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Article

Face Mask as a Versatile Sampling Device for the Assessment of Personal Exposure to 54 Toxic Compounds in Environmental Tobacco Smoke

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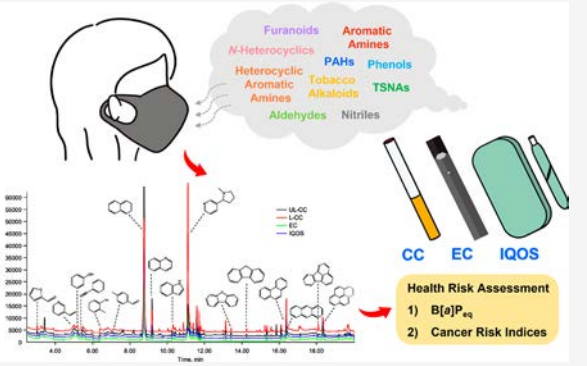
ABSTRACT: Exposure to environmental tobacco smoke (ETS), which contains hundreds of toxic compounds, significantly increases the risk of developing many human diseases, including lung cancer. The most common method of assessing personal exposure to ETS-borne toxicants is by sampling sidestream smoke generated by a smoking machine through a sorbent tube or filter, followed by solvent extraction and instrumental analysis. However, the ETS sampled may not truly represent the ETS in the ambient environment, due to complicating factors from the smoke released by the burning end of the cigarette and from the absorption of the chemicals in the respiratory tract of the smoker. In this study, we developed and validated an alternative air sampling method involving breathing through a face mask to simultaneously determine personal exposure to 54 ETS-borne compounds, including polycyclic aromatic hydrocarbons, aromatic amines, alkaloids, and phenolic compounds in real smoking scenarios. The newly developed method was used to evaluate the risk associated with exposure to ETS released from conventional cigarettes (CCs) and that from novel tobacco products such as e-cigarettes (ECs) and heated tobacco products (HTPs), with the observation of cancer risk associated with exposure to ETS released from CCs significantly higher than that from ECs and HTPs. It is anticipated that this method offers a convenient and sensitive way to collect samples for assessing the health impacts of ETS exposure.



INTRODUCTION

Environmental tobacco smoke (ETS), the collective fumes from the exhaled breath of smokers and that from the lit end of burning cigarettes, is known to adversely affect indoor air quality and pose serious health concerns.[1,2] ETS contains thousands of chemical species, including over 40 carcinogens such as formaldehyde and benzene, as well as many other toxicants that can increase the risk of various human diseases, including lung cancer, stroke, diabetes, and heart diseases.[3−7] In particular, prolonged exposure to ETS is estimated to increase the risk of developing stroke and heart disease by 85% and 25−30%, respectively.[8] Furthermore, ETS causes nearly 34 000 deaths from heart disease and over 7000 premature deaths from lung cancer annually among nonsmokers in the United States.[9] Due to the clear scientific evidence linking ETS to serious health issues like lung cancer, the International Agency for Research on Cancer (IARC) has classified ETS as a Group 1 carcinogen.[10]

ETS contains a complex mixture of 93 harmful and potentially harmful chemical constituents (HPHCs).[11,12] The majority of harmful constituents in ETS are volatile and semivolatile organic compounds (VOCs and SVOCs) produced by the combustion of tobacco during smoking.[13−15] Specific carcinogens in ETS include polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and *N*-nitrosamines, to which epidemiological studies have established a clear link between exposure and disease risk.[16−18] Although the harmful effects of these chemicals are well documented, the exact mechanisms by which ETS exposure leads to adverse health outcomes remain unclear, and there is not a single mechanism/chemical that could fully explain the observed toxicological outcomes of ETS.[19]

Recent research has revealed that the health effects of ETS may be exacerbated by synergistic interactions between its various chemical constituents.[20−22] For example, several ETS chemicals, including catechol, undecane, pyrene, and fluoranthene, have been shown to act as co-carcinogens that enhance the carcinogenicity of benzo[*a*]pyrene (B[*a*]P).[23] These synergistic effects indicate that the toxicity of ETS

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Table 1. Summary of the Collection Efficiencies, Desorption Efficiencies, and Correction Factors for the 54 ETS-Borne VOCs and SVOCs

chemical	toxicity classification	collection efficiency, %	desorption efficiency, %	correction factor	chemical	toxicity classification	collection efficiency, %	desorption efficiency, %	correction factor
2-ethylpyrrole		82 ± 2.9	80 ± 1.8	1.51	fluoranthene (Fluo)	IARC Group 3	59 ± 8.9	101 ± 0.9	1.68
indole		81 ± 10	103 ± 1.1	1.20	pyrene (Pyr)	IARC Group 3	51 ± 1.2	97 ± 1.0	2.02
quinoline	HPHC, IARC Group 2B	85 ± 11	86 ± 7.8	1.36	benz[*a*]anthracene (B[*a*]A)	HPHC, IARC Group 2B	88 ± 3.5	101 ± 5.8	1.12
2-methylindole		89 ± 3.3	113 ± 1.0	0.98	chrysene	HPHC, IARC Group 2B	54 ± 8.3	87 ± 9.5	2.13
1-indanone		85 ± 13	89 ± 7.3	1.32	2-methylnaphthalene		66 ± 6.5	103 ± 0.3	1.47
3-VP		43 ± 3.3	93 ± 9.0	2.47	1-methylnaphthalene		58 ± 3.2	102 ± 1.3	1.67
2-phenoxyethanol		69 ± 6.8	93 ± 8.2	1.56	3-tolualdehyde		86 ± 17	101 ± 4.8	1.16
2,4-dimethylphenol		95 ± 8.8	115 ± 6.3	0.92	4-tolualdehyde		66 ± 6.4	80 ± 1.3	1.88
phenol	HPHC, IARC Group 3	95 ± 13	94 ± 5.7	1.12	nicotine	HPHC	84 ± 6.4	85 ± 1.0	1.41
4-cresol	HPHC	95 ± 10	91 ± 7.0	1.16	aniline	IARC Group 2A	87 ± 11	90 ± 1.2	1.27
2-cresol	HPHC	96 ± 13	86 ± 9.2	1.22	4-toluidine		85 ± 5.1	87 ± 7.6	1.35
3-pyridinecarbonitrile		89 ± 3.8	96 ± 1.7	1.16	3-toluidine		73 ± 5.6	83 ± 3.8	1.66
benzonitrile		69 ± 12	91 ± 5.7	1.59	2-toluidine	HPHC, IARC Group 1	55 ± 1.3	92 ± 4.6	1.99
phenylacetonitrile		95 ± 7.5	102 ± 8.6	1.04	2-anisidine	HPHC, IARC Group 2A	70 ± 7.8	91 ± 1.9	1.57
benzofuran	HPHC, IARC Group 2B	52 ± 3.7	91 ± 5.7	2.11	2,6-dimethylaniline (2,6-DMA)	HPHC, IARC Group 2B	50 ± 6.0	91 ± 5.0	2.21
furfural	IARC Group 3	66 ± 11	91 ± 8.4	1.66	1-naphthylamine (1-NA)	HPHC, IARC Group 3	80 ± 5.8	84 ± 10	1.50
2-furyl methyl ketone		88 ± 6.4	118 ± 8.5	0.96	2-naphthylamine (2-NA)	HPHC, IARC Group 1	66 ± 8.6	102 ± 2.3	1.49
furfuryl alcohol	IARC Group 2B	79 ± 4.2	92 ± 5.8	1.37	2-aminobiphenyl (2-ABP)		92 ± 9.0	98 ± 5.9	1.11
5-methylfurfural		79 ± 5.5	92 ± 4.9	1.36	4-aminobiphenyl (4-ABP)	HPHC, IARC Group 1	87 ± 7.7	92 ± 3.3	1.25
dibenzofuran		66 ± 3.9	105 ± 1.7	1.44	norharman		45 ± 4.9	89 ± 1.1	2.49
naphthalene (Naph)	HPHC, IARC Group 2B	53 ± 4.1	90 ± 7.4	2.11	harman		43 ± 1.7	91 ± 1.3	2.56
acenaphthylene (Acyl)		81 ± 13	125 ± 2.2	0.99	2-amino-9*H*-pyrido[2,3-*b*]indole (A-alpha-C)	HPHC, IARC Group 2B	33 ± 2.2	89 ± 4.2	3.40
acenaphthene (Ace)	IARC Group 3	78 ± 15	105 ± 9.2	1.23	NNN	HPHC, IARC Group 1	79 ± 8.4	98 ± 2.2	1.29
2,6-dimethylnaphthalene		95 ± 6.7	104 ± 6.5	1.01	NNK	HPHC, IARC Group 1	63 ± 13	95 ± 5.8	1.68
fluorene (Flu)	IARC Group 3	70 ± 14	111 ± 1.5	1.29	cotinine		74 ± 4.8	96 ± 7.6	1.42
phenanthrene (Phen)	IARC Group 3	68 ± 11	103 ± 1.9	1.42	anabasine	HPHC	66 ± 3.8	80 ± 5.1	1.91
anthracene (Ant)	IARC Group 2B	79 ± 11	125 ± 2.0	1.01	nornicotine	HPHC	97 ± 15	87 ± 16	1.19

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cannot be attributed to individual chemicals alone, but rather the complex interactions between its diverse components. Therefore, accurately quantifying the wide range of chemicals in ETS is essential to understanding toxicity mechanisms and assessing disease risks.

Current methods for personal ETS exposure assessment involve collecting and analyzing particulate-borne chemicals in the mainstream smoke generated by smoking machines.[24−27] However, few studies have analyzed the chemical composition of ETS comprehensively under real smoking scenarios. This is particularly true for novel tobacco products like e-cigarettes (ECs) and heated tobacco products (HTPs).[28−32] This lack of analysis is likely due to the lack of sampling and analytical methods that are capable of simultaneously monitoring a broad range of constituents that are usually present at trace levels and tend to get diluted in the environment.[33−35] Further research employing advanced chemical analysis techniques is urgently needed to determine the composition of ETS to better understand how its diverse components act synergistically to impact health.

The aim of this study was twofold: (1) to develop an effective, reliable, and user-friendly sample collection method that is capable of simultaneous monitoring of personal exposure to VOCs and SVOCs in ETS; and (2) to define the air concentrations and the associated carcinogenic risks of ETS-borne VOCs and SVOCs from different tobacco products, including conventional cigarettes (CCs) with different tar levels and novel tobacco products, such as ECs and HTPs, under real smoking scenarios. Our prior work has shown that polyurethane foam (PUF)-based materials can trap both VOCs and SVOCs and face masks (especially those made of PUF) can efficiently retain tobacco smoke-specific tracers, i.e., nicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and *N*′-nitrosonornicotine (NNN).[36−39] In this work, we further deployed PUF-based face masks as a personalized air sampling device for a wide array of harmful VOCs and SVOCs in ETS, which were subsequently analyzed using liquid chromatography−tandem mass spectrometry (LC−MS/MS) and gas chromatography−mass spectrometry (GC−MS).

We determined the personal exposure to 54 representative tobacco smoke-borne chemicals of 10 chemical classes, including aromatic amines, heterocyclic aromatic amines, tobacco-specific nitrosamines, tobacco alkaloids, furanoids, phenols, *N*-heterocyclics, PAHs, nitriles, and aldehydes, in ETS generated by smokers of different brands of CCs, ECs, and HTPs. After correction by their corresponding trapping and desorption efficiencies on the mask during the air sampling and extraction process, we were able to assess the health risk impacts associated with real-life exposure to the multiple ETS-borne chemicals emitted from the above-mentioned cigarette products down to the individual level.

MATERIALS AND METHODS

Caution. Used masks may be pathogenic and should be handled in biosafety cabinets.

Chemicals and Materials. Chemical standards (Table 1) and reagents used were of the highest purity available and were used without further purification unless otherwise specified. HPLC-grade isopropyl alcohol (IPA), ethanol, and acetonitrile were obtained from Tedia (Fairfield, OH). Deionized water was further purified by a Pall Cascada laboratory water purification system (Port Washington, NY) and used in all experiments. ORBO 43 Supelpak-20 specially treated Amberlite XAD-2 (20/40; 100/50 mg) sorbent tubes were obtained from Sigma-Aldrich (St. Louis, MO). PUF masks were purchased from a local pharmacy in Hong Kong, washed sequentially using IPA, ethanol, and water, dried at a 100 °C oven, sealed with aluminum foil, and kept in a dry place until used in sample collection. Cigarettes with 1−12 mg/cigarette tar yields were purchased from local grocery stores in Hong Kong. Electronic cigarettes and an IQOS device (Tobacco Heating Device 3 DUO, Philip Morris Products S.A.), as the representative HTP device, were purchased online. Detailed information of the tobacco products, e.g., ultralight cigarettes (UL-CC; 1−6 mg tar/cigarette), light cigarettes (L-CC; 7−12 mg tar/cigarette), e-cigarettes, e-liquids, IQOS devices, and heatsticks, is shown in Table S1.

Collection and Desorption Efficiencies. The collection efficiencies of PUF face masks for the 54 ETS-borne organic molecules were determined as reported previously.[39−41] In brief, volunteers (n = 3) wearing three layers of identical PUF masks sitting in a 10 m^3 research laboratory with smoldering cigarettes for 30 min, and the amounts of individual compounds in each mask were determined separately by GC−MS or LC−MS/MS. The collection efficiency was calculated according to the following equation:

$$\text{collection efficiency \%} = [(\text{amount of target analyte collected on the outermost layer mask})/(\text{total amount of target analyte trapped on all three layers of masks})] \times 100$$

The extraction efficiencies of target analytes from the masks were determined by spiking 50 μL standard solution mixture of known concentrations evenly to an unused mask (n = 3), air-dried, followed by extraction and instrumental analysis to quantitate the amounts of analytes recovered from the extraction. The yields of individual analytes trapped on masks were corrected by their respective loss during the mask processing steps, i.e., sample collection and extraction, to quantify the final amount. The collection efficiencies, desorption efficiencies, and correction factors for target compounds are listed in Table 1.

Method Validation. Results of the PUF-mask sampling method were compared with that obtained by an active sampling method using sorbent tubes. Specifically, while volunteers wore PUF masks for sampling, air samples were collected in parallel with XAD-2 sorbent tubes at a flow rate of 1.0 L/min using a personal sampling pump (Airchek Sampler, SKC Inc.; Eighty Four, PA) in various scenarios, i.e., a research laboratory with smoldering cigarettes; a domestic household with an active smoker; and a domestic home with aging ETS after smoking events. Sampling durations for both sampling methods were 20 min in all situations. The tidal volume and breathing rate of individual volunteers were determined to be 0.48 ± 0.05 L/breath and 16.0 ± 0.4 breath/min, respectively.[41] Field blanks were also collected by exposing precleaned masks and XAD-2 sorbent tubes to air for 1 min before smoking. Air concentrations of target analytes quantified by the mask sampling method were compared with that from the sorbent tube-based sampling method after background subtraction.

Sample Collection. *Time-Dependent Accumulation.* Time-dependent accumulation of the target analytes on masks was conducted by volunteers (n = 3) wearing PUF masks for 5, 10, 20, and 30 min, at 0.5 m away from smoldering cigarettes in the research lab. The amounts of individual analytes trapped on the after-use mask are quantitated by LC−MS/MS or GC−MS, as described below.

ETS from Different Tobacco Products. The developed sampling method was applied to quantitate personal exposure to the 54 target analytes in ETS under real smoking scenarios. Indoor smoking events were arranged in a typical domestic household (a 45 m^3 living room with an air recirculation system: air temperature at around 25 °C; 60% relative humidity; wind speed less than 0.5 m/s), as described previously.[39] Different types of tobacco products, including conventional cigarettes (16 different kinds), e-cigarettes (5 kinds), and IQOS (5 kinds), were consumed by recruited volunteers (n = 3; healthy male smokers over the age of 21). Puff counts and smoking time by different smokers were recorded, varying from 10 to 15 puffs and 5−8

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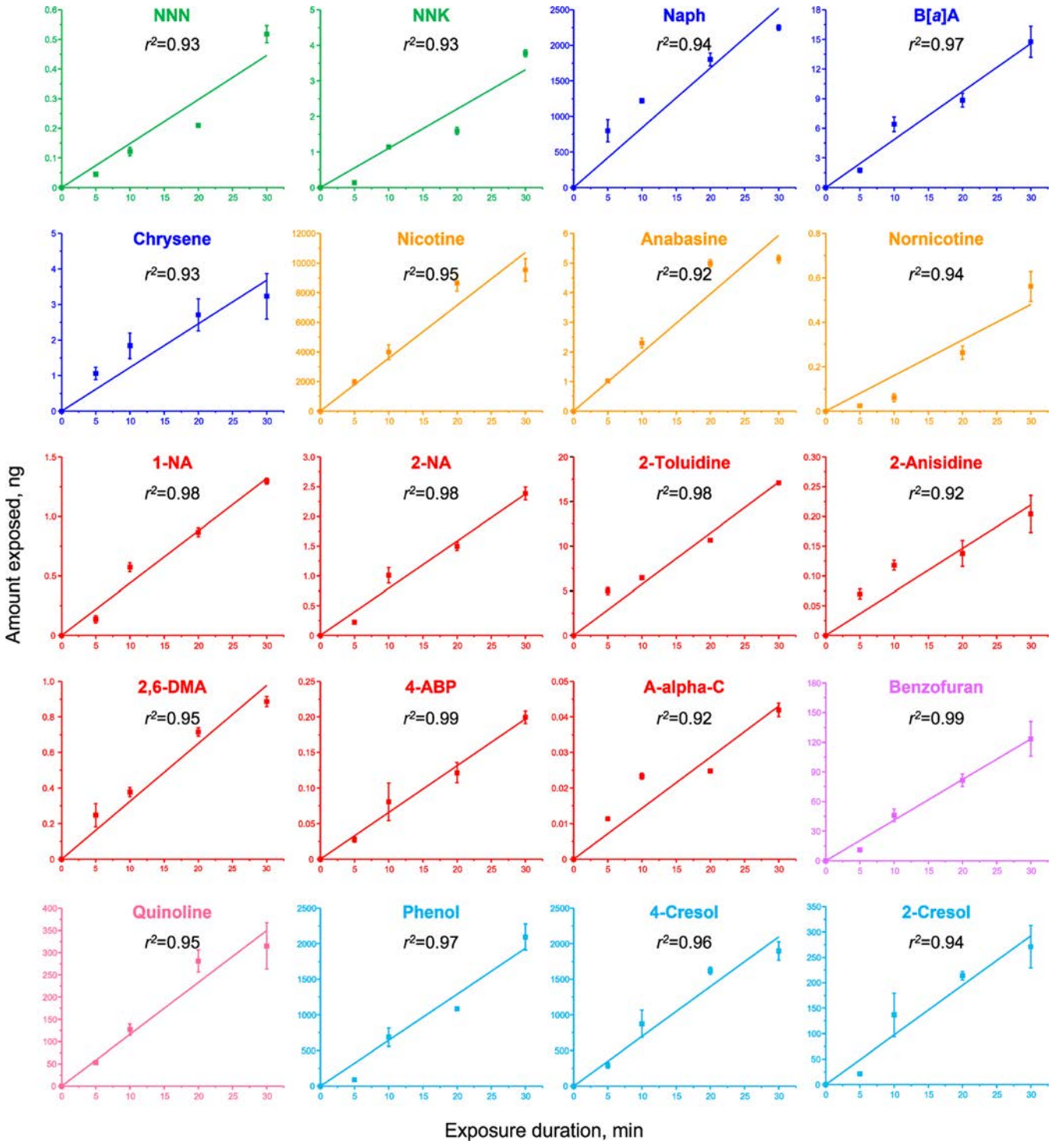

Figure 1. Amount of HPHCs trapped on PUF masks worn by volunteers for four different durations in an air-conditioned room with smoldering cigarettes. Results of constituents in the same chemical categories are shown in the same color. The data represent mean value ± SD for three independent experiments.

min per cigarette. Briefly, tobacco products were used as the following pattern for each event: conventional cigarettes: one cigarette; e-cigarettes: 10 puffs; IQOS: one stick. Concentrations of target analytes trapped by PUF masks were normalized as amounts per 10 puffs for easy comparison.

A low-tar cigarette (yielded 2 mg of tar/cigarette) was smoked as quality control at the beginning, in the middle, and at the end of each smoking event. For environmental background correction, air samples were also collected by volunteers wearing precleaned masks for 5 min at the domestic household before the smoking event started. All mask samples were immediately transported to the research laboratory, sterilized by spraying on both sides with 75% ethanol, wrapped in prebaked aluminum foil, sealed in glass tubes, and stored at a −20 °C freezer prior to analysis.

Sample Preparation. Prior to instrumental analysis, mask samples were divided into two equal portions, with one-half cut into 1 × 1 cm slices and the other half stored at −20 °C for potential reanalysis. The mask pieces were then soaked with 30 mL of

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acetonitrile at room temperature. Afterward, 990 μL of the extraction solutions were transferred to an HPLC vial, and 10 μL of aniline-d_5 and NNN-d_4 mixture (10 and 1 ng/mL in acetonitrile, respectively) was added as internal standards prior to LC−MS/MS analysis. To another 990 μL of extraction solutions, 10 μL of furfural-d_4, phenol-d_6, naphthalene-d_8 (1 μg/mL in acetonitrile), and pyrene-d_{10} (10 ng/mL in acetonitrile) internal standard mixture was added, vortex-mixed, and air-dried before the residue was redissolved in 100 μL of acetonitrile for GC−MS analysis.

Instrumental Analysis. *LC−MS/MS.* Quantitative analysis of aromatic amines, heterocyclic aromatic amines, tobacco alkaloids (excluding nicotine), and tobacco-specific nitrosamines was conducted on a Waters TQ-XS triple quadrupole LC−MS/MS system equipped with a standard ESI interface coupled to an ACQUITY UPLC system. Ten microliters of the samples were injected into a Phenomenex Luna C18 column (100 × 2 mm, 3 μm) thermostated at 40 °C. The column was eluted with a binary solvent mixture of solvent A (12 mM ammonium acetate buffer, pH 4.2) and solvent B (acetonitrile) at a constant flow rate of 0.3 mL/min according to the following gradient: 0 min, 1% B; 5 min, 100% B, and kept for 4 min before reconditioning. Table S2 summarizes the optimized ESI-MS parameters and the multiple-reaction monitoring (MRM) transitions used in the analysis.

GC−MS. Quantitative analysis of furanoids, phenols, *N*-heterocyclics, PAHs, nitriles, aldehydes, and nicotine was performed on an Agilent 7890A GC system equipped with a 5975C mass selective detector (Santa Clara, CA). One microliter of sample extract was injected into the GC inlet, which was heated at 250 °C and operated in pulsed splitless mode (pressure at 35 psi and held for 0.75 min). A DB-5MS column (30 m × 0.25 mm i.d. × 0.25 μm film thickness; J&W Scientific; Folsom, CA) eluted under the following temperature program was used for the chromatography: initially at 75 °C, held for 3 min, increased to 200 °C at 10 °C/min, then ramped to 300 °C at 30 °C/min and held for 8 min, before reconditioned to the initial temperature. Ultrapure helium at a constant volume flow of 1.2 mL/min was used as the carrier gas. The MS was operated in synchronous scan/selected ion monitoring (SIM) mode, with electron impact ionization operated at 70 eV. The MS transfer line, ion source, and quadrupole temperatures were set at 270, 230, and 150 °C, respectively. Table S3 summarizes the MS parameters used for the quantitative and confirmatory analyses.

Calibration and Detection Limits. Working standard solutions for quantitative analysis of the above-mentioned 54 analytes were prepared by adding a fixed amount of internal standards to standard solution mixtures of different analyte concentrations prepared in blank sample extracts. While the detection limits (MDLs) for analytes that were detected in the blank sample extracts were estimated as the amount of analyte that generated a signal 3 times the standard derivation from replicated analyses plus the mean blank signal from replicated analysis (n = 7) of a blank sample extract, MDLs for analytes that were not detected in the blank sample extracts were estimated based on the amounts of analytes that generated a signal 3 times the noise level. These values, after applying their correction factors, were converted to amounts of VOCs and SVOCs per face mask, which were then translated to ng/m^3 levels for a sample volume of 38.4 L, i.e., 5 min sampling at 7.68 L/min. Table S4 summarizes the linear regression parameters of calibration curves and MDLs of the target analytes.

Cancer Risk Indices (CRI). With the assumption of 100 puffs per day as a moderate smoking scenario,[30] the total CRI for daily intake was calculated as follows

$$\mathrm{CRI} = \sum_{i=1}^{n} (\mathrm{CPF}_i \times C_i) \times 10$$

where CRI is the total cancer risk indices for individual products; CPF_i is the cancer potency factor for the specific compound reported by the California Environmental Protection Agency (Table S5);[42] and C_i is the air concentration of the specific compound, which is calculated by dividing amounts of analytes trapped by masks in 10-puff duration by the volumes of air breathed in a 5 min interval.

Statistical Analysis. Assessment of differences in the exposure levels of HPHCs or various classes of chemicals in ETS produced by different tobacco products was performed by Kruskal−Wallis one-way analysis in IBM SPSS (version 28). Data were considered statistically significant at $p < 0.05$. For multivariate data analysis, the processed data of the amounts of different ETS-borne VOCs or SVOCs in ETS emitted from four classes of different tobacco products were analyzed by partial least squares discriminant analysis (PLS-DA) using SIMCA-P 14.0.

RESULTS AND DISCUSSION

Collection and Desorption Efficiencies. A suitable sampling device should be able to trap the analytes efficiently and yet be able to release them quantitatively when extracted for analysis. The trapping efficiency of PUF masks for the 54 target analytes, as determined using the method stated in the Materials and Methods section, was generally high, with an average collection efficiency of 73.9%. Nevertheless, collection efficiencies varied between chemicals of different families. In particular, collection efficiencies for phenolic compounds are remarkably good (≥95%; Table 1), whereas that for 3-vinylpyridine (3-VP) and heterocyclic aromatic amines (harman, norharman, and A-alpha-C) were below 50%. For chemicals in other families, including aromatic amines, tobacco-specific nitrosamines, tobacco alkaloids, furanoids, *N*-heterocyclics, PAHs, nitriles, and aldehydes, the average collection efficiency of each class ranged from 69.3 to 84.4%, indicating that PUF-based mask sampling method could be applied to assess personal exposure of multiclasses of ETS components. The variable collection efficiencies among chemicals of different functional groups suggest a combination of chemisorption (e.g., hydrogen bond, for analytes in the gaseous phase) and physical filtration (for particle-bounded analytes) as analyte trapping processes in the carbamate-based PUF material. Probably, both polar and nonpolar interactions among the gaseous analytes and the PUF material facilitated their collection on the mask surface.

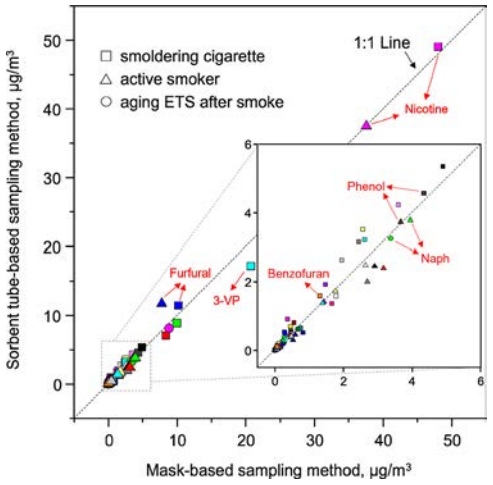

Figure 2. Comparative analysis of ETS-borne VOCs and SVOCs determined using the face mask- and sorbent tube-based sampling methods in an air-conditioned room with different smoking scenarios. Symbols in different colors represent different compounds.

Results from analysis of PUF masks that were spiked with different amounts of the 54 target analytes revealed that

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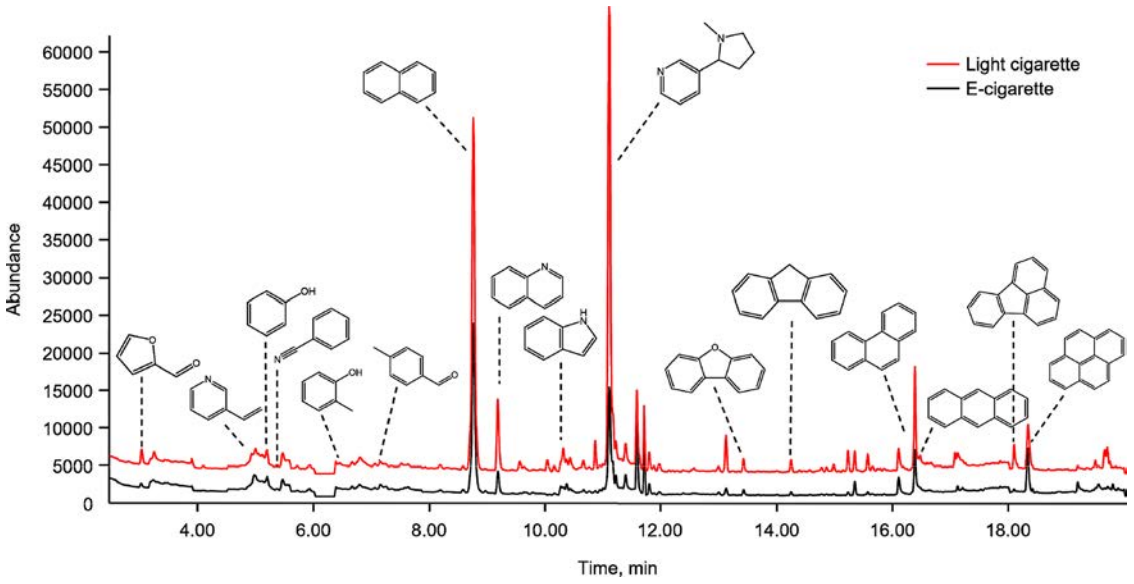

Figure 3. Typical chromatograms obtained from GC−MS (scheduled SIM) analysis of face mask samples worn by a volunteer in an air-conditioned room with ETS generated from light cigarette and e-cigarette consumption, respectively. Shown in the chromatograms are the chemical structures of representative compounds in the categories of furanoids, phenols, *N*-heterocyclics, PAHs, nitriles, aldehydes, and nicotine.

acetonitrile is highly efficient in extracting them from the masks, with extraction efficiencies of >80% for most of the target analytes (Table 1). Together with the above-mentioned results that showed PUF-based masks are highly efficient in trapping the target analytes, these results indicated that the PUF-based mask is a suitable air sampling device for assessing personal exposure to VOCs and SVOCs in ETS. Nevertheless, these results provide correction factors for the loss of analytes during the sample collection and extraction process. Results from subsequent studies were corrected by these factors to achieve their respective total amount trapped on masks.

Time-Dependent Accumulation. Analysis of masks worn by volunteers for four different durations (5, 10, 20, and 30 min) in an air-conditioned room with smoldering cigarettes revealed highly linear relationships (r^2 = 0.87−0.99) between amounts of analytes trapped on masks and mask-wearing time, which again demonstrated the feasibility of using a PUF mask as a sampling device for assessing personal exposure to ETS-borne VOCs and SVOCs. Figure 1 shows the amount of 20 HPHCs trapped on the PUF mask versus sampling time.

Method Comparison. After confirming the feasibility of using PUF-based face masks as a sampling device for ETS-borne VOCs and SVOCs, we evaluated the performance of PUF-based face masks as an air sampling device by parallel analysis with the traditional sorbent tube-based sampling method. To this end, VOCs and SVOCs in ETS were collected in parallel by both PUF masks worn by volunteers and sorbent tubes using a personal sampling pump in an air-conditioned room with smoldering cigarettes, a domestic household with an active smoker, and a domestic home with aging ETS after smoking events. Using LC−MS/MS and GC−MS methods described in the Materials and Methods section, the amounts of VOCs and SVOCs trapped on masks and in the air sampling tubes were quantitated.

After normalizing to the corresponding sampling volume, concentrations of individual analytes in ETS were determined for both the face mask-based sampling method and the sorbent tube-based sampling method. Results showed that air concentrations of the ETS-borne VOCs and SVOCs sampled by the PUF mask were in reasonable agreement with that determined by the XAD sorbent tube-based sampling method (Figure 2), with relative standard deviations <10%. Because the comparative study involved ETS in different scenarios and the sorbent tubes-based sampling method is a widely used air sampling method for sampling different kinds of airborne pollutants, these data indicated that the developed face mask-based sampling method is quantitative and can be used for assessing personal exposure to ETS-borne VOC and SVOCs.

Quantitation of Personal Exposure to VOCs and SVOCs in ETS Generated from Different Tobacco Products. The validated face mask-based sampling method was then used to quantitate personal exposure to the above-mentioned 54 compounds in the categories of PAHs, aromatic amines, alkaloids, and phenolic compounds, in ETS generated from consuming different tobacco products by smoking volunteers. With the exception of B[*a*]A, chrysene, and A-alpha-C, the analysis detected quantifiable levels of all constituents in ETS from most types of tobacco-smoking devices. Among them, 17 were classified as "harmful" or "potentially harmful" by the U.S. Food and Drug Administration (Table 1). Figures 3 and S1 show typical chromatograms obtained from GC−MS analysis of face mask samples worn in an air-conditioned room with ETS generated from different tobacco products, while typical LC−MS/MS chromatograms are shown in Figure S2.

While exposure to HPHCs through ETS produced from burning UL-CC and L-CC were not significantly different, quantitative analysis revealed significant differences (by SPSS; $p < 0.05$) in the VOC/SVOC composition when comparing exposure to ETS released from burning CCs and novel tobacco products. In particular, results showed exposure to HPHCs through ETS generated from CCs was in general 2−10 times higher than that from EC and IQOS. These observations were similar to that reported previously.[43,44] Furthermore, it is worth mentioning that nicotine exposure was the highest through ETS produced from high-tar cigarettes.

Despite the significantly reduced nicotine emission from EC and IQOS compared to that from CCs, emissions of some

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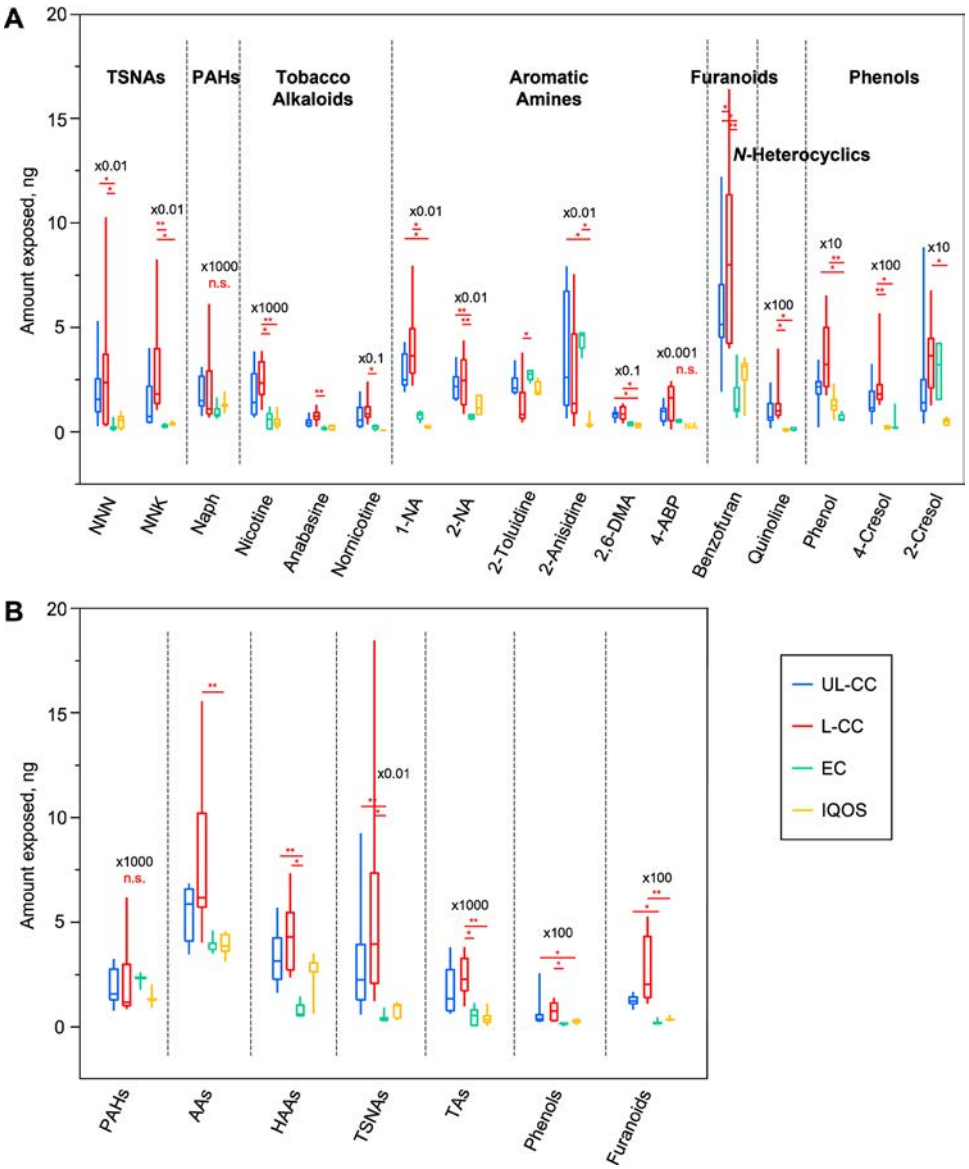

Figure 4. Box and whisker plots of personal exposure to (A) HPHCs and (B) different classes of chemicals, including PAHs, aromatic amines (AAs), heterocyclic aromatic amines (HAAs), tobacco-specific nitrosamines (TSNAs), tobacco alkaloids (TAs), phenols, and furanoids, through ETS emitted from ultralight cigarettes (UL-CC), light cigarettes (L-CC), e-cigarettes (EC), and IQOS as sampled by the PUF-mask-based method. The whiskers, box plot edges, and center line represent the 10th and 90th, 25th and 75th, and median (50th) percentiles of the distribution, respectively. Significant differences were tested by Kruskal–Wallis one-way analysis by SPSS (n.s., $p > 0.05$; *, $p < 0.05$; **, $p < 0.01$). The multiplying folds were marked on the plots. Data were presented as amounts per 10-puff volume.

ETS-borne HPHCs, such as naphthalene and 4-ABP (IARC group 1 carcinogen), did not significantly differ among the various smoking products. Furthermore, results showed that ETS produced from ECs contain the highest concentrations of 2-toluidine (IARC group 1 Carcinogen) and 2-anisidine (IARC group 2A Carcinogen). The box and whisker plots in Figure 4A present the personal exposure to the 17 HPHCs in ETS emitted from the four tobacco products, after normalizing to a 10-puff smoking volume.

It is worth mentioning that our sampling method of breathing through face masks, in combination with LC–MS/MS and GC–MS analysis, is sensitive enough to estimate personal exposure to trace levels of ETS-borne human carcinogens (IARC group 1), i.e., NNN, NNK, and 2-NA in ETS released from EC and IQOS under real-life smoking microenvironments, which could provide valuable preliminary data for apportioning ETS-borne toxicant contributions to their toxicity and carcinogenesis. Table S6 summarizes the amounts of personal exposure to the 54 ETS-borne chemicals determined by the face mask-based sampling method.

We then evaluated personal exposure to ETS-borne VOCs and SVOCs based on chemical classes. Results showed personal exposure to most classes of ETS-borne VOCs and SVOCs that are demonstrated as the contributors to tobacco-related carcinogenesis, including aromatic amines, heterocyclic aromatic amines, tobacco-specific nitrosamines, tobacco alkaloids, phenols, and furanoids,[16] were significantly lower in ETS produced by EC and IQOS than that by the CCs (Figure 4B), which was consistent with the results of previous studies.[45]

While naphthalene was detected as the most abundant PAH in ETS, personal exposure to total PAHs through smoke

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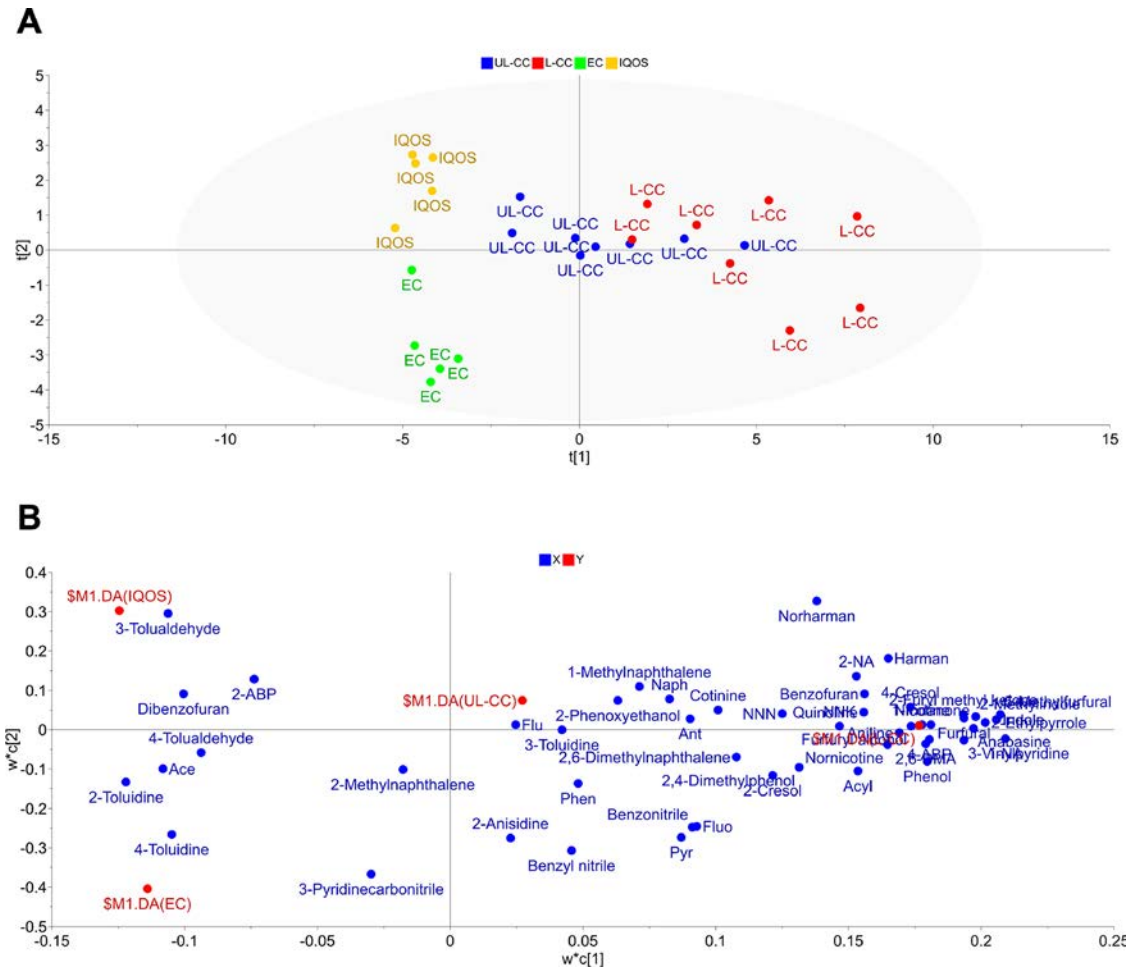

Figure 5. PLS-DA ($p < 0.01$) (A) scores and (B) loading plots from analysis of ETS-borne VOCs and SVOC components in ETS generated by ultralight cigarettes (UL-CC), light cigarettes (L-CC), e-cigarettes (EC), and IQOS. The ellipse in the score plot represents Hotelling's T^2 (0.05).

produced from consuming conventional cigarettes, EC, and IQOS were not significantly different. This phenomenon could be explained by the prior observation that naphthalene is one of the major PAHs present in e-liquids and the aerosols generated from ECs and HTPs.[46,47]

Multivariate Statistical Analysis. The data from the analysis of the 54 ETS-borne VOCs and SVOCs in ETS generated by the different tobacco products were then analyzed by partial least squares discriminant analysis (PLS-DA), a supervised multivariate data analysis model for data visualization and discriminative variable identification. As illustrated by the score plot (Figure 5A), EC and IQOS were completely separated from the other two CC groups, whereas UL-CC and L-CC overlapped to some small extent. These results are consistent with the findings described above, indicating that chemical profiles in EC and IQOS are significantly different from that of UL-CC and L-CC, whereas chemical composition in UL-CC and L-CC are similar.

Figure 5B shows the loading plot of features, i.e., the amount of different ETS-borne VOCs or SVOCs, responsible for the clustering of different groups observed in the score plot. While the tobacco smoke-specific markers (nicotine and 3-VP), phenols, heterocyclic aromatic amines, tobacco alkaloids, and carcinogenic aromatic amines (2-NA and 4-ABP) could be used to differentiate L-CC from other tobacco products, 3-tolualdehyde, dibenzofuran, and 2-ABP were identified as the most significant contributors for differentiating IQOS from other types of tobacco products, whereas 4-toluidine, 2-toluidine, and 3-pyridinecarbonitrile were identified as the variables responsible for differentiating ETS from EC and other tobacco products.

Health Risk Assessment. *B[a]P$_{eq}$.* Since PAHs are known to be one of the major classes of toxic compounds responsible for the carcinogenicity of tobacco smoke, including ETS, we compared the health risks associated with exposure to ETS from different tobacco products using benzo[*a*]pyrene equivalent (B[*a*]P$_{eq}$), a commonly used metric for assessing total PAH carcinogenicity. B[*a*]P$_{eq}$ is calculated by multiplying the concentrations of individual PAHs by their corresponding toxicity equivalency factors, as reported previously.[48]

The results of this study on CCs indicated no clear correlation between B[*a*]P$_{eq}$ and tar levels for CCs, which is consistent with previous research.[26,49] In particular, although the analysis revealed that the highest B[*a*]P$_{eq}$ values were associated with exposure to ETS from the burning of light cigarettes with high tar yields (such as L-CC-4 and L-CC-6), the mean values for UL-CC and L-CC groups were close (0.051 and 0.058, respectively). However, the values were in turn slightly higher than those from e-cigarettes and IQOS, which contain virtually no tar (as shown in Figure 6A).

CRI. We then estimated and compared the CRI that is associated with exposure to ETS-borne carcinogens in ETS of

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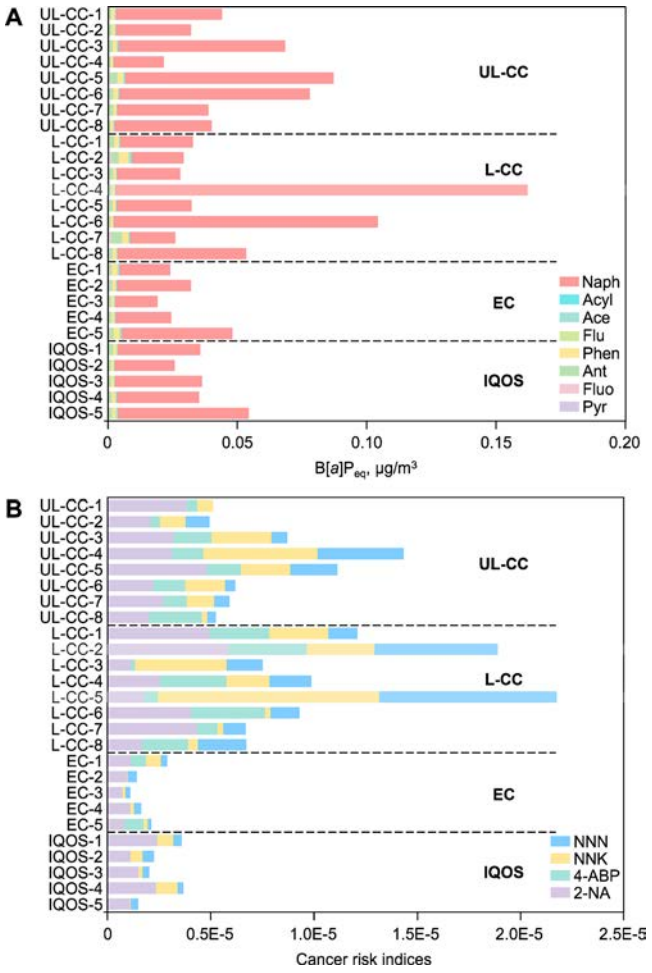

Figure 6. (A) B[*a*]P_{eq} ($\mu g/m^3$) and (B) cancer risk indices of ETS emissions of ultralight cigarettes (UL-CC), light cigarettes (L-CC), e-cigarettes (EC), and IQOS.

various sources using the cancer potency factors of individual carcinogens using the method described in the Materials and Methods section. Figure 6B summarizes the CRI associated with exposure to NNN, NNK, 4-ABP, and 2-NA in ETS generated from different tobacco products, with the observation of total CRI associated with exposure to ETS released from conventional cigarettes significantly higher than that from EC and IQOS.

Similar to that reported previously,[50,51] the CRIs that are associated with exposure to ETS-borne, tobacco-specific nitrosamines NNN and NNK are significantly higher for conventional cigarettes than those for novel tobacco devices, while the values for IQOS emissions are generally higher than those for EC emissions. It is also worth mentioning that 2-NA, because of its high concentration in ETS, contributed to over half of the total CRIs of ETS from all of the tested IQOS and most of the EC devices, whereas 4-ABP accounted for a higher proportion of total CRIs for ETS from some of the ECs than IQOS.

IMPLICATIONS

Using our newly developed face mask-based sampling method in combination with LC−MS/MS and GC−MS analysis, we quantitated personal exposure to 54 chemical components of 10 different classes in ETS generated from conventional cigarettes, as well as novel tobacco products, including ECs and HTPs, in real-life scenarios. Results showed that exposure to ETS generated by novel tobacco products (ECs and HTPs) is considerably less carcinogenic than that from conventional cigarettes, in terms of both B[*a*]P_{eq} and CRI. These results are in line with the general belief that novel tobacco products contain fewer toxic chemicals than conventional cigarettes. It is anticipated that the newly developed face mask-based sampling method shall find wide application in assessing personal exposure and the associated health risk of ETS exposure in a user-friendly way.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemrestox.3c00114.

Detailed information on different tobacco products tested in this study; instrumental parameters for LC−MS/MS analysis of target analytes; monitored quantifier and qualifier ions for target analytes in GC−MS analysis; linear regression parameters of calibration curves and MDLs for the target analytes; cancer potency factor (CPF) of NNN, NNK, 4-ABP, and 2-NA; amounts of personal exposure to the ETS-borne VOCs and SVOCs determined by the face mask-based sampling method; and typical GC−MS and LC−MS/MS chromatograms of representative samples of UL-CC and IQOS (PDF)

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Author Contributions

CRediT: **Wanlin Guo** conceptualization, formal analysis, methodology, writing-original draft; **Jian Zhen Yu** writing-review & editing; **Wan Chan** conceptualization, funding acquisition, project administration, supervision, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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