Distribution of toxic chemicals in particles of various sizes from mainstream cigarette smoke

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Abstract
To accurately estimate the risk of inhaling cigarette smoke containing toxic chemicals, it is important that the distribution of these chemicals is accurately measured in cigarette smoke aerosol particles of various sizes. In this study, a single-channel smoking machine was directly coupled to an electrical low-pressure impactor. The particles of mainstream cigarette smoke were collected using 12 polyester films, and the particulate matter (PM) was characterized. Nicotine, tobacco-specific N-nitrosamines (TSNAs, including NNN, NAT, NAB, and NNK), polycyclic aromatic hydrocarbons (PAHs, including benzo(a)pyrene (BaP), benzo(a)anthracene, and chrysene), and heavy metals (including Cr, As, Cd, and Pb) present in the particles of different sizes were analyzed by GC, HPLC-MS/MS, GC/MS, or ICP-MS, respectively. The results demonstrated that the nicotine, TSNAs, PAHs, and heavy metals in mainstream cigarette smoke were dispersed over a particle size ranging from 0.1 μm to 2.0 μm, and the concentration of these toxic chemicals initially increased and then decreased as the particle size grew. The distribution of nicotine was uniform for the PM in the size ranges of less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm, TSNAs and heavy metals in particles of less than 0.1 μm were more abundant, and PAHs in fine particles were also more abundant.

Keywords
mainstream cigarette smoke, nicotine, particle size, particulate matter, toxic chemicals

Introduction
It is well known that cigarette smoke is a complex and dynamic aerosol composed of tiny liquid- and solid-suspended particles with large specific surface areas. In addition to nicotine, many toxic chemicals (HCN, NH3, TSNAs, PAHs, heavy metals, etc.) are contained particulate matter (PM) in cigarette smoke. The particle size distribution of atmospheric aerosols is closely related to the chemical compositions of PM (Berner & Marek, 1967; Gowadia et al., 2009; Ishizu et al., 1978; Jenkins et al., 1979; Morie & Baggett, 1977; Owen et al., 1969). Cigarette smoke particles may deposit in the human respiratory tract and cause disease (Robinson & Yu, 2001). PM, especially fine particles, have been associated with a variety of adverse health effects, so necessary to study the distribution of toxic chemicals in PM of mainstream cigarette smoke.

Currently, studying tobacco-related cancer etiology requires the knowledge of cigarette smoke particle deposition in the respiratory tract. The particle size distribution of the aerosol is an important factor in predicting the deposition fraction of inhaled particles in the human respiratory tract (Chang et al., 1985; Robinson & Yu, 2001; Sahu et al., 2013). In the last century, researchers have investigated particle size distributions of mainstream cigarette smoke (Ingelbrethsen, 1984; Owen et al., 1969). Chang et al. (1985) studied this distribution in mainstream cigarette smoke undergoing dilution and reported that the composition of the dilution stream did not significantly affect the size distribution of particulates for a given primary dilution ratio. The volume distribution was bimodal, with median diameters for the two modes of approximately 0.25 and 5 μm. However, Ingelbrethsen (1986) and Bernstein (2004) have reported a wide range of mainstream cigarette smoke size distributions ranging from approximately 160 nm to 600 nm. Chen et al. (1990) characterized cigarette smoke aerosol generated from a Walton smoke machine. This group found that based on simple monodisperse coagulation, the mass median aerodynamic diameter was calculated to be 0.45 μm using a dilution ratio of 21.7, and the count median diameter was estimated to be 0.22 μm. Adam et al. (2009) performed an on-line particle size analysis by using differential electrical mobility particle spectrometry (DMS 500) with a matter engineering smoking engine to measure the particle size distribution of cigarette smoke aerosol. Here, it was found that count median diameters ranged from 180 nm to 280 nm with...
regard to the electric mobility diameter. Kane et al. (2010) used a custom-designed smoke sampling system and a Dekati Ltd. (Tampere, Finland) electrical low-pressure impactor (ELPI) to measure particle size distribution, and reported count median diameters ranging from 140 nm to 240 nm aerodynamic diameter. Alderman & Ingebrethsen (2011) characterized mainstream cigarette smoke particle size distributions from commercial cigarettes using a DMS 500, and found that the count median diameter values averaged over all puffs ranged from 152 nm to 174 nm, with this measurement falling between 145 nm and 189 nm in 60/30/2 or 35/30/2 regime for all products analyzed. More recently, Sahu et al. (2013) also studied particle size distribution of mainstream cigarette smoke by an SMPS-C (Sequential Mobility Particle Size Analyzer Series 5.400) manufactured by GRIMM (Ainring, Germany), and they found that cigarette smoke particles were mostly distributed in a submicron size range from 0.01 μm to 1.0 μm. The above research provides evidence that explains the particle size distribution of the smoke aerosol and collectively shows that the variety of techniques, dilution ratios, and aging times are contributing factors that contribute to a lack of agreement among these measurements (Alderman & Ingebrethsen, 2011). However, the value of count median diameter varied little, and particle size distribution of the smoke aerosol ranged from 0.01 μm to 1.0 μm in these studies.

Nevertheless, it is unfortunate that the chemical characteristics of smoke aerosol particles with different sizes are not well known, and there is little information available in the literature that describes the distribution of toxic chemicals with respect to smoke aerosol particle size. Jenkins et al. (1979) studied chemical variability of mainstream cigarette smoke as a function of aerodynamic particle size, and thought that chemical differences exist between the various particle sizes of mainstream cigarette smoke. Morie & Baggett (1977) observed on the distribution of certain tobacco smoke components with respect to particle size, and obtained the distribution of nicotine, indole, diethyl phthalate, total PM in the particle size of 0.25, 0.50, 0.75, and 1.00 μm. As society grows and technology advances, there is an urgent need to gain this crucial information. ELPI is a real-time particle size spectrometer for measuring aerosol particle size distributions (Keskinen et al., 1992; Marjamaki et al., 2000) and was widely used in the study on the distribution of particle size in air, cigarette smoke, coal-fired power plants and automobile exhaust. Liu et al. (2011) reported that real-world operation conditions and on-road emissions of Beijing diesel buses measured by using portable emission measurement system and ELPI, and thought that nanometer size PM make significant contribution to total particle number but play a minor role to total particle mass. Furthermore, the size distribution of aerosols can be studied by adapting research methods used for atmospheric aerosols (Chen et al., 1990; Davies, 1988). Particle sizes and the concentrations of smoke aerosols of mainstream cigarette smoke have been examined using this technique.

The aim of the present study is to better understand the distribution of toxic chemicals with respect to the size of particles produced from mainstream cigarette smoke. We focused our work on the distribution of nicotine and toxic chemicals including tobacco-specific N-nitrosamines (TSNAs, including N-nitrosonornicotine (NNN), NNnitosoanatabine (NAT), NNnitosoanatabasine (NAB), and 4-(methylene)aminoaniline-1-(3-pyridyl)-1-butanone (NNK)), polycyclic aromatic hydrocarbons (PAHs, including benzo[a]pyrene (BaP), benzo[a]anthracene (BaA), and chrysene (CHR)), and heavy metals (including Cr, As, Cd, and Pb) in particles of various sizes (such as PM2.5 and even smaller particles). For these experiments, a single-channel smoking machine connected to an electrostatic low-pressure impactor was used. First, PM of various sizes from a Kentucky 3R4F cigarette smoke reference was divided into 12 stages using ELPI and simultaneously collected in 12 polyester films. The samples were then analyzed using gas chromatography (GC), gas chromatography coupled to mass spectrometry (GC/MS), high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) or inductively coupled plasma-mass spectrometry (ICP-MS). Herein, we analyzed the contents of PM, nicotine, TSNAs, BaP, and heavy metals (Cr, As, Cd, and Pb) in the cigarette smoke aerosol and identified a relationship between the amount of each chemical and smoke particle sizes. These results may provide scientific evidence for improved evaluations of the health risks of inhaling cigarette smoke.

Materials and methods

Cigarettes

Kentucky 3R4F reference cigarettes were obtained from the University of Kentucky (Lexington, KY). The cigarettes were conditioned at 22 ± 1 °C and 60 ± 3% relative humidity for at least 48 h before being smoked according to the ISO 3402 (ISO, 1999). The contents of TPM and nicotine from 3R4F reference cigarettes are 11.0 mg/cig and 0.7 mg/cig, respectively (Roemer et al., 2012).

Mainstream cigarette smoke generation and collection

The parameters of single cigarette smoking machine before being smoked were set up according to the ISO 3308 (ISO, 2000a). The puff volume was 35 mL, the puff duration 2 s, and the puff frequency 60 s. The puff profile was a square curve. The generation and collection of different sized particles from mainstream cigarette smoke was achieved using a single-channel smoking machine connected to an ELPI (Figure 1). Figure 1 shows the process used to collect PM of different sizes from mainstream cigarette smoke. Additionally, 35 mL of mainstream smoke, in smoke puff durations of 0–2 s, was rapidly diluted and introduced into the ELPI. PM from the 3R4F reference cigarette smoke was trapped by the instrument by 12 polyester films. In this work, the aerodynamic diameter was addressed using Di (the geometric mean channel size) in Table 1. The count median diameters and mass median aerodynamic diameter were calculated by ELPIXL4.05 in Excel 2007. Count median diameters were measured and ranged from 130 nm to 160 nm aerodynamic diameter, which was in agreement with Kane et al. (2010) and Alderman & Ingebrethsen (2011).
Analysis of particulate matter and nicotine

PM and nicotine identification was performed using ISO 4387 (ISO, 2000b) and ISO 10315 (ISO, 2008), respectively. PM mass was determined by an electronic balance (0.01 mg, Model: BT 125D, German Sartorius AG). The concentrations of nicotine in each stage were determined according to the following equation: \[ \text{nicotine} (\text{mg/g}) = \frac{\text{average of (content of nicotine (mg/cig)/content of PM (mg/cig))}}{\text{PM (mg/cig)}} \]. The concentration of TSNAs, PAHs, and heavy metals were calculated by the same method.

Analysis of toxic chemicals in particle of varying sizes from smoke aerosol

Analysis of tobacco-specific N-nitrosamines

After particles of varying sizes were collected from the aerosol, the polyester films were extracted for 30 min by an oscillator with 10 mL of a 0.10 M ammonium acetate solution, which contained deuterated tobacco-specific N-nitrosamines as an internal standard. Samples, standards, and blanks were analyzed using HPLC-MS/MS with an electronic balance (0.01 mg, Model: BT 125D, German Sartorius AG). The concentrations of nicotine in each stage were determined according to the following equation: \[ \text{nicotine} (\text{mg/g}) = \frac{\text{average of (content of nicotine (mg/cig)/content of PM (mg/cig))}}{\text{PM (mg/cig)}} \]. The concentration of TSNAs, PAHs, and heavy metals were calculated by the same method.

Table 1. PM and nicotine from particle of different sizes from mainstream cigarette smoke (10 cigarettes were smoked each experiment, and PM and nicotine were determined 6 times).

| Stage | Diameter (μm) | Average (mg/10 cigarette) | RSD/% | Average (mg/10 cigarette) | RSD/% |
|-------|---------------|--------------------------|-------|--------------------------|-------|
| 1     | 0.018         | ND                       | 0     | ND                       | 0     |
| 2     | 0.027         | 0.45                     | 7.0   | ND                       | 0     |
| 3     | 0.039         | 1.05                     | 5.0   | 0.08                     | 3.7   |
| 4     | 0.07          | 3.75                     | 5.0   | 0.30                     | 6.3   |
| 5     | 0.144         | 19.8                     | 4.0   | 1.32                     | 3.1   |
| 6     | 0.261         | 45.5                     | 3.3   | 3.45                     | 6.1   |
| 7     | 0.431         | 15.0                     | 3.9   | 1.16                     | 5.9   |
| 8     | 0.722         | 12.0                     | 6.7   | 1.09                     | 6.4   |
| 9     | 1.166         | 5.85                     | 7.7   | 0.46                     | 3.4   |
| 10    | 1.851         | 0.75                     | 4.4   | 0.06                     | 3.6   |
| 11    | 2.927         | 0.75                     | 5.8   | ND                       | 0     |
| 12    | 5.959         | 0.15                     | 7.5   | ND                       | 0     |

PM, particulate matter; cig., cigarette; RSD, relative standard deviation.

Analysis of polycyclic aromatic hydrocarbons

After the particles were collected, the polyester films were extracted for 40 min using ultrasonic extraction with 40 mL of cyclohexane containing deuterated benzo[a]pyrene as an internal standard. Moreover, 10 mL of the extraction solution was then transferred to the cartridge and passed through with a flow rate of approximately 2 mL/min under positive pressure. Elution was performed with 30 mL of cyclohexane. The entire 40-mL cyclohexane solution was reduced to approximately 0.5 mL using a rotary evaporator at 55 °C at 300 mbar. Samples, standards, and blanks were analyzed by GC/MS (Agilent 6890-5973, Santa Clara, CA). The following conditions were suitable for this analysis: separation was achieved with a DB-5MS column (30 m × 0.25 mm, 0.25 μm) at an initial column temperature of 150 °C; then, the temperature was increased to 260 °C at a rate of 6 °C/min, followed by an increase to 280 °C at a rate of 2 °C/min. Temperature was then held at 280 °C for 20 min. The inlet temperature was 280 °C, the mode was constant flow, the initial flow was 1.2 mL/min, the splitless injection was 1 μL, and the transfer line temperature was 280 °C. These chromatographic conditions were adapted to obtain suitable resolution of the B[a]P and B[a]P-d12 peaks (Xia et al., 2004).

Analysis of heavy metal (Cr, As, Cd, and Pb)

Following particle collection, the polyester films were digested with 5 mL of HNO₃ (65%) and 1 mL of H₂O₂ (35%) using a microwave dissolver (MARs-5, USA CEM). The digested sample was then transferred and washed in a 30-mL PET bottle. Samples, standards, and blanks were analyzed using an inductively coupled plasma-mass spectrometer (ICP-MS) (Agilent 7500a, Santa Clara, CA).

Results

Release of PM and nicotine in different sized particles from mainstream cigarette smoke

As shown in Table 1, the relative standard deviation (RSD) of PM and nicotine in this experimental method was less than 10%, indicating that it is suitable for the study of the distribution of PM and the toxic chemicals found in the analyzed particles. PM and nicotine was distributed in particles ranging from 0.027 μm to 1.851 μm in diameter. The amount present initially increased and then decreased with increasing particle size (Supplementary materials). The maximum values are shown for particles with a mean particle diameter of 0.261 μm. The total yield of PM in all stages was 105 mg/10 cigarette, and nicotine was found at 7.9 mg/10 cigarette. These results are in accordance with the data from studies that used a Cambridge filter pad method (Roemer...
et al., 2012). In that report, the yield of TPM was 110 mg/10 cigarette and the yield of nicotine was 7.0 mg/10 cigarette. Furthermore, the RSD was less than 8% in six tests, indicated that the method used in this report is precise.

Concentrations of nicotine in PM less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm in size

Figure 2 shows the concentrations of nicotine in PM in the size ranges of less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm from the 3R4F reference cigarettes analyzed. The results demonstrate that the concentration of nicotine does not significantly change for different PM size ranges, which indicates that the distribution of nicotine is uniform throughout different particle regardless of size.

Concentration of TSNAs in PM with sizes of less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm fractions

Figure 3 shows the concentrations of TSNAs in PM in the size ranges of less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm from the 3R4F reference cigarettes. The concentrations of TSNAs in PM declined gradually with increasing particle size (Supplementary materials). This result indicates that TSNAs are present in greater concentrations in finer particles.

Concentration of PAHs in PM with sizes of less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm fractions

Figure 4 shows the concentrations of PAHs in PM in the size ranges of less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm. The concentrations of PAHs increased gradually with increasing particle size (Supplementary materials), indicating that PAHs are more abundant in larger-sized particles.

Concentration of heavy metals in PM with sizes of less 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm fractions

Figure 5 shows the concentrations of heavy metals in PM in the size ranges of less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm. The concentrations of the heavy metals declined gradually with increasing particle size (Supplementary materials), indicating that heavy metals are present in greater concentrations in finer particles.

Discussion

Tobacco smoke is a complex and dynamic matrix consisting of gaseous compounds and particulate material, in which over 4800 constituents have been identified (Baker, 1999). It is well known that the PM fraction of dilute, non-hygroscopic aerosols with sizes similar to cigarette smoke particles have approximately a 20% mass deposition efficiency in the respiratory tract. Ishizu et al. (1978) studied changes in the particle size and the concentration of mainstream cigarette smoke particles, and they found that these changes are caused by coagulation and filtration. Physical mechanisms (such as hygroscopic growth, evaporation, and coagulation) are expected to have the largest influence on cigarette smoke particle deposition (Kane et al., 2010). Jenkins et al. (1979) studied chemical variability of mainstream cigarette smoke as a function of aerodynamic particle size, and concluded that volatile compounds were lost due to evaporation.
It is clear that particle size measurements of filter exit cigarette smoke alone are not sufficient for predicting regional or total deposition rates and that other factors play a role in respiratory deposition of smoke. Therefore, major factors affecting particle size distribution measurements are the techniques utilized, dilution ratios, and aging times. Chemical differences (including levels of nicotine, PM, potassium, scopolin, neophytadiene, indole, and others) between various particle sizes of mainstream cigarette smoke have been studied recently. Regarding the distribution of nicotine, Berner & Marek (1967) reported that chemical composition was correlated to the particle size of smoke aerosol under non-diluted smoke, that the distribution of nicotine was not uniform in particles of various sizes and that the maximum amount of nicotine was in particle sizes of 0.6 μm. This group also reported that the levels of potassium grew with increasing particle size. Owen et al. (1969) studied the distribution of chemicals in particles of mainstream cigarette smoke that had been diluted by 150-fold, and found that nicotine levels were highest in particle sizes ranging from 0.5 μm to 0.6 μm. In contrast, Jones et al. (1975) reported that the distribution of nicotine was not dependent on particle size and that it was uniform throughout particles of varying sizes.

Morie & Baggett (1977) studied particle size distribution of nicotine, PM, indole, and other compounds using a cascade impactor, and found that the distribution of nicotine and PM were higher in medium size particles (0.5–0.75 μm) than in small or large particles (0.25–1.0 μm). In the present work, we collected PM of various sizes from 3R4F cigarette smoke using a single-channel smoking machine and an ELPI and analyzed the distribution of several compounds. The data obtained represent a further study on the distribution of PM and nicotine. In our study, nicotine was present in particle sizes ranging from 0.14 μm to 0.72 μm, but the maximum amount identified was in a particle size of 0.261 μm.

Particles of PM_{10} (coarse), PM_{2.5} (fine) or PM_{0.1} (ultrafine) have caused concern in recent years. Ultrafine underground dust is as rich in toxic chemicals as coarse and fine PM, which may have important implications for hazards evaluations of PM in the underground railway stations (Matthew et al., 2013; Yang et al., 2002). Based on the wide variations of size in smoke aerosol particles, it is necessary to compare the yield of nicotine and toxic chemicals in fractions containing different particle sizes (including less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm).

Because PM is a liquid droplet, and solid, and nonvolatile nuclei may comprise make up a minor fraction of the particle mass. In past years, the risks of exposure to cigarette smoke have been expressed by a variety of methods, these include the toxicity of chemicals, the amount of toxic chemicals and the hazard index of mainstream cigarette smoke. The release of toxic chemicals present in mainstream cigarette smoke typically indicates harm to human health. A novel hazard index for mainstream cigarette smoke was developed using the correlation between studies from 29 toxic chemicals and four toxicity assays performed by Xie et al. (2009). This index has been applied successfully to evaluate risk of cigarette products and is widely recognized in the tobacco industry (Xie et al., 2009). In the present study, PM was divided into three categories according to particle size (less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm). The results herein demonstrate that the distribution of nicotine is uniform across the different sized particles, and the main reason may be that a large amount of nicotine volatilizing from tobacco is rapidly cooled, adsorbed and saturated onto the surface of these particles. TSNAs and heavy metals are more abundant in particles with sizes less than 0.1 μm, indicating that these compounds may be easily absorbed by ultrafine particles. In contrast, the results of PAHs differed from those of the TSNAs and heavy metals. PAHs are more prevalent in particles 1.0–2.0 μm in size than in particles outside this range; this is mainly because PAHs are nonvolatile and easily condensate and coagulate during the cooling process. Currently, we have no evidence to explain this phenomenon and need to further investigate these results.

In this study, we collected cigarette smoke particles of varying sizes and analyzed the distribution of toxic chemicals with respect to the size of the particles. The results demonstrate a preliminary correlation between particle size and distribution of the analyzed compounds in mainstream cigarette smoke, and provide an investigation of cigarette smoke aerosol on the micron scale. Nevertheless, our work has some limitation: First, there is relatively high particle loss in the charging section of the commercial ELPI units (Baltensperger et al., 2001), and PM may be lost in the dilution and transmission processes. However, this was expected to be for all experiments performed and should not affect the results of testing under identical conditions. Second, smoke ageing, coagulation, and collection during smoke aerosol generation were unable to be avoided. Finally, only smoke from the 3R4F reference cigarette was studied. Therefore, it is important to repeat this study using a greater number of cigarette brands to confirm these results. Furthermore, the analysis of many other toxic chemicals in smoke PM should be considered, and improvements to analytical methods of determining the amount of toxic chemicals should also be considered to increase the understanding of the chemical properties of cigarette smoke aerosols.

**Conclusions**

The content of toxic chemicals in cigarette mainstream smoke (PM, nicotine, TSNAs, PAHs, heavy metals) was analyzed for cigarette smoke particles of different sizes. The results show that the toxic chemicals in this study existed primarily in cigarette smoke particles less than 2.0 μm in size, which is already considered a risk category for mainstream cigarette smoke. In addition, the distribution of toxic chemicals appeared to first increase and then decrease with increasing smoke aerosol particle size, with a peak chemical release observed in particles 0.261 μm in size. Finally, the distribution of nicotine in PM in the ranges of less than 0.1 μm, 0.1–1.0 μm, and 1.0–2.0 μm was uniform. TSNAs and heavy metals in particles with sizes of less than 0.1 μm in size were more abundant than in other particles, and PAHs were most abundant in fine PM.

**Declaration of interest**

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Supplementary material available online.