Superior
Health Council

NEW TOBACCO PRODUCTS: HEATED TOBACCO PRODUCTS

APRIL 2020
SHC № 9538

.be

Federal Public Service Health, Food Chain Safety and Environment

Superior Health Council
Place Victor Horta 40 bte 10
B-1060 Bruxelles

Tel.: 02/524 97 97
E-mail: info.hgr-css@health.belgium.be

Please cite this document as follows:
Superior Health Council. New Tobacco Products: Heated Tobacco Products. Brussels: SHC; 2020. Report 9538

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Superior Health Council

ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9538

New Tobacco Products: Heated Tobacco Products

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides a risk assessment for heated tobacco products for smokers and non-smokers.

This report aims at providing politicians, public health authorities, healthcare providers, teachers, youngsters, smokers and non-smokers with specific recommendations on the toxicity and safety of heated tobacco products (versus traditional tobacco cigarettes).

This version was validated by the Board on
April 2020 / Published November 2020[1]

I INTRODUCTION

In February 2019, the Superior Health Council (SHC) received a request from the policy unit of Minister Maggie De Block to formulate an opinion on "*heated tobacco products*" (HTP) which are expected to be on the Belgian market in the near future and which fall under Article 14 of the Royal Decree (RD) of 5 February 2016 on tobacco products. These **heated tobacco products** include the IQOS by *Philip Morris International*, the GLO by *British American Tobacco* and PloomTech by *Japan Tobacco International*. These are products in which tobacco is heated, not burned, and which are presented by the companies as a better health alternative to traditional tobacco products.

In view of the novelty of these products and the positive image portrayed by their manufacturers, the Minister sought the opinion of the SHC on the harmful health aspects of using this new type of products, with a view to subsequently defining the legislative provisions to be applied to these products as effectively as possible.

A few months later, the SHC was informed by the "Consumer Products Inspection" department of the FPS Public Health[2] of a request relating to electronic cigarettes and, in particular, of a request for revision of its opinion 9265 of 2015[3]. Although issues related to the consumption of new tobacco products and new electronic cigarettes may possibly entail similar approaches, the SHC preferred to handle the two cases separately. The present opinion is therefore limited to new tobacco products and an assessment of their risks.

[1] The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.
[2] FPS: Federal Public Service for Public Health, Safety of the Food Chain and Environment - Directorate-General for Animals, Plants and Food
[3] SHC 9265: State of play: electronic cigarettes - 2015

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II CONCLUSIONS AND RECOMMENDATIONS

1. Background

The SHC wishes to reiterate that abstention from all forms of tobacco consumption is a public health priority and that legislation must contribute to this.

The SHC would like to point out that the majority of the reports and articles currently available come from and/or have been funded by the tobacco industry. Few independent publications without any links to the tobacco industry are available.

The new tobacco products are, as their name implies, tobacco-based products and must therefore meet the regulatory requirements for new tobacco products. According to the legislation currently in force, these are:

- a ban on advertising,
- a ban on sales to minors under 18 years of age,
- a ban on smoking in enclosed areas accessible to the public,
- notification to the authorities of new tobacco products and devices,
- regulation of ingredients, labelling, product presentation, and distance selling.

2. Categories of new heated tobacco products

The new "***heated tobacco products"*** are complex systems containing nicotine and additives. There are various types, and they can be classified into 3 categories:

1. processed tobacco heated directly to produce vapour (conduction systems) such as IQOS, GLO systems,
2. processed tobacco designed to be heated in a vaporiser (convection systems), such as PAX,
3. devices that produce vapour from non-tobacco sources, where the vapour is then passed over processed tobacco in order to flavour the vapour, and add nicotine such as the PloomTech system**.**

Irrespective of the fact that there are different heating methods, the basic idea is always to heat and not to burn the tobacco. The heating range for tobacco is also very wide for the different devices, ranging from 30 to 40°C for category 3 products to 350°C for category 1 products. For carbon heated tobacco products, referred to in point 2, these temperatures may be even higher. The temperatures at which the tobacco is heated will, of course, influence the emissions and the number and quantity of toxic substances contained in the vapours.

3. Detection, emissions and exposure

Among the substances detected in aerosols of new heated tobacco products are nicotine and various constituents that are harmful and potentially harmful even at lower temperatures. The levels of emissions and exposure to these products (excluding nicotine) are significantly lower for heated tobacco products than for conventional cigarettes. Moreover, the aerosols emitted by the new tobacco products are often characterised by a high water and glycerol content. In the case of heated tobacco products, tar (defined as the nicotine-free dry solid material retained on the filter) contains proportionally fewer toxic contaminants and more humectants than the tar in conventional cigarettes. **This results in the smaller but not necessarily**

negligible exposure of users of heated tobacco products to a range of harmful products generated by conventional cigarettes. However, in addition to these compounds, according to the FDA[4], new heated tobacco products emit 80 other compounds that are not detected or detected at lower levels than in conventional cigarettes. Of these compounds, 4 **are possible carcinogens**, 30 are identified as GRAS (*Generally Recognised as Safe*) and 46 are additional compounds, generally related to flavours. These are authorised for ingestion but have never been tested for inhalation toxicity.

As regards passive exposure, opinions differ. The FDA concludes on the basis of the information provided by *Philip Morris International* that emissions from heated tobacco products into the ambient air lead to passive exposure that could be considered negligible. The authors of an independent study (Ruprecht et al., 2027) concluded that ambient air emissions from heated tobacco products are significantly lower than those detected in the tobacco smoke from conventional cigarettes. However, they highlight the fact that the presence of carbonyls in ambient air emissions from heated tobacco products might have consequences and adversely affect the health of persons subject to passive exposure. With regard to particulate matter emitted, the conclusions of the various studies diverge as to the relevance of the low levels detected.

4. Toxicity of new tobacco products

Despite the methodological limitations of the tests, the *in vitro* studies generally show a decrease in the induction potency of cytotoxicity and mutagenicity due to exposure to a heated tobacco product, compared to conventional cigarettes.

Sub-chronic *in vivo* exposure to the aerosols of IQOS produces little or less severe histopathological changes than sub-chronic exposure to conventional cigarettes. However, the correlation between these effects and clinical changes in humans is not known.

In clinical studies, following a switch from conventional cigarettes to heated tobacco products (IQOS or GLO), significant decreases in biomarker levels of exposure to harmful and potentially harmful constituents have been observed, although they are not considered to be completely safe. Favourable changes have also been noted in several biomarkers with biological impact, suggesting that there is potential for a decreased risk of disease if smokers switch from conventional cigarettes to heated tobacco products.

However, the observed asymptotic dose-response relationship implies that even if the intensity of exposure to heated tobacco products does not exceed 5% of the exposure to tobacco smoke, the risk of these devices is far from negligible.

The few independent studies that exist indicate some potentially harmful consequences of exposure to the aerosols from heated tobacco products and several shortcomings in the studies conducted for and by the tobacco industry.

There is currently no evidence regarding the long-term effects on health (e.g., the carcinogenic potential) of using heated tobacco products compared to smoking conventional cigarettes.

[4] FDA: Food and Drug Administration

More independent molecular-epidemiological research [5]based on human studies needs to be conducted to assess the short- and long-term health effects of using heated tobacco products.

The risk associated with the various unique carcinogens in the aerosols of heated tobacco products needs to be further characterised (effect of inhalation, etc.).

The presence of certain potentially carcinogenic compounds in aerosol emissions from heated tobacco products in concentrations (significantly) higher than those measured in conventional cigarette emissions (e.g., glycidol) raises questions. Notwithstanding, all *in vitro* and *in vivo* tests performed to assess the toxicity of aerosols lead to reduced toxicity compared to smoking cigarettes. In the case of non-threshold carcinogens, however, **a significant risk may still be present even with a reduced dose**. It is therefore desirable to further characterise the risk for the different carcinogenic compounds detected in aerosols of heated tobacco products.

5. Comparison of different systems

There appear to be differences between emissions from different product categories and between products in the same category. However, few studies, except one on IQOS by *Philip Morris International*, have been conducted into the composition of emissions from heated tobacco products and there are currently no international standards for conducting such experiments. **All the results should therefore be interpreted with caution**. Current scientific knowledge does not allow a conclusion to be drawn on these differences in terms of harm to health. The same applies to the toxicity studies themselves; there is not enough scientific research to formulate a clear answer to the question of toxicity according to the category of the heated tobacco product and according to the maximum temperature reached during use.

6. Evolution and characteristics of use, behavioural aspects

These tobacco products are not yet available for sale in Belgium but have been on the market for some years in other countries, notably Japan. Since their launch, there has been a growing interest in this type of system, especially among young adults. Indeed, these products have a sleek, trendy appearance that makes them attractive. The interest in these products primarily comes from smokers, but also from ex-smokers and non-smokers.

It is currently difficult to assess the risk of there being a gateway to conventional smoking for non-smokers and young people. Independent longitudinal studies are necessary in this regard. The same applies to the evaluation of toxicity, particularly in the case of mixed consumption (conventional cigarette and new heated tobacco products).

Bearing in mind that these heated tobacco products have an addictive potential comparable to that of a conventional cigarette, these products can be considered an alternative to the conventional cigarette which is highly likely to be less harmful. The role of heated tobacco products as a means of smoking cessation is currently disputed and requires further investigation.

[5] Molecular epidemiology involves identifying and measuring the biological effects (mutations, changes in hormone concentrations, changes in gene expression, epigenetic changes, changes in the immune system or protein concentrations, changes in the functioning of the nervous system) before linking them to the exposure, external conditions or internal exposure that apply to the individuals concerned.

It is therefore advisable to scrutinise the strategy for placing these products on the market.

7. Recommendations of the SHC*[6]

In the context of the policy for smoking cessation, the SHC is of the opinion that all the means available are useful in achieving this objective. All systems currently on the market that are less toxic should therefore be taken into consideration. Heated tobacco products appear to have a more favourable toxicity profile than conventional tobacco products. However, they cannot be considered risk-free In view of the short- and long-term uncertainties of heated tobacco products, the toxic effects of dual use (conventional cigarettes and heated tobacco products) and given the existence of approved tools for smoking cessation (nicotine substitutes, etc.), the SHC considers that consumption of these products should not be encouraged by measures which would make them more attractive than conventional tobacco products, such as more favourable taxation, better accessibility of the products for potential consumers, or tolerance regarding advertising. The current regulations for cigarettes should therefore apply to heated tobacco products.

Finally, the SHC draws attention to the responsibility of the federated entities and the competent authorities to ensure transparent and impartial communication on the absolute and relative risks associated with the use of new heated tobacco products.

[6] One of the experts of the working group wishes to distance himself from the chapter "Recommendations of the SHC". His position is detailed in Annex 2 to the present opinion.

Keywords and MeSH *descriptor terms*[7]

MeSH terms*	Keywords	Sleutelwoorden	Mots clés	Schlüsselwörter
Tobacco	Tobacco	Tabak	Tabac	Tabak
Smoke	Smoke	Roken	Fumer	Rauchen
Smoking cessation,	Smoking cessation	Stoppen met roken Tabaksontwenning	Arrêt tabagisme	Raucherentwöhnung
Behavior, addictive	Addiction	Verslaving	Assuétude	Sucht
Cigarettes	Cigarette	Sigaret	Cigarette	Zigarette
Tobacco products	Heated tobacco product	Verhit tabaksproduct	Produit à base de tabac chauffé	erhitztes Tabakerzeugnis
Tobacco products	Heated tobacco system	Verhit tabakssysteem	Système à base de tabac chauffé	erhitztes Tabaksystem
Tobacco products	Heat not burn tobacco product	Niet-verbrand tabaksproduct	Produit à base de tabac non brûlé	Nicht-verbranntes Tabakerzeugnis

MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed http://www.ncbi.nlm.nih.gov/mesh.

III METHODOLOGY

After analysing the request, the Board and working group identified the necessary fields of expertise. An *ad hoc* working group was then set up which included experts in psychology, tobaccology, toxicology, smoking prevention, health promotion, cancer prevention, pneumology, pharmacology and contaminant chemistry. The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.

Once the advisory report was endorsed by the working group, it was ultimately validated by the Board.

[7] The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".

IV ELABORATION AND ARGUMENTATION

List of abbreviations used

ALT	Alanine aminotransferase
AOR	Adjusted odds ratio
BMDL	Benchmark Dose Lower Confidence Limit
BAT	British American Tobacco
BOE	Biomarker of Exposure
CI	Confidence interval
IARC	International Agency for Research on Cancer
EFSA	European Food Safety Authority
ENDS	Electronic nicotine delivery systems
EPA	Environmental Protection Agency
FCTC	Framework Convention Tobacco Control
FDA	Food and Drug Administration
FPS	Federal Public Service
FTND	Fagerstrom Test for Nicotine Dependence
GRAS	Generally Recognized as Safe
HPHC	Harmful & Potentially Harmful Constituents
HTP	Heated tobacco products
ICH	International Conference on Harmonisation
IQOS	I-Quit-Ordinary-Smoking
ISO	International Organization for Standardization
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JTI	Japan Tobacco International
MRTPA	Modified Risk Tobacco Product Application
MCEQ	Modified Cigarette Evaluation Questionnaire
MLA	Mouse lymphoma assay
MNWS	Minnesota Nicotine Withdrawal Scale
MoE	Margin of Exposure ou biomarqueur d'exposition
MRTP	Modified-Risk Tobacco Product
NGP	Next generation products
NNK	Nicotine-derived nitrosamine ketone
NNN	N-nitrosonornicotine
NST	Nicotine substitution therapy
OECD	Organisation for Economic Co-operation and Development
PBA	Perception and Behavior Assessment
PHE	Public Health England
PMI	Philip Morris International
PMTA	Premarket Tobacco Product Application
RD	Royal Decree
RR	Relative risk
SHC	Superior Health Council
THS	Tobacco heating system
THP	Tobacco heating product
TPM	Total Particular Matter (teneur en particules totales)
TTFC	Time to first cigarette
WHO	World Health Organization

1 Introduction

In the wake of regulations on tobacco products and confronted with a shrinking market for conventional cigarettes, so-called *Next generation products* (NGPs) have been introduced on the market. These are primarily *Heated tobacco products* (HTP).

Heated tobacco products are complex systems and there are many different types.
In 2017, the UK authorities proposed making a distinction between three categories:

1. processed tobacco heated directly to produce vapour (conduction systems),
2. processed tobacco designed to be heated in a vaporiser (convection systems),
3. devices that produce vapour from non-tobacco sources, where the vapour is then passed over processed tobacco in order to flavour the vapour (and add nicotine) (HM Treasury, 2018).

In general, these products produce nicotine-containing vapour by heating the tobacco to a maximum temperature of 350°C, lower than the combustion temperature of 600°C of conventional tobacco products. The product is heated using a battery-operated heating system placed in a device and used as an external heating system to create an aerosol from specific products such as, for example, tobacco sticks, or via a heating chamber in which an aerosol containing nicotine is created directly from the tobacco. Another principle consists of heating a liquid without (or with) nicotine to create an aerosol which is then passed over tobacco in order to impregnate it with nicotine and flavours.

1.1 Preliminary considerations

The SHC wishes to define various key concepts.

Smoking: by "smoking", the SHC means the consumption of tobacco products by inhalation of smoke or aerosols.

Heated tobacco products (HTP) or *tobacco heating products* (THP) or *heat not burn tobacco products* are heated tobacco products or tobacco products which are not burned. These are aerosol-generating products containing nicotine and other chemicals, which the consumer inhales through their mouth. They therefore contain nicotine, but also (often flavoured) additives (WHO,[8]). In this opinion, it was decided to use the term "heated tobacco products".

HPHC: *Harmful and Potentially Harmful Constituents*.

1.2 Regulatory framework

1.2.1 General regulations

The new tobacco products are, as their name implies, tobacco-based products. The general rules concerning these products apply as regards:

- the ban on advertising (article 7§2bis of the law of 24 January 1977 on the protection of consumer health with regard to foodstuffs and other products),
- the ban on sales to minors under 18 years of age (Article 6§4 of the law of 24 January 1977, Royal Decree (RD) of 3 February 2005 on the prohibition of the sale of tobacco

[8] https://www.who.int/publications/i/item/WHO-HEP-HPR-2020.2

products to persons under 16 years of age via automatic dispensing machines, Article 2 of the Law of 12 July 2019 amending the Law of 24 January 1977[9]),

- the ban on smoking in enclosed places accessible to the public (law of 22 December 2009 introducing general regulations on the ban on smoking in enclosed places accessible to the public and on the protection of workers from tobacco smoke).

1.2.2 Specific regulations

New tobacco products are specifically regulated by the RD of 5 February 2016 on the manufacture and placing on the market of tobacco products and herbal smoking products.

These are defined in the RD as (Article 2, 14°) (translated):

> a tobacco product that:
>
> a) does not fall under any of the following categories: cigarette, hand-rolling tobacco, pipe tobacco, water-pipe tobacco, cigar, cigarillo, chewing tobacco, snuff or oral tobacco; and
> b) is placed on the market after 19 May 2014.

The Belgian legislator has also incorporated a definition of device in its RD (Article 2, 14/1°) (translated):

> "any device or component of such a device necessary for the consumption and/or use of a new tobacco product".

As such, Article 14 of the RD applies to new tobacco products as well as to devices. Paragraphs 1 to 4 stipulate that new tobacco products and devices must be notified to the FPS [10]Public Health in accordance with special rules (notification 6 months before placing on the market, information and studies to be provided, fee of EUR 4,000).

Moreover, paragraph 5 of this Article states that Articles 4, 5, 6, 11, 12 §3 and 13 of the RD apply to new products and devices (general rules on notification, rules on ingredients, general rules on labelling, rules on product presentation and rules on distance selling).

As regards the specific rules concerning labelling, the Minister determines which of the provisions of Articles 7, 8, 9 and 10 apply. This implies that the Minister will determine for each new product whether it is to be considered for labelling as a smoking product or a smokeless tobacco product.

1.2.3 Additional regulations

Since the RD of 13 April 2019, Belgium has been obliged to introduce neutral packaging for cigarettes, hand-rolling tobacco and water pipe tobacco. It does not currently apply to heated tobacco products. Since the recommendation is to treat heated tobacco products in the same way as conventional cigarettes, there should also be a requirement for plain packaging and the same combined health warnings, consisting of text and illustrations, for heated tobacco products as for conventional cigarettes.

[9] Law 12 July 2019 entered into force on 1 November 2019
[10] FPS: Federal Public Service

Since the RD of 5 February 2016, certain ingredients have been banned (see article 5: Regulations on ingredients).[11]

Article 5, paragraph 6, specifies that tobacco products other than cigarettes and hand-rolling tobacco are exempted from the prohibitions referred to in paragraphs 1 and 4. This means that new tobacco products may contain a distinctive flavour (§1) and that their components (such as filters, paper, packaging and capsules) may contain flavourings.

As it is recommended that heated tobacco products should be treated in the same way as conventional cigarettes, vitamins and other additives mentioned above, flavourings and additives facilitating the inhalation or absorption of nicotine should also be prohibited for heated tobacco products.

[11] Art. 5.§ 1. It is prohibited to place on the market [1 tobacco products]1 containing a distinctive flavour.
§ 2. It is prohibited to place on the market [1 tobacco products]1 for oral use as laid down in article 2, 9°.
§ 3. It is prohibited to place on the market [1 tobacco products]1 containing the following additives:
1° vitamins or other additives which create the impression that a [1 tobacco product]1 has beneficial effects on health or that its health risks have been reduced;
2° caffeine or taurine or other additives and stimulants associated with energy and vitality;
3° additives which impart colouring properties to emissions;
4° in respect of smoking tobacco, additives which facilitate the inhalation or absorption of nicotine;
5° additives which, without combustion, have CMR properties.
§ 4. It is prohibited to place on the market [1 tobacco products]1 containing flavourings in any of their components such as filters, paper, wrappers and capsules, or any technical device that modifies the aroma or flavour of the [1 tobacco products]1 concerned or their intensity of combustion. The filters, paper and capsules must not contain tobacco or nicotine.
§ 5. It is prohibited to place on the market [1 tobacco products]1 containing additives in quantities which increase, upon consumption, significantly or measurably on the basis of scientific data, their toxic or addictive effects or their CMR properties. The Minister may request an opinion from the Superior Health Council in order to identify these products.
§ 6. The [1 tobacco products]1 other than cigarettes and rolling tobacco are exempt from the prohibitions referred to in paragraphs 1 and 4.
§ 7. The [1 tobacco products]1 containing a particular distinctive flavouring, with an EU-wide sales volume of 3% or more in a given product group, shall be exempted from the provisions of this Article until 20 May 2020.
§ 8. The Service may collect proportionate fees from manufacturers and importers of tobacco products to assess whether a [1]1 tobacco product contains a characterising flavour, whether prohibited additives or flavourings are used and whether a [1 tobacco product]1 contains additives in quantities that significantly and measurably increase its toxic effects, addictiveness or CMR properties.
[2 § 9. It is prohibited to place on the market any technical element, such as filters and papers, which makes it possible to modify the combustion intensity, colour of emissions, aroma or taste of tobacco products. Furthermore, this element may not contain the additives mentioned in paragraph 3 of this Article.]2
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2 Different categories of new heated tobacco products

Although, for the time being, only a limited number of products are available, a distinction must be made between the different categories. All products are based on heating rather than burning tobacco or tobacco products.

In 2017, the UK authorities proposed making a distinction between three categories:

1. processed tobacco heated directly to produce vapour (conduction systems),
2. processed tobacco designed to be heated in a vaporiser (convection systems),
3. devices that produce vapour from non-tobacco sources, where the vapour is then passed over processed tobacco in order to flavour the vapour (and add nicotine) (HM Treasury, 2018).

A typical example of the first category is **IQOS** from the company *Philip Morris International*. This product actually consists of three parts, which are essential for its functioning.
The first part is the socket, which contains the heating system, which will heat the tobacco, and the rechargeable battery. The tobacco is heated via an electronically controlled heating pin. This pin is made of gold or platinum and has a ceramic coating. The electronics regulate the temperature and heat the tobacco to temperatures below 350°C without combustion.
The second part is the charger, which allows the battery to be recharged, and the third part is the *tobacco stick*, also called "*HeatSticks*" or "HEETS". This stick consists of a filter part and a tobacco part, the tobacco part consisting of tobacco, glycerine, water, cellulose, guar gum and possible flavours. The classic flavours are synthetic tobacco, mint and fruit flavours (blueberry-flavoured HEETS).

After charging the device, the stick must be inserted with the filter facing outwards. The device must then heat up, after which steam can be produced for 6 minutes or 14 puffs. The device also has a safety feature to prevent the stick from overheating[12].

Another example in this category is the product **GLO** by *British American Tobacco*, which is based on the same principle, but is only heated to 240°C. A variant of this principle is the device **IUOC** by the *Shenzhen Yukan Technology Co*. This device follows all the principles of the first category and of the IQOS device with the difference that it does not use "*tobacco sticks*", but traditional cigarettes, which are inserted into the device and are therefore not burnt, but heated[13].

The second category includes, for example, the products **PAX** by Pax Labs. These products are based on the principle of an oven. The devices consist of three parts, namely a plastic mouthpiece, a rechargeable battery and an oven.
Bulk tobacco (10-20 mg), but also other (medicinal) herbs can be placed in the oven. Specially designed concentrates can also be used. The battery provides energy to heat the oven, as the tobacco is heated by the hot air produced; therefore there is no direct contact between the heating element and the tobacco. This heating principle is called convection. The devices can be set to four temperatures, namely 182, 193, 205 and 215°C, and they heat up in 15 seconds.

[12] https://www.pmi.com/smoke-free-products/iqos-our-tobacco-heating-system; IQOS3 user guide https://d2vhuecemjogou.cloudfront.net/images/userguides/IQOS_3_Combined_Userguide_EN.pdf
[13] https://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOAWUGNJ; http://www.iuoctech.com/en#wqd1461130731144serial

The device has a safety function that allows it to cool down as soon as no more vapour is produced. A fully charged battery is sufficient for 10 vapour production sessions.
Other examples are the ***Firefly** 2* by the company *Firefly Vapor*, **the *iSmoke OneHitter*** by the company iSmoke and the **V2 pro series** by the company V2 pro[14].

A typical example of the third category is **PloomTech** by *Japan Tobacco International*. This device also consists of three parts, namely a battery, a cartridge and a tobacco capsule. The tobacco capsule contains a form of granulated tobacco and is available in different flavours. The cartridge contains a nicotine-free liquid composed of propylene glycol, glycerine, flavourings and water. The battery provides the current needed to heat the liquid to produce the vapour. This vapour passes through the capsule and comes into contact with the tobacco, causing the vapour to absorb nicotine and flavours. There is therefore no direct heating of the tobacco and the company claims that the temperature inside the capsule never exceeds 40°C. Both the tobacco cartridges and capsules are available separately and are not reusable. One battery charge is sufficient for the production of vapour for five tobacco capsules or 50 puffs. This device will also automatically turn off after six minutes of inactivity. Another device in this category is the ***Lil vaporiser*** from the *Korean Tobacco & Ginseng Corporation[15].*

Besides these three main types of devices, there are also different variants on the market. Examples include the GLO **iFuse** by *British American Tobacco* and the **Lil Hybrid** by *Korean Tobacco & Ginseng Corporation*. They are hybrid products, halfway between a heated tobacco product and an e-cigarette. The principle is, in fact, similar to that of PloomTech, but in this case a solution containing nicotine is used, which is evaporated and then passed over the tobacco in order to collect the flavour.
There are also so-called *carbon heated tobacco products*, manufactured by *British American Tobacco* and *Philip Morris International* (TEEPS). These products consist of a carbon tip, a tobacco compartment and a filter. The carbon is ignited, heating the tobacco in the tobacco compartment. The aim is to simulate the sensation of a conventional cigarette[16]. Although these devices are considered as hybrid products, their principle is identical to that of conduction systems. Only the method of heating is different, i.e. the combustion of the carbon tip rather than an electric heating element.

In conclusion, we can observe that, although there are different heating methods, the basic idea is always to heat and not to burn the tobacco. The heating range for tobacco is also very wide for the different devices, ranging from 30 to 40°C for category 3 products to 350°C for category 1 products. For carbon heated tobacco products, these temperatures may be even higher. The temperatures at which the tobacco is heated will, of course, influence the emissions and the number and quantity of toxic substances contained in the vapours.

[14] https://www.pax.com/pages/pax-3-how-to-guide Firefly user manual (https://www.thefirefly.com/media/Firefly2-UserManual_3.13.18.pdf)
[15] https://www.jt.com/media/news/2018/pdf/20181002_E02.pdf
[16] https://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOAWUGNJ; https://www.pmi.com/smoke-free-products/teeps-carbon-heated-tobacco-product

3 Conventional cigarette versus new tobacco products

3.1 Compounds present in the conventional cigarette

3.1.1 Detection, emissions and exposure

Besides nicotine, various HPHC (*harmful and potentially harmful constituents*), can be detected in aerosols produced by heated tobacco product-type devices, despite the fact that with these devices the temperature is limited to around 350°C, which limits their synthesis. It is primarily in the main flow inhaled by the user (active exposure) that these compounds are detected. Nevertheless, ambient air can also be contaminated by secondary flows (passive exposure due to non-inhaled fumes generated by the device or exhaled by the user).

3.1.1.1. Levels of harmful and potentially harmful constituents in the main flow and biomarkers of exposure

The **levels of harmful and potentially harmful constituents** in the main flow are measured in the laboratory using specially designed machines. Two methodologies were used in the different studies reviewed: the HCI inhalation regimen (majority of studies) and the ISO regimen.
It has been observed, however, that emission levels estimated using these machines tend to provide proportionately higher abatement rates than those observed in human containment studies where reductions in biomarkers of exposure are observed (Simonavicius et al., 2018). In addition, in order to make comparisons between studies, benchmarks are defined in relation to conventional cigarettes, but the nature of these benchmarks may differ between studies. Due to differences in inhalation regimes and the choice of a benchmark, rigorous comparisons between two different studies are often not possible (PHE, 2018). For all these reasons (underestimation of emissions from machines and difficulties in comparing studies with each other), it is preferable to assess the level of exposure among users by means of biomarkers of exposure.

Measurements in the main flow using inhalation machines.
The **quantities of water** measured in the main flow emanating from IQOS-type devices are significantly increased (94-131%) compared to the aerosols of conventional cigarettes (FDA, 2017). There is also an increase (20-32%) in the **total particulate matter** (TPM) content which is the consequence of the higher water and glycerol content in the aerosol composition. On the other hand, there is a decrease in tar emissions of 35.8 to 40.4% per cigarette and nitrogen oxide emissions of 97 to 99% (FDA, 2017). In this case, tar is defined as the fraction collected on the filter (ISO 4 387: 2 000). The tar in heated tobacco products contains proportionally fewer toxic contaminants and more humectants than the tar in conventional cigarettes. It is also called NFDPM (*Nicotine Free Dry Particulate Matter*): the solid and liquid residue of the smoke/aerosol after extraction of water and nicotine.

As regards **nicotine**, emissions (per unit consumed) are only slightly reduced with the IQOS device (less than 50%) (Table 1) (FDA, 2017). This reduction rate can reach higher values for other heated tobacco product systems: 77% for the GLO device and 81% for iFuse (Simonavicius et al., 2018).

Table 1: Comparison of levels of harmful and potentially harmful constituents (HPHC) found in aerosols from heated tobacco systems and conventionally smoked cigarettes (source FDA (2017) based on data provided by *Philip Morris International* for 3 IQOS type devices (PM00000424-425-426).

HPHC	Unit	31 US Brands	IQOS PM0000424			IQOS PM0000425			IQOS PM0000426		
		Mean ± SD[1]	Mean ± SD[2]	Change (per stick)	Change (per nicotine)[3]	Mean ± SD[1]	Change (per stick)	Change (per nicotine)[3]	Mean ± SD[1]	Change (per stick)	Change (per nicotine)[3]
Nicotine	mg/cig	2.03 ± 0.45	1.29 ± 0.047	↓36.4%	N/A	1.19 ± 0.05	↓41.4%	N/A	1.17 ± 0.03	↓42.4%	N/A
Tar	mg/cig	30.61 ± 5.78	19.4 ± 1.62	↓36.1%	↓0,6%	19.5 ± 1.3	↓35.8%	↓1.1%	18.1 ± 1.1	↓40.4%	↓6.2%
Water	mg/cig	15.65 ± 2.42	30.2 ± 2.17	↑93.8%	↑204.9%	35.6 ± 0.59	↑128.4%	↑259.4%	36.0 ± 0.49	↑131.0%	↑263.5%
1,3-butadiene	µg/cig	116.46 ± 19.14	0.207 ± 0.016	↓99.8%	↓99.7%	0.223 ± 0.030	↓99.8%	↓99.7%	0.192 ± 0.006	↓99.8%	↓99.7%
1-aminonaphthalene	ng/cig	34.55 ± 9.39	0.0427 ± 0.0513	↓99.9%	↓99.8%	0.043 ± 0.012	↓99.9%	↓99.8%	0.060 ± 0.003	↓99.8%	↓99.7%
2-aminonaphthalene	ng/cig	21.20 ± 5.02	0.0223 ± 0.00321	↓99.9%	↓99.8%	0.022 ± 0.007	↓99.9%	↓99.8%	0.031 ± 0.009	↓99.9%	↓99.8%
4-aminobiphenyl	ng/cig	3.45 ± 0.76	0.0087 ± 0.0012	↓99.7%	↓99.6%	0.009 ± 0.002	↓99.7%	↓99.6%	0.010 ± 0.002	↓99.7%	↓99.5%
Acetaldehyde	µg/cig	1443.41 ± 218.35	192 ± 11.6	↓86.7%	↓79.1%	206 ± 6	↓85.7%	↓77.5%	192 ± 9	↓86.7%	↓79.1%
Acrolein	µg/cig	157.59 ± 17.91	8.32 ± 0.755	↓94.7%	↓91.7%	9.79 ± 1.66	↓93.8%	↓90.2%	9.32 ± 0.569	↓94.1%	↓90.7%
Acrylonitrile	µg/cig	24.05 ± 3.67	0.145 ± 0.0112	↓94.4%	↓99.1%	0.127 ± 0.017	↓99.5%	↓99.2%	< 0.107 (LOQ)	unknown	unknown
Ammonia	µg/cig	32.01 ± 9.95	12.2 ± 0.973	↓40.0%	↓38.2%	11.1 ± 1.1	↓65.3%	↓45.4%	10.7 ± 0.943	↓66.6%	↓47.4%
Benzene	µg/cig	86.18 ± 11.99	0.452 ± 0.0395	↓99.5%	↓99.2%	0.453 ± 0.046	↓99.5%	↓99.2%	0.473 ± 0.036	↓99.5%	↓99.1%
Benzo[a]pyrene	ng/cig	14.95 ± 3.12	0.736 ± 0.0973	↓95.1%	↓92.3%	0.539 ± 0.081	↓96.4%	↓93.9%	0.448 ± 0.073	↓97.0%	↓95.3%
Carbon monoxide	mg/cig	28.95 ± 3.60	0.347 ± 0.0462	↓98.8%	↓98.1%	0.32 ± 0.00	↓98.9%	↓98.3%	0.48 ± 0.000	↓98.3%	↓97.4%
Crotonaldehyde	µg/cig	51.07 ± 6.25	< 3.29 (LOQ)	unknown	unknown	< 3.29 (LOQ)	unknown	unknown	< 3.29 (LOQ)	unknown	unknown
Formaldehyde	µg/cig	98.23 ± 35.09	14,1 ± 0.43	↓85.6%	↓77,4%	15.2 ± 0.0	↓84.5%	↓75.7%	10.0 ± 0.773	↓89.8%	↓84.0%
Isoprene	µg/cig	1031.85 ± 155.79	1.51 ± 0.129	↓99.9%	↓99.8%	1.51 ± 0.31	↓99.9%	↓99.8%	1.27 ± 0.281	↓99.9%	↓99.8%
NNN*	ng/cig	178.67 ± 57.79	10.1 ± 0.205	↓94.3%	↓91.1%	7.01 ± 0.51	↓96.1%	↓93.8%	7.75 ± 0.766	↓95.7%	↓93.2%
NNK**	ng/cig	128.32 ± 34.76	7.80 ± 0.423	↓93.9%	↓90.4%	6.63 ± 0.53	↓94.8%	↓91.9%	5.52 ± 0.34	↓95.7%	↓93.2%
Toluene	µg/cig	149.18 ± 23.81	1.42 ± 0.162	↓99.0%	98.5%	1.28 ± 0.12	↓99.1%	↓98.6%	1.03 ± 0.272	↓99.3%	↓98.9%

[1] source MR0000085 ; [2] values from tables 2,3,4 ; [3] Normalized to nicotine yield; * N-nitrosonornicotine; ** nicotine-derived nitrosamine ketone

As for other harmful and potentially harmful constituents, studies conducted on IQOS (FDA, 2017) report significant reductions in emissions (Table 1). For a large number of compounds (1,3-butadiene, 1-aminonaphtalene, 2-aminonaphthalene,
4-aminophenyl, benzene, isoprene and toluene) the abatement rate expressed per unit of cigarette exceeds 99% but is lower for ammonia (40.0-66.6%), acetaldehyde (85.7-86.7%), formaldehyde (84.5-89,8%) and, to a lesser extent for carbon monoxide (98.3-98.9%), acrolein (93.8-94.7%), NNN (N-nitrosonornicotine) (94.3-96.1%), NNK (*nicotine-derived nitrosamine ketone*) (93.9-95.7%) and benzo(a)pyrene (95.1-97.0%).

These results on IQOS are corroborated by other studies cited in a literature review by Simonavicius et al. (2018), which also includes other studies on GLO and iFuse devices characterised by emissions of the same order of magnitude, except, in the case of iFuse, some lower abatement values for 3-aminonaphthalene and 3-aminophenyl (97% vs > 99%) and especially for carbon monoxide (79% vs > 98%).

Finally, it should be added that in a report by *Philip Morris International* (Helen et al., 2018), the authors provide additional information on certain other compounds such as phenols (92% reduction in emissions) and various metals (>95% reduction) such as lead and cadmium. For mercury, however, the abatement rate of the metal from emissions is lower (64%).

Furthermore, the review conducted by *Public Health England* (PHE, 2018) also corroborates the main trends noted above but nonetheless highlights some disparities that can be explained by differences in methodology (notably the choice of benchmark for expressing the abatement rate). As such, for three of the carbonyl derivatives, the abatement rates as measured by Auer et al. (2017) are significantly lower than those reported in the above-mentioned reviews. Indeed, whereas for acetaldehyde, formaldehyde and acrolein the abatement rate exceeded the value of 85 and even 90% in the above-mentioned reviews, it is now only 78, 26 and 18% respectively in the study by Auer et al. (2017), which admittedly uses another benchmark. The latter is characterised by lower emission rates, leading to higher abatement rates (expressed in %) than in other studies.

Estimation of exposure of harmful and potentially harmful constituents using biomarkers of exposure.

Exposure of IQOS users to harmful and potentially harmful constituents was further investigated in human models in containment studies (5 days) followed by analysis of biomarkers in the different groups tested (IQOS versus conventional or mentholated cigarettes versus abstinence). The results of 5 of these studies conducted by *Philip Morris International* were analysed in a systematic literature review by Simonavicius et al (2018). The results show that, with respect to the different nicotine markers, there is no significant difference between the various groups (from -15 to +15% compared to smokers of conventional or mentholated cigarettes). With respect to other harmful and potentially harmful constituents, there was a fairly significant but variable decrease from one study to another in the various biomarkers analysed. A summary of the results is presented in Table 2. It should be noted that reductions in biomarkers of exposure are not as high as those observed in the analysis of the main flow constituents during experiments conducted using inhalation machines (Table 1). One reason for this is that the effects of previous exposure to harmful and potentially harmful constituents may persist for some time, and even in abstinent individuals, biomarker levels are not always zero.

Table 2: Summary of results of biomarker analyses of harmful and potentially harmful constituents in containment studies
(IQOS versus cigarette for 5 days) (Simonavicius et al., 2018)

Harmful & Potentially Harmful Constituents	Number of studies	Abatement rate of biomarkers of exposure in the event of a switch to heated tobacco products, compared to maintaining the conventional cigarette (average)	Number of studies	Abatement rate of biomarkers of exposure in the event of complete abstinence, compared to maintaining the conventional cigarette (average)	Relative average of abatement rate of the biomarker of exposure in the event of a switch to heated tobacco products vs. complete abstinence
1,3-Butadiene	5	77 - 92 % (86.8 %)	3	80 – 90 % (85.7 %)	101.3 %
1-Aminonaphthalene	3	94 – 96 % (95.3 %)	2	95 – 96 % (95.5 %)	99.8 %
2-Aminonaphthalene	5	81 - 89 % (85.2 %)	3	68 – 86 % (79.0 %)	107.8 %
4-Aminobiphenyl	5	59 – 85 % (77.8 %)	3	77 – 83 % (81.0 %)	96.0 %
Acrolein	5	47 – 74 % (59.8 %)	3	67 – 84 % (73.0 %)	81.9 %
Acrylonitrile	4	79 – 87 % (80.8 %)	2	83 – 84 % (83.5 %)	96.8 %
Benzene	3	84 – 94 % (88.8 %)	3	85 – 91 % (87.7 %)	101.3 %
Benzo(a)pyrene	3	70 – 72 % (71.3 %)	2	75 – 76 % (75.5 %)	94.4 %
Crotonaldehyde	3	57 – 77 % (65.3 %)	2	60 – 70 % (65.0 %)	100.5 %
C Monoxide	5	53 – 77 % (74.4 %)	3	54 – 81 % (63.3 %)	117.5 %
NNN*	4	70 – 88 % (76.3 %)	2	96 – 96 % (96.0 %)	79.4 %
NNK**	5	48 – 67 % (55.6 %)	3	55 – 66 % (61.3 %)	90.7 %
Ethylene oxide	3	49 – 68 % (56.7 %)	2	50 – 62 % (56.0 %)	101.2 %
Pyrene	5	43 – 62 % (54.4 %)	3	45 – 67 % (56.7 %)	95.9 %
o-Toluidine	5	42 – 59 % (51.8 %)	3	50 – 62 % (54.7 %)	94.7 %

* N-nitrosonornicotine; ** nicotine-derived nitrosamine ketone

In conclusion, it appears that the levels of emissions and exposure to harmful and potentially harmful constituents (with the exception of nicotine) are significantly lower in the case of heated tobacco products compared to conventional cigarettes, although abatement levels of emissions measured on machines tend to be overestimated compared to human studies using biomarkers of exposure. This results in smaller but not necessarily negligible exposure of users of heated tobacco products. The reductions observed in biomarkers of exposure are close to the reductions observed with complete abstinence over the same time period.

3.1.1.2 Levels of harmful and potentially harmful constituents in ambient air (passive exposure)

According to the *Food and Drug Administration* (FDA), based mainly on studies provided by the manufacturer *Philip Morris International*, passive absorption can be considered negligible even though the presence of some compounds can still be detected in secondary flows supplying the ambient air (FDA, 2017).

On the other hand, an independent study (Protano et al., 2016) found that the heated tobacco product device generated submicron particles in the ambient air, an indicator of passive smoking. However, these levels appear to be four times lower than those generated by tobacco smoke from conventional cigarettes. Despite the low level of emissions, the authors of the study concluded that these products would still pose health risks to users and third parties (Protano et al., 2016).

Another independent study (Ruprecht et al., 2017) reported levels of particles of various sizes (> 1.0 µm > 0.3 µm and 10-1000 nm) and levels of harmful and potentially harmful constituents in emissions of heated tobacco products into ambient air. Under simulated indoor conditions with 1.54 air changes per hour, emissions of nanoscale (10-1 000 nm) particles can reach up to 23.8% of the levels detected in ambient cigarette smoke. Ambient air concentrations of particles of different sizes range from 0.7% to 7.3% compared to conventional cigarettes. It should be noted, however, that the relevance of the number of particles may be called into question on account of their composition and physical state (presence of water and glycerol in greater relative proportions) and because of the absence of soot particles (*black carbon*) in the aerosols generated by heated tobacco products (Ruprecht et al., 2017). For harmful and potentially harmful constituents in emissions from heated tobacco products into ambient air, acrolein can reach concentrations of 1.8% to 2.3% of the levels detected in cigarette smoke, while acetaldehyde is in the range of 5.0% to 5.9% and formaldehyde between 6.9% and 7.1%.

Finally, a study funded by *Imperial Tobacco Company* concluded that IQOS has ambient air emissions, unlike electronic cigarettes and nicotine inhalation devices (Forster et al., 2018). However, it seems reasonable to conclude that the use of IQOS in an environment complying with legal air ventilation requirements does not adversely affect the quality of the indoor atmosphere (Cancelada et al., 2019; Mitova et al., 2019).

In conclusion, while the FDA concludes on the basis of information provided by *Philip Morris International* that emissions from heated tobacco products into the ambient air leads to passive exposure that could be considered negligible, the same is not true for the authors of an independent study (Ruprecht et al., 2017) that concluded that emissions into the ambient air from heated tobacco products are significantly higher than those from an electronic cigarette but significantly lower than those detected in tobacco smoke produced by a conventional cigarette. The authors of the study highlight the fact that the presence of carbonyls in ambient air emissions from heated tobacco products might have consequences and adversely affect the health of persons subject to passive exposure. As regards the particulate matter emitted, the conclusions of the various studies diverge as to the relevance of the low levels detected**.**

3.2 Compounds unique to new tobacco products

3.2.1 Detection, emissions and exposure

The FDA reports that, according to records provided by *Philip Morris International* for the evaluation of IQOS-type devices, 80 compounds can be detected in emissions that are not detected or detected at lower levels in conventional cigarettes. Of these compounds, 4 are possible carcinogens, 30 are identified as GRAS (*Generally Recognised as Safe*) and 46 are additional compounds, generally related to flavours. It is currently unknown what adverse effects these aromas may have upon inhalation. The 4 potentially carcinogenic compounds are glycidol, 3-chloro-1,2-propanediol [3-MCPD], 2-furanemethanol and furfural (Table 3).

Table 3: Potentially carcinogenic compounds according to the classification of the IARC[17] and levels determined per unit (tobacco stick introduced into the IQOS device) (Source: Helen et al., 2018).

Name	IARC Classification	Average content (µg/unit)
Glycidol	2A (probable carcinogen)	5.71
3-Monochloro-1,2-propanediol	2B (possible carcinogen)	9.94
2-Furanmethanol	2B (possible carcinogen)	39.18
Furfural	3 (unclassifiable as to carcinogenic effects)	31.08

Furthermore, according to Auer et al. 2017 (cited in PHE 2018), a polycyclic aromatic hydrocarbon (acenaphthalene) is emitted by IQOS at much higher concentrations (3-6 times higher depending on the reference used) than in the conventional cigarette. These observations are not confirmed by the studies conducted by the manufacturers (PHE, 2018).

In addition, the publication of (Helen et al., 2018) indicates that, with respect to emissions of the IQOS compared to smoking a conventional cigarette, the data from *Philip Morris International* also indicate significantly higher concentrations of several substances that are not recognised as harmful or potentially harmful constituents by the FDA. The impact of these substances on the general toxicity or adverse effects of IQOS is not known. (Helen et al., 2018). Nevertheless, the overall conclusion of *Philip Morris International* (but also the FDA) is largely based on the levels of harmful and potentially harmful constituents, despite the fact that *Philip Morris International* has not examined all harmful and potentially harmful constituents. The present opinion should therefore also focus on the latter substances (harmful and potentially harmful constituents at higher concentrations than conventional cigarettes in the emissions of IQOS) and their potential harmful effects.

These constituents also include flavourings, for which little information is available. The WHO stated in 2019 that evidence obtained for e-liquid flavours suggests that flavour chemicals can have toxic effects. It is important to understand that the wording "generally recognized as safe" (GRAS[18]) for the use of a flavour in food, however, does not automatically apply to its use in tobacco products, particularly products that are inhaled, such as heated tobacco products and electronic cigarettes (WHO, 2019). In response to the St Helen's study (2018), *Philip Morris International* confirms that several substances are specific to IQOS. However, this phenomenon is expected due to differences in composition (menthol and other flavours) compared to the conventional cigarette. However, *Philip Morris International* is still unaware of their potential toxic effects.

On the other hand, *Philip Morris International* claims, based on a complete non-targeted differential screening of the aerosol in the heated tobacco system, that the heated tobacco system is characterised by less compositional complexity and significantly fewer compounds than the conventional cigarette (Baker et al., 2019). The same study leads to the observation that the aerosol of the heated tobacco system is characterised by the presence of 85 compounds present in higher amounts than in cigarette smoke, including 4 compounds

[17] IARC: International Agency for Research on Cancer
[18] GRAS, *generally recognized as safe*

(glycidol, 3-MCPD[19], 2-furanemethanol and furfural), the relevance of which is discussed in section 4.3.4 of the present opinion.

[19] 3-chloro-1,2-propanediol

4 Toxicity of tobacco products

4.1 Toxicity of tobacco

As detailed in the opinion on e-cigarettes of the SHC (9265, 2015) and shown below, both active and passive smoking are harmful to health.

Active smoking is indeed directly responsible for the development of chronic lung diseases (chronic obstructive pulmonary disease and emphysema, but also lung cancer (Forey et al., 2011). Smoking is a risk factor for cancer (lung, larynx, oesophagus, stomach, liver, mouth, pancreas, colon-rectum, kidney, stomach, liver, breast, prostate-Torre et al., 2015). Smoking increases the risk of inflammatory diseases of the digestive system (Crohn's disease) (Coward et al., 2015).

Smoking is associated with an increased risk of developing cardiovascular disease (heart attack, stroke, high blood pressure, peripheral arterial disease - Ambrose & Barua, 2004; Barnoya& Glantz, 2005; Tunstall-Pedoe, 2003). Smokers have a higher risk of developing type 2 diabetes (Willi et al., 2007), kidney disease (Speeckaer et al., 2013), and more complications from these conditions. Smoking increases the risk of osteoporosis. Smoking is associated with an increased risk of infectious diseases (Leung et al., 2015; Nuorti et al., 2000); aggravates certain neurological diseases (multiple sclerosis - Ragamopalan et al., 2013). Smoking is associated with an increased risk of gum and dental disease (Ojima & Hanioka, 2010). Smoking increases the risk of complications during surgery under general anaesthesia (Rodrigo, 2000).

Passive smoking refers to the inhalation of environmental tobacco smoke in the ambient air in enclosed and covered areas.

Short-term exposure to environmental smoke has immediate effects on the respiratory tract, resulting in symptoms of irritation of the mucous membranes of the eyes, nasopharynx and bronchus (Flouris et al., 2009). At the cardiovascular level, brief exposure increases blood pressure and activates blood platelets (Davis et al., 1989).

Chronic exposure to environmental tobacco smoke damages child health by increasing the risk of bronchitis, bronchiolitis, pneumonia in children under 2 years of age (Jones et al., 2011), the risk of sudden infant death syndrome (Golding, 1997), the risk of lower respiratory tract disease (Burke et al., 2012), asthma (Vork et al., 2007), and otitis in children over 2 years of age (Jones et al., 2012). Moreover, exposed children are at greater risk of respiratory complications during general anaesthesia (Seyidov et al., 2011; von Ungern-Sternberg et al., 2010), and are less able to defend themselves against serious infections (den Boon et al., 2007; Murray et al., 2012). Passive smoking aggravates the evolution of chronic diseases in children, with a demonstrated effect for asthma, cystic fibrosis (Collaco et al., 2008), type 1 diabetes.

Chronic exposure to environmental tobacco smoke harms adult health by increasing the risk of cardiovascular disease (Barnoya et al., 2005) both in terms of premature death (Gallo et al., 2010; Pell et al., 2009) and coronary heart disease (increased risk of heart attack, recurrent heart attack - Hamer et al, 2010), stroke (Lee et al., 2006), peripheral arterial disease

(He et al., 2008), high blood pressure (Vozoris et al., 2008); and the risk of respiratory diseases (chronic obstructive pulmonary disease, emphysema, asthma, chronic cough - Ebbert et al., 2007; Hooper et al., 2012; Jaakkola et al., 2003). Finally, passive smoking increases the risk of adult cancer, particularly lung cancer (Taylor et al., 2007), breast cancer (Johnson et al., 2008), cervical cancer (Tsai et al., 2007), pancreatic cancer (Vrieling et al., 2010) and laryngeal cancer (Lee et al., 2008).

4.2 Toxicity of nicotine

As already stated in the opinion on "e-cigarettes" (SHC 9265, 2015), little is known about the long-term harm of pure nicotine.

Numerous animal studies of nicotine toxicity have concluded that nicotine toxicity is vascular, hepatic and pulmonary (Fahim et al., 2014; Wang et al., 2012; Yokohira et al., 2012), renal (Arany et al., 2011) and neurological (Gould et al., 2014). In addition, a study on animals has shown that administration of nicotine can promote the growth of pre-implanted tumours and the formation of metastases (Davis et al., 2009). *In utero* exposure to nicotine results in neurological consequences (Schneider et al., 2010; Gould et al., 2014) and perinatal exposure may promote asthma in subsequent generations of rats (transgenerational transmission - Bruin et al., 2010; Dwyer et al., 2009).

The data currently available in the literature do not provide conclusive evidence of long-term toxicity (more focused on carcinogenesis) with regular use of isolated nicotine (Haussmann HJ & Fariss MW, 2016).

In addition, there are various and well-validated data on the impact of nicotine in sensitising the reward circuit. Nicotine acts by usurping the cellular mechanisms of synaptic plasticity (Gould et al., 2014). Nicotine is a highly addictive alkaloid which, by sensitising the reward circuit, can lead to a disruption of motivational behaviour and sensitisation to other psychotropic drugs (such as alcohol).

Nicotine is therefore clearly not a product without health consequences, but the risk associated with nicotine is limited compared to the risks associated with tobacco smoke.

4.3 Toxicity of conventional cigarettes versus new tobacco products

4.3.1 Toxicity in vitro

Philip Morris International has performed *in vitro* tests using the Ames test, the *mouse lymphoma assay* (MLA) and the nuclear red capture test. The latter test determines cytotoxicity by measuring the absorption of neutral red in viable cells. These tests showed a limited cytotoxic risk for IQOS compared to conventional cigarettes. Similar results were obtained with this *in vitro* test for HTP1.0/GLO and Neostick from *British American Tobacco* (Jaunky et al., 2018; Crooks et al., 2018; Thorne et al., 2018; Murphy et al., 2018).

The Ames test detects chemicals that induce mutations in bacteria to restore the functional ability to synthesize an essential amino acid (e.g. histidine). The bacteria that undergo these mutations are called revertants. The more revertants there are, the more mutagenic the substance is. In these studies, *Philip Morris International* exposed several strains to varying

concentrations of total particulate matter (TPM) from aerosols of IQOS, as well as to conventional cigarettes. This fraction of IQOS produced no positive mutagenic response at any dose used in the Ames test in contrast to conventional cigarettes. The same results were observed for HTP1.0 and Neostick (*British American Tobacco*) (Crooks et al., 2018, Thorne et al., 2018, Murphy et al., 2018). However, the study reports did not contain information from an Ames test with the gas and vapour phase of the IQOS or conventional cigarettes, whereas the information on harmful and potentially harmful constituents submitted by *Philip Morris International* indicates that the IQOS contains mutagens that are typically found in this phase (e.g., formaldehyde, propylene oxide). As such, an Ames test with the gas and vapour phase of the heated tobacco product and tobacco smoke would provide additional information on the mutagenic potential of the products.

The mouse lymphoma assay is a qualitative test that can determine clastogenicity and mutagenicity in a mammalian cell line by measuring resistance to a lethal pyrimidine analogue (triflurothymidine). The frequency at which these mutations occur (i.e., mutant frequency) is usually expressed as the number of mutants per million (10^6) viable cells. In these tests, *Philip Morris International* reported both relative total growth (measured for cytotoxicity) and mutant frequencies (based on the plating efficiency of cells grown in selective and non-selective triflurothymidine media). Both IQOS and cigarette aerosols generated similar peak concentrations of cytotoxicity (15-20% relative total growth) in the mouse lymphoma assay, but those from the conventional cigarette produced these effects at much lower concentrations (13-29x), indicating greater cytotoxic potency. Similar results were obtained with this *in vitro* test for HTP1.0 from *British American Tobacco* (Thorne et al., 2018).

Similar results were observed for mutagenicity with an 8 to 30-fold difference in potency for the IQOS compared to the conventional cigarette. *Philip Morris International* indicates that this difference in potency is an index of potential (reduced) mutagenicity. However, guidelines from major public health resources (e.g., OECD[20], ICH[21], Health Canada, EPA[22]) do not support this method of relative comparison of mutagenic/genotoxic potency between tobacco products (or other chemicals).

The FDA has concluded that there are limitations to these *in vitro* tests (in general, but also due to the configuration of the test) and that they influence the conclusions that can be drawn from these *in vitro* tests. **Despite these limitations, the *in vitro* studies generally show a decrease in the induction potency of cytotoxicity and mutagenicity due to exposure to the IQOS, compared to conventional cigarettes**. As indicated above, the concentration of substance required to produce these effects may not be an accurate indicator of mutagenic potency. Consequently, it is difficult to determine from these *in vitro* evaluations whether long-term use of IQOS will have the same carcinogenic potential as smoking conventional cigarettes (FDA, 2019).

There is little in the way of information available on the toxicity of heated tobacco products belonging to other categories, such as IQOS and GLO. In this regard, a study by *Japan Tobacco International* showed that their new tobacco vapour product showed

[20] OECD: Organisation for Economic Co-operation and Development
[21] ICH: International Council on Harmonization
[22] EPA: Environmental Protection Agency

responses to oxidative stress in human bronchial epithelial cells, but with less potency than conventional cigarettes (Munakata et al., 2018).

4.3.2 In vivo toxicity

In vivo studies conducted by *Philip Morris International* consisted of two 90-day nasal inhalation studies in rats only, an 18-month carcinogenicity study in mice, systems toxicology studies with acute and repeated exposures to human organotypic tissues, and a study on changed treatment in mice.

The 90-day inhalation studies showed that changes due to exposure to the aerosol of the IQOS were not observed or were much less severe than changes due to exposure to smoking conventional cigarettes. Urinary biomarker concentrations of the harmful and potentially harmful constituents NNK[23], acrolein, benzene and acrylonitrile were generally lower in rats exposed to aerosols of the IQOS than in rats exposed to conventional cigarette smoke, and similar to the dummy control. In addition, the incidence of basal cell hyperplasia and squamous cell hyperplasia was similar in rats exposed to either the aerosols of the IQOS or a conventional cigarette, whereas caliciform cell hyperplasia/hypertrophy (lung) and macrophage aggregation (lung) were observed only in rats exposed to the conventional cigarette. Hyperplasia, metaplasia and immune cell infiltration are adaptive responses to acute stress factors, which are often reversible once the causative agent is eliminated.

However, with continued exposure, as with smoking, hyperplasia and metaplasia can be interpreted as pre-neoplastic changes, whereas intra-alveolar macrophage aggregation may be an early indicator of fibrosis and caliciform cell hyperplasia may be an early sign of chronic bronchitis. *Philip Morris International* attributes these effects to the high doses of nicotine to which laboratory animals were exposed under IQOS conditions and considers these results to be adaptive responses, as they partially reverse during the recovery period, but according to the FDA, the data suggest that not all effects are reversible. It is important to note that after 90 days of exposure, liver weight and blood alanine aminotransferase (ALT) levels were not addressed by *Philip Morris International* in their registration application, they were significantly higher with IQOS than with conventional cigarettes in female rats. Alanine aminotransferase is an enzyme released into the blood by hepatocytes during hepatocellular injury. The weight of the liver is a sensitive measure of hepatocellular hypertrophy (Chun et al., 2018). Moreover, hepatocellular vacuolation, a sign of acute liver injury, was significantly higher in female rats exposed to IQOS, an effect not observed in the animals exposed to cigarettes. These results could indicate potential hepatotoxicity due to the use of IQOS (Chun et al., 2018).

The interim report of *Philip Morris International* of an 18-month carcinogenicity study shows that the incidence of neoplastic lesions is higher in the aerosol of the IQOS and conventional cigarette groups than in the dummy control group. However, in the final study report, *Philip Morris International* concluded that this long-term study did not show an increased risk of lung cancer due to exposure to the aerosol of the IQOS compared to the dummy control group. According to *Philip Morris International*, toxicity is limited to adaptive responses in the upper respiratory tract. As an inhaled tobacco product, IQOS may cause an inflammatory response

[23] NNK: *Nicotine-derived nitrosamine ketone*

in the respiratory tract, but this study does not provide definitive information on the carcinogenic risk in humans.

Philip Morris International used five separate *in vitro* organotypic studies to assess the effects of acute and repeated exposure to the aerosols of IQOS and regular smoke on cultures of gingival, buccal, nasal, bronchial and coronary artery epithelium in humans. Both aerosols produce toxicity (e.g. oxidative stress, DNA damage, increased pro-inflammatory mediators) in human gingival, bronchial, oral, nasal and small airway tissues, as well as in epithelial tissues of human coronary arteries. The toxic effects produced by conventional cigarette smoke were generally (but somewhat variable) worse than those produced by the aerosols of the IQOS. However, the experimental approach adopted in these studies included the use of exploratory methods, which have not been independently validated and have no known utility for regulatory use. *Philip Morris International* tries to make assumptions from acute exposure studies with naïve tissues that have little or no genetic variability in order to predict toxicity in a diverse population with a history of smoking. This approach limits the use of these data.

Philip Morris International also conducted an 8-month study on the change in treatment and smoking cessation (designed to model continued smoking versus a switch to IQOS versus smoking cessation) with female ApoE-/- mice.
In this study, the mice were exposed to conventional cigarette smoke, to the aerosols of IQOS or dummy conditions 3 hours per day, 5 days per week for 8 months. Other groups of mice were exposed to conventional cigarette smoke in the same pattern, but switched to the aerosols of IQOS (the "change group") or filtered air (the "cessation group") after 2 months. However, limitations in the study design affected the interpretation of the data. Specifically, no male A/J mice were used in this study, and the period of exposure to conventional cigarettes for the change group may have been too short to determine the extent to which IQOS aerosols influence the progression of toxic effects caused by cigarette smoke. The histopathological changes observed in the change group were similar to the cessation group, but it is not clear that a longer period of smoking would lead to the same result. The overall pattern of change from switching from conventional smoking to IQOS was positive. Although the results of exposure to the IQOS were not identical to those of the dummy exposure (or smoking abstinence), some effects observed after exposure to conventional cigarettes were either less significant or occurred less frequently in mice that switched to the IQOS, indicating that switching to the IQOS may be beneficial for smokers. Dual exposure to cigarette smoke and IQOS aerosol was not assessed.

The FDA concluded that the data presented by *Philip Morris International* indicate that sub-chronic exposure to IQOS aerosols produces little or less severe histopathological changes than sub-chronic exposure to similar concentrations of conventional cigarettes. However, the correlation between these effects and clinical changes in humans is not known. As with the *in vitro* studies, it is difficult to determine the carcinogenic potential of long-term exposure to IQOS aerosols from these evaluations.
Moreover, the experimental approach adopted in the organotypic studies featured methods that were considered exploratory and were not independently validated; consequently, the usefulness of the data is limited. The 8-month treatment change/cessation study suggested that switching to IQOS after a short period of exposure to conventional cigarette smoke led to similar histopathological changes upon smoking cessation; however, certain design limitations reduce the validity of these data.

A major disadvantage of the toxicity evaluation of heated tobacco products is that most of the studies relate to the IQOS and not to other types of heated tobacco products, as the results for these other types may differ. Furthermore, most of these studies are funded by *Philip Morris International* (Schaller et al., 2016). *Public Health England* (PHE, 2018) has also highlighted these facts. **Further independent research is clearly needed.**

A study by Nabavizadeh et al. (2018), in a more relevant physiological model for endothelial function, shows that the IQOS harms endothelial function as much as conventional cigarettes. In this study, anaesthetised rats (n=8/group) were acutely exposed nasally to the aerosol of the IQOS, or to the main smoke from conventional cigarettes, or clean air. Flow-mediated dilation before and after exposure was measured. The change in flow-mediated dilation during acute exposure to the aerosol of the IQOS is comparable to that associated with exposure to cigarette smoke, but does not achieve exposure to clean air. In a response to this study, *Philip Morris International* states that the effects observed in the study by Nabavizadeh et al. are actually short-term sympathomimetic effects which are expected from nicotine, and not predictive of the development of cardiovascular disease in humans. Nevertheless, the difference with clean air cannot be denied.
Furthermore, the results of studies funded by *Philip Morris International* may not address all effects as shown by (Chun et al., 2018) with respect to hepatotoxicity.

4.3.3 Clinical studies

To back up the clinical evaluation of the IQOS, *Philip Morris International* provided kinetic studies, reduced exposure studies, a summary of adverse events, a review of the published literature and pharmacovigilance reports, and an actual use study that assessed the abuse of the products and overall use patterns in a "real world" environment.

Overall, the clinical studies show that exclusively using the IQOS is likely to reduce adverse health effects compared to smoking a conventional cigarette. The IQOS provides nicotine in concentrations similar to a conventional cigarette, which relieves nicotine cravings and withdrawal symptoms. The short (5-day) studies show an improvement in biomarkers of exposure for people who make the complete switch, indicating a reduction in exposure to harmful and potentially harmful constituents. This general improvement continued in the 90-day studies, even though some participants had reduced compliance and were likely using other tobacco products in addition to the IQOS. Although not demonstrated in these studies by *Philip Morris International*, reducing exposure to harmful and potentially harmful constituents may lead to a reduction in the risk of tobacco-related disease. Although dual use was common in the US studies, the clinical study submitted in June 2018 (Lüdicke et al., 2019) showed a reduction in dual use over time (six months) and a general trend towards improvement in biomarkers of potential harm (significant effect for five of the eight biomarkers of effect measured) also during the 6-month study period. Abusing a product does not occur often and the design of the product makes abusing it unsatisfactory. According to the FDA, clinical studies and literature searches have not identified specific short-term health problems associated solely with the use of these products. (FDA, 2019).
This is consistent with what was reported by *Public Health England* (PHE, 2018). The researchers at PHE concluded that, compared to cigarettes, heated tobacco products are likely to expose users and bystanders to lower concentrations of harmful and potentially

harmful particles and compounds, although the magnitude of the reduction observed varies among studies.

However, one important shortcoming should be noted: *Philip Morris International* **did not assess systemic exposure to inorganic compounds, phenols and metals**, perhaps due to the fact that there are no valid biomarkers for certain substances or because the temporal evolution of biomarkers may not be optimal for studies of the duration used by *Philip Morris International* (St Helen, 2018).

The human clinical data submitted by *Philip Morris International* to the FDA raise additional concerns. Increased plasma bilirubin may point to cholestatic liver injury with altered hepatic bile flow, accelerated red blood cell destruction, or decreased bilirubin metabolism. After 5 days of exposure to IQOS, conventional cigarettes or smoking abstinence, plasma bilirubin levels were elevated in 8.8% of IQOS subjects compared to 0% of smokers and 2.6% of abstainers. In another 5-day study, the mean increase in ALT[24] was higher with IQOS than with conventional cigarettes or with smoking abstinence (4.5, 2.9 and 1.6 IU/l, respectively). In a 90-day study of exposure to IQOS, exposure to cigarettes, or smoking abstinence, the rate of increase in Grade 1 (mild) ALT after 60 days of exposure was highest with IQOS and was 6.3% compared to 0% for conventional cigarettes.

Considered together, the preclinical (*in vivo)* and clinical data from *Philip Morris International* represent a worrying pattern for possible hepatotoxicity, particularly given the short exposure period. These results indicate that the IQOS may exhibit unexpected organ toxicity that was not associated with cigarettes (Chun et al., 2018). In response to this study, *Philip Morris International* confirms the above observations, but suggests that the effects reported in the preclinical studies are due to a different set-up and exposure conditions (e.g., higher nicotine concentration in rats subjected to "heated tobacco products" than in rats subjected to "conventional cigarettes"). Despite the clinical data suggesting possible hepatotoxicity, *Philip Morris International* still claims there is no hepatotoxicity and indicates that the clinical diagnosis of hepatotoxicity requires a combined evaluation of various positive parameters/tests as they evolve over time, rather than the individual/isolated parameters mentioned above at specific points in time. Due to the short-term nature of the experiments, however, the absence of hepatotoxicity cannot be confirmed.

Recently, a systematic review (Drovandi et al., 2019) was conducted on studies evaluating the comparative concentrations of biomarkers of exposure (BoE) in humans using conventional cigarettes or new heated tobacco products. As such, out of ten studies, 12 biomarkers of exposure analysed showed significantly lower concentrations in participants using heated tobacco products compared to those using conventional cigarettes. These reductions in biomarkers of exposure were largest for several known carcinogens, including carboxyhaemoglobin, 2-aminonaphthalene, 4-aminobiphenyl and 2-cyanoethylmercapturic acid, indicating the potential for a significant reduction in adverse effects when using heated tobacco products compared to conventional cigarettes. Moreover, the concentrations of 8 of the 12 biomarkers of exposure were statistically equivalent between heated tobacco products and abstinent participants, although the concentrations of some other carcinogenic biomarkers of exposure were significantly higher. Heated tobacco products can therefore play

[24] ALT: Alanine aminotransferase

a role in reducing exposure, but should not be considered totally safe. The significant involvement of tobacco manufacturers in these studies demonstrates the need for caution in interpreting these results and the need for independent research to confirm or refute them.

These findings are consistent with those of the systematic review of (Jankowski et al., 2019). **They conclude that a significant decrease in exposure levels to harmful and potentially harmful constituents was observed after the switch from conventional cigarettes to heated tobacco products (IQOS or GLO). However, while the studies sponsored by the tobacco industry have primarily demonstrated health benefits with respect to switching from using conventional cigarettes to using heated tobacco products, the few existing independent studies indicate several potentially adverse consequences of exposure to the aerosols from heated tobacco products**. These authors also point out that the sponsored studies are conducted with new, clean heated tobacco products, and it can therefore be assumed that the lack of adequate cleaning can lead to an accumulation of undesirable substances in the unit, which influences the heating conditions and the chemical composition of the aerosol produced. **In conclusion, they state that there is currently no evidence for the long-term health effects of the use of heated tobacco products**. **There is a need for independent research in the future, in particular human studies, to assess the short and long-term health effects of using heated tobacco products**.

Another shortcoming in the research on the effects of heated tobacco products on human health is the effects in the event of dual use. This risk of dual use exists in the case of heated tobacco products as described in the study by (Jankowski et al., 2019), among others.

An interesting study by Stephens (2017) based on unit risk values for carcinogenic potency for 15 of the 18 compounds present in tobacco smoke (eleven compounds classified by the IARC[25] as carcinogenic to humans in Group 1 and seven others as possibly carcinogenic to humans in Group 2B) concluded that **heated tobacco products (15 sticks per day) are associated with 2.4% of the carcinogenic risk of consuming 15 cigarettes per day. Stephens also calculated that smoking 15 cigarettes a day would result in a 2.4% additional lifetime risk of cancer**. However, both calculations by Stephens (2017) are almost certainly underestimated.

The lifetime risk of cancer[26] incurred by regular smoking is estimated to be in the order of 10%. Although epidemiological studies may overestimate the consequences of the relatively easily quantifiable parameter "smoking", while other environmental parameters that are more difficult to identify and quantify also contribute to the same diseases, many studies clearly establish that smoking is a very important cause of various types of cancer. In Korea, **20,239 (20.9%) incident cancer cases and 14,377 (32.9%) cancer deaths in adult men, as well as 1,930 (2.1%) incident cancer cases and 1,351 (5.2%) cancer deaths in adult women were attributed to tobacco in 2009 (Park et al., 2014).** A systematic review with meta-analysis of articles published prior to 2000 demonstrated a link between smoking and lung cancer risk,

[25] IARC: International Agency for Research on Cancer

[26] All pathologies taken together, including those unrelated to smoking. The percentage of cancers attributable to smoking in Europe in 2008 was 34.9%. (Agudo et al., 2012).

clearly observed for a lifetime smoker (random effects RR[27] 5.50, CI[28] 5.07-5.96), a current smoker (8.43,7.63-9.31), an ex-smoker (4.30, 3.93-4.71), and a person who smokes only pipes/cigars (2.92,2.38-3.57) (Lee et al, 2012). According to Sasco, one third of all cancer deaths in various Western countries are attributable to smoking. It has been estimated that tobacco can kill all other smokers prematurely (Sasco, 2004). In addition, the risk from **heated tobacco products is probably greater than 2.4% of the risk associated with smoking, since the use of tobacco products exposes users to more toxic and carcinogenic substances than the 15 substances considered in the calculations of Stephens (2017) and, more importantly, the effect of particulate matter was not taken into account. Furthermore, the use of heated tobacco products also exposes users to four carcinogens that are not present in tobacco smoke. Another important aspect is that the dose-response curve for exposure to tobacco smoke is asymptotic. The most intense effect per unit dose is in the lower exposure range. As such, exposure to one to four cigarettes per day is already associated with a relative risk of dying from lung cancer of 2.79 (0.94 to 8.28) in men and 5.03 (1.81 to 13.98) in women and a relative risk of dying from ischemic heart disease of 2.74 (2.07 to 3.61) in men and 2.94 (1.75 to 4.95) in women** (Bjartveit and Tverdal 2005). The study by Choi et al (2017) showed that smoking less than one cigarette per day was already associated with a hazard ratio of 10.73 for lung cancer, rising to 18.38 and 36.83 for consumption of 1-10 cigarettes per day and more than 30 cigarettes per day, respectively. Similarly, the hazard ratio for cardiovascular or pulmonary disease already increases significantly, in relative terms, in individuals who smoke only a few cigarettes per day (Choi et al., 2017). (Pirie et al., 2012), who did not, however, collect data for occasional smokers and used consumption of 1-10 cigarettes per day for the lower category, observed an increase in relative risk proportional to smoking intensity, but this increase was relatively less pronounced for ischemic heart disease than for lung cancer.

The fact that less exposure to tobacco smoke results in a relatively small decrease in the associated health risk also suggests that even limited exposure to tobacco smoke is associated with a substantial increase in health risk. (Lee et al. 2013) identified 14 studies examining the effects of reduced cigarette consumption on lung cancer, cardiovascular disease, chronic obstructive pulmonary disease and decline in lung function. Compared to individuals who did not reduce their consumption, the meta-analysis (random effects) showed a significantly reduced risk of lung cancer (RR 0.81, 95% CI 0.74-0.88 for any reduction, and RR 0.78, 0.66-0.92 for the greatest reduction). Four cohort studies showed cardiovascular outcomes, with the combined RR of 0.93 (0.84-1.03) for any reduction being non-significant. In the case of reduction, an effect was not consistently observed for chronic obstructive pulmonary disease or decline in lung function. Four cohort studies reported all-cause mortality results, with the combined RR of 0.92 (0.85-1.01) being non-significant. The RR of 0.95 (0.88-1.02) for all smoking-related cancers from three studies was also non-significant. **The observed asymptotic dose-response relationship implies that even if the intensity of exposure to heated tobacco products does not exceed 5% of the exposure to tobacco smoke, the risk of these devices is far from negligible.**

[27] RR: Relative risk
[28] CI: confidence interval

4.3.4 Potential toxicity of compounds unique to heated tobacco products

The presence of several potentially carcinogenic compounds in emissions from heated tobacco products at concentrations (significantly) higher than those measured in cigarette emissions raises questions, even though all *in vitro* and *in vivo* tests conducted to assess the toxicity of the aerosols generated by heated tobacco products result in reduced toxicity compared to cigarette smoke (Helen et al., 2018). According to the FDA, the levels of exposure to the 4 potentially carcinogenic compounds appear to be low and, taken together with other data, would not preclude the conclusion that "*heated tobacco products are appropriate for the protection of public health*" (FDA, 2019).

In the case of non-threshold carcinogens, however, a significant risk may persist even if the dose has been reduced.

As such, taking glycidol as an example, studies in rats have shown that glycidol has primarily chronic toxic effects that target the reproductive system of male rats. The effects vary according to the dose administered and may even cause infertility (EFSA, 2016). Furthermore, glycidol is "probably carcinogenic to humans" (Group 2A) (IARC, 2000) and confirmed as carcinogenic in rats and mice (EFSA, 2016). According to the *European Food Safety Authority*, (EFSA, 2016), its mode of action is most likely genotoxic. The EFSA (2016) and JECFA (*Joint FAO/WHO Expert Committee on Food Additives*, 2017) considered carcinogenicity induced in the event of long-term exposure as a critical effect with a toxicological reference point (T25, dose causing 25% tumours in the tissues studied) of 10,200 µg/kg body weight per day for peritoneal mesothelioma in male rats (EFSA, 2016). Given the genotoxic and carcinogenic potential of glycidol, a margin of exposure estimation approach is applied (EFSA, 2017). Margin of exposure estimates were calculated by dividing the reference point of 10,200 µg/kg body weight per day by the exposure levels. Given the glycidol content per unit (tobacco stick) introduced into the system (5.71 µg, see Table 3), it follows that the potential exposure of a heavy user consuming 40 units daily can be estimated at 228.4 µg/day or 3.81 µg/kg bw/day for a 60 kg individual. Therefore, the margin of exposure can be estimated to be 10,200/3,81 = 2 680. According to the EFSA (2016) a margin of exposure equal to or greater than 25,000 is considered to have low health concern. It should be noted, however, that the margin of exposure values proposed for characterising risk from dietary exposure are not appropriate for assessing risk from inhalation exposure. Indeed, the most sensitive effects and target organs may differ depending on whether a toxicant is ingested or inhaled. In addition, differences in toxicokinetics and distinct effects at the point of entry of the toxicant are not taken into account. However, despite all the uncertainties raised, it is clear that the margin of exposure is particularly small compared to the value considered to be of low health concern (2,680 versus 25,000). **It is therefore desirable to further characterise the risk for the different carcinogenic compounds detected in the aerosols of heated tobacco products.** For the sake of completeness and to illustrate their potential risk, the classification of the other 3 potentially carcinogenic substances, as well as that of acenaphthylene, is shown in Table 4.

Table 4: Toxic properties of substances unique to heated tobacco products

Compound	Acute inhalation toxicity*	Repeated dose toxicity*	Carcinogenic, mutagenic, reprotoxic*.	Genotoxicity*	Critical effect
Glycidol	**H331** Toxic if inhaled H335 May cause respiratory irritation.	/ **H315**: Causes skin irritation (with repeated exposure)	Probably carcinogenic to humans (Group 2A, IARC) **H350**: May cause cancer	**H341**: Suspected of causing genetic defects	T25 value of 10.2 mg/kg bw per day for neoplastic effects in rats (EFSA 2016)
3-Monochloro-1,2-propanediol	**H331** Toxic if inhaled	**H372**: Causes damage to organs through prolonged or repeated exposure	Probably carcinogenic to humans (Group 2B, IARC) **H351**: Suspected of causing cancer **H360**: May damage fertility or the unborn child	/ (no genotoxicity *in vivo*)	$BMDL_{10}$[29] value for 3-MCPD of 0.077 mg/kg bw per day for induction of nephrotoxicity in rats and derived from a tolerable daily intake of 0.8 µg/kg bw per day (EFSA, 2016)
2-Furanmethanol	**H331** Toxic if inhaled **H335** May cause respiratory irritation	**H373**: May cause damage to organs through prolonged or repeated exposure	Probably carcinogenic to humans (Group 2B, IARC) **H351**: Suspected of causing cancer	/ (no genotoxicity *in vivo*)	
2-Furfural	**H331** Toxic if inhaled **H335** May cause respiratory irritation	/	Not classifiable as to its carcinogenicity to humans (Group 3, IARC) H351: Suspected of causing cancer	/ (no genotoxicity *in vitro* and *in vivo*)	
Acenaphthylene	**H330** Fatal if inhaled **H335** May cause respiratory irritation		Not classifiable as to human carcinogenicity. (no study)	Inadequate database for evaluation	

*PubChem was used as the source

4.3.5 Conclusions

- Despite the methodological limitations of the tests, the *in vitro* studies generally show a decrease in the induction potency of cytotoxicity and mutagenicity due to exposure to a heated tobacco product, compared to conventional cigarettes.

[29] BMDL: *Benchmark Dose Lower Confidence Limit*

- Sub-chronic *in vivo* exposure to IQOS aerosols produces little or less severe histopathological changes than sub-chronic exposure at similar concentrations to conventional cigarettes. However, the correlation between these effects and clinical changes in humans is not known.
- In clinical studies, following a switch from conventional cigarettes to heated tobacco products (IQOS or GLO), significant decreases in biomarker levels of exposure to harmful and potentially harmful constituents have been observed, although they cannot be considered to be completely safe. The same deduction can be made in light of the asymptotic relationship between dose and effect of tobacco smoke, which suggests that even if the intensity of exposure to heated tobacco products is no more than 5% of the exposure to tobacco smoke, the risk associated with the use of these products should clearly not be overlooked.
- The few independent studies that exist indicate some potentially harmful consequences of exposure to aerosols from heated tobacco products and/or several shortcomings in the studies conducted for the tobacco industry.
- It is currently not possible to draw conclusions on the long-term and medium-term effects on health (cfr., the carcinogenic potential) of using heated tobacco products compared to smoking conventional cigarettes.
- Independent research must be conducted in the future, in particular human studies, to assess the short- and long-term health effects of using heated tobacco products.
- The risk associated with the various unique carcinogens in aerosols of heated tobacco products needs to be further examined (effect of inhalation, etc.).

5 Comparison of the different categories of new heated tobacco products

5.1 Emission levels of different compounds according to the category of heated tobacco products

There are no reliable studies comparing the composition of emissions from different types of heated tobacco products. Rather, the studies compare the composition of emissions with a conventional cigarette and use a smoking machine to this end. Two different standards are used for these comparative studies: ISO 3308 and the HCI standard, used in Canada. In terms of general parameters such as temperature and humidity, the two standards are comparable, but factors such as puff volume, frequency and degree of pore blockage differ. The latter factor ensures that a comparison of the composition of emissions between different heated tobacco products based on data in the literature should be made with caution, and that in the absence of a standard for conducting such tests, the value of such a comparison is debatable (Dautzenberg & Dautzenberg, 2019).

For products in the first category, IQOS-type products, reviews have already been written that provide an overview of the composition of emissions relative to a conventional cigarette (Simonavicius et al., 2018), using the HCI standard. The following table summarises the different values that could be found in the literature. For IQOS and GLO, values are taken from the benchmark (Simonavicius et al., 2018).

Table 5: Percentage of emissions of various harmful and potentially harmful constituents (HPHC) compared to conventional cigarettes based on independent studies of various heated tobacco products.

HPHC	IQOS (Simonavicius et al., 2018)	GLO (Simonavicius et al., 2018)	PloomTech (Poynton et al., 2017)	iFuse (Poynton et al., 2017)
1,3-butadiene	< 1 %	< 1 %	< 1 %	< 1 %
1-Aminonaphtalene	< 1 %	< 1 %	<1.5 %	< 1 %
2-Aminonaphtalene	< 1 %	< 1 %	< 1 %	3 %
4-Aminobiphenyl	< 2 %	< 1 %	< 2 %	3 %
Acetaldehyde	**12-14 %**	**5 %**	**< 1 %**	**< 1 %**
Acrolein	**6-7 %**	**1-2 %**	**< 1 %**	**5 %**
Acrylonitrile	≤ 1 %	< 1 %	< 1 %	< 1 %
Ammonia	**35-38 %**	**12-15 %**	**42 %**	**< 50 %**
Benzene	< 1 %	< 1 %	< 1 %	< 1 %
Benzopyrene	6-9 %	2-3 %	< 4 %	< 7 %
C Monoxide	1-2 %	< 1 %	≤ 1.5 %	21 %
Crotonaldehyde	5-6 %	1-2 %	≤ 3.5 %	< 3 %
Formaldehyde	**8-11 %**	**6-7 %**	**6.4 %**	**13 %**
Isoprene	< 1 %	< 1 %	< 1 %	< 1 %
N-nitrosonornicotine	4-8 %	7-9 %	< 1 %	< 1 %
Nicotine-derived nitrosamone ketone	2-5 %	2 %	< 1 %	< 1 %
Toluene	1-2 %	< 1 %	< 1 %	2 %
Nicotine	**57-73 %**	**18-23 %**	**54.7 %**	**139 %**
Water	168-350 %	71-80 %	74.2 %	-

Glycerol	**163-203 %**	**101-129 %**	**84 %**	-
Total particulate matter	89-135 %	54-56 %	-	-
Tar/nicotine-free dry particulate matter	39-79 %	46-48 %	-	-

The products requiring special attention in terms of toxicology are shown in **bold**.

The first two products in Table 5 belong to the first category described in point 2. Both products are conduction systems that directly heat the tobacco. There is therefore contact between the processed tobacco (tobacco stick) and the heating element. If we compare the emission values of the two products, it should be noted that comparable levels are observed for most harmful and potentially harmful constituents. Significantly lower values can only be obtained for acetaldehyde, acrolein, ammonia, benzopyrene, crotonaldehyde, nicotine and water. This may be due to the fact that in the GLO device, the stick is only heated to 240°C, compared to the IQOS which uses temperatures around 350°C. Here again, it should be pointed out that these tests were not carried out together and not exactly under the same conditions. As such, the observed differences may be the result of differences in the experimental set-up.

For the second category described in point 2, the so-called convection systems, no emission values could be found in the literature.

PloomTech is the typical example found in the third category, where a liquid that does not contain nicotine is heated and then passed over the tobacco. When the emission values are compared to the IQOS, the most studied product in the literature, it is striking that similar values are found for most harmful and potentially harmful constituents. Clearly lower values are found in the literature for acetaldehyde and acrolein and possibly significantly lower values for benzopyrene, NNN[30], NNK[31], nicotine and water. Here too, possible differences due to the experimental set-up should be taken into consideration. It should also be noted that the values for PloomTech are closer to those found for GLO, although GLO and IQOS are based on the same principle. It is possible that temperature is the cause of these differences.

Finally, values were found in the literature for iFuse, a hybrid device in which a nicotine-containing liquid, comparable to the liquids in electronic cigarettes, is heated and passed over the tobacco in order to capture the necessary "tobacco flavours". Compared to IQOS, lower values were found for acetaldehyde, crotonaldehyde, NNN and NNK. Values comparable to PloomTech were obtained for all these components, which may be logical given the similar way they function. However, for 2-aminonaphthalene, ammonia, carbon monoxide and nicotine, higher values are obtained compared to the IQOS. This is fairly surprising for acrolein and carbon monoxide, as these values are also significantly higher than those found for PloomTech. The differences in ammonia levels are probably not significant compared to PloomTech. With respect to nicotine, the higher emission may possibly be explained by the fact that it is present in the liquid in purified form and the sole purpose is to extract the flavour from the tobacco, unlike other products, where all the nicotine in the emissions comes from heated tobacco.

[30] NNN : *N-nitrosonornicotine*

[31] NNK: *Nicotine-derived nitrosamine ketone*

In general, it can be said that, with the exception of IQOS and its predecessors at *Philip Morris International*, few studies have been conducted on the composition of emissions from heated tobacco products. Moreover, there are currently no international standards for conducting such experiments, which makes it difficult to compare the data in the literature and means that they must be interpreted with caution. Although all the studies on which Table 5 is based were carried out in accordance with the HCI standard, there may still be differences in the experimental set-up, which would influence the emissions and thus the measured values. In these tests, it should also be noted that greater reductions in harmful and potentially harmful constituents are observed with a smoking robot than in randomised studies with users. It should be noted that reductions in biomarkers of exposure are not as high as those observed in the analysis of the main flow constituents during experiments conducted using inhalation machines (Table 1). One reason for this is that the effects of previous exposure to harmful and potentially harmful constituents may persist for some time, and even in abstinent individuals, biomarker levels are not always zero.

Nevertheless, the values in Table 5 indicate that there are effectively differences between emissions from different product categories and between products in the same category, cfr. IQOS and GLO. Current scientific knowledge does not allow a conclusion to be drawn on these differences in terms of harm to health. Standardised analytical protocols for these products as well as good comparative studies in the same laboratory and under the same conditions are necessary to achieve this. Moreover, the discrepancy between the results obtained with smoking robots and the *in vivo* situation must be taken into account. In order to make any assertions in this regard, exposure studies with smokers/vapers should in fact be carried out and long-term health risk monitoring should be ensured.

It is clear from the data in Table 5 that, as noted above, emissions of harmful and potentially harmful constituents are significantly lower with heated tobacco products than with conventional cigarettes. **However, the literature indicates the presence of various unidentified constituents in the emission profiles of heated tobacco products**. Here too, unknown toxic substances may currently be present (Savareear et al., 2017).

5.2 Harmfulness of heated tobacco products according to category

There is not enough scientific research to formulate a clear answer to the question of toxicity according to the category of the heated tobacco product. Based on what is currently available in the literature, we can deduce that the emission of toxic substances is primarily related to the temperature at which the tobacco is heated. As such, with IQOS (350°C), emissions of harmful and potentially harmful constituents are higher than with GLO (250°C), although both belong to the same product category. On this basis, it could be asserted that the largest amount of harmful and potentially harmful constituents released is found in conduction systems (category 1), followed by convection systems (category 2) and products based on heating a liquid (category 3). Category 1 would therefore be the most harmful, but is still much less harmful than conventional cigarettes. However, this hypothesis must be qualified. On the one hand, by the fact that testing with a smoking robot clearly underestimates exposure to harmful and potentially harmful constituents. On the other hand, the literature indicates (Savareear et al., 2017) that in a chromatographic analysis of the emission of a heated tobacco product, 205 different signals, and thus chemical constituents, were detected. Most of these have not yet been identified. The constituents, which are also present in the smoke of

conventional cigarettes, are present at much lower concentrations in the vapours of heated tobacco products. Many of the unidentified constituents may therefore be toxic and special attention should clearly be paid to those constituents that are specific to heated tobacco products, which have been less studied and which may therefore, in the long term, lead to unexpected health risks.

6 Evolution and characteristics of use, behavioural aspects related to heated tobacco products

6.1 Trends in the use and familiarity of heated tobacco products

To our knowledge, no data are currently available regarding the use of heated tobacco products in Belgium. Officially, the sale of heated tobacco products such as IQOS is not yet available in shops, supermarkets, etc. in Belgium at the time of publication of this opinion[32]. However, these products are likely to be purchased online, on foreign *websites*. International data show increasing awareness and use of heated tobacco products.

Given the history of sales of heated tobacco products in Japan, this country can be considered a test case for the analysis of trends in use and awareness of, and relationship to smoking status, and sales of cigarettes.

Japan Tobacco International started selling PloomTech in December 2013. The launch of IQOS was phased, it was introduced in Nagoya in 2014, then in 12 of the 47 prefectures in September 2015 and finally in the remaining prefectures in April 2016[33]. *British American Tobacco* launched the GLO in December 2016.

Tabuchi has studied awareness and use of heated tobacco products using online surveys (Tabuchi et al., 2015; Tabuchi et al., 2018; Tabuchi et al., 2019) (Table 5). In 2015, 0.3% of respondents (n = 8,240) had used the IQOS in the month preceding the survey and 0.3% had used the PloomTech during the same period. By 2017, use of the IQOS had increased to 3.6% (a tenfold increase), use of the PloomTech to 1.2% and use of the GLO to 0.8%. In these studies, no details were requested on the frequency of use of the products (one-off, occasional, weekly, daily).

The prevalence of the use of heated tobacco products relative to smoking status was as follows:

- persons who have never smoked:
  IQOS: 0.1% in 2015; 1.3% in 2017,
  PloomTech: 0.1% in 2015; 0.6% in 2017,
- ex-smokers:
  IQOS: 1.1% in 2015; 2.1% in 2017,
  PloomTech: 1.0% in 2015; 0.9% in 2017,
- current smokers with intention to quit:
  IQOS: 1.2% in 2015; 18.8% in 2017,
  PloomTech: 0.7% in 2015; 6.4% in 2017,
- current smokers with no intention to quit:
  IQOS: 0.2% in 2015; 10.3% in 2017,
  PloomTech: 0.2% in 2015; 2.2% in 2017,

[32] The notification procedure for IQOS was launched within the FPS Public Health in October 2019.
[33] https://tobaccoatlas.org/2019/06/17/heated-tobacco-products-replaced-iqos-japan/

Dual use (the combined use of conventional cigarettes and at least one heated tobacco product or electronic cigarette) increased from 0.8% in 2015 to 3.4% in 2017 (Tabuchi et al., 2019). Dual use among smokers with intention to quit increased from 2.6% in 2015 to 23.4% in 2017. Among smokers with no intention of quitting, dual use increased from 4.1% to 9.6% over the same period. Among participants who did not smoke until 2015, dual use was also reported in 2016 and 2017: 0.4% in 2016 and 1.1% in 2017. Among ex-smokers, dual use was observed among 2.2% in 2016 and 1.6% in 2017. Ex-smokers or people who had never smoked (re)started smoking in 2016 and 2017 and immediately added a heated tobacco product and/or electronic cigarette product to conventional cigarettes.
Prevalence was apparently higher in the younger age category (mainly 20-39 years) than in the older age categories (Tabuchi et al., 2018).
However, statistical analysis could not select age as a significant predictor of current use (with the exception of the >60 age category, where current use of heated tobacco products was lower). Significant predictors of current use of heated tobacco products were: male, age > 60 years, current smoker (with or without intention to quit), history of use of heated tobacco products or electronic cigarettes, current "drinker" (without further precision) (less likely than someone who had never "drunk"), television program in which the IQOS was presented, awareness of tobacco industry promotional campaigns.
The same study population was used to illuminate a sub-aspect (Tabuchi et al., 2019). "*Since e-cigarettes and heated tobacco products have been marketed to consumers as an aid for smoking cessation, regardless of the truth of such claims, we need to investigate the effect of e-cigarettes and heated tobacco products on combustible cigarette cessation"* (Tabuchi et al., 2019). These data were reported by Hirano et al (2017). In the latter study, however, the association between heated tobacco products and smoking cessation disappeared and the focus was solely on the association between electronic cigarettes and smoking cessation.

By analogy with the intention to use an electronic cigarette, the increase in the use of the IQOS was triggered by a popular television programme which featured the product (Amin et al., 2019).

A trend related to age (higher rate of use of PloomTech and IQOS in the 15-39 age group compared to the 40-69 age group) was also found in an earlier survey by the same author (Tabuchi), in both men and women. Even non-smokers had used the products at some point (3.51% of men; 1.25% of women) or in the month prior to the survey (0.60% of men; 0.27% of women) (Tabuchi et al., 2015).

Table 6: Current rate of use (used in the last 30 days) of heated tobacco products/electronic cigarettes (Tabuchi et al., 2018).

Characteristics at 2015 baseline	e-cigarette			IQOS			Ploom/PloomTech			GLO	Any product			Dual use		
	2015	2016	2017	2015	2016	2017	2015	2016	2017	2017	2015	2016	2017	2015	2016	2017
Overall	1.3	1.4	1.9	0.3	0.6	3.6	0.3	0.3	1.2	0.8	1.4	1.8	4.7	0.8	1.2	3.4
Sex																
Man	1.9	1.8	2.9	0.4	1.0	5.4	0.3	0.5	1.9	1.3	1.9	2.2	7.0	1.3	1.8	5.3
Woman	0.8	1.1	0.8	0.2	0.3	1.8	0.2	0.0	0.4	0.4	0.8	1.4	2.4	0.4	0.6	1.5
Any Groups years																
15-19	1.5	4.0	1.8	0.6	2.3	2.0	0.6	0.1	1.3	1.8	1.5	4.1	2.0	0.8	4.0	1.5
20-29	3.6	3.2	3.7	1.0	0.6	5.8	1.1	0.4	1.5	1.0	3.7	3.9	8.7	2.4	1.9	4.4
30-39	1.5	1.2	1.7	0.3	0.9	5.4	0.2	0.6	1.2	1.2	1.5	2.0	6.1	0.8	1.5	4.7
40-49	0.9	0.7	1.2	0.0	0.1	3.9	0.0	0.3	1.2	1.0	0.9	0.8	4.8	0.6	0.4	3.9
50-59	0.2	0.2	2.4	0.0	0.4	3.7	0.0	0.0	0.9	0.2	0.3	0.5	4.2	0.2	0.2	3.7
60-69	0.4	0.1	0.4	0.0	0.1	0.0	0.0	0.0	0.7	0.0	0.4	0.2	1.2	0.2	0.1	1.2
Smoking status																
Never-smoker	0.4	0.5	0.9	0.1	0.1	1.3	0.1	0.1	0.6	0.6	0.4	0.7	1.5	-	0.4	1.1
Former smoker	1.5	3.5	1.5	1.1	1.7	2.1	1.0	0.5	0.9	0.9	1.6	4.0	2.8	-	2.2	1.6
Current smoker with intention to quit	2.1	5.1	10.0	1.2	0.2	18.8	0.7	0.6	6.4	1.6	2.6	5.5	25.4	2.6	5.5	23.4

Previous surveys (Tabuchi et al., 2015; Tabuchi et al., 2018; Tabuchi et al., 2019) evaluated the prevalence and change in use of heated tobacco products and electronic cigarettes over several years, in the context of the same study. For some analyses, these two categories were grouped together.

A recent crossover study conducted online (Sutano et al., 2019) examined the prevalence and certain characteristics of users of heated tobacco products (not electronic cigarettes!) in Japan over the period February to March 2018. A representative group of n = 4,684 participants was involved. The prevalence of heated tobacco products was 2.7%, of which 0.9% used only heated tobacco products (= no dual use). However, dual use was strongly prevalent among a large proportion of users of heated tobacco products: n = 859 used heated tobacco products, of which n = 170 used only heated tobacco products. These figures imply dual use among 689/859 (= 80.2%) of the users of heated tobacco products in the study. Among users of heated tobacco products, 67.8% were current smokers, 25.0% were ex-smokers, and 1.0% had never smoked. 63.4% used heated tobacco products daily, predominantly people who used only heated tobacco products (88.3%). There were also indications of higher nicotine dependence among users of heated tobacco products (higher nicotine dependence defined by the use of heated tobacco products between 6 and 30 minutes after waking (high TTFC - Time To First Cigarette)).

The authors expressed concern about the high number of users of heated tobacco products among non-smokers and ex-smokers and the risk of taking up smoking among young people. "*As a heated tobacco product user is still exposed to harmful constituents, the uptake of heated tobacco product-use among never smokers and former smokers is a crucial data point to continue assessing into the future".* (Sutano et al., 2019).

According to the author, the high number of dual users suggests that "*that heated tobacco products may often serve as complementary products, rather than substitutes for cigarette smoking… Still, substantial dual use of cigarettes and heated tobacco products warrants skepticism toward industry claims of risk-reduction"*. The theoretical potential of risk reduction of heated tobacco products will likely depend on the ratio of heated tobacco products to conventional cigarettes in the total dual-use category.

Three years after the authorisation of IQOS in Italy, an increase in awareness of, use and sale of heated tobacco products has also been observed. In 2017, sales grew exponentially (Liu et al., 2018). In a representative survey (n = 3,086), 1 in 5 respondents were aware of the product, 1.4% had already tried it ("tried" was not specified in terms of frequency of use, but it seems clear that this was a result of having smoked a heated tobacco product more than once*)*, including 1% of non-smokers, 0.8% of ex-smokers and 3.1% of current smokers. For the Italian population as a whole, this means that by the time of publication in 2017, 739,000 people had already tried IQOS, including 329,000 non-smokers (Liu et al., 2019). Moreover, 1,205,000 additional Italians, including 619,000 non-smokers (never having smoked or ex-smokers), reported that they intend to try the IQOS in the future (Liu et al., 2019). The author is concerned about the favourable tax regime for these products and the circumvention of existing tobacco control measures (health warnings on packages, smoking bans in public places and product advertising). The author attributes these favourable measures to the "*alleged belief in HNB harm reduction'.* Almost half (45%) of current users and 51% of those interested in IQOS had never smoked. Liu describes the IQOS as "*gateway to nicotine addiction among never smokers rather than a harm reduction substitution for current smokers"* (2019). The author's reasoning might raise questions. Firstly, on account of doubts as to the validity of the gateway theory (Etter, 2017). Secondly, due in particular to the PMTA[34], on the basis of which the FDA gave the green light for the sale of IQOS in the United States in 2019, which states that "*authorizing these products for the US market is appropriate for the protection of the public health because……the products produce fewer or lower levels of some toxins than combustible cigarettes".* At the same time, however, the FDA warns that "*it does not mean these products are safe or ''FDA approved"'*[35] In light of this, Liu's (2019) concerns are understandable.

Also in the United States, there is increasing awareness and use of heated tobacco products among adults (Nyman et al. 2018). Between 2016 and 2017, awareness of heated tobacco products increased from 9.3% to 12.4%. The group of participants who had previously used heated tobacco products was subdivided into "never", "ex" and "current use". "Current use" was described as "daily", "some days", "rarely". "Current use" increased from 0.5% in 2016 to 1.1% in 2017. A further breakdown according to frequency of current use was not made. Heated tobacco products were used by 3.1% of current smokers (AOR[36] for sex, age, education, race and income - expresses risk of use relative to a non-smoker: 1.57; CI[37]: 0.81-3.04), by 0.5% of former smokers (AOR of use for a non-smoker: 1.25; CI: 0.51-3.04) and by 0.3% of non-smokers. The AOR values do not confirm a higher risk of use by smokers and ex-smokers compared to non-smokers.

[34] PMTA: Premarket Tobacco Product Application

[35] https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway

[36] AOR: Adjusted Odds Ratio

[37] CI: confidence interval

Use was (statistically significantly) higher among ex-smokers, smokers who had failed a cessation attempt in the past (statistically insignificant compared to smokers who had never tried to quit), and smokers who intended to make a cessation attempt in the next six months (statistically significant compared to no intention to quit). Heated tobacco products are clearly seen as an aid in a future attempt to quit smoking.

Use was also higher among younger age groups (1.5% among 18-29 year olds; 1.2% among 30-44 year olds; 0.3% among those 45 years of age and older). However, the higher AOR values for young people compared to those over 45 years of age were not statistically significant.

An age gradient was also observed in 2017 in an online survey (n = 4,107) conducted by Marynak in the United States (Marynak et al., 2018) and Brose in the United Kingdom (Brose et al., 2018): 1.6% use by those < 30 years of age compared to 0.5% use by those > 30 years of age. The product was used by 0.5% of non-smokers. In an online survey (n = 12,696) conducted in the UK, both awareness and use were found to be age-related: both awareness and use decrease with age (Brose et al., 2018).

Kang & Cho (2019) observed in South Korea that 2.8% of surveyed adolescents (n = 59,532; 12-18 years) had ever used heated tobacco products, including 75.5% of current tobacco smokers, 45.6% of electronic cigarette smokers, and 40.3% of dual users (tobacco + electronic cigarette). The use of heated tobacco products was not found to be associated with an increase in the number of cessation attempts. The author calls for a ban on all advertising for heated tobacco products which claim harm reduction.

An online survey was also conducted in Korea, three months after the introduction of the IQOS, with a limited sample of n = 228 young adults aged 19-24 years (Kim, 2018). 38.1% (n = 87) were aware of the IQOS, 5.7% (n = 13) had previously used the IQOS, and 3.5% (n = 8) were using the IQOS at the time of the survey. Conventional cigarette smokers were more aware of the IQOS and were more likely to use the IQOS than were non-smokers.

A telephone survey conducted in 2017 in Hong Kong (where heated tobacco products have not been officially marketed but can be purchased freely in shops or online) with 5,131 participants revealed that n = 115 people had ever used heated tobacco products, including 108 current smokers, 6 ex-smokers and 1 non-smoker. Of the respondents who had never used heated tobacco products, n = 72 intended to use them: 3 non-smokers, 6 ex-smokers, and 63 current smokers (Wu et al., 2019). The highest rates of use were observed in the 30-39 age group (2.3%), compared to 0.9% in the 15-29 age group. Among those who had never used heated tobacco products, 15% of 30-39 year olds intended to use them, compared to 6.6% of 15-29 year olds.

In particular, Farsalinos (2019) surveyed the smoking status of n = 174 customers of two stores selling IQOS in Athens, who purchased products in the stores. Most (97.1%) were current or ex-smokers, 5 participants were non-smokers.

Correlation between the use of heated tobacco products and the sale of conventional cigarettes and smoking prevalence

Japan Tobacco International, one of the three manufacturers of heated tobacco products in Japan, publishes domestic sales figures for its conventional cigarettes (expressed in trillions)[38] (see Table 7). These figures, compared to the situation at the time of the introduction of heated tobacco products, can give an indication of the influence of heated tobacco products on the use of conventional cigarettes.

Table 7: Sales of conventional cigarettes in Japan (sold by *Japan Tobacco International*)

Period	Sales volumes of conventional cigarettes (in trillions)	Increase or decrease (%) over the same period in the previous year
April – November 2010	97.1	-6.1%
April – November 2011	70.1	-27.8%
April – November 2012	79.1	+12.8%
April – November 2013*	79.3	+0.3%
January – December 2014**	112.4	-3.6%
January – December 2015***	109.2	-2.8%
January – December 2016****	96.6	-2.7%
January – November 2017	84.0	-12.1%
January – November 2018	75.2	-11.4%
January – July 2019	44.0	-7.2%

*December 2013: launch of PloomTech; ** November 2014: launch of IQOS; *** September 2015: launch of IQOS; **** April 2016: launch of IQOS; **** November 2016: launch of GLO

Table 7 shows the sales volumes of conventional cigarettes (expressed in trillions) during the indicated period, as well as the change, in percentage terms, from the same period in the previous year.

Since the launch of heated tobacco products in 2013, there has been an annual decline in domestic sales of conventional cigarettes in Japan, with a significant decline in 2017 and 2018. However, there were also unusual movements in sales figures, both up and down, in the years before the launch of heated tobacco products: a sharp increase in 2012 (+12.8%), a decrease in 2010 (-6.1%) and a very large decrease in 2011 (-27.8%). Other determinants (price, taxation...?) probably also influenced these figures for sales of conventional cigarettes in Japan.

By way of comparison, the sales figures for conventional tobacco products in Belgium are shown. These data are kept updated by the FPS[39] Finance. Sales figures are presented from 1998 onwards. The official at the FPS Finance reports that the method of recording was slightly modified as from 2011. Until 2010, it is the number of cigarettes for which 'vignettes' were issued. From 2011, it is the number of cigarettes released for consumption in Belgium via an excise declaration. However, the two methods provide largely comparable quantities.

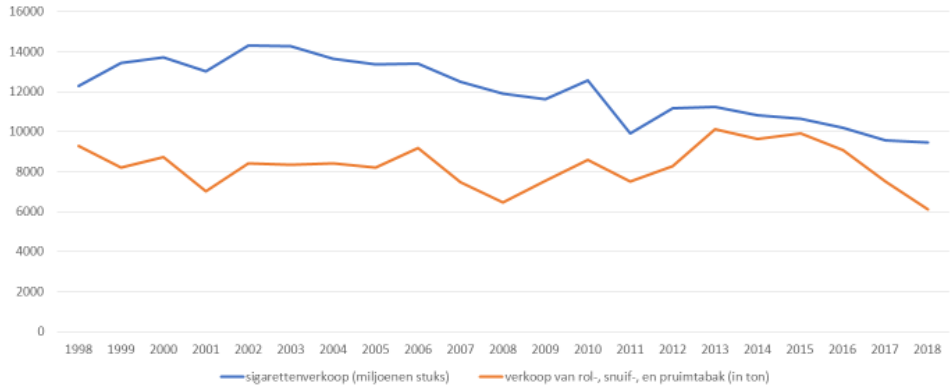
[38] https://www.jt.com/media/news/index.html

[39] FPS: Federal Public Service

Table 8: Sales figures for conventional tobacco products in Belgium - Source: FPS Finance

Year	Cigarettes (in millions of units)	Sale of cigars (in millions of units)	Sale of hand-rolling, snuff and chewing tobacco (in tonnes)
1998	12,294.8	561.6	9,286.5
1999	13,448.5	602.9	8,216.8
2000	13,732.1	596.5	8,716.2
2001	13,029.6	542.5	7,016.9
2002	14,314.4	628.6	8,417.0
2003	14,287.3	527.8	8,326.7
2004	13,634.5	552.9	8,429.0
2005	13,384.6	542.1	8,197.8
2006	13,385.1	543.8	9,168.3
2007	12,492.6	512.7	7,477.7
2008	11,916.3	487.6	6,647.5
2009	11,616.8	414.0	7,548.2
2010	12,557.6	400.1	8,579.2
2011	9,906.9	312.6	7,499.0
2012	11,177.0	373.2	8,261.9
2013	11,222.1	346.3	10,110.6
2014	10,820.9	342.1	9,635.0
2015	10,647.1	312.1	9,925.7
2016	10,176.5	283.3	9,061.3
2017	9,554.1	272.4	7,507.1
2018	9,443.8	257.5	6,098.4

Figure 1: Change in sales (in millions of units) of cigarettes (blue line) and hand-rolling, snuff and chewing tobacco (orange line) (in tonnes), between 1998 and 2018, in Belgium



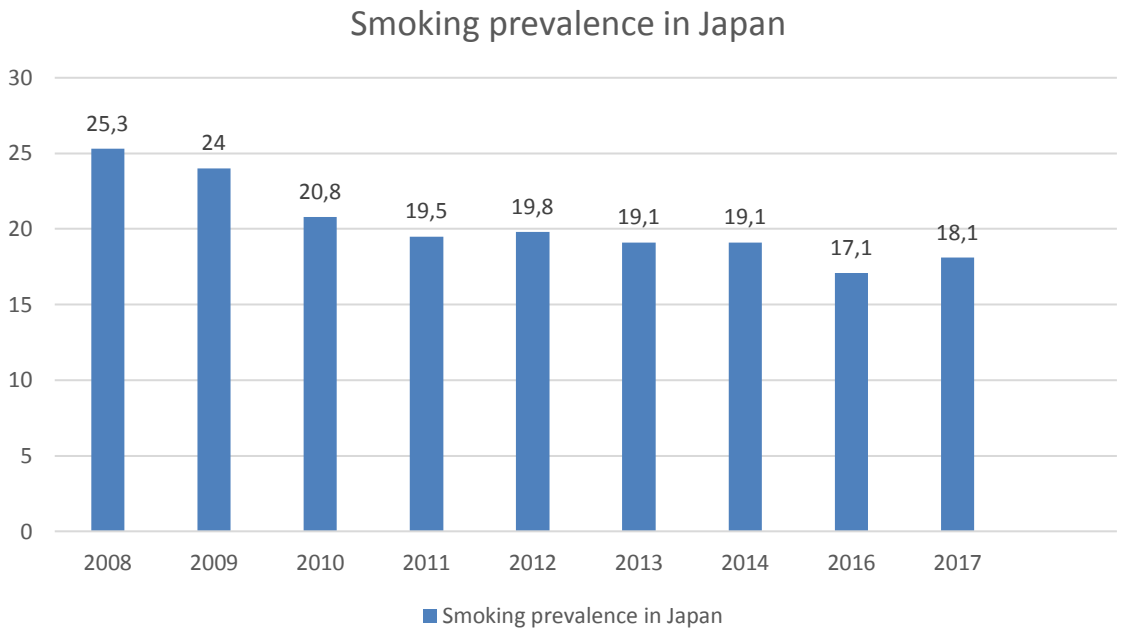
Also in Belgium, there has been a decline in sales of conventional cigarettes from 2002 to the present. This decrease appears to be somewhat offset by a temporary increase in sales of hand-rolling, snuff and chewing tobacco between 2011 and 2015, followed by a decrease from 2016 to 2018 (inclusive). Cigar sales show an almost uniform decline.

Stoklosa (2019) assessed cigarette sales in Japan after the launch of IQOS and found that cigarette sales declined in the months following the introduction of IQOS. This decrease occurred later in the prefectures where IQOS was introduced later on. The author concluded that this decrease could only be explained by the introduction of IQOS and not by other factors such as a national campaign, legislation, price or chance.

According to Euromonitor International[40], the overall decline in cigarette sales in Japan, which was 1.8% per year before the introduction of heated tobacco products, has been 9.5% per year since the introduction.
It is questionable whether this decrease in cigarette sales is also reflected in changes in smoking prevalence.

The global prevalence of smoking (number of conventional cigarette smokers) declined between 2000 and 2015, except in a few countries[41].
In Japan, smoking prevalence also decreased between 2008 and 2017. [42]

Figure 2: Smoking prevalence in Japan



The study involved n = 20,000 participants (> 18 years of age) in 2008 and n = 30,000 in 2017 and showed a steady decrease in smoking prevalence from 2008 to 2010, a stabilisation between 2011 and 2014, a decrease in 2016 and an increase in 2017. During the study period, smoking prevalence went from 25.3% in 2008 to 18.1% in 2017. If we break the figures down into periods before and after the introduction of heated tobacco products, the following data are observed:

- from 25.3% in 2008 to 19.1% in 2013 (-6.2%),
- from 19.1% in 2014 to 18.1% in 2017 (-1%).

Smoking prevalence had already decreased before the introduction of the IQOS and has remained relatively stable since then. In conclusion, it seems unlikely that the IQOS contributed significantly to the decline in conventional cigarette consumption. Moreover, we have no insight into the sales and possible countervailing effect of other tobacco or nicotine products in Japan.

[40] https://www.pmi.com/smoke-free-life/substantially-declining-cigarette-sales-in-Japan
[41] World Bank, http://blogs.worldbank.org/opendata/global-state-smoking-5-charts
WHO https://www.who.int/gho/tobacco/use/en/
[42] https://www.kantarhealth.com/docs/publications-citations/sternbach-annunziata-et-al-smoking-trends-in-japan-from-2008-2017.pdf?sfvrsn=0 & sfvrsn=0)

6.2 Behavioural characteristics when using the product

In the MRTPA[43], submitted to the FDA, *Philip Morris International* describes the results of a number of studies conducted by the company itself (PBA[44]) on the behavioural characteristics of IQOS use. These studies are part of the approval requirement of the FDA that heated tobacco products "*as it is actually used by consumers will benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products*".

Philip Morris International mentions the main observations regarding the impact of heated tobacco products:

a. among current users of conventional tobacco products:
   - Adult smokers, with no intention of quitting, show interest in using heated tobacco products (between 20.2% and 38.9%).
   - The instructions for use by *Philip Morris International* are precise enough to allow the correct use of heated tobacco products with minimal risk of misuse.
   - When smokers wishing to quit are confronted with messages about heated tobacco products, this (only) slightly reduces their desire to quit (between 1.1% and 11.8%).
   - User satisfaction with these products is comparable to user satisfaction with conventional cigarettes. This plays an important role in the potential switch from conventional cigarettes to heated tobacco products.
   - The potential for abuse when using heated tobacco products is no greater than when using conventional cigarettes. This abuse liability is described in the MRTPA as "*the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product (USDHHS 2012). Thus, the FDA Center for Tobacco Products' (CTP) use of the term abuse liability is similar to assessing nicotine dependence using DSM-IV/DSM-V[45] diagnostic (medica) criteria and defines it as dependence liability: nicotine use is characterized, both, as for a substance use disorder (dependence/abuse), and for a substance-induced disorder (withdrawal symptoms)*[46]'.
     In concrete terms, this means that *Philip Morris International* puts forward arguments showing that the risk of addiction to heated tobacco products does not exceed that of conventional tobacco products (conventional cigarettes). According to *Philip Morris International*, heated tobacco products are not attractive to non-users of conventional tobacco products.
   - *Philip Morris International* also indicates that the risk of incorrectly using heated tobacco products is low.
     "Incorrectly using" covers two possibilities here:
     1. lighting the stick like a conventional cigarette, without the device, found in 47/985 or 4.8% of study participants, and
     2. using heated tobacco products with conventional cigarettes or tobacco other than the intended sticks, observed in 2/985 participants.

[43] MRTPA: Modified Risk Tobacco Product Application
[44] PBA: Perception and Behavior Assessment
[45] DSM: Diagnostic and Statistical Manual of Mental Disorders
[46] The source is 'Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications. 24 May 2017 https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications#6

- Smokers who use heated tobacco products in combination with other products containing tobacco and nicotine do not increase their total tobacco consumption.
- Smokers who switch completely to heated tobacco products are unlikely to subsequently return to smoking conventional cigarettes.
- Dual use was limited in studies conducted in Japan (almost 85% used only IQOS), but was higher in studies conducted in the United States (between 55% and 63.8% used only IQOS). The differences were likely due to the characteristics of the study (including the nature of the instructions given).
- The craving curve shows a similar pattern among smokers of heated tobacco products and conventional cigarettes: a sharp increase just before smoking a cigarette/using a heated tobacco product, followed by a sharp decrease just after use, and then a gradual return to the initial level.
- Studies show no difference between IQOS and conventional cigarettes in MNWS-Revised scores (the *Minnesota Nicotine Withdrawal Scale* measures the presence of withdrawal symptoms).
- After 90 days, no difference is observed between IQOS users and conventional cigarette users in terms of level of dependence (measured using the FTND[47]) and intention to quit smoking (measured using the *Prochaska Stages of Change' Questionnaire*). An earlier study into the Eclipse (one of the predecessors of the current heated tobacco products) found users' perception of harm reduction, but also a lower intention to quit smoking (Shiffman et al., 2004; Shiffman et al., 2007).
- The EQSM[48] gives a lower score for the IQOS just after use, compared to conventional cigarettes, for four parameters: reduced craving, feeling of pleasure in the airways, psychological reward and smoking satisfaction. The differences between the two products had disappeared after 90 days, suggesting a period of adaptation to the new product.

b. *Philip Morris International* reports the key findings on the impact of heated tobacco products in adults who do not use tobacco products (non-smokers or ex-smokers):
   - Non-smokers show no interest in heated tobacco products after hearing information about the product, the harm reduction claim, the explanations regarding the potential risk and the fact that heated tobacco products contain tobacco.
   - The intention of non-smokers and ex-smokers to use or try these products was very minimal.
   - Neither the explanations for the use of the products nor the claim of reduced risk or reduced exposure influenced the intention to use or try the product.

c. *Philip Morris International* also points out that the ambient air is not negatively influenced and stresses the reduced fire risk.

d. *Philip Morris International* also reports the results of the study regarding consumers' correct understanding of products and risk perception:

[47] FTND: *Fagerstrom Test for Nicotine Dependence*
[48] MCEQ: *Modified Cigarette Evaluation Questionnaire*

- The marketing material developed by *Philip Morris International* for its heated tobacco product allows consumers to understand all the information about reduced risk and reduced exposure.
- The public attributes a medium risk to heated tobacco products: lower risk than conventional cigarettes, but not an absence of risk. It perceives the health and dependence risks of heated tobacco products to be lower than those of conventional cigarettes, but higher than those of NRT (*Nicotine Replacement Therapy*) or complete smoking cessation.
- Additional information is needed to inform consumers that reduced exposure following a complete switch to heated tobacco products does not systematically imply a reduction in the risk of tobacco-related diseases.

The fact that the results of these scientific studies were produced by the industry itself (*Philip Morris International*), that no peer review was conducted and that any conflict of interest could not be ruled out is highlighted.
These findings would be more credible if the same conclusions could be reproduced by neutral study sources. This is not (yet) the case at present, except at a very early stage.
Public Health England reports on the capacity of heated tobacco products to reduce urgency (McNeill et al., 2018). Craving reduction and cessation are also reported by Adriaens after using a heated tobacco product (Adriaens et al., 2018). Nevertheless, a conventional cigarette would have a more satisfying effect than heated tobacco products (McNeill et al., 2018).
Based on the TTFC[49], Queloz & Etter (2019) found a comparable dependent potential of heated tobacco products and conventional cigarettes.

According to a laboratory study in Japan, satisfaction with heated tobacco products declines more rapidly than with conventional cigarettes. In the long term, this difference disappears. In Poland, a similar evaluation of satisfaction showed a larger and significant difference between heated tobacco products and conventional cigarettes, which, according to the WHO, means that the observations cannot be generalised, but may differ by region (WHO, 2019).

6.3 Perception of the product (especially among adolescents and young adults)

In 2018, heated tobacco products were launched around the world, in particular with the industry's argument of reduced harm due to lower exposure to toxic compounds (compared to traditional tobacco smoke), as long as the smoker made the complete switch from conventional cigarettes to heated tobacco products. However, this last point is questioned by McKelvey (2018), who concludes that *Philip Morris International* does not sufficiently demonstrate that potential users of heated tobacco products have undeniably understood the absolute necessity of switching completely in order to obtain the claimed health benefits. "*Rather, they are likely to misunderstand the unsupported claims of reduced risks to mean IQOS are harm-free"*.

The (hypothetical) assumption of completely switching from conventional cigarettes to heated tobacco products has so far been contradicted in a (limited) study (n = 228 young adults aged 19-24) conducted by Kim (Kim et al., 2018) in Korea three months after the introduction of IQOS. Kim observed that none of the IQOS users used the IQOS exclusively, but

[49] TTFC: *time to first cigarette*

simultaneously consumed conventional cigarettes and/or used electronic cigarettes (dual or triple use). One participant who had previously used IQOS was a non-smoker of conventional cigarettes "*Current IQOS users were more likely to smoke conventional cigarettes and/or e-cigarettes, which contradicts the tobacco industry's claims that conventional cigarette smokers will switch to heated tobacco products".* The arguments in favour of using the IQOS were the belief of reduced harm and use as a means of smoking cessation. One of the reasons they used the product was because they were convinced that it was less harmful and that it would be a way to stop smoking (conventional cigarettes).

An evaluation of the arguments given by *Philip Morris International* in the MRTP documents[50] prompted McKelvey to conclude "*that the introduction of IQOS will result in adolescent and young adult non-users initiating tobacco use with IQOS and could also increase poly-use of IQOS along with other tobacco products"* (McKelvey et al., 2018). According to McKelvey, the way the IQOS is presented to consumers is such that it is primarily young people who are attracted, in particular on account of the attractive packaging and shops, and the striking similarities with the packaging and sales environments of popular digital products such as Apple's iPhone. According to the author, *Philip Morris International* also does not present data on the impact on young people (<18 years) in its MRTP application, in particular with respect to their smoking preferences (limited prediction of "intentions" of use among adolescents, rather than "willingness"), preference for flavourings added in electronic cigarettes, etc., despite the existence of extensive literature on the subject. It also notes that the claimed health benefits can only be achieved after switching completely to IQOS, which however contradicts the observation that few people switch completely, but switch to dual use at most. Finally, *Philip Morris International* fails, in the author's opinion, to demonstrate that adolescents have fully understood the health claims, health risks, smoking cessation potential, etc.

A qualitative consumer survey, including expert interviews, product and marketing analyses, and focus groups with adults in Switzerland and Japan, indicates that IQOS has been commercialised "*as a sophisticated, high tech and aspirational product*. *Because youth and young adults are more interested in such product positioning, this approach raises some concern about youth appeal*". The study also highlights cultural factors that may explain a difference in prevalence and use between different countries (Hair et al., 2018).

In addition, a recent 8-week observational study among conventional cigarette smokers who were willing to use heated tobacco products showed higher "uptake" (defined as 70% use of heated tobacco products in combination with tobacco products in week 6 of the study) among age groups older than the younger age category: 18-24 years old: 10.8%; 25-44 years old: 16.3%; > 44 years old: 15.3% An obvious conclusion from this study might indicate that young people who are willing to use heated tobacco products take up the product to a lesser extent than those over 25 years of age. It should be noted, however, that the study was conducted by the industry and that four reviewers, three of whom were also active in the tobacco industry, added comments. It is probably no coincidence that the only "independent" reviewer (with limited ties to the electronic cigarette industry) made the most critical comments about the methodology used. This study should therefore be treated with the necessary caution.

[50] MRTP: *Modified-Risk Tobacco Product*

The *International Tobacco Control Youth Tobacco and E-cigarette Survey* (Czoli et al., 2019) is an online study of 12,064 young people aged 16-19 years old in Canada, England and the United States, that assessed three aspects:

- awareness of the existence of the IQOS (measured using the question "*Have you heard of a product called IQOS, which heats a stick of tobacco instead of burning it"* with response options "*yes/no*"),
- interest in trying the IQOS (measured using the question "*Would you be interested in trying this product?'"* with response options "*definitely not/ probably not/ probably yes/definitely yes")*
- and willingness to try it (measured using the question "*'If one of your best friends were to offer you this product, would you try it?"* with response options *"definitely not/ probably not/ probably yes/definitely yes"*).

7% were aware of the existence of the product; 38.6% were interested in trying it; 25.1% were willing to try it. All parameters were observed more frequently in current and/or former smokers than in non-smokers. It is striking, however, that young non-smokers not only knew about the product, but also showed an interest in it and were willing to use it.

The predecessors (Accord, Eclipse) of the current generation of heated tobacco products were evaluated negatively by consumers on account of their taste and sensory characteristics, compared to their usual brand of cigarettes. According to consumers, they also contain too little nicotine to satisfy their craving. In any case, they would not recommend these products to other smokers (WHO, 2019).

The influence of current heated tobacco products on the intention and ability to quit smoking conventional cigarettes has not been directly studied much. The available data on this subject are mentioned in several points in the current text. The possible influence of the predecessors of the current means (Eclipse) on the intention to stop smoking has already been examined by Shiffman (cf. above).

However, health considerations (harm reduction and method of smoking cessation) are arguments in favour of IQOS use, according to a UK study of 30 adults (18-56 years) that assessed factors influencing IQOS use (Hitchman et al., 2019). Other arguments for hindering or stimulating the use of IQOS included cost (rather a hindrance) and the possibility of using IQOS in public places (allowed in the UK). Other factors in favour of the IQOS were the nicotine shoot, which was described as comparable to a cigarette, as well as the attractive look of the stores, the device and the packaging. In this study, IQOS was described as a status symbol.

6.4 Conclusions

- Following the introduction of heated tobacco products in different countries, awareness of their existence, willingness to use them and actual use has steadily increased. Most studies show an age gradient, with a tendency for higher use among the young adult and youth category compared to the older category. Some studies did not find this association or did not find statistical significance.
- The use and intention to use heated tobacco products is influenced by exposure to advertising for the product.

- In Japan, a drop in cigarette sales of more than 30% was observed following the launch of IQOS. Other influencing factors apart from the launch of IQOS were negligible. However, in 2011, sales were also down nearly 30% compared to the same period in 2010. It was not possible to assess whether or not this fall was offset by the sale of other products containing tobacco and/or nicotine. Smoking prevalence, which has been declining for several years both globally and in Japan, has not changed dramatically since the introduction of heated tobacco products. The introduction of IQOS in Japan has clearly led to a decline in sales of conventional tobacco products, but not to an accelerated decrease in smoking prevalence. In Belgium, too, there was an almost uniform downward trend in sales of conventional cigarettes and cigars between 1998 and 2018. With the exception of a temporary increase between 2011 and 2016, sales of hand-rolling tobacco, chewing tobacco and snuff are also declining in Belgium.
- Heated tobacco products are the most commonly used products in the group of current and ex-smokers, both single and dual-use. However, a limited and significant number of non-smokers also use the products and this is in contradiction with the findings of *Philip Morris International*.
- Caution is advisable with regard to the strategies used by producers when placing heated tobacco products on the market. The attractive and *trendy* look of the stores, device, packaging, etc., comparable to that of digital cameras, encourages use. Young people in particular are attracted to these features. Cost is more of a hindrance.
- Heated tobacco products remain both harmful (although probably less harmful than the conventional cigarette, but more harmful than smoking abstinence) and addictive; in addition, there is a risk that smokers may switch to heated tobacco products instead of quitting (*Pisinger & ERS Tobacco Control Committee*). In this case, several scenarios can be envisaged: either fewer smokers make a smoking cessation attempt, which increases long-term mortality and morbidity; or more smokers switch to a less harmful product, which may (perhaps) generate longitudinal health gains. However, this is only possible in the case of a complete switch to heated tobacco products only. The high prevalence of dual use, with a rather limited to complete absence of health benefit, however, reduces the likelihood of the second scenario occurring. In any case, the high level of dual use raises doubts as to whether the alleged health benefits of heated tobacco products can be achieved. In addition, dual use has been observed in a higher percentage of users in epidemiological studies than in the experimental studies conducted by *Philip Morris International* in the context of the PMTA[51] application. A study conducted in South Korea also provides arguments in favour of the first scenario.
- The addictive potential of heated tobacco products is considered to be comparable to that of conventional cigarettes.
- The high incidence of dual use indicates complementary use of heated tobacco products rather than a substitution of conventional tobacco products. It is suggested here that smokers use heated tobacco products as a supplement to, rather than a substitute for, conventional cigarettes.
- At present, it is not possible to comment on the usefulness of the product as a way of limiting harm or as a means of smoking cessation, although users and the tobacco industry make such claims in order to use the product and place it on the market. Rather, several

[51] PMTA: Premarket Tobacco Product Application

studies indicate a negative association between heated tobacco products and smoking cessation/intention to quit.

- The low/negligible risk of use by non-smokers and ex-smokers claimed by industry is contradicted in the epidemiological and observational studies currently available. The comparable sense of satisfaction between heated tobacco products and conventional cigarettes, as claimed by *Philip Morris International* in its MRTPA[52], has not been confirmed either in a neutral study (Adriaens, among others).
- A neutral study of the various behavioural issues and epidemiological data from neutral research organisations are urgently needed to deepen and broaden knowledge on these important questions, in order to make informed judgements. Indeed, various key points (uptake of heated tobacco products by non-smokers or ex-smokers, high prevalence of dual use, use of heated tobacco products as a means of smoking cessation, long-term health risks, etc.) diverge in their conclusions depending on whether they are issued by independent research groups or by sources close to the tobacco industry. Moreover, the WHO[53], in its "*Report on the global tobacco epidemic, 2019*", also calls for a critical approach on the part of the Authorities towards claims made by the tobacco industry in favour of heated tobacco products, as well as towards the aggressive marketing associated with them (Annex 1: WHO position on the potential role of electronic cigarettes and heated tobacco products in smoking cessation).

[52] MRTPA: Modified Risk Tobacco Product Application
[53] https://apps.who.int/iris/bitstream/handle/10665/326043/9789241516204-eng.pdf?ua=1

7 Recommendations of the SHC[54]

In this chapter, the SHC develops recommendations on authorisation, communication and the regulatory framework for **tobacco products**. The SHC wishes to distinguish between tobacco products and Electronic Nicotine Delivery Systems (ENDS or electronic cigarettes). These will be the subject of a separate opinion (SHC 9549) in the near future in the context of the revision of Opinion 9265 of the SHC.

The SHC believes that a coherent tobacco control policy should be developed and implemented which involves a reduction in the consumption of tobacco products and the associated risks by all available means, due to the considerable negative effects on public health.
New heated tobacco products are to be considered as tobacco products and the rules to be applied must be identical to those for tobacco products.

1. In order to further reduce smoking prevalence, the SHC calls for additional smoking prevention measures, namely:

    - An ambitious tobacco control plan with a clearly articulated target, such as a "*tobacco end game*" (i.e., less than 5% smokers) by 2040, and supported by an inter-ministerial conference to bring all political levels together to work towards this goal.
    - A drastic increase in excise duty on tobacco products in order to strongly discourage consumption.
    - A limitation on the number of sales outlets and a ban on online sales.
    - Following the recently approved total ban on advertising in sales outlets, a ban on the visible presentation and display of tobacco products is also needed to prevent young people from taking up smoking and to help smokers quit.
    - Specific tailored measures to reduce smoking among groups with a low level of education are one of the main ways of reducing health inequalities between socio-economic groups in society (the health gap).
    - Investing in major campaigns for smoking cessation, such as "Stoptober" in the UK and the Netherlands and "*Le mois sans Tabac*" in France.
    - Discourage the positive image of smoking in series, films and on social networks.

2. The use of heated tobacco products could contribute to reducing health risks to the extent that the absence of combustion is accompanied by an overall reduction in harmful and potentially harmful constituents in inhaled aerosols compared to those emitted by conventional cigarettes and other combustion-based tobacco products. However, there are various unknowns regarding the potential for reducing the harmful effects among consumers of heated tobacco products and about the effectiveness of such devices in a smoking cessation strategy.

[54] One of the experts of the working group wishes to distance himself from the chapter "Recommendations of the SHC". His position is detailed in Annex 2 to the present opinion.

2.1. Potential to reduce harmful effects

- Although heated tobacco products do not burn the tobacco, they do release nicotine and harmful and potentially harmful constituents. The emissions and exposure levels of these products are lower, but not necessarily negligible, compared to conventional cigarettes. Moreover, other compounds - either not present or in small amounts, including possible carcinogens - have been detected in these new heated tobacco products.
- Although positive biological changes in a few biomarkers have been observed in clinical studies, suggesting a potential reduction in risk, it is not yet known to what extent heated tobacco products are less risky than conventional cigarettes or whether they will contribute to a reduction in tobacco-related diseases. Additional short- and long-term health studies, molecular-epidemiological research and, above all, more independent research, are needed.
- There is no evidence that heated tobacco products will be used exclusively as substitutes for conventional cigarettes. Rather, dual use (conventional cigarettes and heated tobacco products) appears to be the norm among smokers who make the switch (in Japan, sales of cigarettes have decreased significantly since the introduction of heated tobacco products, but smoking prevalence has not decreased; this is probably due to the dual use of conventional cigarettes among smokers who switched to heated tobacco products).
- Heated tobacco products do not appear able to play any role in smoking cessation and Public Health England does not attribute any role to these products in this regard. They are actually nicotine replacement products.

2.2. Smoking cessation strategy

Tobacco products are marketed as consumer products and not as medical devices. A notification procedure and rules on the safety, quality and quantity of nicotine exist, as well as rules on packaging and labelling. In Belgium, alternative tobacco products are considered to be the same as conventional tobacco products. In other words, they are subject to a ban on use in enclosed public places, a ban on advertising and a ban on terms such as "helps to quit smoking" in marketing material. However, the European Union has allowed the possibility of marketing new tobacco products through the "*medicinal licence*". Products recognised as medicines would then be sold in pharmacies. However, to date, none of these new tobacco products are available as licensed smoking cessation products (including in the UK or France, for example).

In Belgium, following an opinion of the SHC, Minister De Block decided to authorise the marketing of new tobacco products, but to regulate them relatively strictly (cf. 15 February 2016)[55]. As such, no products can be sold online and manufacturers cannot make claims about harm reduction or smoking cessation results.

3. In addition, there are recognised pharmacological aids for smoking cessation (e.g. controlled nicotine delivery devices / nicotine substitutes) for which the effectiveness has been demonstrated and which are marketed as such, i.e. as medical devices and

[55] Royal Decree on the manufacture and placing on the market of electronic cigarettes

not as consumer products. Heated tobacco products cannot be used in a smoking cessation process. They are substitutes for conventional tobacco products.

4. For these reasons, while being aware that heated tobacco products have a more favourable appearance than conventional tobacco products, the SHC is of the opinion that consumption should not be encouraged by measures which would make them more attractive than conventional tobacco products, such as more favourable taxation, better accessibility of the products for potential consumers, tolerance in advertising, etc.

Finally, the SHC draws attention to the responsibility of the federated entities and the competent authorities to ensure transparent and impartial communication on the absolute and relative risks associated with the use of new heated tobacco products.

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V COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group ***in a private capacity***. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Luc PUSSEMIER**; the scientific secretary was Muriel Baltes.

BAEYENS Frank	Psychology	KULeuven
BARTSCH Pierre	Pneumology	ULG
BODO Martial	Psychology, tobaccology	Bordet
BOUDREZ Hedwig	Psychology, tobaccology	UZ Gent
DECONINCK Eric	Chemistry, additives, contaminant	Sciensano
DEMAEGDT Heidi	Toxicologie in vitro, contaminant, micro-nutrient	Sciensano
GABRIELS Suzanne	Psychology, tobaccology and smoking prevention	Fondation contre le cancer
HENDRICKX Stefaan	Smoking prevention, tobaccology, health promotion, health inequalities	Vlaams Instituut Gezond Leven
NACKAERTS Kristiaan	Pneumology	KULeuven
PUSSEMIER Luc	Chemistry, additives, contaminant	Ex- CERVA
VAN LAREBEKE-ARSCHODT Nicolas	Toxicology, carcinogenesis and primary prevention of cancer	ex-UGent

The following administrations and/or ministerial cabinets were heard:

CAPOUET Mathieu	Tobacco policy	FPS APF- Tobacco unit
REMUE Eline	Electronic cigarette, tobacco product notification	FPS APF - Tobacco unit

This advisory report was translated by an external translation agency.

VII APPENDIXES

Appendix 1*: WHO position on the potential role of electronic cigarettes and heated tobacco products in smoking cessation

In July 2019, the WHO released its "*Report on the Global Tobacco Epidemic, 2019*"[56], which warns of the possible negative effects of ENDS[57] (primarily electronic cigarettes), *Heated Tobacco Products* such as IQOS) and a *Tobacco Harm Reduction* approach. The WHO calls for clear regulations for these new tobacco products and ENDS. However, the report makes a clear distinction between heated tobacco products on the one hand, and ENDS on the other. The WHO envisages the possibility of positive effects of electronic cigarettes (ENDS) in the context of smoking cessation - more specifically the "*limited evidence that may support some forms of ENDS as a cessation aid under certain conditions*", but calls for more studies on the subject. The WHO states here that the basis for recommending ENDS as a means of smoking cessation at the population level is currently insufficient.

A separate chapter provides an overview of the tobacco industry's strategies with respect to these new products that interfere with smoking cessation (policy). In summary, according to the authors of this report, these tobacco industry strategies amount to the following:

- Much of the available literature on the *tobacco harm reduction* approach is funded by manufacturers, such as the tobacco industry, whose commercial interests are an inevitable source of conflict of interest.
- In the case of heated tobacco products: Switching from conventional cigarettes to heated tobacco products is not considered smoking cessation by the WHO, as both are tobacco products. In this context, there is a risk that the industry's marketing strategies focusing on "cessation" and "switching" could lead to confusion of the two concepts among consumers, regulators and policy makers. Given this confusion between different types of products, the "*limited evidence*" regarding ENDS as a means of smoking cessation could also be wrongly attributed to heated tobacco products, according to the WHO. In countries that have rather flexible ENDS regulations (due to the positive evaluation of the role of ENDS as a means of smoking cessation), the tobacco industry abuses this framework by presenting heated tobacco products as similar products, in order to negotiate similar regulations for them. All these elements create confusion between the two categories of products.
- The aggressive marketing designed for new tobacco products (remark by the SHC: prohibited by law in Belgium) can negatively influence the intention of smoking cessation on the part of smokers who want to quit. Smokers are encouraged to continue using tobacco or nicotine instead of quitting. This approach may also have implications for "evidence-based" smoking cessation methods, as smokers will opt for these new tobacco products rather than evidence-based methods.
- The recent positioning of the major tobacco manufacturers in favour of tobacco harm reduction is a means of influencing public opinion, the press and policy makers. Their image, which was becoming strongly negative (cf. the *Tobacco Free Portfolios* initiative, in which banks and insurance companies no longer negotiate with the

[56] https://apps.who.int/iris/bitstream/handle/10665/326043/9789241516204-eng.pdf?ua=1
[57] ENDS: Electronic Nicotine Delivery Systems

tobacco industry), is improving thanks to their advocacy for tobacco harm reduction, in particular as responsible partners in the fight against smoking.

- The tobacco industry is actively lobbying to have new tobacco products excluded from existing tobacco legislation.
- Through promotion and lobbying through its front groups such as the *Foundation for a Smoke Free World*, *Philip Morris International* aims to put pressure on governments so that IQOS is authorised on the domestic market and is, moreover, not subject to tobacco control regulations (e.g. ban on advertising, excise duties and bans on smoking in public places). This weakens tobacco control initiatives and undermines the implementation of the WHO FCTC[58].

Another WHO report was published a few months later, in November 2019[59]. This report summarises the discussions of a study group on "*tobacco product regulation*" at the end of 2017. It provides a scientific basis for tobacco product regulation. A separate chapter is devoted to heated tobacco products. This second report is more positive than the "*Report on the Global Tobacco Epidemic, 2019*" with regard to the electronic cigarette. For example, it states the following:
"Consider a nicotine reduction policy (nb: in conventional cigarette) coordinated with policies that allow adequate access to nicotine replacement therapies and other products, if and as approved by relevant authorities and with appropriate safeguards. This should be supported by population surveillance, monitoring and testing of products, enforcement of product standards, and a strong focus on protecting children and young people." (pg.258).
"Continuing research is required to monitor product development and use, promotional strategies and other activities of the tobacco and related industry to build intelligence to protect public health" (p. 259).

In the WHO[60] "*Report on the Global Tobacco Epidemic, 2019*" specific recommendations are made on page 54 with regard to policy on heated tobacco products.
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- *HTPs contain tobacco and should be regulated like tobacco products.*
- *HTPs produce toxic emissions, many of which are similar to toxicants found in cigarette smoke.*
- *HTP users are exposed to toxic emissions from the products, and bystanders could also be exposed to these toxic secondhand emissions.*
- *Although the levels of several toxicants in HTPs are lower than those found in conventional cigarettes, the levels of others are higher. A lower level of some toxicants does not necessarily mean a reduction in health risk.*
- *HTPs contain nicotine. Nicotine is highly addictive and linked to health harms, particularly in children, pregnant women and adolescents.*
- *The long-term health impacts of HTP use and exposure to their emissions remain unknown. There is currently insufficient independent evidence on the relative and absolute risk. Independent studies are needed to determine the health risk they pose to users and bystanders.*

[58] FCTC: *Framework Convention Tobacco Control*
[59] https://www.who.int/publications-detail/who-study-group-on-tobacco-product-regulation-report-on-the-scientific-basis-of-tobacco-product-regulation-seventh-report-of-a-who-study-group
[60] https://apps.who.int/iris/bitstream/handle/10665/326043/9789241516204-eng.pdf?ua=1

- *The new tobacco products are tobacco-based products. This means that the obligations under the WHO FCTC apply to heated tobacco products in the same way as they apply to conventional cigarettes.*

According to Article 5.3. of the WHO Framework Convention (FCTC[61]), there is a fundamental and irreconcilable conflict between the interests of the tobacco industry and the interests of public health policy.

In a letter addressed to the United Nations, in the context of the 2030 Sustainable Development Goals, ASH[62], the FCA[63], the CTFK[64] and STOP[65] declared that it is impossible to manufacture, market and sell tobacco products in a way that is compatible with public health or the agenda of the UN's *Sustainable Development Goals*[66].

61 *Framework Convention Tobacco Control*
62 *Action on Smoking and Health*
63 *Framework Convention Alliance*
64 *Campaign for Tobacco Free Kids*
65 *Stopping Tobacco Organizations and Products*
66 https://www.fctc.org/joint-letter-to-the-un-sg-re-the-role-of-the-tobacco-industry-in-the-2030-agenda-for-sustainable-development/

Appendix 2: Minority position of Frank Baeyens

Prof. Frank Baeyens distances himself from the group of experts, based on the results reported in Part IV, Chapters 1 to 6, from the recommendations made in Chapter 7, and advocates a tobacco harm reduction approach for a policy that encourages the use and complete switch to heated tobacco products among smokers who are unable or unwilling to quit any form of smoking and who are unwilling or unable to make the transition to electronic cigarettes or other low-risk nicotine products.

He calls for a legal framework specific to heated tobacco products that is proportional to the risks and takes into account the unintended harmful consequences of the measures, treating conventional cigarettes and heated tobacco products in the same way. In particular, he calls for a legal framework for heated tobacco products which does not apply:

- any excise duty in proportion or not to the risk,
- any obligation of neutral packaging,
- any ban on advertising or information at the sales outlet and no ban on product presentation, endorsement and demonstration,
- any general ban on use in enclosed public places,

and which allows distance selling to people over 18 years

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

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