Appendix 6: Indoor Air Quality

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Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality

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ABSTRACT

The impact of the Tobacco Heating System 2.2 (THS 2.2) on indoor air quality was evaluated in an environmentally controlled room using ventilation conditions recommended for simulating "Office", "Residential" and "Hospitality" environments and was compared with smoking a lit-end cigarette (*Marlboro Gold*) under identical experimental conditions. The concentrations of eighteen indoor air constituents (respirable suspended particles (RSP) < 2.5 μm in diameter), ultraviolet particulate matter (UVPM), fluorescent particulate matter (FPM), solanesol, 3-ethenylpyridine, nicotine, 1,3-butadiene, acrylonitrile, benzene, isoprene, toluene, acetaldehyde, acrolein, crotonaldehyde, formaldehyde, carbon monoxide, nitrogen oxide, and combined oxides of nitrogen) were measured. In simulations evaluating THS 2.2, the concentrations of most studied analytes did not exceed the background concentrations determined when non-smoking panelists were present in the environmentally controlled room under equivalent conditions. Only acetaldehyde and nicotine concentrations were increased above background concentrations in the "Office" (3.65 and 1.10 μg/m^3), "Residential" (5.09 and 1.81 μg/m^3) and "Hospitality" (1.40 and 0.66 μg/m^3) simulations, respectively. Smoking *Marlboro Gold* resulted in greater increases in the concentrations of acetaldehyde (58.8, 83.8 and 33.1 μg/m^3) and nicotine (34.7, 29.1 and 34.6 μg/m^3) as well as all other measured indoor air constituents in the "Office", "Residential" and "Hospitality" simulations, respectively.

1. Introduction

There is an overwhelming medical and scientific consensus that cigarette smoking is causally related to lung cancer, heart disease, emphysema and other serious diseases in smokers (U.S. Department of Health and Human Services, 2014). Cigarette smoke from a lit-end cigarette is a complex, dynamic aerosol containing over 8000 identified chemicals produced by distillation, pyrolysis and combustion reactions when tobacco is burnt during both the smoldering and puffing of a cigarette (Rodgman and Perfetti, 2013). Public health authorities and their representatives have proposed more than 100 harmful and potentially harmful constituents (HPHC) in mainstream cigarette smoke as possible causes of smoking-related diseases (Health Canada, 2000; Food and Drug Administration, 2012a; Talhout et al., 2011) and health agencies worldwide have also concluded that exposure to environmental tobacco smoke (ETS) causes diseases including lung cancer and heart disease in adult nonsmokers, sudden infant death syndrome as well as asthma, respiratory infections, cough, wheeze, and otitis media (middle ear infection) in children (California Environmental Protection Agency, 1997; U.S. Environmental Protection Agency, 1992; International Agency for Research on Cancer , 2004; U.S. Department of Health and Human Services, 2006, United States Pharmacopeia, 2014).

Abbreviations: BKG, Background; DNPH, 2,4-dinitrophenylhydrazine; ETS, Environmental Tobacco Smoke; FSPTCA, Family Smoking Prevention and Tobacco Control Act; FPM, Fluorescent Particulate Matter; HCI, Health Canada Intense; HPHC, Harmful and Potentially Harmful Constituents; IAQ, Indoor Air Quality; ISO, International Organization for Standardization; LOD, Limit of Detection; LWRL, Lower Working Range Limit; MRTP, Modified Risk Tobacco Products; NIOSH, National Institute for Occupational Safety and Health; RSP, Respirable Suspended Particles; THBP, 2,2′,4,4′-tetrahydroxybenzophenone; THS, Tobacco Heating System; UWRL, Upper Working Range Limit; UVPM, Ultraviolet Particulate Matter; VOC, Volatile Organic Compounds.

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Several approaches have been developed over the last couple of decades to reduce the yields of HPHCs in mainstream cigarette smoke, including the use of novel filter technologies and tobacco blends to selectively reduce specific chemical classes in tobacco smoke (Gaworski et al., 2009; Branton and Bradley, 2010; Branton et al., 2011; Dittrich et al., 2014; Crooks et al., 2015). However, no progress has been reported to demonstrate reduction in HPHC yields in sidestream cigarette smoke. One approach under investigation by Philip Morris International (PMI) is to heat instead of burn tobacco, resulting in an aerosol containing lower concentrations of HPHCs (https://www.pmiscience.com). The heat-not-burn Tobacco Heating System 2.2 (THS 2.2) evaluated in this study is a more advanced version of a previous heat-not-burn product using an electrical heating device to generate an aerosol on a puff-by-puff basis when used by the consumer (Schorp et al., 2012). The THS 2.2 system (Fig. 1) consists of (i) a Tobacco Stick, which contains a tobacco plug consisting of processed tobacco cast leaf covered by a paper wrap, and (ii) a Tobacco Heating Device which consists of a Holder into which the Tobacco Stick is inserted and a Charger to recharge the Holder after each use. When activated, the Holder heats the tobacco plug using an electrically controlled heater element. The energy capacity of the Holder is sufficient for consuming a single Tobacco Stick and the Charger stores sufficient energy for the consumption of approximately 20 Tobacco Sticks. The Tobacco Stick is specifically designed for the THS 2.2 system which heats the tobacco at a temperature not exceeding 300 °C to generate an aerosol consisting mainly of water (76%), glycerin (10%) and nicotine (3%), without combustion of the tobacco.

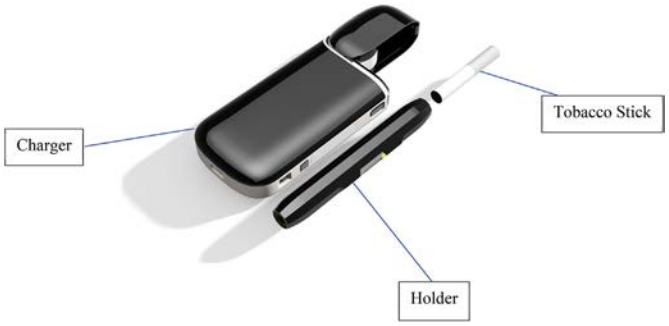

Fig. 1. Tobacco Heating System 2.2.

The objective of the current study was to compare the concentrations of representative particulate and gas–vapor phase ETS constituents (Guerin et al., 1992) when smoking a cigarette (*Marlboro Gold*) versus using the regular (non-menthol) THS 2.2 in an environmentally controlled room under simulated "Office", "Residential" and "Hospitality" conditions. Indoor air concentrations of respirable suspended particles (RSP) less than 2.5 μm in diameter; tobacco smoke-related markers of combustion (ultraviolet particulate matter [UVPM], fluorescent particulate matter [FPM], solanesol); gas-phase tobacco-specific markers (3-ethenylpyridine, nicotine); volatile organic compounds (VOCs: 1,3-butadiene, acrylonitrile, benzene, isoprene, toluene); low molecular weight carbonyls (acetaldehyde, acrolein, crotonaldehyde, formaldehyde); and gases (carbon monoxide [CO], nitrogen oxide [NO], combined oxides of nitrogen [NO_x]) were determined.

2. Methods

2.1. Study design

Three scenarios representing "Office", "Residential" and "Hospitality" environments were simulated in a 'walk-in' environmentally controlled room (size: 24.1 m^2, 72.3 m^3) equipped with an airlock (Fig. 2). The occupant density was set at 8 m^2/person (2 volunteer panelists and one PMI staff member) for the "Office" and "Residential" simulations and 4.8 m^2/person (4 volunteer smoking panelists and one non-smoking PMI staff member) for the "Hospitality" simulation. The ventilation rates ("Office": 156 m^3/h, 2.16

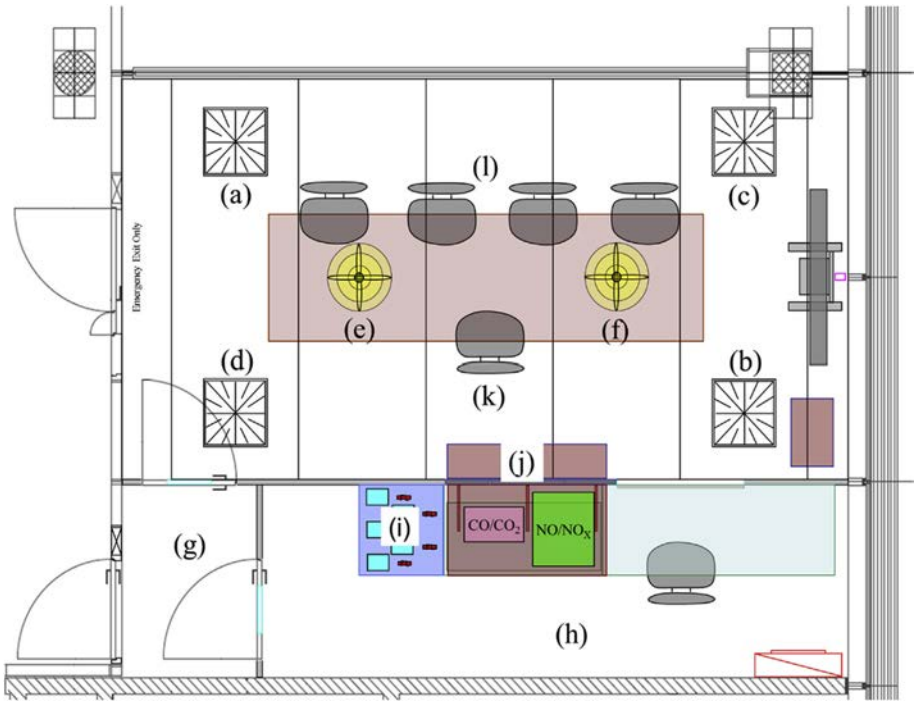

Fig. 2. Layout of the environmentally controlled room and adjacent technical room. Air inlet ducts: **a** and **b**; air outlet ducts: **c** and **d**; electrical fans: **e** and **f**; air lock: **g**; technical room: **h**; membrane sampling pumps: **i**; sampling traps: **j**; PMI staff representative chair: **k**; volunteer panelist chairs: **l**.

air changes/h; "Residential": 87 m^3/h, 1.20 air changes/h; "Hospitality": 555 m^3/h, 7.68 air changes/h) were based on the European ventilation performance standard EN 15251 (European Committee for Standardization, 2006). The simulation conditions were used to compare the indoor air quality (IAQ) when smoking panelists used either the THS 2.2 or when they smoked *Marlboro Gold* to the background levels. All assessments (per simulation) lasted for 5 h during which time the smoking panelists used the test products (THS 2.2 or *Marlboro Gold*) according to a pre-defined time schedule. For the "Office" simulation, panelist 1 started to use the test product immediately at the beginning of the assessment period (t = 0 min) and used a new test product at intervals of 30 min; smoking panelist 2 started to use the test product at t = 15 min and used a new test product at intervals of 30 min (total of 4 test products per hour). The same time schedule was used for the "Hospitality" simulation with 4 smoking panelists, panelists 1 and 2 started to use the test product immediately at the beginning of the assessment period (t = 0 min) and used a new test product at intervals of 30 min; smoking panelists 3 and 4 started to use the test product at t = 15 min and used a new test product at intervals of 30 min (total of 8 test products per hour). For the "Residential" simulation, panelist 1 used a test product at t = 0 min and then a new test product at intervals of 40 min; smoking panelist 2 began using a test product at t = 20 min and used a new test product at intervals of 40 min (total of 3 test products per hour).

Air sampling was performed for 4 h starting at time t = 60 min to ensure a stable indoor air atmosphere. "Background" measurements of IAQ were performed for 4 h using the same ventilation conditions as described in the "Office", "Residential" and "Hospitality" simulations, but no test products were used. After each "background" session, a tracer gas method was used (Burratti et al., 2011) according to the International Organization for Standardization (ISO) standard method ISO 16000-8 (International Organization for Standardization, 2007) to confirm the ventilation rate in the environmentally controlled room. The room was flooded with carbon dioxide (CO_2) up to a concentration of 1% and the decay rate of CO_2 was measured over 8 h using a non-dispersive infrared instrument (X-Stream™ Process Gas Analyzer, Emerson Electric Co., St. Louis, MO, USA).

Each assessment (per simulation) was performed on a separate day starting at approximately 9:30 h on week 1 (Monday: Background; Tuesday: THS 2.2; Thursday: *Marlboro Gold*) and repeated on week 2. The environmental room was air washed between the individual assessments using the maximum flow of filtered fresh air overnight (750 m^3/h; 10.4 air changes/h). Prior to the study and between each of the three simulations the walls, floor, ceiling and furniture were washed with a water/ethanol mixture (80:20, v/v).

2.2. Test products

Using the Health Canada Intense (HCI) testing method (Health Canada, 2000), the aerosol of the THS 2.2 yields 1.32 mg of nicotine and 0.53 mg of CO, while under ISO testing conditions (International Organization for Standardization, 2000) 0.5 mg nicotine and 0.3 mg CO were determined. The *Marlboro Gold* sold on the Swiss market was selected as a representative cigarette and has mainstream smoke yields of 1.70 mg nicotine and 22.9 mg CO under HCI testing conditions. The mainstream smoke yields of *Marlboro Gold* according to ISO testing conditions are 6 mg tar, 0.5 mg nicotine and 7 mg CO.

2.3. Subjects

Adult smokers of cigarettes (age: 21–60 years) with a regular daily cigarette consumption of at least 10 cigarettes with a 6 mg ISO tar yield were recruited for participation in the study by a consumer panel recruiting agency (RANDOM SA, Morges, Switzerland). The panelists were informed about the sponsor, the aims and course of the study, and the voluntary nature of their participation in both written and verbal form. All panelists were also informed about the possible health consequences of smoking. The panelists gave their written informed consent for their participation prior to the study commencing. Before participating in the assessments in which THS 2.2 was used, each panelist was allowed to use the test product under the instruction and supervision of PMI staff.

A PMI representative was present during all assessments to ensure the panelists use the test products according to the established schedule (refer to Study Design). The PMI representatives for the background and THS 2.2 assessments were non-smokers, while those for the *Marlboro Gold* assessments were adult smokers of cigarettes. The PMI representatives did not smoke or use any test products during the assessments.

2.4. Environmentally controlled room

A schematic representation of the environmentally controlled room layout and an adjacent technical room is shown in Fig. 2. The environmentally controlled room was equipped with a variable mixing ventilation system, which allowed the supply of fresh air between 87 and 879 m^3/h, and furnished with a central table and chairs. The ventilation rate was maintained by adjusting the flow of inlet air, which was controlled by sensors. All simulations were performed using 100% filtered outdoor air, purified by sequentially passing through a filter assembly (Unifil AG Filtertechnik, Niederlenz, Switzerland) to remove particles and VOCs using an activated charcoal filter (AKT-305-P-Kombi, class F7, Unifil AG Filtertechnik), fine dust particles (≥1 μm; TU 97-305, class F9, Unifil AG Filtertechnik) and micro particles (≥0.3 μm, TUTS2 305, class E11, Unifil AG Filtertechnik). Filtered air entered the environmentally controlled room through two ventilation ducts (Fig. 2: a and b) situated in the ceiling at diametrically opposed corners of the room. Two exhaust ducts (Fig. 2: c and d) situated in the other ceiling corners removed air from the room. Two electric fans were used to mix and circulate the indoor air. The room temperature was maintained and controlled at 23 ± 3° C by either heating or cooling the inlet air and the relative humidity was monitored. All sampling filter assemblies and sampling lines were positioned near to the breathing height of a seated person (approximately 120 cm above floor level) and connected with polyethylene tubes to 26 membrane sampling pumps (N022AVE, Type PM25578-022, KNF Neuberger GmbH, Freiburg im Breisgau, Germany) housed in the adjacent technical room. Individual pumps were dedicated to a specific sampling method using eight sampling pumps for determination of environmental tobacco smoke particulate-phase markers (RSP, UVPM, FPM, solanesol) and six sampling pumps each for determination of carbonyls (acetaldehyde, acrolein, crotonaldehyde, formaldehyde), VOCs (acrylonitrile, benzene, 1,3-butadiene, isoprene, toluene) and tobacco-specific gas-phase markers (3-ethenylpyridine, nicotine). Indoor air for online measurements were drawn through two independent online sensors specific for CO/CO_2 and NO/NO_x.

2.5. Determination of indoor air constituents

Particulate phase markers for ETS were determined according to ISO methods: ISO 15593 for gravimetric RSP, UVPM and FPM (International Organization for Standardization, 2001), and ISO 18144 for solanesol (International Organization for Standardization, 2003a). Briefly, RSP was determined by weighing a polytetrafluoroethylene filter (37 mm diameter, 1 μm pore size) in triplicate on a microbalance (XP2U, Mettler Toledo, Greifensee, Switzerland)

after overnight conditioning at 50 ± 5% humidity. The average of the triplicate determinations was taken as the filter weight. After air sampling, the procedure was repeated, and the mass increase was reported as RSP. UVPM, FPM and solanesol were determined after extraction of the filter with 3 mL methanol for background and THS 2.2 assessments and 6 mL for assessments using *Marlboro Gold*. UVPM and FPM were determined simultaneously using ultra performance liquid chromatography (UPLC) with ultraviolet (UV) and fluorescence detection (Acquity, Waters Corporation, Milford, Massachusetts, USA). UVPM was determined at a wavelength of 325 nm, and FPM at 300 nm excitation and 420 nm emission wavelengths. 2,2′,4,4′-Tetrahydroxybenzophenone and scopoletin were used as surrogate standards for UVPM and FPM, respectively. The determination of solanesol was performed using UPLC with UV detection at a wavelength of 205 nm (Acquity, Waters Corporation, Milford, Massachusetts, USA). 3-Ethenylpyridine and nicotine were determined using an adaption of the standard method ISO 18145 (International Organization for Standardization, 2003b) for use with gas chromatography-mass spectrometry (GC-MS; QP 2010 Ultra, Shimadzu Corporation, Kyoto, Japan). The analysis of VOCs (1,3-butadiene, acrylonitrile, benzene, isoprene, toluene) was performed using a method based on the National Institute for Occupational Safety and Health (NIOSH) standards 1024 (1994) and 1501 (2003) adapted for the inclusion of acrylonitrile and isoprene (which were not previously determined in the standard methods) in a single method. The air was sampled through a charcoal sorbent tube (Anasorb CSC, SKC, Blandford, UK), which was extracted with dichloromethane (1.5 mL) containing stable isotope-labelled internal standards (acrylonitrile-d_3, benzene-d_6, 1,3-butadiene-d_6, toluene-d_8), prior to analysis by GC-MS (QP-2010 Ultra; Shimadzu Corporation, Kyoto, Japan) operated in electron impact ionization (EI) mode. Low molecular weight carbonyl compounds (acetaldehyde, acrolein, crotonaldehyde, formaldehyde) were trapped on a 2,4-dinitrophenylhydrazine (DNPH)-coated silica cartridge (Waters Corporation, Nilford, MA, USA) using a method based on ISO standard 16000-3 (International Organization for Standardization, 2011). The cartridge was eluted with acetonitrile (2 mL) and the DNPH-derivatives analyzed by liquid chromatography–tandem mass spectrometry using atmospheric pressure chemical ionization (Triple Quad 5500; ABSciex, Framingham, MA, USA). CO was measured continuously using a nondispersive infrared detector (X-Stream™ Process Gas Analyzer, Emerson, Baar, Switzerland) calibrated using a certified gas standard (Carbagas AG, Guemlingen, Switzerland). NO and NO_x were measured continuously using a chemiluminescence detector (APNA 370 Ambient NO_x Monitor; Horiba, Baden, Switzerland) calibrated with certified gas standards (Messer Schweitz AG, Lenzburg, Switzerland).

All offline methods were validated using the accuracy profile procedure, which is based on the concept of total error (bias and standard deviation), as it ensures the performance of the methods under routine use and guarantees that a known proportion of future results obtained with the method will be within accuracy limits when measurements are conducted under the same experimental conditions as those used during method validation (Hubert et al., 2004, 2007a, 2007b). A more detailed description of the analytical methods and their validation has been reported (Mottier et al., 2016). All methods were accredited in 2014 (Accreditation number STS 0045) according to ISO 17025 (International Organization for Standardization, 2005) by the Swiss Accreditation Service (SAS, Bern, Switzerland).

2.6. Data treatment

All data were reported if measured values were between the lower working range limit (LWRL) and the upper working range limit (UWRL) of the analytical method. For analytes detected below the LWRL, the LWRL was reported.

The results were converted to [μg/m^3] using Equation (1).

$$C\left[\mu g/m^3\right] = C[\mu g/mL].\frac{V_{ext}}{V_{air}}.Df \quad (1)$$

Where:

$C\ [\mu g/m^3]$ = target compound concentration in air [μg/m^3]
$C\ [\mu g/mL]$ = target compound concentration in measurement solution [μg/mL]
V_{ext} = volume of solvent used for extraction [mL]
V_{air} = volume of air sampled on collection tube [m^3] = trapping time [min] x trapping flow [L/min] x 0.001
Df = dilution factor applied to measurement solution

The RSP weight determined by the gravimetric measurement was converted to μg/m^3 by dividing the measured mass of RSP on the filter expressed in μg by the volume of sampled air (V_{air}=*trapping time [min] x trapping flow [L/min] x 0.001*).

Potential data outliers were identified using the modified Z score proposed by Iglewicz and Hoaglin (1993) and absolute values greater than 3.5 were treated as potential outliers and removed from the data set only if a root cause by an analytical or laboratory error could be identified.

The main objective of the statistical analysis was to assess the impact on the background IAQ (i.e., concentrations of measured indoor air constituents) in the environmentally controlled room when either THS 2.2 or *Marlboro Gold* were used under identical experimental conditions. In order to increase the power of the statistical conclusions, confidence intervals (United States Pharmacopeia, 2014) were used as follows: comparisons were performed by calculating a confidence interval for the difference in means, where the difference was estimated by the sample mean measured in sessions with either THS 2.2 or *Marlboro Gold* minus the sample mean of the background. Thus, for THS 2.2 Equation (2) was used.

$$Lower\ limit = (M_{THS2.2} - M_{BKG}) - t_{1-\alpha/2,(n_{THS2.2}-1)+(n_{BKG}-1)} * \sqrt{\frac{S^2_{THS2.2}}{n_{THS2.2}} + \frac{S^2_{BKG}}{n_{BKG}}} \quad (2)$$

$$Upper\ limit = (M_{THS2.2} - M_{BKG}) + t_{1-\alpha/2,(n_{THS2.2}-1)+(n_{BKG}-1)} * \sqrt{\frac{S^2_{THS2.2}}{n_{THS2.2}} + \frac{S^2_{BKG}}{n_{BKG}}}$$

Where n is the number of results, S^2 is the variance, t is the Student distribution, and α is the type I error which was fixed at 5%.

If the confidence interval was outside the defined acceptance limits, differences between THS 2.2 and background or between *Marlboro Gold* and background were deemed significant. If the confidence interval for the difference could not be distinguished from the acceptance limits then the samples were considered equivalent. The acceptance limit applied for statistical analysis was defined based on the accuracy acceptance limits of ±25% used during method validation (Mottier et al., 2016). For measurements with values below the LWRL of the analytical method, where a significant uncertainty is associated with quantification at this level, the mean values of the two samples were considered equivalent and no further statistical analysis was performed. No statistical analysis was performed if the concentration levels of the analytes for the assessments of either THS 2.2 or *Marlboro Gold* were below the concentration levels determined for background.

3. Results

3.1. "Office" simulation

For both the background and THS 2.2 sessions in the "Office" simulations (Table 1), the indoor air concentrations of RSP, UVPM, FPM, solanesol, 3-ethenylpyridine, acrolein, crotonaldehyde, acrylonitrile, 1,3-butadiene and NO were below the lower working range limits of the respective analytical methods, and CO was below the limit of detection (LOD). Formaldehyde, benzene, isoprene, toluene, nicotine, acetaldehyde and NO_x were quantified in the background and during sessions with THS 2.2. The median isoprene concentration determined during the background sessions when panelists did not use the THS 2.2 exceeded the measured concentrations of isoprene determined in the THS 2.2 sessions. The concentrations of all measured indoor air constituents were significantly higher in the *Marlboro Gold*, compared to the background and THS 2.2 sessions.

The variability of concentration data for the replicate sessions of most offline markers did not exceed 23.6% with the exception of toluene for the background and THS 2.2 sessions. A substantial spread in toluene values during the THS 2.2 assessments was observed - the median toluene values for the THS 2.2 assessments were 7.78 μg/m^3 and 1.11 μg/m^3 in the first and second weeks, respectively.

Fig. 3 shows a representative trace of the online measurement of CO. The online traces of CO, NO and NO_x for the *Marlboro Gold* sessions showed several maxima, reflecting the times at which the panelists smoked cigarettes. The online traces of CO, NO and NO_x during the background and THS 2.2 sessions were similar showing a 'flat line'. No noticeable maxima in the traces were observed when the THS 2.2 was used. The median measured CO concentrations were below the LOD and NO concentrations below the quantification limits.

The confidence interval for the difference in mean concentrations of formaldehyde, benzene, isoprene and NO_x in the background and THS 2.2 sessions was not larger than the defined acceptance interval therefore the concentrations between the two sessions were not statistically different at the 95% confidence level, while the confidence interval for the mean difference of nicotine, acetaldehyde and toluene in the background and THS 2.2 sessions were outside the acceptance limits and the differences between the sessions were significant. The statistical analyses of data for all indoor air constituents indicated significant differences between the background and *Marlboro Gold* sessions, and between the THS 2.2 and *Marlboro Gold* sessions.

3.2. "Residential" simulation

The results for the "Residential" simulations (Table 2) resembled those reported for the "Office" simulations (Table 1). The

Table 1
Measured indoor air constituents in the simulated "Office" condition.

Constituent[a]	Background		THS 2.2		*Marlboro Gold*	
	Median	[Q1-Q3][b]	Median	[Q1-Q3][b]	Median	[Q1-Q3][b]
ETS Markers						
RSP [μg/m^3]	<14.7	NA[c]	<14.7	NA	204	181–278
UVPM [μg/m^3]	<0.789	NA	<0.789	NA	38.5	33.3–43.1
FPM [μg/m^3]	<0.064	NA	<0.064	NA	7.88	7.25–8.66
Solanesol [μg/m^3]	<0.466	NA	<0.466	NA	10.2	9.09–11.3
3-Ethenylpyridine [μg/m^3]	<0.243	NA	<0.243	NA	6.39	5.66–7.22
Nicotine [μg/m^3]	0.51	0.43–0.63	1.61	1.53–1.65	35.2	31.4–39.1
Carbonyls						
Acetaldehyde [μg/m^3]	5.77	5.04–6.54	9.42	8.56–10.2	64.6	60.0–74.0
Acrolein [μg/m^3]	<0.146	NA	<0.146	NA	6.42	5.36–7.68
Crotonaldehyde [μg/m^3]	<0.207	NA	<0.182	NA	2.04	1.86–2.33
Formaldehyde [μg/m^3]	13.9	13.7–14.4	14.0	13.9–14.2	42.8	37.4–49.0
VOCs						
Acrylonitrile [μg/m^3]	<0.270	NA	<0.270	NA	2.61	2.37–2.89
Benzene [μg/m^3]	0.244	0.233–0.253	0.245	0.218–0.313	6.82	6.56–7.95
1,3-Butadiene [μg/m^3]	<1.14	NA	<1.14	NA	12.6	11.8–13.5
Isoprene [μg/m^3]	4.11	3.61–4.72	3.63	3.52–4.01	80.1	75.2–87.2
Toluene [μg/m^3]	1.69	0.92–1.95	3.79	1.11–7.72	16.6	14.5–20.1
Gases						
Carbon monoxide [ppm]	<0.270[d]	NA	<0.270[d]	NA	1.58[d]	1.44–1.72[d]
Nitrogen oxide [ppb]	1.94[d]	1.35–2.61[d]	2.20[d]	1.60–2.95[d]	27.0[d]	23.7–30.6[d]
Nitrogen oxides [ppb]	3.13	2.38–3.94	3.53	2.73–4.45	32.5	29.1–36.3

[a] Abbreviations: ETS, environmental tobacco smoke; FPM, fluorescent particulate matter (expressed as scopoletin equivalents); RSP, respirable suspended particles (determined by gravimetry); UVPM, ultra-violet particulate matter (expressed as 2,2′,4,4′-tetrahydroxybenzophenone equivalents); VOCs, volatile organic compounds.
[b] Q1: first quartile, Q3: third quartile; the interval Q1-Q3 contains 50% of the data.
[c] NA: not applicable (Q1-Q3 not reported when median < lower working range limit (LWRL).
[d] Conversion in μg/m^3 (ambient pressure of 1 atm and temperature of 25 °C; median (Q1-Q3)): Background CO < 0.309 mg/m^3, NO 2.38 μg/m^3 (1.66–3.20 μg/m^3); THS 2.2 CO < 0.309 mg/m^3, NO 2.70 μg/m^3 (1.96–3.62 μg/m^3); *Marlboro Gold* CO 1.81 mg/m^3 (1.65–1.97 mg/m^3), NO 33.1 μg/m^3 (29.1–37.6 μg/m^3).

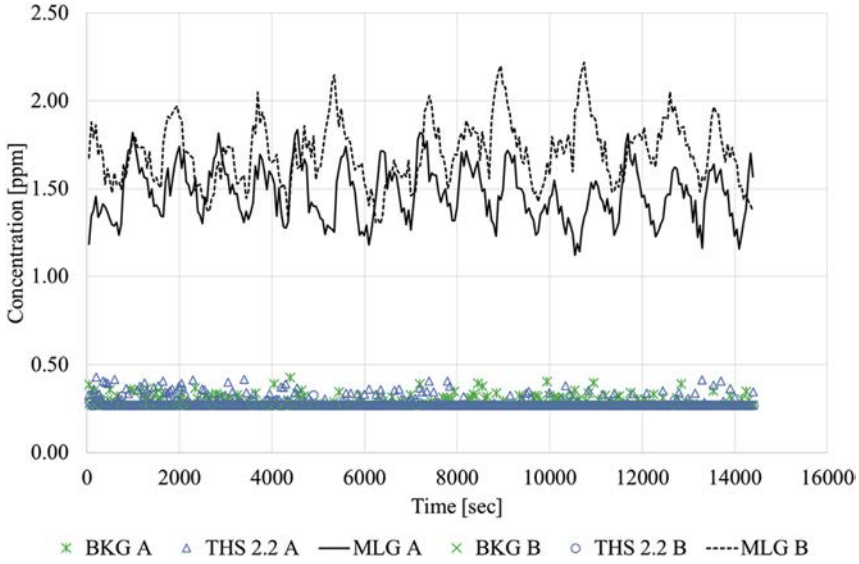

Fig. 3. Online measurements for carbon monoxide [ppm] for the 'office' simulations. BKG: Background; THS 2.2: Tobacco Heating System 2.2; MLG: *Marlboro Gold*, A: week 1; B: week 2.

Table 2
Measured indoor air constituents in the simulated "Residential" condition.

Constituent[a]	Background		THS 2.2		*Marlboro Gold*	
	Median	[Q1-Q3][b]	Median	[Q1-Q3][b]	Median	[Q1-Q3][b]
ETS Markers						
RSP [μg/m^3]	<14.7	NA[c]	<14.7	NA	268	240–299
UVPM [μg/m^3]	<0.789	NA	<0.789	NA	40.8	39.6–42.9
FPM [μg/m^3]	<0.064	NA	<0.064	NA	8.50	8.44–8.67
Solanesol [μg/m^3]	<0.466	NA	<0.466	NA	9.84	8.30–11.3
3-Ethenylpyridine [μg/m^3]	<0.243	NA	<0.243	NA	7.61	6.54–8.67
Nicotine [μg/m^3]	0.855	0.687–1.07	2.66	1.56–4.21	29.9	29.3–33.3
Carbonyls						
Acetaldehyde [μg/m^3]	7.44	7.39–7.50	12.5	10.3–15.1	91.3	86.0–98.4
Acrolein [μg/m^3]	<0.146	NA	<0.146	NA	5.65	2.44–8.94
Crotonaldehyde [μg/m^3]	<0.207	NA	<0.182	NA	2.11	1.85–2.41
Formaldehyde [μg/m^3]	19.7	19.0–21.8	22.4	21.8–23.7	55.3	46.8–66.0
VOCs						
Acrylonitrile [μg/m^3]	<0.270	NA	<0.270	NA	3.61	3.21–3.96
Benzene [μg/m^3]	0.407	0.387–0.427	0.567	0.438–0.673	9.64	8.17–11.0
1,3-Butadiene [μg/m^3]	<1.14	NA	<1.14	NA	16.8	16.3–17.6
Isoprene [μg/m^3]	9.05	8.74–10.8	6.70	5.77–7.95	108	99.1–119
Toluene [μg/m^3]	3.57	1.93–6.69	2.61	1.86–3.29	29.7	18.8–40.5
Gases						
Carbon monoxide [ppm]	0.386[d]	0.313–0.465[d]	0.454[d]	0.408–0.504[d]	2.17[d]	1.95–2.42[d]
Nitrogen oxide [ppb]	3.21[d]	1.74–6.53[d]	2.58[d]	1.92–3.29[d]	38.8[d]	34.1–43.2[d]
Nitrogen oxides [ppb]	5.97	4.09–9.24	5.21	4.36–6.05	45.6	41.2–49.7

[a] Abbreviations: ETS, environmental tobacco smoke; FPM, fluorescent particulate matter (expressed as scopoletin equivalents); RSP, respirable suspended particles (determined by gravimetry); UVPM, ultra-violet particulate matter (expressed as 2,2′,4,4′-tetrahydroxybenzophenone equivalents); VOCs, volatile organic compounds.
[b] Q1: first quartile, Q3: third quartile; the interval Q1-Q3 contains 50% of the data.
[c] NA: not applicable (Q1-Q3 not reported when median < lower working range limit (LWRL).
[d] Conversion in μg/m^3 (ambient pressure of 1 atm and temperature of 25 °C; median (Q1-Q3)): Background CO 0.442 mg/m^3 (0.359–0.533 mg/m^3), NO 3.94 μg/m^3 (2.14–8.01 μg/m^3); THS 2.2 CO 0.520 mg/m^3 (0.467–0.577 mg/m^3), NO 3.17 μg/m^3 (2.36–4.04 μg/m^3); *Marlboro Gold* CO 2.49 mg/m^3 (2.23–2.77 mg/m^3), NO 47.6 μg/m^3 (41.9–53.0 μg/m^3).

concentrations of ten indoor air constituents (RSP, UVPM, FPM, solanesol, 3-ethenylpyridine, acrolein, crotonaldehyde, acrylonitrile, 1,3-butadiene and CO) were below the quantification limits of the analytical methods during the background and THS 2.2 sessions, while the concentrations of eight indoor air constituents (nicotine, acetaldehyde, formaldehyde, benzene, isoprene, toluene, NO and NO_x) were quantifiable (Table 2). Isoprene, toluene, NO and NO_x concentrations in the background sessions were higher than those measured in the THS 2.2 sessions. When *Marlboro Gold* was smoked a significant increase in the concentrations of all measured indoor air constituents was observed.

Similar to the online measurements of CO, NO and NO_x in the "Office" simulations, the traces obtained during the *Marlboro Gold* sessions showed several maxima, reflecting the smoking pattern of the panelists, compared to the flat line trace for the background and THS 2.2 sessions.

For most measured offline indoor air constituents the data spread between replicate sessions was similar to the "Office" simulations. Significant variability in the measured toluene concentrations in both the background and THS 2.2 sessions were noted,

and for nicotine and acrolein between the THS 2.2 and *Marlboro Gold* sessions, respectively.

No statistically significant differences at the 95% confidence level between the concentrations of formaldehyde, benzene, isoprene, toluene, NO and NO_x in the background and THS 2.2 sessions were observed, whilst statistical differences for acetaldehyde and nicotine between the background and THS 2.2 sessions were found.

Similar to the "Office" simulations, smoking *Marlboro Gold* led to significant increases in the concentrations of all eighteen measured indoor air constituents when compared to either the background or THS 2.2 sessions.

3.3. "Hospitality" simulation

The results for the "Hospitality" simulations were similar to both the "Office" and "Residential" simulations; however, the measured concentrations of indoor air constituents during the background, THS 2.2 and *Marlboro Gold* assessments were generally lower. As in the "Office" and "Residential" simulations, the concentrations of most indoor air constituents (UVPM, FPM, solanesol, 3-ethenylpyridine, acrolein, crotonaldehyde, acrylonitrile, 1,3-butadiene, CO and NO) were below the quantification limits for both the background and THS 2.2 sessions (Table 3). RSP, formaldehyde, benzene, isoprene and toluene were quantified during the THS 2.2 sessions; however, the 95% confidence interval for the difference of means between THS 2.2 and background was not outside the acceptable difference. The reported concentrations of nicotine, acetaldehyde and NO_x in the THS 2.2 sessions were statistically higher at the 95% confidence level than found in the background sessions. A statistically significant increase in the concentrations of all measured indoor air constituents was found when smoking *Marlboro Gold*, compared to both the background and THS 2.2 sessions.

Similar to the online measurements of CO, NO and NO_x in the "Office" and "Residential" simulations, the smoking pattern of the panelists when smoking *Marlboro Gold* was reflected in the online traces of gases which showed several maxima while a flat line trace was monitored during the background and THS 2.2 sessions.

A larger data variability between replicate sessions was observed only for acetaldehyde and benzene in the background sessions, and toluene in both the background and THS 2.2 sessions.

4. Discussion

A significant development in tobacco control in the U.S. has been the enactment of the Family Smoking Prevention and Tobacco Control Act (FSPTCA, 2009), which empowers the U.S. Food and Drug Administration (FDA) to evaluate and regulate Modified Risk Tobacco Products (MRTPs) (Deyton et al., 2010). The FSPTCA defines an MRTP as 'any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products.' The FDA has also been charged to issue guidance or regulation on the scientific evidence required for the assessment and ongoing review of potential MRTPs in consultation with the U.S. Institute of Medicine (IOM), and has published Draft Guidance on 'Modified Risk Tobacco Product Applications' (Food and Drug Administration, 2012b). The guidance requires demonstration that the MRTP, as actually used, will: (i) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (ii) benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. Since THS 2.2 is a candidate MRTP, the reported study was performed specifically to address public health concerns about the indoor use of THS 2.2 and the presence of toxicants in indoor air which may present an exposure source to persons who do not use tobacco products.

ETS is an aged and diluted mixture of sidestream smoke emitted from the lit end of a smoldering cigarette and exhaled mainstream

Table 3
Measured indoor air constituents in the simulated "Hospitality" condition.

Constituent[a]	Background		THS 2.2		*Marlboro Gold*	
	Median	[Q1-Q3][b]	Median	[Q1-Q3][b]	Median	[Q1-Q3][b]
ETS Markers						
RSP [μg/m^3]	<14.7	NA[c]	15.5	<14.7–17.1	147	135–156
UVPM [μg/m^3]	<0.789	NA	<0.789	NA	18.4	17.1–19.8
FPM [μg/m^3]	<0.064	NA	<0.064	NA	4.04	3.75–4.36
Solanesol [μg/m^3]	<0.466	NA	<0.466	NA	4.68	4.16–5.01
3-Ethenylpyridine [μg/m^3]	<0.243	NA	<0.243	NA	3.94	3.78–4.17
Nicotine [μg/m^3]	0.438	0.426–0.460	1.09	0.906–1.31	35.0	33.9–36.7
Carbonyls						
Acetaldehyde [μg/m^3]	2.65	2.00–3.33	4.05	3.47–4.61	35.7	35.1–36.8
Acrolein [μg/m^3]	<0.146	NA	<0.146	NA	3.03	2.98–3.09
Crotonaldehyde [μg/m^3]	<0.207	NA	<0.182	NA	0.989	0.959–1.06
Formaldehyde [μg/m^3]	7.98	5.89–9.83	7.09	6.34–7.56	25.4	25.0–25.7
VOCs						
Acrylonitrile [μg/m^3]	<0.270	NA	<0.270	NA	1.36	1.26–1.44
Benzene [μg/m^3]	0.268	0.177–0.369	0.248	0.184–0.295	3.76	3.68–4.00
1,3-Butadiene [μg/m^3]	<1.14	NA	<1.14	NA	5.79	5.15–6.34
Isoprene [μg/m^3]	2.31	2.27–2.33	2.28	2.24–2.34	39.3	36.9–40.1
Toluene [μg/m^3]	1.09	0.783–1.48	1.08	0.783–1.42	9.85	8.42–11.3
Gases						
Carbon monoxide [ppm]	<0.270[d]	NA	<0.270[d]	NA	0.688[d]	0.494–0.892[d]
Nitrogen oxide [ppb]	1.95[d]	1.39–2.50[d]	2.32[d]	1.62–3.11[d]	14.8[d]	11.0–19.3[d]
Nitrogen oxides [ppb]	2.32[d]	1.69–2.90[d]	2.84[d]	2.02–3.83[d]	17.6[d]	13.4–22.3[d]

[a] Abbreviations: ETS, environmental tobacco smoke; FPM, fluorescent particulate matter (expressed as scopoletin equivalents); RSP, respirable suspended particles (determined by gravimetry); UVPM, ultra-violet particulate matter (expressed as 2,2′,4,4′-tetrahydroxybenzophenone equivalents); VOCs, volatile organic compounds.
[b] Q1: first quartile, Q3: third quartile; the interval Q1-Q3 contains 50% of the data.
[c] NA: not applicable (Q1-Q3 not reported when median < lower working range limit (LWRL).
[d] Conversion in μg/m^3 (ambient pressure of 1 atm and temperature of 25 °C; median (Q1-Q3)): Background CO < 0.309 mg/m^3, NO 2.39 μg/m^3 (1.71–3.07 μg/m^3); THS 2.2 CO < 0.309 mg/m^3, NO 2.85 μg/m^3 (1.99–3.82 μg/m^3); *Marlboro Gold* CO 0.788 mg/m^3 (0.566–1.02 mg/m^3), NO 18.2 μg/m^3 (13.5–23.7 μg/m^3).

smoke from the smoker. In addition, cigarette smoke spilled from the mouth prior to inhalation (mouth-spill) may also contribute to ETS (St. Charles et al., 2013).

Comparative studies on the composition of ETS produced by smoking cigarettes and the environmental aerosol produced by using THS 2.2 in the "real-world" would be difficult to perform due to the non-specificity of most smoking-related markers of IAQ (Guerin et al., 1992). Therefore, the presented comparisons were performed using simulations of "real-world" conditions under strictly controlled ventilation conditions. For comparative studies, this approach has one major advantage: absorbent media and particle filters can be used to minimize and control additional environmental sources of indoor air constituents (de Blas et al., 2012). This approach has been reported in a previous comparison of the impact of using either *Marlboro Gold* or an earlier version of the THS 2.2 on smoking-related markers (Tricker et al., 2009). Nelson et al. (1998) have also reported a similar approach, but an unventilated, controlled environmental chamber was used to compare ETS generated by smoking different market cigarettes and a cigarette prototype that primarily heats tobacco. The range of measured indoor air pollutants differed between the two reported studies (Nelson et al., 1998; Tricker et al., 2009) and the current study selected smoking-related markers based on the known mainstream smoke chemistry of *Marlboro Gold* and the mainstream aerosol of THS 2.2 (unpublished data). Unlike the study by Nelson et al. (1998), no biological endpoints such as bacterial mutagenicity of RSP were determined since the expected RSP concentration in indoor air due to use of THS 2.2 was predicted to be too small to allow collection of sufficient RSP mass for performing biological assays.

The concentrations of indoor air constituents determined in simulations using *Marlboro Gold* were in good agreement with reported real-world concentrations of ETS markers in offices, homes and hospitality venues where smoking occurred. Similar values as those measured in our study for *Marlboro Gold* in the "Office" simulations (Table 1), were published by Jenkins et al. (2001a) who reported median concentrations of 46.4 μg/m^3 RSP, 44.1 μg/m^3 UVPM, 71.1 μg/m^3 FPM, 27.5 μg/m^3 solanesol, 5.5 μg/m^3 nicotine and 1.8 μg/m^3 3-ethenylpyridine in indoor air samples collected from four offices where smoking was unrestricted. Comparable median values for RSP, UVPM, FPM, solanesol, nicotine and 3-ethenylpyridine in offices occupied by smokers were also published by Oldaker et al. (1995) and Sterling et al. (1996).

Heavner et al. (1995) reported median concentrations of 0.95 μg/m^3 3-ethenylpyridine, 4.03 μg/m^3 benzene and 23.8 μg/m^3 toluene in 24 US homes in which smoking occurred. Kraev et al. (2009) reported a median concentration of 0.13 μg/m^3 nicotine (mean concentrations of 2.20 μg/m^3 nicotine) in multi-unit housing in the Greater Boston Area. While Kim et al. (2001) reported median concentrations of 0.3 μg/m^3 3-ethenylpyridine, 11.4 μg/m^3 benzene, 0.7 μg/m^3 1,3-butadiene and 28.4 μg/m^3 toluene in 6 UK homes. Thus, the reported real-world values for nicotine, 3-ethenylpyridine and 1,3-butadiene are lower than those quantified in the current study, while the values for benzene and toluene are similar to those determined in the "Residential" simulations (Table 2).

Jenkins et al. (2001b) reported that nicotine concentrations ranged from 12 to 22 μg/m^3 and 3-ethenylpyridine ranged from 2 to 5 μg/m^3 in 2 US restaurants where smoking occurred. Median concentrations of 15.0 μg/m^3 nicotine, 3.2 μg/m^3 3-ethenylpyridine, 0.7 μg/m^3 acrylonitrile, 8.9 μg/m^3 benzene, 0.3 μg/m^3 1,3-butadiene, 48.5 μg/m^3 acetaldehyde and 17.0 μg/m^3 formaldehyde were reported in 11 German restaurants (Bolte et al., 2008). These data are also consistent with the measured indoor air concentrations of ETS markers in *Marlboro Gold* sessions in the "Hospitality" simulations (Table 3). Thus, literature data suggests that the concentrations of ETS markers (Guerin et al., 1992) reached in this study for simulations with *Marlboro Gold* are indeed representative of real-life smoking environments.

Compared to the impact of smoking cigarettes on IAQ, little is known about the impact of heat-not-burn tobacco products. Studies investigating the use of Electrically Heated Cigarette Smoking Systems (EHCSSs), predecessors of the current THS 2.2, demonstrate that heat-not-burn based products have less impact on IAQ than smoking cigarette (Roethig et al., 1995; Oey et al., 2008; Frost-Pineda et al., 2008; Tricker et al., 2009). One experimental study very similar to the current reported study measured 29 indoor air constituents in a 65 m^3 environmentally controlled room simulating an "Office" condition using three different ventilation rates (72, 180, and 288 m^3/h) or a "Hospitality" condition with a ventilation rate of 576 m^3/h (Tricker et al., 2009). In a direct comparison between the simulations using either EHCSS or *Marlboro Gold* cigarettes, 24 of 29 measured indoor air constituents (83%) showed mean reductions of greater than 90%, and 5 constituents (17%) showed mean reductions between 80% and 90% when smoking EHCSS. Specific ETS markers for the gas-vapor phase of ETS (3-ethenylpyridine, nicotine) were reduced by an average of 97% (range 94–99%) when the EHCSS was smoked compared to *Marlboro Gold*. Similarly, ETS markers for the particulate phase (solanesol, UVPM, FPM) were reduced by 93% (range 85–97%). Total RSP was reduced by 90% (range 82–100%). The mean and standard deviation of the reduction of all constituents was 94 ± 4%.

The outcome of the current study further supports the conclusion that the use of heat-not-burn tobacco products in indoor environments results not only in substantial reductions of pollutants in comparison to smoking cigarettes but, more importantly, most of the measured indoor air constituent concentrations were very similar to those found in the absence of tobacco product use. No measurable increases in any particulate-phase markers, either measured gravimetrically or as combustion markers such as UVPM and FPM or as a specific marker such as solanesol, were determined for THS 2.2 sessions in the three simulation conditions (Tables 1–3). Twelve of the fourteen studied gas-phase ETS markers in the THS 2.2 sessions did not exceed those found in the background. In particular, 3-ethenylpyridine, a specific gas-phase marker of ETS formed by thermal decomposition of nicotine during tobacco combustion (Vainiotalo et al., 2001), was not detected during the THS 2.2 assessments. The non-specific vapor-phase ETS compounds formaldehyde, benzene, isoprene and toluene were found at very similar concentrations in both the background and during the use of THS 2.2. In fact, the measured concentrations of these compounds were sometimes higher in the background than during the THS 2.2 sessions. This suggests that additional sources such as the environmentally controlled room itself or the panelists and their personal items contributed to the background concentrations. Several potential sources of formaldehyde and benzene have been reported (Haghighat and De Bellis, 1998; Hodgson et al., 2002; Kelly et al., 1999; Salthammer et al., 2010; Hodgson and Levin, 2003; Yu and Crump, 2003). Similarly, toluene is a common indoor air pollutant (Fishbein, 1985; Low et al., 1988). Isoprene, the major hydrocarbon found in human breath (Gelmont et al., 1981), and low amounts of formaldehyde (Riess et al., 2010) may also be exhaled by the study panelists.

Similar to the response of the background measurements, the online measurement of gases (CO, NO and NO_x) gave a 'flat' profile when THS 2.2 was used during all three studied simulations. The data show that THS 2.2 did not contribute to the measured indoor concentrations of gases, otherwise several maxima reflecting the times when panelists used the THS 2.2 would have been observed (see Fig. 3). Most of the measured median values for CO, NO and

NO_x in the background and THS 2.2 assessments remained either below or close to the reporting limits in the "Office" and "Hospitality" simulations (Tables 1 and 3). Only for the "Hospitality" simulations, an increase of NO_x levels above the background was recorded when THS 2.2 was used (THS 2.2 Q1 - Q3: 2.02–3.83 ppb>background Q1 - Q3: 1.69–2.90 ppb, Table 3); however, the measured values were close to the reporting limits of the method (Limit of Quantification = 2.35 ppb for NO_x) and therefore at levels with significant measurement uncertainty. This fact together with the lack of maxima in the online trace of NO_x, led us to conclude that THS 2.2 did not contribute to NO_x concentrations. In addition, some variability in the background levels of gasses was noted. For example, in the "Residential" simulations the quantified levels of NO and NO_x were marginally higher in the background (NO Q1 - Q3: 1.74–6.53 ppb; NO_x Q1 - Q3: 4.09–9.24 ppb) than in the THS 2.2 sessions (NO Q1 - Q3: 1.92–3.29 ppb; NO_x Q1 - Q3: 4.36–6.05 ppb) (Table 2).

The only two indoor air constituents that were quantified above background in assessments using THS 2.2 under "Office", "Residential" and "Hospitality" conditions were acetaldehyde and nicotine (Table 4). After adjustment for background concentrations the measured indoor air concentrations of acetaldehyde and nicotine in the "Office" simulations (3.65 [range 2.79–4.44] and 1.10 [range 1.03–1.14] $\mu g/m^3$, respectively) were higher than in the "Hospitality" simulations (1.40 [0.82–1.97] and 0.66 [0.47–0.88] $\mu g/m^3$, respectively), but lower than in the "Residential" simulations (5.09 [2.83–7.70] and 1.81 [0.70–3.36] $\mu g/m^3$, respectively). Considerably higher median concentrations of both acetaldehyde (58.8, 83.8, and 33.1 $\mu g/m^3$) and nicotine (34.7, 29.1, and 34.6 $\mu g/m^3$) were found under the "Office", "Residential" and "Hospitality" simulations using *Marlboro Gold*, respectively.

On average, a smokers retains about 90–100% of nicotine, 55–80% of CO, 100% of NO and 90–100% of carbonyls on inhalation of mainstream cigarette smoke into the respiratory tract (Armitage et al., 2004; Baker and Dixon, 2006; Feng et al., 2007; Moldoveanu et al., 2007). Retention of individual compounds is influenced by several factors including mouth-spill, inhalation volume, depth of inhalation and breath-hold. Acetaldehyde is a product of human metabolism and a common constituent in exhaled breath (Jurvelin et al., 2001). Acetaldehyde and the tobacco-specific constituent nicotine are both known to occur in exhaled breath of cigarette smokers (Baker and Dixon, 2006; Feng et al., 2007; Riess et al., 2010). Thus, it is plausible that when THS 2.2 is used, exhaled breath may contribute to the indoor air concentrations of both acetaldehyde and nicotine. However, the levels of all the determined markers in the three simulations using *Marlboro Gold* are clearly driven by the contribution of sidestream smoke emissions in addition to the contribution made by exhalation of mainstream cigarette smoke. Since THS 2.2 does not emit a true sidestream aerosol, the main source of impact on indoor air quality when THS 2.2 is used is exhalation of non-retained mainstream aerosol constituents by the THS 2.2 user.

The measured acetaldehyde concentrations during use of THS 2.2 under the "Office", "Residential" and "Hospitality" simulations (Table 4) were below the minimal risk level for chronic exposure (140 $\mu g/m^3$; 80 ppb acetaldehyde) listed by the California Office of Environmental Health Hazard Assessment (2008) and the proposed exposure limit of 200 $\mu g/m^3$ in the European Union (Kotzias et al., 2005). The World Health Organization (World Health Organization, 2010) considers acetaldehyde as an air pollutant of potential interest for regulation.

The measured nicotine concentrations during use of THS 2.2 under the three studied simulations (Table 4) were well below the indicative occupational exposure limit values of 500 $\mu g/m^3$ in the European Union (European Agency for Safety and Health at Work, 2006) and the permissible exposure limit of 500 $\mu g/m^3$ defined by the U.S. Occupational Safety and Health Administration (Occupational Safety and Health Administration, 1978).

Table 4
Contribution of THS 2.2 and *Marlboro Gold* to indoor air quality.

Constituent[a]	Office (median Q1 –Q3)[b]		Residential (median Q1 –Q3)[b]		Hospitality (median Q1 –Q3)[b]	
	THS $2.2_{adjusted}$	*Marlboro Gold*$_{adjusted}$	THS $2.2_{adjusted}$	*Marlboro Gold*$_{adjusted}$	THS $2.2_{adjusted}$	*Marlboro Gold*$_{adjusted}$
ETS Markers	-[c]		-[c]			
RSP [$\mu g/m^3$]	-[c]	204 (181–278)[d]	-[c]	268 (240–299)[d]	-[c]	147 (135–156)[d]
UVPM [$\mu g/m^3$]	-[c]	38.5 (33.3–43.1)[d]	-[c]	40.8 (39.6–42.9)[d]	-[c]	18.4 (17.1–19.8)[d]
FPM [$\mu g/m^3$]	-[c]	7.88 (7.25–8.66)[d]	-[c]	8.50 (8.44–8.67)[d]	-[c]	4.04 (3.75–4.36)[d]
Solanesol [$\mu g/m^3$]	-[c]	10.2 (9.09–11.3)[d]	-[c]	9.84 (8.30–11.3)[d]	-[c]	4.68 (4.16–5.01)[d]
3-Ethenylpyridine [$\mu g/m^3$]	-[c]	6.39 (5.66–7.22)[d]	-[c]	7.61 (6.54–8.67)[d]	-[c]	3.94 (3.78–4.17)[d]
Nicotine [$\mu g/m^3$]	1.10 (1.03–1.14)	34.7 (30.9–38.6)	1.81 (0.70–3.36)	29.1 (28.4–32.4)	0.66 (0.47–0.88)	34.6 (33.4–36.3)
Carbonyls						
Acetaldehyde [$\mu g/m^3$]	3.65 (2.79–4.44)	58.8 (54.3–68.2)	5.09 (2.83–7.70)	83.8 (78.6–91.0)	1.40 (0.82–1.97)	33.1 (32.5–34.1)
Acrolein [$\mu g/m^3$]	-[c]	6.42 (5.36–7.68)[d]	-[c]	5.65 (2.44–8.94)[d]	-[c]	3.03 (2.98–3.09)[d]
Crotonaldehyde [$\mu g/m^3$]	-[c]	2.04 (1.86–2.33)[d]	-[c]	2.11 (1.85–2.41)[d]	-[c]	0.99 (0.96–1.06)[d]
Formaldehyde [$\mu g/m^3$]	-[c]	28.9 (23.4–35.1)	-[c]	35.5 (27.0–46.2)	-[c]	17.5 (17.1–17.8)
VOC	-[c]		-[c]		-[c]	
Acrylonitrile [$\mu g/m^3$]	-[c]	2.61 (2.37–2.89)[d]	-[c]	3.61 (3.21–3.96)[d]	-[c]	1.36 (1.26–1.44)[d]
Benzene [$\mu g/m^3$]	-[c]	6.58 (6.32–7.70)	-[c]	9.24 (7.76–10.6)	-[c]	3.50 (3.41–3.73)
1,3-Butadiene [$\mu g/m^3$]	-[c]	12.6 (11.8–13.5)[d]	-[c]	16.8 (16.3–17.6)[d]	-[c]	5.79 (5.15–6.34)[d]
Isoprene [$\mu g/m^3$]	-[c]	75.9 (71.1–83.1)	-[c]	99.4 (90.0–110)	-[c]	37.0 (34.6–37.8)
Toluene [$\mu g/m^3$]	-[c]	14.9 (12.9–18.4)	-[c]	26.1 (15.3–37.0)	-[c]	8.76 (7.33–10.2)
Gases	-[c]		-[c]		-[c]	
Carbon monoxide [ppm]	-[c]	1.58 (1.44–1.72)[d]	-[c]	2.17 (1.95–2.42)[d]	-[c]	0.69 (0.49–0.89)[d]
Nitrogen oxide [ppb]	-[c]	27.0 (23.7–30.6)[d]	-[c]	35.6 (30.9–40.0)	-[c]	14.8 (11.0–19.3)[d]
Nitrogen oxides [ppb]	-[c]	29.4 (26.0–33.2)	-[c]	39.7 (35.3–43.7)	0.52 (<0.70[e]–1.51)	15.3 (11.1–20.0)

[a] Abbreviations: ETS, environmental tobacco smoke; FPM, fluorescent particulate matter (expressed as scopoletin equivalents); RSP, respirable suspended particles (determined by gravimetry); UVPM, ultra-violet particulate matter (expressed as 2,2′,4,4′-tetrahydroxybenzophenone equivalents); VOC, volatile organic compound.

[b] Q1: first quartile, Q3: third quartile; the interval Q1-Q3 contains 50% of the data. THS $2.2_{adjusted}$ and *Marlboro Gold*$_{adjusted}$ refer to measurements corrected for the median concentration of the analyte in the background.

[c] Analyte concentration equivalent to background.

[d] Background not subtracted (background concentration < lower working range limit [LWRL] of analytical method).

[e] The median of the background for NO_x is below the measured value for the Q1 of THS 2.2, LOD is reported (0.704 ppb).

5. Conclusions

Statistical evaluation of the data showed that the concentrations of RSP, UVPM, FPM, solanesol, 3-ethenylpyridine, formaldehyde, acrolein, crotonaldehyde, acrylonitrile, benzene, 1,3-butadiene, isoprene, toluene, CO, NO and NO_x in the assessments with THS 2.2 under three environmental conditions were equivalent to the concentrations found in background indoor air. Only acetaldehyde and nicotine concentrations in indoor air were increased in assessments with THS 2.2, but the concentrations were considerably lower than found in assessments with *Marlboro Gold*. Qualitative differences exist between the environmental aerosol resulting from use of the heat-not-burn THS 2.2 product and ETS produced by smoking a cigarette, namely, lower concentrations of all markers associated with tobacco combustion and less volatile and semi-volatile constituents are released by use of THS 2.2 into indoor air. Under the simulated conditions the concentrations of most measured indoor air constituents with the exception of acetaldehyde and nicotine during use of THS 2.2 were similar to background levels, suggesting no negative impact on the IAQ when using THS 2.2 in an indoor environment.

Conflict of interest statement

All authors were Philip Morris International employees at the time of the study which was funded by PMI R&D.

Transparency document

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