Scientific substantiation of the absence of Environmental Tobacco Smoke (ETS) emission during use of the Electrically Heated Tobacco System (EHTS)

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1 Executive summary

This report consolidates scientific evidence substantiating that there is no Environmental Tobacco Smoke (ETS) emitted during use of Philip Morris International's (PMI) Electrically Heated Tobacco System (EHTS, also known as the Tobacco Heating System 2.2 and marketed in various countries under the brand name *IQOS*) and that EHTS use has no adverse effect on the air quality according to threshold limits established by existing air quality guidelines and when used in a setting where regulatory norms of adequate ventilation are respected.

In summary:

- ETS is generated by the combustion of tobacco products. It is composed of sidestream smoke (SS), emitted from the smoldering tobacco between puffs, and exhaled mainstream smoke (MS) from the smoker.
- The absence of combustion of the tobacco contained in the Electrically Heated Tobacco Product (EHTP), when used as intended in the EHTS Holder, and the fact that the aerosol generated during EHTS use is not smoke were scientifically substantiated and the available evidence has been summarized and discussed in a report by Nordlund et al., 2019 [1].
- The scientific substantiation is based on a review of technical and scientific definitions, an extensive set of published scientific evidence, and expert opinions issued by third-party scientific experts in numerous countries as well as by independent research organizations.
- As there is no smoke (neither SS nor MS) generated by the EHTP when used as intended in the EHTS Holder, there is no ETS emitted during EHTS use.
- As the tobacco contained in the EHTP is heated and not burned, the mainstream aerosol generated during EHTS use contains >90% lower levels of harmful and potentially harmful constituents, on average, compared with the MS of a 3R4F reference cigarette.
- The environmental EHTS aerosol (predominantly emitted from exhalation of EHTS mainstream aerosol constituents during EHTS use) is, by nature, different from the ETS emissions from cigarette smoking.
- In addition to demonstrating that the EHTS aerosol is not smoke and that no ETS is emitted during EHTS use, it is important to assess the impact of the environmental EHTS aerosol on air quality. PMI conducted scientific studies in a dedicated air quality assessment room under simulated environmental conditions.
- These studies demonstrated that only three compounds were above the background levels in air (nicotine, glycerol, and acetaldehyde) and could be attributed to EHTS use. However, glycerol is not an air pollutant and the concentrations of nicotine and acetaldehyde were much lower than the levels measured after cigarette smoking and far below the limits established by existing air quality guidelines.
- Scientific studies conducted by independent researchers on EHTS (as well as certain e-vapor products (EVP)) use in indoor environments generally corroborated these results. Moreover, the use of EHTS as well as the EVP tested resulted in the lowest concentrations of formaldehyde, benzene, toluene, and particulate matter (PM) $PM_{2.5}$

when compared with cigarettes, waterpipes, and some common sources of indoor pollution (incense, mosquito coils). Significantly higher levels of benzene, toluene, and formaldehyde can be detected in public environments, where no EHTS or EVP was used, especially in transport micro-environments (Kauneliene et al., 2018 [2]).

- To better understand the impact of day-to-day activities on air quality and to prepare the assessment of the impact of EHTS use in real-life settings, PMI conducted studies on the impact of activities of daily living, such as using cosmetics, preparing food on a table-top appliance, or simply the prolonged presence of people, on air quality in an indoor environment. The results of these studies showed that day-to-day activities lead to significant emissions of volatile organic compounds and PM, which would need to be considered when assessing the impact of EHTS use on bystanders in real-life settings.
- PMI scientific studies in real-life settings, such as coffee rooms and in *IQOS* stores, where EHTS use is allowed demonstrated that no quantifiable amounts of $PM_{2.5}$ were present and that the environmental aerosol emissions of the measured compounds during EHTS use were far below the limits set by existing air quality guidelines.
- In a study conducted in Japan, in a restaurant where EHTS use was allowed but cigarette smoking was not, the results indicated that:
    - The use of EHTS did not generate ETS and had no adverse effect on air quality as measured by nicotine, tobacco-specific nitrosamines (TSNA), and respirable suspended particles as well as the carbonyls acrolein, crotonaldehyde, acetaldehyde, and formaldehyde in air in a real-life setting where regulatory norms for occupational exposure in terms of adequate ventilation were respected.
    - Non-smokers did not have an increase in exposure to nicotine and TSNAs due to passive exposure to the environmental EHTS aerosol by means of assessing their urinary biomarkers of exposure.
    - Non-smokers were not exposed to higher levels of acrolein, crotonaldehyde, ethylene oxide, and benzene in a real-life setting due to passive exposure to the environmental EHTS aerosol by means of assessing their urinary biomarkers of exposure.
- These results were further corroborated by independent scientific studies on air quality conducted in real-life settings in a nightclub and in a catering and entertainment establishment. The studies showed that:
    - The particle number concentration was found to be higher when the nightclub was in full operation with no humans present and no use of EHTS compared with what could be measured when EHTS was used and the nightclub was not in operation.
    - The levels of all compounds measured in the catering and entertainment establishment during EHTS use were far below threshold limits established by existing air quality guidelines.

- Moreover, the results of an independent study performed in Germany were in line with the results of PMI studies on air quality, with cigarette smoking leading to the greatest impact on air quality. EHTS use resulted in detectable levels of nicotine, but no other chemical markers of contamination were detected, including the absence of markers for secondhand smoke. The confined environment of the car and the proximity of the sample collection to the product user resulted in detection of small liquid droplets in the nanoscale range when EHTS was used in the car.

To summarize, the scientific evidence comprehensively demonstrates that there is no ETS emitted during use of the EHTS and that EHTS use has no adverse effect on air quality and bystanders' exposure considering threshold limits set by existing air quality guidelines and when used in a setting where regulatory norms of adequate ventilation are respected. Furthermore, it is important to consider exposure to air pollutants existing in the current real-life environment to contextualize the impact of products such as EHTS or EVPs in this context.

2 Introduction

Various chemicals are emitted into the air from both natural and man-made sources, leading to air pollution. Natural air pollution stems from various biotic and abiotic sources, such as plants, radiological decomposition, forest fires, volcanoes and other geothermal sources, and emissions from land and water. Man-made air pollution sources include emissions from various industrial processes and emissions from fuel-burning processes in the transport sector as well as emissions from building materials, furniture, furnishings and equipment, heating and ventilation systems, occupants, cleaning, household burning processes (candles, gas burners, wood fires, etc.), and, if smoking occurs, Environmental Tobacco Smoke (ETS, also called secondhand smoke) [3]. ETS is composed largely of sidestream tobacco smoke (SS), the smoke emitted by the smoldering end of a cigarette between puffs, with minor contributions from exhaled mainstream smoke (MS, the smoke that is directly exhaled by a smoker) and mouth spill (any smoke that escapes during puffing by a smoker) [3, 4].

More than 6,000 chemical compounds have been identified in MS [5]. ETS has been characterized based on a much smaller number of compounds, possibly due to both its significant dilution in indoor environments as compared with MS and the lack of specificity of many ETS constituents. Generally speaking, particulate matter (PM) (respirable suspended particles (RSP), PM_{10}, $PM_{2.5}$, ETS-RSP), carbon monoxide (CO), nicotine, 3-ethenylpyridine, selected volatile organic compounds (VOC) (e.g., benzene, toluene, xylenes, 1,3-butadiene, aldehydes), and polycyclic aromatic hydrocarbons (PAH) have been used to "characterize" ETS [6-9]. As a consequence, International Organization for Standardization (ISO) norms have been set up to specifically measure ETS.

Public health authorities, including the World Health Organization (WHO), have concluded that ETS (secondhand smoke) causes diseases, including lung cancer and heart disease, in non-smoking adults as well as conditions in children, such as asthma, respiratory infections, cough, wheezing, otitis media (middle ear infection), and sudden infant death syndrome [3]. In

addition, secondhand smoke can also exacerbate adult asthma and cause eye, throat, and nasal irritation [3].

The purpose of this report is to review the definition of ETS and to summarize scientific evidence demonstrating that there is no ETS emitted during use of the Electrically Heated Tobacco System (EHTS, also known as the Tobacco Heating System (THS) 2.2, marketed in various countries under the brand name *IQOS*), a heat-not-burn technology, and that EHTS use has no adverse effect on air quality when compared with common air pollution sources and threshold limits set by existing air quality guidelines.

It is important to note that the purpose of Philip Morris International's (PMI) studies on the impact of EHTS on air quality was not to establish evidence in support of overcoming existing, already implemented smoking bans in any country but to fully characterize the impact of EHTS on the environment and on bystanders as well as to provide scientific evidence to support the creation and implementation of science-based policies for new emerging, less-harmful products, such as the EHTS.

3 Electrically Heated Tobacco System

3.1 Product description

The EHTS, developed by PMI, has three distinct components that perform different functions: (i) an Electrically Heated Tobacco Product (EHTP), a multicomponent product containing a specially formulated tobacco material made from tobacco powder, water, glycerol, guar gum, and cellulose fibers; (ii) a Holder, into which the EHTP is inserted and that heats the tobacco portion of the EHTP by means of an electrically controlled Heater; and (iii) a Charger, which is used to recharge the battery in the Holder after each 360-second heating cycle or 14 puffs, whichever comes first. A schematic of the EHTS and of the multiple components of the EHTP inserted into the Holder (heating device) are shown in Figure 1(a) and Figure 1(b), respectively.

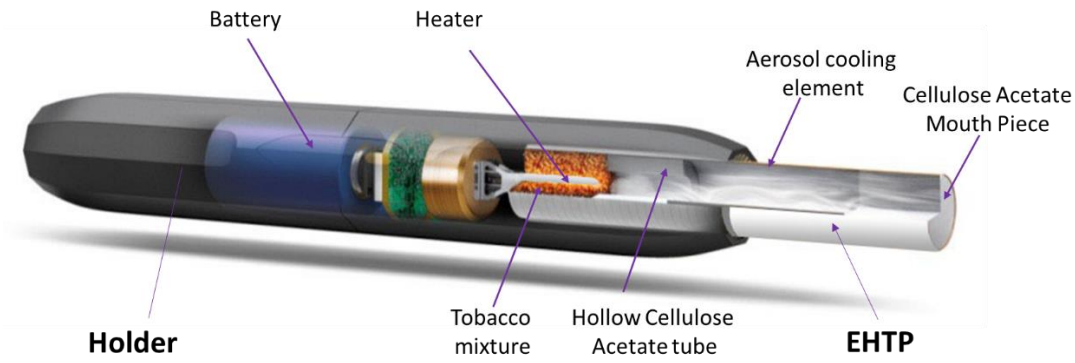
3.2 Product operation

To operate the EHTS device, an EHTP is inserted into the Holder, and a 360-second heating cycle is initiated. The Holder contains a Heater that heats the tobacco material in the EHTP from the center of the tobacco plug radially outwards (see Figure 1(b)). During a puff, air enters the Holder through a gap between the outer and inner device walls and then exits through the components of the EHTP. The Heater (heating blade) consists of a platinum track encased in a ceramic substrate. Heat is supplied to the tobacco material for a fixed period of 360 seconds and allows for up to 14 puffs to be taken. The device switches off after 14 puffs or 360 seconds, whichever comes first. The temperature profile of the Heater is electrically controlled by a firmware and a micro-controller, and the electrical current supplied to the Heater is continuously monitored by the device throughout the 360-second heating cycle. The electrically controlled Heater in the Holder is programmed to reach an average temperature over the Heater surface between 320°C and 350°C according to a predefined profile. If its operating temperature exceeds 350°C, the energy supply to the Heater is cut. During the controlled heating process, volatile compounds vaporize from the tobacco material, and

thermal decomposition reactions occur; however, combustion and high-temperature pyrolysis reactions are avoided [1, 10]. When cooled down in the EHTP, a nicotine-containing aerosol that is not smoke is formed [1], containing significantly lower levels of harmful and potentially harmful constituents (HPHC) compared with those measured in cigarette smoke [11-13].

More information on the design and the operation of the EHTS during use can be found in [14].

(a)



(b)

Figure 1. (a) The three components of the EHTS and (b) a schematic of the cross-sectional view of the EHTP and its components when inserted into the Holder.

4 Definition of ETS

According to WHO: "Environmental tobacco smoke (ETS) is generated by the combustion of tobacco products. It is composed of sidestream smoke (SS), emitted from the smouldering tobacco between puffs, and exhaled mainstream smoke (MS) from the smoker" [3]. This definition is in line with the common definition of smoke being a product of combustion [15-20], as reviewed in detail in a report by Nordlund et al., 2019 [1]. Smoldering is a flameless combustion process [21]. As stated by WHO [3], ETS comprises both SS and exhaled MS.

5 Scientific substantiation of the absence of ETS emission

This section summarizes the scientific evidence demonstrating that no ETS is emitted during EHTS use and that the environmental EHTS aerosol (predominantly emitted from exhalation of EHTS mainstream aerosol constituents) is, by nature, different from the ETS emissions from cigarette smoking. In addition, scientific studies assessing the overall impact of EHTS use on air quality in both research and real-life environments are presented and discussed. Furthermore, exposure to air pollutants existing in the current real-life environment are presented and used to contextualize the impact of products such as EHTS or e-vapor products (EVP) in that context.

5.1 Absence of combustion and no smoke formation in the EHTP

As discussed in Section 4, for ETS to be emitted during use of a tobacco product, combustion of the tobacco must occur according to the definition of ETS by WHO, and smoke (SS and MS) must be generated [3]. The absence of combustion of the tobacco contained in the EHTP, when used as intended in the EHTS Holder, and the fact that the aerosol generated is not smoke were scientifically substantiated and the available evidence has been summarized and discussed in a report by Nordlund et al., 2019 [1]. This report includes a review of technical and scientific definitions of key terms (including smoke, combustion, pyrolysis, and aerosol), an extensive set of published scientific evidence, and expert opinions issued by third-party scientific experts in numerous countries as well as by independent research organizations. All these elements comprehensively demonstrated that no combustion and high-temperature pyrolysis of the EHTP tobacco material occurs during intended use of the EHTS and that the aerosol generated from tobacco contained in the EHTP is not smoke [1]. As there is no smoke (SS and MS) generated by the EHTP when used as intended in the EHTS Holder [1], there is no ETS emitted during EHTS use according to the WHO definition of ETS [3].

5.2 Reduced toxicant levels in EHTS mainstream aerosol

As no combustion and high-temperature pyrolysis occurs in the EHTP during use in the EHTS Holder, and as the maximum temperature measured in the EHTP tobacco material during EHTS operation is 320°C (at the Heater surface), with most of the tobacco material at much lower temperatures, both the toxicant levels and complexity of the aerosol composition are strongly reduced compared with cigarette smoke, which is generated when tobacco is burning at temperatures reaching above 850°C [22].

The quantification of 54 HPHCs (including all of the prioritized HPHCs listed by regulatory authorities, such as the abbreviated list from the U.S. Food and Drug Administration (FDA), Health Canada, and the WHO) shows that the levels of these HPHCs were reduced by more than 90%, on average, in the EHTS mainstream aerosol compared with the MS from a 3R4F reference cigarette [13]. The same level of reduction was also observed when all compounds specified in the complete list of 93 HPHCs established by U.S. FDA [23] were considered (90.5% reduction, on average [24]) as well as when compared with the MS from commercially available cigarettes [25]. Moreover, similar levels of reduction of HPHCs in EHTS aerosol compared with cigarette smoke have also been reported by independent research on EHTS aerosol chemistry [11, 26-29]. The compositions of 3R4F reference cigarette smoke and EHTS aerosol are very different, as most of the EHTS aerosol mass is attributed to water, glycerol, and nicotine, whereas for the 3R4F reference cigarette smoke, the largest mass fraction is comprised of compounds other than water, glycerol, and nicotine [13].

The EHTP, when used as intended in the EHTS Holder, does not generate solid particles, as demonstrated by detailed experiments involving scanning electron microscopy (SEM) analysis [30]. As discussed by Nordlund et al., 2019 [1], thermodenuder and thermodilution techniques are not able to determine the presence of solid particles alone without being combined with microscopy analysis, such as SEM.

5.3 Impact of EHTS use on air quality under controlled environmental conditions

Unlike the lit end of a cigarette, which smolders between puffs and emits SS, which is the main contributor to air pollution caused by cigarettes, the EHTS does not emit SS. The environmental EHTS aerosol is instead predominantly emitted from exhalation of EHTS mainstream aerosol constituents. Furthermore, the levels of HPHCs were reduced by more than 90%, on average, in the EHTS mainstream aerosol compared with the MS from a 3R4F reference cigarette (see Section 5.2). Therefore, by design, the use of EHTS is expected to have substantially lower impact on the air quality compared with cigarette smoking. During use of the EHTS, a particular smell inherent with the product use (resulting from the heating of the tobacco material in the EHTP) can be noticed. A particular smell does not, however, unambiguously mean that harmful constituents are released or that the levels of emitted compounds are above the exposure limits set by air quality guidelines, in the same way as the smell from cooking, toasting, etc. do not necessarily mean that the air quality is compromised.

5.3.1 Air quality guidelines for exposure limits of compounds in air

To evaluate if the concentrations of emitted compounds in air are of concern, it is relevant to review threshold limits of exposure for compounds listed in air quality guidelines. Table 1 lists threshold limits of exposure for a selection of compounds in air as defined in air quality guidelines. For comparison, occupational exposure guidelines (OSHA, EU-OSHA) are included together with guidelines for non-industrial environments (OEHHA, EU, MHLW). The maximum allowable contaminant levels specified in occupational exposure standards apply for healthy adult individuals, controlled exposures, and normal workweek exposure duration (typically 40 hours per week/168 days per year). In the absence of an alternative, more effective method and as indicative of levels also in non-industrial indoor spaces, occupational exposure limit

Table 1. Limits of exposure levels for compounds in air defined in regulatory air quality

Substance		OSHA PEL[a]	OEHHA REL [b] acute [1 h]	OEHHA REL[b] 8-hr	OEHHA REL[b] chronic	EU-OSHA[c]	EU[d,e]	MHLW[f] / MOE[g]
RSP (PM 2.5)	[µg/m³]	5000	-	-	12 [1y]	-	25[d]	15[g]
Nicotine	[µg/m³]	500	-	-	-	500	-	-
Acetaldehyde	[µg/m³]	360000	470	300	140	-	200[e]	48[f]
Acrolein	[µg/m³]	250	2.5	0.7	0.35	50	-	-
Crotonaldehyde	[µg/m³]	6000	-	-	-	-	-	-
Formaldehyde	[µg/m³]	920 [8h]	55	9	9	250	30[e,h]	100[f]
Acrylonitrile	[µg/m³]	4340 [8h]	-	-	5	-	-	-
Benzene	[µg/m³]	3190 [8h]	27	3	3	<3250 [8h]	5[e]	-
1,3-Butadiene	[µg/m³]	2000	660	9	2	<225 [8h]	-	-
Isoprene	[µg/m³]	-	-	-	-	-	-	-
Toluene	[µg/m³]	754000	37000	-	300	192000	300[e]	260[f]
TVOC	[µg/m³]	-	-	-	-	-	-	400[f]
Glycerol[i]	[µg/m³]	-	-	-	-	-	-	-
Propylene glycol[j]	[µg/m³]	-	-	-	-	-	-	-
NNK	[µg/m³]	-	-	-	-	-	-	-
NNN	[µg/m³]	-	-	-	-	-	-	-
CO	[ppm]	50	20	-	-	20	10[e]	10[f]
NO	[ppb]	25000	-	-	-	2000	-	-
NO_2	[ppb]	5000[k]	250	-	-	500	20[e]	60[f]

[a] U.S. Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PEL) [33]

[b] U.S. Office of Environmental Health Hazard Assessment (OEHHA) Reference Exposure Levels (REL) [34]

[c] European Agency for Safety and Health at Work (EU-OSHA) [35]

[d] European Union (EU) [36]

[e] Koistinen et al., 2005 [32] – The INDEX project

[f] Ministry of Health, Labour and Welfare (MHLW) Japan [37] – Indoor/Housing (Living room/Bed room)

[g] Ministry of Environment (MOE) Japan [38]

[h] NOAL: no observed adverse effect level is not equivalent to exposure limit, but used in deriving it.

[i] American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (guideline value for average industrial worker) for glycerol concentration in air of 10 000 µg/m³ [39]

[j] American Industrial Hygiene Association (AIHA) Occupational guideline value for propylene glycol concentration in air of 10 000 µg/m³ [40]

[k] Ceiling value: should not be exceeded at any time

values divided by 10 have sometimes been used to allow for a much longer exposure time and heterogeneous target population [31, 32].

5.3.2 Air quality studies in controlled environmental conditions

To enhance knowledge of the impact of the environmental aerosol generated during EHTS use on air quality, PMI conducted scientific studies in simulated environments in a room under controlled environmental conditions (also referred to as the Indoor Air Quality (IAQ) room) located in the PMI Research & Development facilities in Neuchâtel, Switzerland [41-43]. All testing methods, including the IAQ room, are validated and ISO 17025-accredited. Figure 2 shows a representation of the IAQ room. To assess the specific impact of EHTS use on air quality, relevant norms and defined protocols were strictly followed. For example, participants of the studies were not allowed to wear cosmetics or perfumes or eat during the sessions. These restricted conditions are necessary to correctly attribute measured quantities to the product used during the session and to avoid attributing non-product-related contaminates to product use. However, while being appropriate for comparative studies between different products in scientific studies, these conditions are not fully representative of real-life situations.

The ventilation conditions for simulations representative for "Office," "Residential," and "Hospitality" environments were specified according to European ventilation performance standard EN 15251 [44]. The impacts of both cigarette smoking and EHTS use on air quality were evaluated and compared to conditions when no tobacco product was used.

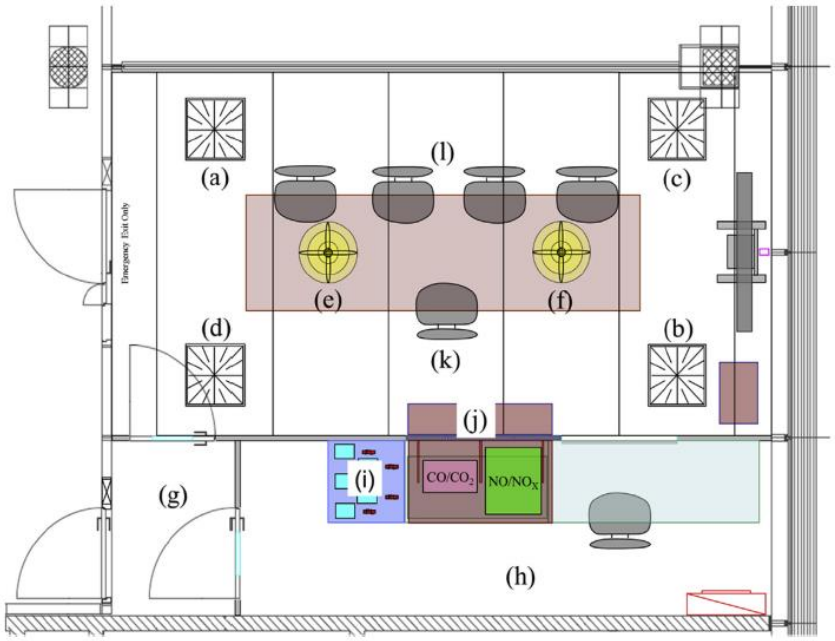


Figure 2. Layout of the environmentally controlled room and adjacent technical room. Air inlet ducts: a and b; air outlet ducts: c and d; electrical fans: e and f; air lock: g; technical room: h; membrane sampling pumps: i; sampling traps: j; PMI staff representative chair: k; volunteer panelist chairs: l [42].

The concentrations of 23 compounds representative of seven categories (ISO measurement standards for ETS, ISO measurement standards for total volatile organic compounds (TVOC), carbonyls, VOCs, tobacco-specific nitrosamines (TSNA), product-specific compounds (aerosol formers), and gases) were measured. The measured constituents were:

- RSP < 2.5 µm in diameter (off-line and/or real-time measurement)
- Particulate phase markers (ultraviolet particulate matter (UVPM), fluorescent particulate matter (FPM), solanesol)
- Gas-phase tobacco-specific markers (3-ethenylpyridine, nicotine)
- VOCs (1,3-butadiene, acrylonitrile, benzene, isoprene, toluene)
- Low-molecular weight carbonyls (acetaldehyde, acrolein, crotonaldehyde, formaldehyde)
- TSNAs (*N*-nitrosonornicotine (NNN), nicotine-derived nitrosamine ketone (NNK))
- Product-specific markers (glycerol, propylene glycol (PG))
- Gases (CO, nitrogen oxide (NO), and combined oxides of nitrogen (NO_x)).

Table 2. Impact of EHTS (referred to as THS 2.2 in the table) use and smoking Marlboro Gold cigarettes on the air quality measured in a dedicated room under controlled environmental conditions [42, 43].

Analyte [unit]	THS vs Background (difference in units)					Cigarette vs Background (difference in units)				
	Residential I	Residential II	Residential III	Office	Hospitality	Residential I	Residential II	Residential III	Office	Hospitality
RSP gravimetric [µg/m³]						236	268	642	204	147
UVPM-THBP [µg/m³]						39.6	40.8	92.1	38.5	18.4
FPM-scopoletin [µg/m³]						8.05	8.5	20.4	7.88	4.04
Solanesol [µg/m³]						10.2	9.84	23.8	10.2	4.68
3-Ethenylpyridine [µg/m³]						6.02	7.61	10.5	6.39	3.94
Nicotine [µg/m³]	0.69	1.81	0.70	1.10	0.66	29.7	29.1	49.8	34.7	34.6
Acetaldehyde [µg/m³]	2.66	5.09	3.26	3.65	1.40	70.2	83.8	123	58.8	33.1
Acrolein [µg/m³]						6.94	5.65	11.6	6.42	3.03
Crotonaldehyde [µg/m³]						2.19	2.11	3.54	2.04	0.99
Formaldehyde [µg/m³]						27.1	35.5	58.4	28.9	17.5
Acrylonitrile [µg/m³]						2.53	3.61	5.26	2.61	1.36
Benzene [µg/m³]						7.09	9.24	14.4	6.58	3.5
1,3-Butadiene [µg/m³]						13	16.8	17.4	12.6	5.79
Isoprene [µg/m³]						71.5	99.4	164	75.9	37
Toluene [µg/m³]						11.1	26.1	25	14.9	8.76
TVOC [µg/m³]							144	451		
NNN [ng/m³]								8.89		
NNK [ng/m³]								1.49		
Glycerin [µg/m³]			12.1					10.3		
Propylene glycol [µg/m³]								60.5		
CO [ppm]						1.63	2.17	2.66	1.58	0.92
NO [ppb]						26.2	35.6	59.4	27	14.8
NO_x [ppb]					0.52	29.4	39.7	62.8	29.4	15.3

µg/m³: 0, 1, 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 400, 650

*The data are background subtracted; THS 2.2: numerical value not shown if the concentration of the constituent in air is not increased above background

Table 2 summarizes the results of the measurements. The impact of EHTS use was calculated as the difference in median concentrations between the test product use and background

sessions. Background concentrations of all constituents were determined when the panelists were present in the room under equivalent conditions but did not smoke cigarettes or use EHTS.

Qualitative and quantitative differences exist between the environmental aerosol resulting from EHTS use and ETS produced when smoking cigarettes. Only three of the compounds measured (nicotine, acetaldehyde, and glycerol) were increased above the background levels and could be attributed to the use of EHTS. However, the levels of these compounds measured in the room were below the maximum exposure levels as defined in existing air quality guidelines. For example, the maximum acetaldehyde concentration during EHTS use in all simulated conditions was significantly below the limit for chronic exposure set by OEHHA (140 µg/m^3) [34] as well as the lowest limit specified for acetaldehyde in Table 1 (48 µg/m^3) by MHLW in Japan. Similarly, the maximum nicotine concentration during EHTS use was well below the occupational exposure limit (500 µg/m^3) defined by OSHA PEL [33] and EU-OSHA [35] (Table 1). Also, the glycerol concentration measured during EHTS use is well below the reference level established by ACGIH (10,000 µg/m^3) [39]. Acetaldehyde is a product of human metabolism and a common constituent in exhaled breath [45]. Human presence and day-to-day activities were shown to increase the acetaldehyde concentration in air in the study by [46] (described in more detail in Section 5.4.1). Acetaldehyde and the tobacco-specific constituent nicotine are both known to occur in the exhaled breath of cigarette smokers [47-49]. Thus, it is plausible that exhaled breath may contribute to the measured concentrations of both acetaldehyde and nicotine. Furthermore, the levels of NO_x were for most simulated environments either below or close to the limit of quantification (LOQ) of the method, with the exception of the "hospitality" environment, where it was slightly above, as shown in Table 2. However, the authors concluded that EHTS use did not contribute to the measured indoor concentrations of NO_x, due to the lack of maxima in the measurement signal, when EHTS was used, and the proximity of the measured levels to the LOQ of the method [42].

Moreover, the chemical compositions of the background air and the environmental aerosol of EHTS were essentially similar in contrast to the ETS emitted during cigarette smoking, as shown by the TVOC profiles in Figure 3. TVOC provides both a quantitative value and a fingerprinting of VOCs with boiling points from 69°C to 287°C. On average, the TVOC was 20.4 µg/m^3 for the background session and 22.2 µg/m^3 for the session where EHTS was used. In comparison, the TVOC for the session in which cigarettes were smoked was 479 µg/m^3, on average [50].

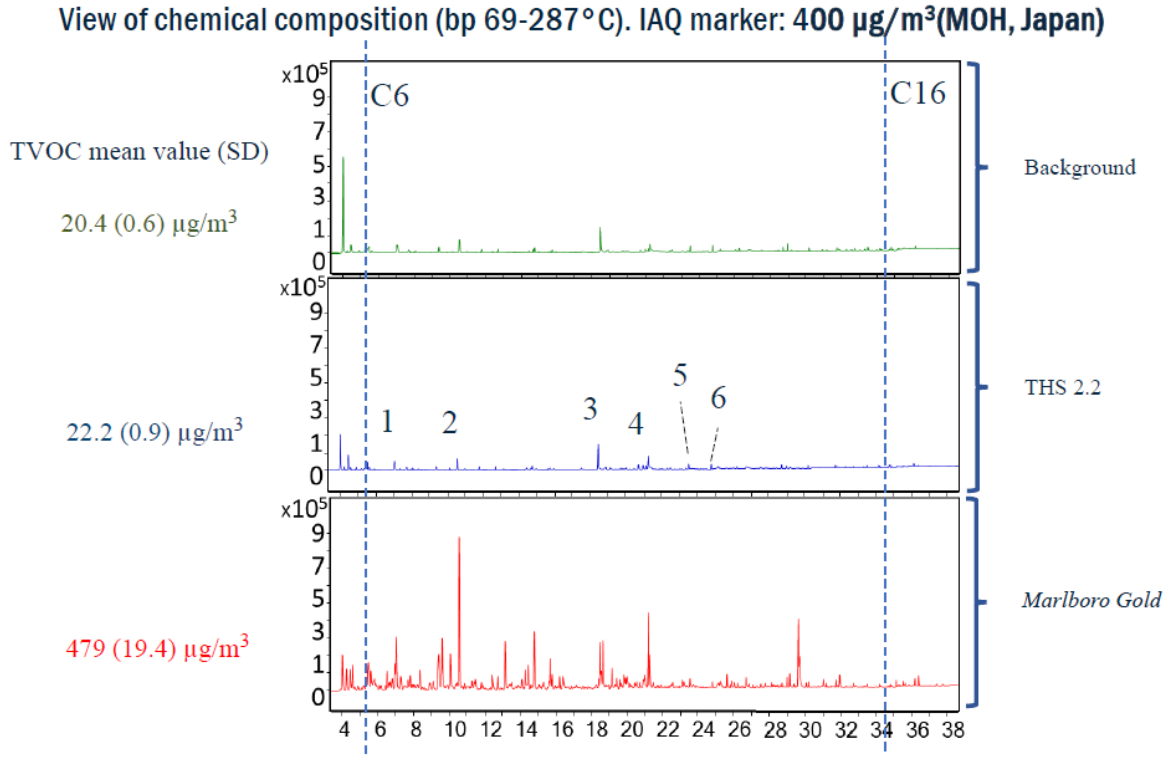


Figure 3. TVOC chromatograms. Compounds above 2 µg/m³: butanol (1), cyclotrisiloxane (2), benzaldehyde (3), benzyl alcohol (4), nonanal (5), decamethylpentasiloxane (6) [50]. EHTS is referred to as THS 2.2 in the figure, and cigarettes are represented by Marlboro Gold. SD refers to standard deviation.

5.3.3 Air quality study in an apartment environment

Another study was carried out in an apartment environment by Ruprecht et al. (2017) [51], where the effects on air quality of EHTS and EVP use, as well as cigarette smoking, were studied. A room in an apartment owned by habitual smokers, furnished with typical home appliances, was used for this study. Two to three persons occupied the room during the experiments. Concentrations of particulate metals and organic compounds, as well as gas-phase aldehydes emitted from EHTS, EVP, and cigarettes, were measured in the air. In contrast to the study by [41-43, 50], where ventilation conditions were strictly controlled, the air exchange rate (ventilation condition) in the study by [51] was not controlled and was instead estimated. Moreover, the influence of variations in outdoor pollution entering the apartment during the experiments could not be controlled, as the ventilation air was unfiltered. The results from the measurements showed that PAHs were mostly undetectable in the VOC emissions from both the EHTS and EVP [51]. Metal concentrations were similar to the background levels and lower during EHTS use compared with both EVP use and cigarette smoking. Concentrations of aldehydes in the environmental aerosol emitted by the EHTS during use were higher in comparison with the environmental aerosol from EVP use; however, the levels were substantially lower compared with the ETS from cigarette smoking. For example, EHTS use resulted in average levels of formaldehyde of 2.7 µg/m³ [51], whereas the level of formaldehyde was equivalent to the background for all simulated environments reported in

Table 2 extracted from the studies by [42, 43]. The reported formaldehyde concentrations by Ruprecht et al. (2017) [51] was computed based on the difference between simultaneous indoor and outdoor measurements, and no additional baseline control of the indoor levels without product use was done. Indoor environments are known to have higher levels of formaldehyde compared to the outdoor levels due to emissions from furniture and furnishings, fabrics, and personal care products and due to the normal metabolism of the panelists [52]. Outdoor air typically has formaldehyde concentrations around 1–4 µg/m^3 due to fast photo-oxidation of formaldehyde in sunlight to carbon dioxide (CO_2) [53]. In contrast, the median indoor concentration of formaldehyde in the European Union in non-smoking environments is typically 26±6 µg/m^3 [32]. Thus, the difference in the result for formaldehyde between the two studies by Ruprecht et al. (2017) [51] and Mitova et al. (2016) [42] may result from the fact that background measurement was only partially performed in the study by Ruprecht et al. (2017) [51]. The average level of acetaldehyde measured by Ruprecht et al. (2017) [51] when EHTS was used was 3.5 µg/m^3, which was within the range (1.4–5.09 µg/m^3) reported in Table 2 for all simulated environments in the studies by [42, 43]. Such low levels of formaldehyde and acetaldehyde are an order of magnitude lower than the levels measured when cigarettes were smoked under the same environmental conditions [42, 51]. Furthermore, in the apartment environment, $PM_{2.5}$ was reported to be 6.5 µg/m^3 when EHTS was used [51], whereas Mitova et al. (2016) [42] did not find PM (represented by the RSP concentration) above the LOQ (14.7 µg/m^3). Moreover, Ruprecht et al. (2017) [51] also reported that concentrations of particle-phase alkanes, organic acids, and levoglucosan (none of which are included in the U.S. FDA list of tobacco aerosol HPHCs [23]) from the use of EHTS were well below the levels associated with ETS emitted from cigarette smoking. As no explicit baseline control of the indoor levels without product use was done by Ruprecht et al. (2017) [51] and the values reported were computed based on the difference between simultaneous indoor and outdoor measurements, it is not possible to know if the measured values were related to the indoor environment or directly effects of the product use.

As shown by the studies under controlled environmental conditions [41-43, 50, 51], the environmental aerosol emissions from EHTS use (predominantly emitted from exhalation of the EHTS mainstream aerosol) were far below the emissions from smoldering cigarettes and did not adversely affect air quality, considering the exposure limits set by air quality guidelines (Table 1).

5.4 Impact of EHTS use on air quality in real-life environments

As mentioned previously, relevant norms and defined protocols were used in the assessments by [41-43, 50] to evaluate the specific impact that EHTS use has on air quality and how the emissions compared with those in ETS from cigarette smoke under controlled environmental conditions. The rigorousness and adherence to relevant norms and defined protocols reduces the risk of drawing erroneous conclusions related to the impact a tested product has on the measured air quality. While being instrumental for the evaluation of the impact of specific products, such restricted conditions do not, however, represent real-life conditions. To assess the impact of EHTS use in real-life settings, where activities of daily living, such as cooking, wearing cosmetics, and burning candles or incense, or simply the presence of people, may influence the air quality and produce significant levels of pollutants (such as $PM_{2.5}$,

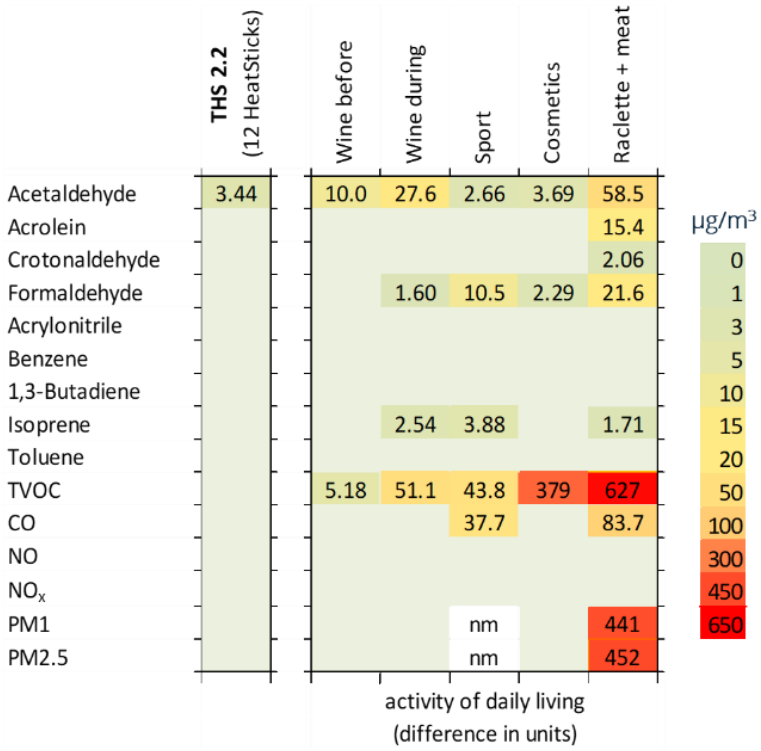
acetaldehyde, or noxious gases), studies in real-life settings have also been carried out to reflect a variety of scenarios and environments. The studies described in sections 5.4.1 and 5.4.2 were conducted with the objective to help contextualize the impact of EHTS when used in real-life settings and when interpreting results obtained from scientific studies on EHTS in a real-life environment.

5.4.1 Impact of human presence and activities on air quality

To examine how the presence of people, activities of daily living, and air without preceding purification (unfiltered air) influence the concentrations of selected air quality and non-specific ETS markers in air, a study was performed and reported by Mitova et al. (2017) [46]. During the experiments, all the volunteers and IAQ room operators were non-smokers, used products from a special hypoallergenic non-perfumed cosmetic kit, and were asked to not use perfume or aftershave, nor to wear new clothes (i.e. clothes which had yet not been washed following purchase) or new footwear during the sessions to, as much as possible, minimize the emissions of pollutants that could impact the background levels. The study demonstrated that the simple presence of people led to increases in the concentrations above the levels measured in an empty room for formaldehyde (50%–65% increase) and acetaldehyde (39%–49% increase) in air (Table 3). Similarly, the TVOC level increased by three to five times above the level measured in an empty room, whereas isoprene increased by five to eight times. Moreover, the study also showed that the presence of people did not influence the concentrations of acrolein, crotonaldehyde, toluene, NO, and NO_x in air.

The four selected activities of daily living (drinking wine, practicing sport, using cosmetics, and preparing food on a table-top appliance (melted cheese dish known as raclette)) caused an increase in the concentrations of several of the assessed constituents. The concentrations of acetaldehyde in air increased during all experiments, with the highest concentrations observed during the raclette and wine drinking sessions. As ethanol is metabolized mostly to acetaldehyde, elevated amounts of this compound are found in the exhaled breath of consumers of alcohol-containing drinks. In non-smoking environments, alcoholic beverages are one of the main sources of exposure to acetaldehyde for the general population [32]. Formaldehyde was increased during the sport, cosmetic use, and raclette sessions. Acrolein, crotonaldehyde, PM_1, and $PM_{2.5}$ levels rose significantly during the raclette session (by more than two orders of magnitude for acrolein, PM_1, and $PM_{2.5}$). These findings were consistent with literature data indicating that cooking vapors may contain carbonyls and PM [54, 55]. TVOC concentrations in toluene equivalents rose in all experiments. In conclusion, as all of these activities led to significant emissions of VOCs and PM, this study provides evidence that when experiments with EHTS use are run in real-life settings (homes, restaurant, bars, etc.), careful monitoring of background levels and day-to-day activities during measurements (i.e., alcohol consumption and dining) must be performed to understand and separate the effects of EHTS use on air quality from those already existing in today's real-life environment and to help avoid drawing erroneous conclusions from the acquired data.

Table 3. Summary of concentrations [µg/m³] of constituents measured in air in the experiments assessing the influence of activities of daily living on IAQ in comparison to EHTS use [46, 56]. The EHTS is referred to as THS 2.2 and EHTP as HeatSticks in the table. The values for EHTS are extracted from Mitova et al. 2016 [42].



5.4.2 Impact of EHTS use versus common pollution sources on the air quality

To contextualize the contribution of EHTS use has on measured air quality in real-life settings, it is also important to understand the impact that commonly used products have on air quality. Smoking cigarettes is associated with indoor air pollution, and awareness of its impact is high, whereas awareness of the impact of other commonly burned organic materials, such as wood burned for cooking or heating and burning of candles, incense, and mosquito coils, is generally lower [53, 57].

To further evaluate the contribution EHTS use has on measured compounds in air in real-life settings, PMI conducted a study [58] in which the impact of pollutant emissions from two commonly used combustible products (incense and candles (so-called “tea-lights”)) were investigated using the PMI IAQ room (Figure 2) under controlled environmental conditions. The tests were carried out under the simulated ventilation condition (0.5 air changes/hour; “Residential category III” environment; European ventilation performance standard EN 15251 [44]) representative of residential buildings with natural ventilation. All applied methods were validated and accredited under ISO 17025 scope B (accreditation number STS 0045, Swiss Accreditation Service, Bern, Switzerland).

Sixteen compounds were selected to be analyzed based on their potential to differentiate combustion from heating or because they are known to be emitted during the specific product use. The selected compounds were RSP by gravimetric measurement, UVPM, FPM, carbonyls (acetaldehyde, acrolein, crotonalehyde, formaldehyde), VOCs (acrylonitrile, benzene, 1,3-butadiene, isoprene, toluene), TVOC (expressed as toluene equivalent), CO, NO, and NO_x. To collect sufficient mass to allow for extraction and characterization of the composition of the samples collected, offline measurements (trapping of samples prior to analysis) were used for all compounds, except for the noxious gases CO, NO, and NO_x.

Table 4 summarizes the results of the measurements, where the background subtracted emissions after burning candles and incense were compared with data on environmental aerosol emitted by the EHTS during use and ETS emitted when smoking cigarettes (extracted from Mitova et al., 2016 [42]). In the conditions of the experiment ("Residential category III" environment and two hours measurement duration), burning of three "tea-lights" led to an increase of CO, NO, and NO_x above the background levels, with the level of NO being equivalent to the levels measured when 12 cigarettes were smoked and the level of NO_x being even higher than for when cigarettes were smoked. The burning of one incense stick resulted in an augmentation above the background levels of all compounds measured. For TVOC, the measured level was equivalent to the level measured when 12 cigarettes were smoked. Moreover, the emissions of one incense stick also resulted in substantially higher concentrations compared to the smoking of two cigarettes for benzene (24 times greater), acrolein, formaldehyde, and 1,3-butadiene. As a comparison, at the same environmental condition, EHTS use (12 EHTPs/two hours) resulted in a completely different influence on the air quality. Out of the compounds measured in this study, only acetaldehyde was slightly increased above the background levels after EHTS use, while all the other measured constituents remained at background levels [42].

These results demonstrate that burning candles or incense has a considerable impact on air quality (even equivalent or higher than cigarette smoking for some of the compounds analyzed) in the conditions of the experiment and that the impact is generally higher than the effect of EHTS use. It is therefore important to pay special attention to the measurement conditions when carrying out air quality measurements in real-life settings, and to carefully monitor background levels and account for them in the data analysis to understand and separate the effects of EHTS use on air quality from those already existing in today's real-life environment.

In addition to the PMI study on the impact of burning candles and incense on the air reported above, Kaunelienė, et al. 2018 [2] carried out a comprehensive comparative analysis of changes in air quality as a consequence of EHTS use versus the use of EVP, smoking cigarettes, and waterpipe as well as burning of incense and mosquito coils in various environments, especially with combustion-based pollution sources present. Two types of environments were considered: "controlled" (i.e., performed under controlled environmental conditions) and "real-life" (i.e., residential, public, or transport environments). Aldehydes (formaldehyde and acetaldehyde), monoaromatic hydrocarbons (benzene and toluene), and $PM_{2.5}$ were analyzed. As shown in Figure 4, EHTS use generally resulted in lower or comparable environmental aerosol constituent concentrations compared with the researched air pollution sources (cigarettes, waterpipe, incense, and mosquito coils). For example, in a controlled environment, the use of EHTS (as well as EVP) resulted in lower concentrations of formaldehyde, benzene,

toluene, and $PM_{2.5}$ compared with most of the researched pollution sources. For example, burning mosquito coils resulted in a high concentration of $PM_{2.5}$ (4,324 µg/m^3), while it was below the LOQ (<14.7 µg/m^3) when EHTS was used. Moreover, compared with EHTS use, real-life public and transport environments yielded equivalent or significantly higher levels of formaldehyde, acetaldehyde, benzene, and toluene, as shown in Figure 5. For instance, the toluene concentration inside a new vehicle was reported as high as 1,220.0 µg/m^3, whereas it was below 1 µg/m^3 during EHTS use [2].

Table 4. Summary of concentrations [µg/m^3] of constituents measured in air during the experiments when combustible products as well as EHTS (12 EHTPs) were used under low ventilation conditions (0.5 air changes per hour) [58]. nm: not measured. The EHTS is referred to as THS 2.2 and EHTP as HeatSticks in the table. The values for EHTS and Marlboro Gold (MLG) cigarettes are extracted from Mitova et al. 2016 [42].

	THS 2.2 (12 HeatSticks)	Tea-lights (3 candles)	Incense (1 stick)	Cigarettes (12MLG)	Cigarettes (2 MLG)
RSP-gravimetry		nm	162	631	119
UVPM-THBP		nm	13.9	92.9	17.7
FPM-scopoletin		nm	3.62	20.4	4.20
Acetaldehyde	3.44	nm	22.2	122	26.2
Acrolein		nm	5.31	12.4	2.75
Crotonaldehyde		nm	0.86	3.57	0.80
Formaldehyde		nm	29.0	58.9	9.71
Acrylonitrile		nm	0.68	5.28	1.23
Benzene		nm	75.2	14.2	3.11
1,3-Butadiene		nm	11.6	17.6	4.17
Isoprene		nm	9.05	164	39.9
Toluene		nm	11.6	25.2	5.15
TVOC		nm	323	445	33.4
CO		309	1497	2920	611
NO		70.8	13.7	71.8	
NO_x		127	21.0	94.6	

combustion product (difference in units)

µg/m^3: 0, 1, 3, 5, 10, 15, 20, 30, 50, 60, 90, 120, 150, 450, 650, 1500, 2000, 2990

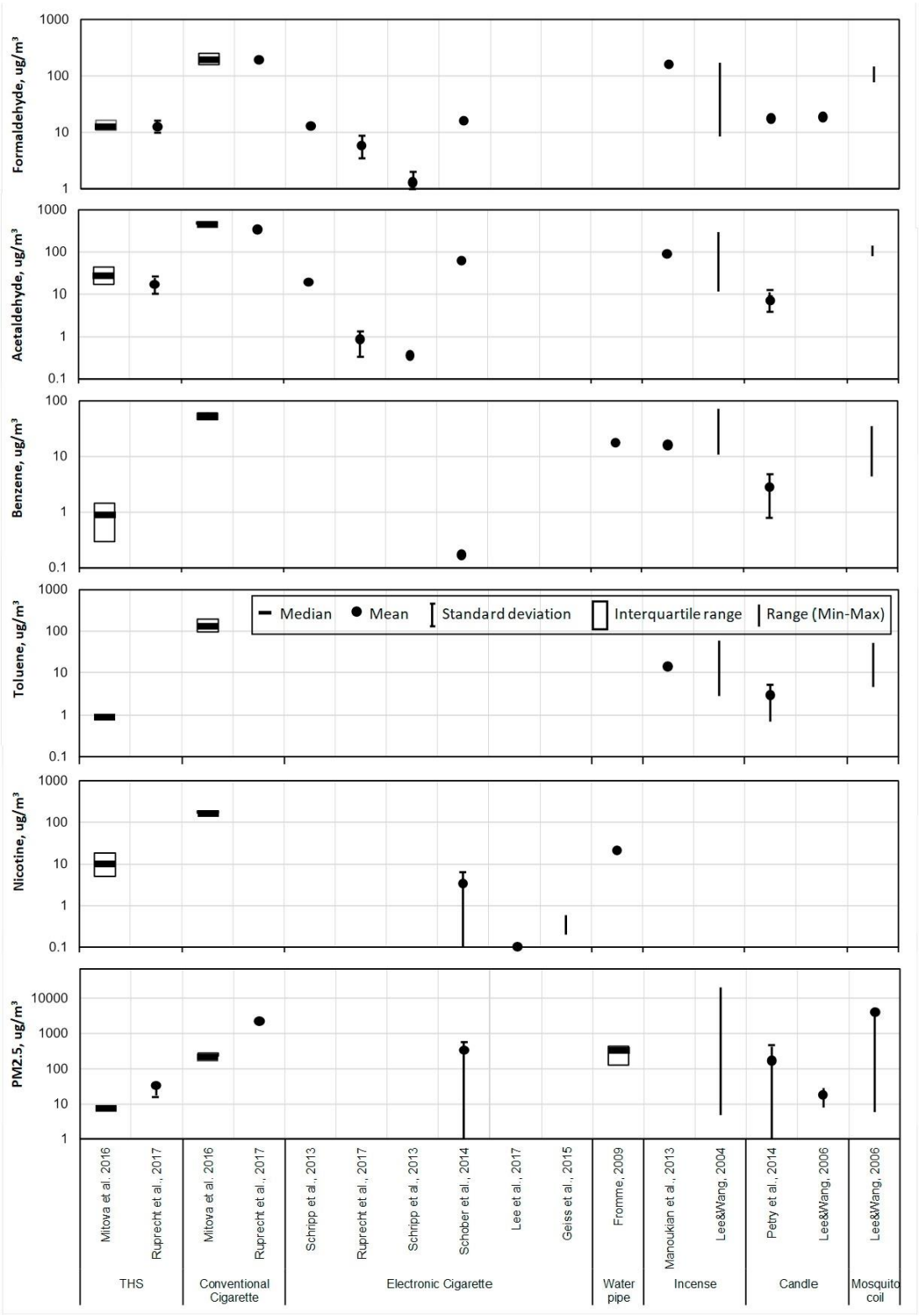


Figure 4. Concentrations of airborne formaldehyde, acetaldehyde, benzene, toluene, nicotine, and $PM_{2.5}$ as reported in chambers where EHTS and EVP were used, cigarettes were smoked, or common pollution sources were active [2]. EHTS is referred to as THS and EVP as Electronic Cigarette in the figure.

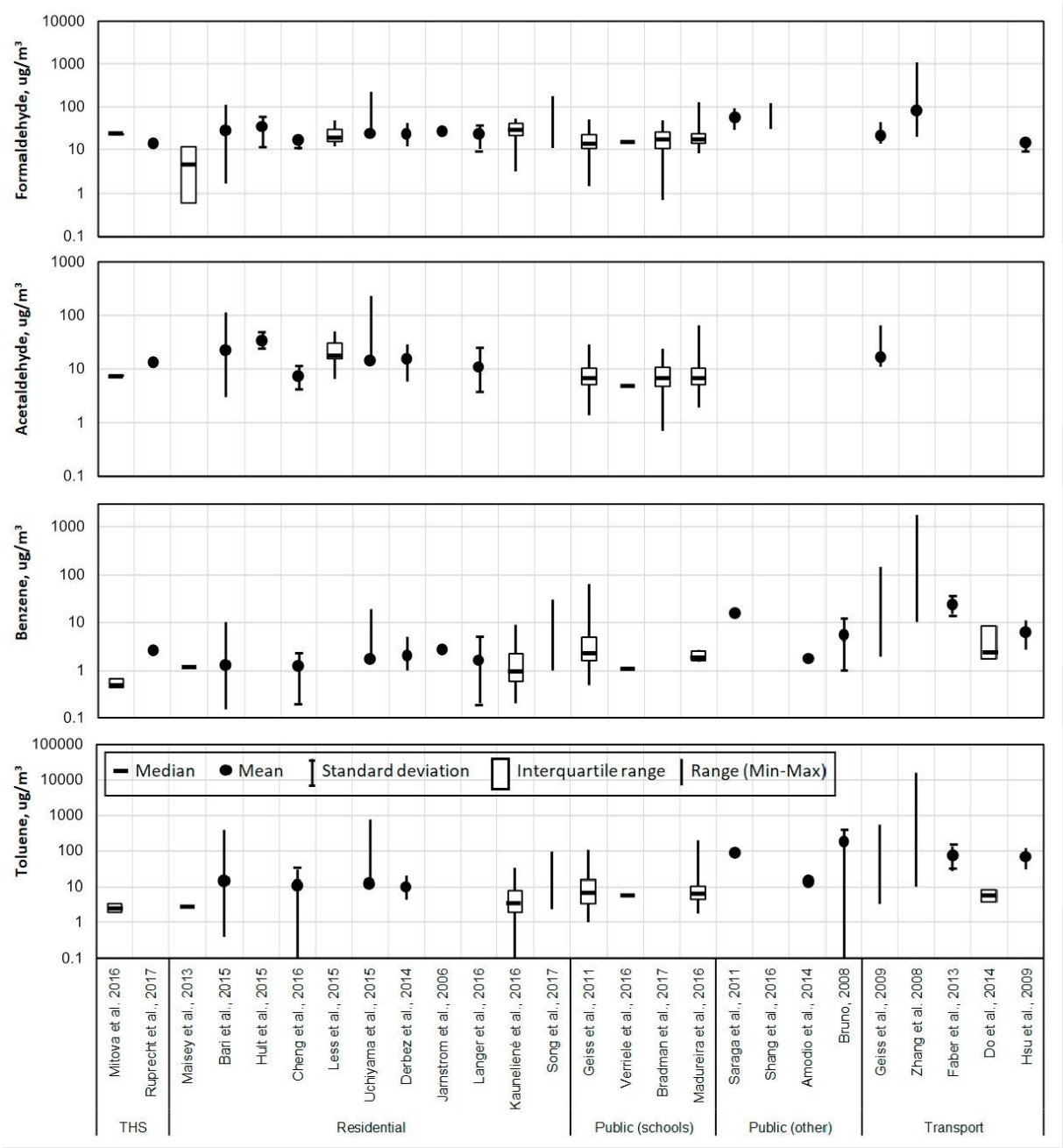


Figure 5. Concentrations of airborne formaldehyde, acetaldehyde, benzene, and toluene as reported in various indoor environments [2]. EHTS is referred to as THS in the figure.

5.4.3 Air quality study in a workplace coffee corner environment

A study was carried out at a coffee corner area, where the use of EHTS is allowed, at Philip Morris Japan (PMJ, part of the PMI group of companies), Sanno Park Tower, Tokyo, Japan (Figure 6) [59, 60]. The study was performed by the Analytisch-Biologisches Forschungslabor (ABF), Germany, a certified bioanalytical contract research laboratory with clients from the occupational, environmental, food, tobacco, and pharmaceutical fields. Three air quality measurement sessions were held within one representative working day. PM_1 and $PM_{2.5}$ as well as nicotine, 3-ethenylpyridine, TSNAs, and carbonyls (acetaldehyde, acrolein, crotonaldehyde, and formaldehyde) were measured by qualified technicians and scientists using certified equipment.

Figure 6. Picture of the PMJ coffee corner. The instruments used for air quality measurements are located on both sides of the room (PMJ 1, PMJ 2) [59].

First, the background concentrations of the selected constituents were measured in the air during two hours (from 08:00 to 10:00) when the room was empty of people. Thereafter, PMJ employees were allowed to enter and leave the room as they wished to use EHTS, relax, snack, or socialize. Concentrations of the selected constituents were continuously measured in the air during two two-hour sessions (11:00 to 13:00 and 14:00 to 16:00). In total, 239 EHTPs were consumed (approximately 60 EHTPs per hour), and on average, 22 people were present in the room at any one moment.

Subsequent analysis of the acquired data showed that no quantifiable amounts of $PM_{2.5}$ were present in any of the sessions (LOQ: 15 µg/m^3). Out of nicotine, 3-ethenylpyridine, and TSNAs, only nicotine was found at a quantifiable, but negligible, level (below 5 µg/m^3) during human presence and EHTS use. In comparison, the level of nicotine measured was two orders of

magnitude lower than the occupational exposure limit (500 µg/m^3) defined in the air quality guidelines listed in Table 1. Moreover, carbonyls were detected at low levels in all sessions (including the background session without people in the room). For example, formaldehyde and acetaldehyde concentrations were generally below 15 µg/m^3, while acrolein and crotonaldehyde were both below 1 µg/m^3 in the session to assess building background concentrations of the selected analytes. When the room was occupied and EHTS was used, no significant increases in acrolein, crotonaldehyde, and formaldehyde concentrations were observed. A slight increase in the acetaldehyde concentration was noted during human presence and EHTS use. On average, the acetaldehyde concentration was 10.4 µg/m^3 (range: 9.0–11.6 µg/m^3) during the session to assess the background levels, whereas it increased to 16.1 µg/m^3, on average (range: 13.2–23.1 µg/m^3), during the sessions with human presence and EHTS use. As acetaldehyde is a product of human metabolism and a common constituent in exhaled breath [45], the observed increase in the acetaldehyde concentration from the background level during the session with human presence and EHTS use makes it challenging to distinguish what part of the increase in acetaldehyde comes from the human presence or the EHTS use. All measured carbonyls were far below the levels defined by air quality guidelines [32, 33, 35-38].

5.4.4 Air quality studies in *IQOS* stores

A study assessing the air quality in a real-life setting was conducted in the *IQOS* store in Ginza, Tokyo, Japan (Figure 7) in collaboration with ABF, Germany [59, 61]. Four air quality measurement sessions, each lasting three hours, were conducted over two days during periods representative of customer affluence (i.e., from 12:00 to 15:00 and from 17:00 to 20:00). PM_1 and $PM_{2.5}$ as well as nicotine, 3-ethenylpyridine, TSNAs, and carbonyls (acetaldehyde, acrolein, crotonaldehyde and formaldehyde) were measured by qualified technicians and scientists using certified equipment.

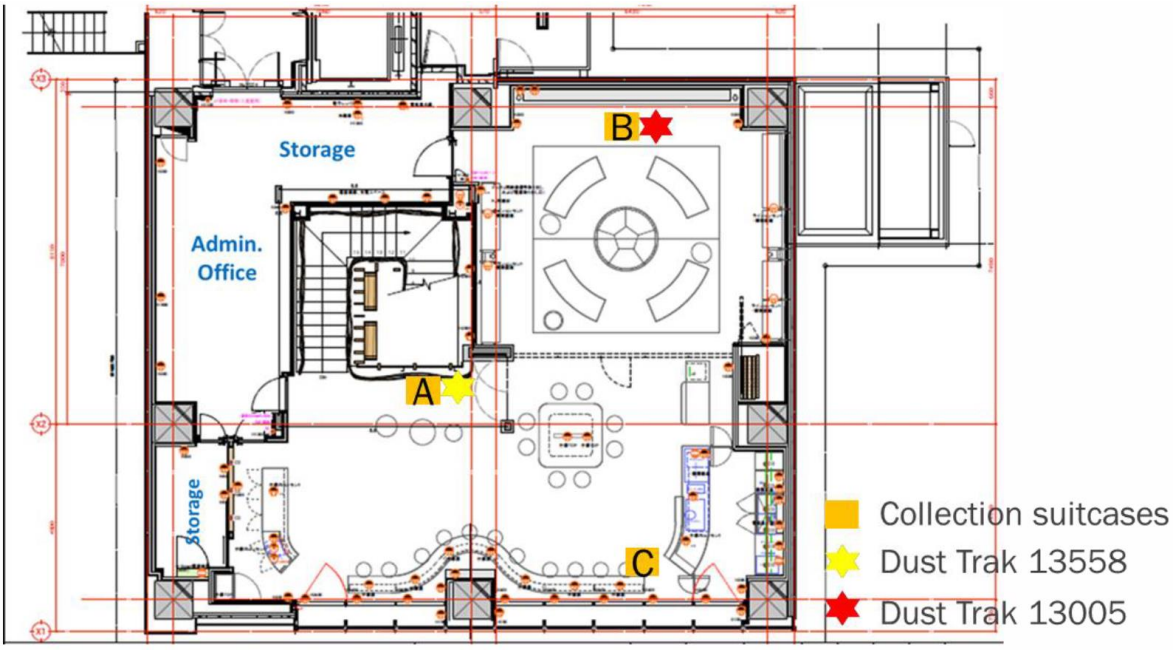


Figure 7. Layout of the IQOS store, second floor. The instruments used for IAQ measurements were located in three areas (A,B,C) [59].

Subsequent analysis of the acquired data showed that no quantifiable amounts of $PM_{2.5}$ were detected in any of the sessions (LOQ: 15 µg/m^3). Similarly to the study in the PMJ coffee room, out of nicotine, 3-ethenylpyridine, and TSNAs, only nicotine was detected at negligible levels (not exceeding 0.85 µg/m^3) during the periods where humans were present and were using EHTS. The levels of nicotine measured were two orders of magnitude lower than the occupational exposure limit (500 µg/m^3) defined in the air quality guidelines listed in Table 1. Similarly to the study carried out in the coffee corner area at the PMJ premises, carbonyls were detected at low levels in all sessions (including the background session without people in the room). For example, formaldehyde and acetaldehyde concentrations were generally below 8 µg/m^3 (on average 5.4 µg/m^3) and 20 µg/m^3 (on average 12.3 µg/m^3), respectively, while acrolein and crotonaldehyde were both generally below 0.1 µg/m^3. All measured carbonyls were far below the levels defined in the air quality guidelines presented in Table 1.

Another air quality study conducted in an *IQOS* store in Zürich, Switzerland, was performed together with ABF, Germany [62]. The aim of the study was to evaluate the levels of nicotine, formaldehyde, acetaldehyde, acrolein, and crotonaldehyde in air during intensive use of EHTS and to compare them to the maximum allowable concentrations for the selected compounds at workplaces. In addition, 3-ethenylpyridine (a specific marker for gas-phase ETS) was monitored, although there is no specific exposure limit defined for this compound.

The *IQOS* store consisted of two areas (Figure 8): one was assigned as a control area (shop: 108 m^2, 395.3 m^3, sampling height of 170 cm), where the use of tobacco products was forbidden; the other area was assigned as a trial area (lounge: 62 m^2, 226.9 m^3, sampling height of 142 cm), where only EHTS use was allowed. The two areas were separated by sliding doors. No restrictions were placed on the customers present in the store, nor on the staff, except for the

requirement to use only EHTS in the trial area. The customers were allowed to move freely between both areas and to consume drinks and snacks. Thus, the number of persons in the store as well as the number of EHTPs consumed varied for the different measurement sessions and days. The consumption of EHTPs was monitored throughout the course of the four-hour sample collection periods (Day 1: 161 EHTPs, Day 2: 33 EHTPs, Day 3: 118 EHTPs, Day 4: 231 EHTPs). No mechanical ventilation was installed in the store. The shop was aerated through windows (natural ventilation), and two air purifiers were installed to compensate for the absence of windows in the lounge.

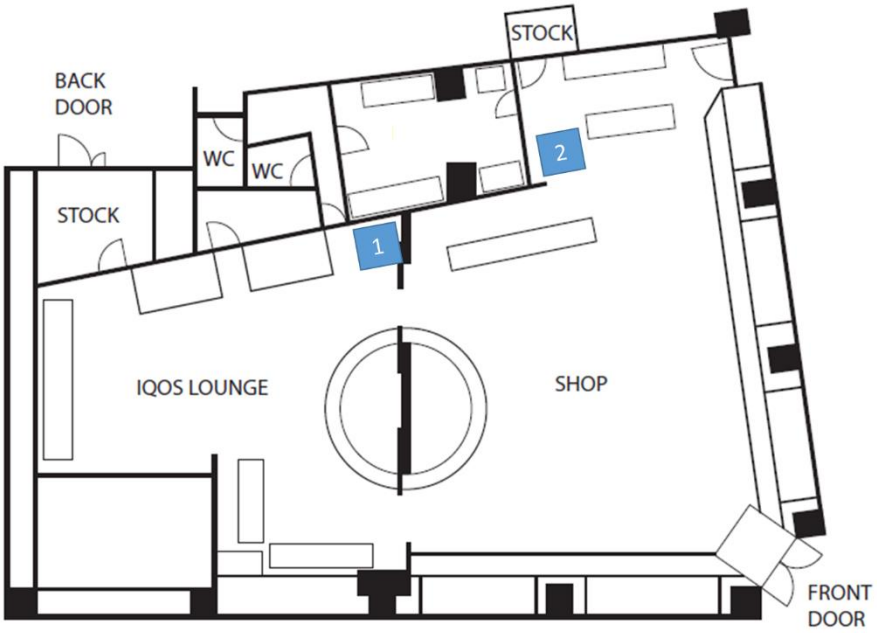


Figure 8. Graphical representation of the IQOS Store in Zürich, Switzerland, with the positions of the sampling locations in the trial area (1) and in the control area (2) [62].

The nicotine concentrations in the air of the trial area were slightly increased to levels above the background and were correlated with the number of used EHTPs. However, the nicotine concentrations did not exceed 3.1 µg/m^3 in the trial area during the four-hour collection period for all four trial days, which is around 160 times below the occupational exposure limit for nicotine of 500 µg/m^3 (Table 1) for the highest amounts measured during the study.

Higher levels of formaldehyde were observed in the trial area compared with the control area; however, no correlation between EHTS use and formaldehyde concentrations was evident. These results are best explained by other environmental factors, such as the number of persons or the residence time in the room, which may have had a more pronounced contribution to the formaldehyde concentrations measured compared to the use of EHTS considering the results of the human signature study in a controlled environment reported by Mitova et al. (2017) [46]. In contrast, no differences were observed between the trial and control area for 3-ethenylpyridine (below the LOQ in the trial area), acetaldehyde, acrolein, and crotonaldehyde.

The concentrations of all measured carbonyls were far below the defined threshold limits listed in Table 1.

Once again, in view of the intensive conditions of EHTS use (up to 231 sticks for four hours of collection), only nicotine values could be attributed to the use of EHTS. The concentrations measured for nicotine were, however, far below the maximum allowed levels of exposure as defined by air quality guidelines for Switzerland. In contrast to the studies conducted in controlled environments under simulated environmental conditions [42, 51], acetaldehyde, a non-specific marker of environmental aerosol emitted by EHTS, was not quantified at higher than background levels under the conditions of the experiment.

5.4.5 Air quality studies in a nightclub environment

An air quality study aimed at assessing the use of EHTS in a real-life nightclub environment (Figure 9) was carried out by Martuzevičius et al. (2018) [63]. The study included up to 30 persons (10 or 30 persons) using the EHTS simultaneously 1) at a confined space of a nightclub in Lithuania, without additional occupancy or activities and 2) during full operation of the nightclub. Cigarette smoking and the use of EVP was prohibited in the nightclub during the study.

The measured median background particle number concentration (PNC) was 5×10^3–3.5×10^4 #/cm^3 in the case when the nightclub was empty (no human presence) and not operating. In the case when 10 humans were present in the non-operating nightclub (not using EHTS), the median background PNC was 7×10^3–3×10^4 #/cm^3, and when 30 humans were present (not using the EHTS), the median background PNC was increased to 4×10^4–5×10^4 #/cm^3, as shown in Figure 10.

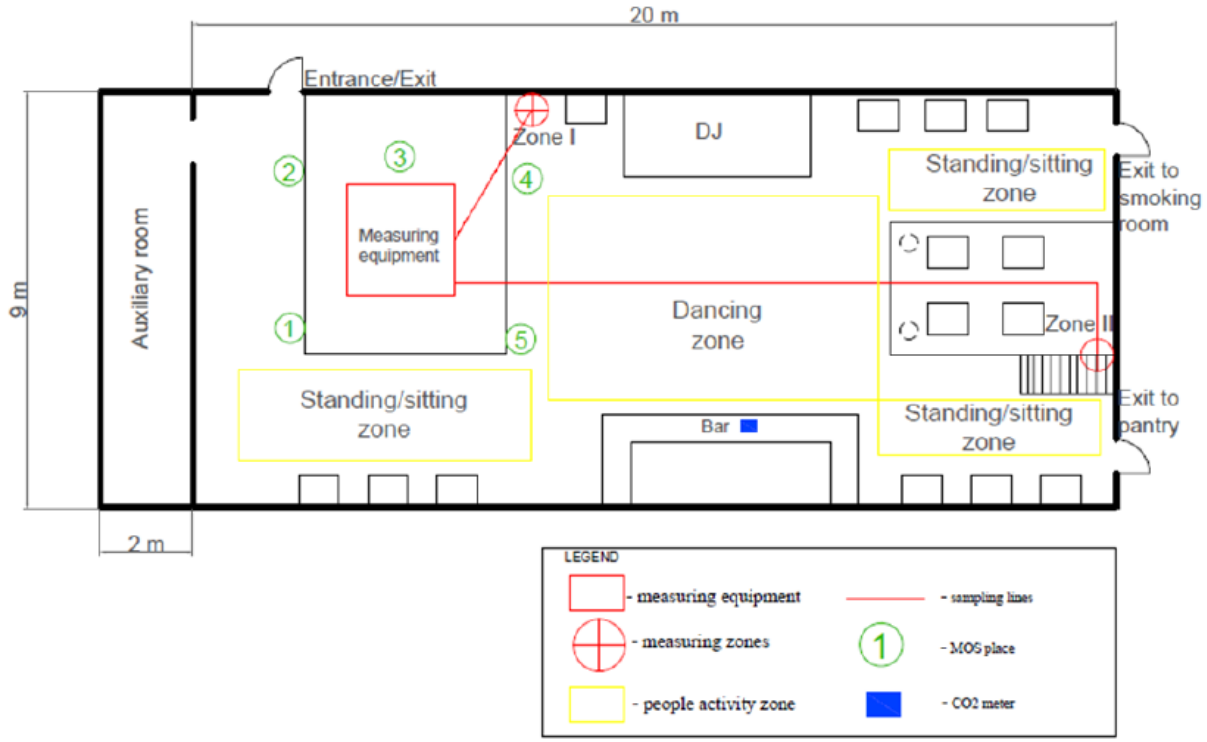


Figure 9. Nightclub scheme where air quality was measured. The surface area of the nightclub was approximately 198 m^2, and its volume was approximately 800 m^3 [63].

Moreover, in the case when 10 EHTS were used simultaneously, the median PNC was 5×10^3–7×10^4 #/cm^3, whereas it was 4×10^4–2.5×10^5 #/cm^3 in the case when 30 EHTS were used simultaneously. As shown in Figure 10, EHTS use in the non-operating nightclub slightly increased the PNC above the background, especially in the situation when 30 persons used the EHTS simultaneously. However, when put into the context of an operating nightclub, the median PNC levels measured when 30 EHTS were used simultaneously and the nightclub was not operating were even below the median background levels (but within a similar range) when the nightclub was operating without human presence, as shown in Figure 10. When the nightclub was operating with human presence, including EHTS use, the median PNC (measured over several days) was between 5×10^5 and 1×10^6 #/cm^3. The nightclub in operation resulted in an order of magnitude higher levels of PNC compared to EHTS use measured when the nightclub was not in operation. The high levels of PNC measured when the nightclub was operating were attributed to the fog machine operation and fugitive emissions from the smoking room where cigarettes were smoked [63]. The authors of the study concluded that EHTS may not be a distinguishable source of particles in crowded real-life environments even when used indoors, as compared to other thermal aerosol sources and as opposed to cigarette smoking [63].

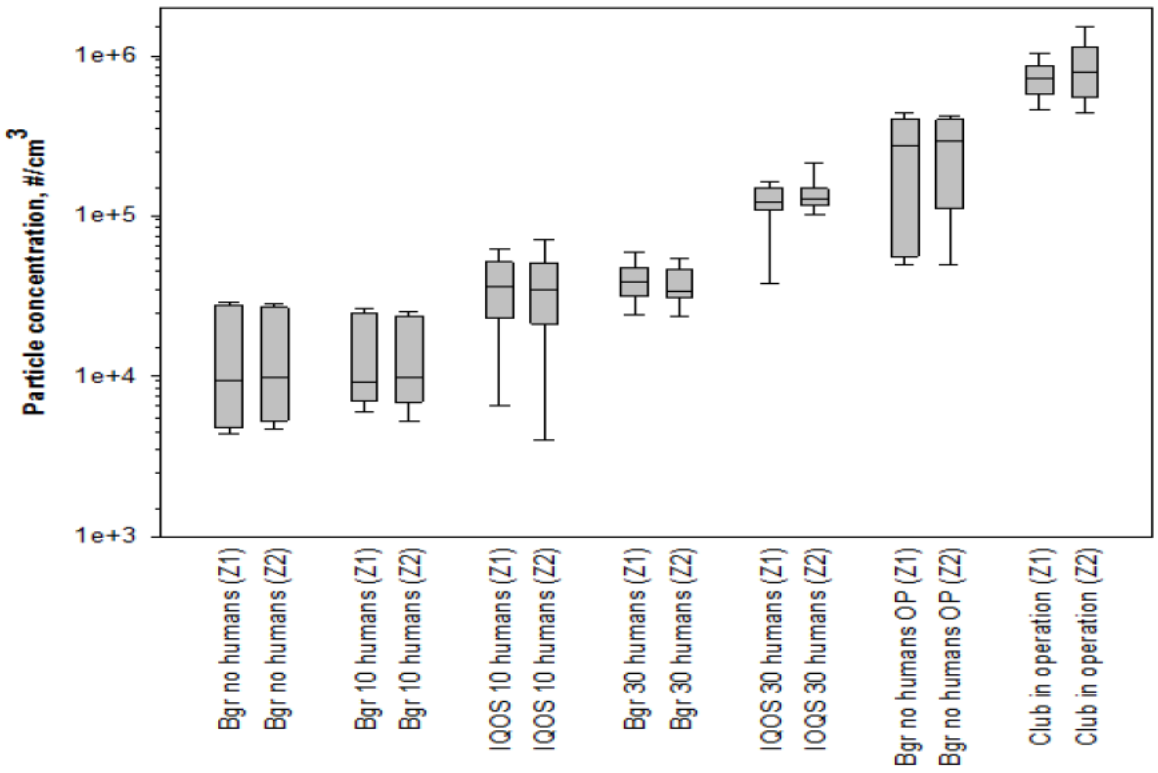


Figure 10. Comparison of particle concentration distributions between background (Bgr), EHTS use in an non-operating nightclub and when the nightclub is in operation [63]. EHTS is referred to as IQOS in the figure.

5.4.6 Air quality studies in a catering and entertainment environment

In another air quality study conducted in a catering and entertainment establishment (in Kiev, Ukraine), the quality and pollution level of indoor air were evaluated before, during, and after EHTS use and cigarette smoking [64, 65]. The study was commissioned by the Ukrainian Ministry of Health and carried out by L.I.Medved's Research Center of Preventive Toxicology, Food and Chemical Safety. The experiments were run in a catering and entertainment establishment (250 m^2, 625 m^3) (Figure 11) with 80 participants (20 participants either used EHTS or smoked cigarettes, while 60 participants did not use any tobacco products during the experiments). The participants were engaged in recreation activities, including playing billiards, snacking, watching TV, and chatting. Measurements were conducted during four consecutive one-hour sessions: 1) indoor space background session (no human presence), 2) background session with participants (recreation activities without use of any tobacco product), 3) sessions with EHTS use or cigarette smoking, and 4) background session with participants after the use of tobacco products (recreation activities without use of any tobacco product).

During the sessions where tobacco products were used, 20 participants used four EHTPs during EHTS use session or four cigarettes during the smoking session. During the first experimental day, EHTS was used, while cigarettes were smoked on the second day. The establishment was cleaned and aerated before and after each experimental day. No natural or mechanical ventilation systems were used during the experiments. The conditions of the establishment

met the regulatory requirements stipulated by [66]. Concentrations of six compounds were evaluated (CO, CO_2, nicotine, benzo(a)pyrene, formaldehyde, and ammonia) using analytical methods accredited under ISO 17025:2005.

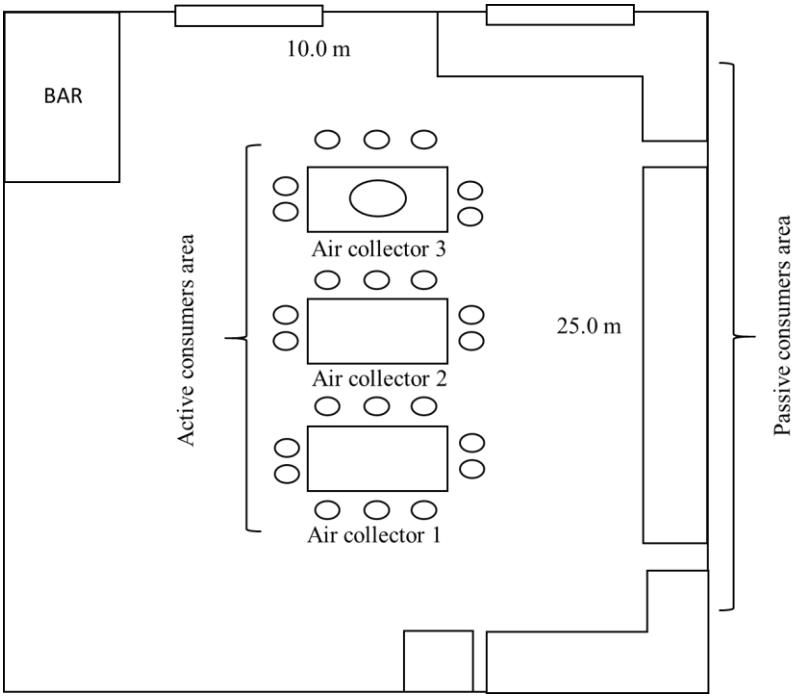


Figure 11. Plan of the catering and entertainment establishment and the locations of the air collectors [65].

No benzo(a)pyrene, nicotine, or ammonia were detected in the collected indoor air during and after the EHTS session (where 80 EHTPs were consumed), whereas a slight increase in CO, CO_2, and formaldehyde concentrations were observed. The authors of the study inferred that the slight increases in CO, CO_2, and formaldehyde levels were not caused by EHTS use, but from intensified breathing of the participants during their activities [64]. Slight increases in formaldehyde are known to occur during prolonged residence in indoor places as a result of human metabolism [46, 67]. The concentrations of all measured indoor air pollutants were far below the threshold limit values established in air quality guidelines. In addition to the chemical analysis, the participants reported that they subjectively perceived the indoor air during and after EHTS use as being practically the same as before EHTS use [67].

In contrast to the EHTS sessions, the levels of all measured compounds were increased in the indoor air during and after the smoking of 80 cigarettes in the smoking session. All participants, both smokers and bystanders, described the indoor air as smoke-laden, suffocating, and of a nature to cause choking and, sometimes, mild eye irritation. The threshold limit values of hazardous substances in air at a workplace were exceeded for all measured substances, except for ammonia.

Thus, considering that this study was performed under intensive conditions of EHTS use (80 EHTPs in one hour without ventilation), it was concluded by [64, 65] that significant qualitative as well as quantitative differences exist between the composition of indoor air after cigarettes

have been smoked and after EHTS have been used. The concentrations of air quality indicators in indoor air during and after EHTS use did not exceed regulatory levels for ambient air, whereas the same indicators exceeded the regulatory levels when cigarettes were smoked.

5.4.7 Air quality and passive exposure study in a restaurant setting

In addition to the air quality studies carried out in real-life settings presented above, a study was conducted aiming to assess if passive exposure to the environmental aerosol emitted during EHTS use in a real-life restaurant setting in Japan during dinner events, where food and alcohol were served, had an adverse effect on air quality and on non-smoking bystanders [68]. It is important to remark that at the time of the study, the use of tobacco and nicotine-containing products in restaurants and bars in Japan was permitted at the discretion of the restaurant owner. Dinner events of about a four-hour duration, where no tobacco- or nicotine-containing product use was allowed (non-exposure events) or only EHTS use was allowed (exposure events), were conducted in a restaurant in Tokyo, Japan, where the use of EHTS but no cigarette smoking was allowed. One hundred and thirty seven (137) persons completed the two non-exposure events, and 260 persons completed the four exposure events. The group of study participants during the non-exposure events was composed of non-smokers, EHTS users not using EHTS or any other tobacco- or nicotine-containing product, and cigarette smokers not using cigarettes or any other tobacco- or nicotine-containing product for the duration of the events. During the exposure events, a group of EHTS users that were allowed to use EHTS during the events was added.

Air quality was assessed during the events by measuring concentrations of selected environmental aerosol constituents in the air, and urinary levels of biomarkers of exposure to selected HPHCs were measured in all groups prior to and after the events. The combination of air quality assessment and measurements of urinary levels of biomarkers of exposure in participants during the events helped to understand and characterize the potential source of exposure (i.e., EHTS use versus background exposure in the building, study participants, food, and beverages).

Results from the study show that during the non-exposure events, nicotine levels were below the lower limit of detection and the lower limit of quantification, except for two replicates that showed nicotine levels in air of 0.13 µg/m^3 and 0.1 µg/m^3. During the second non-exposure event, nicotine was detected with a maximum value of 0.18 µg/m^3. The highest average nicotine concentration recorded in the air during any of the exposure events was about 1.5 µg/m^3 (maximum of 2.26 µg/m^3 in any event), which is far below existing occupational air quality guidelines of 500 µg/m^3 [35, 69] and in line with the levels reported in Table 2 for simulated environments.

Nicotine, at very low and similar levels, was detected in urine before and at the end (at slightly increased levels) of both the non-exposure and the exposure events in the non-smokers group. The presence of measurable levels of nicotine and the small increase in the levels of exposure in non-smokers can be best explained by the presence of participants who were users of tobacco or nicotine-containing products in their day-to-day life (cigarette smokers and EHTS passive users), as nicotine is known to be found on surfaces touched or on clothes worn by users of tobacco or nicotine-containing products [70, 71]. These results show that a low level

of exposure to nicotine exists in the current public setting and that non-smokers passively exposed to the environmental aerosol emitted during EHTS use are not exposed to an increased amount of nicotine compared to non-smokers not being passively exposed to EHTS use.

Furthermore, no quantifiable levels of TSNAs (NNN and NNK), potent carcinogenic compounds and the only tobacco-specific HPHCs known to date, were found in the air during the non-exposure events or, more importantly, during the exposure events. Furthermore, and consistent with the results of the air quality measurements, exposure to NNN and NNK was not quantifiable in the urine of non-smokers after any event (non-exposure and exposure events).

The concentrations of all four carbonyls measured as part of the air quality assessment (acrolein, formaldehyde, crotonaldehyde, and acetaldehyde) are not specific to exposure to tobacco or nicotine-containing products, and many other sources of exposure exist in day-to-day life, as discussed in Section 5.4.1 [46]. Extensive analyses and cross-correlations between various sources (including the number of EHTPs used, food and alcohol consumption, etc.) present during the events indicate that in a real-life setting, EHTS use was not a major source of any of the measured carbonyls in air [68]. Based on the results of previous studies, a minor contribution of EHTS to the concentrations of acetaldehyde in indoor air could be assumed [42, 43]. However, these levels are negligible considering the exposure to these compounds that already exists in today's real-life environment, as discussed by Kaunelienė et al., 2018 [2].

In addition to the air quality assessment, the exposure patterns observed in the urinary levels of the biomarkers of exposure for acrolein and crotonaldehyde, as well as for benzene and ethylene oxide, in the participants provide further evidence that EHTS use is not a major contributor to any of the assessed compounds in a real-life setting.

In summary, the results of this study indicate that [68]:

- The use of EHTS did not generate ETS and had no adverse effect on air quality as measured by nicotine, TSNAs, and RSP as well as the carbonyls acrolein, crotonaldehyde, acetaldehyde, and formaldehyde in air in a real-life setting where regulatory norms for occupational exposure in terms of adequate ventilation were respected.
- Non-smokers did not have an increase in exposure to nicotine and TSNAs due to passive exposure to the environmental EHTS aerosol by means of assessing their urinary biomarkers of exposure.
- Non-smokers were not exposed to higher levels of acrolein, crotonaldehyde, ethylene oxide, and benzene in a real-life setting due to passive exposure to the environmental EHTS aerosol by means of assessing their urinary biomarkers of exposure.

5.4.8 Air quality study in passenger car environments

A study commissioned by the German Federal Ministry for Public Health was carried out by [72] with the aim of investigating concentrations of fine particulates and VOC emissions from the use of EHTS, an EVP, and cigarettes in passenger car interiors. Measurements of the quality of interior air during rides with and without product use were taken in seven different car models (classified as either having large, average, or small interior volumes). The car rides all took place

at the same time of day (09:00 to 13:00) on seven consecutive working days in Munich, Germany, in November 2017. On every measurement day, one vehicle was driven along an 8.5 km inner-city route (using a predefined circuit, lasting reproducibly 20–23 minutes). Of the two persons in the car, only the passenger was consuming the various test products. Prior to the first measurement and in between rides, all doors of the vehicles were opened, with the interiors shock ventilated for 10 minutes. Measuring instruments were stored on the back seat behind the passenger, with sensors positioned in the breathing zone typical for a child passenger. Measurements of the interior climate (temperature, relative humidity, atmospheric pressure, CO, CO_2), PNC (within the range from 25 nm to 300 nm as well as $PM_{2.5}$ and 15 different particle sizes within a range from 300nm to >20µm), VOC emissions (e.g., nicotine, 3-ethenylpyridine, PG), and carbonyls (e.g., acrolein, acetaldehyde, formaldehyde, 2-butanone) were performed.

Results show that the concentration of CO was within the background range, with a slight increase only observed when cigarettes were smoked in the car. The different ventilation conditions imposed by opening the passenger side window by either 5 cm or 2 cm had no significant impact on the level of particle loads measured.

EHTS use had almost no impact on the median PNC of microscale particles and on $PM_{2.5}$ concentration in the interior. On the other hand, PNC in the range from 25 nm to 300 nm was significantly increased above background levels during EHTS use in all passenger cars tested. The increased number of small droplets is a sign that the water in the EHTS aerosol droplets (EHTS aerosol droplets are comprised mostly of water [13]) evaporates in the air, leaving behind less volatile compounds that take longer to evaporate (such as glycerol) in droplets largely reduced in size. In contrast to the PM measured during EHTS use, EVP use showed a steep increase in $PM_{2.5}$ concentration in five of the seven sampled passenger cars, releasing greater amounts of larger particles (>300 nm) into the interior air than EHTS, whereas the median PNC in the range from 25 nm to 300 nm tended to be higher during EHTS use. As expected, cigarette smoking resulted in the highest particle load for all PNC ranges, with an increase of the PNC of nanoscale particles by 1.3 to 17 times the background. It is important to recognize that the PM in EHTS as well as in EVP aerosols are liquid-based droplets formed from supersaturated glycerol and/or PG vapor and as shown by [1, 30, 73, 74] no solid particles are formed, in contrast to cigarette smoke, which contains solid particles (soot) [75].

Out of the measured VOCs, only the nicotine concentration level was observed to increase (4–12 µg/m^3) during EHTS use in three out of the seven passenger cars. In contrast, EVP use led to an increase in PG concentration in addition to the increase in nicotine. The PG concentration in five car interiors rose to levels of 50–762 µg/m^3, exceeding the guideline value for PG (60 µg/m^3) [76] in three car interiors. In four vehicles, EVP use resulted in increases in nicotine levels (similar to that found during EHTS use). In contrast to EHTS and EVP use, cigarette smoking led to the highest nicotine levels and to increases in 3-ethenylpyridine concentrations (a marker for ETS) as well as benzene, toluene, and furfural. Increases in the other VOCs measured were similar to the levels measured from EHTS and EVP use and partly within the range of background levels.

Cigarette smoking resulted in increased concentrations of formaldehyde, acetaldehyde, and acetone in the interior air. For both EHTS and EVP use, there were no significant changes in the concentrations of the measured carbonyls compared with the background levels.

6 Conclusions

The scientific evidence summarized in this report substantiates that there is no ETS emitted during use of the EHTS and that EHTS use has no adverse effect on air quality according to threshold limits established by existing air quality guidelines and when used in a setting where regulatory norms of adequate ventilation are respected.

Key takeaways of this report include the following:

- According to WHO, "Environmental tobacco smoke (ETS) is generated by the combustion of tobacco products. It is composed of sidestream smoke (SS), emitted from the smouldering tobacco between puffs, and exhaled mainstream smoke (MS) from the smoker" [3].
- The absence of combustion of the tobacco material in the EHTP when used as intended in the EHTS Holder and the fact that the aerosol generated is not smoke were scientifically substantiated and the available evidence has been summarized and discussed in a report by Nordlund et al., 2019 [1].
- The substantiation was based on a review of technical and scientific definitions, an extensive set of published scientific evidence, and expert opinions issued by third-party scientific experts in numerous countries as well as by independent research organizations.
- As there is no smoke (neither SS nor MS) generated by the EHTP when used as intended in the EHTS Holder [1], there is no ETS emitted during EHTS use according to the definition of ETS by WHO [3].
- As the tobacco contained in the EHTP is heated and not burned, the mainstream aerosol generated during EHTS use contains >90% lower levels of HPHCs, on average, compared with the MS of a 3R4F reference cigarette.
- In addition to demonstrating that the EHTS aerosol is not smoke and that no ETS is emitted during EHTS use, it is important to assess the impact of the environmental EHTS aerosol on air quality. PMI conducted scientific studies in a dedicated air quality assessment room under simulated environmental conditions.
- These studies demonstrated that only three compounds were above the background levels in air (nicotine, glycerol, and acetaldehyde) and could be attributed to EHTS use. However, glycerol is not an air pollutant and the concentrations of nicotine and acetaldehyde were much lower than the levels measured after cigarette smoking and far below the limits established by existing air quality guidelines.
- Scientific studies conducted by independent researchers in indoor environments showed that the use of EHTS as well as EVP resulted in the lowest concentrations of formaldehyde, benzene, toluene, and $PM_{2.5}$ when compared with cigarettes,

waterpipes, and some common sources of indoor pollution (incense, mosquito coils). Significantly higher levels of benzene, toluene, and formaldehyde can be detected in public environments, where no EHTS or EVP was used, especially transport micro-environments (Kauneliene et al., 2018 [2]).

- To better understand the impact of day-to-day activities on air quality and to prepare the assessment of the impact of EHTS use in real-life settings, PMI conducted studies on the impact of activities of daily living, such as drinking alcoholic beverages, practicing sport, using cosmetics, preparing food on a table-top appliance, or simply the prolonged presence of people, on air quality in an indoor environment. The results of these studies showed that day-to-day activities lead to significant emissions of volatile organic compounds and PM, which would need to be considered when assessing the impact of EHTS use on bystanders in real-life settings.
- PMI scientific studies conducted in a coffee room and in *IQOS* stores demonstrated that no quantifiable amounts of $PM_{2.5}$ were present in any of the sessions and that the environmental aerosol emissions during EHTS use (predominantly emitted from exhalation of the EHTS mainstream aerosol) were far below the limits set by existing air quality guidelines
- In a study conducted in Japan, in a restaurant where EHTS use was allowed but cigarette smoking was not, the results indicated that:
    - The use of EHTS did not generate ETS and had no adverse effect on air quality as measured by nicotine, TSNA, and RSP as well as the carbonyls acrolein, crotonaldehyde, acetaldehyde, and formaldehyde in air in a real-life setting where regulatory norms for occupational exposure in terms of adequate ventilation were respected.
    - Non-smokers did not have an increase in exposure to nicotine and TSNAs due to passive exposure to the environmental EHTS aerosol by means of assessing their urinary biomarkers of exposure.
    - Non-smokers were not exposed to higher levels of acrolein, crotonaldehyde, ethylene oxide, and benzene in a real-life setting due to passive exposure to the environmental EHTS aerosol by means of assessing their urinary biomarkers of exposure.
- These results were further corroborated by independent scientific studies on air quality conducted in real-life settings in a nightclub and in a catering and entertainment establishment. The studies showed that:
    - The particle number concentration was found to be higher when the nightclub was in full operation with no humans present and no use of EHTS compared with what could be measured when EHTS was used and the nightclub was not in operation.
    - The levels of all compounds measured in the catering and entertainment establishment during EHTS use were far below threshold limits established by existing air quality guidelines.

- Moreover, the results of an independent study performed in Germany were in line with the results of PMI studies on air quality, with cigarette smoking leading to the greatest impact on air quality. EHTS use resulted in detectable levels of nicotine, but no other chemical markers of contamination were detected, including the absence of markers for secondhand smoke. The confined environment of the car and the proximity of the sample collection to the product user resulted in detection of small liquid droplets in the nanoscale range when EHTS was used in the car.

To summarize, the scientific evidence comprehensively demonstrates that there is no ETS emitted during use of the EHTS and that EHTS use has no adverse effect on air quality and bystanders' exposure considering threshold limits set by existing air quality guidelines and when used in a setting where regulatory norms of adequate ventilation are respected. Furthermore, it is important to consider exposure to air pollutants existing in the current real-life environment to contextualize the impact of products such as EHTS or EVP in this context.

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