A Single-Center, Open-Label, Parallel-Cohort Study to Evaluate Environmental Tobacco Smoke Constituents from a Heated Tobacco Product and Combustible Cigarettes

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Abstract

Secondhand smoke (SHS), also known as environmental tobacco smoke, is a significant risk factor for the development of smoking-induced diseases including lung cancer and cardiovascular disease. Limited knowledge is available on heated tobacco product (HTP)-induced secondhand emissions. This poster presents a clinical study design to investigate secondhand emissions resulting from human use of a HTP compared to combustible cigarettes (CC) in an environmental test chamber (ETC). The study was approved by an Institutional Review Board and conducted in compliance with ICH-GCP. This is a single-center, open-label, parallel, 10-cohort study (n=120 subjects) design with several unique features including human use versus machine smoking, the use of menthol and non-menthol products, a 2-week subject acclimation to HTP, five non-smoking blank sessions and five use sessions for statistical power, and subject randomization for each ETC session to reduce bias which may arise from the use of homogeneous session panels. Subjects will be users of non-menthol or menthol CCs, HTPs or dual users, and will be assigned to one of 10 cohorts based upon their flavor preference. Two CC cohorts will use Marlboro Gold Box and Newport Box as non-menthol and menthol comparators, respectively. The remaining 8 cohorts will be distributed among additional types of products/uses to assess two HTP devices with different heating modes, and four tobacco stick variants (3 menthol and 1 non-menthol). Subjects will complete 10 ETC visits over a period of 2 weeks. The endpoints are 8 primary SHS and 19 secondary SHS constituents. SHS constituents detected during non-smoking sessions will serve as controls. By using validated methods for SHS constituents, this plan will increase understanding of secondhand emissions from HTP compared to CCs.

Introduction

Environmental tobacco smoke (ETS), also known as secondhand smoke (SHS), is composed of the aged and diluted combination of smoke exhaled by a smoker (mainstream smoke) and smoke from the lit end of a CC (sidestream smoke). HTPs are different from CCs in that they produce an aerosol when they are being puffed but there is almost no sidestream aerosol when it is not being puffed. The novel HTP used in this study electrically heats tobacco to temperatures ≤ 260°C but does not burn tobacco and uses one of four tobacco stick flavor variants (**Figure 1**). Consequently, significantly fewer chemical toxicants/constituents are formed. The number and level of harmful and potentially harmful constituents (HPHCs) produced during HTP use are expected to be significantly reduced or not present in the HTP aerosol compared to that of CCs. Two recent studies examining the impact of HTP aerosol in an ETC found that selected constituents of HTP aerosol had significantly lower impact on indoor air quality than CC smoke due to the lower emission profiles of aerosol particles, chemical toxicants, and selected volatile organic compounds.[1,2] This study will provide evidence to confirm the hypothesis that HTPs will produce lower quantities of secondhand emissions and HPHCs compared to CCs. Offering less risky tobacco products to consumers is a major focus of the company's tobacco harm reduction (THR) strategy. As HTP use becomes more common in the US and globally, there is a clear and increasing need to evaluate indoor air quality prior to, during, and after HTP use.

Materials and Methods

Two commercially available, market leading CCs, Marlboro Gold Box (non-menthol) and Newport Box (menthol) will be investigated for SHS constituents. Two HTP devices with different, but locked, heating modes (Heating Mode 1 (HM1) and Heating Mode 2 (HM2)) and four tobacco stick variants (3 menthol and 1 non-menthol) will be investigated for the same SHS constituents as measured for CCs. With the HTP device, the user can take an unlimited number of puffs within the allotted heating period, four minutes for HM1 and three minutes for HM2. The tobacco sticks are composed of a tobacco rod of blended tobacco, resembling a super-slim cigarette, but they are designed to be used exclusively with the HTP device and will not support combustion if lit.

The ETC methodology employed in this study is largely based on a previous study that utilized chamber sampling to measure secondhand emissions from CCs and ENDS.[3] ETS constituents will be measured in an ETC (3.04 m × 3.04 m × 3.04 m, approximately 28.3 m^3) maintained and operated by Materials Analytical Services, LLC (MAS) (Suwanee, GA, USA). A schematic of the environmental chamber can be found in **Figure 2**. A stainless-steel manifold in a corner of the chamber will hold sample collection devices attached via tubes to sampling pumps outside the chamber. Tubes will be pre-calibrated and synchronized via digital timer to open or close simultaneously at the sampling start and end times. Determination of SHS constituents will be performed using analytical methods validated according to Good Laboratory Practice (GLP)[4] and in compliance with the Bioanalytical Method Validation Guidance at MAS to ensure the accuracy and reliability of the results. The SHS constituents were selected from among the FDA's established list of harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke required for evaluation and reporting (Federal Register, 2012) and including typical combustion byproducts and markers.

Materials and Methods

Figure 1. HTP device, tobacco stick, and HTP.

HTP device | tobacco stick | HTP

Figure 2. Diagram of Environmental Test Chamber (ETC).

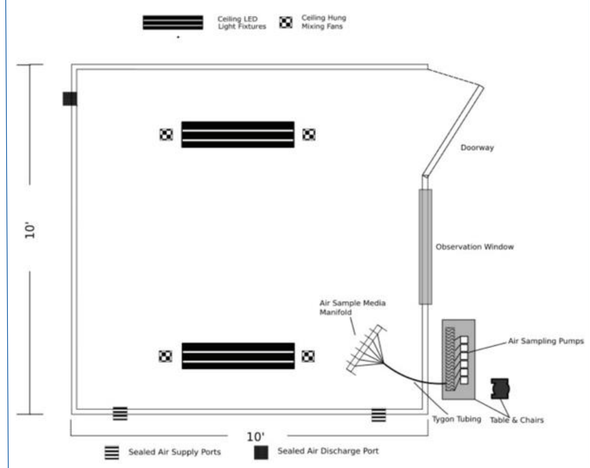
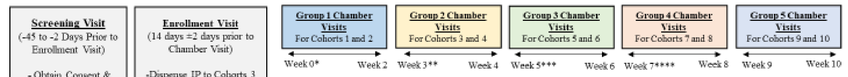


Figure 3. Study Design.



List of Cohorts

1) Marlboro Gold Box Smokers
2) Newport Box Smokers
3) HTP device, Heating Mode 1, Menthol 1 Flavor
4) HTP device, Heating Mode 2, Menthol 1 Flavor
5) HTP device, Heating Mode 1, Menthol 2 Flavor
6) HTP device, Heating Mode 2, Menthol 2 Flavor
7) HTP device, Heating Mode 1, Menthol 3 Flavor
8) HTP device, Heating Mode 2, Menthol 3 Flavor
9) HTP device, Heating Mode 1, Tobacco Flavor
10) HTP device, Heating Mode 2, Tobacco Flavor

* At-home ad lib use for Cohorts 3 & 4
**At-home ad lib use for Cohorts 5 & 6
***At-home ad lib use for Cohorts 7 & 8
****At-home ad lib use for Cohorts 9 & 10

NSB^ = Non-smoking blank

Chamber Visits	1	2	3	4	5	6	7	8	9	10
Weekday	Mon	Tues	Wed	Thurs	Fri	Mon	Tues	Wed	Thurs	Fri
Session Type: • AM Cohort • PM Cohort	• NSB^ • Smoking	• NSB^ • Smoking	• NSB^ • Smoking	• NSB^ • Smoking	• NSB^ • Smoking	• NSB^ • Smoking	• NSB^ • Smoking	• NSB^ • Smoking	• NSB^ • Smoking	• NSB^ • Smoking
Weeks 1 and 2 AM Cohort	1^	2^	1^	2^	1^	2^	1^	2^	1^	2^
Weeks 1 and 2 PM Cohort	2	1	2	1	2	1	2	1	2	1
Weeks 3 and 4 AM Cohort	3^	4^	3^	4^	3^	4^	3^	4^	3^	4^
Weeks 3 and 4 PM Cohort	4	3	4	3	4	3	4	3	4	3
Weeks 5 and 6 AM Cohort	5^	6^	5^	6^	5^	6^	5^	6^	5^	6^
Weeks 5 and 6 PM Cohort	6	5	6	5	6	5	6	5	6	5
Weeks 7 and 8 AM Cohort	7^	8^	7^	8^	7^	8^	7^	8^	7^	8^
Weeks 7 and 8 PM Cohort	8	7	8	7	8	7	8	7	8	7
Weeks 9 and 10 AM Cohort	9^	10^	9^	10^	9^	10^	9^	10^	9^	10^
Weeks 9 and 10 AM Cohort	10	9	10	9	10	9	10	9	10	9

Study Design

Background

- This is a single-center, open-label, parallel-cohort study to measure and compare the levels of selected HTP vs. CC SHS constituents sampled from human smoking sessions in an ETC. Machine smoking will not be used. The study is unblinded by necessity due to the different visual appearances of the investigational products (IPs).
- A sufficient number of chamber visits will be used to detect statistically significant differences between the level of each SHS constituent after human smoking of CCs vs. human use of HTP IP.

Study Population

- The study will recruit healthy smokers of non-menthol and menthol CCs and/or HTPs from all sex, age (21 years of age or older), ethnicity, and race groups from the surrounding Atlanta, GA, USA area. All subjects will provide written informed consent, and the study will be approved by an Institutional Review Board and conducted in compliance with ICH-GCP.

Study Procedures

- Subjects (n = 120) will be assigned to one of 10 study cohorts, 12 subjects per cohort, based on their usual brand (UB) flavor preference (**Table 1**).
- Cohorts 1 and 2 will use their UB CC, Marlboro Gold Box or Newport Box which will serve as non-menthol and menthol CC comparators, respectively.
- The remaining 8 cohorts will be distributed to assess two HTP devices that have different heating modes, and 4 tobacco stick variants (3 menthol flavors and 1 non-menthol tobacco flavor). Subjects in the HTP cohorts will undergo a 2-week acclimation to the HTP for familiarization prior to their ETC visits.
- Over a period of 2 weeks, subjects will complete 10 ETC visits, 5 smoking and 5 non-smoking visits **(Figure 3**). Using a subject randomization scheme, only 4 subjects per ETC visit, of each 12-subject cohort, will be selected to enter the ETC. This plan will reduce any bias that may arise from the use of homogeneous session panels.
- Subjects will enter the ETC for a 20-minute ETC visit, including either a 10-minute "smoking" session (1 UB CC or 1 HTP tobacco stick) or a 20-minute "non-smoking blank session," following which air samples will be collected from the ETC for approximately 2 hours for SHS constituent analysis.
- Real-time SHS measurements and time-weighted average (TWA) samples will be collected.
- Up to two cohorts will be tested per day, with one non-smoking cohort in the morning and one smoking cohort in the afternoon.
- Following completion of Chamber Visit 10, subjects will complete an End of Study Visit.

Table 1. Study Cohorts.

Cohort	Investigational Product	Flavor
1	Marlboro Gold Box CC	Non-Menthol
2	Newport Box CC	Menthol
3	HTP device, HM1, Flavor 1 Menthol	Menthol
4	HTP device, HM2, Flavor 1 Menthol	Menthol
5	HTP device, HM1, Flavor 2 Menthol	Menthol
6	HTP device, HM2, Flavor 2 Menthol	Menthol
7	HTP device, HM1, Flavor 3 Menthol	Menthol
8	HTP device, HM2, Flavor 3 Menthol	Menthol
9	HTP device, HM1, Tobacco Flavor	Non-Menthol
10	HTP device, HM2, Tobacco Flavor	Non-Menthol

CC = Combustible Cigarette; HTP = Heated Tobacco Product; HM1 = Heating Mode 1; HM2 = Heating Mode 2.

Objectives and Endpoints

- The endpoints will include 8 primary SHS and 19 secondary SHS constituents with the SHS constituents detected during non-smoking sessions serving as a control.
- Differences in selected SHS constituents (**Table 2**) from human smoking of each HTP tobacco stick variant in an ETC compared to those from CCs (non-menthol to non-menthol and menthol to menthol) will be determined.
- Differences in selected SHS constituents (**Table 2**) from all cohorts, measured after IP use, compared to the corresponding non-smoking blank sessions will be determined; each cohort serving as its own control.
- Air samples from the ETC atmosphere will be evaluated for measures of real-time and TWA concentrations of secondhand emissions at specified times during the study.

Table 2. Primary and Secondary SHS Constituents.

Primary SHS Constituents	Secondary SHS Constituents	
Acetaldehyde	*o*-,*m*-,*p*-Cresol	Total volatile organic compounds (TVOC)
Ammonia (NH_3)	3-Ethenylpyridine	Ultraviolet particulate matter (UVPM))
Benzene	Fluorescent particulate matter (FPM)	Ethylbenzene
Carbon monoxide	Glycerol	Pyridine
Formaldehyde	Hydroquinone	Pyrrole
Nicotine	Phenol	Styrene
Toluene	Propylene glycol	*o*-,*m*-,*p*-Xylene
Respirable suspended particulates (RSP) ($PM_{2.5}$)	Solanesol	

Results

This study is expected to produce the following results:

- Statistically significant differences in levels of measured secondhand emission analytes after human smoking of each HTP tobacco stick variant compared to after human smoking of CC (non-menthol and menthol variants).
- Statistically significant differences in levels of measured secondhand emission analytes after human subject smoking of each HTP tobacco stick variant compared to after non-smoking blank session.
- Blank-corrected real time and TWA SHS concentrations for the secondhand emission analytes for the 10 cohorts.

Conclusions

The study outcome measures will include findings related to:

- Secondhand emission levels from the HTP flavor variants compared to CCs (non-menthol and menthol variants)
- Secondhand emission levels from the HTP flavor variants compared to background levels.
- Low levels of HTP secondhand emissions would not be expected to contribute significantly to the contamination of indoor air relative to CC.
- Confirmation of the hypothesis that THPs will produce less secondhand HPHCs compared to CCs and would be representative of a THR product.

References

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