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## Estimated Exposure Risks from Carcinogenic Nitrosamines in Urban Airborne Particulate Matter

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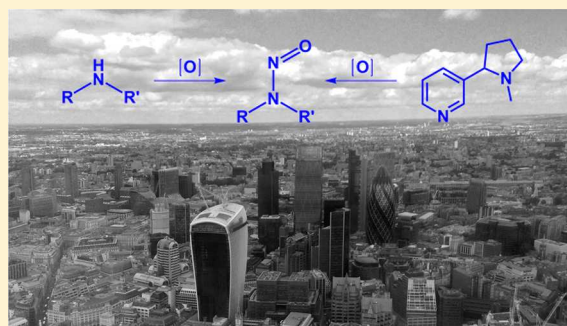
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### S Supporting Information

**ABSTRACT:** Organic nitrogen (ON) compounds are present in atmospheric particulate matter (PM), but compared to their inorganic, hydrocarbon, and oxygenated counterparts, they are difficult to characterize due to their low concentrations in complex matrices. Nitrosamines are a class of ON compounds known to be highly carcinogenic and include species formed from nicotine degradation, but there are no detailed estimates of their abundance in ambient air. We use a highly sensitive analytical method, which is capable of separating over 700 ON compounds, to determine daily variability in nicotine, and 8 nonspecific and 4 tobacco-specific nitrosamines in ambient PM from central London over two periods in winter and summer. The average total nitrosamine concentration was  $5.2 \text{ ng m}^{-3}$ , substantially exceeding a current public recommendation of  $0.3 \text{ ng m}^{-3}$  on a daily basis. The lifetime cancer risk from nitrosamines in urban PM exceeded the U.S. Environmental Protection Agency guideline of 1 excess cancer case per 1 million population exposed after 1 h of exposure to observed concentrations per day over the duration of an adult lifetime. A clear relationship between ambient nitrosamines and total  $\text{PM}_{2.5}$  was observed with  $1.9 \text{ ng m}^{-3} \pm 2.6 \text{ ng m}^{-3}$  (total nitrosamine) per  $10 \mu\text{g m}^{-3} \text{ PM}_{2.5}$ .



### INTRODUCTION

Particulate matter less than  $2.5 \mu\text{m}$  in diameter, termed  $\text{PM}_{2.5}$ , lies within the respirable size range for humans and is therefore considered an important air quality standard.<sup>1</sup> The deposition of particles upon inhalation is largely dependent on size; in general, smaller particles tend to reach lower parts of the respiratory tract, such as the alveolar region where gas exchange occurs. Larger particles, however, are normally trapped in the upper respiratory tract and removed more rapidly.<sup>2</sup> As a result, inhalation of  $\text{PM}_{2.5}$  has particularly adverse effects on human health, contributing to both lung and heart disease and also premature mortality and morbidity, particularly among more sensitive population groups, such as asthmatics, children, and the elderly.<sup>3</sup>

Within the respirable and often toxic chemical constituents in  $\text{PM}_{2.5}$  exist a range of organic nitrogen (ON) compounds. Atmospheric ON is difficult to characterize due to its various complexities; it spans a wide range of volatilities and polarities, originates from both biogenic and anthropogenic sources, and can undergo many biological and photochemical transformations. Although there are extensive studies and reviews of atmospheric ON, there is still no full description of its chemical composition.<sup>4–7</sup> This may be due to the lack of

comparable studies; many different measurement techniques have been used, often targeting different classes of ON compounds. The environmental implications of ON compounds are also important.<sup>8,9</sup> Many species are recognized as essential nutrient sources for marine and terrestrial ecosystems, yet little is known about their potential toxicity.<sup>10</sup> Overall, it is clear that a better understanding of ON chemical composition is required.

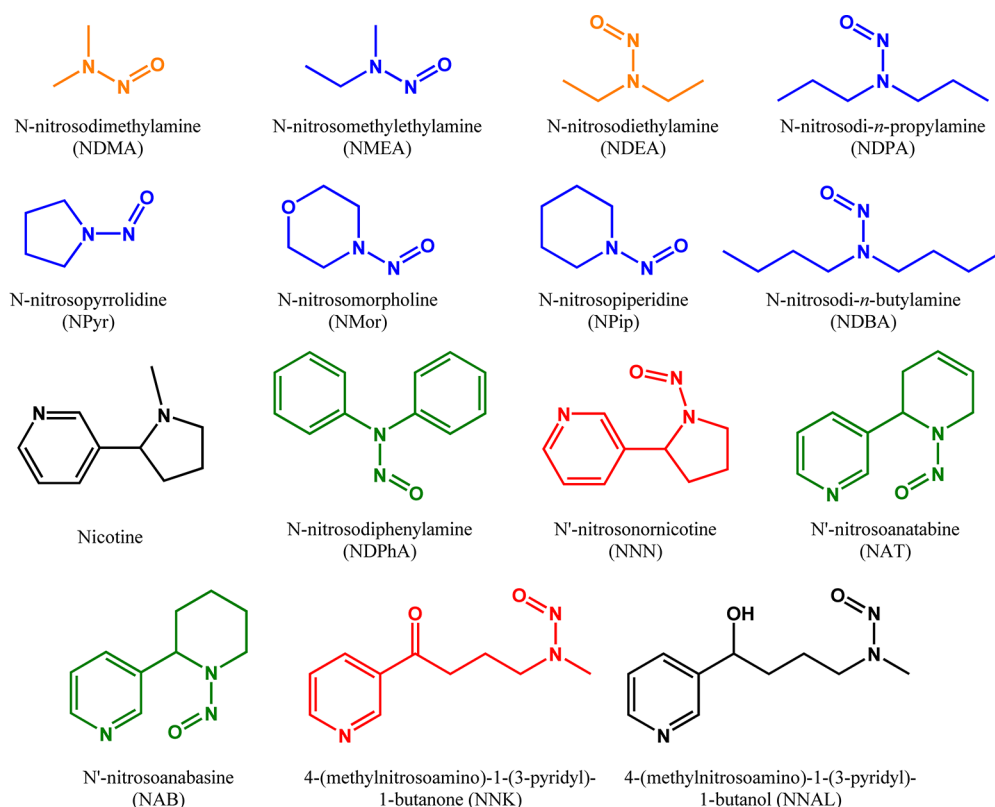
Nitrosamines are a particular class of ON compounds that have been classified by the International Agency for Research on Cancer (IARC) as extremely potent human carcinogens<sup>11</sup> and have been highlighted in recent studies as environmental contaminants of increasing health concern.<sup>12–15</sup> Although the term “nitrosamine” can incorporate an array of N-nitroso compounds, there is one particular group referred to as nonspecific nitrosamines (N-nitrosamines), which are N-nitroso derivatives of secondary amine precursors.<sup>16</sup> They can be emitted to the atmosphere directly, for example, from

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**Figure 1.** Chemical structures of the target N-nitrosamines, TSNAs and nicotine and their respective IARC classifications: (red) group 1, known carcinogen to humans; (orange) group 2A, probable carcinogen to humans; (blue) group 2B, possible carcinogen to humans; and (green) group 3, not classifiable as to its carcinogenicity to humans.<sup>11</sup>

tobacco smoke, cooking, or vehicle emissions; alternatively, they are formed in the atmosphere through oxidation or nitrosation reactions of their precursor amines.<sup>6</sup> N-Nitrosamines have been determined in food products,<sup>17</sup> cosmetic products,<sup>18</sup> house dust,<sup>12</sup> and water,<sup>19</sup> as well as in PM samples.<sup>13,14</sup> Nicotine is the most abundant organic compound emitted during smoking and can react with nitrous acid and other atmospheric oxidants to form a class of special interest nitrosamines, tobacco-specific nitrosamines (TSNAs).<sup>20</sup> TSNAs are some of the most commonly occurring carcinogens in tobacco smoke and can induce lung, oral, esophageal, and pancreatic cancer.<sup>21</sup> In a previous study, Ramirez et al.<sup>15</sup> measured nitrosamines in house dust (which is often contaminated with residual smoke gases and particles, known as third-hand smoke) collected from homes occupied by both smokers and nonsmokers, and reported an increased human cancer risk from exposure to nitrosamines. Interestingly, the presence of N-nitrosamines in nonsmokers' homes, and its lack of correlation with nicotine, indicated that the main source of these compounds was likely to be outdoor ambient air pollution.<sup>15</sup>

To determine trace level compounds such as nitrosamines in complex atmospheric matrices, an extraction method offering high recovery and reproducibility coupled with a highly specific and sensitive measurement method is required. Pressurized liquid extraction (PLE) is suitable for compounds that are sensitive, thermolabile or present in low concentrations. It has been used previously as a suitable technique for atmospheric PM samples, demonstrated by the extraction of contaminants such as N-nitrosamines,<sup>14</sup> PAHs,<sup>22</sup> phthalates, and organophosphate esters.<sup>23</sup> The use of comprehensive two-dimensional

gas chromatography (GC × GC) as an analytical measurement technique provides increased separation power, and offers better peak resolution and sensitivity compared to one-dimensional GC.<sup>24</sup> GC × GC has been successfully coupled to both time-of-flight MS (TOF/MS) and nitrogen chemiluminescence detection (NCD) to analyze ON compounds in urban aerosol, the latter technique offering higher sensitivity and selectivity toward ON, and greater ease of calibration.<sup>25,26</sup>

To extend upon studies which have simply identified the presence of N-nitrosamines in ambient air,<sup>13,14,26</sup> we present more extensive time-resolved measurements of both N-nitrosamines and TSNAs in ambient air. Time-resolved sampling is essential to capture variability in concentration, enabling reasonable estimates of exposure to be calculated. The aim of this study is to develop a PLE-GC × GC-NCD method capable of time-resolved measurement of N-nitrosamines and TSNAs in ambient air PM samples collected during intensive observations in London, as part of the 2012 Clean Air for London (ClearfLo) campaign. The first comparisons between observed ambient nitrosamine levels and recommended guidelines have been made, allowing for an exposure assessment to be carried out to determine the human cancer risk through inhalation of these species.

## EXPERIMENTAL SECTION

**Standards and Solutions.** A mixed standard solution of 9 N-nitrosamines (EPA 8270/Appendix IX Nitrosamines Mix) containing N-nitrosodimethylamine (NDMA), N-nitrosomethylethylamine (NMEA), N-nitrosodiethylamine (NDEA), N-nitrosodi-*n*-propylamine (NDPA), N-nitrosopyrrolidine (NPyr), N-nitrosomorpholine (NMor), N-nitrosopiperidine

(NPip), N-nitrosodi-*n*-butylamine (NDBA), and N-nitrosodiphenylamine (NDPhA) was used (2000 mg L<sup>-1</sup> in methanol). Individual standards of nicotine, N'-nitrosornicotine (NNN), N'-nitrosoanatabine (NAT), N'-nitrosoanabesine (NAB), 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanol (NNAL) were also used. All standards were purchased from Sigma-Aldrich, Ltd. (Dorset, U.K.) and had a minimal purity of 97% except for NNAL, which was ≥92%. Standard solutions were prepared in ethyl acetate (GC grade, 99.9% purity) from VWR International, Ltd. (Leicestershire, U.K.). The chemical structures of the target compounds and their respective carcinogen classifications set out by the IARC are shown in Figure 1.<sup>11</sup>

**Sample Collection and Preparation.** As part of the U.K. Natural Environment Research Council (NERC) funded ClearLo project, 77 PM<sub>2.5</sub> filter samples were collected at the North Kensington site (51°31'16" N, 0°12'48" W) using a High Volume Air Sampler (Ecotech HiVol 3000, Victoria, Australia) operating at 1.13 m<sup>3</sup> min<sup>-1</sup>. 52 samples were collected during winter 2012 between 10/01/2012 and 08/02/2012 throughout both the daytime (09:00–17:00) and the nighttime (17:00–09:00). The remaining 25 samples collected in summer 2012 (July 22–August 16, 2012) were changed at midday and represent 24 h sampling intervals. Further details and a map of the site are provided in the Supporting Information (Figure S1). The PM<sub>2.5</sub> quartz filters (20.3 × 25.4 cm) supplied by Whatman (Maidstone, U.K.) were prebaked at 550 °C for a minimum of 12 h prior to sample collection. After sample collection, the filters were wrapped in aluminum foil and stored at -18 °C until analysis.

**Additional Measurements.** HONO was measured using a highly sensitive, long-path absorption photometer (LOPAP) instrument from the University of Wuppertal, Germany.<sup>27</sup> The instrument was successfully validated against the spectroscopic DOAS technique under urban conditions and in a smog chamber.<sup>28</sup> During the campaign, a detection limit of 1 pptV for a time resolution of 5 min, a precision of 1%, and an accuracy of 10% was obtained. The PM<sub>2.5</sub> filter samples were analyzed for OC and EC using a Sunset thermal-optical carbon analyzer (Sunset Laboratory, Inc.), following the EUSAAR2 thermal protocol.<sup>29</sup> Hourly PM<sub>2.5</sub> data, which was measured at the North Kensington site using a TEOM-FDMS, was supplied by UK-AIR.<sup>30</sup>

**Pressurized Liquid Extraction.** A quarter of each PM<sub>2.5</sub> sample was extracted using an accelerated solvent extraction system (ASE 350, Dionex, Sunnyvale, CA). The base of each 5 mL stainless steel extraction cell was lined with two glass microfibre filter papers (Fisher Scientific, U.K.) and then packed with the sample. Extractions were carried out in ethyl acetate (GC grade, 99.9% purity) at 80 °C and 1500 psi for three consecutive 5 min cycles. A 50% flush volume and 60 s purge time were used. Extracts obtained were held at 0 °C while evaporated under nitrogen to 1 mL and stored at -18 °C prior to analysis. Recovery and optimization tests were performed using a 9 cm<sup>2</sup> portion of the collected PM<sub>2.5</sub> samples, which were heated (300 °C, 1 h) to remove semivolatile compounds and then spiked with a mixed nitrosamine standard (100 μL, 50 ppm). The remaining dead volume in the extraction cell was filled with blank filter paper and extracted under the same conditions previously described. Procedural blanks were carried out, and no detectable amounts of target compounds were found.

**Chromatographic Analysis.** Chromatographic analysis was carried out on a GC × GC-NCD system comprised of an Agilent 7890 gas chromatograph and an Agilent 255 NCD system (Palo Alto, CA). The first column was a nonpolar Ultra Inert DB5 (30 m × 0.32 mm i.d. × 0.25 μm film thickness) from Agilent Technologies, Ltd. (Stockport, U.K.) and the second column a midpolarity BPX50 (2 m × 0.10 mm i.d. × 0.10 μm film thickness) from SGE Analytical Science (Milton Keynes, U.K.). The initial temperature of the first dimension column was 40 °C for 2 min, followed by a heating rate of 7 °C min<sup>-1</sup> to 100 °C for 8 min and then further heating at 7 °C min<sup>-1</sup> until 270 °C was reached and held isothermally for a further 5 min. A temperature offset of 30 °C was applied to the second dimension column throughout the GC temperature program. A liquid nitrogen two-stage cold jet modulation system was used, with a modulation period of 5 s and a +15 °C offset from the primary GC oven temperature. Data was collected at 200 Hz over the entire course of the analysis, and hydrogen was used as a carrier gas at 1.4 mL min<sup>-1</sup>. Injections of 1 μL were performed in splitless mode at an injection temperature of 200 °C using an automated liquid injector (Gerstel, Mülheim an der Ruhr, Germany). Pyrolysis of the analytes in the NCD was carried out at 900 °C under a hydrogen flow rate of 4 mL min<sup>-1</sup> and an oxygen flow rate of 10 mL min<sup>-1</sup>.

**Cancer Risk Assessment.** The cumulative lifetime cancer risk associated with exposure to the target nitrosamine species was determined according to the Superfund Program's updated approach for the determination of inhalation risk; the concentration of the target chemical in air (μg m<sup>-3</sup>) is used as the exposure metric, rather than the intake of a contaminant in air based on inhalation rate and body weight (mg kg<sup>-1</sup> day<sup>-1</sup>).<sup>31</sup>

Initially, the exposure concentration (EC), which is a time-weighted average concentration, is calculated for each individual contaminant according to eq 1:<sup>31</sup>

$$EC_i = (CA_i \times ET \times EF \times ED) / AT \quad (1)$$

where EC<sub>i</sub> is the EC (μg m<sup>-3</sup>) specific for each carcinogen; CA<sub>i</sub> is the target contaminant concentration in air (μg m<sup>-3</sup>); ET is the exposure time (hours day<sup>-1</sup>); EF is the exposure frequency (days year<sup>-1</sup>); ED is the exposure duration (years); and AT is the averaging time (lifetime in years × 365 days year<sup>-1</sup> × 24 h day<sup>-1</sup>).

The cumulative lifetime cancer risk is then calculated using eq 2:<sup>31</sup>

$$\text{risk}_{\text{inhalation}} = \sum_{i=1}^n IUR_i \times EC_i \quad (2)$$

where IUR<sub>i</sub> is the inhalation unit risk specific for each carcinogen (μg m<sup>-3</sup>). The IUR can be defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg m<sup>-3</sup> in air. IUR values were taken from databases provided by the Integration Risk Information System (IRIS)<sup>32</sup> and the Office of Environmental Health Hazard Assessment (OEHA),<sup>33</sup> priority was given to IRIS values. As toxicological values have only been officially established for NDMA, NDEA, NDPA, NPyr, NMor, NPip, NDBA, NDPhA and NNN, the cumulative cancer risk presented is a sum of the risks from these nine compounds only.



Table 1. Median, Mean, and Maximum Nitrosamine Concentrations in PM<sub>2.5</sub> in Winter and Summer

compd	winter				summer				%RSD <sup>b</sup>
	median (ng m <sup>-3</sup> )	mean (ng m <sup>-3</sup> )	maximum (ng m <sup>-3</sup> )	%Qt <sup>a</sup>	median (ng m <sup>-3</sup> )	mean (ng m <sup>-3</sup> )	maximum (ng m <sup>-3</sup> )	%Qt	
NDMA	0.45	1.36	6.37	83	0.24	0.49	3.54	92	8.6
NDEA	0.62	0.89	3.51	96	1.13	2.08	12.33	100	8.7
NDPA	0.05	0.07	0.25	42	0.04	0.05	0.18	72	8.3
NPyr	0.01	0.08	0.48	39	0.02	0.04	0.24	36	8.3
NMor	0.10	0.32	2.27	56	0.13	0.23	1.35	96	11.1
NPip	0.03	0.04	0.28	15	0.03	0.05	0.36	40	8.6
NDBA	0.15	0.18	0.72	60	0.22	0.33	1.26	100	8.5
NDPhA	0.95	1.22	4.08	94	0.34	0.60	2.58	88	9.1
NNN	0.12	0.21	0.75	54	0.14	0.20	0.58	96	7.8
NAT	0.18	0.31	1.94	58	0.14	0.16	0.91	68	6.8
NAB	0.03	0.14	1.21	39	0.06	0.11	0.86	56	7.5
NNK	0.41	0.57	2.35	79	0.25	0.29	0.98	100	13.8

<sup>a</sup>Percentage of samples in which the target species were above the LOQ. <sup>b</sup>Total error associated with each compound.

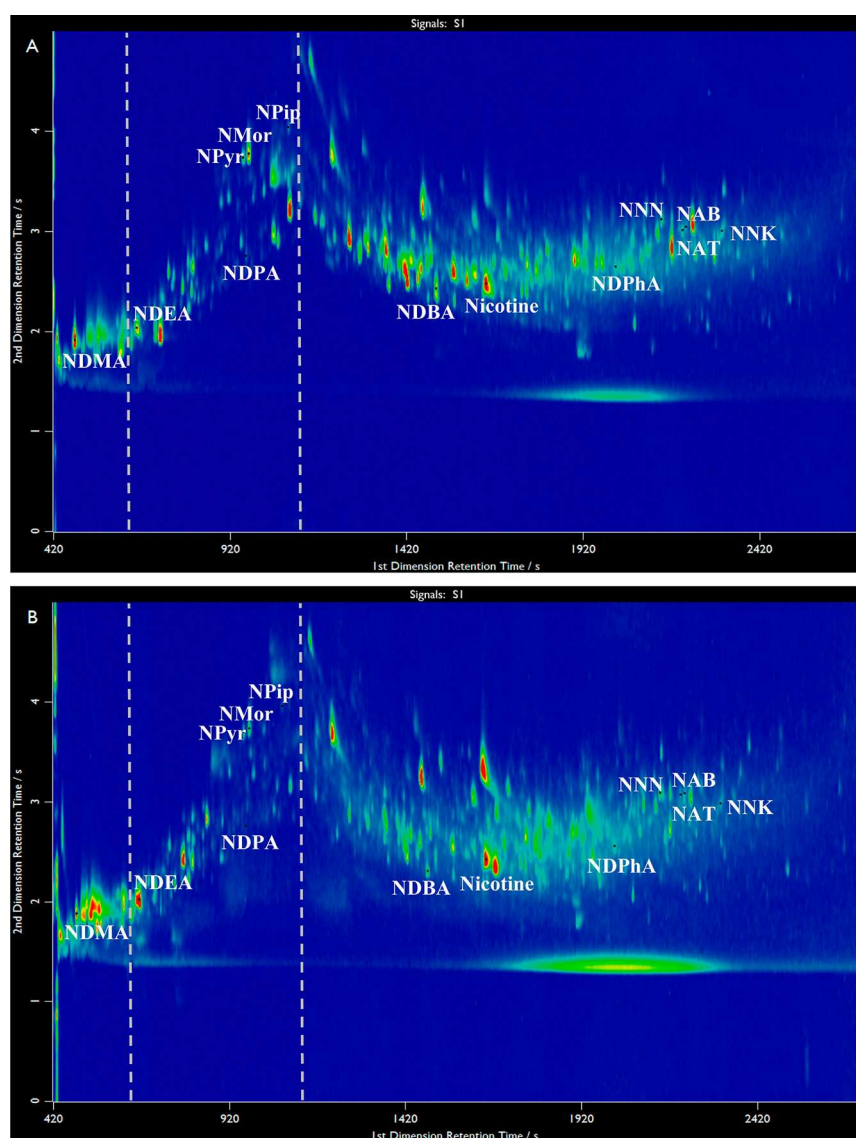


Figure 2. Typical GC × GC-NCD chromatograms of air PM<sub>2.5</sub> samples collected during (A) winter (from 06/02/2012 17:17 to 07/02/2012 08:37) and (B) summer (from 10/08/2012 12:56 to 11/08/2012 11:55).

Chemicals sometimes cause cancer by a mutagenic mode of action (MOA) and therefore pose a higher risk of cancer to humans when exposure occurs during early life. In these cases,

age-dependent adjustment factors (ADAFs) can be applied to assess the additional risk.<sup>34</sup> Eq 2 is altered to include the ADAFs, as shown in eq 3:<sup>31</sup>

$$\text{risk}_{\text{inhalation}} = \sum_{i=1}^n \text{IUR}_i \times \text{EC}_i \times \text{ADAF}_i \quad (3)$$

where ADAF<sub>*i*</sub> is the age-dependent adjustment factor specific for the age group under consideration.

Values for all parameters and chosen age intervals are recommended by the U.S. EPA and are provided in the [Supporting Information](#), Table S1.<sup>35</sup> Nitrosamine concentrations below the limits of detection (LODs) and limits of quantification (LOQs) were replaced with a value equal to half the LOD or half the LOQ, respectively, for all risk assessment calculations, as recommended by the U.S. EPA.<sup>36</sup>

**Statistical Analyses.** Correlations between different variables were assessed by performing multiple linear regression analyses, using RStudio (Boston, MA).

## RESULTS AND DISCUSSION

**PLE Conditions.** In line with previous studies, ethyl acetate was used as the extraction solvent<sup>12,14</sup> and tested at three temperatures (70, 80, and 100 °C) under the chosen PLE conditions. Recovery levels were low at 70 °C, ranging from 1% for nicotine to 20% for NNN, but were considerably higher at both 80 and 100 °C, averaging 66 and 62% respectively. A second set of recovery tests was performed at 80 °C under the same PLE conditions, but the extraction vial was stored at −18 °C before and after the extraction. Furthermore, the extracts were held at 0 °C (rather than previously at room temperature) during evaporation under nitrogen to a final volume of 1 mL. Recovery levels at 80 °C improved dramatically to an average of 91% under the newly modified extraction procedure; recovery levels and the associated errors are provided in [Supporting Information](#), Table S2. Evaporating samples to dryness was avoided as according to previous studies, this can lead to excessive compounds loss, especially those with low vapor pressures.<sup>23</sup>

**Method Validation.** The main instrumental parameters of the GC × GC-NCD system were evaluated and are detailed in the [Supporting Information](#), Table S3. Instrumental LODs and LOQs were calculated according to the EPA protocol 40 CFR 136;<sup>36</sup> multiplying the standard deviation (10 pg, *N* = 10) by the Student *t*-value (*N* = 10, 95% confidence interval) gave the LOD, and multiplying the standard deviation by 10 gave the LOQ. The LODs and LOQs obtained ranged from 2.0 to 10.5 pg and from 7.2 to 37.2 pg, respectively, with the exception of NNAL, which exhibited significantly higher levels of detection. It is clear that combining the GC × GC with the element specific NCD is a successful way of measuring trace level nitrogen-containing compounds. Good correlation coefficient values (*R*<sup>2</sup>) were obtained for the stated linear ranges (0.9697 to 0.9999).

Instrument repeatability was monitored over the course of the sample analysis period using a mixed nitrosamine standard (100 pg, *N* = 19). The precision (%RSD) remained below 13% for all compounds except nicotine and NNAL; this can possibly be attributed to the lack of equimolar response for these species or degradation during pyrolysis. Total errors were estimated by combining errors associated with the instrument and the recovery process and remained below 14% for all compounds except nicotine and NNAL (Table 1).

**Analysis of Ambient Particulate Matter in London.** The UK NERC funded ClearfLo project was set up to provide long-term integrated measurements of the meteorology,

composition, and particulate loading of London's urban atmosphere at both street level and elevated sites. The PM<sub>2.5</sub> filter samples were collected as part of the two 5 week intensive operation periods (IOPs) in the winter and summer of 2012, at the Sion Manning School in North Kensington, London (classified as an urban background site).

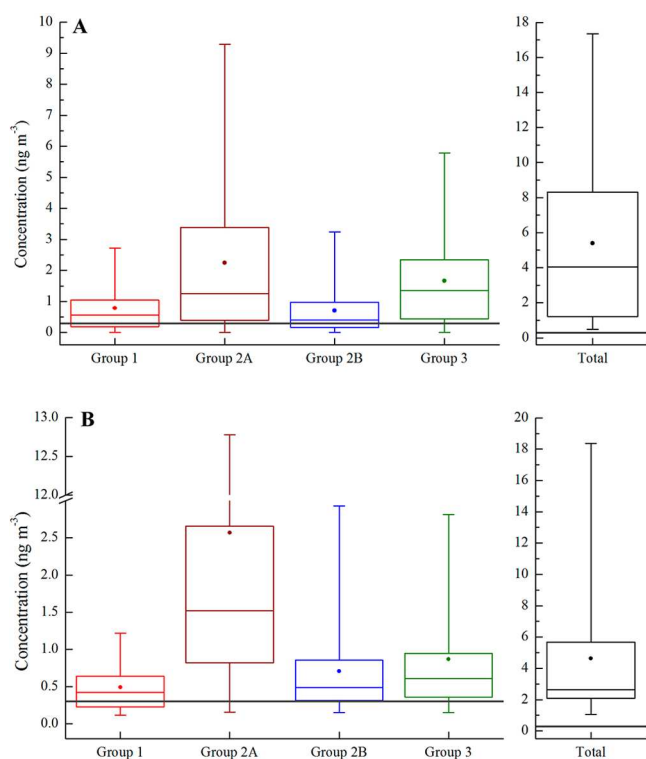
The PLE-GC × GC-NCD method was applied to measure ambient N-nitrosamine, nicotine, and TSNA concentrations in the collected PM<sub>2.5</sub> samples. To ensure accurate quantification of all target compounds, we used individual calibration curves for each compound. GC × GC-NCD chromatograms are shown in [Figure 2](#) for typical samples in both winter and summer 2012. The chromatograms show the complexity of ON in London, and more than over 700 compounds were observed in both samples.

Peak identification was based on direct comparison of retention times on both GC × GC columns to those of individual standards. The method successfully separated and identified the majority of the target compounds; an isothermal period (highlighted within the gray lines on each chromatogram) was introduced to the method to separate NPyr and NMor, which caused some loss of the typical structured chromatograms associated with GC × GC. Although it was possible to detect NMEA, coelution with other ON compounds meant that it was not possible to accurately determine the concentration. It was also difficult to confirm the concentration of NNAL because the levels were close to the LOD and precision was low (RSD = 45%).

Nicotine was the most abundant target compound and was found in all PM<sub>2.5</sub> samples in both winter and summer, with average concentrations of 21.1 and 6.8 ng m<sup>-3</sup>, respectively. Nicotine reached a maximum concentration of 118.1 ng m<sup>-3</sup> in winter and 30.6 ng m<sup>-3</sup> in summer. Although nicotine itself is not classified as carcinogenic,<sup>11</sup> it can undergo a series of atmospheric oxidation reactions to form TSNAs, which are carcinogenic.<sup>20</sup> Elevated exposure of the public to nicotine in ambient PM is primarily of concern due to the potential for coinhalation of its more harmful degradation products.

The median, mean, and maximum nitrosamine concentrations in PM<sub>2.5</sub> in winter and summer are shown in [Table 1](#) (the frequency of occurrence of each compound is also included). Of the eight N-nitrosamines measured during the winter, NDMA and NDPhA had the highest average concentrations of 1.36 and 1.22 ng m<sup>-3</sup>, respectively. Average concentrations were slightly lower for NDEA and NMor, but maximum concentrations reached 3.51 and 2.27 ng m<sup>-3</sup>, respectively. In summer, the highest average concentration was seen for NDEA at 2.08 ng m<sup>-3</sup>, followed by NDPhA at 0.60 ng m<sup>-3</sup> and NDMA at 0.49 ng m<sup>-3</sup>. NNK was the most abundant TSNA measured in both winter (0.58 ng m<sup>-3</sup>) and summer (0.30 ng m<sup>-3</sup>). The concentrations of the other three TSNAs averaged 0.22 and 0.16 ng m<sup>-3</sup> in winter and summer, respectively, but the frequency of occurrence of TSNAs was higher in the summer (56–100%) compared to winter (39–79%).

**Exposure to Nitrosamines.** As shown in [Figure 1](#), the target compounds can be classified according to their carcinogenicity.<sup>11</sup> Box-plot representations of measured nitrosamine concentrations (according to these classifications) are shown in [Figure 3](#) for winter and summer respectively, alongside total nitrosamine concentrations. In 2011, the Norwegian Institute of Public Health (NIPH) recommended



**Figure 3.** Ambient particle-borne nitrosamine concentrations categorized according to their IARC classifications in (A) winter and (B) summer. Separate box plots are given for total nitrosamine concentrations. Each box plot represents the 25th and 75th percentiles of the observed concentrations, and the bottom and top lines indicate minimum and maximum concentrations, respectively. The circle is the mean concentration, and the horizontal line inside the box represents the median concentration. The horizontal black line at  $0.3 \text{ ng m}^{-3}$  represents the NIPH recommended level.<sup>37</sup>

that the total amount of nitrosamines in ambient air should not exceed  $0.3 \text{ ng m}^{-3}$ .<sup>37</sup>

In both seasons, the lowest recorded total nitrosamine concentration exceeded  $0.3 \text{ ng m}^{-3}$ , with average total nitrosamine concentrations of  $5.40$  and  $4.63 \text{ ng m}^{-3}$  for winter and summer, respectively. Furthermore, in both winter and summer, average nitrosamine concentrations of compounds in each IARC group classification exceeded  $0.3 \text{ ng m}^{-3}$ . Of the four different classifications, group 2A carcinogens were observed at the highest levels, with average concentrations of  $2.24$  and  $2.57 \text{ ng m}^{-3}$ , and maximum concentrations of  $9.29$  and  $12.78 \text{ ng m}^{-3}$  in winter and summer, respectively. This direct comparison of measured ambient atmospheric nitrosamine concentrations with recommended air quality guidelines indicates that the ambient concentrations, at least in London, are currently at levels that are likely to pose a significant long-term cancer risk. We find no obvious reason why London would be an abnormal or unrepresentative urban environment for ON in general or nitrosamines specifically.

The nitrosamine concentrations observed in London demonstrate a prima facie case that a cancer risk assessment of exposure via inhalation is necessary. The World Health Organization (WHO) states that inhalation is the only concernable route of exposure when considering the direct effects of atmospheric PM on human health.<sup>38</sup> Toxicological data is only available for nine of the target nitrosamines;

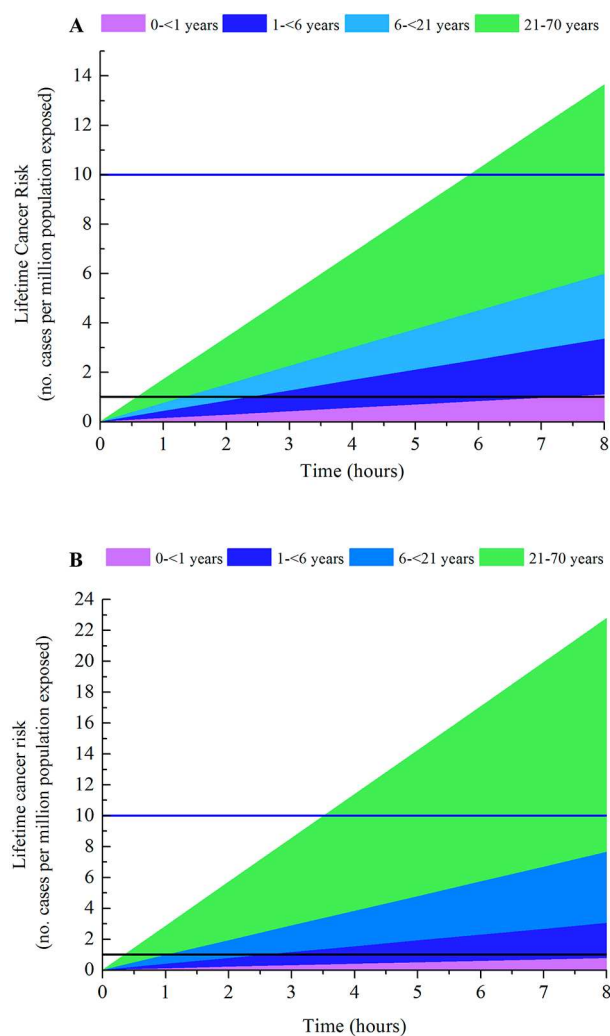
therefore, the carcinogenic risk assessed here using IRIS guidelines only accounts for these compounds.

The original approach used to estimate exposure to inhaled contaminants in air was outlined in the U.S. EPA's Risk Assessment Guidance for Superfund (RAGS) Part A.<sup>39</sup> Using a function of the concentration of the chemical in air (CA), inhalation rate (IR), body weight (BW), and exposure scenario, this approach allows for the estimation of the daily intake of a contaminant in air ( $\text{mg kg}^{-1} \text{ day}^{-1}$ ). However, this approach was developed before the release of the U.S. EPA's Inhalation Dosimetry Methodology (IDM), which provides details of the interpretation of occupational exposures of humans to airborne chemicals.<sup>40</sup> Under this methodology, human equivalent concentrations (HECs) can be extrapolated from experimental exposures, which in turn can be used to develop the inhalation unit risk (IUR) values required for cancer risk assessments. In response to the IDM, the Superfund Program released an updated approach for estimating cancer risk via inhalation. The new approach relies on the concentration of the chemical in air as the exposure metric ( $\mu\text{g m}^{-3}$ ), rather than the intake of a contaminant in air ( $\text{mg kg}^{-1} \text{ day}^{-1}$ ).<sup>31</sup> The new approach is considered more accurate as it accounts for the fact that the amount of chemical reaching the target site is not a simple function of IR and BW. In fact, important considerations of the anatomy and physiology of the respiratory system and the characteristics of the inhaled agent are required, to account for the fact that the amount of pollutant entering the body through the upper respiratory tract and lung is less than the amount measured at the boundary of the body. An estimation of exposure time (ET) is also required to assess lifetime cancer risks using this approach. In this analysis, we assume that an individual is only exposed to the observed values when outside and that indoor exposure is zero, due to lack of available data. The ET was increased from 1 to 8 h in 1 h increments to represent a range of different individual scenarios, and the corresponding EC's were estimated using eq 1. Values for all parameters at the chosen age intervals are provided in the Supporting Information, Table S1. The cumulative lifetime cancer risk was then calculated using eq 2, and age-dependent adjustment factors (ADAF's) were applied if necessary using eq 3. Figure 4A,B show estimated cumulative cancer risks as a function of ET (0–8 h), expressed as the number of excess cancer cases per million population exposed. The corresponding data is given in the Supporting Information, Table S4.

This initial assessment shows that the cancer risk associated with nitrosamine exposure is most prevalent in adults; all of the lifetime cancer risks calculated for this age group (21 to 70 years) exceeded the U.S. EPA guideline of negligible risk (1 excess cancer cases per 1 million population exposed).<sup>35</sup> Additionally in the summer, the minimal cancer risk (defined by the U.S. EPA as 10 excess cancer cases per 1 million population exposed)<sup>35</sup> is exceeded after 4 h of exposure to outdoor ambient air. The risk is slightly lower in winter for the adult age group, with the "minimal cancer risk" level reached after 6 h. After 8 h, the cancer risk reaches 1 excess cancer case per 1 million population of exposed 0 to <1 year olds in winter but in summer remains below 1 excess cancer case. One excess cancer case is predicted within 2 to 3 h in both winter and summer for 1 to <6 and 6 to <21 year olds.

The relevance of the presented risk estimates can be assessed by comparing the values to estimates of other carcinogens in urban air. For example, benzo(a)pyrene (BaP) is a commonly occurring polycyclic aromatic hydrocarbon (PAH) in ambient





**Figure 4.** Average cumulative lifetime cancer risk estimations for different age groups as a function of ED for the inhalation of NDMA, NDEA, NDPA, NPyr, NMor, NPip, NDBA, NDPhA, and NNN, expressed as the number of excess cancer cases per million population exposed in both (A) winter and (B) summer. The horizontal black and blue lines indicate the US EPA guidelines of 1 and 10 excess cancer cases per 1 million population exposed, respectively.<sup>35</sup>

air and is used as a single indicator carcinogen to represent the carcinogenic potential of the complex mixture of PAHs.<sup>41</sup> The current EU guideline value for BaP is 1 ng/m<sup>3</sup>, which corresponds to a lifetime cancer risk of 100 excess cancer cases per 1 million population exposed.<sup>42</sup> However, this value is considered somewhat high, and in 1999 the UK expert panel on air quality standards recommended that the level should be lowered to 0.25 ng/m<sup>3</sup> (i.e., 25 cancer cases per 1 million people).<sup>43</sup> The estimates of cancer risks in this study from nitrosamine exposure are approximately 41 and 68 excess cancer cases per 1 million people in winter and summer respectively (assuming 24 h exposure per day for average adult lifetime in the same way as for BaP). These values are actually higher than the recent recommendation, and therefore, they can be considered relevant and of concern.

Inevitably, there are limitations and uncertainties associated with the presented cancer risk evaluation. Currently, the U.S. EPA recommends that a simple additive approach is applied when calculating cumulative cancer risks less than 10<sup>-1</sup>. However, this assumes independence of action by the

compounds involved (i.e., that there are no synergistic or antagonistic chemical interactions and that all chemicals produce the same effect, cancer).<sup>39</sup> Also, the assessment presented only accounts for carcinogenic effects, but realistically, some compounds may also pose chronic and acute noncarcinogenic effects. Nitrosamine concentrations below the LODs and LOQs were replaced with a value equal to half the LOD or LOQ, which can possibly overestimate the calculated risk.<sup>36</sup> To quantify the potential overestimation, we have also calculated the risks when the concentrations below the LODs and LOQs are replaced with zero values (Table S4). This analysis shows that the potential for overestimation is low; on average the risk is only 0.27% lower, with a maximum reduction of 0.55%. A key limitation is the lack of data available for indoor air; this means that we assume indoor exposure is zero and only estimate the outdoor air contribution to total exposure. As people spend a considerable amount of time indoors on a daily basis, it is likely that the exposure risks are significantly higher, indicating that the risk presented is almost certainly an underestimate of true exposure. Currently, there is no appropriate toxicological data available for some nitrosamines (NAT, NAB, and NNN), and so, these are not included in the exposure assessment. Furthermore, it is likely that the nitrosamines of higher volatility also exist in the gas phase, which would add an additional cancer risk.<sup>44</sup> Overall, the calculated risks are likely to be underestimates, indicating that ambient nitrosamine concentrations have the potential to adversely affect human health in urban areas to a greater extent than presented here. Despite these limitations, this study presents the first estimation of the cancer risk associated with inhalation of nitrosamines in ambient outdoor air.

**Nitrosamine Correlations.** Time series of N-nitrosamines, TSNAs, nicotine, nitrous acid (HONO), OC and PM<sub>2.5</sub> for both winter and summer are provided in the Supporting Information, Figures S2 and S3. HONO and PM<sub>2.5</sub> measurements have been time-averaged to the filter paper sampling times. Strong positive correlation between nicotine and total TSNA concentration was seen in both winter ( $R = 0.73$ ,  $p < 0.001$ ) and summer ( $R = 0.82$ ,  $p < 0.001$ ). This trend may be attributed to both the coemission of nicotine and TSNAs during smoking, and the formation of TSNAs in urban air (nicotine is the sole precursor for TSNAs that are not emitted directly).<sup>20</sup> As expected, the correlation between nicotine and total N-nitrosamine concentration is weaker in both winter ( $R = 0.48$ ,  $p < 0.001$ ) and summer ( $R = 0.47$ ,  $p < 0.02$ ), as N-nitrosamines are either emitted directly or formed from the oxidation of a range of secondary amines.<sup>6</sup> Interestingly, a degree of positive correlation between total N-nitrosamine concentration and total TSNA concentration is seen;  $R = 0.68$  ( $p < 0.001$ ) in winter and  $R = 0.66$  ( $p < 0.001$ ) in summer. The positive relationship between N-nitrosamine and TSNA concentration indicates that the pollutants are probably influenced by common atmospheric factors, such as boundary layer height/dilution, deposition rate, atmospheric chemistry, and meteorological conditions. A moderate to strong correlation was also observed between total nitrosamine (nonspecific and tobacco-specific) concentration and particle mass, both PM<sub>2.5</sub> ( $R = 0.84$ ,  $p < 0.001$  in winter and  $R = 0.67$ ,  $p < 0.001$  in summer) and the OC mass ( $R = 0.80$ ,  $p < 0.001$  in winter and  $R = 0.78$ ,  $p < 0.001$  in summer). This suggests that gas-particle partitioning and the amount of available absorbing mass limits the particle phase concentration of nitrosamines.<sup>45</sup>



Scatter plots of these correlations can be found in the Supporting Information, Figures S4 and S5.

The time series show that the temporal variation of HONO is similar to the nitrosamine observations. Correlations between HONO and N-nitrosamine concentrations were observed in winter ( $R = 0.62$ ,  $p < 0.001$ ) and summer ( $R = 0.74$ ,  $p < 0.001$ ). Stronger positive correlation was found between HONO and TSNA concentrations;  $R = 0.88$  ( $p < 0.001$ ) in winter and  $R = 0.79$  ( $p < 0.001$ ) in summer; it is possible that this correlation arises from the fact that HONO is thought to be a key atmospheric oxidant for nitrosamine formation.<sup>20</sup>

The observed correlations may be useful in predicting nitrosamine levels and the resulting exposure to human health. The relatively strong correlation to PM<sub>2.5</sub> in winter, a pollutant which is continually monitored at various urban sites in London and indeed very many other cities around the world, could allow for nitrosamine levels to be estimated at other urban locations over different periods of time. Where direct measurements of nitrosamines are not available, a value of  $1.88 \pm 2.60 \text{ ng m}^{-3}$  (total nitrosamine) per  $10 \mu\text{g m}^{-3}$  PM<sub>2.5</sub> is recommended for estimates of exposure.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.5b01620.

Details of the ClearLo project and sampling site; location of the North Kensington site; parameters used for the cancer risk assessment; recovery levels under the final PLE conditions; instrumental parameters for the GC × GC-NCD system; cancer risk estimations; time series of N-nitrosamines, TSNA and nicotine; time series of HONO, OC and PM<sub>2.5</sub>; correlations for winter 2012 measurements; correlations for summer 2012 measurements (PDF)

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### Notes

The authors declare no competing financial interest.

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