Expert opinion on heated tobacco products

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Preface

This expert opinion document is prepared on request of the Public Health Agency of Sweden by reviewing available scientific literature to guide all stakeholders towards developing risk assessment strategies for the safety of the recently launched heated tobacco products. The document in this regard aims to discuss the operational technology (heating versus combustion), composition of mainstream emissions, biomarkers of exposure, and potential adverse health effects of heated tobacco products.

Contents

Abbreviations

2-AN	2-Aminoaphthalene
3-HPMA	3-Hydroxypropylmercaptauric acid
cal	Calorie
CD4	Cluster of differentiation 4
CEMA	3-Cyanoethylmercapturic acid
CO	Carbon monoxide
CO_2	Carbon dioxide
COHb	Carboxyhemoglobin
COPD	Chronic obstructive pulmonary disease
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CRP	C-reactive protein
ECIG	Electronic cigarette
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCI	Health Canada Intense (a smoking machine test regime)
H_2O	Water
HPHC	Harmful and potentially harmful constituent
IL	Interleukin
IQOS	I Quit Ordinary Smoking (a HTP product)
ISO	International Organization for Standardization
J	Joule
NAB	N-Nitrosoanabasine
NAT	N´-Nitrosoanatabine
NNAL	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	Nicotine derived nitrosoamine ketone
NNN	N-Nitrosonornicotine
O_2	Oxygen
PAH	Polycyclic aromatic hydrocarbon
PMI	Philip Morris International
TCC	Traditional combustible cigarette
TNeq	Total nicotine equivalents
TSNA	Tobacco specific nitrosamine
VOC	Volatile organic compound
WHO	World Health Organization

Keywords

Combustion

Electronic cigarette

Exposure

Health effects

Heat not burn

Heated tobacco products

Heating

Tobacco

1. Introduction

Heated tobacco products (HTP) are a new category of tobacco products that heat processed tobacco leaf to about 350 °C to generate nicotine containing aerosol. This contrast[i]s burning of traditional combustible cigarettes (TCC), where temperatures up to 900 °C are reached [1-4]. In some HTP products, temperatures of around 550 °C have been reported [1]. HTP tobacco products are currently available in about 40 countries including Sweden [1,4,5]. The total sale of HTP products is expected to reach nearly 18 billion USD during 2021, a nine-fold increase during previous five years[1].

Table 1 lists some of the commonly available HTP products. Most of the HTP research data currently available were obtained with tobacco heating system 2.2 which has been marketed as "IQOS" (I Quit Ordinary Smoking) by Philip Morris International (PMI) [5]. The IQOS is operated by a battery-powered heating device with a heating blade that is inserted into a tobacco stick containing processed tobacco leaf (HTP sticks) [4]. The HTP sticks comes in different flavours (eg. menthol) as do electronic cigarette (ECIG) liquids. However, the HTP device heats actual tobacco leaf whereas the ECIG heats a liquid that may or may not contain nicotine [1-3]. The products "iFuse", "PloomTech", "lil hybrid", and "lil vapor" are hybrids between HTP and ECIG.

Heating versus combustion is the claimed operational difference between heated tobacco products and traditional combustible cigarettes.

Heating versus combustion is the basic operational difference between HTP and TCC. In this context it is important to note article 2, definition 5 of the 2014 European Union tobacco directive [6]:

> *"'smokeless tobacco product' means a tobacco product not involving a combustion process, including chewing tobacco, nasal tobacco and tobacco for oral use;"*

The directive further states (Article 2, definitions 9 and 10):

> *"'tobacco products for smoking' as tobacco products other than a smokeless tobacco product;"*
>
> *a 'cigarette' as a roll of tobacco that can be consumed via a combustion process;".*

Based on the above information, we have divided this expert opinion document in four sections to provide an overall idea about HTP tobacco products:

1. Heating versus combustion
2. Composition of mainstream HTP emissions
3. Biomarkers of exposure
4. Health effects of exposure to mainstream HTP emissions

Table 1. Examples of various HTP tobacco products [1-5]. Hybrid is a combination of features of HTP products and electronic cigarettes.

Product name	Company	Type
Accord	Philip Morris International	HTP
Eclipse	RJ Reynolds Tobacco Company	HTP
iFuse	British American Tobacco	Hybrid
IQOS	Philip Morris International	HTP
Kent Glo	British American Tobacco	HTP
lil hybrid, lil vapor	The Korea Tobacco and Ginseng Corporation	Hybrid
lil plus, lil mini	The Korea Tobacco and Ginseng Corporation	HTP
PloomTech	Japan Tobacco International	Hybrid
Premier	RJ Reynolds Tobacco Company	HTP

2. Heating versus combustion

Heat is energy transferred form a hotter to a cooler body due to a temperature gradient [7]. This leads to increased temperature, *heating*, of the object receiving the energy. The heat energy (thermal energy) is expressed in calories (cal) or joules (J).

Combustion is an exothermic chemical reaction between substances, usually including oxygen. *Exothermic* means that there is a net production of energy during the reaction, leading to increased temperature. Examples of definitions and descriptions of the term combustion are given in Table 2.

- Heating (sv upphettning): energy is added, leading to increased temperature (oxygen not needed). The process is endothermic as the object absorbs heat energy.
- Combustion (sv förbränning): energy is produced (usually by oxidation with oxygen), leading to increased temperature. The process is exothermic as the process releases heat energy.

Complete combustion requires an optimum combination of fuel and oxygen (O_2). During the complete combustion process, the fuel is completely burned in oxygen, leaving no or little byproducts. Thus, when a "pure" organic compound, such as a hydrocarbon is burned in oxygen, the reactions lead to production of carbon dioxide (CO_2) and water (H_2O). When other elements are burned, they typically produce the corresponding oxides. Burning of carbon will produce carbon dioxide, nitrogen leads to nitrogen dioxide and sulfur forms sulfur dioxide.

However, burning of biomass (including tobacco) is a complex process that involves many chemical reactions. The major steps may be summarized by the following pathways (adapted from Rein 2016 [8]):

1. **Pyrolysis (charring):**

   Fuel (solid) + Heat → Pyrolyzate (gas) + Char (solid) + Ash (solid)

2. **Heterogenous oxidation (smoldering combustion):**

   Char (solid) + O_2 (gas) → Heat + CO_2 + H_2O + Other gases + Ash (solid)

3. **Gas-phase oxidation (flaming combustion):**

   Pyrolyzate (gas) + O_2 → Heat + CO_2 + H_2O + Other gases

As indicated in the above pathways, a number of processes are involved. These may vary depending on a variety of factors including the composition and size of the burning material, the temperature, and the availability of oxygen. Accordingly, a variety of terms are used to describe the processes. The major ones are described in the following section, as they may be relevant for heating or burning of tobacco. It should be noted that some of these terms are partly overlapping.

Smoldering, or smoldering combustion, is the slow, low temperature, flameless burning of solid fuels. Unlike flaming combustion, smoldering occurs as oxygen reacts directly with the surface of the fuel. The heat released and the temperature during smoldering (typically 6-12 kJ/g and 450-700 °C) is lower than during flaming combustion (typically 16-30 kJ/g and around 1500 °C) [8].

In *flaming combustion* there are visible flames. Solid and liquid fuels are first heated and converted to gas. The combustion occurs in the gas near the solid or liquid [9].

Incomplete combustion (*pyrolysis*, see Table 3 for examples of definitions and descriptions) occurs when there is not enough oxygen for the fuel to fully react. In this case, not only carbon dioxide and water are produced, but also numerous byproducts. For example, when smoking a TCC, the smoke will include carbon monoxide, soot, tar, polycyclic aromatic hydrocarbons (PAH), nitrosamines and many other substances. Actually, over 5000 substances have been identified in TCC smoke (Rodgman and Perfetti 2009, cited in [10]). As with combustion, pyrolysis may be exothermic at some conditions [11].

Charring is the formation of char by heating (typically 430 °C or higher, see Table 4 for examples of definitions and descriptions) organic material such as wood under limited access of oxygen, which is a form of pyrolysis. The heat first removes water vapour and volatile organic compounds (VOC). Thereafter, hydrogen and oxygen are removed, so that primarily carbon remains. Charring can occur naturally in fires but can also be a deliberate reaction as in the production of coke and charcoal. Charring may be strongly exothermic [12].

Torrefaction of biomass is a mild form of pyrolysis occurring at 200-320 °C. Torrefaction changes the material for instance via Maillard reactions, reactions between amino compounds (amines, proteins etc.) and carbohydrates (sugars, cellulose etc.) such as in toasting bread. The decomposition of tobacco ingredients starts at different temperatures, beginning at about 150 °C for lignin and above 300 °C for cellulose. Torrefaction may be both endothermic (consuming energy) and exothermic (producing energy), depending on the temperature. For example, torrefaction of wood samples (5 mm) were endothermic up to about 270 °C and mainly exothermic at higher temperatures [13].

Soot production takes place at high temperatures (>1000 °C) during fuel combustion or biomass burning. The soot is formed by condensation of organic vapors, mainly PAH [14].

Most materials require a relatively high input of energy (high temperature) to start the combustion process. Exceptions are so called pyrophoric materials such as those used to create sparks in cigarette lighters and flintlock mechanisms in firearms. The temperature needed (ignition temperature) varies depending on the properties of the material as well as the partial pressure of oxygen. Ignition temperatures of some cigarette related materials are given in Table 5. For complex materials such as wood, the ignition temperature depends not only on the composition of the test material (which varies between wood species) but also its size, as illustrated by the different ignition temperatures between wood and saw dust, and between saw dust slabs of different thickness (Table 5).

For comparison, the average temperature in the burning zone of a TCC has been reported to 650 °C (470-812 °C) [15].The maximum temperature in the IQOS heating device is stated to be 320-350 °C, while the boiling point of nicotine is 247 °C [16]. A graphical comparison of TCC related processes is given in Figure 1.

Notably, HTP emission contains many of the VOC, PAH and inorganic compounds that are found in TCC smoke, some at levels not far lower or even exceeding that in the latter (see Table 8) [17]. It is unclear to what extent these compounds are formed by charring or torrefaction of the tobacco.

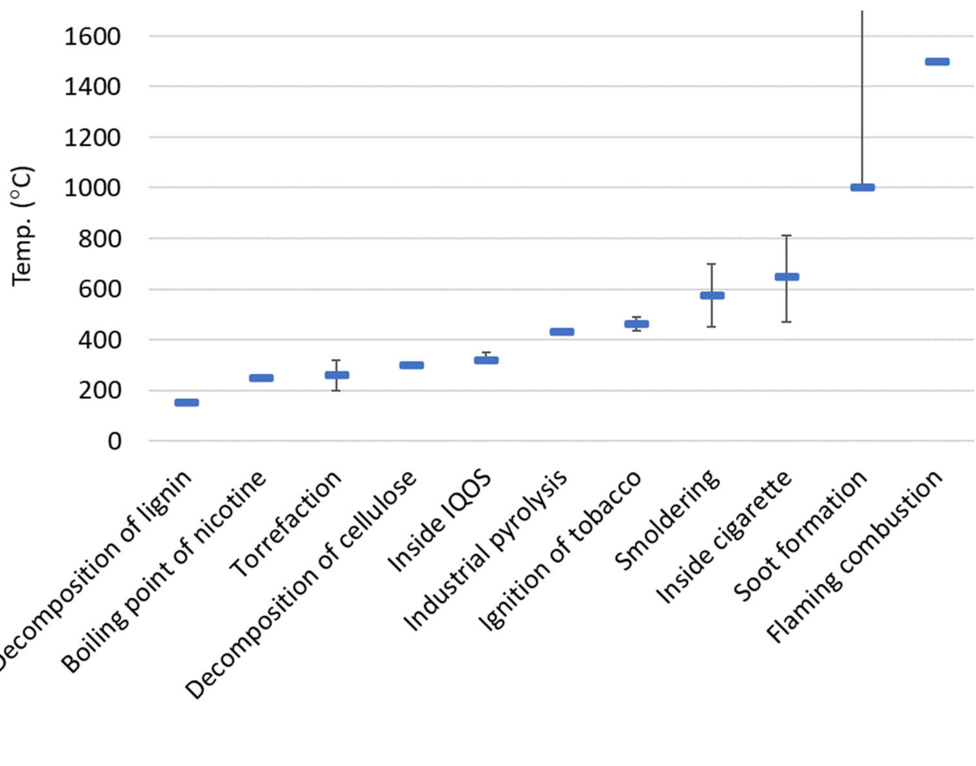

Figure 1. *Comparison of temperatures in cigarette-related heating processes.*

It is well known that oxidation with consumption of oxygen and generation of heat, carbon dioxide and carbon monoxide (CO) occurs also at low temperatures (ambient air temperatures or slightly higher). For example, in an experimental study with bituminous coal heated under 19 % oxygen, the amounts of carbon monoxide generated at 60, 70, 80 and 90 °C were 2, 9, 64 and 146 mg CO/kg coal respectively [18].

When organic material is stored in large volumes, as in wood chip piles, landfills, haystacks and coal mines, this low temperature oxidation may be significant already at "normal" ambient temperatures such as 20 °C and cause a self-heating process with accelerated oxidation, as the heat generation supersedes the heat loss to the environment. Eventually, when sufficiently high temperatures are reached, this will result in self-ignition and smoldering (if poor access to O_2) or flaming (if rich access to O_2) combustion.

No information on low temperature oxidation of tobacco leaves or cured tobacco was found in the literature, perhaps because tobacco is not stored in large enough piles to cause self-ignition. Nevertheless, it is reasonable to assume that tobacco in similarity with other organic materials is also oxidized already at low temperatures. This assumption is supported by the presence of carbon monoxide in the HTP aerosol.

In conclusion, exothermic oxidation is most likely present during heating of the HTP stick to 320-350 °C. Whether this process should be termed combustion depends on how the word is defined. Among the sources quoted in Table 2, all mention two characteristics of combustion, namely heat production and oxidation (with oxygen in the case of organic materials). One source also state that combustion is accompanied by generation of light (Oxford Dictionary [20]) while three state that it is usually or may be accompanied by generation of light (Encyclopedia Brittanica [19], Svensk ordbok [20], ThoughtCo [21]). A fifth source does not mention light (Nationalencyklopedin [22]).

In the absence of a clear definition of combustion, rather than looking at the presence or absence of light or the temperature, it seems wiser to look at the composition of the HTP aerosol compared to TCC smoke. This comparison (see chapter 3) reveals that carbon monoxide and a number of other TCC smoke constituents are present also in HTP aerosol, although mostly at lower concentrations, suggesting that processes comparable with low grade combustion are at hand in the HTP stick.

Table 2. Definitions and descriptions of combustion.

Source	Definition/description
Encyclopedia Brittanica [19]	Combustion, a chemical reaction between substances, usually including oxygen and usually accompanied by the generation of heat and light in the form of flame. The rate or speed at which the reactants combine is high, in part because of the nature of the chemical reaction itself and in part because more energy is generated than can escape into the surrounding medium, with the result that the temperature of the reactants is raised to accelerate the reaction even more.
Nationalencyklopedin [22]	Förbränning, exoterm kemisk reaktion där ett brännbart ämne (kol, väte, svavel, fosfor etc.) förenar sig med syre till en förbränningsprodukt (rökgas). Förbränning av t.ex. kol skrivs på följande sätt: $C + O_2 \Rightarrow CO_2$ + värme. Förbränning är alltså en oxidationsprocess i vilken kemiskt bunden energi överförs till värme. Förbränning kan starta med att värme tillförs utifrån så att bränslet uppvärms till antändningstemperaturen. Om lufttillförseln som svarar för reaktionens syrebehov är tillräcklig, fortsätter förbränningen av sig själv genom att det bildade värmet håller temperaturen uppe över antändningstemperaturen.
Oxford Dictionary [23]	Rapid chemical combination of a substance with oxygen, involving the production of heat and light.
Svensk ordbok [20]	Förbränning - kemisk reaktion mellan syre och ett eller flera andra ämnen vanligen under utveckling av värme el. eld.
ThoughtCo. [21]	Combustion is a chemical reaction that occurs between a fuel and an oxidizing agent that produces energy, usually in the form of heat and light. Combustion is considered an exergonic or exothermic chemical reaction. It is also known as burning. Combustion is considered to be one of the first chemical reactions intentionally controlled by humans. The reason combustion releases heat is because the double bond between oxygen atoms in O_2 is weaker than the single bonds or other double bonds. So, although energy is absorbed in the reaction, it is released when the stronger bonds are formed to make carbon dioxide (CO_2) and water (H_2O). While the fuel plays a role in the energy of the reaction, it's minor in comparison because the chemical bonds in the fuel are comparable to the energy of the bonds in the products.

Table 3. Definitions and descriptions of pyrolysis.

Source	Definition/description
Encyclopedia Brittanica [19]	Pyrolysis, the chemical decomposition of organic (carbon-based) materials through the application of heat. Pyrolysis, which is also the first step in gasification and combustion, occurs in the absence or near absence of oxygen, and it is thus distinct from combustion (burning), which can take place only if sufficient oxygen is present. The rate of pyrolysis increases with temperature. In industrial applications the temperatures used are often 430 °C (about 800 °F) or higher, whereas in smaller-scale operations the temperature may be much lower. Two well-known products created by pyrolysis are a form of charcoal called biochar, created by heating wood, and coke (which is used as an industrial fuel and a heat shield), created by heating coal. Pyrolysis also produces condensable liquids (or tar) and noncondensable gases. Pyrolysis transforms organic materials into their gaseous components, a solid residue of carbon and ash, and a liquid called pyrolytic oil (or bio-oil). Pyrolysis has two primary methods for removing contaminants from a substance: destruction and removal. In destruction, the organic contaminants are broken down into compounds with lower molecular weight, whereas in the removal process, they are not destroyed but are separated from the contaminated material. Pyrolysis is a useful process for treating organic materials that “crack” or decompose under the presence of heat; examples include polychlorinated biphenyls, dioxins, and PAHs. Although pyrolysis is not useful for removing or destroying inorganic materials such as metals, it can be used in techniques that render those materials inert.
Nationalencyklopedin [22]	Process vid vilken ett ämne upphettas utan närvaro av syre. Industriellt används pyrolys t.ex. vid torrdestillation av fasta bränslen i syfte att överföra dem i gasformiga produkter (se förgasning) och vid råvaruåtervinning av plast. På laboratorier används blixtvakuumpyrolys för att mycket snabbt sönderdela en organisk förening i gasfas, följt av uppsamling av de önskade produkterna på kylda ytor, vanligen vid flytande kväves temperatur. Liknande teknik används för att inom någon mikrosekund förgasa och pyrolysera ett analysprov, t.ex. av en polymer; vilka reaktionsprodukter som bildats bestäms med gaskromatografi (pyrolys-gaskromatografi).
Oxford Dictionary [23]	Decomposition brought about by high temperatures.
IUPAC Goldbook [7]	Thermolysis, usually associated with exposure to a high temperature. Notes: The term generally refers to reaction in an inert environment. Pyrolysis is the commonly used term for a high-temperature treatment that converts a ceramic precursor to a ceramic. Modified from previous definition. The definition proposed here is more explicit about the elevated temperatures involved.

ACI Controls [24]	Combustion is a technical term for burning, which is a chemical process that occurs when a fuel reacts with an oxidant to produce heat. Some common examples of combustion include burning wood to heat a home, the burning of petrol to run a car and the combustion of natural gas to cook on a stovetop. The process of combustion can be broken down into different classifications based on the energy it needs to occur and the byproducts of the reaction. Here is a closer look at five types of combustion: 1. Complete Combustion Complete combustion requires a combination of fuel and oxygen. During the combustion process, the reactant is completely burned in oxygen, leaving a limited amount of byproduct. When a hydrocarbon is burned in oxygen, the reaction will usually lead to the production of carbon dioxide and water. When other elements are burned, they typically leave commonly known oxides leftover. For example, carbon will produce carbon dioxide, nitrogen leads to nitrogen dioxide and sulfur will yield sulfur dioxide. 2. Incomplete Combustion Incomplete combustion occurs when there is not enough oxygen for the fuel to fully react. In this case, the byproducts, carbon dioxide and water, are not produced. Instead, the reaction will leave behind carbon monoxide and soot. Incomplete combustion also produces less energy than complete combustion, making it less efficient overall. 3. Rapid Combustion When rapid energy requires external heat energy for a reaction to occur, it is classified as rapid combustion. This reaction will continue to remain live until all of the fuel is burned up. As a byproduct, this form of combustion produces large amounts of heat and light energy at a rapid pace. One common example of this occurs when you light a candle. The combustion reaction takes place when a flame ignites the wick, producing a constant light that doesn't stop until all of the wax has been burned through. 4. Spontaneous Combustion Spontaneous combustion received its name because no outside energy is required for the reaction to begin. It occurs spontaneously. During spontaneous combustion, an increase in temperature due to an internal reaction, followed by thermal runaway and the presence of sufficient oxygen will start the process. Once the fuel reaches a temperature that is high enough, it will ignite all on its own. For example, phosphorus will self-ignite at room temperature without any application of heat. 5. Explosive Combustion Explosive combustion is exactly what you would expect; an explosion. This type of combustion occurs at an extremely rapid pace. When a force is used to ignite the fuel, heat, light and sound energy are produced immediately. One common example of this can be seen in fireworks. When a spark lights the fuse, the fireworks explode, causing heat, light and sound.

Table 4. Definitions and descriptions of charring.

Source	Definition/description
Oxford Dictionary [23]	Decomposition brought about by high temperatures.
IUPAC Goldbook [7]	Pyrolysis of samples containing organic matter. In the presence of oxygen this is referred to as ashing.
Collins Dictionary [25]	1. to burn or be burned partially, so as to blacken the surface; scorch 2. (transitive) to reduce (wood) to charcoal by partial combustion
The Free Dictionary [26]	Charring is a chemical process of incomplete combustion of certain solids when subjected to high heat. The resulting residue matter is called char. By the action of heat, charring removes hydrogen and oxygen from the solid, so that the remaining char is composed primarily of carbon. Polymers like thermoset, or most solid organic compounds like wood or biological tissue, exhibit charring behaviour. Charring can result from naturally occurring processes like fire; it is also a deliberate and controlled reaction used in the manufacturing of certain products. The mechanism of charring is part of the normal burning of certain solid fuels like wood. During normal combustion, the volatile compounds created by charring are consumed at the flames within the fire or released to the atmosphere, while combustion of char can be seen as glowing red coals or embers which burn without the presence of flames. A substance that has been scorched, burned, or reduced to charcoal.

Table 5. Ignition temperatures in normal atmosphere of tobacco and some cellulose materials.

Material	Ignition temperature	Reference
Paper (unspecified)	218 – 245 °C (may vary more depending on thickness, material and moisture)	27
Tobacco (dried, <60 mesh)	435 – 455 °C 442 – 488 °C	28 29
Wood, solid	200 – 489 °C Best estimate 250 °C	30
Wood sawdust (dried, 35-60 mesh)	61 cm slab: 118 – 142 °C 20 cm slab: 147 – 167 °C	31

3. Composition of mainstream HTP emissions

This chapter compares the composition in mainstream HTP aerosol and mainstream cigarette smoke (Figure 2; Tables 6, 7) with respect to several harmful and potentially harmful constituents (HPHC) including e.g. nicotine, tobacco specific nitrosamines (TSNA), tar, carbon monoxide (CO), aromatic amines, hydrogen cyanide, ammonia, phenol, VOC, PAH, reactive oxygen species, carbonyls [4,32-37]. The contents are given as mass per stick or cigarette. The contents in ECIG aerosol are also given in cases where simultaneous measurements along with HTP aerosol and TCC aerosol have been reported under comparable puffing regimes [4,33-35].

The nicotine content in the tobacco fillers (per cigarette) is higher in the TCC than the HTP sticks [4]. Similarly, the TSNA levels are also higher in TCC. Correspondingly, the TSNA content in HTP aerosol is lower by 7-17 times compared to TCC smoke [35]. The range of nicotine content in HTP aerosol (0.5-1.50 mg/cigarette) is lower compared to TCC smoke (0.7-2.1 mg/cigarette) (Table 6) [1]. However, some studies reported comparable nicotine content in HTP aerosol and TCC smoke [36]. Based on the surveyed literature [4,32-37], the range of total particulate matter in the HTP aerosol is higher compared to the TCC smoke. Percentage of free base is comparable among HTP aerosol and TCC smoke. Tar content is lower in case of HTP aerosol compared to TCC smoke [1] although some reports suggest comparable tar emissions [36]. Propylene glycol and glycerin are detected in HTP aerosol. CO levels in HTP aerosol is 40-60 times lower than in TCC smoke. Aromatic amines were not detected in HTP aerosol but present in TCC smoke [36]. Total particulate and gas phase radicals as well as reactive oxygen species are 40-80 and 1.5-8 times higher in TCC smoke compared to HTP aerosol respectively (Table 6). The overall carbonyl content in TCC smoke is 3-16 times higher than in HTP aerosol (Table 6 and 7). Similarly, levels of VOC are also much higher in TCC smoke than in HTP aerosol (Table 6). Highly toxic formaldehyde cyanohydrin is detected in HTP aerosol [38]. Almost three times higher levels of potentially carcinogenic acenapthene in HTP aerosol than in TCC smoke have also been reported [17]. Evidence of pyrolysis products have been reported in HTP aerosol following simulated experiments [36,38]. Analysis of literature further shows the influence of puffing topography such as puff volume, puff duration, inter-puff interval (eg. ISO - International Organization for Standardization, HCI - Health Canada Intense puffing regimens, CORTESA- Cooperation Centre for Scientific Research Relative to Tobacco) on the toxic emissions of HTP aerosol, ECIG aerosol, and TCC smoke. The flavour (e.g. variations of menthol) and brand (University of Kentucky reference cigarette [39]: 3R4F, 1R6F etc.; commercially available: Marlboro Red 100 etc.] also influences the HTP, ECIG, and TCC emission constituents [4,32-37] (Supplementary tables S1-S4).

The current scientific literature on HTP is dominated by tobacco industry sponsored research [5,40] warranting more independent studies on this topic. Independent examination of PMI's IQOS emission data [41] on US Food and Drug Administration's HPHC list revealed 56 constituents to be higher in HTP aerosol (Marlboro HTP sticks) compared to TCC smoke (3R4F cigarettes). PMI reported levels of only 40 of 93 of these HPHC on US Food and Drug Administration's list. Among the not reported HPHC, fifteen were two-fold or more and seven were more than ten-fold higher in HTP aerosol compared to TCC smoke [41] (Table 8). Some researchers recommend testing of other tobacco-related PAH such as monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) in addition to the commonly tested 1-hydroxypyrene in HTP aerosol [41]. The above reviewed data suggests HTP aerosol may expose users to lower levels of some toxicants than TCC smoke on one hand, and on the other hand, they also expose users to comparable as well as higher amounts of certain toxicants [40].

Some studies reported comparable nicotine and tar levels in HTP aerosol and TCC smoke. Fifteen HPHCs were more than 2-fold higher, whereof seven were more than 10-fold higher in HTP aerosol than in TCC smoke. Currently available data on HTP is dominated by tobacco industry thereby warranting more independent studies.

When comparing the HTP and TCC, it should be kept in mind that the HTP sticks are smaller (at least half the size) than the TCC, reflected as a lower nicotine content. The small size of the HTP sticks may lead to increased consumption, i.e. two sticks replacing one cigarette, to obtain a similar nicotine dose. The strive to reach a certain nicotine dose may explain why the widely popular IQOS device comes in two varieties, one where the battery discharges approximately after 6 minutes allowing use of one HTP sticks in a smoking session, and one where the battery supports use of two consecutive HTP sticks [42].

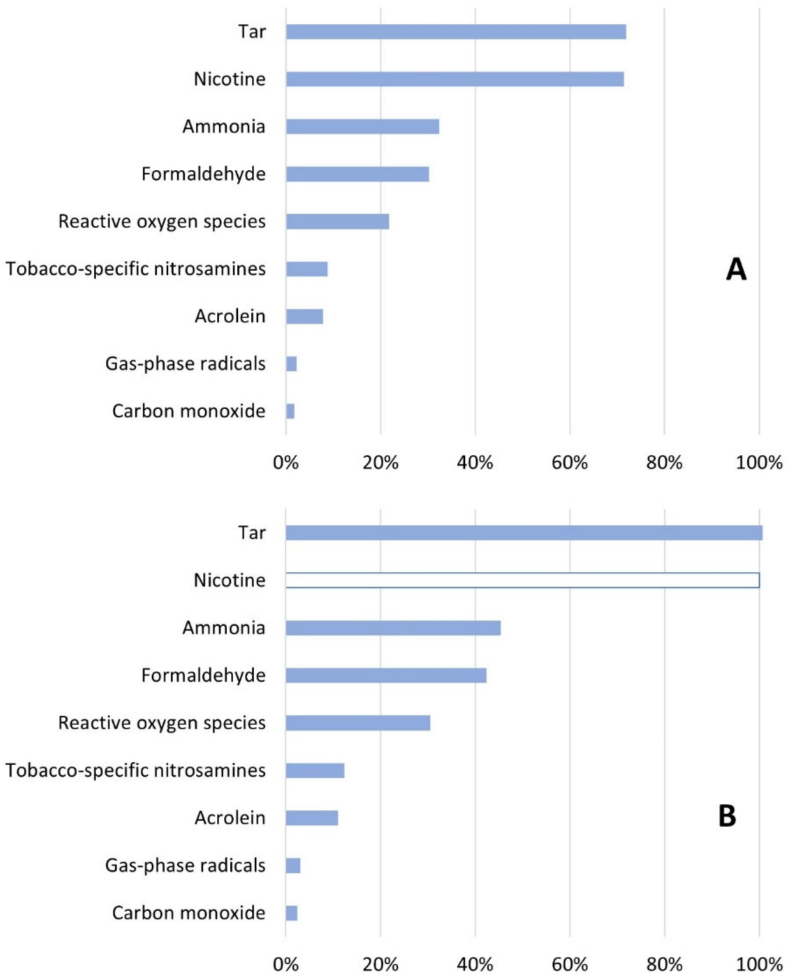

Figure 2: *Graphical representation of the average amount of few selected harmful and potentially harmful constituents in the mainstream heated tobacco product (HTP) emissions from:* ***A:*** *One HTP sticks relative to mainstream smoke from one traditional combustible cigarette.* ***B:*** *Same as A, normalized for nicotine. Averages were calculated based on the midpoints (maximum-minimum / 2) of each chemical shown in tables 6 and 7.*

Table 6: Comparative range of harmful and potentially harmful constituents (HPHC; per stick or cigarette) present in the heated tobacco product mainstream aerosol (HTP aerosol) and mainstream smoke of traditional combustible cigarettes (TCC smoke) [4,32-37]. Blanks (-) indicate not reported/not quantified/below level of detection. Single values are provided where ranges could not be obtained. ISO, HCI and CORESTA puffing regimes were used. Reported HTP aerosol data was obtained from tobacco and menthol flavoured HTP sticks. TCC smoke data was obtained from reference grade (3R4F, 1R6F) and Marlboro Red 100 cigarettes.

	HTP stick	**TCC cigarette**
Nicotine (mg)	4.7 – 5.1	8.7 – 15.0
Tobacco specific nitrosamines (TSNA) (ng)		
N-Nitrosonornicotine (NNN)	94.4 – 101.0	1899.0 – 1691.0
N´-Nitrosoanatabine (NAT)	94.5 – 99.8	913.0 – 1341.0
N-Nitrosoanabasine (NAB)	2.6 – 5.6	46.0 – 65.0
Nicotine derived nitrosoamine ketone (NNK)	51.1 – 58.2	412.0 – 532.0
	HTP aerosol	**TCC smoke**
Total particulate matter (mg)	12.9 – 55.8	9.8 – 37.7
% Free Base	5.7 – 13.6	5.8 – 14.5
Tar (mg)	7.5 – 16.6	8.0 – 25.50
Propylene glycol (mg)	0.2 – 0.6	-
Glycerin (mg)	1.6 – 3.8	0.80 – 2.3
Nicotine (mg)	0.5 – 1.5	0.7 – 2.1
Carbon monoxide (mg)	0.3 – 0.5	11.2 – 33.0
TSNA (ng)		
NNN	5.00 – 24.9	92.1 – 311.1
NAT	6.1 – 37.2	92.9 – 246.4
NAB	2.6 – 5.5	9.60 – 30.4
NNK	3.5 – 13.8	85.50 – 250.4
Aromatic amines (ng)		
1-Aminonaphthalene	-	10.6 – 21.6
2-Aminonaphthalene	-	5.7 – 10.1
3-Aminobiphenyl	-	2.0 – 4.2
4-Aminobiphenyl	-	1.0 – 2.2
Hydrogen cyanide (µg)	-	70.9 – 319.0
Ammonia (µg)	2.4 – 10.5	11.1 – 28.7
Phenol (µg)	1.2	7.0 – 14.8

Polycyclic aromatic hydrocarbon (PAH) Benzo(a)pyrene (ng)	-	6.7 – 16.2
Reactive oxygen species (nmol H_2O_2)	6.3	10.7 – 46.8
Gas phase	1.9	2.3 – 2210
Particle Phase	4.3	7.8 – 24.7
Particulate phase radicals (pmol)	-	79.4
Volatile organic compounds (μg)		
1,3-Butadiene	0.5	38.5 – 76.5
Isoprene	0.6 – 3.0	395.0 – 863.0
Acrylonitrile	0.2	26.4 – 67.0
Benzene	0.1 –0.6	47.7 – 104.0
Toluene	0.8 – 2.5	73.6 – 208.0

Table 7: Comparative range of harmful and potentially harmful constituents (HPHC, per cigarette) present in the heated tobacco product mainstream aerosol (HTP aerosol), mainstream smoke of traditional combustible cigarettes (TCC smoke), and electronic cigarette mainstream aerosol (ECIG aerosol) [4,32-37]. Blanks (-) indicate not reported/not quantified/below level of detection. Single values are provided where range could not be obtained. ISO, HCI and CORESTA puffing regimes were used. Reported HTP aerosol data was obtained from tobacco and menthol flavoured HTP sticks, TCC smoke data was obtained from reference grade (3R4F, 1R6F) and Marlboro Red 100 cigarettes, ECIG aerosol data was obtained from tobacco flavoured ECIG liquid using 1st and 2nd generation ECIG devices at 10 and 14 wattage.

HPHC	HTP aerosol	TCC smoke	ECIG aerosol
Nicotine (mg)	0.5 – 1.5	0.7 – 2.1	0.07 – 1.73
Total gas phase radicals (pmol)	12.5 – 12.6	567.6	5.3 – 47.8
Non-polar	13.9 – 14.3	449.9	2.4 – 19.2
Polar	6.8 – 8.2	9.6	5.9 – 43.3
Carbonyls (μg)			
Formaldehyde	0.9 – 22.6	3.2 – 74.4	0.5 – 3.7
Acetaldehyde	128.5 – 301. 5	567.0 – 1534	0.8 – 2.9
Acetone	18.8 – 48.37	210 – 775.6	-
Acrolein	4.0 – 13.1	56.7 – 160.9	0.3 – 1.1
Propionaldehyde	9.6 – 22.3	48.4 – 124.0	-
Crotonaldehyde	1.4 – 6.4	10.10 – 65.7	-
Methacrolein	6.5	85.5	-
Butyraldehyde	14.9 – 30.7	22.2 – 65.0	-
Valeraldehyde	20.1	-	-
Glyoxal	3.1	-	-
Methyl glyoxal	33.5	-	-
2-Butanone	4.2 – 6.5	11.0 – 220.5	-

Table 8. List of harmful and potentially harmful constituents (HPHC) reported to be more than two-fold higher in heated tobacco product mainstream aerosol (HTP aerosol) compared to mainstream smoke of traditional combustible cigarettes (TCC smoke) (adapted from St Helen et al. 2018) [41].

	HPHC	Fold increase in HTP aerosol compared to TCC smoke
1	1,4-Dioxane, 2-ethyl-5-methyl-	137
2	Hexadecanoic acid, ethyl ester	60
3	Trans-4-hydroxymethyl-2-methyl-1,3-dioxolane	47
4	Stearate, ethyl-	24
5	12,14-Labdadiene-7,8-diol, (8a,12E)	21
6	Butylated hydroxytoluene	18
7	Ethyl linoleate	16
8	Labdane-8,15-diol, (13S)	9
9	Propylene glycol	6
10	2-Furanmethanol	4
11	Butyrolactone	5
12	Methyl furoate	4
13	2-Cyclopentene-1,4-dione	4
14	2-Furanmethanol, 5-methyl-	3
15	Ethyl linolenate	3
16	2-Methylcyclobutane-1,3-dione	3
17	Lanost-8-en-3-ol, 24-methylene-, (3beta)	3
18	2-Furancarboxaldehyde, 5-methyl-	3
19	Eicosane, 2-methyl-	3
20	1,2,3-Propanetriol, diacetate (diacetin)	2
21	Glycidol	2
22	Heneicosane, 2-methyl-	2

4. Biomarkers of exposure

Evaluation of 12 commonly reported biomarkers of exposure among 1766 subjects involving 10 studies comparing TCC smokers and HTP users revealed lower levels of all the twelve biomarkers among latter. The measured biomarkers were: 1-hydroxypyrene, 2-aminoaphthalene (2-AN), 3-cyanoethylmercapturic acid (CEMA), 3-hydroxypropylmercaptauric acid (3-HPMA), 4-aminobiphenyl (4-ABP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), carboxyhemoglobin (COHb), monohydroxybutenyl-mercapturic acid, n-nitrosonornicotine (NNN), o-toluidine, phenylmercapturic acid, and total nicotine equivalents (TNeq). The reductions were most prominent for COHb, 2-AN, 4-ABP, and CEMA. Figure 3 shows biomarker effect sizes for the HTP group versus the TCC group. Compared to smoking abstinence, eight biomarkers were unaffected among HTP users while that of four (3-HPMA, NNN, NNAL, and TNeq) were significantly elevated [43] (Table 9). The findings that the levels of all the 12 evaluated biomarkers of exposure being significantly lower among the HTP users compared to the TCC users supports the tobacco industry claim regarding reduced risk of HTP devices. On the other hand, the findings that the levels of 8 of the 12 biomarkers of exposure among HTP participants were not significantly different compared to the smoking abstinence group, indicate that the complete safety of HTP devices is not assured. Moreover, considering the small number of studies included and the limited range of biomarkers of exposure assessed warrant further independent research on the safety of HTP use [43].

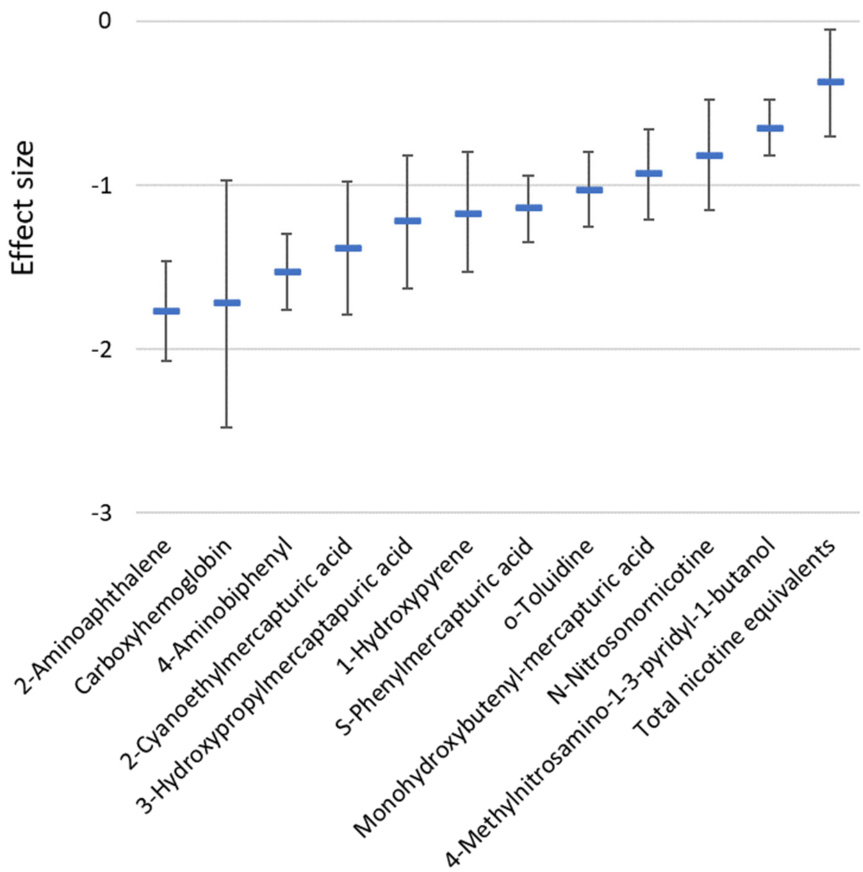

Figure 3: *Biomarkers of exposure effect sizes (expressed relative to the variation) and their 95% confidence interval in a group of heated tobacco product users versus a group of traditional combustible cigarette smokers (data from Drovandi et al. 2020 [43], table 2)*

Table 9. *Significantly elevated biomarkers of exposure effect sizes (expressed relative to the variance) and their 95% confidence intervals for heated tobacco product users compared smoking abstinence groups (data from Drovandi et al 2020* [43]*, table 2).*

Biomarkers of exposure	Effect size	p-value
3-Hydroxypropylmercaptauric acid (3-HPMA)	0.21 (0.02, 0.40)	0.027
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	0.11 (0.03, 0.18)	0.005
N-Nitrosonornicotine (NNN)	0.22 (0.01, 0.43)	0.041
Total nicotine equivalents (TNeq)	1.91 (1.40, 2.41)	<0.001

5. Health effects of exposure to mainstream HTP emissions

Current state of knowledge on the plausible adverse health outcomes of exposure to HTP aerosol is primarily on the pulmonary and cardiovascular systems. However, there is a paucity of long-term toxicity data on the use of HTP products.

5.1. Pulmonary effects

Independent analysis of publicly available tobacco industry data revealed a significant reduction of white blood cells among adult smokers (Japan based study) when they switched to HTP (n=148; inclusion criteria: asymptomatic with at least 10 cigarettes/day for 3 years). However, no improvement of pulmonary function (forced expiratory volume in 1 second) and no reduction of the systemic acute phase inflammatory marker C-reactive protein (CRP) were observed [44,45]. A three year follow up study among smokers with chronic obstructive pulmonary disease (COPD) (n=38 subjects; age and sex matched) who abstained from smoking or switched to HTP observed consistent improvement in pulmonary function, exercise tolerance (6 minute walk distance), quality of life (COPD assessment test score), and rate of disease exacerbations (GOLD- Global Initiative for Chronic Obstructive Lung Disease grading) compared to COPD patients who continued smoking [46]. Another study (50 male subjects) evaluating the acute pulmonary effects of HTP aerosol exposure detected significantly increased exhaled CO and airway resistance (respiratory impedance and respiratory resistance). Significantly decreased oxygen saturation, forced expiratory flow at 25% and 50% of vital capacity, peak expiratory flow, and diffusion lung capacity for CO were detected [47]. The changes detected were not at magnitudes of immediate clinical importance but enough to raise concern about the safety regarding the long-term use of HTP products. Two case reports of HTP use associated acute eosinophilic pneumonia have been reported. In both these case reports the subjects were male (age: 16 and 20 years) who were not cigarette smokers and started using HTP tobacco products since 2 weeks and 6 months (20 HTP sticks/day and doubled the consumption in last 2 weeks), respectively, prior to hospitalization [48-50].

Inhalation exposure of HTP aerosol in female rats for 90 days (6 hours/day; targeted nicotine dose: 23 µg/L of aerosol; 7-10 rats/group) resulted in significantly increased lung weight, bronchoalveolar lavage inflammatory cell recruitment, epithelial hyperplasia and metaplasia, and elevated levels of bronchoalveolar lavage inflammatory markers (monocyte chemoattractant protein, macrophage inflammatory protein, myeloperoxidase; plasminogen activator inhibitor) in the airways compared to control. However, the inflammatory response was significantly lower when compared to female rats exposed to TCC smoke [44,45]. Short term (5 hours/day for 14 days; HCI puffing regime) inhalation exposure to HTP aerosol in mice resulted in increased albumin in the bronchoalveolar lavage fluid indicating lung epithelial barrier leakage and infiltration of leukocytes in the lung. Increased numbers of cluster of differentiation 4 $(CD4)^+$ and interleukin (IL)-17A$^+$ T cells (marker of T cell immune response) as well as increased numbers of CD4$^+$ and RAR-related orphan receptor gamma-t$^+$ T cells (an inflammatory T cell subtype expressing the transcription factor essential for promoting differentiation into pro-inflammatory Th17 cells); and elevated levels of several proinflammatory cytokines [chemokine ligand-4, 5, 11; chemokine (C-X-C motif) ligand 1; IL-2, IL-5, IL-9, IL-13; interferon gamma; and tumor necrosis factor alpha] in the bronchoalveolar lavage fluid compared to sham exposed controls were detected [51].

Several studies using human bronchial epithelial cells demonstrated that HTP exposure resulted in oxidative stress and pro-inflammatory response [44,52]. Higher cytotoxicity was also reported in human bronchial epithelial cells following HTP exposure compared to corresponding sham and ECIG exposure [44,51-53]. These observations are attributable to the presence of tar, VOC, PAH, carbonyl compounds, and other HPHC in HTP aerosol resulting in increased free radical exposure [52]. Altered mitochondrial respiration have also been reported following exposure to HTP in human bronchial epithelial cells and airway smooth muscle cells [54,55].

5.2. Cardiovascular effects

Effects of exposure to mainstream HTP emissions are regarded as potentially harmful to cardiovascular health though less than that of TCC smoke [56]. Acute effects on heart rate, blood pressure, and arterial stiffness have been reported among HTP users similar to TCC smokers [56]. One study involving 22 current TCC smokers with no comorbidities, exhibited similar acute effects of HTP products and TCC based on evaluation of a panel of cardiovascular assessments: heart rate, blood pressure, carotid–femoral pulse wave velocity, and brachial–ankle pulse wave velocity which were significantly elevated from baseline [56,57]. Another study including twenty active, healthy smokers (10 men and 10 women) were studied to assess the acute effect of HTP use on arterial stiffness in comparison to ECIG use and TCC smoking. Peripheral systolic blood pressure and mean arterial pressure increased significantly within the TCC, ECIG, and HTP groups by more than 3% compared to before exposure. Heart rate increased by more than 9% in the TCC and HTP groups. The augmentation index, a measure of arterial stiffness was also significantly increased in the HTP group after 5 minutes, whereas in the TCC group increased phenomenon were observed till 15 minutes after smoking. The pulse wave velocity parameter, another measure of arterial stiffness, showed only a trend of alteration in HTP and ECIG group and was significantly altered in the TCC group 15 minutes after exposure [58].

> Preclinical indicators of cardiovascular diseases such as blood pressure, heart rate, and arterial stiffness are altered due to HTP aerosol exposure.

A study in rats indicated that acute exposure to HTP aerosol impairs the arterial flow-mediated dilation. The studies also demonstrated that HTP aerosol can rapidly and substantially impair the endothelial function comparably to TCC smoke. The post-exposure serum nicotine levels were more than 4-fold higher in the HTP aerosol exposed rats compared to those exposed to TCC smoke [59]. Independent evaluation of tobacco industry sponsored research data in a Japanese cohort (70 HTP users, 41 TCC smokers, and 37 smoking abstinent) identified significant improvement of only 4 out of 13 systemic biomarkers of harm. In an American cohort (47 HTP users, 32 TCC smokers, and 9 smoking abstinent), significant improvement of only one out of 24 measured systemic biomarkers of harm was improved. Systemic biomarkers exhibiting significant improvement among individuals switching to HTP from TCC included an increase in high-density lipoprotein and reduction of inflammatory indicators [white blood cell count, soluble intercellular adhesion molecule 1, and prostaglandin F2 alpha [40].

5.3. Other effects

Data from tobacco industry indicate immunomodulatory effects of HTP aerosol exposure. Rats (7-10/group) exposed to HTP aerosol developed 270% and 75% higher systemic neutrophilia compared to sham and TCC smoke exposed rats. In female rats, following a 6-week recovery period, the blood neutrophil counts remained elevated compared to both sham and TCC exposed animals. HTP exposed rats also exhibited higher levels of thymic atrophy (by gross organ weight and histology) than both sham and TCC smoke exposed groups [45]. Independent examination of tobacco industry data further revealed significant increases in alanine amino transferase activity, liver weight, and hepatocellular vascularization (in females only) following 90 days exposure of HTP aerosol to male and female rats compared to sham exposed indicating possible hepatoxicity [60,61]. Discoloration in the enamel, dentin, and composite resin restorations from baseline was observed following 3 weeks of HTP aerosol exposure though to a significantly lesser extent compared to TCC smoke exposure in tobacco industry sponsored research [62,63].

6. Conclusions

Heated tobacco products (HTP) are novel products that allow the user to inhale nicotine by heating the tobacco rather than burning it at high temperature, as in conventional cigarettes. As there is no clear definition of combustion/burning, it seems wiser to look at the composition of the HTP aerosol rather than dichotomizing between heating and burning. The presence of carbon monoxide and a number of other TCC smoke constituents in the HTP aerosol indeed corresponds to what would be expected from slight combustion.

The HTP stick has a smaller size and lower amount of tobacco than the traditional combustible cigarette (TCC). Therefore, the amount of nicotine delivered in the mainstream emission from the HTP stick is generally lower than that delivered in the mainstream smoke from the TCC. However, technological advancements of the HTP product, such as improvement of the battery capacity may result in increased rather than reduced consumption, e.g. by shifting from one to two sticks per smoking session.

Apart from nicotine and carbon monoxide, several other chemicals are also present in the HTP aerosol, including a number of so called harmful and potentially harmful constituents (HPHC). The levels of these HPHC are influenced e.g. by the puffing regime, the HTP device, and additives to the HTP stick. Several HPHC have been detected in higher concentrations in HTP aerosol than in TCC smoke.

Currently there is not sufficient evidence from independent sources to conclude on health effects from long-term use of HTP sticks. Few independent studies reported short-term pathophysiological effects of HTP use.

According to the European Union tobacco directive, Article 2, a ‘novel tobacco product’ is a tobacco product which does not fall into any of the following categories: cigarettes, roll-your-own tobacco, pipe tobacco, waterpipe tobacco, cigars, cigarillos, chewing tobacco, nasal tobacco or tobacco for oral use; and is placed on the market after 19 May 2014 [6]. In this context, it is important to note that HTP products are a conceptual and technological evolution of similar products marketed by tobacco industry during 1980-1990s [1]. The directive also identified the importance to monitor the developments of novel tobacco products.

Multiple tobacco industry sponsored studies on human bronchial epithelial cells, coronary arterial endothelial cells, 3-D nasal culture model, gingival epithelial organotypic cultures, monocytic cells, and mouse models indicate lower toxicity of HTP aerosol compared to TCC smoke [61]. Currently available independent research findings follow a similar line. In general, the tobacco industry sponsored research highlights the findings of HTP emission exposure mainly in comparison to TCC smoke. However, it is important to note that potential adverse effects have been observed while comparing HTP emission exposed groups compared to unexposed groups. Thus, comprehensive studies addressing the safety profiling related to long-term HTP use is required.

Nevertheless, it needs to be accounted that HTP aerosol does contain nicotine allowing users to inhale nicotine. Nicotine is highly addictive and exposure to nicotine is harmful to the adolescent brain (the brain develops until about age 25 years), particularly in the regions controlling attention, learning, mood, and impulse control. Use of nicotine among adolescents may also act as a gateway for future use and addiction to other drugs. Nicotine is toxic to developing fetuses and harmful for pregnant women. Use of nicotine is also harmful for adults [2,3]. Therefore, more independent and long-term research is necessary for evaluating the safety of HTP tobacco products.

In conclusion, the health effects of short-term and, in particular, long-term use of HTP sticks are uncertain. Accordingly, the European Respiratory Society recommended against the use of any product including HTP tobacco products that can potentially damage the lungs and human health [64].

Disclaimer statement: *We based our expert opinion article primarily on the interpretation of research, review articles, and reports without affiliation to tobacco industry and independent reviews of tobacco industry data.*

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