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Harm reduction of heated tobacco in outdoor spaces in place of burnt tobacco smoking

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The effect of heat-not-burn (HnB) tobacco in smoking practices has been evaluated in outdoor scenarios by using gas sensors. The data obtained confirmed that the use of HnB tobacco has a minimal impact on ambient suspended particles, that is, PM_{10} and $PM_{2.5}$ levels, resulting in approximately half the effect of combustion tobacco, in line with harm reduction principles. In addition, using HnB products outdoors did not lead to high levels of VOCs in the surrounding air nor in the breath of people who use them, whether directly or through passive exposure. This contrasts sharply with the increased levels found in the breath of both active and passive users of traditional tobacco cigarettes. On the other hand, liquid chromatography high resolution mass spectrometry (LC-HRMS) analysis of HnB passive volunteers' exhaled breath extracts showed typical compounds of tobacco manufacturing products.

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1 Introduction

The inhalation of traditional tobacco can potentially produce physiological harm across all of the human organism, and is one of the main etiological agents of early mortality on a global scale.[1] As reported by the World Health Organization (WHO), habitual tobacco smoking causes millions of deaths annually, and its associated mortality exceeds that of pathologies such as human immunodeficiency virus (HIV), tuberculosis, and malaria.[2]

Tobacco smoke is linked to pathological conditions, such as neoplastic transformations, cardiovascular dysfunction, and pulmonary impairment.[3] For instance, smoking contributes to systemic inflammation and the generation of reactive oxygen species, increasing the progression of health disorders.[3,4] Since 2009, multiple governmental and transnational regulatory bodies have intensified efforts to surveil and regulate the constituents of tobacco-related products.[5,6] In 2017, and to date, the U.S. Food and Drug Administration (FDA) has released a comprehensive inventory of 20 harmful and potentially harmful constituents (HPHCs) found in tobacco and its combustion byproducts. These include nicotine and related alkaloids, carbon monoxide, tobacco-specific nitrosamines (TSNAs), polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), aromatic amines with carcinogenic potential, and trace metals.[6] Table S1 indicates representative HPHCs identified in tobacco and tobacco smoke together with their associated disease outcomes.

Tobacco dependence arises from the rapid translocation of nicotine to the central nervous system (CNS), where it produces intense neuropharmacological reinforcement.[5] Nevertheless, the extensive pathological outcomes associated with smoking are due to smoke and the toxicants generated during the burning of tobacco. So, there is a social need to reduce drastically the number of smokers, by avoiding the recruitment of new consumers and offering a way out to reluctant tobacco smokers. In addition to traditional systems to facilitate the ingestion of nicotine by oral or dermal methods, new inhaling systems—like e-cigarettes and heat-not-burn tobacco—have raised harm-reduction possibilities in an attractive format for smokers.

The concentration of nicotine in low-temperature aerosols remains significant,[7] but the overall load of harmful and carcinogenic agents is lower than in cigarette smoke.[8] However, analytical studies examining the aerosol profiles of these new devices have identified the presence of harmful substances, such as reactive carbonyl species, tobacco-specific nitrosamines, acrolein, and acrylamide.[7–11] Also, toxicological compounds have been detected in some e-liquids used for vaping.[10,12,13,14] Consequently, the vapors emitted by electronic nicotine systems could constitute a significant non-occupational vector, and it is important to evaluate their use both indoors and in the open air.

In HnB products, inserts are heated by electrical induction at sub-combustion temperatures (<300 °C), thereby avoiding the pyrolysis of organic substrates and resulting in the emission of an inhalable aerosol consisting predominantly of water vapor (76%), propan-1,2-diol (glycerol, 10%), and nicotine alkaloids

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(3%).[15] Marketed as a smoke-free innovation, HnB technologies are promoted to preserve the sensory experience of tobacco smoking while minimizing particulate emissions, ash residue, and olfactory impact.[16] Despite their limited visible emissions and the enforcement of comprehensive smoke-free regulations in numerous jurisdictions,[17–20] exposure to environmental aerosols from these systems must be controlled. Empirical studies have demonstrated the presence of potential risk during HnB use in indoor ambient air,[21–25] with VOC values close to 50 ppm and particulate matter (PM) concentration in the range between 6.5 and 8.1 μg m^{-3}.[23–25] Regarding outdoors, there is increased concern regarding the use of nicotine delivery systems, even leading to the proposal of laws to ban them in such spaces, including HnB systems.[26] However, there are no precedents in the literature regarding their effect on passive smokers when they are exposed to HnB second-hand vapor/smoke in outdoor scenarios.

The aim of this work is to evaluate, using portable sensing devices, the concentrations of classical parameters such as PM and VOCs in the exhaled breath of smokers and non-smokers exposed to second-hand HnB vapors in outdoor scenarios. Similarly, nicotine concentration in the exhaled breath of tobacco and HnB users and passive smokers were determined. Additionally, untargeted analysis of the exhaled breath of tobacco and HnB users and passive smokers was performed in order to identify non-studied compounds.

2 Materials and methods

2.1 Experimental setup

To evaluate the effect of the consumption of traditional tobacco/HnB devices in outdoor terraces on passive smokers, participants were arranged at square tables of 0.48 m^2, with four volunteers (one active and three passive smokers), located as shown in Fig. 1A. The population under study was composed of volunteers who were traditional tobacco smokers, HnB users or non-smokers, constituted by men and women in the age range from 25 to 70 years.

Two identical IQOS ILUMA HnB devices manufactured by Philip Morris Inc. (Neuchâtel, Switzerland), were obtained from the local market and employed following the instructions. TEREA type HnB sticks, from Smartcore Induction Systems®, were used.

PM and VOCs were measured in exhaled breath by placing the sensor probes 1.5 cm from each volunteer's mouth for 1 minute (see Fig. 1B). Measurements were conducted first for the active participants, followed by the passive person located in front, then the passive person placed to the left and finally the passive person placed to the right, and measurements were made both before and after each session, in all cases using the same procedure. In all cases, ambient conditions, such as wind speed and humidity, were not controlled, in order to reproduce real-life exposure situations. Moreover, to perform ambient measurements, gas sensors were placed in the center of the table equidistant from all participants in each experiment. This measurement process was carried out during the entire time required for the consumption of a traditional tobacco cigarette or an HnB stick. The exhaled breath after consumption was recorded in the same sampling order and the same conditions were employed for the initial measurements.

2.2 Sampling and analysis

2.2.1. Particulate matter (PM_{10} and $PM_{2.5}$) and volatile organic compounds (VOCs). To determine the presence of pollutants in the ambient air and exhaled breath, two portable air quality monitor loggers, coupled to PM_{10}, $PM_{2.5}$, and VOCs Aeroqual Series 500 sensors from PCE Instruments (Tobarra, Spain), were employed. These instruments were regularly calibrated and used after a stabilization period. Table 1 summarizes the technical characteristics of the instruments.

A data set concerning the concentration of the evaluated parameters in ambient air, the exhaled breath of smokers and HnB users before tobacco/HnB consumption and the exhaled breath of active and passive smokers after smoking/exposition processes were recorded, together with data from the ambient air during the tobacco/HnB consumption.

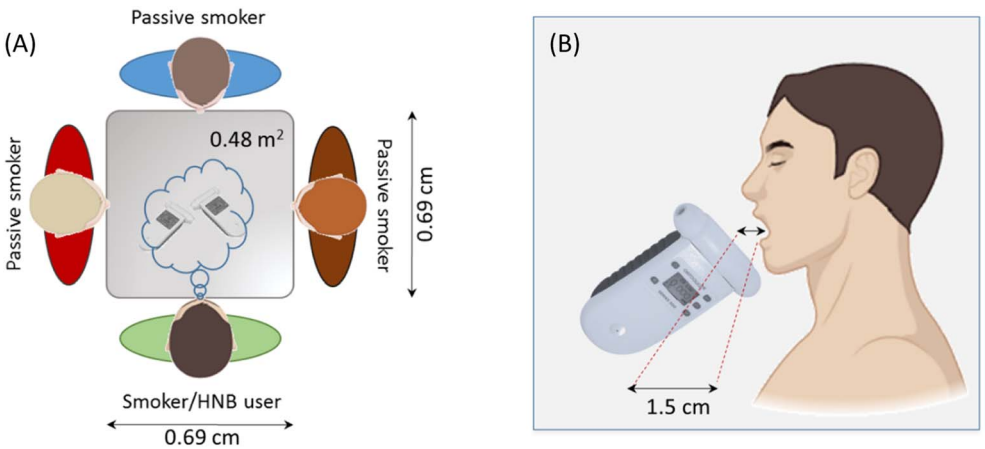

Fig. 1 Distribution of volunteers and gas sensors for the control of particulate matter (PM) and volatile organic compounds (VOCs) in air from open places (A) and for testing the exhaled breath of both active smokers/HNB users and passive ones (B).

Table 1 Characteristics and performance of gas sensors employed in this study

	VOCs	PM_{10}	$PM_{2.5}$
Working range	0–30 ppm	0–1 mg m^{-3}	0–1 mg m^{-3}
Sensor type	Photoionization detector	Laser particle counter	Laser particle counter
Minimum detection limit	0.01 ppm	0.001 mg m^{-3}	0.001 mg m^{-3}
Accuracy of factory calibration	<±0.02 ppm + 10%	±(0.005 mg m^{-3} + 15% of reading)	±(0.005 mg m^{-3} + 15% of reading)
Resolution	0.01 ppm	0.001 mg m^{-3}	0.001 mg m^{-3}
Response time	30 s	5 s	5 s
Temperature working range	0–40 °C	0–40 °C	0–40 °C
Relative humidity working range	0–95%	0–90% non-condensating	0–90% non-condensating

A set of 244 and 436 total measurements were recorded for ambient air in the case of traditional tobacco and HnB use, respectively. Regarding traditional tobacco, measurements from 55 active smokers and 145 passive smokers were evaluated, before and after the smoking practice. For HnB, 98 and 292 measurements were made in the case of active and passive users before HnB use, respectively, while 196 and 292 measurements were obtained for active and passive HnB smokers after HnB use. In addition, data for temperature, wind and humidity were recorded to study the sampling process.

2.2.2. Determination of nicotine in exhaled breath. The presence of nicotine exhaled in the breath of passive and active HnB smokers was assessed by using the bubbling collection device shown in Fig. S1. One-minute exhaled breath samples were collected directly from the mouths of active HnB smokers and passive HnB smokers in a 25 mL ethanol trap. Additionally, exhaled breath from consumption of a whole HnB stick and a whole traditional cigarette were collected. The samples of exhaled breath collected in the ethanol trap, taken in 25 mL volumetric flasks, were pre-concentrated under a low-pressure rotary evaporator at 60 °C and under N_2 flow and reconstituted in 0.5 mL of ethanol to increase the sensitivity before being analyzed by gas chromatography mass spectrometry (GC-MS). To carry out the nicotine extraction, ethanol GC of ultra-trace analysis grade from Scharlau (Barcelona, Spain) was employed.

The exhaled breath from each puff from an active HnB consumer was collected in the ethanol trap. The resulting solution was treated in the aforementioned way before being analyzed through chromatography. The same was done for an active classical smoker after the total consumption of a cigarette.

In all cases, the glass material was decontaminated before each sampling. The decontamination procedure was as follows: the material was cleaned in an ultrasound bath and gently soaked with solvents of different polarity, from methanol to hexane, in order to remove any possible contaminants. Once the material was cleaned, the last hexane fraction was analyzed by GC-MS in order to ensure that the material was free of contaminants. Furthermore, the clean glass material was then heat-treated at 300 °C for 24 hours in order to remove any trace of organic compound. Silicone tubes were replaced by new ones before each sampling in order to avoid any possible cross-contamination from previous assays.

The analysis of exhaled compounds, including nicotine, was performed using an Agilent 7890A series gas chromatograph equipped with a 5975C inert XL EI/CI MSD mass detector (Palo Alto, CA, USA) and a ZB-5MS column (30 m × 0.25 mm × 0.25 mm). For the chromatographic separation, 1 μL of each concentrated collected sample solution was injected in the splitless mode at 250 °C, using a constant helium flow rate of 1.1 mL min^{-1} as the carrier gas. Chromatographic separation was achieved with the following oven program: an initial temperature of 70 °C followed by an increase to 230 °C at a rate of 25 °C min^{-1}, maintaining this temperature for 3 minutes. Subsequently, the temperature was increased to 250 °C at a rate of 10 °C min^{-1}, which was held for 10 minutes. Transfer line, ion source, and quadrupole temperatures were set at 280 °C, 276 °C, and 150 °C, respectively. The detection of the analytes by MS was carried out in electron impact (EI) mode, using an ionization energy of 70 eV. The analysis was performed in full scan mode, monitoring the *m*/*z* value of 84.1 for nicotine.

The determination of nicotine by ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) was performed using a Vanquish UHPLC system (Thermo Scientific, Bremen, Germany) equipped with a quaternary pump, a refrigerated autosampler (10 °C) and a column compartment (40 °C). For chromatographic separation, a Kinetex® C_{18} column (100.0 × 2.1 mm, 1.72.6 μm) was employed. The UHPLC system was coupled to a Finnigan TSQ Quantum Ultra triple quadrupole mass spectrometer with electrospray ionization (ESI), from Thermo Fisher Scientific (Bremen, Germany). Subsequently, 10 μL of extracts were injected into the UHPLC system. The mobile phases consisted of an aqueous solution containing 0.1% formic acid (A) and methanol with 0.1% formic acid (B). The eluent gradient profile was as follows: 0 min: 20% B, 8 min: 95% B, 12 min: 95% B, 13 min: 95% B, 22 min: 20% B, and the flow rate was set at 0.3 mL min^{-1}. The triple quadrupole mass spectrometer was operated in positive ESI mode, using the following parameters: spray voltage of 3 kV, sheath gas pressure of 10 a.u., auxiliary gas pressure of 15 a.u., and capillary temperature of 280 °C. The monitored ion transitions were 163 *m*/*z* (quantifier ion), and 132 and 130 *m*/*z* (ion qualifiers) for nicotine, and 167 *m*/*z* (ion quantifier) and 132 *m*/*z* (ion qualifier) for deuterated nicotine as internal standard. Data processing was conducted using Xcalibur™ version 2.2.

To quantify the amount of nicotine in the exhaled breath, 1 mg mL^{-1} (−)-nicotine from Sigma-Aldrich (St. Louis, MO, USA), 100 μg per mL nicotine-d_4 standard solution in acetonitrile from Sigma-Aldrich (St. Louis, MO, USA) and ethanol for LC-MS (Scharlau, Barcelona, Spain) were employed to prepare calibration solutions in the range from 1 ng mL^{-1} to 100 ng mL^{-1}.

2.2.3. Screening of potential compounds in the second hand tobacco smoke (SHS). Untargeted analysis of the exhaled breath was performed in order to compare traditional tobacco smokers, HnB users and passive smokers. The exhaled breath from (i) a whole cigarette smoked, (ii) after consumption of a complete HnB stick and (iii) the passive smoker breath, were taken at time intervals of 5 minutes, which corresponds to the time to smoke a traditional tobacco cigarette. Samples were collected by bubbling onto a 25 mL ethanol trap (Fig. S1) and processed, as indicated in Section 2.2.2, for analysis by liquid chromatography coupled to high resolution mass spectrometry (LC-HRMS).

The analysis of extracts was performed using a SCIEX TripleTOF™ 6600plus UHPLC/MS/MS System (Framingham, MA, U.S.A.) A UHPLC Exion LC AD from SCIEX (Framingham, MA, U.S.A.) was equipped with a micro volume binary pump, a refrigerated autosampler (4 °C) and a column compartment. For chromatographic separation, a Kinetex® XB-C_{18} (2.1 × 100 mm, 1.7 μm) column from Phenomenex (Torrance, CA, U.S.A.) was employed. The UHPLC system was coupled to a SCIEX TripleTOF™ 6600 plus time-of-flight mass spectrometer with ESI in the positive mode, from Sciex (Framingham, MA, U.S.A.). Then, 10 μL of extracts were injected into the UHPLC system. The mobile phases consisted of an aqueous solution containing 0.2% formic acid and 2 mM ammonium formate (A), and an aqueous solution containing acetonitrile with 0.2% formic acid and 2 mM ammonium formate (B). The eluent gradient profile was as follows: 0 min: 10% B, 5 min: 10% B, 12 min: 95% B, 20 min: 95% B, 20.1 min: 10% B and 23 min: 10% B. The flow rate was set at 0.4 mL min^{-1}. The data acquisition was performed in positive mode, over a mass range of 100–700 *m*/*z*. Mass spectrometer conditions were as follows: (i) 60 psi ion source gas 1, 60 psi ion source gas 2, 40 psi for curtain gas, ion spray voltage 5500 V and thermostatting at 450 °C. The accumulation time was set to 240 ms. Automated calibration was performed using an external calibrant delivery system (CDS) which infuses calibration solution prior to sample introduction. The MS used data independent acquisition (DIA) mode with: survey scan type (TOF-MS) and dependent scan type (product ion) using 35 V of collision energy. Data was qualitatively evaluated using PeakView™ software and the identification criterion followed for non-target analysis was a match with the spectral libraries.

3 Results and discussion

3.1 Levels of particulate matter (PM_{10} and $PM_{2.5}$) and volatile organic compounds (VOCs)

3.1.1. Ambient air. Table 2 indicates the concentrations of VOCs, PM_{10} and $PM_{2.5}$ determined in ambient air before and after traditional tobacco/HnB use. As can be seen, the concentrations determined using traditional tobacco increase the concentration of the three evaluated analytes in the ambient air after the smoking practice, corresponding to average values of 0.778 ± 0.773 ppm for VOCs, 0.511 ± 0.333 mg m^{-3} for PM_{10} and 0.359 ± 0.215 mg m^{-3} for $PM_{2.5}$. It should be highlighted that values obtained for $PM_{2.5}$ concentrations are in good agreement with those reported in the literature,[27] being an intermediate situation between completely open air and a semi-closed air scenario. In the same way, when the HnB practice was evaluated, it could be seen that the PM_{10} levels decreased in ambient air, compared with classical tobacco, at 0.315 ± 0.238 mg m^{-3}, involving a reduction of 38% of the values obtained for traditional smoking practices. Statistical analysis provided a *p*-value lower than 0.05 (95% significance), indicating no statistical difference between the two situations. $PM_{2.5}$ values decreased to 0.167 ± 0.135 mg m^{-3}, indicating an average reduction of 53% compared with burned tobacco smoking. However, the statistical analysis provided a *p*-value lower than 0.05 (95% significance), indicating that there was no significant difference between the two situations, probably due

Table 2 Concentration of VOCs, PM_{10} and $PM_{2.5}$ determined in ambient air before and after traditional tobacco/HnB smoking[a]

Traditional tobacco					Increased concentration after practice		
	N	VOCs (ppm)	PM_{10} (mg m^{-3})	$PM_{2.5}$ (mg m^{-3})	ΔVOCs (ppm)	ΔPM_{10} (mg m^{-3})	$\Delta PM_{2.5}$ (mg m^{-3})
Before	57	0.116 ± 0.047	0.016 ± 0.004	0.007 ± 0.007	0.778	0.511	0.359
After	187	0.894 ± 0.751	0.543 ± 0.333	0.366 ± 0.221	$p < 0.05$	$p > 0.05$	$p > 0.05$
HnB					Increased concentration after practice		
	N	VOCs (ppm)	PM_{10} (mg m^{-3})	$PM_{2.5}$ (mg m^{-3})	ΔVOCs (ppm)	ΔPM_{10} (mg m^{-3})	$\Delta PM_{2.5}$ (mg m^{-3})
Before	80	0.124 ± 0.053	0.019 ± 0.006	0.004 ± 0.003	0.000	0.315	0.167
After	356	0.121 ± 0.042	0.333 ± 0.238	0.170 ± 0.135	$p < 0.05$	$p > 0.05$	$p > 0.05$

[a] *N*: number of independent measurements.

Table 3 Concentration of VOCs, PM_{10} and $PM_{2.5}$ determined in ambient air and exhaled breath of traditional tobacco smokers/HnB users and passive users before and after both practices[a]

Traditional tobacco							
Active smokers' breath					Increased concentration after practice		
	N	VOCs (ppm)	PM_{10} (mg m^{-3})	$PM_{2.5}$ (mg m^{-3})	ΔVOCs (ppm)	ΔPM_{10} (mg m^{-3})	$\Delta PM_{2.5}$ (mg m^{-3})
Before	55	0.121 ± 0.088	0.020 ± 0.007	0.017 ± 0.014	0.219	0.040	0.039
After	55	0.339 ± 0.189	0.061 ± 0.059	0.056 ± 0.024	$p > 0.05$	$p < 0.05$	$p < 0.05$
Passive smokers breath					Increased concentration after practice		
	N	VOCs (ppm)	PM_{10} (mg m^{-3})	$PM_{2.5}$ (mg m^{-3})	ΔVOCs (ppm)	ΔPM_{10} (mg m^{-3})	$\Delta PM_{2.5}$ (mg m^{-3})
Before	145	0.141 ± 0.038	0.018 ± 0.017	0.004 ± 0.003	0.052	0.0076	0.018
After	145	0.193 ± 0.077	0.026 ± 0.013	0.023 ± 0.021	$p < 0.05$	$p < 0.05$	$p < 0.05$
HnB tobacco							
Active users breath					Increased concentration after practice		
	N	VOCs (ppm)	PM_{10} (mg m^{-3})	$PM_{2.5}$ (mg m^{-3})	ΔVOCs (ppm)	ΔPM_{10} (mg m^{-3})	$\Delta PM_{2.5}$ (mg m^{-3})
Before	98	0.154 ± 0.067	0.017 ± 0.005	0.004 ± 0.005	0.000	0.003	0.003
After	196	0.151 ± 0.072	0.020 ± 0.006	0.007 ± 0.007	$p < 0.05$	$p < 0.05$	$p < 0.05$
Passive users breath					Increased concentration after practice		
	N	VOCs (ppm)	PM_{10} (mg m^{-3})	$PM_{2.5}$ (mg m^{-3})	ΔVOCs (ppm)	ΔPM_{10} (mg m^{-3})	$\Delta PM_{2.5}$ (mg m^{-3})
Before	292	0.133 ± 0.054	0.028 ± 0.051	0.010 ± 0.028	0.000	0.000	0.000
After	292	0.134 ± 0.048	0.027 ± 0.046	0.009 ± 0.024	$p < 0.05$	$p < 0.05$	$p < 0.05$

[a] *N*: number of independent measurements.

the high variability in the obtained data. On the other hand, the use of HnB devices did not affect VOC concentrations in air. It should be noted that the measurements performed in outdoor ambient air were drastically affected by high variability, probably due to the high-dilution open-air effect and by meteorological conditions.

3.1.2. Exhaled breath. Table 3 indicates the concentrations of VOCs, PM_{10} and $PM_{2.5}$ determined in the exhaled breath of traditional tobacco smokers/HnB users and passive volunteers before and after both practices.

The study of the breath of passive smokers gave no evidence of difference as a function of their relative position. Thus, the increased amount of target analytes was calculated from data from all passive participants. The exhaled breath of active traditional tobacco smokers showed an increment (exhaled concentrations after smoking practices minus those found before) with a VOC concentration of 0.219 ppm, while the concentrations of PM_{10} and $PM_{2.5}$ remained practically constant, with average values of 0.04 ± 0.06 and 0.039 ± 0.043 mg m^{-3}. The concentration values were found to be of the same order of magnitude as those obtained by Gallart-Mateu *et al.* (2021) in the exhaled breath of smokers in indoor scenarios.[21]

A similar situation was found for the exhaled breath of passive traditional tobacco smokers after smoking practices, and a non-substantial increase was detected in all measured parameters. The averaged data found from 145 measurements performed for passive smokers were 0.052 ± 0.086 ppm for VOCs, 0.008 ± 0.022 mg m^{-3} for PM_{10} and 0.018 ± 0.021 mg m^{-3} for $PM_{2.5}$, where the high standard deviation values are

Table 4 Amount of nicotine in exhaled breath (μg) of active and passive HnB users compared with the amount found for traditional tobacco smoker exhaled breath

	$\mu g_{nicotine}$ exhaled	Standard deviation	RSD (%)
Extract from 1 minute passive exhaled breath	2.77	0.05	16
Extract from 1 minute active exhaled breath	5.7	0.7	13
Extract from the whole HNB stick exhaled breath	10.3	0.7	7
Extract of a whole traditional cigarette exhaled breath	44.9	3.2	7

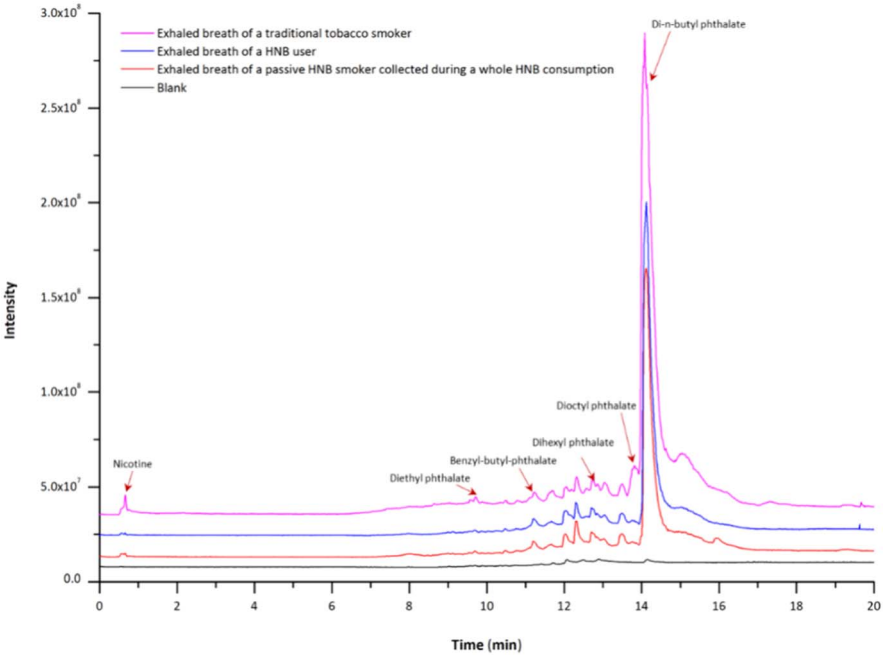

Fig. 2 UHPLC-TOF-MS/MS full-scan chromatograms obtained for the extracts belonging to the complete exhaled breath of a traditional tobacco smoker (pink), the complete exhaled breath of an HNB user (blue), the exhaled breath of a passive HNB smoker collected during a whole of an HNB stick consumption (red), and measurements blank (black).

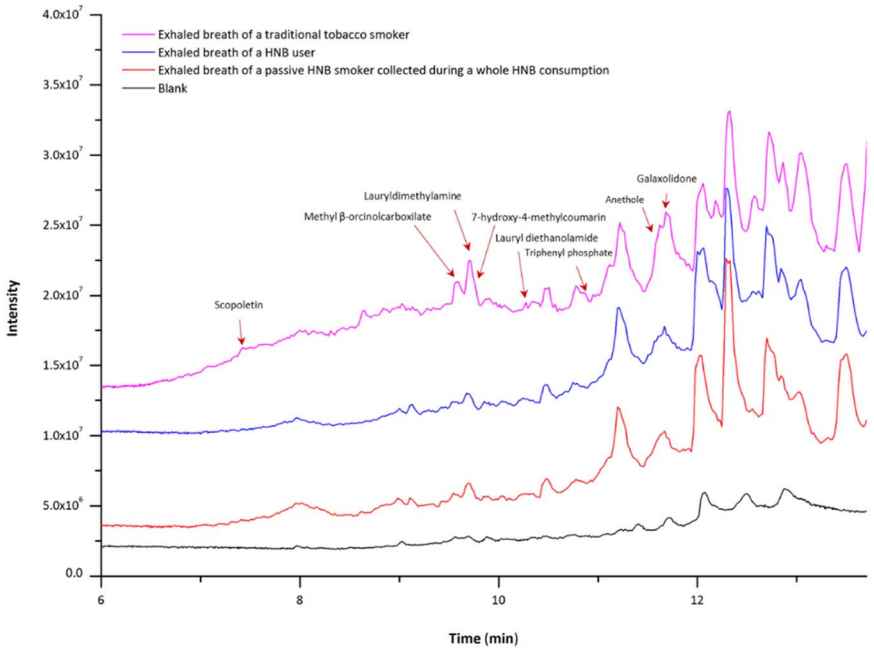

Fig. 3 UHPLC-TOF-MS/MS full-scan chromatograms obtained for the extracts belonging to the complete exhaled breath of a traditional tobacco smoker (pink), the complete exhaled breath of an HNB user (blue) and the exhaled breath of a passive HNB smoker collected during a whole HNB consumption (red) in the range between 6.5 and 14 minutes.

probably due to the change in ambient conditions of open air. Nevertheless, those values involve a severe reduction compared with those found for passive smokers in indoor scenarios[21] and the $PM_{2.5}$ concentrations found in outdoor scenarios.[28]

On the other hand, the use of an HnB stick provided no differences in VOCs between the concentrations detected before and after the use of this device for any of the subjects or with the concentration in the ambient air before its use. Furthermore, similar situations were detected for VOCs, $PM_{2.5}$ and PM_{10}

Table 5 Tentative identification of substances found in the exhaled breath after smoking practices

m/z	Retention time (min)	Spectral match	Similarity (%)	Peak intensity	Mass error (ppm)	Presence/possible cause
163.1237	0.61	Nicotine	98.2	High	0.6	Tobacco active principle
193.0500	7.43	Scopoletin	96.3	High	0.4	Active principle from tobacco
197.0814	9.54	Methyl β-orcinolcarboxylate	98.4	High	0.8	Flavouring agent
230.2494	9.69	Lauryldimethylamine	97.8	High	−1.2	Tobacco anti-suckering thermal decomposition product
177.0550	9.87	7-Hydroxy-4-methylcoumarin	58.6	Low	11	Derived from coumarin, present on leaves
223.0972	9.87	Diethyl phthalate	98.8	High	1	Present on leaves and device
288.2542	10.33	Lauryl diethanolamide	97.8	High	−0.9	Moisturizing agent
327.0789	11.05	Triphenyl phosphate	74.5	Medium	7.2	OPEs in tobacco leaves
313.1446	11.52	Benzyl-butyl-phthalate	98.8	High	−0.8	Present on leaves and device
149.0236	11.61	Anethole	58.4	Low	13	Flavouring agent
273.1856	11.73	Galaxolidone	87.7	Medium	6.4	Flavouring agent
179.0703	12.62	4-Methoxycinnamic acid	91.0	High	2.1	Pesticide contamination
335.2230	12.88	Dihexyl phthalate	93.1	High	1.1	Present on leaves and device
391.2857	13.88	Dioctyl phthalate	87.9	Medium	−5.3	Present on leaves and device
279.1599	14.07	Di-*n*-butyl phthalate	98.9	High	1.3	Present on leaves and device

levels present in the breath of HnB passive users, which were practically nonexistent before HnB practice.

3.2 Presence of nicotine in exhaled breath

Table 4 indicates the nicotine results in the breath samples. In addition, the whole exhaled breath of a traditional tobacco smoker while smoking a cigarette was collected under the same conditions as the other extracts and pre-concentrated following the same procedure.

As can be seen in Table 4, the amount of nicotine exhaled by a passive HnB smoker in 1 minute is approximately half the amount found in the breath exhaled by an active HnB user, showing an average of 2.77 ± 0.05 μg of nicotine in the exhaled breath after HnB passive exposition, while the active HnB user showed 5.7 ± 0.7 μg nicotine in the exhaled breath after HnB use. On the other hand, analysis of the extract from the exhaled breath from a whole HnB stick revealed an average value of 10.3 ± 0.7 μg nicotine, approximately four times higher than that found in the passive HnB smoker and twice as high as that in the active smoker after HnB stick consumption. From a comparison with the nicotine exhaled by a traditional tobacco smoker, an HnB user exhales approximately four times less nicotine than a traditional tobacco smoker. It must be taken into consideration that the aforementioned results correspond to absolute values not corrected by previous contents determined in the breath before tobacco consumption.

3.3 Screening of compounds in the second-hand tobacco smoke (SHS)

To perform a tentative identification of compounds present in breath, LC-HRMS chromatograms were obtained for extracts belonging to the exhaled breath of a traditional tobacco smoker, an HnB user and a passive HnB smoker collected during consumption of a whole HnB (see Fig. 2 and 3). Mzmine® software and the North America Mass Bank (MoNA) spectral libraries were employed for data processing. In this regard, the MoNA LC-MS/MS spectral library and the MoNA LC-MS/MS QTOF spectral library, constituted by 150 231 and 49 541 spectra respectively, and updated in May 2025, were selected for the tentative identification. Table 5 indicates some of the compounds identified by the libraries, together with their respective retention times in the chromatogram, the similarity with the spectral library data and the exact masses found.

Similar chromatographic profiles were obtained for the exhaled breath from classical tobacco smokers, HnB users and passive HnB smokers, where the intensity of the chromatogram peaks were higher in the case of classical tobacco extract than those obtained in active HnB exhaled breath or passive HnB. Considering this fact, different tobacco principles have been identified in all extracts analyzed, such as nicotine, scopoletin or 7-hydroxy-4-methylcoumarin, the last being derived from coumarin and present on tobacco leaves.[29] In the same way, different tobacco plant contaminants were tentatively identified. This is the case for phthalates, which can be found in tobacco leaves[30] and in exhaled breath after smoking.[31] Other compounds detected, such as lauryldimethylamine, triphenyl phosphate and 4-methoxycinnamic acid, are related to contamination of tobacco leaves, especially as thermal decomposition products from tobacco anti-suckering treatments,[32] organophosphate esters (OPEs) in tobacco leaves[33] and pesticide-related contamination,[34] respectively.

Other compounds, such as methyl β-orcinolcarboxylate, anethole and galaxolidone, were tentatively identified, being employed as flavouring agents,[35] while the presence of lauryl diethanolamide could be justified by its use as a moisturizing agent in the treatment of tobacco leaves.

4 Conclusions

This study has revealed that the use of HnB tobacco in outdoor scenarios has a very limited effect on the presence of PM_{10} and

$PM_{2.5}$ in ambient air, involving a reduction of two times compared with the effect of burning tobacco, consistent with the harm reduction criteria. On the other hand, the use of HnB in the open air does not increase the ambient level of VOCs nor the level of VOCs, PM_{10} and $PM_{2.5}$ in the breath of passive and active HnB smokers; which indicates a large difference with the measured levels found in the exhaled breath of active and passive traditional burnt tobacco smokers.

Preliminary studies using GC-MS and UHPLC-MS/MS evidenced the absence of additional molecules at measurable concentration levels in HnB users' breath, as also confirmed by a large reduction in the amount of nicotine in the exhaled breath of active HnB smokers.

Informed consent statement

All participants were informed regarding the objective of the study and provided their informed consent to include the analytical data derived from their participation this study.

Author contributions

D. Gallart-Mateu: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, supervision, validation, visualization, writing-original draft, writing-review & edition. E. Fuentes-Ferragud: data curation, formal analysis, investigation, methodology, software, writing-original draft. C. Coscollà: data curation, formal analysis, investigation, methodology, software, supervision, writing-original draft. M. de la Guardia: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, software, supervision, validation, visualization, writing-original draft, writing-review & edition.

Conflicts of interest

The authors declare that there is no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be available on request.

Supplementary information contains: the potentially harmful compounds found in tobacco and tobacco smoke (Table S1) and a picture of the ethanol trap employed to collect the exhaled (Fig. S1). See DOI: **https://doi.org/10.1039/d5ay00954e**.

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