S2 in the Supplementary Material, in summary, the range of airborne nicotelline mean concentration in 2010 was  $31.3\text{--}37.9 \text{ pgm}^{-3}$  for four sites but for Canebrake the concentration was very low  $0.6 \text{ pgm}^{-3}$  as already discussed. However, at all the CARB sites the concentration of nicotelline was higher in fall (September–November) and winter (December–February) compared to the other seasons. In fact, the airborne nicotelline concentration in the colder seasons is approximately 2 to 3 times higher than the warmer seasons, consistent with poorer dispersion conditions typical of the cooler months of the year.

For the CARB dataset, a Spearman-rho correlation analysis (Table S5) indicated that nicotelline exhibits a correlation of  $R = -0.147$

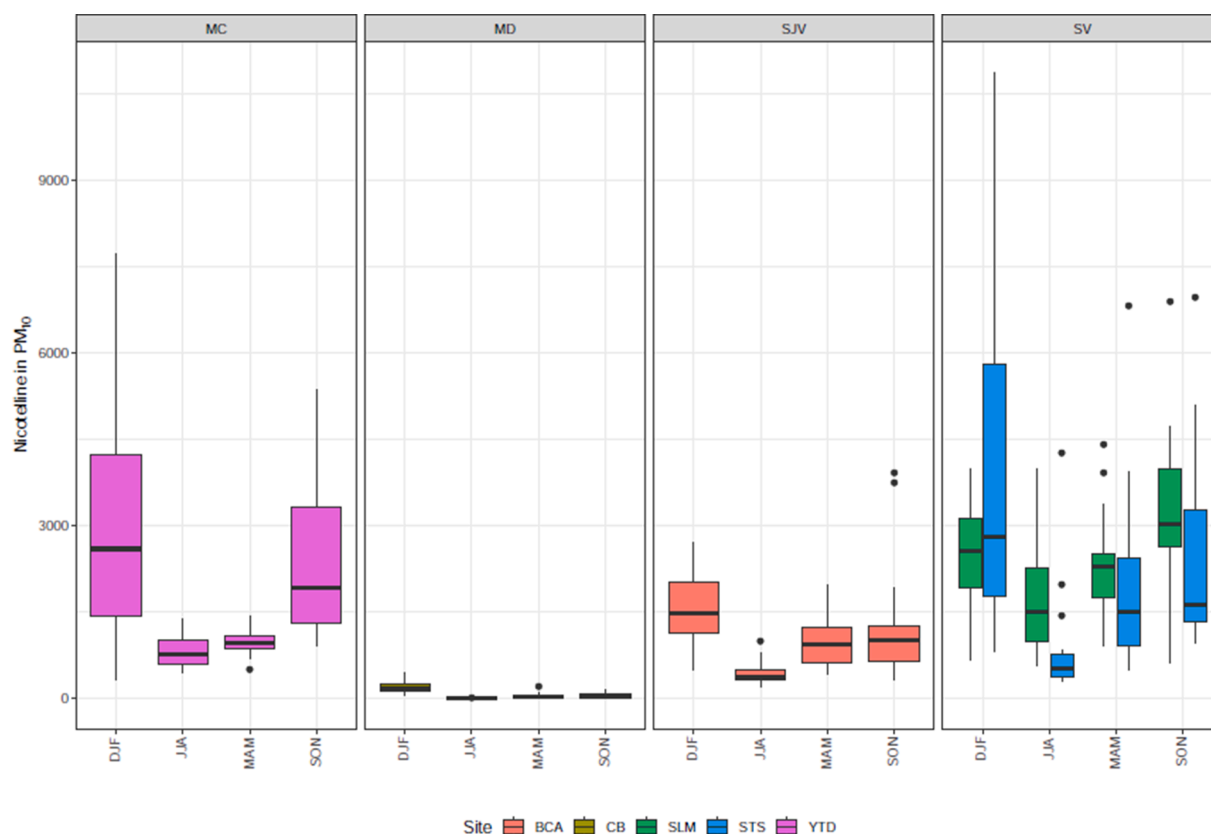


Fig. 4. Seasonal variability of nicotelline in PM<sub>10</sub> (ng/g) for each CARB site by the air basin.

( $p < 0.011$ , 2-tailed) and  $R = -0.718$  ( $p < 0.000$ , 2-tailed) with ambient temperature (T) and relative humidity (RH) respectively. The correlation with wind speed (ws) is very weak,  $R = 0.070$  and not statistically significant ( $p < 0.227$ , 2-tailed).

### 3.4.3. Nicotelline in different campaigns

Table S3 in the Supplementary Material reports descriptive statistics of nicotelline levels in different PM fractions collected on untreated filters from other six sites in four countries between 2014 and 2018.

From the three sites in Hong Kong, it appears that the median nicotelline concentration at Tseung Kwan O Industrial Estate (MA - landfill site) is lower ( $10.2 \pm 7.6 \text{ pgm}^{-3}$ ) than the other two sites because the PM composition in MA is most probably of construction material origin given that in the last years it has been accepting only construction waste. At Tin Shui Wai (TSW) the median concentration is higher as is the variability, however given that both Tin Shui Wai and Tseung Kwan O (TKO) are urban sites in a mix of residential and commercial areas, the nicotelline concentrations are similar, at TSW ( $47.9 \pm 30.6 \text{ pgm}^{-3}$ ) and at TKO ( $37.9 \pm 14.7 \text{ pgm}^{-3}$ ).

For the limited dataset collected in Birmingham, PM<sub>2.5</sub> and PM<sub>10</sub> were collected concurrently. The overall median concentrations were  $2.3 \pm 0.1 \text{ pgm}^{-3}$  and  $8.6 \pm 3.0 \text{ pgm}^{-3}$  respectively, somewhat expected given the background location and the low airborne nicotine levels detected in Birmingham (noted also in Fig. 2).

In 2016, the datasets from Msida correspond to two sampling periods spanning from March to July, collecting PM<sub>2.5</sub> and from July to September, collecting PM<sub>10</sub>. The median concentration in the two fractions were  $13.4 \pm 8.7 \text{ pgm}^{-3}$  and  $19.8 \pm 6.7 \text{ pgm}^{-3}$  respectively. In Malta, airborne PM does not show seasonality (Fenech and Aquilina, 2020), so although the different size fractions were not collected concurrently, the difference in the median hints that nicotelline is found in both fractions. This observation can be also deduced from the Birmingham samples however this claim warrants further investigation. In

2018, the median nicotelline concentration was  $85.3 \pm 85.0 \text{ pgm}^{-3}$  when sampling PM<sub>2.5</sub> in the colder months from November to December. The difference between the 2016 and 2018 samples on untreated filters could be attributed to different atmospheric conditions across the warm and colder months, in a similar way that was observed from the CARB samples.

The samples collected in San Francisco in 2016 were Total Suspended Particulate (TSP) and the median concentration was  $7.9 \pm 1.8 \text{ pgm}^{-3}$ . Although it well known that the tobacco smoking prevalence in San Francisco is low (12.3% in 2012) (SFTFPM.org, 2018), these were the only samples collected on a 5-storey building, which could explain the lower mean nicotelline concentrations obtained, even though the samples from this site were representing TSP, for which higher levels of nicotelline might have been expected. Knowing that PM concentration profiles change vertically (e.g. (Colls and Micallef, 1999; Wu et al., 2002)), the apparent lower median concentration in a relatively densely populated city is not unexpected.

### 3.5. Percentage of PM derived from tobacco smoke

Due to the reactivity or partitioning from particle to gas phase of nicotine or most of the other alkaloids emitted from commercial cigarettes, as shown in experiments carried out by (Jacob et al., 2013), the percentage of tobacco smoke in PM could not be calculated using these compounds. However, from the same experiments, it was shown that given the stable nature of nicotelline in the particle-phase PM, an apportionment factor of 1589 ng/mg was calculated and it will be used to calculate the attributable fraction of tobacco smoke in airborne PM samples (Jacob et al., 2013). Fig. 5 and Table S4 shows details of the variability of the percentage of tobacco smoke particulate in PM for the countries considered. The highest variability was obtained for samples from the USA and China, but the overall median for these four countries varies from 0.03 to 0.08% (mean 0.06%). For the USA, the calculation of



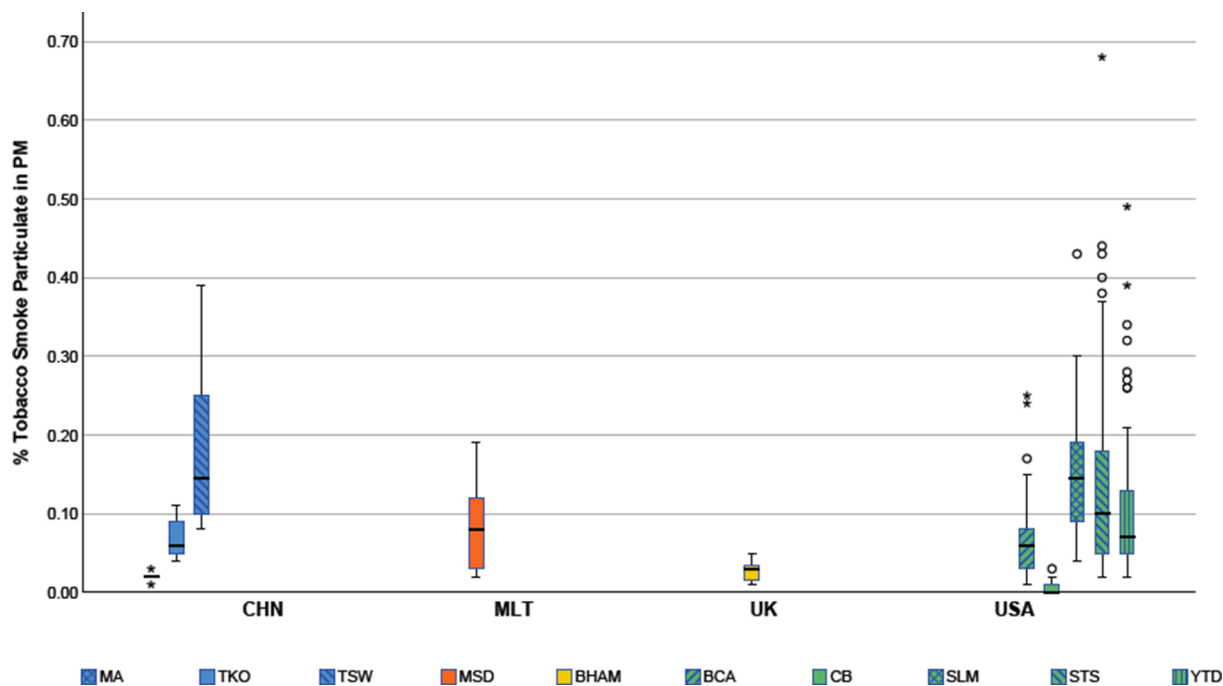


Fig. 5. Variability of Percentage Tobacco Smoke particulate in PM in all cities, by country.

the percentage tobacco smoke particulate in PM and hence its range and variability is driven mainly by the load of nicotelline in PM (reference is made to Fig. 4 in comparison to the % tobacco smoke particulate in PM in the USA sites in Fig. 5).

Although a limited number of samples collected over a span of years, were available from other countries, the range of the percentage tobacco smoke particulate in PM is of the same order of magnitude of the results obtained from the USA dataset.

From the knowledge of the tobacco smoking prevalence patterns associated with the different countries considered in this study, the smoking prevalence of adults in Birmingham (18.4% in 2014) (Local Government Association, 2018) is comparable to that in Malta (20.0% in 2017) (WHO FCTC, 2017). Although in Hong Kong the smoking prevalence was 11.4% in 2015 (Hong Kong Council on Smoking and Health, 2018), the mean nicotelline concentration and the percentage of tobacco smoke in PM was along the same levels obtained for the other countries.

An analysis of the nicotelline pollution roses (Fig. S3) from all sites except from Birmingham (as no wind data was available), indicates that in most cases the higher nicotelline concentration is associated with long-range transport of PM, representing well mixed air masses, hence the median values of percentage tobacco smoke particulate in PM are associated with a geographical variability that is linked to the population densities and smoking prevalence in cities. This strengthens our argumentation that nicotelline can be considered as a suitable marker for tobacco smoke particulate in airborne PM and its ubiquitous presence represents a tobacco-smoke contamination of PM.

#### 4. Conclusions

The aims of this study were to determine if nicotelline has the adequate characteristics to be considered as a suitable marker of tobacco smoke particulate in PM, and if so, if it could be used to estimate the fraction of airborne PM attributable to tobacco smoke.

This was the first comprehensive study to show the ubiquitous presence of nicotelline in outdoor PM. Results from year-long datasets indicated that nicotelline in PM exhibits a seasonal variation modulated by the variability in the PM levels. The spatial variability on the other hand was more driven by the areas chosen, the associated population

densities and the tobacco smoking prevalence patterns.

A stability study carried out to determine if nicotelline decomposes during sampling indicated that decomposition is negligible and loss is dependent on the PM levels, and not on other atmospheric conditions, unlike nicotine that is highly affected by oxidant levels.

Evidence of specificity for tobacco smoke was strengthened by simultaneously measuring nicotine, using an established method of using quartz fiber filters treated with sodium bisulfate to sample PM, in order to also collect total airborne nicotine which exists in both in the gas and particle phase. The results demonstrated that total airborne nicotine, the primary marker of tobacco smoke, is directly proportional to airborne nicotelline in the various localities tested, confirming its specificity for SHS.

The nicotelline collection efficiency on the bisulfate-treated filter showed that a treated filter is only slightly more efficient in collecting nicotelline and allows simultaneous sampling of nicotine as well. Although the specific sampling site microenvironment characteristics determine the overall atmospheric concentrations detected, in all sites, even in the cleanest environments, nicotelline could be detected with confidence, another important property of a suitable marker.

The main limitation of this study was that there was not enough information to understand why nicotelline was found in different PM size fractions. In the future, analysing untreated filters collected by air quality networks from densely populated cities over the world would give a better understanding of the scale of tobacco-smoke contamination of PM and its implications mentioned hereunder.

The range of the median percentage tobacco smoke particulate in PM calculated through the nicotelline load in PM across the four countries varied from 0.03 to 0.08%, acknowledging that these calculations were based on relatively small datasets.

Although these values in themselves are low, they set a new standard for evaluating a possible chronic exposure to SHS through inhalation of PM even in non-smoking environments. There is also considerable interest in determining exposure to and the health effects of tobacco smoke residues remaining indoors in places where smoking once occurred. These residues have been termed Thirdhand Smoke (Acuff et al., 2016; Jacob et al., 2017; Matt et al., 2011). Unlike the major SHS exposure pathway which is by direct smoke inhalation, these Thirdhand

Smoke components have additional exposure pathways, including dermal uptake, hand-to-mouth transfer and by inhalation of secondary particles that form after re-emission from surfaces (Petrick et al., 2011). Therefore, in studies of exposure, it is important to utilize markers for PM, such as nicotelline, as well as gas-phase markers such as nicotine. Both phases contain numerous toxic substances and of particular concern in the particle phase are the highly carcinogenic tobacco specific nitrosamines.

Determining background atmospheric levels of tobacco smoke would be of particular importance for assessing Thirdhand Smoke contamination of indoor venues, to distinguish the contribution of past indoor smoking from what is an unavoidable contamination originating outdoors. The results of this comprehensive study should be useful in addressing this issue.

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### CRediT authorship contribution statement

**Noel J. Aquilina:** Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft. **Christopher M. Havel:** Formal analysis, Methodology. **Polly Cheung:** Formal analysis. **Roy M. Harrison:** Data curation, Methodology, Writing - review & editing. **Kin-Fai Ho:** Data curation, Writing - review & editing. **Neal L. Benowitz:** Supervision, Writing - review & editing. **Peyton Jacob III:** Conceptualization, Writing - review & editing.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2021.106417>.

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