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REVIEW ARTICLE

Analytical Evaluation of the Chemical Content of HTPs Compared to Conventional Cigarettes

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Analytical Evaluation of the Chemical Content of HTPs Compared to Conventional Cigarettes

SUMMARY

Smoking is a major public health problem and one of the leading causes of preventable death in the world today. Despite well-known health risks, quitting remains a challenge for many smokers. This review aims to critically assess heated tobacco products (HTPs) as potentially less harmful alternatives to traditional cigarettes. This mini-review synthesizes findings from over 400 articles published in high-impact journals. Studies funded by tobacco companies or those with potential conflicts of interest were excluded to ensure unbiased results. Comprehensive analysis indicates that HTPs contain substantially fewer harmful and potentially harmful compounds (HPHCs) than conventional cigarettes. Because HTPs heat the tobacco instead of burning it, they prevent the production of harmful combustion byproducts. Nicotine levels in HTPs were found to be comparable to those in conventional cigarettes, offering similar experiences for users. HTPs are not entirely free of harmful substances, and they contain significantly fewer HPHCs due to the absence of combustion. The current body of evidence suggests that HTPs could serve as safer substitutes for smokers who have difficulty quitting. HTPs appear to be a promising option for harm reduction, mainly since they do not produce combustion byproducts, which are a significant source of carcinogens in traditional cigarettes.

Key Words: *Electronic cigarette, heated tobacco products, nicotine, tar, tobacco harm reduction, tobacco-specific nitrosamines*

Geleneksel Sigaralara Kıyasla HTP'lerin Kimyasal İçeriğinin Analitik Değerlendirmesi

ÖZ

Sigara içmek önemli bir halk sağlığı sorunudur ve dünya çapında önlenebilir ölümlerin önde gelen nedenlerinden biridir. İyi bilinen sağlık risklerine rağmen, sigarayı bırakmak birçok sigara içicisi için bir zorluk olmaya devam etmektedir. Bu derleme, geleneksel sigaralara potansiyel olarak daha az zararlı alternatifler olarak ısıtılmış tütün ürünlerini (HTP'ler) eleştirel bir şekilde değerlendirmeyi amaçlamaktadır. Bu mini derleme, yüksek etkili dergilerde yayınlanan 400'den fazla makaleden elde edilen bulguları sentezlemektedir. Tütün şirketleri tarafından finanse edilen veya potansiyel çıkar çatışması olan çalışmalar, tarafsız sonuçlar elde etmek için hariç tutulmuştur. Kapsamlı analiz, HTP'lerin geleneksel sigaralara kıyasla önemli ölçüde daha az zararlı ve potansiyel olarak zararlı bileşikler (HPHC'ler) içerdiğini göstermektedir. HTP'ler tütünü yakmak yerine ısıttığından, zararlı yanma yan ürünlerinin üretimini önler. HTP'lerdeki nikotin seviyelerinin geleneksel sigaralardakilerle karşılaştırılabilir olduğu ve kullanıcılar için benzer deneyimler sunduğu bulunmuştur. HTP'ler tamamen zararlı maddelerden arınmış değildir, yanma olmadığından önemli ölçüde daha az HPHC içerirler. Mevcut kanıtlar, HTP'lerin sigarayı bırakmakta zorluk çeken tiryakiler için daha güvenli ikameler olarak hizmet edebileceğini göstermektedir. HTP'ler, özellikle geleneksel sigaralarda önemli bir karsinojen kaynağı olan yanma yan ürünleri üretmedikleri için, zarar azaltma konusunda umut verici bir seçenek olarak görünmektedir.

Anahtar Kelimeler: *Elektronik sigara, ısıtılmış tütün ürünleri, nikotin, katran, tütün zararlarının azaltılması, tütüne özgü nitrozaminler*

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INTRODUCTION

Cigarette smoking is a serious public health problem and one of the primary preventable causes of death worldwide. Health risks (lung cancer, bladder cancer, respiratory system disorders, cardiovascular disorders, etc.) related to tobacco use have been well-established for more than 50 years. It harms nearly every organ of the body, leading to many diseases, including cancer, heart disease, stroke, asthma, and emphysema. According to the 2019 Global Burden of Disease Study, more than 1.1 billion people smoke worldwide, and 7.7 million people die every year from smoking-related diseases (GBD 2019 Tobacco Collaborators, 2009). It is expected that the number of smoking-related deaths that occur annually will continue to increase even after tobacco use starts to decrease since smoking-related diseases develop over time (WHO, 2019). Smoking, the traditional method of obtaining nicotine through the combustion of tobacco, produces emissions that contain more than 7000 chemicals. Of these chemicals, at least 250 compounds, such as hydrogen cyanide, carbon monoxide, polycyclic aromatic hydrocarbons (PAHs), and ammonia, are harmful to health (NIH, 2017). PAHs are a class of compounds composed of two or more fused benzenoid rings. They have carcinogenic and mutagenic properties. PAHs are formed due to incomplete combustion, and benzo(a)pyrene is a biomarker of them. Most PAHs are found in cigarette smoke (Vu et al., 2015). Second-hand smoke, also known as ETS, is a mixture of the smoke resulting from the burning of tobacco products during smoldering (sidestream smoke) and the part of the mainstream smoke exhaled by active smokers. Hence, not only tobacco smokers but also smokers are exposed to these chemicals and thus at risk for tobacco-related diseases. Second-hand smoke causes premature deaths among nonsmokers as well as numerous health problems such as ear infections, asthma attacks, sudden infant death syndrome, and respiratory infections, especially in infants, and children (EPA, 2021). Due to the severe health risks of smoking, undoubtedly, the best solution to prevent the harms and health risks of smoking is to quit smoking. However, some smokers do not succeed in quitting smoking for many reasons. Due to the severe health effects of cigarettes, an alternative to cigarettes was sought for less harmful products. Over time, various products have been released to the market. These products were made to contain nicotine or to meet the ritual of smoking and were made attractive with certain flavors. Heated tobacco products (HTPs) and electronic cigarettes (e-cigarettes) were widely sold. HTPs were introduced to the market as advantageous products because they heat the tobacco at high temperatures but do not burn the tobacco, thus avoiding the formation of combustion products and providing the smoking ritual due to the tobacco it contains. Studies have been conducted to evaluate these products regarding the chemicals they contain, their emissions, and potential health risks, but with conflicting results (Bekki et al., 2017; Lu et al., 2021; Phillips et al., 2018; Titz et al., 2018).

In the present review, as mentioned above, although there are many alternatives to cigarettes, only HTPs will be mentioned because it is well-known that there are significant differences between HTPs and other alternatives (such as e-cigarettes, which are close to the smoking ritual). Nevertheless, as different possibilities are addressed in some of the studies referenced in the review, these will be briefly outlined. It should be noted, however, that the review also encompasses other subjects.

Heated tobacco products versus conventional cigarette

Nicotine is the primary psychoactive substance in tobacco products that leads people to use tobacco products. Given that nicotine is a natural component of tobacco, any product that contains tobacco, of course, contains nicotine. Nicotine is a highly addictive substance, preventing even smokers who would like to quit smoking from giving up smoking.

Millions of people die every year due to smoking-related diseases. Today, however, it is not the nicotine that causes illness and death but the harmful and potentially harmful compounds (HPHCs) formed by the combustion of tobacco (FDA, 2021). Exposure to conventional tobacco smoke has no safe level. The tobacco found in a conventional cigarette transforms into ash and smoke as it burns between 400°C and above 1000°C. Three elements, i.e., tobacco, oxygen, and the necessary amount of heat to activate the reaction, should be available for combustion. Incomplete combustion, i.e., pyrolysis, of traditional cigarettes, primarily due to insufficient oxygen, also leads to the formation of HPHCs due to thermogenic degradation (Aver et al., 2017).

For smokers who cannot quit smoking for various reasons or have repeatedly tried to quit smoking but failed, novel products, such as heated tobacco products with unique mechanisms preventing the combustion of tobacco, are developed and released to the market as safer alternatives to cigarettes. Heat-not-burn tobacco (HnB) products which is a type of HTP, snus, and e-cigarettes, are other alternatives and are also referred to as new-generation products (NGPs). HnB tobacco products heat the processed tobacco instead of combusting or burning it. HTPs are not the same as e-cigarettes since e-cigarettes heat liquids that usually contain nicotine derived from tobacco; while HTPs heat tobacco leaves, e-cigarettes do not contain tobacco. This is the first and most fundamental difference between e-cigarettes and HTPs, but when examined, it will be observed that there are significant differences between them.

HTPs are commercially available systems consisting of a charger, a holder, tobacco sticks, plugs, or capsules (Simonavicius et al., 2019; Auer et al., 2017). Among HTPs are IQOS (Phillip Morris International), PAX (PAX Labs), Glo (British American Tobacco), and Ploom (Japan Tobacco International) brand products, all of which produce aerosols that contain nicotine and other chemicals. Table 1 summarizes new generation products and leading tobacco companies. HTPs allow the users to mimic typical smoking and give the real taste of tobacco. In addition, the fact that they do not produce fire or ash is another reason smokers prefer HTPs.

Table 1. New generation products and main tobacco companies

Year	Company	[1]Brand Name/Slogan	Current (C) / Discontinued (D)
1980s	Tobacco companies first developed HTP technology		
1988	ATC-RJR	Premier	D (1989) Not like taste and smell.
1996	ATC-RJR	Eclipse/ “imagine the unimaginable”	D (up to 2014)
1998	PMI	Accord/ “the time is right”	D (up to 2006) Difficult to use, not good taste; Not as satisfying as traditional cigarettes
2005	BAT	iFuse (similar to PloomTech) A hybrid product	D no longer available and was superseded by “Glo”.
2007	PMI	Heatbar (Accord is rebranded)	D Not obtaining any significant user reception; discontinued from Sweden and Australia.
2010	JTI	Ploom	D
2014	RJR (bought by BAT)	Revo (New version of “Eclipse”)	
2014	PMI	IQOS/ (New version of “Accord”) “This changes everything”	C
The second half of 2014	PMI	IQOS/ “I Quit Ordinary Smoke” The use of misleading term” according to the TCRs	C
February 2015	JTI	Ploom (later rebranded as Pax Labs)	JTI and Ploom Inc. ended their partnership
December 2016	PMI	IQOS	Applied to FDA to classify IQOS as MRTP
In February 2018	PMI	IQOS	C Around 30 countries
Early 2018	[2]All transnational TC	Ploom Three products available	D They remained on the market until 2019
2019	PMI	IQOS FDA partially* authorized MRTP application.	C “reduced exposure to harmful substances” and “*not reduce the risk of disease and death.”
2019	IT (Now IB)	Pulze	C
2019	BAT	Glo / 3 versions (hybrid like the iFuse) Glo Pro, glo Nano, glo Sens “a real game changer for consumers”	D
By 2019	BAT and PMI-tested devices using carbon tips as the heat source		
By July 2020	BAT	Glo Latest brand “GloHper”	C Glo website is linked to retail sites in 17 countries other than Canada.
July 2020	PMI	IQOS	partial approval applying to the marketing of IQOS
By 2021	PMI	IQOS	C 64 markets

[1]Brand names may vary in different countries; [2]Except IT included HTPs their portfolio; TC, Tobacco Company, ATC, American Tobacco Company; RJR, RJ Reynolds; TCRs, Tobacco Control researchers; PMI, Phillip Morris International; BAT, British American Tobacco; IT, Imperial Tobacco; IB, Imperial Brand; JTI, Japan Tobacco International; US, United States; FDA, Food and Drug Administration; MRTP, Modified Reduced Tobacco products;

Classification of Heated Tobacco Products

The British Government categorized HTPs into three categories. In addition to these three categories, the World Health Organization (WHO) also included the new carbon-tipped devices in HTPs (WHO, 2020). These three different classes of HTPs produce vapor from tobacco or non-tobacco sources are:

1. Directly heating the processed tobacco,

2. Heating the processed tobacco in a vaporizer or

3. Passing the vapor from non-tobacco sources over processed tobacco to obtain the flavor. The HTPs that use the vapor from non-tobacco sources are called the HTP "hybrids" (Treasury, 2018).

The absence of combustion is critical in HTPs that do not produce HPHCs, including carbon monoxide. The WHO Framework Convention on Tobacco Control (FCTC) has addressed the health effects of second-hand smoke. In this regard, WHO stated in its "2018 HTPs fact sheet" that data on the health effects of second-hand exposure to HTPs are insufficient (WHO, 2018). Environmental Protection Agency (EPA) stated that second-hand smoke causes some diseases and has numerous harmful effects on nonsmoking adults and children. EPA classified second-hand smoke as a Group A carcinogen in humans (EPA, 2021). In line with EPA, the Centers for Disease Control and Prevention (CDC) reported that among nonsmoking adults, exposure to second-hand smoke contributes to death and causes diseases (stroke, lung cancer, coronary heart diseases, etc.) and in infants it causes sudden deaths (CDC, 2020). Second-hand smoke is addictive because of the nicotine alkaloid. Further independent studies are needed to clarify the health effects of second-hand exposure.

The US Family Smoking Prevention and Tobacco Control Act (FSPTCA) requires premarket authorization for all tobacco products (Section 910). It does not allow manufacturers to market tobacco products on the basis that they reduce the risk of developing tobacco-related diseases. HTPs cannot be marketed unless authorized by the Food and Drug Administration (FDA) since FSPTCA stipulates that all tobacco products, including modified-risk tobacco products (MRTPs) such as HTPs, are regulated by FDA. For this reason, manufacturers must scientifically prove that their products reduce the risk of tobacco-related diseases before marketing them and submitting an MRTP application (Section 911) to the FDA (Lempert and Glantz, 2018). FSPTCA defines an "MRTP" as "any tobacco product sold or distributed for use to reduce harm or the risk of tobacco-related diseases associated with commercially marketed tobacco products" (FDA, 2020). Only one HTP system (IQOS and three of its tobacco-containing heat-stick products) was authorized to be marketed as MRTPs by the FDA on July 7th, 2020, since it was scientifically proven that these products heat tobacco without burning, they reduce the formation of HPHCs, and switching from regular cigarettes to these products reduces the exposure to HPHCs (FDA New Release, 2020).

It is essential to understand the health effects of HTPs that substitute cigarettes, particularly on chronic obstructive pulmonary disease (COPD) patients. However, considering that smoking is a habit with long-term exposure, there are not enough studies that compare the long-term health effects of HTPs with those of conventional cigarettes. Bekki et al. (2017) conducted the first study evaluating HTPs at the National Institute of Public Health in Japan. They measured basic HPHCs such as carbon monoxide, tar, nicotine, and tobacco-specific nitrosamines in the mainstream smoke of IQOS and its tobacco filler as well as conventional combustion cigarettes, i.e.,3R4F, a relatively high yield cigarette and 1R5F, a low yield cigarette, since nicotine and tar amounts were written on the conventional tobacco packages in Japan, but not on IQOS packages. They found that the nicotine levels in IQOS were almost the same as those in conventional cigarettes. On the other hand, the tar levels of IQOS were half or less than half of those of conventional cigarettes, and the carbon monoxide levels of IQOS were approximately one-hundredth of conventional cigarettes. In summary, they concluded that the amounts of hazardous compounds in the mainstream smoke of IQOS were much less than those in conventional cigarettes (Bekki et al., 2017).

The previous study on the long-term health effects of HTPs was performed by Polosa et al. (2021) on two groups of patients. Group 1 consisted of 19 COPD patients who significantly reduced or stopped smoking after switching to HTPs. Group 2 consisted of 19 COPD patients with age and gender characteristics that matched the patients in Group 1 and who used HTPs for 12, 24, and 36 months. Parameters such as the number of cigarettes smoked daily, disease exacerbations, lung function test results, self-reported outcomes, and distance walked in 6 minutes were monitored in both groups for three years. Consequently, significant improvements were recorded in respiratory symptoms, and all other parameters in patients who used HTPs (Polosa et al., 2021), supporting the hypothesis asserted by tobacco companies that avoiding exposure to chemicals produced by the combustion of cigarettes by switching to HTPs will improve patients' health. It was also suggested that switching from conventional cigarettes to HTPs might be a safer alternative to conventional cigarettes (Szymanski et al., 2021). In a randomized, controlled study conducted with 180 Japanese subjects, the biomarkers of exposure (excluding nicotine and including exhaled carbon monoxide) were analyzed on day five after switching from conventional cigarettes to using glo™/THP1.0 or IQOS/THS, resulting in a reduction in smoke toxicants (Gale et al., 2018). The harm is expected to be higher when this data obtained from acute exposure is used in long-term chronic studies. Unfortunately, there have been no epidemiological studies on these products, unlike conventional cigarettes. This makes it impossible to assess the safety of not only HTPs but also other alternative products. Evaluations are currently based on acute exposures or animal experiments.

Tobacco-specific nitrosamines and carbonyl compounds regulated by WHO were also detected in the mainstream smoke of HTPs, yet in lesser amounts than conventional cigarettes. Furans derived from flavorings and pyrimidines are in lesser amounts in HTPs than conventional cigarettes. As in foods, furans in HTPs are produced by the Maillard reaction, the reaction of sugar and amino acids in tobacco leaves. Both furan and pyrimidine concentrations are lower in HTPs than in conventional cigarettes (Bekki et al., 2021). HTPs are generally used in combination with other products (including tobacco cigarettes by the youth and people who never smoke (Znyk et al., 2021). It is not possible to distinguish whether tobacco cigarettes or HTPs are responsible for any adverse health effects observed with such combined use. Independent studies have proven that harmful chemicals emitted from HTPs are less than conventional cigarettes (Znyk et al., 2021; Cancelada et al., 2019; Mallock et al., 2018); however, they have not been completely eliminated (Uchiyama et al., 2018). A study investigated whether IQOS, an HTP, was less harmful than conventional products and assessed its impact on indoor air quality. Consumable tobacco plugs were analyzed by gas chromatography-mass spectrometer (GC-MS) to quantify 33 volatile organic compounds in mainstream and side stream emissions of IQOS. Consequently, fewer harmful products were found in IQOS than in conventional products and that IQOS was a weak indoor air polluter (Cancelada et al., 2019). Total particulate matter (TPM), water, aldehydes, nicotine, and other volatile organic compounds (VOCs) generated with the Health Canada Intense smoking regimen in HTP emissions were analyzed, and the nicotine levels in HTP emissions were found to be comparable to those of combusted cigarettes. In addition, it was observed that the aldehyde levels (approximately 80–95%) and VOCs (97% to 99%) were also lower in HTP emissions than in the emissions of combusted cigarettes (Mallock et al., 2018). Phillip Morris International (PMI) conducted a 90-day OECD TG 413 rat inhalation study using carbon HTP (CHTP1.2) to determine whether, compared to combusted cigarettes, CHTP1.2 results in reduced exposure to harmful constituents and reduced respiratory tract irritation and systemic and pathological effects. CHTP is a single-use, disposable tobacco product that is similar in appearance and use to cigarettes. The CHTP device uses a fast-burning carbon heat source to heat the tobacco plug inside a specially designed rod, producing an aerosol containing nicotine and tobacco flavoring. During use, the temperature of the tobacco within the tobacco stick does not exceed a well-defined threshold, which serves to prevent combustion and, as a consequence, markedly restricts the formation and transfer of harmful smoke constituents into the aerosol. As a consequence, they found that CHTP1.2 aerosol contained approximately one-third TPM, one-twenty-fifth CO, two-fifth formaldehyde, one-eighth acetaldehyde, and one-sixth acrolein compared to those of combusted cigarettes at the same nicotine concentrations (Phillips et al., 2018).

METHODS

Review the PRISMA flow diagram

Simonavicius et al. (2019) conducted a systematic review of the literature published between 2009 and 2017 and indexed by databases such as Web of Science and Scopus, etc., to determine the differences between the independent and tobacco industry-funded studies on available HTPs (Figure 1 and Table 2). They found that HTP emissions under the Health Canada Intense (HCI) regimen contained 18% to 73% less nicotine, ≥98% less CO, and ≥62% fewer HPHCs and tar than cigarettes. One of the independent studies reported significantly less tar and more tobacco-specific nitrosamines in HTPs than tobacco industry-funded studies. There were heterogeneities between the 31 reviewed studies depending on the tobacco company that funded the study. A study conducted with users and bystanders exposed to the toxicants revealed lesser amounts of harmful chemicals in HTPs than in conventional cigarettes. In this review of studies published up to November 2017, nicotine levels and HPHCs in mainstream HnB emissions compared to conventional cigarettes are reported (Simonavicius et al., 2019). In comparison, this study featured a systematic review of the literature published in the English language between January 2018 and April 2022 and indexed by PubMed, Scopus, and Elsevier databases. For this purpose, databases were searched using various synonyms and combinations of keywords such as "heat does not burn", "heated tobacco products", "less harmful heated tobacco products" and brand names (IQOS, Ploom, glo) and 447 publications were obtained. With the keywords given in PubMed, Scopus, Web of Science, and Elsevier databases, 447 articles were found from January 2018. The number of articles decreased to 423 after excluding articles without English text and articles outside the study's scope. After excluding irrelevant articles in terms of title, abstract, and content, the number of articles decreased to 407. The number of articles decreased to 16, especially when studies measuring HPHC content and the most commonly used smoking regimen Health Canada Intense (HCI) (i.e., 55 ml puff volume, 2 sec. duration, 30 sec. puff interval) were included. Figure 1 summarizes the study's inclusion and exclusion criteria (Figure 1). In addition, only independent studies were considered, and the studies carried out or sponsored by the tobacco companies, as well as the studies deemed to give rise to a conflict of interest potentially, were excluded.

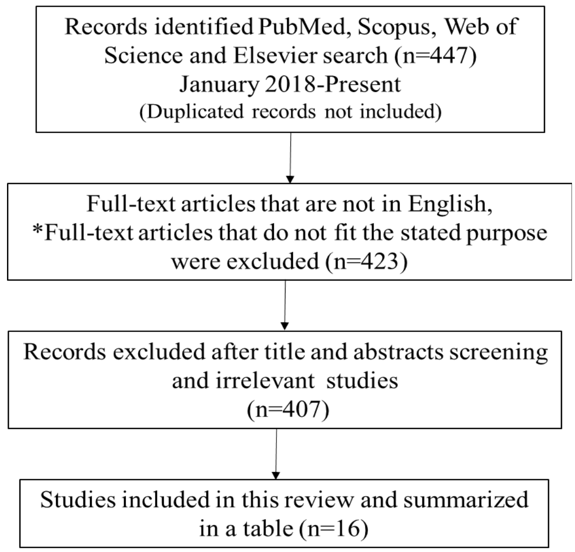

Figure 1. Systematic review PRISMA flow diagram according to inclusion criteria

** Full-text articles that do not fit the stated purpose are awareness of HTPs usage, the use of HTPs and disease relation, method development for measuring HTPs etc.*

Table 2. Studies comparing nicotine and HPHC levels in emissions of HTPs with conventional cigarettes over the last 5 years

Authors, year of publication	Heated Tobacco Products (HTPs)		Conventional Tobacco Cigarette (CTC)	Method	Results
Farsalinos et al ., 2018	Formaldehyde: 5-6,4 µg/stick Acetaldehyde:144,1-175,7 µg/stick ACR: 10,4-10,8 µg/stick PA:11,0-12,8 µg/stick CA :1,9-2,0 µg/stick	Formaldehyde:0,5-1,0µg/12 puffs Acetaldehyde:0,8-1,5µg/12 puffs ACR :0,3-0,4 µg/12 puffs PA and CA (N.D)	Nic. levels (1.99 ± 0.20 mg/cig) were higher than HTPs and not statistically different from e-cigarettes.	GC-NPD	CTC levels in HTPs were lower (85-95%) than CTC and higher than e-cigarettes.
Leigh et al., 2018	HTP aerosols (IQOs, Amber, Tobacco flavor) TSNA was 8–22 times lower HTP aerosols than in CTC smoke. Nic: 1.4±0.2 mg from a single HeatStick (12 puffs)	Nic: 1.3±0.2 mg per 55 puffs-	Nic 2.1±0.1 mg per cigarette (8 puffs)	GC-NPD	TSNA levels respectively, (except N-Nitrosonornicotine ketone (4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone) (NNK) CTC>HTPs>e-cigarettes (per puff)
Caponnetto et al., 2018	IQOS Median exhaled breath CO (eCO) level (95%CI) reaching a max peak at 15 min with 4.9 (4.1;5.6) ppm	Glo Med eCO level (95%CI) reaching a max peak at 45 min with 4.5 (3.9;5.2) ppm	12 control smokers≥10 CTC/day, 5 years CTC≥10 ppm for at least 30 min.	A hand-held eCO meter	Baseline eCO<5 ppm No significant changes between HTPs and Glo. Significant differences between (iQOS/GLO and CT were found.
Uchiyama et al., 2018	IQOS Total gaseous and particulate matter: 42mg/sticks Nic: 1200 µg/sticks Acetaldehyde: 360 µg/sticks Mean heating ^{0}C=210 Mainstream smoke PG: 240–850 µg/stick ACT: 140–260 µg/stick Nic content: 5.2 mg/stick, generated 1200 µg/stick	Glo Total gaseous and particulate matter: 29mg/sticks Nic: 510 µg/sticks Acetaldehyde: 520 µg/sticks Mean heating ^{0}C= 170 PloomTECH Total gaseous and particulate matter: 18mg/sticks Nic: 230 µg/sticks Acetaldehyde: 5900 µg/sticks Mean heating ^{0}C= 23 °C Nic Content: 1.7 mg/stick; generated 510 µg/stick	Total gaseous and particulate matter: 31mg/sticks Nic: 1900 µg/sticks Acetaldehyde: 18 µg/sticks Mean heating ^{0}C=460 PG: 11–28 µg/stick ACT: 50–110µg/stick Nic content: 6.5 mg/stick; generated 230µg/stick	GC-MS, GC-TCD	Chemicals from HTP were less than those from CTCs, except water, propylene glycol, glycerol, and acetol.
Farsalinos et al., 2018	IQOS Regular Tobacco Nic content: 15.2 ± 1.1 mg/g tobacco Menthol Tobacco Nic content: 15.6 ± 1.7 mg/g tobacco Regular Tobacco Nic (aerosol): 1.40 ± 0.16 mg/12 puffs Menthol Tobacco Nic (aerosol): 1.38 ± 0.11 mg/12 puffs	(Ciga-like, eGo-style, and variable wattage) Custom-made liquid: 2% nicotine	Nic 1.99 ± 0.20 mg/cigarette		Although the Nic content in HTP was similar to in CTC, HTP yielded higher levels of Nic than aerosolized e-cigarettes but lower than CTC.

Cancelada et al., 2019	Blue, Amber, and Yellow Label Heatsticks 33 VOC quantified Acetaldehyde, DAAN, PA, BA, benzaldehyde, mACR, CA, and BUTA, IQOS emissions were higher than e-cigarettes.		Isoprene, phenol, pyridine, benzene, acrylonitrile, cresols, and quinolone emissions> IQOS CC emissions from CTCs were higher than IQOS emissions, except for BUTA and CA, which were similar to IQOS and CTC.	Headspace GC-MS	VOC and Nic increased with temperature (IQOS heatstick -at three different headspace temperatures; 180, 200, and 220°C).
Ishizaki and Kataoka, 2019	TSNAs IQOS (Marlboro) (ng/cig.) Mainstream smoke NNK, NNN, NAT, NAB 0.42 ± 0.01; 0.55 ± 0.03; 0.38 ± 0.07;0 .04 ± 0.00 Sidestream smoke NNK, NNN, NAT, NAB: -;-;-;-	Glo (Kent) (ng/cig.) Mainstream smoke NNK, NNN, NAT NAB 0.18 ± 0.01; ND; ND; ND Sidestream smoke NNK, NNN, NAT, NAB: -;-;-;- PloomTECH (Mevius) (ng/cig.) NNK, NNN, NAT: NAB ND 0.16 ± 0.01 0.09 ± 0.01 ND Sidestream smoke NNK, NNN,NAT, NAB: -;-;-;-	TSNAs Mainstream smoke Marlboro-regular Regular: NNK, NNN, NAT, NAB (4.00 ± 0.21; 4.11 ± 0.28; 3.73 ± 0.07; 0.59 ± 0.03) Sidestream smoke Regular 2.63 ± 0.20;1.63 ± 0.05; 0.88 ± 0.06; 0.28 ± 0.02 ***Marlboro (Menthol), MEVIUS (Menthol, Superlight, Original); not presented***	LC-MSMS	TSNAs in sidestream smoke NNK > NNN > NAT > NAB The TSNA contents were significantly lower in the mainstream smoke of HTPs than in the mainstream smoke of CTCs. CTCs are more harmful than HTPs. The TSNA content in the sidestream smoke of CTCs is relatively high and both smokers and non-smokers are exposed it. Cancer risk is higher than not only in smokers but in non-smokers exposed to CTCs.
Le Godec et al., 2019		Flavored Neostick (mg/stick) Total Particulate Matter:16,24±1,71 0,41±007 Gly:3,46±0,62 Unflavored Neostick (mg/stick) Total Particulate Matter:16,05±2,01 0,40±0,07 Gly:3,44±0,68	3R4F (mg/stick) Total Particulate Matter:36,89±1,51 Nic 1,90±0,1 Gly:2,36±0,22	Ames Test	Flavored and unflavored neosticks-Not mutagenic (Ames test) Flavored and unflavored neosticks-Induced mutagenicity less than 3R4F (MLA test)
Bentley et al., 2019	THS 2.2. (IQOS) in mainstream aerosol 529 chemicals (majority particulate and Gas vapor) at concentrations ≥100ng items (excluding water, Gly, Nic) Only a few compounds in THS2.2 aerosol exceeded concentrations measured in 3R4F reference cigarette smoke.	contains all 529 compounds that were present in THS2.2 aerosol (at concentrations ≥ 100 ng/item),	3R4F in mainstream smoke contain 529 compounds	GCxGC-TOF MS, LC+HRAM-MS (untargeted screening)	The complete list was not presented. Total reduction in the number and quantity of chemical components, including known HPHCs, in THS 2.2.
Li et al., 2019	THS 2.2. (IQOS) Total Particulate Matter, water, tar, Hydrogene cyanide; Ammonia, NAs, phenol, and PAHs, which are carcinogenic and mutagenic. Simulated pyrolysis of THS 2.2 heating sticks		CTCs	GC × GC-MS	Not presented all amounts on compounds Other than some carbonyls, ammonia, NAB at least 80% lower in THS 2.2. than CTCs. Tar and nicotine were similar.

Salman et al., 2019	IQOS aerosol Total Nic, PG, Veg. Gly. ROS: 6,26±2,72 nmol H_2O_2 /cigarette CCs: 472.4 ±19.35 µg/cigarette		CTCs-Marlboro red CCs:2033±35.72 µg/cigarette ROS: 46.83 ± 9.6 nmol H_2O_2 / cigarette (Only ISO regimen data)	HPLC, GC	ROS and CC levels were 85% and 77% lower than levels emitted by CTCs. Total Nic, PG, Veg. Gly were similar.
Hirn et al., 2020	Max usage level of 400 puffs, i.e., approximately 8 HTP tobacco capsules or 40 CTCs) HTP aerosol Ammonia: 20,1±1,1 PG: 25,2±60 Gly: 27,6±6 Formaldehyde: 0,74±0,099 Nic: 1,97±1,7 ACT:1,55±0,85		3R4F Ammonia:30±1,7 PG: 0,034±0,003 Gly: 2,23±0,08 Formaldehyde: 46,8±2,5 Nic: 1,97±1,7		The HTP aerosol was compared to 3R4F using a quantitative risk assessment approach. (Total 54 analytes). >90% reduction in non-cancer and cancer risk for HTP compared to 3R4F.
Hirano et al., 2020	Nic, 25,9-257µg/m³ (Tobacco Cigarette (TC): 3 µg/m³) Nic>TC $PM_{2,5}$<standard value of 15µg/m³/year $PM_{2,5}$ 492 and 413 µg/m³ (SD = 667, 466) at 1.0 and 1.8 m Indoor Nic: 2.6 and 2.7 µg/m³(at 1.5 and 2.5 m from the user) $PM_{2,5}$: 7.0 and 6.9 µg/m3 (SD = 11.6, 4.0)	$PM_{2,5}$<standard value of 15µg/m³/year Glo is slightly higher for $PM_{2,5}$ PloomTECH, at 21 and 10 µg/m³(SD) = 55, 6.6); Glo 330 and 99 µg/m3 (SD = 564, 119) at 1.0 and 1.8 m Indoor Nic: 2 2.3 and 3.0 µg/m3 (at 1.5 and 2.5 m from the user) PloomTECH $PM_{2,5}$: 6.5 and 7.0 µg/m³ (SD = 5.8, 2.7) Glo $PM_{2,5}$: 102 and 56 mg/m³ (SD = 95, 56)	$PM_{2,5>}$ 10,700 and >5800 µg/m3 (at 1.0 and 1.8 m from the user) Indoor Nic: 130 and 160 µg/m3	LC-MSMS	Nic>Tolarable Concentration PM 2,5m³-Hazard PM 2,5m³>IQOS>Glo
Kim et al., 2020	Three major brands of HTP sticks and devices have been used to produce HTP aerosol. HTP-Heating materials **Sample A** Formaldehyde: 0.138 ± 0.016 µg/stick Acetaldehyde: 0,616 ± 0.732 µg/stick ACR: 0.121 ± 0.109 µg/stick AT: 0.181 ± 0.200 µg/stick PA: 0.102 ± 0.119 µg/stick **Sample B** Formaldehyde: 0.945 ± 0.214 µg/stick Acetaldehyde: 1.21 ± 0.650 µg/stick ACR: 0.519 ± 0.379 µg/stick AT: 0.580 ± 0.305 µg/stick PA: 0.291 ± 0.139 µg/stick **Sample C** Formaldehyde: 0.641 ± 0.092 µg/stick Acetaldehyde:63,5 ± 18,4 µg/stick ACR: 0.220 ± 0102 µg/stick AT….NA PA: 1,710 ± 0.123 µg/stick	Tobacco sticks for HTP-HTP brands **Sample A** Formaldehyde: 0.640 ± 0.528 µg/stick Acetaldehyde: 26,4 ± 42,9 µg/stick ACR: 0.473 ± 0.4029 µg/stick AT: 0.348 ± 0.480 µg/stick PA: 0.783 ± 0.7719 µg/stick **Sample B** Formaldehyde: 0.546 ± 0.364 µg/stick Acetaldehyde: 14,4 ± 24,3 µg/stick ACR: 0.143 ± 0.047µg/stick AT: 0.317 ± 0.286 µg/stick PA: 0.682 ± 1.017139 µg/stick **Sample C** Formaldehyde: 0.539 ± 0.363 µg/stick Acetaldehyde: 24.5 ± 41.2µg/stick ACR: 0.243 ± 0.214µg/stick AT: 0.096 ± 0.166µg/stick PA: 0.291 ± 0.139 µg/stick Acetaldehyde:63.5 ± 18.4 µg/stick PA: 0.641 ± 0.854 µg/stick			Harmful compounds were come from the filter, not tobacco sticks. Heated tobacco stick filters had higher. Formaldehyde and ACR concentrations (0.945 ± 0.214 µg/stick and 0.519 ± 0.379 µg/stick) than the aerosols generated from heated tobacco consumable The amount of acetaldehyde and PA were higher in the heated filter than in the aerosol produced from heated tobacco consumable.

Bitzer et al., 2020.	IQOS 122 ± 9.6 µg/puff) 156 ± 44,6 µg/puff Glo (72± 10.6 µg/puff) 156 ± 44,6 µg/puff Ploom 18 ± 0 µg/puff SREC 71 ± 8.2 µg/puff) Mod: ND	156 ± 44,6 µg/puff The hybrid (Ploom)	Research Cigarette-1R6F Nic 190 ± 7,9 µg/puff (except Juul) 73.9 ± 7.5 pmol GPR:2982 ± 251 pmol/mg PPR: 392 ± 61.1 pmol/mg **e-cigarettes** Jull 5,3 ±0,5 pmol/ml SREC 40 ±0,8 pmol/puff Mod 48 ±1,8 pmol/puff	GC/ FID, EPR spectroscopy	No differences among HTPs (IQOS, Kent, Glo) HTPs emitted more radical than Jull. There was no particulate phase radical with IQOS, Glo, Ploom, SREC e-cigarettes emitted more radical than IQOS. 1R6F produced significantly more gas-phase radicals/ and more particulate-phase radicals than any other devices. No difference was among QOS, Glo, and SREC for Nic. The Juul and the IQOS were not different for Nic.
Protano et al., 2020	Data on indoor air-In a test room, measurements of 10, 4, 2.5, 1 µm (PM10, PM4, PM2.5, PM1) PM pollution was obtained from IQOS (n=6), Glo (n=4), Juul (n=3)in different flavors and Marlboro Gold.	Before and during each experiment (10–12 puff for about 5–6 min)			They worsen indoor air quality. Indoor PM1 was at lower conc.s than CTCs.

Table abbreviations; HPHC, harmful and potentially harmful constituents; HTPs, Heated Tobacco Products; CTC, Conventional tobacco cigarettes, Med, Median; TC, Tolerable concentration; ND, Not Detected; NA, Not Available.

Test Shower Cubicle (length 0.80 m × width 0.80 m × height 2.24 m); Test Room 25m^3 (length 3,44 m × width 7.26 m)

HeatSticks, regular", "balanced regular", "mint", and "menthol" tobacco sticks; NeoSticks, "bright tobacco", "fresh mix", and "intensely fresh" tobacco sticks; Tobacco caps, "Mevius Legular", "Cooler Green", and "Cooler Purple" liquid capsules.

ACR, acrolein, PA, Propionaldehyde; CA, Crotonaldehyde, eg., Regular; Ment., Menthol, Nic, Nicotine; CCs, Carbonyl compounds, TSNA, tobacco-specific nitrosamines; NAB, N'-nitroso anabasine; NAT, N'-nitrosoanatabine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosonornicotine, CO, Carbon monoxide; PG, Propylene glycol; ACT, Acetol; BUTA, Butanal; DAAN, Diacetylaceton; ACT, Aceton, BA, benzaldehyde; mACR, methacrolein; Gly, Glycerol, Veg. Gly., Vegetable glycerol; 3R4F, Reference Cigarette, AAs, Aromatic amines; VOCs, Volatile compounds ; Nas, N-nitrosamine; PAH, Polycyclic aromatic hydrocarbons; PPR, Particulate phase radical; GPR, Gas Phase Radical

GC-NPD, Gas Chromatography equipped with Nitrogen—Phosphorous Detector; GC-MS, as chromatography–mass spectrometry; GC-TCD, gas chromatograph/ thermal conductivity detector; GCxGC-TOF MS, LC+HRAM-MS, Liquid chromatography with high-resolution accurate mass spectrometry; Two-dimensional gas chromatography with time of flight mass spectrometry; MLA, Mouse Lymphoma Assay; ISO, International Organization of Standardization; GC/FID, gas-chromatography with flame-ionization detection

RESULTS and DISCUSSION

Carbonyl compounds in HTPs were 77-95% less than in conventional tobacco cigarettes (CTC) (Farsalinos et al., 2018; Salman et al., 2019). HPHCs (Uchiyama et al., 2018; Salman et al., 2019) and particulate matter (PM) (indoor) were also less in HTPs than in CTCs (Protano et al., 2020). Tobacco-specific nitrosamines (TSNAs) were 8–22 times less in HTP aerosols than in CTC smoke. CTCs had the highest amount of TSNAs, except 4-(methyltyramine)-1-(3-pyridyl)-1-butanone (NNK), which was followed by HTPs and then e-cigarettes (Leigh et al.,2018; Ishizaki et al., 2019). Caponnetto et al. conducted a study of exhaled breath carbon monoxide (eCO) as a combustion marker after using IQOS, Glo, and CTC. In their study, a total of 12 healthy smokers (6 Men, 6 Women) who smoked ≥10 conventional cigarettes per day for at least 5 years were recruited. During the screening, participants provided a baseline eCO≥10 ppm (ppm) and were trained for at least 30 minutes according to the recommendations of the HTP manufacturers. Participants were asked not to smoke for at least 12 hours before each training session. By the eligibility criteria, abstinence from smoking was verified by eCO measurements of ≤10 ppm obtained with a single breath using a handheld eCO meter (Micro CO; Micro Medical Ltd., UK). Once a baseline value was obtained, eCO was recorded at 5, 10, 15, 30, and 45 minutes after the first puff of the first round. eCO concentration was significantly different ($p<0.0001$) for both HTPs (IQOS and Glo) compared to conventional smoking, but not for iQOS compared to GLO. In eCO concentrations versus time, eCO concentrations of HTPs remained below 5ppm. The point at which the eCO concentration of conventional cigarettes did not increase, i.e. 5 ppm, represents the widely accepted eCO reference range for non-smokers (Caponnetto et al., 2018).

Significant differences were observed in nicotine levels between iQOS/GLO and CTC but not between HTPs and Glo. Nicotine levels in HTPs are similar to those of CTCs (Caponnetto et al., 2018). The amount of nicotine in HTP aerosols was higher than in e-cigarettes but lower than in CTCs (Farsalinos et al., 2018; Salman et al., 2019; Li et al., 2019). Volatile organic compounds (VOCs) and nicotine levels increase with temperature (180°C, 200°C, and 220°C) (23). E-cigarettes reportedly emit more radicals than IQOS, whereas HTPs emit more radicals than Jull. IQOS, Kent, and Glo have similar levels of radicals (Bitzer et al., 2020). The comparison of heated tobacco sticks and heated tobacco aerosol in terms of some chemicals, such as acrolein and formaldehyde levels, revealed that the levels of these chemicals were higher in the sticks than in aerosol (Kim et al., 2020).

It is well-established that tobacco smoking causes many diseases, including cancer, and that it is the nicotine that induces tobacco use. HTPs and e-cigarettes could be less harmful smoke/aerosol alternatives that satisfy users in terms of nicotine yet minimize the health risks caused by the harmful substances found in cigarette smoke. There is also evidence that these products help smokers quit tobacco smoking. It is not the nicotine that causes harm in tobacco cigarettes, but the HPHCs formed due to incomplete combustion. It has been demonstrated that HTPs also contain HPHCs in varying proportions, similar to those found in conventional cigarettes. However, the chemical composition of these HPHCs is significantly reduced or absent due to the absence of combustion in HTPs. Since different types of harmful substances are prominent in HTPs, the possible risk assessment of these substances should be made in detail. The studies conducted in vitro and animal experiments provide limited data for the safety of HTPs. Moreover, the absence of epidemiological studies that provide the most scientifically valuable data precludes making definitive judgments about the safety of HTPs. However, HTPs, which do not contain combustion products because they do not burn, are considered to be less harmful than conventional cigarettes and may be preferable for individuals who cannot quit smoking and have severe chronic diseases (such as cardiovascular disease).

AUTHOR CONTRIBUTION STATEMENT

Conception and design, data collection, analysis and interpretation, literature search, and preparing the text (BK).

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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