

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 1 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

Cp'pgz '4/3<'<

Uk p'k'hec p'v' H'k'p'f k'p'i u'q'p' U'el'g'p'v'k'k'le' R'w'd'k'ec v'k'q'p'u'

FDA STN No.	Tobacco Product Name
PM0000424 - MR00000059	<i>Marlboro Amber HeatSticks</i>
PM0000425 - MR00000060	<i>Marlboro Green Menthol HeatSticks</i>
PM0000426 - MR00000061	<i>Marlboro Blue Menthol HeatSticks</i>
PM0000479 - MR0000133	<i>IQOS System Holder and Charger</i>
PM0000634 - MR0000192 ¹	<i>IQOS 3 System Holder and Charger</i>
PM0004691.PD1	<i>Marlboro Amber HeatSticks</i>
PM0004337.PD1	<i>Marlboro Sienna HeatSticks</i>
PM0004337.PD2 ²	<i>Marlboro Bronze HeatSticks</i>
EX0002940.PD1 ³	<i>Marlboro Amber HeatSticks</i>
EX0002940.PD3	<i>Marlboro Green Menthol HeatSticks</i>
EX0002940.PD5	<i>Marlboro Blue Menthol HeatSticks</i>
EX0003036.PD1	<i>Marlboro Bronze HeatSticks</i>
EX0003036.PD3	<i>Marlboro Sienna HeatSticks</i>
Reporting Period	March 1, 2023 to February 29, 2024

¹ a02 is responsive to the April 30, 2019 Marketing Order for PM0000424-PM0000426 and PM0000479, the December 7, 2020 Marketing Granted Order for PM0000634 and the January 26, 2023 Marketing Granted Order for PM0004691.PD1 and PM0004337.PD1-PD2. We refer to all orders collectively here as the “Marketing Orders”.

² a02 corresponds to Appendix C Section 9a and 9b of the January 26, 2023 Marketing Granted Order for PM0004691.PD1 and PM0004337.PD1-PD2.

³ a02 corresponds to Appendix A of the January 19, 2024 Exemption Request Granted Order. There has been no sale or distribution of the products under this Exemption Request Granted Order for EX0002940.PD3, EX0002940.PD5, EX0003036.PD1, EX0003036.PD3 or EX0002940.PD1 in the US during the Reporting Period so there is no new data to discuss in this Annual Report. These products may be referred to as HEETS in future reports in which will be communicated via 30 Day Submission before the product name is updated.

Eq'p'h'f g'p'v'k'k'le' U'c'v'g'o g'p'v'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 2 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

TABLE OF CONTENTS

1	Overview	3
2	Significant Findings by Scientific Area.....	3
2.1	Aerosol Chemistry and Physics & Indoor Air Quality	4
2.1.1	Aerosol Chemistry and Physics	4
2.1.2	Indoor Air Quality	16
2.2	Standard and Systems Toxicology	16
2.2.1	Respiratory	16
2.2.2	Non-respiratory	22
2.2.3	Dental.....	28
2.3	Clinical.....	30
2.3.1	Health effects of HTPs.....	30
2.3.2	Biomarkers of exposure and biomarkers of potential harm.....	45
2.3.3	Abuse liability	51
2.3.4	Methodology, consensus statements, guidelines	53
2.4	Perception & Behavioral Studies and Post-Market Studies.....	55
2.4.1	HTP Prevalence and Use Pattern	55
2.4.2	Youth and Young Adult Usage and Behavior	65
2.4.3	Smoking Cessation	70
2.4.4	Consumer perception	71
2.4.5	Tobacco Policy and Broader Research Topics	81

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 3 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

1 OVERVIEW

Significant findings from scientific publications are presented in an integrated manner by scientific area in this section for the period from March 1, 2023, to February 29, 2024.

Throughout this Annex, we reference publications that are related to the *IQOS* THS generally. PMP S.A. sells modified versions of the *IQOS* System Holder and Charger and additional variants of *HeatSticks* in markets outside of the U.S. The publications in this section may be related to versions of the *IQOS* System Holder and Charger and *HeatSticks* other than the Authorized Products, as PMP S.A. believes it is important to provide this information because those other versions are designed to have the same principles of operation and performance as the Authorized Products.

2 SIGNIFICANT FINDINGS BY SCIENTIFIC AREA

A systematic literature search and review of retrieved articles was conducted and originally identified 152 publications that reported information related to Heated Tobacco Products (HTPs).

41 publications have been excluded from reporting as they a) did not represent original research in a scientific discipline, b) did not represent a systematic review, c) were not available in English, or d) mentioned HTPs, but upon review, did not include HTP-related data. Studies related to the COVID-19 pandemics were also excluded as this exceptional situation is considered a case in itself, not representative of the reality of smoking behaviors, or use of smoke-free systems.

The remaining 111 publications are listed in Annex 2-2. The literature summary provided below gives an overview of those publications presenting significant findings that were not previously reported.

The publications included in our literature summary encompass various scientific fields including:

- Aerosol chemistry and physics, including data on product properties related to non-combustion, emissions of harmful and potentially harmful constituent (HPHCs), non-targeted analysis of the emissions from the product, indoor air quality and secondhand exposure;
- Standard and systems toxicology including *in-vitro* toxicology testing, *in-vivo* inhalation studies, and animal models of disease;
- Clinical studies on exposure reduction to HPHCs, effect on biomarkers of potential harm (BoPH) and early marker of disease risk;
- Observational studies on trends related to the potential impact of the product on smoking-related diseases;

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 4 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

- Both perception/behavioral and post-market studies, primarily outside the U.S., to assess the impact of the *IQOS* Tobacco Heating System on product use trajectories, impact on former and never smokers, impact on cessation, product acceptability and the impact of marketing approaches;

2.1 Aerosol Chemistry and Physics & Indoor Air Quality

2.1.1 Aerosol Chemistry and Physics

2.1.1.1 Desorgher et al., (2023) Dosimetry in the lungs of α -particles (^{210}Po) and β -particles (^{210}Pb) present in the tobacco smoke of conventional cigarettes and heated tobacco products, *Journal of Environmental Radioactivity*

The purpose of this research was to investigate the radioactive risk associated with heated tobacco products (HTPs) and compare it to that of conventional cigarettes. The study was conducted in Switzerland and funded by the Swiss Federal Office of Public Health. The authors utilized data from their previous research (Berthet et al., 2022) and implemented the recent ICRP intake models for natural polonium-210 (^{210}Po) and lead-210 (^{210}Pb) in their dosimetry code. The models considered slow and moderate absorption scenarios into the blood. The researchers aimed to estimate the annual effective dose induced by smoking one pack of cigarettes per day (equivalent to 20 cigarettes) and a corresponding pack of heated tobacco product Heets⁴ (IQOS).

In their investigation, the authors measured the ^{210}Po and ^{210}Pb content in tobacco leaves of various cigarette brands, including Heets. They also employed a smoking machine to determine the transfer of radioactive elements to the mainstream smoke, both for conventional cigarettes and the IQOS system.

The results demonstrated that conventional smoking of one pack per day led to an estimated lung dose of approximately 0.3 mSv/year. In contrast, the use of the IQOS system resulted in a significant dose reduction by a factor of ten, to 0.03 mSv/year. The reduction in effective dose seen with the IQOS system primarily stemmed from the lower percentage of tobacco being heated (15%) to the target temperature (330 °C), rather than offering inherent protection against radioactive elements.

The authors found that when heated homogeneously to 300 °C, both conventional cigarettes and IQOS release about 80% of ^{210}Po from the tobacco, leading to similar doses to lungs. The study also highlights the presence of ^{210}Po and ^{210}Pb in tobacco leaves, which are potential carcinogenic components of lung cancer and contribute to the high mortality rate from lung cancer found in smokers.

The authors conclude that “*there is room for new studies of ^{210}Po and ^{210}Pb deposition in the lungs to increase the accuracy of dosimetric modelling.*”

⁴HEETS is brand name used internationally for the Marlboro *HeatSticks*

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 5 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.1.1.2 Liang et al., (2023) Co-pyrolysis behavior of polylactic acid and biomass from heated tobacco products, Biomass Conversion and Biorefinery

HTP comprise of three main components: reconstituted tobacco treated with humectant, an acetate fiber filter rod, and a polylactic acid (PLA) polymer film; the latter distinguishing HTP from traditional cigarettes. While recent studies have focused on the pyrolysis process of individual HTP waste material,^{4,5} Liang et al., (2023) focused on the co-pyrolysis behavior of PLA and waste tobacco. This independent study aimed to understand the synergistic mechanism during the co-pyrolysis process of PLA and waste tobacco from HTP.

Thermogravimetric analysis (TG), thermogravimetric-fourier infrared spectroscopy (TG-FTIR), and pyrolyzer-gas chromatography/mass spectroscopy (Py-GC/MS) techniques were used to analyze the pyrolytic kinetic parameters and product distribution to gain insights into the co-pyrolysis behavior. After HTP use, waste tobacco and PLA were removed from the tobacco sticks by grinding and screening to obtain particles less than 500 µm. PLA and waste tobacco were blended in ratios of 1:3, 1:1, and 3:1 to study their interaction during the co-pyrolysis process.

The results suggest that the co-pyrolysis of PLA and waste tobacco from HTPs has a synergistic effect (PLA reduced the T_{\max} from 367.5 to 303.8–314.1°C), which reduces the activation energy required for the pyrolysis reaction and promotes ester product formation. The addition of waste tobacco improved the thermal activity of PLA and enhanced the reaction, particularly at 25%wt of waste tobacco addition (activation energy reduced from 166.38 to 111.20 KJ/mol). Additionally, the results show that the yield of lactide was significantly increased under specific conditions, indicating the significant impact of the synergistic effect. Furthermore, the pyrolytic products detected by TG-FTIR showed that the addition of waste tobacco promoted free radical reactions during the co-pyrolysis process, as reflected by the reduction of CO and aldehyde. The synergistic effect also reduced the input of external power and potential environmental pollution problems, making it an effective method for resource recovery.

2.1.1.3 Mušić et al., (2023) Influence of Weathering on the Degradation of Cellulose Acetate Microplastics Obtained from Used Cigarette Butts, Polymers

Microplastics, i.e., particles smaller than 1 mm, are considered a global problem in both aquatic and terrestrial habitats. Despite the waste generated by cigarette butts, they are often overlooked as a source of microplastics. In this independent research, Mušić et al. (2023) aimed to compare the effects of accelerated aging, using UV light, on the degradation of cellulose acetate (CA) microplastics following their use and disposal in nature. Used filters from

⁴ Chien YC, Liang CJ, Yang SH (2011) Exploratory study on the pyrolysis and PAH emissions of polylactic acid. Atmos Environ 45:123–127. <https://doi.org/10.1016/j.atmosenv.2010.09.035>

⁵ Zhang F, Sun Y, Li J, Su H, Zhu Z, Yan B, Cheng Z, Chen G (2022) Pyrolysis of 3D printed polylactic acid waste: a kinetic study via TG-FTIR/GC-MS analysis. J Anal Appl Pyrolysis 166:105631. <https://doi.org/10.1016/j.jaap.2022.105631>

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 6 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

conventional cigarettes and HTP *HeatSticks* (IQOS HEETS) were collected and processed using a vibrational ball mill to create two types of CA microplastics in powder form.

The results of the bulk density measurements showed how the materials changed after being exposed to weathering. In classic cigarettes, CA experienced a 29.6% decrease in density, while in IQOS HEETS, the decrease was 16.7% for CA and 0.3% for polylactic acid (PLA). Particle size analysis revealed that as CA from classic cigarettes and the ground CA filter from IQOS cigarettes aged in the Xenon chamber, their particle sizes decreased. Prior to aging, the majority of particles were distributed between 20 µm and 100 µm in size for both. However, after aging, the particle size distribution narrowed, with 80% of particles now falling between 16 µm and 100 µm for both CA types. These findings suggest that CA filters, including PLA film used in IQOS HEETS, are not only UV-unstable but also not biodegradable. Interestingly, the PLA film showed better stability than CA filters when exposed to UV light. Its bulk density changed only slightly, suggesting that it will take a longer time to decompose compared to CA filters before it breaks down in the environment.

2.1.1.4 Li Zhiqiang et al., (2023) Optimization of Control System for Electromagnetic Heating Cigarette Device, Journal of Physics

China Tobacco have previously reported that the control system for electromagnetic heating cigarettes has deficiencies in heating speed and temperature control accuracy.⁶ In this paper, Li Zhiqiang et al. (2023) describe the optimization of the control system of the MOK device. The study focused on the resonance modes and control modes of electromagnetic heating systems. The research employed a half-bridge push-pull double resonant capacitor design, which demonstrated nearly double the heating power compared to the original double-tube single-capacitor resonant circuit. By optimizing the main working circuit and designing the resonant circuit, the researchers were able to significantly improve the heating speed and temperature control accuracy of the electromagnetic heating control system. The test results revealed that the eddy current heating system achieved a preheating time of 7 seconds to 350°C, with an average rate of 44.33°C/s. During the constant temperature stage, the maximum temperature deviation did not exceed 5°C, and the temperature control accuracy remained within ±1.47%. Additionally, in the suction stage, the system quickly returned from 280°C to 340°C in just 3 seconds, with an average temperature return speed of 17.0°C/s.

The findings of this research provide a methodological framework and data basis for the development and design of vortex heating cigarette control systems. The optimized heating system design offers enhanced heating power, fast preheating, precise temperature control, and rapid temperature recovery, addressing the limitations reported by China Tobacco.

⁶ Xianqing Z, Donglin H, Yuchuan H, Yong D, Yun Z, Li X, Kai L, Lei T, Sheng L, Yunhong Z (2021) Development and prospect of lithium-ion battery for heated tobacco products. *Acta Tabacaria Sinica* 27(6):112-119. <https://doi.org/10.16472/j.chinatobacco.2021.085>

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 7 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.1.1.5 Guo et al., (2023) Face Mask as a Versatile Sampling Device for the Assessment of Personal Exposure to 54 Toxic Compounds in Environmental Tobacco Smoke, Chemical research in Toxicology

The primary approach to evaluating individual exposure to harmful toxins carried by Environmental Tobacco Smoke (ETS) involves acquiring smoke through a sorbent tube or filter via a smoking machine, which is then subjected to solvent extraction and instrumental analysis. In this independent research paper, Guo et al. (2023) suggest the primary methodology may not capture the true representation of ETS and, therefore, developed and validated an alternative air sampling method. The new method involved breathing through a face mask to simultaneously determine personal exposure to 54 ETS-borne compounds, including polycyclic aromatic hydrocarbons, aromatic amines, alkaloids, and phenolic compounds in real smoking scenarios. In the experiments, three types of cigarettes were used: cigarettes with tar yields ranging from 1 to 12 mg per cigarette (n=16), electronic cigarettes (n=5), and IQOS THS 3.0 DUO *HeatSticks* (n=5). The study involved 3 volunteers who wore 3 layers of identical PUF masks while sitting in a 10 m³ research laboratory where smoldering cigarettes were present (0.5 m away) for a duration of 30 minutes. The researchers then conducted separate analyses using mass spectrometry to determine the quantities of individual compounds present in each mask.

The study results indicated that exposure to ETS from novel tobacco products such as electronic cigarettes and HTPs is substantially less carcinogenic than exposure from conventional cigarettes, as demonstrated by both benzo[a]pyrene equivalent (a commonly used metric for assessing total polycyclic aromatic hydrocarbon carcinogenicity) and cancer risk indices measurements. These findings align with the general notion that novel tobacco products have a lower concentration of toxic chemicals when compared to conventional cigarettes. The study authors anticipate that the newly developed sampling technique relying on face masks will become widely used in evaluating personal exposure levels and the related health risks associated with exposure to ETS, as it is user-friendly.

2.1.1.6 Kim et al., (2023) Development and validation of a method for preparing heated tobacco product aerosol condensate (HTPAC) for large-scale toxicity data acquisition. Ecotoxicology and Environmental Safety

Kim et al., (2023) developed a method for preparing HTP aerosol condensate (HTPAC) to expedite HTP toxicity evaluation. HTPAC involves collecting HTP particles and vapor using Cambridge filter pads and Dulbecco's phosphate buffered saline (DPBS). The HTPAC preparation method underwent validation, with the procedures for HTP aerosol sampling and pretreatment divided into six stages (Exps 1-6):

- Exp 1 tested the mass of HTP aerosol that could be collected by the Cambridge filter without breakthrough.
- Exp 2 evaluated the efficiency of methanol extraction for HTP aerosol (SVOCs) collected by the Cambridge filter.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 8 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

- Exp 3 assessed the efficiency of DPBS in absorbing HTP vapor (VOCs).
- Exp 4 examined SVOC loss from the extract when methanol, the solvent for HTP aerosol extraction, was removed using nitrogen flow.
- Exp 5 evaluated the solubility of HTP aerosol in DMSO.
- Exp 6 analyzed the concentrations of OCs (SVOCs and VOCs) and carbonyl compounds in HTPAC.

The study found that key compounds such as nicotine and formaldehyde were present in HTPAC at levels similar to those found in HTP aerosols. The efficiency of different solvents for extracting specific compounds was also assessed, with methanol achieving over 90% extraction efficiency. However, analysis revealed that the sensitivity for some compounds was lower in DPBS and DMSO solvents. HTPAC concentrations of various compounds closely matched those in HTP aerosol, indicating the effectiveness of the method. The study concludes that HTPAC has the potential to contribute to safety evaluations of different HTP types, but further research is needed to optimize the method and investigate the impact of surfactant DMSO. HTPAC can be a valuable tool for formulating safety guidelines for HTP usage.

[2.1.1.7 Sussman et al., \(2023\) Aerosol Emissions from Heated Tobacco Products: A Review Focusing on Carbonyls, Analytical Methods, and Experimental Quality. Toxics](#)

Sussman et al. (2023) conducted a comprehensive review of 17 studies (9 industry-funded and 8 independent) on carbonyl emissions, in particular aldehydes, in aerosol from HTP. They assessed the quality of the experiments, focusing on reproducibility, analytic methods, and puffing regimes. The authors acknowledge that the HTP market is dominated by electronic HTP devices and, as such, the review only included data from studies that examined carbonyl emissions in IQOS™ or Tobacco Heating System 2.2, glo™ or Tobacco Heating Product THP1.0 and Ploom.

PubMed was used to search for relevant articles, focusing on those published after 2018. They screened titles and abstracts, excluding electronic cigarettes and reviews. Selected articles were critically analyzed for compliance with standardized puffing protocols (CORESTA), reproducible methods, and sample storage. The review also assessed physicochemical properties of HTP aerosols.

The majority of studies used the derivatization reaction with 2,4-DNPH to form hydrazones, with pH management and optimal reaction time being crucial for accurate measurements. Some studies used alternative derivatization methods such as DNPH cartridges or O-(2,3,4,5,6-Pentafluorobenzyl)hydroxylamine hydrochloride (PFBHA). High-performance liquid chromatography with ultraviolet detection (HPLC-UV) was commonly used for quantification. Blank analysis and proper storage conditions of aerosol samples were found to be lacking in many studies. The presence of certain compounds in HTP emissions at higher levels than in combustible cigarette smoke does not necessarily indicate significant toxicity, as the

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 9 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

concentrations are often minuscule. However, the authors determined that further monitoring and research on the effects of HTP emissions are needed.

Reliability of the reviewed studies demonstrated that one study was completely unreliable, while three studies had partial reliability due to issues with unit specifications and method validation. The remaining studies were considered reliable, with minor flaws that did not significantly impact their findings.

The main finding was that while HTP contain harmful and potentially harmful constituents (HPHCs), but at substantially lower concentrations than tobacco smoke. The reduction in HPHCs in HTP emissions compared to tobacco smoke was estimated to be around 90%. Regulatory evaluations by organizations such as the US FDA and the WHO supported this significant reduction.

[2.1.1.8 Davigo et al., \(2023\) Impact of More Intense Smoking Parameters and Flavor Variety on Toxicant Levels in Emissions of a Heated Tobacco Product. Nicotine Tobacco Research](#)

Davigo et al., (2023) aimed to assess the link between more intense puffing regimes and toxicant release in IQOS HEETS Yellow aerosol in comparison with cigarette smoke (1R6F and Marlboro Red). Nicotine, particulate matter, carbonyl compounds, and tobacco-specific nitrosamines were measured in emissions from 9 differently flavored IQOS HEETS (Amber, Blue, Bronze, Green, Russet, Sienna, Teak, Turquoise, and Yellow).

Mainstream emissions from cigarettes were generated on a 10-port linear smoking machine and from IQOS HEETS were generated on a 4-port linear vaping machine according to the WHO intense protocol. Chemical determination of analytes was performed in accordance with the WHO TobLabNet standard operating procedures. Carbon monoxide levels were measured with a nondispersive infrared analyzer integrated into the smoking machine. Mainstream emissions from all the assessed tobacco products were collected on a Cambridge glass-fiber filter pad, and nicotine levels were measured by gas chromatography with flame ionization detector.

The study found that HEETS Yellow aerosol contained around 55% less nicotine and 25% less total particulate matter (TPM) than cigarette smoke, whereas carbon monoxide (CO) levels were found to be below the limit of quantification (LOQ). Furthermore, compared with 1R6F and Marlboro Red, HEETS Yellow aerosol contained 63%-89% lower levels of several carbonyl compounds (formaldehyde, acetaldehyde, acetone, acrolein, glyoxal, and methylglyoxal) and 95%-98% less tobacco-specific nitrosamines (TSNAs). More intense smoking parameters increased carbonyls and TSNAs release in 1R6F and Marlboro Red cigarettes, while reducing them in HEETS Yellow aerosols.

When assessing the toxicant levels of different varieties of HEETS, nicotine and TPM concentrations were not significantly different in the aerosol of the assessed products.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 10 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

However, it was observed that HEETS Yellow and Bronze had the lowest levels TSNAs, while other HEETS emitted higher concentrations of certain TSNAs like NNN, NNK, and NAT. NAT was found to be the most abundant TSNA in all variants.

In terms of carbonyl compounds, acetaldehyde was the most abundant compared to other investigated carbonyls. Although no significant differences were noted in the levels of carbonyls released by the different HEETS overall, three variants (Amber, Bronze, and Green) were found to emit higher levels of formaldehyde compared to HEETS Yellow.

The study concluded that while IQOS HEETS emit lower levels of toxicants compared to cigarettes, they are not risk-free and further investigations are needed.

[2.1.1.9 Yang et al., \(2023\) Risk assessment and estimation of controlling safe distance for exposure to particulate matter from outdoor secondhand tobacco smoke.](#) [Air Quality, Atmosphere and Health](#)

Yang et al., (2023) conducted a study on the emission and diffusion of particulate matter (PM₁₀ and PM_{2.5}) and black carbon from different types of cigarettes, aiming to assess the risk of second-hand smoking (SHS) exposure and estimate safe distances for the general population and children. The study recruited 100 male smokers aged 20-40 years old who exclusively used one type of product among combustible cigarettes, heating e-cigarettes, and liquid e-cigarettes. Data from the Seventh Korea National Health and Nutrition Examination Survey (KNHANES VII) was used to identify 1129 nationwide subjects of SHS exposure, 18 of whom were children and 966 were adults.

Additionally, for every three types of cigarette consumption, 10 people (totaling 30 smokers) were invited to participate in an “aerosol emission investigation.” Measurements were taken for various pollutants at different distances from the participants, in light wind conditions. The average wind speed was 0.9 m/s and the average air temperature and humidity were 2.7°C and 38.1%, respectively.

Results showed that liquid e-cigarettes emitted the highest levels of PM₁₀ and PM_{2.5} in the air, followed by combustible cigarettes and heating e-cigarettes. Specifically, liquid e-cigarettes had an average PM₁₀ emission of 124 µg/cigarette, while combustible cigarettes and heating e-cigarettes emitted an average of 90 µg/cigarette and 78 µg/cigarette, respectively. For PM_{2.5}, liquid e-cigarettes emitted an average of 20 µg/cigarette, while combustible cigarettes and heating e-cigarettes emitted averages of 15 µg/cigarette and 12 µg/cigarette, respectively. In terms of black carbon emission, combustible cigarettes had the highest levels with an average emission of 5.6 µg/cigarette. Liquid e-cigarettes emitted an average of 3.9 µg/cigarette, while heating e-cigarettes emitted the lowest amount with an average of 2.5 µg/cigarette.

The aerosol emission investigation assessed the diffusion of particulate matter and found that particulate matter concentration increased within a 10-meter radius from the source of smoking or vaping. Beyond this distance, the concentration gradually decreased, but still remained higher than background levels. Based on the results, the study recommended a safe distance of

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 11 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

10 meters from smokers for the general population. However, for children, the safe distance was suggested to be over 100 meters when vaping liquid e-cigarettes due to their higher emissions.

2.1.1.10 Lang et al. (2024) Nontargeted analytical comparison of a heated tobacco product aerosol against mainstream cigarette smoke: does heating tobacco produce an inherently different set of aerosol constituents? Analytical and Bioanalytical Chemistry

In this industry study conducted by PMI, Lang et al. (2024) used untargeted analytical methods to identify compounds exclusive to THS 2.2 (*IQOS*) aerosol or with higher yields in *IQOS* aerosol than in cigarette smoke. Both test items, *IQOS* heatstick and comparator cigarettes, were produced at PMI using a blend of different tobacco types, including flue-cured tobacco (>60%), Oriental tobacco, and a small fraction of air-cured type tobaccos (<10%). For the comparator cigarette, design parameters and humectant levels in the tobacco were aligned with those of the 1R6F research cigarette. By using *IQOS* *HeatSticks* and comparator cigarettes produced with the same tobacco blend and without added flavors, the study focused exclusively on chemical differences due to heating vs. burning tobacco.

The Health Canada Intense puffing regime was applied to aerosolize *IQOS* and generate smoke from the comparator cigarette. A Cambridge glass fiber filter pad was used to trap aerosol and smoke, followed by two impinger traps filled with solvents and internal standards. Only compounds with significantly higher abundance in *IQOS* aerosol than in cigarette smoke and with a per-item yield of at least 37.5 ng in *IQOS* were identified and reported. Compounds with an *IQOS*/cigarette yield ratio below 1.25 were excluded, as were nicotine, glycerin, propylene glycol, and triacetin.

The results showed that 92.6% of analytical features were either unique for cigarette smoke or significantly higher in cigarette smoke than in *IQOS* aerosol, while 3.5% were unique for *IQOS* aerosol or significantly higher in *IQOS* aerosol than in cigarette smoke. These features with higher abundance in *IQOS* aerosol correspond to 31 distinctive compounds with per-item yields ranging from 0.03 to 81.9 µg. In addition to the non-targeted analysis, which provides only semi-quantitative concentration information, 4 toxicologically relevant compounds were quantified using validated methods, with glycidol, 3-MCPD, and 2-furanmethanol confirmed as increased. Nicotine was also quantified at 1.29 ± 0.04 and 2.55 ± 0.12 mg/item for *IQOS* and the cigarette, respectively. The glycerol content in *IQOS* is higher than in cigarettes, leading to an increased abundance of glycerol reaction products in *IQOS* aerosol. The authors describe how the results demonstrate that heating a glycerol-containing tobacco substrate to the temperatures applied in *IQOS* (i.e., max. 350 °C) does not introduce new compounds in the resulting aerosol compared to cigarette smoke, which are detectable with the method portfolio applied in this study. Overall, the study provides evidence that heating tobacco produces a subset of chemicals found in cigarette smoke, with most constituents being less abundant in *IQOS* aerosol. Further research is needed to understand compound formation mechanisms and evaluate the toxicological risks of HTPs.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 12 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.1.1.11 Zhang et al. (2024) Real-time characterization and quantification of aerosol components for open- and Closed-Ended heated tobacco products. *Microchemical Journal*

Zhang et al. (2024) describe a novel vacuum ultraviolet photoionization time-of-flight mass spectrometer (PI-TOFMS) that was adapted for online chemical analysis of gaseous and particulate aerosol fractions formed from two China Tobacco, HTPs of contrasting airflow designs (open-ended and close-ended). The airflow pathways were compared using electrically resistive heating with a maximum temperature of $240^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Aerosols were generated by a linear smoking machine with 55 mL puff volume, 2 s puff duration and 30 s puff interval (i.e., Health Canada Intense puffing regimen). Nicotine, glycerine, and propylene glycol were additionally quantified using GC-TCD and GC-MS, respectively.

The gaseous phase mass spectra showed that more major components were identified in comparison to the particulate phase aerosol. Peaks at $m/z = 44$ (ethanol, acetaldehyde, or ethylene oxide), $m/z = 58$ (propen-2-ol, acetone, or propanal), $m/z = 72$ (acrylic acid, 2-butanone, or isobutyraldehyde), $m/z = 86$ (2,3-Butanedione) and $m/z = 96$ (3-Furaldehyde or 4-Cyclopentene-1,3-dione) were observed.

35 peaks were detected in the particulate phase and 48 peaks in the gaseous phase in the open-ended and close-ended HTPs, and the relative ratios were different for the two airflow systems. The close-ended HTP had a lower condensation/nucleation rate than the open-ended HTP. The gaseous and particulate phase ratios were different in the close-ended and open-ended HTP configurations, which implied that less formations of aldehydes and ketones were achieved in the close-ended HTP.

Variations of nicotine, glycerine, and propylene glycol signals with puff durations demonstrated that prolonged puff durations lowered the nicotine, glycerine, and propylene glycol deliveries in the close-ended HTP with an approximately linear trend, while no obvious variation was observed for the open-ended HTP. The highest mass intensity was observed at around puff 5-6 for the open-ended HTP and puff 7 for the closed-ended HTP. The study also established regression relationships between the off-line mass values of aerosol chemicals and the on-line signal intensities recorded by the PI-TOF-MS system. This allowed for effective quantification of the yields of nicotine, glycerine, and propylene glycol. The results showed that increasing the puff duration from 2 to 4 seconds reduced the total amount of nicotine delivered by 43% in the closed-ended configuration. The authors suggest that the established quantification method can provide a way to balance the airflow to deliver nicotine, as well as being used to predict the delivery of other aerosol chemicals.

2.1.1.12 Zhao X et al. (2024) Preparation of tobacco pyrolysis liquids in subcritical/supercritical ethanol and their application in the aroma enhancement of heated cigarettes. *Frontiers in chemistry*

In this industry study conducted by China Tobacco, Zhao et al, (2024) explored the use of subcritical and supercritical ethanol to produce pyrolysis liquids from tobacco for use in heated

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 13 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

cigarette aroma enhancement. The authors describe how subcritical and supercritical ethanol has a high solubility that allows them to extract small molecules from tobacco cells, releasing aromas. Additionally, they can also promote the depolymerization and dissolution of cellulose and lignin in tobacco leaves, which accelerates the pyrolysis and liquefaction processes.

The effect of supercritical liquefaction conditions on volatile aroma components and the aroma-enhancing effect of tobacco pyrolysis liquid were analyzed by GC-MS. Tobacco raw materials were crushed and screened, and anhydrous ethanol added. A high-pressure reactor, electronic balance, and rotary evaporator were used in the experiment.

The analysis of tobacco pyrolysis products at different reaction temperatures revealed that temperature plays a crucial role in the pyrolysis process. The main components detected in the pyrolysis products were ethanol derived ethyl-esters, nitrogen-containing heterocycles, phenols, alcohols, aldehydes, ketones, and other substances commonly associated with flavoring. The content of 2-hydroxybutanoic acid ethyl ester, levulinate ethyl ester, butanedioic acid diethyl ester, dibutyl phthalate, and 5-oxo-2-pyrrolidinecarboxylic acid ethyl ester in the tobacco pyrolysis liquid increased as the reaction temperature rose. Nicotine, the primary nitrogen-containing heterocycle in tobacco pyrolysis liquid, exhibited improved peak area ratios with higher reaction temperatures. The nicotine content was further quantitatively analyzed using gas chromatography and was found to increase with higher reaction temperatures. The authors suggest this increase can be attributed to the decomposition of cellulose in subcritical/supercritical ethanol, which disrupts the compact structure of tobacco leaves and facilitates the release of nicotine.

Phenolic compounds were mainly presented at a reaction temperature of 260°C, implying that higher reaction temperatures may be favorable for the depolymerization of lignin. Notable compounds identified include 2-furanmethanol, 5-hydroxymethylfurfural, 5-methyl-2-furancarboxaldehyde, and 3-methyl-1,2-cyclopentanedione, which are important contributors to the aromatic properties of tobacco smoke.

When applying tobacco pyrolysis liquid to the aroma enhancement of heated cigarettes, the researchers found that the tobacco pyrolysis liquid significantly increased the release of volatile substances into the smoke of heated cigarettes, resulting in a higher total particulate matter content (22.4 mg/cig vs. 20.6 mg/cig, respectively) and a slightly higher nicotine content (0.415 mg/cig vs. 0.410 mg/cig, respectively) compared to the heated cigarette without addition of extract. The optimal conditions for preparing tobacco pyrolysis liquid were found to be at a temperature of 220°C with a liquid/solid mass ratio of 15, and a reaction time of 2 hours. Analysis of aroma compounds in smoke showed that tobacco pyrolysis liquid enhances the release of aroma substances and has a significant aroma-enhancing effect.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 14 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.1.1.13 An et al. (2024) Assessment of toxicological validity using tobacco emission condensates: A comparative analysis of emissions and condensates from 3R4F reference cigarettes and heated tobacco products. *Environment International*

In this independent study, An et al., (2024) focused on the importance of tobacco condensate in evaluating the toxicity of tobacco products. The study aimed to quantify and compare the organic compounds (OCs) present in tobacco condensates from combustible cigarettes and HTPs as well as determining the hazard index for tobacco emissions and condensates.

The study examined three HTPs (identified as HTP-A, HTP-B and HTP-C) with the highest market share in South Korea in 2017, which are known to be *IQOS*, Lil, and Glo. To prepare tobacco condensates, 3R4F cigarettes and HTPs emissions were initiated using an SG-300 smoke-generation device, and the particulate phase was collected through a Cambridge filter pad. The gaseous phase was absorbed into Dulbecco's phosphate-buffered saline, and the total particulate matter (TPM) residue was subject to methanol-based solvent extraction and N₂ evaporation.

The authors used 29 previously prepared OCs as final working standards for external calibration and determined the concentration of each compound using the effective carbon number (ECN) method. The concentrations were obtained from predictive equations built upon a linear regression relationship between the experimental response factor values of the 29 target standards and their respective ECNs. The study focused on the quantitative assessment of the concentration and hazards of tobacco condensate, specifically targeting OCs amenable to detection using GC-MS methodology.

The 3R4F sample had the highest diversity of selected targeted organic compounds (OCs) with 108 distinct types, while the HTP samples ranged from 72 to 92 OCs, resulting in an average decrease of 22.2±9.80% in OCs compared to 3R4F. Sixty OCs were found in both 3R4F and HTP samples, making up more than half of the total OCs in each sample. Moreover, 90 OCs were consistently present in all HTP samples, indicating similar OC profiles among different HTP variants. Cyclic, alcohols, and ketones were the most prevalent types of OC functional groups. Nitrogen-bearing OCs were consistently detected in all samples, suggesting the formation of significant nitrogen compounds in HTPs despite lower temperatures compared to traditional cigarette combustion. Specifically, there were 35 nitrogen compounds in 3R4F and an average of 18.0±1.73 in HTPs.

The total OC concentration (TOC) in HTP-A was highest, followed by HTP-C and HTP-B, with 5422 µg stick⁻¹ and 4600 µg stick⁻¹, respectively. However, the 3R4F sample exhibited the lowest TOC, although it contained the greatest diversity of detected OCs. When captured on a Cambridge filter pad, TPM concentration from the 3R4F cigarette was 17,667 µg cig⁻¹ i.e., roughly 1.89 times greater than the average TPM concentration in HTPs, which stood at 9342±1918 µg stick⁻¹. The authors believed the observed differences in TPM and TOC in HTP aerosols are not ascribed solely to tar levels and were instead due to water content, which accounts for 46.4% of TPM in HTP aerosols and elevated levels of propylene glycol and

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 15 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

vegetable glycerin in the HTP aerosols. When evaluating the OC levels in emissions versus condensates, 3R4F showed 30% recovery in its condensed form, with HTP recoveries ranging from 80% to 120%. This results in considerable losses during the 3R4F condensation phase.

Hazard index determination showed that the hazard index of tobacco condensate was highest in the 3R4F sample (45.2), with HTPs ranging from 30.3 (HTP-A) to 40.0 (HTP-C). Nicotine consistently had the highest hazard quotient in all condensate samples, significantly influencing the hazard index. Nicotine and vegetable glycerin had elevated hazard values in tobacco emissions, consistent with condensate findings. Acetaldehyde had a consistently higher hazard value in emissions than in condensates across all samples.

The authors conclude that the study highlights the importance of accurately quantifying OCs in order to effectively evaluate the toxicity of conventional tobacco condensate.

[2.1.1.14 Bechikhi et al. \(2024\) Effect of oxygen on the temperatures and conversion of tobacco in an electrically heated system. Journal of Analytical and Applied Pyrolysis](#)

The aim of this study by Bechikhi et al. (2024), which was funded by PMI, was to investigate the effect of oxygen on the temperature profile inside the tobacco plug of a *IQOS* HEETS using a modified puffing machine, analyze the chemical composition of the solid residue in the tobacco plug after puffing cycles using FTIR spectroscopy, and present the effect of oxygen on the heats of reactions using a fixed bed of tobacco in a 3D-sensor calorimeter.

The researchers controlled the vertical position of the thermocouple in the *IQOS* device by reconstructing it in CAD software. They measured the temperature inside the tobacco stick at different radial distances from the heated lamella (0, 0.2, 0.5, 1.7, 3.4 mm) under N₂ or air, micro-positioning the thermocouple at the targeted radial position.

The temperature profiles were found to be nearly identical for both atmospheres, with only minor influences of oxygen observed (maximum temperatures: 318°C in air, 308°C in N₂, at the end of the puffing cycle). The thermal degradation of the tobacco consistently remained globally endothermic. Principal component analysis of the FTIR spectra clearly differentiated the residues based on their radial positions, regardless of whether air or N₂ was used. Additionally, analysis of the FTIR spectra indicated that the heating of the tobacco in the *IQOS* device was uniform, without any indications of hot spots. Calorimetry of tobacco during pyrolysis or oxidation without being placed in the *IQOS* device showed significant exothermic reactions at ~230°C. When the tobacco stick was used in the *IQOS* device exothermicity was counterbalanced by strong heat losses and a high flow rate of cold air during puffing. Consequently, the net observed degradation of tobacco during *IQOS* operation remained predominantly endothermic.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 16 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.1.2 Indoor Air Quality

2.1.2.1 [Giongo et al., \(2023\) Impact of the use of heated tobacco products \(HTP\) on indoor air quality. Physis](#)

Giongo et al., (2023) conducted a systematic review of studies that evaluate the impact of using HTP indoors on air quality and the health of passively exposed individuals. The researchers conducted a search of multiple databases and selected 21 studies for inclusion in their review using PECO methodology.

The results of the review indicated that HTP are a source of environmental pollution due to the emission of particulate matter. The emissions from HTP also contain substances that are classified as carcinogenic to humans, including as formaldehyde, acetaldehyde, and acrolein. The authors reported that emissions from HTP can worsen air quality and expose people to toxic substances indoors. However, they noted that while there is evidence indicating possible harm to health, such as respiratory system damage and increased cancer risk, there is still no conclusive evidence on the causal relationship between exposure to HTP emissions and the emergence of health problems.

The authors noted that more independent research is needed to understand the full extent of the damage caused by HTP. They also highlighted the need for studies to assess the impacts of HTP on both environmental contamination and health, considering the diverse models and products available.

Based on the evidence evaluated in the review, the authors concluded that HTP should not be used indoors to avoid contaminating non-users. They also suggested the adoption of additional measures to curb the illegal trade of these products and reinforce the inspection of their use indoors, accompanied by information campaigns for the public.

2.2 Standard and Systems Toxicology

2.2.1 Respiratory

2.2.1.1 [Husari et al., \(2023\) The substitution of fifty percent of combustible tobacco smoke exposure with either electronic cigarettes or heated tobacco products did not attenuate acute lung injury in an animal model, Nicotine & Tobacco Research](#)

In this animal study, conducted by researchers at the American University of Beirut, Lebanon, the acute effects on the lungs of C57BL/6 mice were assessed when conventional cigarettes were partially substituted with electronic cigarettes (ECIG) or heated tobacco products (HTP). This study aimed to mimic the approach of dual users and investigate the health implications of combining different tobacco products.

Mice were divided into seven groups, including a control group: air, ECIG, HTP, conventional cigarette smoke (CS), ECIG + CS, HTP + CS, and HTP + ECIG groups. Each group consisted of eight animals. The mice were nose-only exposed to air, CS, ECIG, or HTP for 3 hours in

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 17 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

morning and afternoon sessions for 7 consecutive days. Various measures were used to assess lung injury, including wet-to-dry (W/D) lung weight ratio, albumin concentration in bronchoalveolar lavage fluid, lung expression of pro-inflammatory mediator-encoding genes, lung histopathology examination, reactive oxygen species (ROS) production, and apoptosis.

The study revealed that mice exposed to a combination of 50% CS and 50% HTP or ECIG exhibited similar characteristics of lung injury compared to those solely exposed to 100% CS. These characteristics included increased expression of pro-inflammatory mediators (IL-1 β , IL-6, and TNF- α), elevated albumin leakage into the bronchoalveolar lavage fluid, augmented ROS production, and increased cellular death. Histopathological examination showed inflammatory cell infiltration, reduced air space, thickened alveolar walls, and alveolar edema in these groups. Additionally, Masson trichrome staining indicated collagen fiber accumulation, potentially indicating lung remodeling and future fibrosis.

While apoptosis and oxidative stress data suggested a reduction in lung injury in the dual exposure groups compared to exclusive CS exposure, other parameters did not show significant improvement. The study did not observe any significant lung injury when mice were exposed to a combination of ECIG and HTP.

The authors conclude that their results suggest “*a potentially grave misunderstanding by cigarette users that partially substituting cigarette use with ECIG or HTP use can reduce health risks.*”

2.2.1.2 Muratani et al., (2023) Oxidative stress-mediated EGFR activation by cigarette smoke or heated tobacco aerosol in human primary bronchial epithelial cells from multiple donors, *Journal of Applied Toxicology*

In this study, supported by Japan Tobacco Inc., the researchers aimed to explore the reduced risk potential of HTPs compared to conventional cigarettes in the context of oxidative stress-induced epidermal growth factor receptor (EGFR) activation as described in an Adverse Outcome Pathway (AOP) for decreased lung function. The endpoints assessed included reactive oxygen species (ROS) production, glutathione depletion, EGFR ligand secretion, and EGFR phosphorylation.

The aerosol collected mass (ACM) from the Direct Heating Tobacco System Platform 3 Generation 3 (DT3.0a), as well as other in-market HTPs, and the total particulate matter TPM from combustible cigarettes, were used to expose Primary Normal Human Bronchial Epithelial (NHBE) cells from 4 donors

The results showed that CS TPM treatment induced all tested endpoints, albeit with inter-donor differences, while HTP ACMs elicited most of the biological events only at higher concentrations. However, crucially, EGFR phosphorylation, indicative of EGFR activation, and a feature associated with cancer, was not observed even at five-fold higher HTP ACM concentrations than CS TPM. Overall, the findings suggested that HTPs are less effective than

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 18 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

CS in inducing ROS-mediated EGFR activation, pointing towards their reduced risk potential for EGFR-related diseases.

The authors emphasized the importance of investigating the chronic effects of HTP exposure and further refining the link between in vitro results and real-world situations through quantitative modeling and simulation.

2.2.1.3 Sato and Ishigami (2023) Effects of heated tobacco product aerosol extracts on DNA methylation and gene transcription in lung epithelial cells, Toxicology and Applied Pharmacology

Sato and Ishigami (2023) conducted an independent study to investigate the effects of HTPs (Ploom S and Ploom TECH+, Japan Tobacco) on global DNA methylation in lung epithelial cells, compared to 1R6F reference cigarette smoke extract. Of note, Ploom S is a high temperature (200 °C) heating product, while Ploom TECH+ heats at a lower temperature of 40 °C.

In this study, human lung adenocarcinoma (A549) cells were treated with HTP aerosol extracts or CS extract for 24 or 48 hours, before assessing cell viability, cytotoxicity, gene expression, and DNA methylation.

The results demonstrated that CS extract decreased cell viability at concentrations above 0.1 mg TPM⁷/mL, whereas Ploom S and Ploom TECH+ aerosol extracts increased it (0.1 to 0.4 mg TPM/mL and 0.125 to 2 mg TPM/mL, respectively). CS extract significantly decreased global 5-mC and 5-hmC levels⁸, whereas Ploom S and Ploom TECH+ aerosol extracts did not. Both the CS extract and Ploom S aerosol extract increased TET1⁹ mRNA expression in A549 cells, but this effect was greater with CS extract. Treatment with Ploom S aerosol extract decreased CpG methylation levels compared to control and CS extract. Ploom S aerosol extract affected a smaller number of genes than CS extract, with affected genes contributing to only a small number of varying pathways—contrary to the large number of pathways affected by CS extract. Both extracts had an impact on CYP1A1 mRNA expression and promoter methylation, but CS extract elicited greater changes than HTP aerosol extract.

Overall, the study found that HTP aerosol extracts were less cytotoxic and had less impact on global DNA methylation levels than reference cigarette smoke extracts, although Ploom S aerosol extract altered patterns of CpG methylation and the expression of cancer-related genes such as CYP1A1 albeit to a smaller degree than CS extract. The authors suggest that “*further investigations are necessary to understand the health effects associated with HTP use*”.

⁷ TPM, total particulate matter

⁸ 5-mC, 5-methylcytosine; 5-hmC, 5-hydroxymethylcytosine

⁹ TET1, ten-eleven translocation 1

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 19 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.2.1.4 Bratu et al., (2023) NIR and THz spectroscopy: An experimental investigation toward nicotine-related devices, *Journal of Biophotonics*

This independent research by Bratu et al. (2023) examined the transmission spectra of tobacco and nicotine in nicotine delivery products using terahertz time-domain spectroscopy and breath ethylene with CO₂ laser photoacoustic spectroscopy. The study involved testing three different types of nicotine delivery devices, including traditional cigarettes, electronic cigarettes, and HTP (IQOS with HEETS). Seven healthy male volunteers aged 35-42 were asked to use each device for 4 minutes each (n=15 puffs). Breath samples were collected prior to and immediately after the final puff of each tobacco product, as well as on 2 consecutive days following product use.

The results of the study showed that nicotine delivery devices, specifically HTP and electronic cigarettes, exhibit lower transmission of harmful constituents in the terahertz (THz) region compared to traditional cigarettes. Additionally, the levels of ethylene in breath, which is an indicator of oxidative stress, were lower after using HTP and electronic cigarettes compared to smoking traditional cigarettes. The authors conclude that cigarettes containing more toxic constituents can lead to higher levels of oxidative stress in the body.

2.2.1.5 Kastratovic, et al., (2023) Effects of Combustible Cigarettes and Electronic Nicotine Delivery Systems on the Development and Progression of Chronic Lung Inflammation in Mice. *Nicotine and tobacco research*

Kastratovic et al. (2023) compared the effects of combustible cigarettes (1R6F; CCs) and HTP (IQOS) on lung health in mice, compared to control mice who were exposed to regular air only. The experimental mice were exposed to 5 CC or IQOS sticks every day for four weeks and then placed back into fresh air. The researchers found that the nicotine concentrations in the aqueous aerosol extracts (AqE) of CC and HTP were 12.8 µg/ml and 8.4 µg/ml, respectively. Blood gas analysis showed that mice exposed to CCs experienced severe respiratory dysfunction, while HTP caused moderate respiratory impact on the mice exposed to it. The study also measured the levels of inflammatory cytokines (IL-1β, IL-6, IL-12, and IL-17) in serum samples of mice from control and experimental groups, using commercial enzyme-linked immunosorbent assay (ELISA) sets. The data indicated that mice exposed to HTP had reduced serum concentrations of inflammatory cytokines compared to those exposed to CCs. Additionally, flow cytometry analysis and intracellular staining of immune cells in lung tissues revealed that both CCs and HTP exposure triggered an immune response in the lungs, but that induced by HTP was less severe than that by CCs. HTP exposure resulted in lower recruitment of circulating immune cells in injured lungs compared to CCs. Histological examination further supported these findings, with CCs causing more severe lung injury and inflammation (including partial alveolar wall destruction, widened alveolar septa, capillary dilation and congestion accompanied with significant leucocytes' infiltration) compared to HTP.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 20 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The researchers concluded that although HTP caused significantly less severe lung injury compared to CC, both products caused immune cell-driven lung damage in mice and caution should therefore be exercised in using HTP, and long-term use of HTP should also be avoided.

2.2.1.6 Wang et al., (2024) Evaluation of toxicity of heated tobacco products aerosol and cigarette smoke to BEAS-2B cells based on 3D biomimetic chip model. Toxicology In Vitro

In their study, Wang et al. (2024) used a 3D biomimetic chip model to compare the potential harm reduction of HTP (Hubei, China) to combustible cigarettes (CC). They aimed to assess the toxicity of the aerosol/smoke from each product using the Health Canada Intense machine puffing regime. Cell viability, morphology, and apoptosis were also examined using an optical microscope at different concentrations (25%, 50%, 100%).

The results showed that the nicotine content in CC extract was approximately 1.5-fold higher than HTP ($26.32 \pm 2.26 \mu\text{g}$ vs $17.48 \pm 1.34 \mu\text{g}$, respectively). While there was no significant difference in cell proliferation rate during the first 3 days, a significant difference ($p < 0.001$) was observed on the 5th day. After treatment with aerosolized extract (AqE) from HTP and CC, both HTP_100% and CC groups exhibited noticeable apoptosis and cell necrosis. The CC group showed an increasing apoptosis state with higher smoke extract concentration. Inflammatory factors like LDH, TNF- α , and IL-8 increased in a concentration-dependent manner, with higher cell membrane permeability in CC groups compared to HTP groups.

Even at HTP_100%, the toxic effects on BEAS-2B cells were weaker than those of CC. HTP mainly caused limited inhibition of cell proliferation, apoptosis, necrosis, and inflammatory response, with minor impairment of mitochondrial structure and relatively low impact on gene expression of key enzymes in the TCA cycle. HTP_100% significantly affected the mitochondrial membrane potential of cells compared to the control group, while CC AqE showed a dose-dependent effect on mitochondrial membrane potential. CC AqE significantly affected ATP production at a concentration of 25%. HTP only significantly inhibited ATP production at HTP_100%. HTP_100% down-regulated IDH2 and OGDH genes, while CS gene expression was down-regulated in all HTP experimental groups. CC groups showed a concentration-dependent down-regulation of all TCA-related genes.

In conclusion, the study suggests that HTP may be less harmful than CC, but still causes harm to BEAS-2B cells. The researchers highlighted the usefulness of the 3D biomimetic chip model for evaluating HTP and providing valuable data for tobacco risk assessment. However, they acknowledged that the current limitations of 3D models prevent the evaluation of the numerous compounds present in smoke.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 21 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.2.1.7 Zarcone et al., (2023) Impact of Electronic Cigarettes, Heated Tobacco Products and Conventional Cigarettes on the Generation of Oxidative Stress and Genetic and Epigenetic Lesions in Human Bronchial Epithelial BEAS-2B Cells. Toxics

Zarcone et al. (2023) investigated the effects of e-cigarettes, HTP, and combustible cigarettes on human bronchial epithelial (BEAS-2B) cells, specifically looking at oxidative stress, genetic damage, and epigenetic lesions. The cells were exposed to emissions from each product, and their impact was observed.

The findings revealed that HTP had lower cytotoxicity compared to combustible cigarettes. To reach EC50 (the dose reducing cell viability to 50%), 350 puffs of HTP emissions were required, while only 12 puffs from cigarette smoke were needed, indicating a 29-fold difference. E-cigarettes did not show any significant cytotoxic effects regardless of the power used.

Both HTP and cigarettes triggered oxidative stress and genetic damage through the activation of the Nrf2 pathway. These products caused oxidative DNA damage, DNA strand breaks, and chromosomal abnormalities. In contrast, e-cigarettes did not induce significant DNA damage.

The study demonstrated that HTP, unlike e-cigarettes, have a biological response similar to that of cigarettes. However, this response only occurs with extensive exposure. The doses required to induce oxidative stress were much lower for cigarettes compared to HTP.

The researchers suggested that formaldehyde, acetaldehyde, and benzo-[a]-pyrene, which are well-known DNA-damaging agents found in high concentrations in HTP and cigarettes, may explain the observed oxidative DNA lesions and DNA strand breaks in BEAS-2B cells. In contrast, the measured carbonyl compounds and PAH concentrations in e-cigarette emissions were too low to cause cytotoxicity, nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant response, and genotoxicity in BEAS-2B cells since e-cigarettes do not involve combustion.

While acknowledging that HTP may be less harmful than cigarettes, the researchers cautioned that HTP still pose health risks. They recommended further research using animal models to better understand the tumorigenic potential of these products.

2.2.1.8 Lenski et al. (2024) Metabolomics Provides Novel Insights into the Potential Toxicity Associated with Heated Tobacco Products, Electronic Cigarettes, and Tobacco Cigarettes on Human Bronchial Epithelial BEAS-2B Cells. Toxics

In this independent study, Lenski et al. (2024) used liquid chromatography–high resolution mass spectrometry (LC-HRMS)-based metabolomics to analyze human lung epithelial cells (BEAS-2B) exposed to e-cigarettes, HTP (*IQOS* THS 2.4), or reference cigarette (3R4F) emissions to highlight potential early markers of toxicity.

For each type of tobacco product, the cells were exposed to different doses of nicotine, but the goal was to create similar levels of cell damage (more than 80% cell viability) based on preliminary data: 60 and 120 puffs for e-cigarettes (based on 18W and 30W devices,

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 22 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

respectively), 60 and 120 puffs for HTP, and 2 and 4 puffs for the 3R4F cigarette. To evaluate all products, the Health Canada intense (HCI) puff profile was used for smoke/aerosol generation. The final data matrix from the metabolomic evaluation contained 3591 features, with 2398 compounds from positive electrospray ionization and 1193 compounds from negative electrospray ionization.

Cytotoxicity results showed that emissions from HTP led to higher levels of cell damage after 120 puffs compared to the control groups. Statistical tests indicated significant differences in cytotoxicity levels for the HTP group ($p=0.03$). However, no significant differences were observed in cytotoxicity levels for the other groups tested. Overall, treatment with aerosols from all types of tobacco product resulted in less than 20% cytotoxicity. The authors remark that these results suggests that, under the specific conditions used for the metabolomic analysis, the effects of exposure were attributed to intracellular effects rather than changes caused by cell death.

The metabolome of BEAS-2B cells was significantly affected by 3R4F and HTP emissions, whereas no difference was observed after e-cigarette exposure. Notably, 84% of the compounds deregulated after 3R4F exposure were also deregulated after HTP exposure, corresponding to 43 common compounds.

After exposure to 3R4F cigarettes, 7 compounds were identified as exogenous, while after exposure to HTP, 8 compounds were identified as exogenous. 3-Methylindole was only increased through exposure to HTP emissions. Nicotine levels significantly increased after exposure to both HTP and 3R4F emissions, but not after exposure to e-cigarette emissions. Following exposure to 3R4F cigarette smoke, 13 endogenous compounds were identified, including 8 lipids of the eicosanoid class. After exposure to HTP aerosol, 73 endogenous compounds were identified, including 38 lipids. Furthermore, after 120 puffs of exposure to HTP aerosols, an increase in oxidized glutathione and a decrease in nicotinamide adenine dinucleotide phosphate were observed, both of which are involved in glutathione metabolism.

Overall, the study demonstrated that exposure to both cigarette smoke and HTP aerosol resulted in similar metabolic changes, indicating shared markers between the two tobacco products. The authors suggest that the study identified exogenous compounds, including 3-methylindole (which is speculated, but not proven, to be a carcinogen) as markers of tobacco exposure. However, the study had limitations, including a uniform smoking regimen protocol and the need for further target verification.

2.2.2 Non-respiratory

2.2.2.1 [Ohashi et al., \(2023\) Human vasculature-on-a-chip with macrophage-mediated endothelial activation: The biological effect of aerosol from heated tobacco products on monocyte adhesion, Toxicology in Vitro](#)

In this study, funded by Japan Tobacco Inc., the researchers aimed to investigate the biological effects of aerosol from heated tobacco products (HTPs) on monocyte adhesion, which is a

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 23 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

critical process in the development of atherosclerosis, the predominant form of cardiovascular disease (CVD). The authors developed an in vitro model of monocyte adhesion using an organ-on-a-chip (OoC) that mimicked major aspects of human physiology. The model included a tubule of endothelial cells and flowing monocytes with the consideration of macrophage-mediated endothelial activation.

The study used TPM from a reference conventional cigarette (1R6F) and ACM from 3 commercial heated tobacco products (HTPs), including the Direct Heating Tobacco System Platform 3 Generation 3 (DT3.0a), tobacco heating product (THP), and tobacco heating system (THS), with one representative regular tobacco flavor stick for each HTP purchased from the Japanese market.

The researchers were assessing the importance of proinflammatory cytokines for monocyte adhesion by direct treatment of endothelial tubules with tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β). The reduced risk potential of HTPs for monocyte adhesion was also investigated by considering macrophage-mediated effects, assuming the actual situation of humans.

The authors concluded that IL-1 β contributes more to monocyte recruitment than TNF- α at the early stage of atherosclerosis. They also reported that the study showed that HTPs elicited less pronounced effects on the biological events related to monocyte adhesion even at 3000 $\mu\text{g/mL}$ ACM compared with the cigarette. Furthermore, all three tested HTPs, including the DT3.0a, had comparable biological effects, although they used different tobacco heating mechanisms.

2.2.2.2 Giebe et al., (2023) Comparative study of the effects of cigarette smoke versus next-generation tobacco and nicotine product extracts on inflammatory biomarkers of human monocytes, *European Journal of Physiology*

In this study, funded by British American Tobacco, Giebe et al. examined the effect of next-generation tobacco and nicotine products (NGPs) on human monocytes, with a focus on cell viability, oxidative stress, and the induction of a pro-inflammatory phenotype.

The research evaluated the effect of aqueous smoke extracts (AqE) of a heated tobacco product (HTP), an electronic cigarette (e-cig), a conventional cigarette (3R4F), and pure nicotine on THP-1 monocytes, a commonly used model for mimicking monocyte function in the vasculature. The authors discovered that 3R4F AqE led to a dose-dependent reduction in cell viability, while neither AqE of NGPs nor nicotine affected cell viability.

Further analysis revealed significant changes in mRNA expression for several pro-inflammatory markers. Treatment with 3R4F, HTP, and e-cig AqE resulted in increased expression of genes associated with oxidative stress (*HMOX1*, *NOX2*, and *NQO1*) and pro-inflammatory responses (*CCL2*, *IL1B*, *CXCL8*, and *TNF*), albeit to different degrees. Protein expression of IL1B and IL8 was also elevated. The expression of adhesion molecule ICAM1

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 24 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

was transiently increased following all treatments; however, levels were highly variable and differences between conditions did not reach statistical significance.

When comparing the NGPs to 3R4F, it was observed that NGPs generally induced smaller responses in terms of oxidative stress and pro-inflammatory gene and protein expression. However, at higher doses, all extracts showed greater induction of gene and protein expression, with 3R4F AqE consistently producing stronger responses than AqEs of NGPs.

The authors conclude that *“in vitro stimulation of human monocytes with conventional cigarette leads to onset of antioxidative and pro-inflammatory mechanisms at lower doses, whereas treatment with alternative smoking products leads to reduced activation of the analyzed study parameters: cell viability, cellular oxidative stress response, and inflammatory state.”*

2.2.2.3 Granata et al., (2023) Potential Harm of IQOS Smoke to Rat Liver, International Journal of Molecular Sciences

In this independent *in vivo* study, Granata et al. (2023) explored the potential harmful effects of IQOS on carcinogen-metabolizing enzymes, redox homeostasis, and lipid profile in rat liver by using a total-body exposure model.

Male Sprague Dawley rats (n=24) were housed under standard conditions and exposed to air, IQOS aerosol, or control (n=14). The IQOS group was subject to total-body exposure. The inhalation chamber consisted of a propylene box with a capacity of 19 L, a pump was installed on one side of the box, and two IQOS devices were connected in tandem. Rats were exposed to 904 g nicotine/chamber/day for 5 consecutive days/week for up to for 4 weeks.

The results of the study showed that IQOS aerosol exposure increased oxidative stress in the liver as evidenced by increased reactive oxygen species (ROS) production, carbonylated protein and malondialdehyde levels and reduced glutathione (GSH) levels. There were no significant effects on antioxidant enzymes related to GSH; however, catalase and xanthine oxidase levels increased significantly in the IQOS group. Liver weights remained unchanged, possibly due to the short exposure period. However, analysis of liver mitochondria revealed an increase in mitochondrial mass, suggesting a protective response to counteract ROS-induced damage to oxidative phosphorylation.

Among the detoxifying enzymes, cytochrome P450 (CYP) enzymes and uridine diphosphate-glucuronosyltransferases (UDGPT) were increased, whereas (glutathione S-transferase) GST was decreased in the IQOS group. Furthermore, Nrf2 expression was significantly reduced in the livers of IQOS aerosol-exposed rats.

The study saw a significant lipid peroxidation increase, which is known to be related to membrane function loss, decreased fluidity, protein and DNA damage, disruption of gene functions and promotion of cell death (apoptosis and necrosis) pathways, and can produce liver inflammation and fibrosis, eventually leading to organ failure.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 25 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

Together, the results point toward increased oxidative stress, enhance mitochondrial respiration, active xenobiotic metabolism, and potential lipolysis in the liver of IQOS aerosol-exposed mice.

The authors acknowledge that this study should not be interpreted as a translational study, and the results presented cannot be directly extrapolated to humans. However, they conclude that the IQOS device is harmful not only to primary target organs such as the lungs but also to the liver in rats.

2.2.2.4 Wang et al., (2023) Testicular tissue response following a 90-day sub-chronic exposure to HTP aerosols and cigarette smoke in rats. *Toxicological Research*

Wang et al. (2023) conducted a study to investigate the effects of exposure to HTP aerosols, combustible cigarette smoke, and filtered air on testicular health in male Sprague-Dawley rats over a 90-day period. High-level exposure to HTP aerosol (HTP_50, 50 µg/L nicotine) and combustible cigarette smoke (Cig_23, 23 µg/L nicotine) resulted in oxidative damage to the testes, leading to sperm malformation and decreased serum testosterone levels, with more severe changes in Cig than the HTP group. These high-dose exposure groups also exhibited an increase in tissue IL-1b, IL-6, and TNFa levels and tissue markers associated with pyroptosis, with a greater impact of cigarette smoke than of HTP aerosol exposure. Histopathological examination confirmed damage to the testicular tissue structure in the HTP_50 and Cig_23 groups. In contrast, rats exposed to lower doses of HTP aerosol (HTP_10 and HTP_23, 10 and 23 µg/L nicotine, respectively) showed milder responses compared to the high-exposure groups.

Chemical analysis of the test atmospheres revealed lower concentrations of acrolein, formaldehyde, and acetaldehyde in HTP aerosols compared to combustible cigarette smoke, even when both products contained the same nicotine concentration (23 µg/L).

In summary, the study concluded that high-level exposure to HTP aerosol and cigarette smoke induced oxidative stress, inflammation, and pyroptosis, leading to structural damage in the rat testes and impairing normal testicular function. Lower HTP aerosol doses had fewer adverse effects, with some changes being statistically indistinguishable from the rats exposed to filtered air (control group).

The researchers emphasized the need for further research to investigate the potential health risks associated with HTP usage.

2.2.2.5 Wölkart et al., (2023) Varied effects of tobacco smoke and e-cigarette vapor suggest that nicotine does not affect endothelium-dependent relaxation and nitric oxide signaling. *Scientific Reports*

Wölkart et al. (2023) investigated the impact of chronic smoking on vascular endothelial cells by studying the effects of cigarette smoke extract (CSE), e-cigarette vapor extract (EVE), and

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 26 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

heated tobacco extract (HTE) on vascular relaxation, endothelial nitric oxide signaling, and soluble guanylyl cyclase activity.

The average nicotine concentrations in CSE, EVE, and HTE were 164 µM, 800 µM, and 85 µM, respectively. These concentrations were significantly higher (approximately 1800- (CSE), 900- (HTE), and 4300-fold (EVE) higher) than the average plasma concentration of chronic smokers which is approximately 30 ng/ml. Diluted extracts were used to treat coronary aortic rings, prepared from Sprague-Dawley rats and porcine aortic endothelial cells (PAECs) for 24 hours.

The results of the study showed that CSE at a 1:3 dilution and undiluted HTE significantly inhibited the endothelium-dependent but not the endothelium-independent relaxation of rat and porcine coronary arteries. There was no correlation between the nicotine content of the extracts and the inhibition of acetylcholine-induced aortic ring relaxation, indicating that nicotine is not a mediator of the impaired endothelium-dependent relaxation caused by cigarette smoking.

CSE and HTE caused concentration-dependent decreases in PAEC viability, inhibition of eNOS activity, and endothelial cGMP accumulation, with greater effects seen for CSE than HTE and no obvious impact of EVE on these parameters. This indicated that substances other than nicotine in the aerosols of burned or HTP contributed to the observed effects on endothelial cells.

The study had limitations, including the fact that the extracts tested may not accurately represent the properties of inhaled aerosols, as well as the use of only one type of vaporizer and conditions, which may not reflect the effects of aerosols generated by different devices. Furthermore, the authors acknowledge that while there is evidence that e-cigarette and HTP aerosol increases markers of oxidative stress and inflammation, they induce less pronounced responses compared to tobacco smoke.

[2.2.2.6 Vivarelli et al. \(2024\) Effects of unburned tobacco smoke on inflammatory and oxidative mediators in the rat prefrontal cortex. *Frontiers in Pharmacology*](#)

Independent authors Vivarelli et al. (2024) conducted a chemical analysis of HTP aerosol (*IQOS* THS 2.2) using GC/MS and assessed the inflammatory and oxidative mediators in the rat prefrontal cortex. Sprague-Dawley rats were randomly assigned to either air control (n=6) or HTP exposure (n=6). A puff profile (5s on, 15s off, and 5s on) with an airflow of 4 L/min was set in accordance with previous studies by the authors. Animals were subjected to total-body exposure for 20 minutes.

GC-MS identified carcinogens such as aldehydes and polycyclic aromatic hydrocarbons in HTP mainstream aerosol, indicating thermal degradation and incomplete combustion of tobacco. The recorded concentration of nicotine was significantly lower than the LC₅₀ for vaporized nicotine in rat models (2.3 mg/L).

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 27 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

Significantly elevated levels of several protein/enzymes were seen in the prefrontal cortex of exposed rats compared to the control group including those related to oxidative stress and DNA repair: 8-hydroxy-2'-deoxyguanosine, reactive radical species, nuclear factor erythroid 2-related factor, catalase, SOD-1, xeroderma pigmentosum group C, and 8-oxoguanine DNA glycosylase, as well as increased levels of superoxide dismutase mRNA. No significant changes in the DNA damage marker histone H2AX were observed.

Significant increases in cytochrome P450 (CYP) isoforms were observed in the prefrontal cortex of rats exposed to HTP aerosol, including CYP1A1, CYP2A6, CYP2B6 and CYP2E1. Analysis of protein alterations of c-MYC showed significantly higher levels in exposed rats compared to control (1.92 ± 0.08 vs 1.00 ± 0.08 , $p < 0.0001$). Analysis of inflammatory mediators showed significantly higher levels of NF- κ B, TNF- α , IL-1 β , and IL-6 in the prefrontal cortex of rats exposed to HTP aerosol compared to control, while no significant changes in IL-8 were observed. Lastly, rats exhibited a downregulation in prefrontal cortex mRNA levels of the nuclear receptors PPAR α and PPAR γ in the exposure group compared to the control group, while an increase in gene expression levels of KDM6A was seen in rats exposed to HTP aerosol compared to those exposed to air.

The authors conclude that although HTP release lower concentrations of carcinogenic and neurotoxic compounds compared to conventional cigarettes, HTP consumption can still trigger pathological mechanisms seen in cigarette smoking. These mechanisms include oxidative DNA damage, co-carcinogenesis, and the deregulation of cellular pathways associated with neuroinflammation and neurodegeneration. Additionally, the authors state that nicotine, similar to other drugs of abuse, can alter oxidative and neuroinflammatory mediators, which are key factors in the development of substance use disorders.

[2.2.2.7 Tian et al. \(2024\) Liver toxicity in rats after subchronic exposure to HTP aerosol and cigarette smoke. Toxicology Research](#)

In this industry study by China Tobacco, Tian et al. (2020) investigated the potential health risks of HTP by examining various parameters including liver enzyme activity, inflammatory factors, biomarkers of oxidative stress, and mitochondrial function as part of a 90-day inhalation toxicology study. Sprague Dawley rats were exposed nose-only to control (air), HTP aerosol at varying doses (HTP_10, 23, and 50 μ g nicotine/L), and cigarette smoke (Cig_23 group; 23 μ g nicotine/L). Both cigarette smoke and HTP aerosols were generated using the Health Canada Intense puff regime. The rats inhaled these substances for 90 days, 6 hours per day and 5 days per week.

The study revealed significant increases in hepatic biomarkers, including total protein in female rats and alanine aminotransferase (ALT) in male rats, in the Cig_23 group. Moreover, exposure to HTP resulted in higher ALT levels in female rats in both the HTP_23 and HTP_50 groups compared to the control group.

The findings indicated significant differences in the levels of proinflammatory cytokines, such as IL-1 β , IL-6, and TNF- α , in the livers of the Cig_23 group compared to the control group. In

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 28 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

the HTP groups, exposure to the highest dose also induced inflammation, as evidenced by increased levels of IL-1 β , IL-6, and TNF- α . Notably, when comparing the HTP_23 group to the Cig_23 group, the inflammatory mediator production induced by HTP aerosol exposure was significantly lower than that induced by cigarette smoke exposure, despite both groups receiving equal nicotine levels.

The study found a significant decrease in mitochondria in the Cig_23 group compared to the control group. However, exposure to HTP aerosol at the same nicotine concentration did not yield significant changes. Both cigarette smoke and high-dose HTP aerosol exposure affected adenosine triphosphate (ATP) production, but cigarette smoke had a more significant impact, reducing ATP content compared to the HTP group. Impaired mitochondrial function often accompanies a decrease in ATP production and an increase in reactive oxygen species (ROS) production. The study indicated that both cigarette smoke and the high-dose HTP aerosol exposure induced ROS production, suggesting that high doses of smoke/aerosol may lead to mitochondrial impairment in the liver.

Additionally, cigarette smoke exposure induced elevated malondialdehyde (MDA) levels along with reduced superoxide dismutase (SOD) activity and glutathione (GSH) levels. In comparison to the control group, the HTP_50 group exhibited significantly higher MDA levels. SOD activities in the HTP groups, except for HTP_10, were significantly reduced. The authors noted that both HTP aerosol and cigarette smoke exposure could induce oxidative stress in the liver. Finally, while HTP aerosol did not induce liver apoptosis, cigarette smoke exposure did result in slight apoptosis due to oxidative stress and inflammation.

2.2.3 Dental

2.2.3.1 [Uehara et al., \(2023\) Effects of prolonged stimulation with heated tobacco products \(Ploom TECH+\) on gingival epithelial cells, Journal of Periodontal Research](#)

In this study, conducted at Health Sciences University of Hokkaido, Japan, Uehara et al. aimed to investigate the effect of Ploom TECH+ extract, a specific heated tobacco product (HTP), on gingival epithelial cells.

The researchers collected tobacco leaves from Ploom TECH+ tobacco capsules and processed them by heating in water. The resulting supernatant, referred to as the HTP extract, was used for further analysis. Human gingival epithelial progenitors (HGEPs) were cultured and alternately exposed to the HTP extract or untreated (control) for 1 month.

To comprehensively assess the effects of HTP extract stimulation, the researchers employed RNA sequencing (RNA-seq) and reduced representation bisulfite sequencing (RRBS) techniques to analyze gene expression and DNA methylation, respectively. They also conducted western blotting to examine protein levels.

RNA-seq analysis revealed that 284 differentially expressed genes exhibited a greater than twofold increase, while 145 genes showed a greater than twofold decrease in expression in response to HTP extract stimulation. Changes in the expression of selected genes was

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 29 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

confirmed by qRT-PCR. A heat map and principal component analysis demonstrated differences between the control and HTP groups, indicating distinct gene expression profiles associated with HTP extract exposure. Gene Ontology (GO) analysis identified enrichment of seven biological processes related to keratinocyte differentiation, such as cornification and keratinization, which were induced by long-term HTP extract stimulation. Notably, no inhibition of biological processes was observed.

The RRBS analysis provided insights into DNA methylation patterns. It showed that methylation of CpG islands increased more than twofold in 158 genes and decreased to less than twofold in 171 genes in response to HTP extract stimulation. However, the researchers found no correlation between CpG island methylation and changes in gene expression levels.

The study also compared its findings to a previous in vitro study that examined the effects of IQOS on oral keratinocytes and fibroblasts after 24 hours (Pegano et al., 2021). Unlike the previous study, which reported increased cell proliferation, the HTP extract treatments in this study did not show higher cell counts at any concentration or time point.

The authors conclude that *“because long-term HTP stimulation affects epithelial differentiation and keratinization of gingival epithelial cells, habitual Ploom TECH+ use may be a risk factor for tobacco-related oral mucosal diseases. However, the mechanism underlying the induction of epithelial differentiation and keratinization by HTP remains unclear.”*

2.2.3.2 [Camoni et al., \(2023\) Electronic Cigarettes, Heated Tobacco Products, and Oral Health: A Systematic Review and Meta-Analysis, Applied Sciences](#)

There is evidence to suggest that electronic nicotine delivery systems (ENDS) and HTPs may have negative effects on oral health. To address this, Camoni et al. (2023) conducted a systematic review and meta-analysis to gather and analyze clinical and laboratory data on the potential oral health impacts of ENDS and HTPs. The review aimed to synthesize existing knowledge from both clinical observations and laboratory research to provide a comprehensive understanding of the oral health risks associated with these smoking alternatives.

The review indicated that both ENDS and HTPs can have adverse effects on periodontal and peri-implant parameters, potentially leading to oral health issues. Laboratory studies suggested that e-liquids used in ENDS may induce apoptosis and necrosis biomarkers in oral cells, while flavored e-liquids could promote bacterial adhesion and disrupt the oral microbiome. Despite these findings, the high variability among studies, lack of standardized methodologies, and simplified product comparisons pose challenges in drawing definitive conclusions. Therefore, further research with standardized approaches is needed to better understand the long-term effects of alternative tobacco products on oral health and address these limitations.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 30 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.2.3.3Á Kurachi et al., (2023) Effects of aerosols from heated tobacco products with flavors on the discoloration of bovine tooth enamel, Clinical and Experimental Dental Research

In this industry-sponsored *in vitro* study, Kurachi et al. (2023) aimed to assess the potential for tooth discoloration caused by aerosols generated from 3 different Japan Tobacco Inc HTPs (IT1.0a, IT2.0a, and DT3.0a) compared to smoke from the 1R6F reference cigarette . In addition, 3 flavor variants (regular, menthol, and berry menthol) were selected for each HTP to characterize the effect of flavor types on tooth discoloration using bovine teeth as a proxy.

Six bovine tooth samples were exposed directly to aerosols generated from one pack of each HTP: 350 puffs for IT1.0a, 325 puffs for IT2.0a, and 220 puffs for DT3.0a. Six bovine tooth samples were also exposed to air (350 puffs) and smoke generated from one pack of cigarettes (160 puffs) as negative and positive controls, respectively.

405' Endpleci'

2.3.1Á Health effects of HTPs

2.3.1.1Á Cardiovascular system and diseases

2.3.1.1.1Á Ikonomidis et al., (2023) Differential effects of heat-not-burn, electronic, and conventional cigarettes on endothelial glycocalyx; European Heart Journal

Studies have shown acute negative effects on cardiovascular function after using HTP and electronic cigarettes, however, there is limited knowledge about their impact on endothelial glycocalyx. To address this research gap, Ikonomidis et al. (2023) conducted an independent clinical study involving 100 participants: 50 current smokers were randomized to either HTP use (IQOS with HEETS Amber, n=25) or to e-cigarette use (NOBACCO eGo, n=25) and 50 smokers were used as matched controls (Marlboro Red). Participant demographics were similar across all groups with average daily cigarette consumption at baseline of >25 cigarettes.

CO, endothelial glycocalyx, and blood cotinine were assessed at baseline and after 1 month. The study found that HTP and e-cigarette users showed a significant decrease in CO levels (mean percent change of -55% and -58% respectively, $p < 0.001$), while CO levels remained unchanged in traditional cigarette smokers ($p = 0.312$). The endothelial glycocalyx of conventional cigarette smokers experienced further deterioration after continuing to smoke for one month. In contrast, those who switched to e-cigarettes preserved their glycocalyx integrity, while those who switched to HTPs showed a moderate improvement in micro-vessels ranging from 20 to 25 μm . Cotinine levels, which are indicative of nicotine exposure, were similar across the three groups at baseline and at 1 month, respectively (HTP, 90.34 ng/mL vs. 93.18 ng/mL; e-cigarette, 90.34 ng/mL vs. 91.18 ng/mL; traditional cigarette, 88.13 ng/mL vs. 93.18 ng/mL).

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 31 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

Overall, this study suggests that switching from traditional cigarettes to e-cigarettes or HTPs may have benefits in terms of reducing CO exposure and preserving or improving endothelial glycocalyx integrity.

2.3.1.1.2 Lyytinen et al., (2023) Use of heated tobacco products (IQOS) causes an acute increase in arterial stiffness and platelet thrombus formation. Atherosclerosis

Lyytinen et al. (2023) aimed to assess the impact of HTP usage on vascular function in healthy young adults. In a randomized crossover study, 24 healthy male and female occasional tobacco users, between 18-40 years of age, were exposed to the HTP IQOS 3 Multi, with a control group having no exposure. An additional 8 healthy volunteers were recruited due to data loss. Arterial stiffness and platelet thrombus formation were evaluated through pulse wave velocity, pulse wave analysis, and Total-Thrombus-formation analysis.

The results available for 23 participants showed that HTP exposure caused immediate heightened pulse wave velocity (+0.365m/s, 95% CI: +0.188 to 0.543; p=0.004) and enhanced augmentation index corrected to heart rate (+6.22%, 95% CI: +2.33 to 10.11; p=0.003) compared to the no exposure occasion. Additionally, there were increases in heart rate and diastolic blood pressure after 20 minutes, both compared to baseline and to the no exposure occasion. These effects normalized within 90 minutes. There was also a trend towards a significant increase in systolic blood pressure observed 20 minutes after HTP exposure, which also normalized after 90 minutes. 22 participants had results for platelet thrombus formation which significantly increased following HTP exposure (area under the curve +59.5, 95% CI: +25.6 to 93.4; p<0.001) compared to no-exposure. However, no effect was seen on fibrin-rich thrombus formation following HTP exposure.

The findings suggest that brief HTP use in healthy young adults has immediate adverse effects on vascular function, including increased arterial stiffness, heart rate, and blood pressure. These effects normalize within 90 minutes. These vascular changes are known risk factors for the development of atherosclerosis. The authors underscored the need for further research to address the long-term health impacts of HTP use. The study's limitations include its small size and the need for additional research on HTP aerosol compounds' effects on arterial stiffness and hemostatic function.

2.3.1.1.3 Krysiński et al., (2023) A multicenter prospective randomized controlled trial investigating the effects of combustion-free nicotine alternatives on cardiovascular risk factors and metabolic parameters in individuals with type 2 diabetes who smoke: the DiaSmokeFree study protocol. Internal and Emergency Medicine

Krysiński et al., (2023) discusses a randomized controlled trial called DiaSmokeFree, which aims to investigate the long-term health impact of switching from combustible cigarettes to combustion-free nicotine alternatives (C-F NA) in smokers with type 2 diabetes (T2D). The trial will be conducted in seven sites across four countries (UK, Italy, Poland and Moldova) and will enroll 576 smokers with type 2 diabetes. The primary endpoint of the study is the

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 32 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

change in the proportion of patients with metabolic syndrome between baseline and the 2-year follow-up. The study will also analyze the absolute change in the sum of the individual factors of metabolic syndrome at each study time point. Patient recruitment started in September 2021, and the results will be reported in 2026.

The article emphasizes that the study will focus on cigarette smokers diagnosed with T2D who have been smoking daily for at least 5 years and meet specific inclusion criteria related to glycated hemoglobin percentage and body mass index. While participants will be given access to free smoking cessation programs, randomization will only occur if they decline to join these programs. The article acknowledges that C-F NA are marketed as substitutes for tobacco cigarettes and are promoted for harm reduction and smoking cessation. However, it cautions that these alternatives are not without risks and may have undisclosed adverse health effects. To ensure compliance, the study protocol includes reminders to quit smoking and access to smoking cessation programs, with compliance monitored through biochemical verification and checks of returned consumables. Innovative features of the study include offering participants a range of C-F NA to choose from and incorporating a tracker application to monitor behaviors and enhance adherence. Limitations of the study include potential challenges in subject retention due to the lengthy 2-year follow-up period and the inability to generalize the results to all smokers with diabetes.

In conclusion, the DiaSmokeFree study aims to provide valuable insights into the cardiovascular and metabolic health benefits or risks associated with using C-F NA in individuals with T2D who are seeking alternatives to tobacco cigarette smoking.

2.3.1.2 Pregnancy and reproductive health

2.3.1.2.1 *Galanti et al., (2023) Impact of different typologies of smoking on ovarian reserve and oocyte quality in women performing ICSI cycles: an observational prospective study; European Review for Medical and Pharmacological Sciences*

Galanti et al. (2023) conducted an independent prospective observational study between January 2019 and February 2022 at the Sandro Pertini Hospital in Rome, focusing on 410 women undergoing in vitro fertilization (IVF). The aim of the study was to scrutinize the effects of smoking and alternative tobacco products (e-cigarettes and HTP) on the quality of oocytes during intracytoplasmic sperm injection (ICSI) cycles. Active smokers (n=203) included women who smoked ≥ 10 cigarettes per day or >10 e-cig/HTP per day for at least one year were included (mean, 12 ± 2.3), while non-smokers (n=207) included women who had never smoked or stopped smoking for at least 1 year.

The study revealed noteworthy distinctions between smokers and non-smokers, with smokers exhibiting lower anti-Müllerian hormone levels, necessitating higher gonadotropin doses for hormonal stimulation. Additionally, smokers had statistically significantly fewer retrieved

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 33 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

oocytes ($p = <0.001$), an elevated count of empty zona pellucida oocytes ($p = <0.05$), and a reduced fertilization rate compared to non-smokers ($p = 0.03$). Of significance, no substantial variations in ICSI outcomes emerged between conventional cigarette smokers and users of e-cigarettes or HTP. These findings, however, underscore the adverse repercussions of smoking and alternative tobacco devices on ovarian reserve and quality, emphasizing the utmost importance of reducing exposure to harmful substances from such products, especially for women of reproductive age.

2.3.1.2.2 Incognito et al., (2023) Use of cigarettes and heated tobacco products during pregnancy and maternal-fetal outcomes: a retrospective, monocentric study,; Archives of Gynecology and Obstetrics

In a retrospective study conducted in Italy between July 2021 and July 2022, Incognito et al. (2023) compared a cohort of pregnant women who used the IQOS HTP ($n=138$), with pregnant women smoking traditional cigarettes ($n=120$), ex-smokers ($n=114$) and non-smokers ($n=270$). Women underwent epidemiological evaluation, anxiety/depression tests, and answered questions about smoking habits. Medical records were also used to evaluate pre-pregnancy BMI, difficulty getting pregnant, blood pressure peaks, gestational weeks at birth, type of delivery, and labor induction.

The results showed that women who smoked traditional cigarettes experienced more weight gain and faced difficulties in conceiving. Both smokers and ex-smokers faced higher risks of preterm labor, miscarriages, hypertensive spikes, and cesarean sections. Preterm birth was more common in women who smoked traditional cigarettes and in those who used HTP. Both traditional cigarette smokers and those who used HTP exhibited lower awareness of smoking risk. Furthermore, traditional cigarette smokers were more prone to depression and anxiety. Biochemical parameters showed no significant differences among the groups. Traditional cigarette smokers had the most significant difference in gestational age calculations based on the last menstrual period compared to actual ultrasound age. In addition, the average newborn weight percentile and Apgar scores were lower for cigarette smokers. In conclusion, while traditional cigarette smoking posed greater risks compared to HTP, the study did not recommend HTP due to differing maternal-fetal outcomes compared to non-smokers.

2.3.1.3 Respiratory function and diseases

2.3.1.3.1 Yoshioka et al., (2023) Association between exposure to secondhand aerosol from heated tobacco products and respiratory symptoms among current non-smokers in Japan: a cross-sectional study, BMJ Open

In this study, Yoshioka et al. looked at respiratory symptoms (asthma/asthma-like symptoms and persistent cough) following second-hand aerosol exposure (assuming someone had used an aerosol in their presence) from heated tobacco products (HTPs) in current non-smokers in Japan.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 34 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The study used data relating to non-smokers aged between 15 and 80 years, who had responded to the 2021 Japan ‘Society and New Tobacco’ Internet Survey (JASTIS) carried out from 8 – 16th February of that year. Of the 26,000 people who had responded to the survey, 18,839 current non-smokers were selected. Of those, 4,402 respondents reported that they had second-hand exposure to HTP aerosols in the past year.

The study looked at any asthma attacks/asthma-like symptoms and/or persistent cough these responders had experienced in the last 12 months, following second-hand exposure to HTP aerosols.

The study primary endpoint was asthma-like symptoms or asthma. The secondary endpoint was persistent cough. Weighted, multivariable ‘modified’ Poisson regression models were used to calculate prevalence ratio (PR) and 95% confidence interval (CI).

9.8% (95% confidence interval: 8.2% to 11.7%) and 16.7% (95% CI 14.8% to 18.9%) of the individuals reported experiencing asthma attacks/asthma-like symptoms, along with persistent cough after second-hand exposure to HTP aerosols. This corresponded with a PR of 1.49 (95% CI: 1.21 to 1.85) for asthma attacks/asthma-like symptoms and a PR of 1.44 (95% CI: 1.21 to 1.72) for persistent cough.

In contrast, among the 14,437 people who were not exposed to HTPs in the past year, the prevalence was 4.5% (95% CI: 3.9% to 5.2%) for asthma attacks/asthma-like symptoms and 9.6% (95% CI: 8.4% to 11.0%) for persistent cough.

The findings of the study suggest that second-hand exposure to aerosols from HTPs is linked to an increased risk of asthma attacks/asthma-like symptoms and persistent cough. However, due to the cross-sectional nature of the study, it does not provide definitive evidence of causality.

2.3.1.3.2 Popp et al., (2023) Heated tobacco products and chronic obstructive pulmonary disease: a narrative review of peer-reviewed publications, European Medical Journal

Smoking is a major contributor to COPD, and quitting smoking is the most effective intervention for improving prognosis. However, quitting smoking can be difficult. Over the past two decades, combustion-free nicotine delivery alternatives, including heated tobacco products (HTPs), have been introduced which expose users to lower levels of harmful components than traditional cigarettes. However, to date, research on the potential benefits of HTPs specifically for COPD patients has been limited.

Preclinical studies suggest that HTPs may induce fewer harmful effects than cigarettes, but the clinical evidence is less conclusive. Meta-analyses and systematic reviews indicate that HTP users are exposed to lower levels of harmful constituents. Still, the number of studies investigating the effects of HTPs on human health is limited, particularly for COPD patients.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 35 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

While aerosols from HTPs appear to be less harmful than cigarette smoke, they may still induce changes. Previous research in mice and rats reported effects from HTP exposure, such as apoptosis-mediated pulmonary emphysema in mouse lungs, alterations in lung airways and DNA in rats, and HTP aerosol exposure for 24 weeks increased proinflammatory cytokine levels. However, these changes were generally less significant than those induced by cigarette smoke.

Current evidence from randomized controlled trials assessing HTP safety is limited, with a median follow-up of just 13 weeks. Patient-focused studies on HTP use among individuals with COPD have had small sample sizes, ranging from 19 to 51 subjects, and real-world evidence studies have limitations in establishing causal relationships.

There is a need for further research, including longer-term studies and investigations specific to COPD patients. Surveys, real-world evidence surveillance, and completion of Phase IV trials will provide additional insights. The completion of ongoing clinical trials, such as one assessing the effect of switching to HTPs on disease progression in COPD patients, will contribute to understanding the potential benefits.

A clinical trial sponsored by a tobacco company is currently underway, recruiting subjects with mild to moderate COPD, to assess the effect of switching from cigarettes to HTPs on disease progression. However, this study isn't due to be completed until June 2027.

In conclusion, while recent findings suggest a lower risk of COPD development and progression for smokers who switch to HTPs, the limited number of studies restricts the strength of this conclusion. More research, including longer-term studies, is necessary to fully understand the potential benefits and risks of HTP use for COPD patients.

2.3.1.3.3 Braznell et al., (2023) What can current biomarker data tell us about the risks of lung cancer posed by heated tobacco products? Nicotine & Tobacco Research

The aim of this study, conducted by researchers at the University of Bath, United Kingdom, was to evaluate the existing biomarker data on heated tobacco products (HTPs) and determine its appropriateness in estimating the lung cancer risk posed by HTPs. The researchers also sought to identify the most appropriate data that provides insights into the potential lung cancer risk associated with HTPs. The study was supported by Bloomberg Philanthropies' Stopping Tobacco Organizations and Products, an initiative to prevent misleading advertising efforts.

The researchers previously conducted a systematic review of 40 interventional clinical trials on HTPs published between January 2010 and April 2022 ([Braznell et al., 2022](#)). The current study utilized the data generated from that systematic review, but focused on analyzing the effects of HTPs on biomarkers within cigarette smokers who switched to HTPs and compared them to those who continued smoking or quit.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 36 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The review identified various biomarkers measured in the HTP clinical trials, including biomarkers of exposure, endothelial dysfunction, inflammation, platelet function and coagulation, metabolic syndrome, oxidative stress, oral health, and respiratory health and function. These biomarkers were predominantly measured in urine and blood, except for those related to oral health, respiratory health and function, and sebum.

Out of the 82 biomarkers analyzed, the following 22 biomarkers were associated with tobacco use and lung cancer risk, dose-dependently correlated with smoking, and modifiable upon cessation: monohydroxybutenylmercapturic acid, 4-hydroxybutyl-2-mercapturic acid, 2-hydroxyethylmercapturic acid, nicotine, cotinine, nicotine equivalents, total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, endothelin-1, nitric oxide, high sensitivity C-reactive protein, white blood cell count, fibrinogen, soluble p-selectin, apolipoprotein A1, 4-Hydroxy-2-nonenal, 8-[epi/iso]-prostaglandin F2alpha, malondialdehyde, vitamin E, bleeding on probing, clinical attachment level, periodontal pocket depth, and spirometry measures. However, 4 of these biomarkers were not measured within an appropriate timeframe based on reversibility, and no results data were available for endothelin-1 or 4-Hydroxy-2-nonenal. Among the 16 biomarkers judged to be most appropriate for assessing lung cancer risk, only malondialdehyde and spirometry were measured in non-smokers exposed to HTPs.

The association between tobacco use and most biomarkers was significant, with a few exceptions such as S-benzyl mercapturic acid and blood pressure. Thirty-five biomarkers were associated with lung cancer risk, while the association for 20 biomarkers remained unclear due to insignificant or conflicting findings. However, there was no evidence of an association with lung cancer for 18 biomarkers.

Fifty-nine biomarkers showed a dose-dependent correlation with tobacco exposure, but 6 biomarkers had inconclusive results. Among the biomarkers measured, the effects of smoking on 54 biomarkers deviated from those observed following cessation. The time to deviation ranged from 12 hours to 15 years. Certain biomarkers, such as E-selectin, homocysteine, and soluble CD40 ligand, did not reverse upon cessation. The effects of cessation were unclear for three biomarkers, and time to deviation was uncertain for six biomarkers due to conflicting or insufficient results.

The appropriateness of existing biomarker data in assessing lung cancer risk of HTPs, both relative to cigarettes and their absolute risk, is limited. Furthermore, findings on the most appropriate biomarkers were conflicting across studies and largely showed no improvement following a switch to HTPs.

The authors concluded that the evaluation of existing biomarker data on HTPs indicates that much of the data is *“inadequate for determining the risk of lung cancer posed by HTPs.”* There is a lack of sufficient data on the absolute lung cancer risk of HTPs, which could be obtained by comparing HTP users to smokers who have quit or never smokers exposed to HTPs. The authors state the importance of *“careful consideration of biomarker selection and study design to ensure both are appropriate and will provide valuable data.”*

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS devices & HeatSticks</i>	Page 37 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.3.1.3.4 Majek et al., (2023) Acute health effects of heated tobacco products - comparative analysis with traditional cigarettes and electronic cigarettes in young adults, ERJ Open Research

This study compared the use of Heated Tobacco Products (HTPs) versus cigarettes or electronic cigarettes with regard to the acute health effects on the respiratory and cardiovascular systems during product use.

The study was open to young, healthy adults aged between 18 and 30 years residing in the Silesian voivodeship (regions) of Poland.

160 healthy young adults, of both sexes were recruited. The mean age was 23 years. Participants self-reported their smoking status and were then allocated into one of four groups according to whether they used HTPs, traditional cigarettes, e-cigarettes or were non-smokers.

Of the 160, 40 were HTP users (H-group), 40 were traditional cigarette smokers (T-group), 40 were e-cigarette users (E-group) and 40 were non-smokers (C-group).

Acute health effects on each group were assessed through measuring blood pressure, heart rate, O₂ saturation, the concentration of fractional exhaled nitric oxide (FeNO), carbon monoxide (CO), temperature of exhaled air, and spirometry. Each test was performed immediately after exposure to HTP (IQOS 2.4 device), cigarettes, e-cigarette, or simulated smoking (inhaling air through a paper tube the length of a conventional paper cigarette), and again 30 minutes later.

Immediately after 5 minutes of exposure, FeNO levels were observed to significantly decrease in the **HTP and e-cigarette groups**, from 12.8±5.5ppb to 11.2±5.3ppb and from 16.9±6.5 to 14.2±6.8, p<0.01; respectively. This was also observed to with traditional cigarettes. HTP use did not cause an increase in exhaled air temperature after 30 minutes, unlike cigarette or e-cigarette use (where exhaled air temperature went from 34.1[33.6;34.4]°C to 34.4[34.1;34.6]°C, p=0.02 and from 34.2 [33.9;34.5]°C to 34.4 [33.8;34.6]°C p<0.01; respectively). Carbon monoxide levels increased only after cigarette smoking. All groups using nicotine-containing products experienced a significant increase in heart rate and blood pressure.

The study concluded that the regular use of HTPs may increase the risk of chronic respiratory and cardiovascular diseases.

2.3.1.3.5 Bhat et al., (2023) Do alternative tobacco products induce less adverse respiratory risk than cigarettes? Respiratory Research

The objective of this study was to compare the effects of chronic inhalation of aerosols from electronic cigarettes (EC), HTP, and combustible cigarettes (CC) on lung inflammation responses and vaccine efficacy. Bhat et al., (2023) exposed mice to the aerosols for 8 weeks, and lung inflammation, damage, and oxidative stress were measured. Another group was exposed for 12 weeks, vaccinated and exposed to a bacterial respiratory infection. The effects of the aerosol exposure on antibody titers, bacterial clearance, and lung damage were assessed.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 38 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The results showed that both EC and HTP aerosols induced lung immune cell infiltrates comparable to CC. However, neutrophil numbers increased more with HTP and CC than with EC. All three products led to increased B cells, T cells, and pro-inflammatory IL17A+ T cells in the lungs. Lung antioxidant activity decreased, and epithelial/endothelial damage occurred with all products. Furthermore, EC and HTP impaired vaccination efficacy, but with CC resulting in the highest suppression of bacterial clearance.

The authors of the study put forward that chronic exposure to EC and HTP aerosols has the potential to induce pro-inflammatory lung conditions and damage lung tissues. Although CC smoke leads to more damage, the researchers highlight that exposure to alternative tobacco products is not risk-free. They hope that the study will encourage discussions among clinicians and users about the respiratory health consequences and immune-suppressive effects of alternative tobacco products.

In conclusion, the adverse respiratory effects of chronic HTP inhalation are often comparable to those of CC. Thus, the study underscores the need to carefully consider the potential risks of alternative tobacco products and their interplay with respiratory and immune system health.

2.3.1.3.6 Goebel et al., (2023) Impact of Heated Tobacco Products, E-Cigarettes, and Combustible Cigarettes on Small Airways and Arterial Stiffness. Toxics

Goebel et al., (2023) investigated the acute effects of two HTP (IQOS™ and glo™) on small airway function and arterial stiffness. They compared these products to combustible cigarettes, nicotine-free e-cigarettes, and a sham smoking group. The single-center, crossover study included 17 healthy occasional smokers who were students at the University of Lübeck. The participants were all over the age of 18 years. The order in which the test devices were used by each participant was determined by random selection. Each participant used every device once, and in order for their data to be included in the analysis, they had to assess all four devices (cigarettes, nicotine-free e-cigarettes, IQOS™ and glo™, and sham smoking). Sham smoking was tested in 7 out of the 17 participants and was also included in randomization.

The results of the study revealed that all of the tested products, including both cigarettes and substitute products, caused an increase in small airway obstruction and resistance. Additionally, all nicotine-containing products led to similar increases in blood pressure and arterial stiffness, indicating heightened cardiovascular stress.

The researchers concluded that HTP, notwithstanding their lower concentration of harmful substances compared to cigarettes, still have negative acute effects on small airway function and are associated with an increased risk of cardiovascular problems. Moreover, the study found that IQOS™ and glo™ had more pronounced impacts on small airway function compared to both cigarettes and nicotine-free e-cigarettes.

In light of these findings, the researchers suggest that alternative smoking cessation devices should aim to minimize harm as much as possible. They also stress the importance of

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 39 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

conducting further independent studies to gain a better understanding of the long-term health consequences associated with HTP.

2.3.1.3.7 Seo et al., (2023) Relationship between heated tobacco product use and allergic rhinitis in Korean adults. Tobacco Induced Diseases

This article examined the prevalence of respiratory and allergic diseases among Korean adults in relation to different types of tobacco use. Seo et al., (2023) utilized data from the Korea National Health and Nutrition Examination Survey, involving 18,230 adults over 19 years of age. Three groups were analyzed: current exclusive cigarette (CC) users, current exclusive HTP users, and dual users of CC and HTP. The majority of participants were female (55.7%) with a mean age of 47.80 ± 0.24 years. Among the participants, the prevalence rates were 15% for exclusive CC users (n=2740), 1% for exclusive HTP users (n=182), and 2.4% for dual users (n=435).

The study revealed that past tobacco users had a higher prevalence of chronic obstructive pulmonary disease (COPD) compared to non-users (AOR=2.37; 95% CI: 1.02–5.51). Furthermore, both past tobacco users and exclusive CC users had a higher prevalence of asthma compared to non-users (AOR=1.73; 95% CI: 1.26–2.38 and AOR=1.57; 95% CI: 1.08–2.26, respectively). The prevalence of allergic rhinitis was also higher among past tobacco users (AOR=1.33; 95% CI: 1.13–1.57), and exclusive HTP users had a higher prevalence of allergic rhinitis compared to non-users or exclusive CC users (AOR=1.60; 95% CI: 1.06–2.42 and AOR=1.74; 95% CI: 1.14–2.66, respectively). Current dual users and current exclusive HTP users had a higher prevalence of allergic rhinitis compared to current exclusive CC users (16% and 25.28% vs. 12.02%, respectively; $p=0.022$ and $p<0.001$). However, there were no significant differences in the prevalence of sinusitis and atopic dermatitis among the different tobacco use types. Current dual users had a higher prevalence of atopic dermatitis compared to current exclusive CC users (6.59% vs. 3.53%; $p=0.003$).

In conclusion, the study suggested that exclusive use of HTP was associated with allergic rhinitis in Korean adults. Further longitudinal studies are needed to gain a better understanding of the health risks associated with HTP. It is important to note that the study had some limitations, including its cross-sectional design, reliance on self-reported health information, and a relatively small number of HTP users. The study recommends future research to explore the specific components of HTP that may be related to allergic rhinitis and to conduct longitudinal studies to evaluate the overall health impact of HTP.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 40 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.3.1.4 Dental health

2.3.1.4.1 *Morishita et al., (2023) Effects of heated tobacco products and conventional cigarettes on dental implant wound healing: experimental research, Annals of Medicine and Surgery*

In this study by Morishita et al., conducted in Japan, the authors compared the effects of heated tobacco products (HTPs) and conventional cigarettes (CCs) on wound healing after dental implant placement to assess the role of HTPs in implant failure.

The researchers used L929 mouse fibroblast cells and a scratch wound-healing assay to evaluate the impact of cigarette smoke extract (CSE) obtained from CCs (Marlboro, Philip Morris) and from HTPs (Marlboro Heat Sticks Regular for IQOS, Philip Morris) on cell migration to the wound site. The L929 mouse fibroblast cells were exposed with 2.5% and 5% CSE from HTPs and CCs. The number of cells migrating to the wound site was counted after 12, 24, and 48 hours.

Gas chromatography-mass spectrometry analysis revealed that both CCs and HTPs had a nicotine concentration of 5 ppm in their CSE. The migration of L929 cells decreased after exposure to CSE from both test groups. At a concentration of 2.5% CSE, cell migration in the HTP group was significantly lower than that in the CC group at each time-point. Comparing the 2.5% CC and 2.5% HTP groups as well as the 5% CC and 5% HTP groups, there were significant differences in cell migration after 24 hours. The median cell migration number in the 2.5% CC sample was 334, whereas in the 2.5% HTP sample, it was 221. Similarly, the median cell migration number in the 5.0% CC sample was 213, compared to 257 in the 5.0% HTP sample.

The authors suggest that HTP use may be a risk factor for poor dental implant healing as HTPs may possess a toxic effect even at lower concentrations. Additionally, the authors refer to previous findings that cotinine, a major metabolite of nicotine, can impair the migration and adhesion of fibroblasts to tooth surfaces. The study further demonstrated that HTP had a more significant impact on fibroblast migration to wounds than cigarettes, even at lower concentrations.

The authors conclude that “HTPs may be a risk factor equivalent to CCs for dental implant treatment by inhibiting fibroblast migration to wounds.”

2.3.1.4.2 *Yatabe et al., (2023) Oral-malodor measurement and intention to quit smoking in men: A before-after study; Tobacco Induced Diseases*

In a retrospective, uncontrolled, before-after study conducted in 2019 and 2020, Yatabe et al. (2023) examined the effect of oral malodor measurements on the motivation to quit smoking. Smokers were invited to a workplace health event at the Japan Grand Self-Defense Force where they attended seminars on oral health and smoking cessation aids. Participants (n=241) were male smokers aged 20–54 years with an average age of 33.2 years. 39 participants (16.2%)

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 41 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

were exclusive HTP users, 33 participants (13.7%) were dual cigarette and HTP users, while the remaining 169 participants (70.1%) were exclusive cigarette users. All participants underwent respiratory function tests and oral malodor measurements. The intention to quit smoking was evaluated using questionnaires administered before and after the event.

The results showed that before the event, 8.7% of smokers intended to quit in the next month, 17.0% intended to quit in the next six months, and 74.3% had no intention to quit. After the event, the respective percentages were 17.8%, 26.6%, and 55.6%. The study found that smokers with higher concentrations of methyl mercaptan were more likely to intend to quit in the next month. Those with higher daily tobacco consumption were less likely to intend to quit in the next six months. The study also discussed the relationship between oral malodor, xerostomia (dry mouth), and tobacco smoking. It suggested that social and disease risk information may strongly motivate smoking cessation. It also mentioned the need for comprehensive measurements of halitosis components to motivate more smokers to quit. Overall, the study found that interventions using dental health effects and respiratory function assessments were effective in motivating smoking cessation in men, including users of HTP. The effect was specifically observed in smokers with higher concentrations of methyl mercaptan. However, the study had limitations such as a small sample size and the inclusion of male participants only.

2.3.1.4.3 Abdulla et al., (2023) Smoke and mirrors – does smoking cause discolouration of composite restorations? Evidence-Based Dentistry

This systematic review analyzed in vitro studies on the color stability of resin-based composites (RBCs) exposed to combustible cigarette smoke (CS), tobacco heating systems (THS), and electronic nicotine delivery systems (ENDS). Thirteen studies met the inclusion criteria, with CS being analyzed in all studies, ENDS in four studies, and THS in two studies. The review found that CS caused irreversible discoloration of RBCs, while ENDS and THS caused less color change, which could be reversed with repolishing or bleaching procedures. However, the evidence for ENDS and THS was limited. The authors concluded that further research is needed to understand the long-term effects of CS, ENDS, and THS on RBC discoloration.

In terms of commentary, the authors noted that THS heats tobacco at a lower temperature than combustible cigarettes, while ENDS heat a liquid containing nicotine but not tobacco. The authors highlighted the prevalence of smoking and the popularity of composite resin restorations in dental practice, making this systematic review relevant. However, they acknowledged limitations such as the inclusion of only English-language studies and the high variability in methodology among the included studies. The authors suggested evaluating these findings against patient-reported outcomes of RBC discoloration and conducting further research to understand the effects of CS, THS, and ENDS on RBC color stability.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 42 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.3.1.4.4 Sever et al., (2023) Impact of the Tobacco Heating System and Cigarette Smoking on the Oral Cavity: A Pilot Study. Dentistry Journal (Basel)

In a study conducted by Sever et al. (2023), the effects of combustible cigarettes and a new alternative tobacco heating system (THS) on oral health were examined. This stratified cross-sectional study involved a total of 60 participants aged between 20 and 56 years, recruited from the Clinic of Dental Medicine, Clinical Hospital Center, Rijeka, Croatia, and the Faculty of Dental Medicine in Rijeka, Croatia. The participants were divided into three groups, namely THS smokers (n=20), combustible cigarette smokers (n=20), and non-smokers (n=20), with approximately 85% of them being female.

During the study, the participants completed questionnaires regarding their medical information, smoking habits, oral lesions, and symptoms. They also underwent a clinical examination, salivary flow rate (SFR) test, and an organoleptic assessment of bad breath. Additionally, mucosal swabs were collected to detect the presence of *Candida* spp.

The results indicate that there were significant differences observed between the smoking groups in relation to bad breath, intraoral findings, SFR, and dry mouth. The SFR was significantly lower among smokers compared to non-smokers. Both combustible cigarette smokers and THS smokers reported a higher prevalence of dry mouth compared to non-smokers. However, there were no significant differences observed between THS and combustible cigarette smokers in terms of these oral health outcomes. Additionally, the study found significant differences in subjective, self-reported symptoms between the groups, with combustible smokers and THS smokers reporting dry mouth most frequently. The prevalence of intraoral findings, such as halitosis, was similar in both smoking groups but not present in non-smokers. Oral lesions, including atrophy, inflammation, erosion, mortification, or coated tongue/lingua villosa, were observed in all three groups without significant differences between them. It is worth noting that the presence of oral candidiasis and burning sensation was only observed in a small number of patients and could not be analyzed for significant differences among the groups.

Overall, the study suggests that THS smoking has similar effects on oral health, particularly SFR and bad breath, as combustible cigarette smoking. The study acknowledges the need for more research on the effects of THS products on oral health due to their increasing use, especially among younger populations.

2.3.1.4.5 Gupta et al. (2024) E-cigarettes and heated tobacco products impact on dental color parameters. Heliyon

Gupta et al. (2024) evaluated and compared dental color parameters among five different groups in Italy: current cigarette smokers, former smokers, never smokers, exclusive users of electronic cigarettes, and exclusive users of HTP. The focus of this independent study was to determine if tar-free nicotine delivery technologies have cosmetic benefits in terms of dental appearance.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 43 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

A cross-sectional study was conducted, recruiting a total of 89 subjects from the different groups. The mean age of the participants was 34.39 ± 10.4 years, with 34 of them being female. The groups consisted of 18 current smokers, 18 former smokers, 20 never smokers, 15 HTPs users, and 18 e-cigarette users. The smoking status was confirmed objectively by assessing eCO levels (>7 parts per million [ppm], indicative of smoking status). Participants were requested to abstain from smoking cigarettes for a minimum of 2 h before the eCO measurements.

Dental color assessment was performed using digital spectrophotometry, which measured International Commission on Illumination (CIE) $L^*a^*b^*$ color parameters and calculated Whiteness Index for Dentistry (WID) values. L^* represents the lightness of the teeth, ranging from 0 (black) to 100 (white). The a^* and b^* values indicate the chromaticity measures for green/red and blue/yellow, respectively. To obtain the overall CIE $L^*a^*b^*$ scores for each subject, the individual values of all examined anterior teeth were summed and divided by the number of teeth examined. Data analysis involved comparisons, regression analyses, and ANCOVA.

The study found a significant difference in dental whiteness among different smoking groups. Current smokers had lower dental whiteness (13.38 WID units) compared to both never smokers (19.96 WID units) and former smokers (16.79 WID units). ECs and HTPs users, on the other hand, had notably higher WID values than current smokers, 16.72 WID units and 17.82 WID units respectively indicating better dental whiteness. The visual difference in dental whiteness between e-cigarettes and HTPs users and smokers was noticeable, with a difference of more than 2.90 units. Delta E values also indicated visible color differences, with smokers showing more pronounced effects. Age, gender, and toothbrushing frequency were found to influence dental color measurements.

In conclusion, the exclusive use of e-cigarettes and HTP was associated with improved dental color measurements compared to current smoking, suggesting that tar-free nicotine delivery technologies do not negatively affect dental appearance. The authors suggest the study implies potential cosmetic advantages for smokers, emphasizing the significance of dental aesthetics as a motivational factor for quitting smoking.

2.3.1.4.6 Majid. (2024) How far does feedback on oral malodor assessment influence the decision to quit smoking? Evidence-Based Dentistry

Majid (2024) investigated the influence of feedback on oral malodor assessment on the decision to quit smoking among male smokers aged 20-54 years. The research aimed to assess the relationship between oral malodor measurements and intention to quit smoking, as well as the impact of oral malodor measurements as feedback on motivation for smoking cessation. A total of 241 male smokers participated in a one-day smoking cessation event at their workplace. Among the participants, 70.1% were exclusive cigarette smokers, 16.2% used HTP exclusively, and 13.7% used both cigarettes and HTP.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 44 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

Before and after the event, participants completed a questionnaire to evaluate their smoking cessation intentions, categorizing them as planning to quit within the next month, within the next 6 months, or having no intention to quit. Prior to the event, 8.7% of smokers expressed an intention to quit within the next month, while after the event, this percentage increased to 17.8%. Additionally, individuals with higher daily tobacco consumption (15 or more pieces) were less likely to have an intention to quit smoking within the next 6 months (AOR=0.37, 95% CI: 0.15–0.92, $p=0.032$).

The study revealed that levels of methyl mercaptan concentration in the oral cavity air were significantly associated with a greater likelihood of intending to quit smoking within the next month (AOR=4.24, 95% CI: 1.52–11.84; $p=0.006$).

The authors conclude that the findings highlight the potential of using oral malodor measurements as a motivational tool for quitting smoking.

2.3.1.4.7 Mišković et al. (2024) Periodontal Health Status in Adults Exposed to Tobacco Heating System Aerosol and Cigarette Smoke vs. Non-Smokers: A Cross-Sectional Study. Dentistry Journal

Mišković et al. (2024) conducted an independent study between June 2022 and June 2023 at the Clinic of Dentistry in Rijeka, Croatia. The aim of the study was to investigate the impact of aerosol from HTP compared to combustible cigarette smoke on periodontal tissue in adult smokers. The study included 66 subjects aged 26-56, who were divided into three groups: non-smokers, combustible cigarette smokers, and HTP (*IQOS*) users. The primary research parameters were probing depth and clinical attachment loss (CAL).

The study showed that *IQOS* users generally had lower values of periodontal indices compared to cigarette smokers, but only the CAL parameter showed a significant difference between the two groups ($p=0.011$). Logistic regression analysis indicated that cigarette smoking was the sole predictor of periodontitis, with an odds ratio of 4.7 ($p=0.027$). Cigarette smokers had the highest probing depth and CAL values compared to non-smokers, with a significant difference ($p\leq 0.002$). The Full Mouth Bleeding Score results highlighted a higher prevalence of gum bleeding in cigarette smokers and the least in *IQOS* users. Despite this, *IQOS* users still exhibited worse periodontal conditions than non-smokers, although this difference did not reach statistical significance.

In conclusion, the research suggests that using HTP with nicotine-containing aerosol has a lower impact on periodontal tissues compared to burning tobacco in combustible cigarettes. However, HTP use still has negative effects on the periodontium. The authors highlight the importance for HTP users to prioritize proper oral health care and be aware of the potential risks, despite the reduced harm compared to combustible cigarettes.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 45 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.3.1.5 Neurological conditions

2.3.1.5.1 *Kim et al., (2023) Factors associated with Korean adolescent's e-cigarette use by the severity level of generalized anxiety disorder (GAD-7); Journal of Affective Disorders*

Utilizing a cross-sectional secondary dataset retrieved from the 2020 Korea Youth Risk Behavior Survey, Kim et al. (2023) investigated the correlation between the use of e-cigarettes and anxiety among adolescents aged 13 to 18 years. Of the total sample of 54,948 respondents, four anxiety groups were formed: minimal (score 0-4; n=36,711), mild (score 5-9; n=12,138), moderate (score 10-14; n=4,143), and severe (score above 15; n=1,965).

The total sample consisted of 51.6% male students and 48.4% female students, with 53.1% attending middle school, 37.8% in academic high school, and 9.1% in vocational high school. The overall prevalence of e-cigarette use among Korean adolescents was 2.2% with the average number of smoking days being 2.06 (SD = 1.85) in the whole study population.

The results showed that the prevalence of e-cigarette use increased with the severity of anxiety from minimal to severe levels. While cigarette use was linked to e-cigarette usage in all anxiety groups, individuals with minimal or mild anxiety exhibited a stronger influence from factors such as tobacco accessibility, sexual activity, alcohol consumption, and smartphone addiction. Furthermore, secondhand smoke exposure was a noteworthy factor in all anxiety groups, except for those with moderate anxiety. The authors suggest that future research should first develop reliable and validated intensity measures of e-cigarette use to determine the real differences in e-cigarette usage among anxiety groups. The study had several limitations, such as not being able to examine causal or longitudinal associations between variables, not including drug use as a covariate, and having a small sample size for each anxiety group. Furthermore, vaping is often described as using either HTPs or e-cigarette in Korea, therefore the results from this study do not distinguish between e-cigarette use and HTP use.

2.3.2 Biomarkers of exposure and biomarkers of potential harm

2.3.2.1 *Yingst et al., (2023) Nicotine delivery of a menthol-flavored heat-not-burn tobacco product during directed use; Nicotine and Tobacco*

The recent ban on menthol flavored cigarettes by the FDA raises the question of whether menthol smokers, who can no longer access menthol cigarettes, would consider menthol HTPs, such as IQOS, as an acceptable and potentially less harmful alternative. To answer this, Yingst et al. (2023) aimed to evaluate the nicotine delivery profile and subjective effects associated with naïve IQOS use among current menthol cigarette smokers.

This independent clinical study involved 8 participants with a mean age of 43.9 years. The majority of participants were female (63%) and White (88%). All participants smoked menthol cigarettes at the start, averaging 17.1 cigarettes per day. Baseline measurements showed a mean

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 46 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

exhaled CO of 9.5ppm and a mean blood nicotine level of 1.29 ng/mL, confirming nicotine abstinence prior to the study. During the study, participants were provided an IQOS device and menthol *heatstick* to puff every 20 seconds for a total of 14 puffs after a 14-hour nicotine abstinence period. A puffing protocol designed to mimic cigarette smoking patterns was utilized. Blood was drawn during and after IQOS use at 1, 2, 4, 6, 8, 10, 12, and 15 minutes after the first puff.

After using IQOS, participants experienced a maximum nicotine concentration of 17.25 ng/mL, with a mean nicotine boost of 15.96 ng/mL. The time to reach maximal concentration averaged 5.25 minutes. Exhaled CO did not increase significantly after IQOS use. Participants reported a reduction in total withdrawal score, as well as decreases in specific nicotine-related withdrawal symptoms such as anger, depressed mood/sadness, restlessness, and craving to smoke. Most participants (62.5%) reported no side effects, but for those who did report side effects, dry mouth, throat irritation, dizziness, and headache were mentioned.

Participants found IQOS use to be moderately satisfying, rewarding, and relieving, with no aversive feelings. The satisfaction and reward scores were not significantly correlated with the nicotine boost. When comparing own brand cigarettes with IQOS, there were no significant differences in satisfaction and reward ratings. However, participants rated their own cigarettes as more aversive compared to IQOS. With the ban of menthol in cigarettes, the authors discuss that some menthol smokers may quit smoking, however, others could switch to non-menthol available tobacco products, therefore acceptable cigarette alternatives, like IQOS, could help promote smokers to switch to a less harmful alternative.

2.3.2.2 Yach and Scherer (2023) Applications of biomarkers of exposure and biological effects in users of new generation tobacco and nicotine products: Tentative proposals; Journal of Analytical Toxicology

In this perspective paper, Yach and Scherer (2023) discuss how the use of biomarkers could be applied to support epidemiological research and maximize understanding of the benefits of tobacco harm reduction. The authors acknowledge the scientific contribution to the paper by a principal scientist at British American Tobacco.

Biomarkers enable researchers and regulators to determine the level of exposure to harmful components in new generation tobacco and nicotine products (NGPs). By measuring biomarkers of exposure (BOE), such as exhaled carbon monoxide, cotinine, and N-[2-cyanoethyl]valine, as well as biomarkers of potential harm, termed biomarkers of biological effect (BOBE) in this paper, it becomes possible to evaluate the reduction in exposure to harmful substances compared to combustible cigarettes. Biomarkers also play a crucial role in supplementing epidemiological research by providing objective measures of exposure and biological effects. Unlike self-reported data, biomarkers offer a quantitative and qualitative assessment of tobacco product use, allowing for more accurate comparisons between different user groups. By utilizing verified biomarkers, it becomes possible to detect the positive effects of NGPs more quickly. This has significant implications for public health interventions and

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 47 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

policy-making, as timely and accurate data on harm reduction can inform regulatory decisions and facilitate the transition from combustible cigarettes to less harmful alternatives.

The authors propose that if BOBE can be verified, they could be used to assess the effects of NGPs earlier than classic endpoints such as morbidity and mortality.

The authors suggest that significant further work on BOBE is required before they are able to be used as surrogate endpoints for disease. They stress the importance of expanding and disseminating the existing progress made in developing and validating biomarkers to the broader health and medical community. They propose subsequent discussions and consensus on the most relevant biomarkers for epidemiological research, as well as the establishment of guidelines for their usage. This way, they believe biomarkers can serve as objective tools for assessing tobacco harm reduction and informing public health interventions and regulatory decisions.

2.3.2.3 Li et al., (2023) Comparison of Biomarkers of Exposure in a Controlled Study of Smokers Switched from Conventional Cigarettes to Heated Tobacco Products. Toxics

Li et al. (2023) conducted a study to examine the changes in biomarkers of exposure when individuals switched from smoking combustible cigarettes (CC) to HTP. The study involved a total of 224 smokers aged 20-65 years from four cities in China. The participants were required to have a smoking habit of consuming 5-20 cigarettes with ISO tar yield of 10-12 mg and a nicotine level of 1.0 mg per day for at least 2 years. Additionally, they should have been smoking the same brand for more than 6 months. Urine samples were collected for the purpose of biomarker analysis, and a total of nine biomarkers, including tobacco-specific nitrosamines (TSNAs), volatile organic compounds (VOCs), acrolein, and crotonaldehyde, were measured using UPLC-MS/MS.

The results revealed that individuals who smoked HTP had significantly lower levels of biomarkers in urine samples compared to those who smoked CCs. The sum of the nine biomarkers in CCs was found to be 5.4 and 5.2 times higher than in Original-HTP and Menthol-HTP, respectively. Among the nine biomarkers, 3HPMA and 3HMPMA accounted for the highest proportions. After switching to HTP, the content of all biomarkers decreased significantly, especially the three VOCs. The changes in biomarker levels in urine samples were similar for both men and women who switched from CCs to HTP. The study also observed that subjects aged 20-39 years experienced the greatest reduction in biomarker residues in urine, while those over 60 years had the least reduction. Furthermore, the reduction in biomarker residues was more pronounced in subjects who switched to Original-HTP compared to Menthol-HTP.

In conclusion, this study provides evidence that switching from CCs to HTP leads to significantly lower exposure to harmful substances, as demonstrated by biomarker analysis of urine samples. The findings indicate that both men and women experience similar changes in biomarker levels after making the switch. Moreover, younger subjects benefit more from

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 48 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

reduced biomarker residues compared to older subjects. These results emphasize the importance of further research on the health risks associated with HTP in China.

2.3.2.4 [Harada et al., \(2023\) Metabolomics profiles alterations in cigarette smokers and heated tobacco product users. BMC Pediatrics](#)

Harada et al., (2023) presents the results of a study that aimed to identify plasma metabolites associated with smoking and HTP use in a large Japanese population for improved health risk assessment. The study analyzed metabolomics data from 9,922 participants to determine the association between smoking habits and plasma metabolites, and 3,334 participants from a follow-up survey to examine alterations in smoking-related metabolites among HTP users.

The study found that cigarette smokers had distinct metabolomics profiles compared to never smokers, with 22 polar metabolites identified as candidate biomarkers for smoking. The metabolomics profiles of HTP users were closer to those of cigarette smokers than never smokers. The concentration of glutamate was higher in cigarette smokers, and biomarkers involved in glutamate metabolism were associated with both cigarette smoking and HTP use. Network pathway analysis suggested that smoking and HTP use were associated with the glutamate pathway, which could lead to endothelial dysfunction and atherosclerosis of the vessels.

The authors conclude that the glutamate pathway is affected by habitual smoking and may partly explain the mechanism by which cigarette smoking causes cardiovascular disease. They suggest that HTP use may also contribute to the development of cardiovascular disease through similar mechanisms. The study found strong associations between smoking habits, plasma metabolites, and the glutamate pathway. The authors highlight the need for further research to examine the long-term effects of HTP use and its relationship with cardiovascular disease outcomes.

2.3.2.5 [Nishihara et al., \(2024\) A Randomized Control Study in Healthy Adult Smokers to Assess Reduced Exposure to Selected Cigarette Smoke Constituents in Switching to the Novel Heated Tobacco Product DT3.0a. Clinical Pharmacology in Drug Development](#)

Nishihara et al. (2024) aimed to determine the impact of switching to a new heated tobacco product (direct heating tobacco system, platform 3, generation 3, version a [DT3.0a]) on the exposure to harmful cigarette smoke constituents in healthy adult smokers. This was done through a randomized, controlled, open-label, confinement study carried out at two clinics in Fukuoka, Japan. The study included 60 nonmenthol and 30 menthol cigarette smokers between the ages of 21 and 65, who were randomly assigned to different groups. Participants were instructed to either switch to HTP, continue smoking their regular cigarettes, or quit smoking altogether. Over a period of 5 days, the study assessed the participants' exposure to harmful substances, nicotine levels, and subjective effects.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 49 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The study yielded significant results, demonstrating that both the groups using HTP and those who switched to the menthol variant experienced substantial reductions in harmful substance exposure compared to those who continued smoking. In terms of cigarette consumption, participants in the CC and mCC groups maintained $\pm 10\%$ of their self-reported daily cigarette consumption as required by the protocol, with mean values ranging from 12.9 to 13.3 cigarettes/day and 13.8 to 14.2 cigarettes/day, respectively. Over a period of 5 days, the use of HTP remained relatively consistent, with a percentage change (from Day 1 to Day 5) of 11.9%, 9.2%, and -0.4% for the DT3.0a, THS, and mDT3.0a groups, respectively. These reduction rates were comparable to those observed in the group that completely quit smoking.

Regarding nicotine levels, there were no significant differences between HTP, combustible cigarettes, and the menthol variant, except for the time it took to reach peak nicotine levels in the group using the menthol variant. Participants also reported generally stable or decreased subjective effects when using HTP. The study found no safety concerns associated with the short-term use of HTP. Furthermore, no notable differences were identified between the nonmenthol and menthol flavors of HTP.

However, there are some limitations to this study. The duration of the study was short, and the participants were confined to a certain setting. This raises questions about how these products would be used in the real world and what flavors people would choose. In conclusion, switching to HTP resulted in significant reductions in harmful substance exposure, and there were no notable differences between the different flavors of the product. Further research is needed to evaluate long-term effects and the impact on smoking-related diseases.

[2.3.2.6 Zięba et al., \(2024\) Impact of Smoking on Salivary Lipid Profile and Oxidative Stress in Young Adults: A Comparative Analysis between Traditional Cigarettes, E-Cigarettes, and Heat-Not-Burn Products. Medical Science Monitor](#)

Zięba et al., (2024) examined the effects of smoking combustible cigarettes, e-cigarettes, and heat-not-burn products on the levels of salivary lipids and lipid peroxidation products in young adults who have been smoking for up to 3 years. The researchers compared three groups of 25 smoking patients each to a control group that was similar in terms of age, gender, and oral health. They collected saliva samples from all participants and analyzed them for sphingolipids, ceramides, malondialdehyde (MDA), and 4-hydroxynonenal (4-HNE).

The results showed that all forms of smoking led to a decrease in salivary lipids and an increase in the concentration of MDA and 4-HNE, indicating elevated oxidative stress. Although, it was only in the combustible cigarette users' group versus the control group that this result was statistically significant. This oxidative stress may disrupt the lipid balance in the oral cavity and cause damage to cell membranes. Notably, a decrease in sphingolipids in the saliva of smokers was linked to ongoing issues within the salivary glands, likely caused by toxins in cigarette smoke damaging DNA. The study highlights the importance of sphingolipids in maintaining oral health and emphasizes the negative effects of smoking on the oral environment, which may lead to long-term complications.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 50 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The authors stress the need for further research, particularly focusing on the impact of modern nicotine delivery devices like e-cigarettes and heat-not-burn products.

2.3.2.7 Takagi et al. (2024) Plasma Oxidative State Induced by Exercise in Young Heat-Not-Burn Cigarette Users. *Nicotine & Tobacco Research*

Independent researchers, Takagi et al., (2024) investigated resting and exercise-induced oxidative states in 30 male HTP users, never-smokers, and combustible cigarette (CC) users aged 20-29 years. To ensure the accuracy and validity of the experiment, individuals who exercised daily were excluded from the study, to avoid the confounding effects of regular exercise on oxidative state distorting the study results. Blood samples were collected from each group before and after exercise, and plasma hydroperoxide concentration (a marker of oxidative state) was measured. Participants followed specific protocols, including refraining from smoking cigarettes for 12 hours before the study to avoid the acute effects of smoking on oxidative state.

The results showed that exercise significantly increased plasma hydroperoxide concentration in all participants. Prior to exercise, there were no significant differences in plasma hydroperoxide concentrations between never-smokers, HTP users, and CC users. Following exercise, HTP users exhibited a significantly higher oxidative state compared to never-smokers ($p < 0.005$), indicating a potential risk of acute oxidative damage associated with HTP use. Conversely, HTP users had a significantly lower exercise-induced oxidative state compared to CC smokers ($p < 0.01$). The authors suggest the results indicate HTP use may increase the risk of acute oxidative damage in users compared to never-smokers, but to a lesser extent than CCs.

2.3.2.8 Yamada et al. (2024) Status of home-based second-hand smoke exposure among children and its association with health risks in Japan. *Preventive medicine reports*

Yamada et al. (2024) examined the prevalence of second-hand smoke (SHS) exposure among children under 5 years old in Japan, with a specific focus on the use of HTP and e-cigarettes within households. The study also examined maternal attitudes towards avoiding SHS exposure in children and its association with health risks.

The study utilized a cross-sectional questionnaire-survey, which was administered to 379 mothers raising children under 5 years of age. The findings of the study showed that 31.1% of the surveyed children were exposed to SHS. HTP and e-cigarettes used by mothers or family members were the sources of SHS exposure for 74.2% and 67.0% of the children, respectively. Among the surveyed mothers, 8.2% were daily smokers, and 28.8% of family members were daily smokers. In terms of smoking products, 51.6% of smoking mothers used combustible cigarettes, while 64.5% used HTP, and 9.7% used e-cigarettes.

The most common locations for smoking combustible cigarettes among mothers and family members were the "garden or balcony" (68.8% and 66.1%, respectively), followed by "in the car" (31.2% and 17.9%) and "in the kitchen" (25.0% and 23.2%).

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 51 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

For HTP and e-cigarettes, the most common locations were "in the kitchen" for mothers (56.5%) and family members (39.7%), and "in the car" for mothers (21.7%) and family members (17.8%). Additionally, 8.7% of mothers and 8.2% of family members reported smoking HTPs or e-cigarettes "anywhere at home".

Maternal perceptions played a role in determining the health risks associated with SHS exposure in children, especially among smoking mothers. Children living with smokers at home were more likely to experience respiratory diseases, otitis media, and dental caries ($p=0.049$, $p=0.008$, and $p=0.001$, respectively). Significant differences were found in maternal perceptions of child SHS exposure between smokers and non-smokers ($p<0.05$).

The study emphasized the increasing prevalence of HTP and e-cigarettes in homes, driven by the desire to avoid the odor and air pollution associated with combustible cigarettes. However, individuals using HTP and e-cigarettes were found to be less motivated to quit smoking compared to exclusive smokers, highlighting the need for smoking cessation support. The findings also revealed differences in maternal attitudes between smoking and non-smoking mothers concerning protecting their children from SHS exposure, with non-smoking mothers showing more concern.

While the study had limitations, including its cross-sectional design and reliance on self-reported data, the researchers recommend conducting future longitudinal cohort studies and nationally representative surveys to further strengthen the findings.

2.3.3 Abuse liability

2.3.3.1 [McDermott et al., \(2023\) An assessment of nicotine pharmacokinetics and subjective effects of the pulze heated tobacco system compared with cigarettes; Scientific Reports](#)

McDermott et al. (2023) conducted an open-label, randomized, crossover study in 24 healthy adult smokers to assess the nicotine pharmacokinetics and subjective effects of the Pulze HTP and three consumables (iD sticks: Intense, Regular, and Menthol) compared with the participants usual brand cigarettes. The study was funded, designed, and conducted by Imperial Brands PLC.

Blood samples were collected 5 min prior to initiating product use and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 120, and 240 min following the start of study product use and analyzed using mass spectrometry to determine plasma nicotine concentrations, with a minimum quantifiable limit of 0.2 ng/ml. For subjective assessments, an Intent to Use visual analogue scale (VAS), Urge to Smoke VAS and Product Evaluation Scale (7-point scale) were completed at pre-defined time-points. Subjects were asked to use the product according to a fixed regimen (30 sec intervals between puffs, and 3 sec puff duration).

The maximum concentration (C_{max}) and total exposure (AUC_t) levels were found to be highest for usual brand cigarettes (20.07 ng/mL and 1501 ng*min/mL, respectively) and significantly

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 52 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

lower for each variant of Pulze (Intense= 5.821 ng/mL and 763.1 ng*min/mL; Regular= 5.508 ng/mL and 570.8 ng*min/mL; Menthol= 7.179 ng/mL and 590.3 ng*min/mL). When comparing the Intense to Regular variants, both C_{max} and AUC_t were significantly higher, while AUC_t was also significantly higher for Intense compared to Menthol.

The median time to reach maximum concentration (T_{max}) was lowest for the participants' usual brand cigarettes (6.250 min), indicating faster nicotine delivery, and similar across the iD stick variants, with no statistically significant between-product differences (Regular=7.084 min, Menthol=6.942 min, Intense=6.000 min).

All study products reduced smoking urges, with cigarettes having the greatest effect, although this difference was not statistically significant. Evaluation scores for each Pulze variant in terms of 'satisfaction,' 'psychological reward,' and 'relief' were similar and lower than those for usual brand cigarettes. These findings demonstrate that Pulze effectively delivers nicotine and produces positive subjective effects, including satisfaction and reduced urge to smoke. The authors conclude that Pulze may serve as “an acceptable alternative to cigarettes for adult smokers while having a lower abuse liability than cigarettes”.

2.3.3.2 Vukas et al., (2023) Two Different Heated Tobacco Products vs. Cigarettes: Comparison of Nicotine Delivery and Subjective Effects in Experienced Users; Toxics

In this three-arm crossover study, Vukas et al. (2023) aimed to characterize the potential of two different HTPs (IQOS 3 DUO with HEETS Amber and glo with neo Tobacco Bright) to deliver nicotine and satisfy cravings compared with conventional cigarettes (Marlboro Red) in users who had already switched to HTPs.

Fifteen individuals who were active users of HTPs (non exclusive users of HTPs) consumed the study products according to a predetermined puffing protocol (10 puffs, 3 s puff duration, 30 s puff interval). Blood samples were drawn at predetermined time points and nicotine, cotinine, and trans-3'-hydroxycotinine levels were determined using LC-MS/MS. PK parameters were also calculated and the subjective effects of consumption evaluated.

The nicotine delivery after consumption of both HTPs was not statistically different, with a slightly lower AUC and C_{max} after use of glo HTP. Cigarette consumption led to a statistically significantly higher level of nicotine delivery ($p < 0.005$). The QSU-G assessed changes in smoking urges before and after consumption of cigarettes and HTPs. The results showed significant decreases ($p < 0.05$) after using all study products in factors 1 and 2, which summarize positive and negative reinforcement factors, respectively. However, the differences in reduction levels between the three products were not statistically significant ($p = 0.119$), indicating that all products had a similar effect on reducing smoking urges. Participants reported low levels of side effects, including drowsiness, mouth irritation, throat irritation, and dizziness.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 53 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The authors conclude that “*HTPs do not necessarily need high nicotine deliveries with high addictive potential, as are characteristic of tobacco cigarettes.*”

2.3.4 Methodology, consensus statements, guidelines

2.3.4.1 [Gowda et al., \(2023\) Does India's ban on electronic cigarettes improve public health outcomes? Indian Public Policy Review](#)

This review of an Indian Public Policy looked at the 2019 ban on Electronic Nicotine Delivery Systems (ENDS) in India. ENDS is a broad category comprising electronic cigarettes, vaping devices and heated tobacco products (HTPs).

The 2019 ban was passed as a result of political concern regarding the impact to health, the susceptibility of youth to the marketing and presence of ENDS and the potential of ENDS devices to undermine national tobacco control efforts aimed at improving public health outcomes.

The review included a risk analysis to assess whether the ban would be likely to improve public health outcomes, or whether regulation of ENDS would be a more appropriate approach and looked at the approaches of countries such as the United Kingdom and United States who have different regulatory approaches to these devices as opposed to a blanket ban.

The review recommended that HTPs should be removed from the blanket ENDS ban. The researchers propose that HTPs are instead incorporated within the Cigarettes and Other Tobacco Products Act on the basis that they are tobacco-based, with the aim of encouraging conventional cigarette smokers to switch to the less harmful HTPs, to help reduce the harm to smokers who would otherwise continue, and to provide a device that wean users off nicotine dependence, should they wish to quit.

The authors proposed that making the sale of HTPs to minors (directly or by proxy, and face-to-face or online), a criminal offence would prevent youth uptake of these devices. It would also be appropriate to enforce quality standards for devices, to prevent modification or the adding of illicit additives.

The review argued that the ban may have triggered underground, unregulated markets for ENDS devices that could potentially lead to the purchase of dangerous products, that it prevents the development and evolution of products that could offer smokers a less harmful way of consuming nicotine that may help them to stop using nicotine altogether in the future and that not providing an alternative was likely to encourage youth to experiment with using standard tobacco rather than a less harmful product. The ban also denies the Indian government of legitimate tax revenue and is the result of government interference with its citizens' freedom of choice.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 54 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.3.4.2 Koh et al., (2023) The relationship between heated cigarette smoking and blood white blood cell count: a population-based cross-sectional study, Public Health

In this independent cross-sectional, population-based study, Koh et al. (2023) examined the relationship between cigarette smoking and white blood cell (WBC) count using nationally representative health data from the Korea National Health and Nutrition Examination Survey. The study focused on 9,747 individuals aged 20-79 years, who were divided into four categories of smoking status: non-smokers (n=6,490), ex-smokers (n=1,999), HTP users (n=76), and conventional cigarette smokers (n=1,182).

The results revealed that conventional cigarette smoking led to elevated WBC counts, indicative of increased inflammation. Although HTP use showed no significant increase in WBC count compared to non-smokers, a potential dose-related response was seen in conventional cigarette smokers and HTP users. The authors suggest these results may imply that although HTPs induce less inflammation than conventional cigarette smoking, they may affect WBC count in a dose-response manner. However, they acknowledge further research is needed in this area.

2.3.4.3 Moscone et al., (2023) Does switching from tobacco to reduced-risk products free up hospital resources? British Journal of Healthcare Management

Moscone et al. (2023) examined the potential advantages of shifting from traditional tobacco smoking to reduced-risk alternatives, including vaping and heat-not-burn tobacco products, within the context of ongoing global issues related to tobacco-related mortality. Their research unveiled a notable reduction in the prevalence of smoking among English adults, a shift partly attributed to the growing popularity of vaping and heat-not-burn alternatives, particularly among individuals aged 16-24 years. However, the study also unveiled significant regional differences in smoking rates and hospital admissions for lung cancer, with notable implications for healthcare expenditures. The study emphasized the potential for substantial cost savings, ranging from 2.5% to 13.0% of healthcare spending, through the encouragement of smokers to transition to reduced-risk options. This potential cost reduction is particularly pertinent for regions with elevated admission rates for lung cancer, such as the north-east and Yorkshire. These findings underscore the significance of considering regional variations in the broader strategy to reduce the impact of tobacco smoking in England and work towards the 2030 goal of becoming smoke-free.

2.3.4.4 Udhaya et al. (2024) Warning on every puff: Learning from Canada's innovative tobacco control strategy. Oral oncology reports

Udhaya et al., (2024) conducted an independent examination of Canada's tobacco control strategy and its potential applicability to India. The researchers focused on the benefits that India could derive from adopting some of the tobacco control policies implemented in Canada.

Canada pioneered implementing pictorial warnings on cigarette packages. They have mandated that at least 75% of the display surface of the cigarette pack must be covered by

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 55 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

health pictorial warning labels. The authors highlight this approach as a valuable lesson for India to consider, given that India has the second highest number of tobacco users globally, with 267 million individuals, and a concerning level of second-hand smoke exposure among children. Additionally, the economic costs associated with tobacco consumption in India far surpass the revenue generated from tobacco product taxes. This underscores the urgent need for effective tobacco control measures.

The authors suggest that India's policymakers can significantly reduce the economic and health burden caused by tobacco use by implementing a comprehensive strategy that incorporates various elements. These include pricing mechanisms, awareness campaigns, the provision of easily accessible quitting services, education initiatives, tailored support programs, and health warnings on each cigarette. By studying successful initiatives from Canada and other countries, India can formulate an integrated approach to tobacco control that addresses the unique challenges it faces.

2.4 Perception & Behavioral Studies and Post-Market Studies

2.4.1 HTP Prevalence and Use Pattern

2.4.1.1 [Lee et al., \(2023\) Associations between the frequency and quantity of heated tobacco product use and smoking characteristics among Korean smoking adolescents, Journal of Korean Academy of Nursing](#)

Within this study, conducted in South Korea and funded by the Korean Society of Nursing Science, researchers explored the associations between the frequency and quantity of heated tobacco product (HTP) use and smoking characteristics among Korean adolescents who were current combustible cigarette (CC) smokers. HTP use among adolescents is an emerging public health problem, and little is known about the frequency and quantity of HTP use. The study analyzed data from 2,470 Korean adolescents who were current CC smokers and used multinomial logistic and logistic regression analyses to examine the relationships. A substantial number of patients had been exposed to secondhand smoke at home. The study adjusted for a range of potential factors, including age, gender, household income, parental education level, and perceived stress level.

The study found that daily and heavier CC users had greater likelihoods of more frequent and heavier HTP use. In addition, dual users of CCs and electronic cigarettes (ECs) were more likely to use HTPs more frequently and heavily than CC users who did not use ECs. Daily EC users had the highest risk of frequent and heavy HTP use. The frequency and quantity of HTP use were not associated with attempts to quit smoking. Compared to CC-only use, dual use of CCs and HTPs were not associated with quitting attempts, and triple use of CCs, ECs, and HTPs were associated with a lower likelihood of quitting attempts. This suggests that HTP use was less likely to displace CC use and promote attempts to quit smoking.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 56 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The researchers concluded that *‘the risks of more frequent and heavier HTP use were significantly associated with daily and heavier CC use and daily EC use and the frequency and quantity of HTP use were not associated with attempts to quit smoking’*.

2.4.1.2 Alanazi et al., (2023) The associations between cigarette smoking behavior and the use of heated tobacco products among Arab cigarette smokers: findings from Saudi Arabia, Egypt, Kuwait, and Yemen, Journal of Ethnicity in Substance Abuse

Alanazi et al. examined HTP use among 628 Arab cigarette smokers across multiple countries. A cross-sectional survey comprised questions related to sociodemographic characteristics, cigarette smoking behavior characteristics (quitting attempts and desire to quit cigarette smoking, nicotine dependence, and consideration of switching to nicotine products with reduced health risks), and awareness of, use of, and susceptibility to use of HTPs. The study found that awareness of HTPs was relatively low among Arab cigarette smokers (24.2%) and the proportion of participants who had ever used HTPs or were currently using them was quite low also (10.7% and 5.0%, respectively). A history of quit attempts was associated with more likely lifetime use of HTPs (adjusted odds ratio [AOR] = 2.63, 95% confidence interval [CI] [1.21-5.71]) while nicotine-dependent cigarette smokers were more likely to be susceptible to HTP use (AOR = 1.12, 95% CI [1.01- 1.24]). Moreover, those who would consider switching to a product that provided nicotine and could reduce health risks by 99% were more likely to be susceptible to using HTPs (AOR = 2.17, 95% CI [1.05-4.51]).

2.4.1.3 Sun et al., (2023) Global prevalence of heated tobacco product use, 2015–22: a systematic review and meta-analysis, Addiction

Sun et al. (Sun et al., 2023) aimed to estimate the prevalence of HTP use worldwide from 2015 to 2022. A meta-analysis of 45 studies from 42 countries/areas with a total sample size of 1,096,076 participants found an overall lifetime HTP use of 4.87%, current use of 1.53%, and daily use of 0.79%. HTP use was higher among males, with adolescents having a higher prevalence of lifetime HTP use than adults. Japan and South Korea exhibited the highest current HTP use.

2.4.1.4 Seo et al., (2023) Reasons for initiation and regular use of heated tobacco products among current and former smokers in South Korea: findings from the 2020 ITC Korea survey, International Journal of Environmental Research and Public Health

In a study by Seo et al. (Seo et al., 2023) researchers in South Korea conducted a study to identify why HTP consumers initiated and regularly used HTPs, and whether they intended to use HTPs to quit smoking. Cross-sectional data from the 2020 ITC Korea Survey, involving 1,815 adults, found that the most common reasons for trying HTPs were curiosity, family/friend use and HTP technology. Regular use was driven by features like less odor, reduced harm perception, stress reduction, enjoyment, and social acceptance. Only 35.4% of HTP users cited quitting smoking as a reason.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 57 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.4.1.5 Funk et al., (2023) Concurrent choice assessment of preference and substitutability of e-cigarettes and heated tobacco products for combustible cigarettes among African American and white smokers, *Nicotine & Tobacco Research*

Funk et al. aimed to investigate preferences for e-cigarettes and HTPs in comparison to usual brand combustible cigarettes (UBC), among African American and white smokers in the US. The randomized study included 22 daily smokers who completed a concurrent choice task, earning puffs of each product. Most participants had a subjective preference for UBC, however, the results showed that participants earned significantly more puffs from the alternative products, with a preference for e-cigarettes (42.9%) and HTPs (38.1%) over UBC (19.1%). The study suggests smokers are willing to substitute alternative nicotine delivery products when obtaining cigarettes becomes more difficult.

2.4.1.6 Rabenstein et al., (2023) Usage pattern and nicotine delivery during ad libitum consumption of pod e-cigarettes and heated tobacco products, *Toxics*

The study that was conducted in Germany, aimed to investigate the usage patterns and nicotine delivery of pod e-cigarettes, heated tobacco products (HTPs), and conventional cigarettes when consumed ad libitum. The study was funded by the German Federal Ministry of Food and Agriculture. 15 subjects per product group were recruited, 45 in total, between August 2021 and May 2022 between the ages of 18 and 49 years.

During the study, the participants were allowed to use the product of their choice ad libitum for 90 minutes. The study recorded the usage patterns and puff topography of the participants and collected blood samples to determine nicotine concentrations at predetermined time points. According to the study, the group using pod e-cigarettes took the most puffs 71.9, followed by the HTP group 52.2 and the group using conventional cigarettes 42.3. The study also found that the pod e-cigarette was mostly used with single puffs or in short clusters of 2-5 puffs, whereas the other products were used in medium or long clusters that resembled the consumption behavior of smoking a cigarette. The mean puff duration was longest for pod e-cigs at 2.8 seconds, followed by HTPs 1.9 seconds and CCs 1.8 seconds. The maximum plasma nicotine concentration was highest for conventional cigarettes, followed by HTPs, and then pod e-cigarettes, with 24.0, 17.7, and 8.0 ng/mL, respectively. The study observed a reduction in craving for all products, and it suggests that pod e-cigarettes may be able to satisfy cravings in experienced users without the need for high nicotine delivery.

The authors of the study referred to their own previous work, which investigated the nicotine delivery of pod e-cigarettes in the acute phase during pre-directed use.

In summary, the results indicate that the pod e-cigarettes may be used differently than older generation e-cigarettes and that high nicotine delivery may not be necessary for pod e-cigarettes to satisfy cravings in experienced users.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 58 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.4.1.7 Wan Puteh et al., (2023) Exhaled carbon monoxide level and practices among tobacco and nicotine adult users in Klang Valley, Malaysia, International Journal of Environmental Research and Public Health

A cross-sectional study conducted by Wan Puteh et al. examined the practices, nicotine dependency profile, pulmonary function, and exhaled carbon monoxide (eCO) levels among adult users of electronic cigarettes (EC), heated tobacco products (HTP), conventional cigarettes (CC), and non-users in Malaysia. The study was partially funded by the Malaysian Society of Harm Reduction.

The study included 657 participants aged 18 to 60 years, consisting of single CC users (48.3%), EC users (20.9%), HTP users (3.5%), poly-users (PUs; 27.3%), and non-users (52.1%). Socio-demographic data, smoking profiles, nicotine dependency levels, anthropometry, eCO measurements, and spirometer data were collected.

The findings revealed age disparities in product use. CC use was more prevalent among individuals aged 31–60 years (25.6%), while EC use was higher among those aged 18–30 years (15.6%). In contrast, HTP use was higher among the older age group (2.5%) compared to the younger age group (0.4%). The mean age varied significantly across the groups, with HTP users having the highest mean age (~39 years) and EC users having the lowest mean age (~30 years).

Gender differences were also observed, with 86.7% of females being non-smokers compared to 37.4% of males. Among male users, CC use had the highest prevalence (31.4%), followed by poly-users (17.6%), EC users (11.2%), and HTP users (1.9%). Among female users, EC use was highest (7.3%), followed by CC users (3.1%), poly-users (2.1%), and HTP users (1.0%). Additionally, Malays were more likely to be poly-users (13.7%), while non-Malays had a higher prevalence of HTP use (10.0%).

Regarding usage patterns, CC-only users and PUs initiated product use at the earliest age, with mean ages of 17.41 and 17.16 years, respectively. EC-only users and ECs and HTPs users in PUs began using the products in their late 20s, while HTP-only users had the highest mean age of initiation (35 years). These differences were statistically significant ($p < 0.001$). The duration of product use followed a similar trend, with CC-only users and CC use in the PU group showing the longest mean duration (17.58 and 13.93 years, respectively). HTP users in the PU group exhibited the shortest mean duration (3.43 years), and these group differences were also statistically significant ($p < 0.001$).

No significant differences in nicotine dependency, as measured by the Fagerström score, were found among the user groups ($p = 0.109$). However, the EC-only group had the highest mean score (4.12), while the HTP-only group had the lowest mean score (2.55).

Quit attempts varied significantly among the user groups ($p < 0.001$), with CC users in the PU group showing the highest prevalence of quit attempts (86.0%) and HTP-only users exhibiting

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 59 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

the lowest rate (9.1%). These findings suggest a greater intention among CC users in the PU group to transition to perceived "safer" products.

The authors conclude that the usage patterns of tobacco and nicotine derivative products in this study showed the highest prevalence among CC users, followed by the PU group, EC users, and then HTP users, and the pattern differs according to socio-demographic factors.

[2.4.1.8 Jiménez Ruiz et al., \(2023\) Prevalence, Knowledge and Perceptions of Smoking and Tobacco Products and Vape Among SEPAR Members, Open Respiratory Archives](#)

Jiménez Ruiz et al. (2023) aimed to identify the consumption, knowledge, and perception of tobacco and its emerging products among professionals involved in the treatment of respiratory patients in the Spanish Society of Pneumology and Thoracic Surgery (SEPAR). Between June 1 and October 31 2022, a structured interview was sent periodically on-line. The questionnaire consisted of 21 questions about smoking habits, knowledge, attitudes in aspects related to tobacco control as the electronic cigarettes and heated tobacco. A total of 802 participants completed the online survey between June and October 2022. According to the survey, the prevalence of smoking among SEPAR members was 6.6% (n=53) with current smoking being higher among women (66%). The average age of SEPAR members who smoke was 48 years, and they had a low degree of smoking and nicotine dependence (mean Fagerström Test Cigarette Dependence score of 1.31 ± 2.03).

The survey found that 94.3% of SEPAR members frequently ask about tobacco consumption in their patients, and 95.6% always advise their patients to quit smoking. However, only 52.5% of SEPAR members record tobacco consumption in medical records. Over 75% of SEPAR members did not consider nicotine delivery devices for smoking cessation or harm reduction.

Over 75% of members considered e-cigarettes neither effective nor helpful at minimizing the toxic effects of tobacco. However, 23.1% considered such devices useful in harm reduction. A quarter of SEPAR members are unaware of emerging tobacco products: 22% were unaware of water pipes, and 29% were unaware of HTP.

The authors concluded that prevalence of cigarette smoking is low among SEPAR members, and that there is a need for additional training in smoking cessation and increasing knowledge and awareness of emerging tobacco products, such as HTP, among healthcare professionals.

[2.4.1.9 Marzioni et al., \(2023\) An econometric analysis of the demand for cigarettes in Italy after the introduction of heated tobacco products in 2016, British Food Journal](#)

The regulation and taxation of HTPs vary across countries, and their increasing demand may have an impact on the demand for traditional cigarettes. Marzioni et al. (2023) therefore aimed to examine the long-term structural relationship between demand for combustible cigarettes and HTPs in the Italian market. The study used a statistical model called vector error correction model (VECM) to determine how likely people would switch from traditional cigarettes to HTPs. The VECM included several factors: the number of cigarettes and HTP used, the

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 60 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

average price of cigarettes, the per capita GDP, and a vector loading of alpha elements that represents how quickly the variables change in response to the cointegration equation.

The findings suggest that the price of traditional cigarettes and the per capita GDP positively influence cigarette demand. However, a negative relationship between HTP and traditional cigarette demand was observed, meaning that an increase in HTP demand would likely lead to a decrease in cigarette demand. The analysis showed that the effects of changes in cigarette demand are strongly influenced by the dynamics of the cointegration equation. The study found that the impact of a shock on HTP demand is initially positive but turns negative quickly and becomes persistently negative over time. Through their analysis of forecast error variance decomposition, the authors identified that exogenous shocks on HTP demand affect traditional cigarette demand relatively less than interactions where HTP demand affects traditional cigarette demand. The evidence generated in the study suggests a long-term structural relationship between HTPs and traditional cigarettes, impacting the relationship between price and cigarette demand. The authors suggest that tax-based policies should take into account substitution effects with other toxic and addictive products such as HTP, while regulation should not be excessively mild and tax burden should not be excessively low.

[2.4.1.10 Khelfeh et al., \(2023\) Substance use associated with eating attitudes and behaviors, neglected health issues among Palestinian refugees, Journal of Substance Use](#)

Khelfeh et al. (2023) conducted an independent cross-sectional study between June and August 2022 among male Palestinian refugees (n=270) in the West Bank to explore the relationship between substance use and eating behaviors. A self-administered questionnaire (EAT-26) was used to collect background information and variables related to general health and psychoactive substance use. A urine screening test was also performed. The average age of participants was 26.7 (range, 15 to 51 years). Obesity was highly prevalent, with 52.6% of participants being either obese or overweight. 28.9% of participants tested positive for at least one drug in their urine samples, with benzodiazepines being the most prevalent.

The results showed significant smoking habits with 63.3% reporting cigarette smoking, 31.6% pipe smoking, 6.7% vape smoking, and 3.4% IQOS use. The highest percentage of eating disorders was among cigarette smokers (28.2%), while eating disorders were more prevalent among overweight and obese participants and those with purge behavior. Self-induced vomiting behaviors for weight control were more common among waterpipe smokers (odds ratio [OR] = 8.622, $p < .05$), energy drink users (OR = 11.275, $p < .05$), and vape smokers (OR = 10.373, $p < .05$).

The authors acknowledge that self-reported substance use could underestimate the results because of the refusal rate, the limited time frame to detect substances, and the test used to examine urine does not distinguish between drugs of use and certain medications. However, the study highlights a new challenge for the health system to deal with emerging health conditions among male refugees, such as eating disorders and substance use disorders. The

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 61 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

authors concluded that there is a “need for further research and awareness of eating disorders and substance use among male Palestinian refugees”.

[2.4.1.11 Noguchi et al., \(2023\) Association of cigarette smoking with increased use of heated tobacco products in middle-aged and older adults with self-reported chronic obstructive pulmonary disease, asthma, and asthma-COPD overlap in Japan, 2022: the JASTIS study. BMC Pulmonary Medicine](#)

Noguchi et al. (2023) looked at the relationship between chronic obstructive pulmonary disease (COPD), asthma, asthma-COPD overlap (ACO), and HTP usage in adults aged 40 and above to obtain data on short- and long-term adverse health effects of HTP in this setting.

The study utilized data obtained from the Japan “Society and New Tobacco” Internet Survey (JASTIS) 2022, conducted between February 1, 2022, and February 28, 2022, which included 19,308 participants; 10,900 (56.5%) were never-cigarette smokers, 4,903 (25.4%) were former cigarette smokers, and 3,505 (18.2%) were current cigarette smokers.

The study found that 1,813 (9.4%) of the participants confirmed using HTP (of whom 809 [4.2%] used Ploom TECH, 919 [4.8%] used IQOS, 712 [3.7%] used glo, and 110 [0.6%] used lil HYBRID). 258 (1.3%) stated that they currently had COPD, 2,327 (12.1%) currently had asthma, and 113 (0.6%) currently had ACO.

The researchers provided a breakdown of HTP use in adults with COPD, asthma, and ACO, based on smoking status. In participants with COPD, asthma and ACO respectively, the proportions of HTP use were 2 (3.0%), 7 (0.6%), and 0 (0.0%) in never-cigarette smokers. In past cigarette smokers, the figures were 8 (7.8%) COPD participants, 83 (13.2%) asthma, and 2 (4.4%) ACO. For current smokers, the figures were 45 (50.6%), 161 (16.8%), and 34 (68.0%).

To assess the association between HTP use and respiratory diseases, the researchers categorized the participants into current cigarette smokers; former cigarette smokers; and never-cigarette smokers. Statistical analyzes showed that current cigarette smokers with COPD and ACO had a significantly higher prevalence of HTP use compared to former and never-cigarette smokers. These findings align with previous studies, indicating higher utilization of HTP among current cigarette smokers.

These results highlight the increased likelihood of HTP use among current smokers with COPD and ACO compared to those without respiratory diseases. Conversely, former smokers with COPD, asthma and ACO were generally less likely to use HTP compared to those without these conditions. The authors state they believe complete cessation of both cigarettes and HTP in individuals with COPD, asthma, and ACO, who they found are likely to become dual smokers (of cigarettes and HTP), is required. It also underscores the need for tailored smoking cessation programs that specifically consider the unique characteristics of these respiratory diseases, in light of the observed variations in HTP use across different smoking statuses and conditions.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 62 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The authors note the limitations of the study, such as the self-reported nature of the data and the potential for selection bias and recommend further longitudinal studies are required.

[2.4.1.12 Momosaka et al. \(2024\) Associations of individual characteristics and socioeconomic status with heated tobacco product harmfulness perceptions in Japan: A nationwide cross-sectional study \(INFORM Study 2020\). Journal of Epidemiology](#)

Momosaka et al. (2024) explored the perception of HTPs as being less harmful compared to combustible cigarettes among Japanese individuals aged 20 years or older. To obtain a representative sample, a two-stage stratified random sampling method was used select 10,000 individuals from 500 census areas. Data collection was carried out via mailed invitations and questionnaires were self-administered between August and September 2020.

A total of 9,719 eligible participants were identified, of which 3,605 individuals consented to participate, resulting in a participation rate of 37.1%. Only participants who provided complete data on the questionnaires were included in the final analysis. Of 3,420 participants (2,871 non-tobacco users and 549 tobacco users) with complete data, 40.3% of tobacco users and 18.3% of non-users perceived HTP as less harmful to health than combustible cigarettes. Among participants aged 20 to 39 years, 49.9% of tobacco users and 30.4% of non-users believed HTPs were less harmful than combustible cigarettes.

Among 1,160 non-tobacco users who were familiar with HTPs, approximately 50% of males aged under 39 years and with less than a college education considered HTPs to be less harmful. However, no similar associations were found among tobacco users.

When comparing HTP users to combustible cigarette smokers, 77.8% of HTP users and 55.1% of combustible cigarette smokers perceived HTPs to be less harmful.

The weighted logistic regression analysis identified several factors influencing the perception of HTPs. Non-tobacco users aged 40-59 and 60 years or older, as well as those with higher education, were less likely to view HTPs as less harmful. However, being male increased the likelihood of perceiving HTPs as less harmful. Among tobacco users, those who used HTPs were 3.05 times more likely than cigarette users to hold this perception.

Ultimately, the researchers concluded that male non-tobacco users aged less than 39 years, with a lower education level, and tobacco users were more likely to believe that HTPs are less harmful to health than combustible cigarettes. Trusted cancer education/information sources did not impact the perception of HTP harmfulness among tobacco or non-tobacco users.

[2.4.1.13 Kim and Park. \(2024\) Changes in smoking patterns and characteristics of Koreans using the Korea National Health and Nutrition Examination Survey 2013–2021 data. Public Health](#)

Kim and Park. (2024) conducted a cross-sectional analysis using data from the Korea National Health and Nutrition Examination Survey (KNHANES) spanning from 2013 to 2021. The study

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 63 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

aimed to investigate smoking patterns among Korean adults (<19 years), with a specific focus on the use of e-cigarettes and HTP and the reasons behind initiating these new tobacco products.

Out of the 9,656 current tobacco users, 85% used combustible cigarettes, 7% used both conventional cigarettes and e-cigarettes, and 3% used both combustible cigarettes and HTP. Less than 1% used all three types of tobacco products, while 2% of participants used solely e-cigarettes or solely HTP.

The survey data demonstrated a decrease in the percentage of current tobacco users from 25.54% in 2013 to 23.05% in 2021. More notably, there was an overall decrease in the use of combustible cigarettes from 23.39% in 2013 to 15.77% in 2021, particularly among males and older age groups (those aged 60 years old and above).

Among the new tobacco products, those who were younger, had higher income and education levels, and used dietary supplements were more likely to use HTP or e-cigarettes. 46.68% of HTP users reported that the absence of cigarette smell was the primary reason for using HTP, 19.19% considered HTP less harmful than combustible cigarettes, and 15.04% perceived HTP as a potential aid to quit smoking. On the other hand, 45.19% of e-cigarette users considered them helpful for quitting smoking, followed by 19.98% who viewed them as less harmful than combustible cigarettes.

The authors recommended the implementation of new policies in Korea to protect public health. These policies would require the disclosure of important information regarding the content of new tobacco products, such as nicotine levels, hazardous substances, and heavy metals. The authors believed that by providing this information, consumers would be more informed about the potential health risks associated with these products.

[2.4.1.14 Otsuka et al. \(2024\) Prevalence, knowledge, and concerns regarding the use of heated tobacco products and electronic cigarettes among young Japanese physicians, Tobacco Induced Diseases](#)

In a study conducted by Otsuka et al. (2021), the authors aimed to explore the awareness, knowledge, and concerns surrounding HTP and e-cigarettes among young Japanese physicians (aged 24-39 years). This demographic was chosen due to their potential role in smoking cessation efforts. The research employed a cross-sectional online survey involving 529 physicians, assessing their awareness, smoking status, and knowledge of HTP and e-cigarettes.

The prevalence of current smoking among male physicians was 12.7% and female physicians was 7.4%, with prevalence rates of exclusive combustible cigarette use, e-cigarette use, HTP use, and dual use at 4.3%, 2.9%, 1.9%, and 1.9%, respectively.

The survey results indicated a high level of awareness, with 89.0% of participants familiar with HTP and 71.3% with e-cigarettes. Only 8.3% were unaware of both products. Among those who used these products, male physicians displayed a preference for HTP, while female

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 64 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

physicians favored e-cigarettes. Notably, no female physicians reported HTP use. Traditional news sources, notably newspapers (56.8%) and TV (37.4%), were the primary channels for obtaining information about HTP and e-cigarettes. Approximately 23.1% reported receiving information from tobacco company advertising, while 8.0% gained insights from the scientific literature.

Among non-smokers (89.0%), limited knowledge about HTP and e-cigarettes was observed. Consequently, non-smokers exhibited higher levels of concern about these products, while HTP users expressed the lowest level of concerns. Safety concerns were the most commonly cited type of concern. Based on their findings, the authors concluded that differing levels of concerns about HTPs and e-cigarettes among physicians reflected knowledge gaps, particularly in non-smokers.

[2.4.1.15 Liu and Filippidis. \(2024\) Tobacco market trends in 97 countries between 2007 and 2021. Tobacco Induced Diseases](#)

Liu and Filippidis., (2024) examined the market trends of seven tobacco products in 97 countries between 2007 and 2021: cigarettes, cigars/cigarillos, smoking tobacco, smokeless tobacco, e-cigarettes, HTP, and tobacco-free oral nicotine. Population data for each country was obtained from the United Nations Population Division, representing 88.4% of the world's population in 2021. A total of 5283 retail value data points for the tobacco products across the study countries were analyzed.

The research focused on trends in retail value and global market share, categorized by national income level and individual countries. The analysis revealed that from 2007 to 2021, the total value of tobacco sales across the 97 countries consistently increased, rising from US\$657 billion to US\$906 billion.

During the initial period (2007-2015), cigarette sales dominated the global tobacco market, holding over 91% of the market share. However, starting from 2016, emerging products like e-cigarettes and HTPs, along with non-cigarette combustible products such as cigars, drove most of the growth in global tobacco retail value. By 2021, the market share of cigarettes had decreased to 83%, while cigars/cigarillos and smoking tobacco experienced an increase. E-cigarettes, HTP, and oral nicotine showed small incremental gains in market share, accounting for 2.5%, 3.1%, and 0.3% of the overall tobacco market in 2021, respectively.

High-income countries saw the most substantial increase in the retail value of emerging products. By 2021, the market share of e-cigarettes, HTP, and oral nicotine in high-income countries had reached 3.9%, 5.1%, and 0.7%, respectively. On the other hand, middle- and low-income countries continued to observe growth in cigarette sales. In upper middle-income countries, cigarette sales rose from \$199 billion to \$317 billion from 2007 to 2015 before experiencing a decline in 2016, leading to slower growth thereafter. Meanwhile, the market for cigars/cigarillos expanded rapidly. Lower middle/low-income countries saw a gradual increase in cigarette sales from \$57 billion to \$87 billion between 2007 and 2021. The retail value of

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 65 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

smokeless tobacco declined from \$8.5 billion in 2007 to less than \$1 billion in 2015, continuing to decrease due to reduced sales in countries like India.

The researchers suggested that their data and findings could be valuable for policymakers in terms of tobacco control. They emphasized recent changes in the European Union that restrict the flavoring of HTP aerosols and mandate health warnings on HTP in all member states. The authors recommended ongoing research to monitor the tobacco market, identifying emerging trends in tobacco sales and addressing regulatory gaps.

[2.4.1.16 Ju H et al. \(2024\) The online promotion strategies of e-cigarette and heated tobacco product retailers in South Korea following the COVID-19 pandemic: Implications for regulation. Tobacco Induced Diseases](#)

Ju-H et al., (2024) conducted a study analyzing the marketing strategies of online e-cigarette and HTP retailers in South Korea before and after COVID-19, utilizing data from website pages published before January 2023.

The study encompassed 774 online retailers from eight e-commerce platforms and three search engines. From 2017 to 2022, the number of retailers offering e-cigarettes and HTP rose from 4 to 512. During this period, the average price decreased from US\$76.3 to US\$63.9, and the percentage of retailers offering free shipping increased from 25% to 59.4%. Following the peak of the COVID-19 pandemic in 2021, the number of online retailers surged, growing from 113 in 2021 to 512 in 2022, representing an increase of 399 retail websites.

The most commonly used promotional strategies were 'Stay home and vape' (57.5%, n=445) and 'Trendy' (44.4%, n=344). HTP sellers emphasized 'Stay home and vape' and 'Trendy' more than e-cigarette sellers, with significant usage rate increases observed over the analyzed period.

2.4.2 Youth and Young Adult Usage and Behavior

[2.4.2.1 Chirila et al., \(2023\) Romanian young adult perceptions on using heated tobacco products following exposure to direct marketing methods, Primary Care Respiratory Medicine](#)

In a qualitative study by Chirila et al. (2023), the authors aimed to understand the effects of direct marketing of HTPs on young Romanian adults. Nineteen young adults (age range 18–26), including non-smokers, were interviewed to explore their awareness of HTP marketing and their perceptions of the products. The participants demonstrated high awareness of HTP advertising and perceived HTPs as appealing and potentially having lower health risks compared to cigarettes. Free samples and promotional offers were found to be attractive marketing tactics. However, participants asserted their decision to use HTPs was based on personal choice, downplaying the influence of marketing. Participants also displayed limited knowledge of the specific health risks associated with HTPs. The study emphasized the role of family, peers, and cultural environment in shaping smoking-related attitudes and highlighted

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 66 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

the need for policy-driven demarketing strategies to counteract self-rationalization.

2.4.2.2 Istenic et al., (2023) Prevalence of use and knowledge about tobacco products and their harmful effects among university students in southern Croatia, *Healthcare*

Istenic et al. (Istenic et al., 2023) conducted a cross-sectional survey on the use of conventional cigarettes, e-cigarettes and HTPs by university students. Higher prevalence of HTP use was reported when examining HTP use among adult university students. Specifically, out of 1,184 university students in Croatia, 17.6% of participants reported using HTPs.

2.4.2.3 Affolter et al., (2023) Use of tobacco, nicotine and cannabis products among students in Switzerland, *Frontiers in Public Health*

Similarly, Affolter et al. (Affolter et al., 2023) examined the usage of tobacco, nicotine, and cannabis products among upper-secondary school students in Switzerland. Tobacco products included tobacco cigarettes in commercial packages, self-rolled tobacco cigarettes, hookahs, pipes, cigars, and cigarillos and HTPs. An online survey was conducted with 9,515 participants aged 15 to 21, providing information on their frequency of use for various products. Around 54.8% reported using at least one of the listed products in the past month, with daily use most prevalent for commercially packaged tobacco cigarettes, snus, and smoking cannabis with tobacco. 40.0% of respondents report using tobacco products, of which daily HTP prevalence was less than 0.5%. The study found that Swiss adolescents had higher rates of cigarette consumption compared to other countries. The researchers recommended implementing effective tobacco control policies and developing customized prevention programs for this population. Regular surveys were also suggested to track changes in substance use habits.

2.4.2.4 Cheng et al., (2023) Awareness and use of tobacco products among underage individuals: findings from the Altria client services underage tobacco use survey 2020–2022, *BMC Public Health*

Cheng et al. analyzed data from the Altria Client Services Underage Tobacco Use Survey (UTUS), a repeated cross-sectional survey, that included 14,708 U.S. underage individuals aged 13-20 years old. The study was conducted after the authorization of *IQOS* until it was withdrawn from the U.S. market during quarter 4 of 2021, and analysis included data from the second quarter of 2020 to the third quarter of 2022. The study found that past 30-day use was low for tobacco products (< 2%), with e-cigarettes being the most commonly used tobacco products among underage individuals. In agreement with data from NYTS 2021 and 2022, the study reported limited HTP use among underage individuals (ever use < 1.5% and 5.0% among youth and underage young adults, respectively; past 30-day use < 1% in both youth and underage young adults).

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 67 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.4.2.5 Harlow et al., (2023) Sexual and Gender Identity Disparities in Nicotine and Tobacco Use Susceptibility and Prevalence: Disaggregating Emerging Identities Among Adolescents from California, USA, Nicotine and Tobacco Research

In this study, Harlow et al. (2023) provide a cross-sectional analysis of an ongoing prospective cohort study of behavioral health among students enrolled in 11 Southern California high schools (ADVANCE). The authors claim substantial variation exists in sexual and gender identities that is often not captured in US nicotine and tobacco research. The study therefore aimed to investigate disparities in prevalence of nicotine and tobacco use and susceptibility to tobacco products among youth based on gender identity and sexual identity, with a focus on understanding the tobacco use outcomes among youth with understudied sexual and gender identities.

The sample included 3,795 participants with an average age of 15.2 years. 5.7% identified as both a gender minority and sexual minority, 0.6% identified as a gender minority and heterosexual, 15.9% identified as cisgender and sexual minority, 68.9% identified as cisgender and heterosexual, and 5.4% preferred not to disclose their gender or sexual identity.

4.3% of youth had ever used combustible tobacco (cigarettes, cigars, hookah) and 11.4% had ever used non-combustible tobacco (e-cigarettes, e-hookah, HTP, smokeless/snus, oral nicotine). Non-binary youth had greater prevalence of ever using combustible tobacco than male/masculine youth, and transgender youth had slightly higher prevalence of non-combustible tobacco use than male/masculine youth. Youth identifying as bisexual, gay/lesbian, pansexual, and queer/other identities had greater prevalence of ever using non-combustible tobacco compared to heterosexual youth. Youth who were questioning their sexual identities did not have greater prevalence of ever using combustible or non-combustible tobacco but were considered to have a greater risk of future initiation of tobacco use.

In a subgroup sample of 3,331 participants, tobacco-use susceptibility was assessed. 14.6% were susceptible to future cigarette smoking, 19.5% (n=650) to future e-cigarette use, and 15.3% (n=511) to future oral nicotine product use. Non-binary and transgender youth had a higher susceptibility to future cigarette, e-cigarette, and oral nicotine product use compared to male/masculine youth. Non-binary youth had more than twice the risk. Gender non-conforming youth who preferred not to disclose their gender identity were also more susceptible to cigarette use.

The authors highlight the importance of measuring diversity within the LGBTQ+ community for tobacco use research as the inclusive measurement of a wide range of sexual and gender identities in research and surveillance may inform more precise tobacco control interventions, including education campaigns or programmatic efforts to reduce sexual and gender minority tobacco disparities.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 68 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.4.2.6 Tashakkori et al., (2023) Multiple Tobacco Product Use Among Youth E-Cigarette Users: National Youth Tobacco Survey, 2020, Journal of Adolescent Health

In their cross-sectional study, Tashakkori et al. (2023) analyzed data from the 2020 National Youth Tobacco Survey (NYTS) to compare e-cigarette use behaviors, age at first combustible tobacco use, and tobacco dependence symptoms between dual users (n=573) and exclusive users (n=1,087). The 2020 NYTS was a nationally representative, cross-sectional, school-based, self-administered survey of middle (grades 6 to 8) and high school (grades 9 to 12) students in the United States. 80% of students were in high school (i.e., 14 to 18 years of age). The majority were White or Hispanic (54.1% and 32.4%, respectively).

Among the current e-cigarette users (total, n=1,660), the prevalence of exclusive e-cigarette use was 61.1%, while 38.9% reported using e-cigarettes and other tobacco products. Within the group of multiple product users, 56.0% used combustible only products, and 26.8% used both combustible and noncombustible products. Among those who reported using e-cigarettes and noncombustible tobacco only, 10.3% used e-cigarettes and smokeless tobacco, and 4.0% used e-cigarettes and HTPs.

The study found that more than 60% of the participants reported using their first combustible product at the same age or after they started using e-cigarettes. The prevalence of multiple tobacco product use was higher among non-Hispanic Black students and sexual minority students, highlighting concerns about health disparities in these populations.

It was observed that dual users exhibited more frequent and daily e-cigarette use, higher tobacco dependence symptoms, and had access to e-cigarettes through various sources.

The authors suggest the findings highlight the need to prevent e-cigarette initiation and the transition to multiple tobacco product use, especially combustible tobacco, due to the increased risk of addiction and continued use among young people.

2.4.2.7 Zhang et al. (2024) Dual and poly-nicotine and tobacco use among adolescents in the United States from 2011 to 2022. Addictive Behaviors

Zhang et al., (2024) aimed to assess the prevalence and risk factors of concurrent use of multiple nicotine and tobacco products among US adolescents (aged 9-19 years) from 2011 to 2022, including e-cigarettes, combustible tobacco products, smokeless tobacco, and HTP. The study utilized data from the National Youth Tobacco Survey (NTYS). Adolescent use of 12 nicotine or tobacco products, including e-cigarettes, cigarettes, cigars, waterpipe, chewing tobacco, roll-your-own cigarettes, pipes, snus, dissolvable tobacco products, bidis, HTP, and nicotine pouches were examined. Dual use was defined as current use of ≥ 2 products, and poly use was defined as current use of ≥ 3 products. The authors also examined four categories of dual use: (1) combustible/smokeless, (2) combustible/novel, (3) smokeless/novel, and (4) combustible/noncombustible.

The study sample included 242,637 respondents, with 48.9% being female. In terms of school level, 43.9% were middle-school students. The racial/ethnic breakdown of the sample was as

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 69 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

follows: 53.1% White, 14.9% Black, 16.1% Hispanic, and 10.7% non-Hispanic and other races.

The prevalence of dual and poly use of nicotine and tobacco products varied over time and by product. From 2011 to 2021, the prevalence of dual product use decreased from 9.5% in 2011 to 2.8% in 2021. Similarly, poly use decreased from 5.1% in 2011 to 1.1% in 2021. However, between 2021 and 2022, there was an increase in prevalence for both dual and poly use. The prevalence of dual use was 3.7% in 2022, while poly use prevalence was 1.7% in 2022.

The prevalence of different combinations of dual use also showed variable trends over time. Dual use of at least one combustible and at least one smokeless product declined consistently from 4.0% in 2011 to 0.7% in 2022. In contrast, dual use of smoking and novel products increased from 0.9% in 2011 to 6.8% in 2015, reached another peak in 2019 at 6.6%, and dropped to 2.0% in 2021.

When examining the prevalence of dual and poly use by race/ethnicity, Hispanic respondents had the highest prevalence of dual product use in 2011 (11.2%), followed by White (9.8%), non-Hispanic and other races (9.5%), and Black (7.2%). By 2022, the prevalence had decreased substantially for all groups, with Black individuals having the highest prevalence (4.5%), followed White (3.9%).

In terms of poly use, Hispanic respondents had the highest prevalence in 2011 (6.6%), followed by White (5.3%), non-Hispanic and other races (5.1%), and Black (3.2%). By 2022, the prevalence of poly use remained highest among Hispanic adolescents (2.0%).

Overall, the study shows that while there was a decreasing trend in dual and poly use of nicotine and tobacco products from 2011 to 2021, there was a slight increase in prevalence from 2021 to 2022. Racial and ethnic differences in prevalence also narrowed over time, with Black and Hispanic individuals having the highest prevalence in recent years. While the research offered a comprehensive evaluation, limitations included reliance on self-reported data, potential recall bias, and adjustments in survey administration post-2020.

2.4.2.8 Mott et al. (2024) Exploring the association between the proximity to and density around schools of retailers selling IQOS products and youth use of heated tobacco products: evidence from the 2020-2021 COMPASS study. Health promotion and chronic disease prevention in Canada

Mott et al. (2024) investigated the association between the proximity and density of retailers selling HTP around secondary schools and youth use of HTP in four Canadian provinces. The study utilized data from the 2020-2021 COMPASS study, which included 40,636 students from 120 high schools across British Columbia, Alberta, Ontario, and Quebec.

Students self-reported their past 30-day HTP use, gender, school grade, ethnicity, weekly spending money, cigarette smoking behaviors, and e-cigarette use behaviors. Those who reported smoking in the past 30 days were considered current smokers, and those who reported ever smoking were considered ever smokers.

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 70 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

The prevalence of HTP use among students was found to be 0.80%. Higher rates of HTP use were reported among Grade 12 students, individuals who identified their gender as other or preferred not to answer, and those with other/mixed ethnicity. Additionally, higher rates of HTP use were observed among current smokers and vapers.

The percentage of schools with at least one retailer within 500 m, 1000 m and 1500 m of the school selling *IQOS* devices was 4.2%, 10.0% and 21.7%, respectively. The density of retailers selling *IQOS* devices and HEETS within 500 m, 1000 m and 1500 m of each school was low, whereas the density of retailers selling HEETS was much higher with 35.8% of schools having at least one retailer within 500 meters, increasing to 65.0% within 1000 meters and 77.5% within 1500 meters.

Larger urban areas had a higher proximity and density of retailers compared to smaller or medium-sized urban areas. However, the study found no significant association between the proximity and density of retailers and current HTP use among students.

There was significant between-school variability in the likelihood of currently using an HTP among students ($p < 0.001$). The school-level prevalence of HTP use ranged from 0.02% to 2.90%, with 33 schools having no students reporting HTP use.

Overall, the study found that despite the low overall prevalence of HTP use ($< 1\%$) at the time of the COMPASS survey in 2020-2021, most schools had at least one retailer selling *IQOS* or HEETS within a 1000m radius. However, proximity and density of retailers selling *IQOS* devices and HEETS tobacco sticks near schools were not significantly associated with current HTP use. More HEETS retailers than *IQOS* retailers were present near schools, suggesting students may be able to obtain *IQOS* products through online sources or social sources. The authors recommend continued monitoring of HTP use among youth and the implementation of policies regulating the proximity of tobacco retailers to schools to reduce tobacco use among students.

2.4.3 Smoking Cessation

2.4.3.1 [Noda et al., \(2023\) The usefulness of a smartphone app-based smoking cessation program for conventional cigarette users, heated tobacco product users, and dual users: retrospective study, Journal of Medical Internet Research](#)

Noda et al. (2023), retrospectively examined the usefulness of a smartphone app-based smoking cessation program for exclusive HTP, cigarette and dual users. Data from 2,952 participants participating in the Ascure online smoking cessation program in Japan from June 2019 to February 2021 was used to determine the continuous abstinence rate (CAR) at weeks 21 to 24, biochemically validated using salivary cotinine testing. 52% (1,524/3,478) of participants were in the cigarette group, 35% (1,038/3,478) in the HTP group, and 13% (390/3,478) in the dual use group. Mean age of 43 years. The Ascure smartphone app provided four elements to support smoking cessation: (1) educational video tutorials to enhance the understanding of nicotine dependence, (2) a personalized to-do list for behavior change, (3) a

Confidentiality Statement

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 71 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

digital diary for record keeping, and (4) interactive chat sessions for relief from cravings or withdrawal symptoms. CAR at weeks 21 to 24 showed that exclusive HTP users were more likely to stop tobacco use than exclusive cigarette smokers (CAR 52.6% for cigarette users vs CAR 64.8% for HTP users; odds ratio [OR] 1.17, 95% CI 1.12-1.22; $P < .001$). There were no significant differences between the exclusive cigarette users and the dual users. The program adherence rate at week 24 was 70.7% overall (68.4% for cigarette users, 75% for HTP users, and 67.9% for dual users).

[2.4.3.2Á Martinho et al., \(2023\) Are perceived benefits of heated tobacco products consumption aiding smoking cessation? Social Marketing Quarterly](#)

In Portugal, Martinho et al. (2023) explored the perceived benefits of HTP consumption and its potential in aiding smoking cessation using the Health Belief Model to analyze the results from an online survey. The survey involved 173 smokers and 77 former smokers of the 173 current smokers 95 used HTPs exclusively. The study uncovered that HTPs were not perceived as effective aids for smoking cessation and, in some cases, might lead to an increased dependency on tobacco. Users of HTPs did not view them as safer or more efficient means of quitting smoking, and only a small percentage managed to quit smoking entirely after transitioning to HTPs. Of the 95 HTP users, 58.5% did not intend to stop smoking in the next year, and 59.3% said they increased their tobacco consumption since beginning using HTPs.

[2.4.4Á Consumer perception](#)

[2.4.4.1Á Maglia et al., \(2023\) Qualitative study on the perception of combustible cigarettes, e-cigarettes and heated tobacco cigarettes among pregnant women, Journal of Addictive Diseases](#)

Maglia et al. explored the perceptions of combustible cigarettes, e-cigarettes, and HTPs among 30 pregnant women in Italy. This qualitative study in Italy aimed to explore the psychological reasons behind smoking addiction during pregnancy and perceptions of cigarettes, e-cigarettes, and HTPs. Thirty women, either continuing or quitting smoking during pregnancy, were interviewed. Among them, ten continued smoking (33%) and 20 quit (67%). Of the 30 participants, 6 used HTPs, with only one continuing use during pregnancy (17%). HTPs were perceived as less harmful and more satisfying while cigarettes were seen as riskier. Participants' mistrust of cessation treatments and lack of awareness of risks to the baby were identified.

[2.4.4.2Á Sharma et al. \(2023\) Differences in demographics and behaviors across two web-based survey platforms: observations from a study of risk perceptions of heated tobacco products \(HTPs\), Preventive Medicine Reports](#)

In a US-based study by Sharma et al. (2023), the authors compared 604 participants from Amazon Mechanical Turk (Mturk) and Prime panels to investigate how sources of participants

Equivalency of 'Ucvgv gpv'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 72 of 82"
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

impact study outcomes. The survey assessed participants' perceptions of HTPs, with significant differences between the platforms, including Prime panels having more everyday smokers and greater HTP awareness. Demographic differences existed, including a higher percentage of non-Hispanic whites on Mturk (68.4%) compared to Prime panels but more non-Hispanic Blacks on Prime panels (16% vs. 8% on Mturk). Web-based recruitment platforms were cited as a cost-effective and efficient way of collecting data in behavioral science. However, given the significant differences between platforms, the study highlighted the importance of considering participant demographics and recruitment sources in research on HTPs.

[2.4.4.3 Berg et al., \(2023\) Impact of different health warning label and reduced exposure messages in IQOS ads on perceptions among US and Israeli adults, Preventive Medicine Reports](#)

Berg et al. examined the effectiveness of health warning labels (HWLs) on IQOS in the US and Israel. Researchers conducted an online survey with 2,222 adults aged 18 to 45, analyzing different types of HWLs and ad messages. The results showed that risk-related HWLs increased perceived harm and reduced likelihood of trying IQOS. Slight and clear distancing ads decreased perceived harm and increased likelihood of recommending IQOS, with clear distancing further reducing perceived harm and exposure. The combination of the quitting HWL and clear distancing resulted in the lowest perceived harm.

[2.4.4.4 DeAtley et al., \(2023\) Effects of Modified Tobacco Risk Products with Claims and Nicotine Features on Perceptions among Racial and Ethnic Groups, International Journal of Environmental Research and Public Health](#)

DeAtley et al. (2023) conducted an online experiment spanning from July to October 2022 in which they explored the influence of nicotine content and modified risk tobacco product (MRTP) claims on four tobacco products (Classic White Snus, IQOS, JUUL e-cigarette, and VLN cigarette). The study included an ethnically diverse sample of 1,484 adults aged 21 to 65 (mean, 34 years). Among the participants, 51.9% were female, 63.3% were non-smokers and 36.7% were current combustible cigarette smokers. 23.5% of participants identified as Black, 18.2% as Asian, 24.2% as Latine, and 29.7% as White.

Employing a 2x2x4 mixed factorial design, the study examined participants' responses to tobacco products with varying nicotine content, with and without MRTP claims, focusing on four key outcomes: likelihood of trying the product, concerns about serious disease with regular use, perceived addictiveness, and perceived ease of quitting smoking. The results demonstrated that the absence of an MRTP claim correlated with increased willingness to try a product, reduced apprehensions about serious disease, lower perceptions of addictiveness, and heightened beliefs in smoking cessation ease. Participants identified low-nicotine IQOS products without MRTP claims as less likely to cause serious disease, while low-nicotine JUUL products without claims were deemed less addictive and more supportive of smoking cessation. The study findings also revealed subtle differences in outcomes across various racial and ethnic groups. Asian participants were more interested in low-nicotine IQOS than other

Equity and Inclusion

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 73 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

groups, while Black individuals ranked low nicotine JUUL with no claim as least addictive. Asian and White individuals saw low nicotine JUUL without a claim as the most helpful for quitting smoking, while Black and Latine individuals saw low nicotine VLN cigarettes with a claim as the most helpful. The authors conclude that *“regulatory efforts should be guided by our understanding of how MRTP claims interact with different product characteristics.”*

2.4.4.5 [ÁDuan et al., \(2023\) IQOS marketing strategies and expenditures in the United States from market entrance in 2019 to withdrawal in 2021, Nicotine and Tobacco Research](#)

Duan et al. (2023) examined IQOS and its advertising strategies before and after obtaining modified risk tobacco product authorization (MRTPA) from the FDA. The study, based on Numerator marketing data spanning from August 2019 to the end of 2021, scrutinized advertising occurrences and expenditures, emphasizing headline themes, imagery, and media types. Of a total \$15,451,870 in expenditure, 99.6% was allocated to print media while online display was the primary channel for ad occurrences (73.1%).

There were 685 total ad occurrences: 39.3% pre-MRTPA and 60.7% post-MRTPA. The most prominent pre-MRTPA ad headlines included "The future of tobacco is here" (13.0%), "Get IQOS: real heated tobacco" (10.7%), and "Real tobacco meets innovative technology" (6.3%). Post-MRTPA, new headline themes emerged (i.e., reduced exposure), and some existing headline themes increased in prominence (i.e., switch, "not burned/heat control"), and the theme "distinct from e-cigarettes" emerged. The imagery also evolved, with an increased presence of women in post-MRTPA ads. The data suggest increased targeting of women and young and/or technology-savvy people in media channels.

The authors conclude that *“as the nicotine market in the US expands, further population studies are needed to evaluate the impact of marketing, particularly marketing using reduced risk or exposure language, on consumer understanding, perceptions, and behaviors, including among specific subpopulations.”*

2.4.4.6 [ÁRobichaud et al., \(2023\) How Media Stories in Low- and Middle-Income Countries Discussed the U.S. Food and Drug Administration’s Modified Risk Tobacco Product Order for IQOS, Nicotine and Tobacco Research](#)

In this independent study, Robichaud et al. (2023) assessed how news media in low and middle-income countries (LMICs: AFRO, AMRO, WPRO and EURO¹⁰) discussed the FDA authorization of IQOS as a modified risk tobacco product (MRTP). The study analyzed 50 newsarticles published between July 2020 and January 2021, from 20 LMICs. Twenty-six articles (52%) included reduced risk language while 40 (80%) included reduced exposure

¹⁰ AFRO = World Health Organization (WHO) African Region, which includes all African countries; AMRO = WHO Region of the Americas, which includes North, Central, and South American countries; WPRO = WHO Western Pacific Region, which includes countries in the Western Pacific, such as China, Japan, Australia, and Pacific Island nations; EURO = WHO European Region, which includes European countries, as well as some countries in Central Asia.

Eqplhf gplckrlf 'Ucvgo gpv'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 74 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

language. Twenty-two articles (44%) discussed potential impacts of the MRTP order on regulations in LMICs. Thirty articles (60%) included quotes from tobacco industry representatives, while 6 (12%) included quotes from public health or medical professionals, and 2 (4%) included both.

Of the twenty-two articles discussing the impact of FDA authorization on tobacco product regulations, some articles suggested regulating HTPs differently based on their harmfulness, while others called for a ban on HTPs in India and Mexico. In contrast, some articles argued that the FDA authorization should not influence regulations in their respective countries. Concerns were raised by two government health agencies in Mexico about the potential misuse of FDA authorization to mislead lawmakers and the public. Half of the articles incorrectly reported that the FDA had authorized IQOS as a reduced risk or reduced harm product, indicating potential misrepresentation of reduced exposure in the media. The analysis of non-English language news media articles found that most articles discussing the MRTP order for IQOS were published in AFRO, AMRO, and WPRO regions. It is unclear why there were fewer articles in EURO. Additionally, public health and tobacco control organizations received less media coverage compared to press releases and quotes from PMI leadership in LMICs. The authors emphasize the importance of accurate reporting, balanced perspectives, and continued monitoring of tobacco regulations and industry activities in LMICs.

2.4.4.7 [Wackowski et al., \(2023\) Impact of IQOS modified risk messaging on physicians' product perceptions and recommendations, BMJ](#)

Wackowski et al. (2023) conducted an independent study between May and October 2021 to examine the potential impact of ads for IQOS on physicians in the United States. The study used national survey data from 543 board-certified physicians who were randomly assigned to view 1 of 3 ads: (1) a manipulated IQOS ad with no Modified Risk Tobacco Products (MRTP) message (control group), (2) an ad with an FDA-authorized MRTP message about reduced chemicals (experimental group 1), or (3) both the MRTP message and a reference to FDA authorization (experimental group 2). The primary outcomes were perceived harm of IQOS compared to cigarettes and willingness to recommend switching to IQOS for a patient who smokes but is unwilling to quit.

Out of the 543 respondents, only a small percentage had prior knowledge of IQOS. Specifically, 5.4% reported having heard of IQOS before, 2.1% had seen an IQOS ad, and 0.6% had been asked about IQOS by a patient. These findings suggest that the participants were generally unfamiliar with IQOS, indicating a level of naivety towards the product. The study found that physicians in experimental group 2 (i.e., viewed both the MRTP message and FDA authorization reference) were significantly more willing to recommend switching to IQOS compared to those in the control group (OR=1.69, 95% CI: 1.08 to 2.63, p=0.0213). No significant difference was found between the control group and experimental group 1.

The study suggests that physicians may be influenced by modified exposure claims to recommend novel tobacco products to their smoking patients. However, it also highlights that

Egphf gplckls{ 'Ucvgo gpv'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 75 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

physicians may need to be informed of FDA authorization for MRTP claims to increase their willingness to recommend such products. The authors conclude that given the expected resumption of US IQOS sales and marketing, future research should consider physicians as an important audience group when examining the effects of MRTP ads or interventions.

[2.4.4.8Á Suzuki et al., \(2023\) Comparison of Publications on Heated Tobacco Products With Conventional Cigarettes and Implied Desirability of the Products According to Tobacco Industry Affiliation: A Systematic Review. Nicotine and Tobacco Research](#)

Suzuki et al., (2023) carried out a systematic review to investigate whether studies affiliated with the tobacco industry are more likely to conclude that HTP are more desirable in terms of human health than combustible cigarettes (CC). A total of 134 studies published from January 2017 to March 2022 were analyzed with 64.9% (87 papers) being affiliated with the tobacco industry. The findings revealed that 56.3% (49/87) of industry-affiliated studies concluded that HTP were more desirable than CC, while only 19.1% (9/47) of non-industry-affiliated studies shared this view ($p < .01$).

Suzuki et al. noted that none of the industry-affiliated studies looked at outcomes of clinical relevance, such as disease occurrence, but rather, tended to focus on ‘surrogate outcomes’ such as *laboratory measurements in place of a clinically meaningful outcome*.

The authors concluded that the tobacco industry markets HTP as a reduced harm tobacco product, compared to CC and that it reinforces this message through the majority of tobacco industry-affiliated papers that were written during the period examined. The authors raise concerns about potential bias in favor of HTP and suggest caution is used when interpreting the findings of such studies.

They highlight that of the independent studies examining HTP use, 13 concluded that HTP were harmful to human health and that this was independent of comparison between these devices and CC, on the basis that HTP contain toxicants such as propylene glycol that are known to be harmful to human health. They note further that some of these toxicants are produced in larger quantities in HTP than in CC or other combustible tobacco products.

[2.4.4.9Á Duan et al., \(2023\) Health warning labels on heated tobacco products and their impact on use intentions and risk perceptions: a cross-sectional study of adult tobacco users in the US and Israel. Israel Journal of Health Policy Research](#)

Duan et al. reviewed cross-sectional survey data utilizing information collected via Ipsos Panel from October to December 2021 to examine past month tobacco use and awareness of HTP, obtained from 424 adults (18–45 years) in the United States (n=125) and Israel (n=299). Purposive sampling was used to obtain ~40% tobacco users and sufficient representation of racial/ethnic minorities to allow subgroup analyses. The authors carried out a multivariate analysis that looked at sociodemographics on the impact of health warning labels on HTP and how the health warning labels affected use and perception of HTP.

Eqlhř gplkrlř 'Ucvgg gpl'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 76 of 82"
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

Among adult tobacco users who were aware of HTP, the majority (87.7%) reported noticing HTP health warning labels. Of these, 27.7% reported that they became more concerned about HTP use after reading the health warning labels, 22.6% felt reassured about HTP, and 49.7% reported no effect.

The reported effects of HTP health warning labels were not associated with HTP risk perceptions. Furthermore, participants who reported increased concern or reassurance from HTP health warning labels exhibited greater intention to use HTP. Certain groups, such as other tobacco users, respondents from Israel, females, and those who had a less than college level education, were more likely to be reassured about HTP following reading health warning labels.

The authors stress the importance of interventions such as prevention campaigns aimed at those who are more likely to use tobacco products, on the harmful health effects of HTP. The authors also recommend restrictions on HTP advertising as they conclude that HTP marketing and the wording of many health warning labels being the same as that on combustible cigarette packets, may cause readers to believe that the health warning label

relates to cigarettes and not to HTP. Further research is recommended by the authors, to evaluate the effectiveness of different types of HTP health warning labels in communicating risks and discouraging use.

2.4.4.10 [Goulette et al., \(2023\) Perceptions of harmfulness of heated tobacco and nicotine vaping products compared to cigarettes, and the association of advertising exposure on harm perceptions among adults who smoke in South Korea: Cross-sectional findings from the 2020 ITC Korea Survey. Tobacco Induced Diseases](#)

Goulette et al., (2023) examined adult smoker perceptions of the harmfulness of HTP and nicotine vaping products (NVPs) compared to cigarettes, NVPs to HTP, and self-reported exposure to HTP/NVP advertising in South Korea. They also looked at the association between exposure to marketing and harmfulness perceptions.

The study used data from the 2020 International Tobacco Control Korea Survey. Study participants fell into the following categories: exclusive smokers (n=1,845); individuals who consumed both HTP and cigarettes (n=1,130); individuals who consumed both nicotine vaping products (NVPs) and cigarettes (n=224); and individuals who consumed all three products (n=514).

The study found that 27.5% of respondents believed HTP to be less harmful than cigarettes, and 23.4% perceived NVPs as being less harmful than cigarettes. Exclusive cigarette smokers were less likely to perceive HTP and NVPs as less harmful to health, compared to dual HTP + cigarette consumers, dual NVP + cigarette consumers, and triple consumers (all p<0.001). Half of respondents perceived NVPs as being equally harmful as HTP.

The authors found that exposure to HTP/NVP advertising was associated with perceiving these products as less harmful than cigarettes. The highest odds of perceiving HTP/NVPs as less

Equivalency of 'Ucvgv' and 'Ucvgv'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 77 of 82"
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

harmful than cigarettes were associated with exposure to transportation ads, newspapers/magazines, and stores where tobacco is sold.

The study concluded that approximately a quarter of adult Korean cigarette smokers perceive HTP and NVPs as less harmful than cigarettes and reported that this is consistent with studies by Kim et al and of smokers in Japan.

2.4.4.11 [LoParco et al., \(2023\) Associations Between Pro/Anti-Tobacco Media and Messaging Exposure and Knowledge and Support of Smoke-Free Policy Among Adults in Armenia and Georgia. Journal of Public Health Management and Practice](#)

LoParco et al., (2023) analyzed survey data from 1468 adults (31.6% past-month smokers) in 28 communities in Armenia and Georgia, two low- and middle-income countries that recently implemented national smoke-free policies. The surveys were conducted in 2022, with 763 participants from Armenia and 705 participants from Georgia. The average age of the participants was 42.92 years, and 51.4% of the respondents were female. The aim of the study was to examine the associations between exposure to pro- and anti-tobacco media and knowledge and support for smoke-free policies applying to alternative tobacco products (e-cigarettes and HTP) and various settings.

The study found that 79.2% of participants were aware that smoke-free policies applied to e-cigarettes and HTP, indicating a good level of knowledge. Moreover, the majority of participants expressed support for these policies applying to e-cigarettes and HTP and different settings. Exposure to media and community-based action supporting smoke-free policies was associated with greater knowledge and support for the policies. On the other hand, exposure to news opposing smoke-free policies and tobacco advertising was linked to reduced support.

These findings suggest that media campaigns and community mobilization efforts play a crucial role in increasing knowledge and support for smoke-free policies concerning e-cigarettes and HTP and their expansion.

2.4.4.12 [Seidenberg, et al., \(2023\) Effects of Modified Risk Tobacco Product Claims on Consumer Responses. Nicotine and Tobacco Research](#)

Seidenberg et al. (2023) conducted a study in the United States in August 2019 to examine how the specificity and content of modified risk tobacco product (MRTP) claims influenced consumer perceptions of tobacco products. The study included 3161 participants who were adult cigarette smokers. Among the participants, 63.9% were female, with an average age of 41.7 years. The sample consisted of 82.9% white participants and 9.2% Hispanic participants. Notably, there was low awareness of IQOS among all participants, with only 8.8% being familiar with it.

Using a 2 × 2 factorial design with an independent control, the participants were randomly assigned to view different MRTP claim conditions, specifically describing the benefits of switching to IQOS. The findings of the study indicated that participants viewing MRTP claims reported a slightly higher willingness to try IQOS compared to those in the control group (litter

English version of 'Ucvgv gpv'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 78 of 82"
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

message) ($d = 0.09$). Additionally, participants viewing any MRTP claim had lower scores for perceived risk ($d = -0.32$) and perceived exposure from complete switching from cigarettes to IQOS ($d = -0.31$).

However, the study also indicated that MRTP claims not only influenced perceptions of complete switching but also resulted in reduced perceived risk and exposure from partial switching. It is worth noting that the MRTP claims, regardless of their specificity, had a positive impact on consumer perceptions. However, participants found the claims to be less believable and easy to understand.

In conclusion, the study demonstrated that MRTP claims can effectively influence consumer perceptions, leading to a decrease in perceived risk and exposure while increasing the willingness to try IQOS.

[2.4.4.13 Kozii-Bredelieva et al., \(2023\) Levels of nicotine addiction in consumers of the latest tobacco products. Acta Medica Leopoliensia](#)

Kozii-Bredelieva et al., (2023) examined nicotine addiction levels in consumers of different tobacco products in the Lviv region. A survey was conducted among 817 individuals aged 18 to 45. The focus groups included 96 electronic cigarettes with nicotine (e-cigarette) users and 93 users of tobacco products for electric heating HTP. Nicotine addiction was assessed using the Fagerström test, and various analysis methods were employed.

Results showed that the average nicotine addiction score was slightly higher for HTP users (4.00) compared to combustible cigarette smokers (3.00) and e-cigarette users (3.00). Among HTP users, around 23.66% had a high level of nicotine addiction. For combustible cigarette and e-cigarette users, the percentages were 19.74% and 16.67% respectively. Combustible cigarette smokers had the highest percentage of individuals with an average level of nicotine addiction (21.05%), followed by HTP users (19.35%) and e-cigarette users (14.58%). Gender differences were observed, with HTP users having the highest proportion of individuals with a high level of nicotine addiction among male smokers (36.36%), while e-cigarette users had the lowest percentage (4.76%). Among female smokers, e-cigarette users had the highest percentage with a high level of nicotine addiction (25.93%), followed by combustible cigarette smokers (16.07%) and HTP users (12.24%). There was a negative correlation between the age of e-cigarette smokers and nicotine addiction levels, indicating that younger e-cigarette users establish a strong addiction quicker. HTP users showed a positive correlation between age and nicotine addiction, similar to smokers of combustible cigarettes.

In conclusion, this study highlights the higher nicotine addiction levels in TPEH smokers compared to combustible cigarette smokers and e-cigarette users. Gender differences were observed, with HTP users having the highest proportions of individuals with a high level of nicotine addiction among male smokers, while e-cigarette users had the highest percentage among female smokers. The findings emphasize the need for personalized prevention strategies to address the rise in new tobacco consumption methods and improve care for smokers in the region.

Eqlhf gplcklsf 'Ucvgo gpv'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 79 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

2.4.4.14 Wang et al., (2023) Profiles of tobacco product use and related consumer characteristics in the US and Israel: A multiple-group latent class analysis. *Global Public Health*

In their 2023 study, Wang et al. aimed to explore tobacco use profiles and consumer values among adults in the US and Israel. They employed latent class analysis and collected data from 382 participants in the US and 561 in Israel, focusing on seven tobacco products. The classes identified in the US were primarily cigarette users (58.1%), e-cigarette–no cigarette users (17.5%), primarily cigar users (14.9%), and poly-product users (9.9%). In Israel, the classes included primarily cigarette users (39.0%), moderate poly-product users (40.3%), high poly-product users (13.4%), and hookah users (7.3%). Data was collected from a cross-sectional online survey conducted between October and December 2021, specifically focusing on tobacco use and its associated factors. The study found a correlation between consumer values like innovation and e-cigarette and poly-product use in both countries. Demographic factors also played a role, with younger age linked to e-cigarette use and higher education associated with primarily cigar use. The study emphasized the importance of considering country-specific factors in understanding tobacco use patterns, as there were differences in use profiles and correlates between the US and Israel. These findings highlight the need to examine the targeting of different consumer segments in diverse tobacco markets and the influence of sociopolitical contexts on tobacco use.

2.4.4.15 Sharma et al. (2024) Exposure to IQOS ads and reduced exposure claims, and association with perceived risk from COVID-19 on IQOS purchase and use intentions: results from a web-based survey. *Frontiers in Public Health*

Sharma et al. (2024) conducted a cross-sectional online survey involving 604 adult participants aged 18-45 years in the US. The study aimed to investigate the impact of reduced exposure marketing claims on the likelihood of trying and purchasing *IQOS*. Participants were randomly assigned to view one of six *IQOS* advertisements that either included or excluded reduced exposure claims. They were then asked to complete a survey to assess their opinions on product appeal and their likelihood to purchase *IQOS*.

The study found that 32% of participants found the reduced exposure claims most appealing, while 27% found the picture of the *IQOS* device most appealing. Additionally, 20% of participants found the product description appealing, and 7% found each of the device name, health warning, and surgeon general's warning most appealing.

Current smokers showed a significantly higher appeal for reduced exposure claims, the device picture, and the device name compared to former or never-smokers. Former e-cigarette users also found reduced exposure claims and the device picture more appealing than current e-cigarette users, although this difference was not statistically significant.

In the ad condition without health warnings (ad condition A), 28% of participants found reduced exposure claims most appealing, while in the ad condition with health warnings (ad condition B), this figure rose to 35%. Participants who currently smoked displayed

Equity and Justice

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 80 of 82"
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

significantly higher average ratings for product appeal, intentions to purchase, and intentions to try *IQOS* compared to those who had never smoked or were former smokers. Additionally, former e-cigarette users reported higher product appeal, intentions to purchase, and intentions to try *IQOS* compared to everyday, someday, and never e-cigarette users.

A higher perceived appeal of *IQOS* was associated with a greater likelihood of purchasing and trying *IQOS* among participants. Among the participants who were aware of HTP, there was a higher product appeal and an increased likelihood of trying *IQOS* compared to those who were unaware. While there were variations in appeal and intentions among different smoker and e-cigarette user categories, no significant differences were found between the different ad conditions.

The researchers concluded that *IQOS* uptake is more likely in current smokers as well as a small number of those who have never smoked.

2.4.4.16 [Henderson et al., \(2024\) Content analysis of IQOS direct mail and email marketing in the US, Preventive medicine reports](#)

In their research, Henderson et al. (2024) conducted an examination of the direct mail and email marketing content of *IQOS* in the United States (US). The study focused on the period between September 2019 and July 2021 and was carried out in Atlanta, Georgia, which served as the initial test market for *IQOS* in the US.

The research team consisted of seven members who voluntarily registered for *IQOS* mail and email from PMI. They created accounts on IQOS.com, confirmed their status as adult smokers, and underwent an identity verification process. The registrations were conducted at different timepoints, with four team members signing up between August and September 2019, two between December 2019 and January 2020, and one in January 2021. Throughout the study, the team collected the *IQOS* mail and email marketing items they received and documented the details in a database. During the period of receiving marketing mail, two team members purchased an *IQOS* device, while another team member bought *HeatSticks* for non-study-related research purposes.

A total of 101 marketing items were collected, consisting of 88 direct emails and 13 mailed items. Out of these, 59 were distinct or unique. The recipients experienced significant variation in the frequency of marketing items, ranging from fewer than 5 to as many as 55 items during the study period. Among the unique items, 89.8% displayed images of the *IQOS* device or *HeatSticks*, while 10.2% showcased accessories. Approximately 67.8% of the items featured one or more individuals referred to as "models." Within the items that featured models, 82.5% showcased their faces, and within that subset, 93.9% portrayed a positive facial expression. The researchers also found that 70% of the items featuring people appeared to represent racial/ethnic minority groups, while 86.8% had at least one female-presenting model. Additionally, 37.5% of the items featured models that appeared to be young adults between the ages of 18 and 29 years.

Eqlhř gplcrhř 'Ucvgo gpv'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: IQOS devices & HeatSticks	Page 81 of 82"
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

Upon examining the contents of the marketing materials, the researchers reported that a significant majority of the items (91.5%) contained links or URLs leading to the official website or social media pages. These sites often provided online services such as online ordering (54.2%), social media engagement (44.1%), user experience information (49.2%), and details on where to purchase the devices (37.3%). Notably, 96.6% of the items prominently displayed nicotine warnings, while 94.9% included at least one Surgeon General's warning. However, the researchers noted that in 96.4% of cases, these warnings were not displayed prominently. It is also worth mentioning that the majority (94.9%) of the IQOS marketing items contained age restriction language.

Based on their findings, the researchers concluded that the direct marketing materials obtained during the study for IQOS contained elements that suggested potential race- and sex-based targeting. They acknowledged that this may have been influenced by the demographics of Atlanta. However, they emphasized the need for further research to comprehensively assess marketing practices, particularly for novel products, and to understand their impact on consumer interest and usage patterns.

2.4.5Á Tobacco Policy and Broader Research Topics

2.4.5.1Á Miyoshi et al. (2024) Foods and Beverages Associated with Smoking Craving in Heated Tobacco Product and Cigarette Smokers: A Cross-sectional Study. Tobacco Induced Diseases

Miyoshi et al. (2024) aimed to investigate the association between food and beverage types and smoking craving among Japanese adults between the ages of 40 and 69 who smoke cigarettes or use HTP. The authors also examined food preference variations associated with smoking craving between cigarette smokers and HTP users to gain insights into correlations between dietary habits and smoking behavior for potential use in smoking cessation interventions and public health strategies.

The study utilized a self-administered questionnaire, which was sent via mail. 800 participants were initially enrolled, and complete data was collected from 657 participants (response rate of 82.1%), including 178 never-smokers, 242 cigarette smokers, and 237 HTP users. Approximately half of the participants were female (n=335), and the median ages of men and women were 53 years and 52 years, respectively.

The study found that alcoholic beverages, coffee, and foods high in fat were significantly associated with a higher likelihood of smoking cravings, whereas fruits, dairy, and sweet and sour tastes were linked to a lower likelihood of experiencing smoking cravings.

Moreover, there were significant differences in dietary intake between the different smoking groups. Both cigarette and HTP smokers had significantly higher alcohol consumption compared to never-smokers, and the intake of dairy products and fruits was significantly lower in both groups compared to never-smokers. In terms of food preferences, HTP users

Eqlhř gplcrlř{ 'Ucvgř gpv'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.

Philip Morris Products S.A.	Confidential
2024 Annual Report: <i>IQOS</i> devices & <i>HeatSticks</i>	Page 82 of 82
Annex 2-1: Significant Findings on Scientific Publications	Version 1.0

demonstrated a higher preference for items such as ramen noodles, grilled meat, sauces with bitter, hot, spicy, and oily flavors, as well as Western and Korean cuisine categories.

The authors concluded that their study showed dietary disparities associated with smoking behavior between cigarette and HTP users and between never-smokers and smokers. They recommended that the study findings be considered when giving smoking cessation advice to smokers and HTP users. However, they also acknowledged that further research is necessary to determine the physiological mechanisms behind specific foods and drinks triggering a craving to smoke among smokers and HTP users.

2.4.5.2 Kang et al. (2024) Public support for tobacco endgame policies in South Korea: Findings from the 2020 International Tobacco Control Korea Survey. Tobacco Control

Kang et al. (2024) conducted a study to explore public support for six tobacco endgame policies in South Korea, using data from 4,740 participants who completed the 2020 International Tobacco Control (ITC) Korea Survey. The study categorized participants into four groups based on their nicotine use: (1) non-nicotine users, (2) users of vapes and/or HTP but not cigarettes, (3) exclusive cigarette smokers, and (4) dual users of cigarettes and vapes/HTP. The study assessed attitudes towards the policies, classifying responses as supportive, undecided, or opposed.

The largest groups of participants were exclusive smokers (n=1899, 40.1%) and dual users (n=1864, 39.3%). The study found that there was strong overall support for most policies, particularly for limiting nicotine content in cigarettes, with 68.4% (95% CI 64.6% to 72.3%) of participants showing support for this measure. There was also significant support for limiting the number of retailers permitted to sell cigarettes, with 68.1% (95% CI 64.5% to 71.7%) of participants in favor of this measure. However, support for banning cigarette sales if alternative products were available was lower, with only 45.0% (95% CI 40.9% to 49.1%) in favor of the policy.

Non-nicotine users showed the highest support across all policies, except for the policy of banning cigarettes if alternative products were available. Participants who responded as ‘undecided’ ranged from 13% to 25% for all policies.

The authors concluded that there is strong public support for tobacco control policies in South Korea and recommended further research on developing strategies to effectively implement well-supported policies.

English version of 'Ucvgv gpv'

Data and information contained in this document are considered to constitute trade secrets and confidential commercial information, and the legal protections provided to such trade secrets and confidential information are hereby claimed under the applicable provisions of United States law. No part of this document may be publicly disclosed without the written consent of Philip Morris Products S.A.