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Summary and recommendations

A clear definition of heated tobacco products (HTPs) is not currently available. EHN therefore follows the WHO description, which defines HTP as ‘tobacco products that produce an emission containing nicotine and other chemicals, which is then inhaled by users.’

This report concludes that heated tobacco products are not healthy alternatives to conventional cigarettes. Studies show that they have a negative impact on the cardiovascular system. They increase heart rate and blood pressure and when looking at these two parameters, there is no difference between the impact of HTPs and conventional cigarettes. HTPs cause oxidative stress, negatively impact on endothelial function, and cause arterial stiffness. Here too, there is hardly any difference between the impact of HTPs and conventional cigarettes. Furthermore, when looking at platelets there is again no difference between the impact of HTPs and conventional cigarettes: they both have a negative effect on platelet function.

The use of HTPs also leads to particulate matter emissions, which have a devastating effect on CVD. Potential consequences of compensatory puffing (which is common in HTP users) include more consumption or more intense smoking to gain equal doses of nicotine, which can be associated with intake of higher levels of non-nicotine toxins, leading to increased tobacco-associated diseases such as cardiovascular disease.

Although their use is still limited in Europe, worrying trends like increased use in younger generations and uptake among non-smokers are noticed. Moreover, in Europe, awareness of addictiveness and toxicity of HTPs among users is low and needs to be improved.

HTPs cannot be considered as a nicotine replacement product or a quit aid. Quite the opposite, HTPs should be considered a gateway to smoking. Last but not least, heated tobacco products produce relevant amounts of side stream and second-hand emissions which contain harmful and potentially harmful substances, although the quantity of emission is lower than in conventional cigarettes.
EHN’s recommendations on Heated Tobacco Products are:

- A clear definition of HTPs is imperative.
- Users of HTPs suffer from similar, devastating effects on cardiovascular health as conventional cigarettes. They can therefore not be recommended as safe alternatives, nicotine replacement therapies or quit aids.
- HTPs produce second-hand smoke, both indoors and outdoors and can therefore not be considered safe for non-users.
- Considering the similarities in CVD outcome in users of HTPs and conventional cigarettes, both should be subject to the full effect of the Tobacco Products Directive. In countries where the TPD does not apply, HTPs should be subject to the same smoke free legislation.
- Considering the similarities in CVD outcome in users of HTPs and conventional cigarettes, taxes and excise duties on HTPs should be at the same level as for conventional cigarettes.

Aim of the paper

In 2019, the European Heart Network published its position paper on electronic cigarettes (e-cigarettes). Heated tobacco products (HTPs) were deliberately disregarded from that position paper, as the scientific evidence for HTP products was not clear yet. However, the body of evidence on HTP products is growing and the aim of this paper is to draw attention to the current evidence and provide our recommendations for regulation on heated tobacco products.

In view of the current revision of the Tobacco Taxation Directive (TTD), and the upcoming review of the Tobacco Products Directive (TPD), this report provides evidence on why HTPs should be included in the TPD, should not be exempt from smoke free legislation and should be taxed in the same way as conventional cigarettes.

Cardiovascular disease

Cardiovascular disease (CVD) – the main forms of which are coronary heart disease and stroke – is the main cause of death in Europe as well as in the European Union (EU), where it is responsible for 3.9 million and 1.8 million deaths respectively every year.\(^1\) CVD is also a major cause of disability and a significant economic burden across the EU, estimated to cost the EU economy almost 210 billion euros every year.\(^2\)

Leading risk factors for CVD are tobacco use, high blood pressure, high cholesterol, overweight and obesity, physical inactivity, diabetes, unhealthy diets, and harmful use of alcohol. It is estimated that smoking is responsible for over 16% of all cardiovascular deaths in the WHO European region (almost 700 000 deaths) and 12.8% in the European Union (almost 260 000 deaths).\(^3\)

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\(^3\) Data from the Global Burden of Disease database (2019) https://vizhub.healthdata.org/gbd-compare/
Introduction

Note of Caution

When assessing the literature in the field of heated tobacco products (HTPs), the influence of the tobacco industry must be considered. The majority of the HTP-papers published had authors affiliated or linked with tobacco industry.\(^4\)\(^5\) As the tobacco industry is confronted with declining sales volume of conventional cigarettes, it wants to promote HTPs as a healthier alternative to conventional cigarettes (CC).\(^6\)\(^7\) Clinical trials conducted by the tobacco industry focused on comparison of HTP with conventional cigarettes (CC), concluding that HTPs yield less harmful and potential harmful compounds, leading to improved biomarker profiles compared to CC.\(^8\)\(^9\)\(^10\)\(^11\) Although these conclusions are partly supported as well by independent trials, HTPs are associated with unfavorable outcomes when compared to non-smoking.

However, although methodology and statistics of tobacco industry funded studies are mostly correct, trial design and outcomes are intentionally set to have a positive outcome for the tobacco industry. Stakeholders should be aware of where funding comes from and the affiliations of authors when assessing evidence for HTPs. There is a great need for independent research addressing HTPs.\(^12\) Moreover, the comparison of HTPs with non-smoking should be the Gold Standard for judging tobacco products, as long as non-inferiority to non-smoking cannot be proven. Furthermore, outcome parameters should be represented by (hard) clinical endpoints (such as nonfatal stroke, nonfatal myocardial infarction, cardiovascular death, all-cause death) rather than surrogate parameters (such as biomarkers)\(^13\)\(^14\).

What are heated tobacco products?

In this paper the phrase ‘heated tobacco products’ (HTPs) is used. In many other studies, mainly industry funded publications, the term ‘heat-not-burn’ products is used. They refer to the same products as ‘heated tobacco products. We consistently use ‘heated tobacco products’ in this paper.

\(^7\) Bialous SA, Glantz SA. Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control. Tob Control 2018;27:s111–s117.
\(^12\) Patanavanich R, Glantz SA. How to combat efforts to overturn bans on electronic nicotine delivery systems: lessons from tobacco industry efforts during the 1980s to open closed cigarette markets in Thailand. BMJ Glob Health 2021;6:e004288.
In its document ‘Heated Tobacco Products – A brief’, WHO states that ‘smoking, the traditional way of extracting nicotine by burning tobacco, results in smoke containing thousands of compounds, many of which are harmful to health. HTPs are based on the principle that burning tobacco is unnecessary to liberate nicotine. In smoking, aerosolizing nicotine is achieved by igniting tobacco, reaching temperatures of up to 900°C in the burning cone, but a similar release is attained in HTPs by the volatilisation and even pyrolysis of tobacco at temperatures of around 350°C, although in some products it may reach up to 550 °C. The lower temperature at which nicotine is volatilised is expected to expose the user to emissions that have fewer toxicants and in smaller amounts than in conventional cigarette smoking’.

In the same brief, WHO defines HTP as ‘tobacco products that produce an emission containing nicotine and other chemicals, which is then inhaled by users.’ However, an official definition of heated tobacco products does not exist and is urgently needed.

Recommendation: an official and recognised definition of ‘heated tobacco products’ should be formulated.

Effects of heated tobacco products on the cardiovascular system

Impact on the cardiovascular system

In a study published on 20 October 2020 on ‘Heat-not-burn tobacco products: an emerging threat to cardiovascular health’ the authors show that heated tobacco products produce mainstream and second-hand emissions of harmful chemicals, including nicotine, particulate matter, benzene, acrolein, and tobacco-specific nitrosamines. The levels of these emissions, despite being less than those of traditional cigarettes, are potentially harmful to cardiovascular health.18

- Heart rate and blood pressure

Studies show that HTPs resulted in increased heart rate, increased blood pressure, pulse wave velocity and augmentation index immediately after smoking without relevant differences to conventional cigarettes (CC).19,20

Nicotine inhaled by users of HTPs raises blood pressure and heart rate and is associated with right ventricular remodeling and increased right ventricular filling pressures.\textsuperscript{21,22} Cardiac dysfunction, cardiotoxicity and fibrosis was reported in preclinical trials.\textsuperscript{23}

Nicotine levels in mainstream HTPs emissions are high and approximately 57\% to 83\% of CC. Extracting nicotine from tobacco is more effective with the HTP device compared to combustion in CCs.\textsuperscript{24,25,26,27,28,29,30} Therefore, it can be concluded that nicotine inhaled from HTPs could be more harmful than from CC as nicotine degradation is different in HTPs\textsuperscript{31} indicating that HTPs are more harmful than is commonly assumed.\textsuperscript{32}

**Conclusion**

*When looking at heart rate and blood pressure there is no difference between the impact of HTPs and conventional cigarettes.*

- **Oxidative stress, endothelial function, and arterial stiffness**


\textsuperscript{22} Oakes JM, Xu J, Morris TM, Fried ND, Pearson CS, Lobell TD, Gilpin NW, Lazartigues E, Gardner JD, Yue X. Effects of Chronic Nicotine Inhalation on Systemic and Pulmonary Blood Pressure and Right Ventricular Remodeling in Mice. *Hypertension* 2020;\textbf{75}:1305–1314


Vascular-endothelial dysfunction was measurable by ultrasound after consuming HTPs, and participants suffered from oxidative stress and dysfunction of platelet aggregation. These effects are comparable to conventional cigarettes.

HTPs produce acrolein, which is associated with vascular endothelial dysfunction and oxidative stress. HTPs also produce benzene which is associated with increased low-density lipoprotein, decreased circulating of angiogenic cells, increased cardiovascular risk scores. Conclusion

Vascular endothelial dysfunction and oxidative stress is evident in HTPs and can be explained by the emitted acrolein and other toxins. There is hardly any difference between the impact of HTPs and conventional cigarettes.

The negative impact of HTPs on platelet function could be demonstrated in biomarker studies. Two studies were conducted by the tobacco industry, reporting high levels of biomarkers for platelet activation in HTPs users, putting consumers of HTPs at risk for increased platelet activation.

Platelets

The negative impact of HTPs on platelet function could be demonstrated in biomarker studies. Two studies were conducted by the tobacco industry, reporting high levels of biomarkers for platelet activation in HTPs users, putting consumers of HTPs at risk for increased platelet activation.


44 Lüdicke F, Picavet P, Baker G, Haziza C, Pouix V, Lama N, Weitkunat R. Effects of Switching to the Menthol Tobacco Heating System 2.2, Smoking Abstinence, or Continued Cigarette Smoking on Clinically Relevant Risk Markers: A Randomized, Controlled,
negative effects of CCs on platelet function and thrombosis are well documented and there is no reason why HTPs should not be associated with similar effects.\textsuperscript{45}

Acrolein in CCs is associated with increased platelet aggregation and platelet-leukocyte aggregate formation, and induced formation of platelet factor 4, which augments endothelial activation and exacerbation of atherosclerosis.\textsuperscript{46,47,48} As acrolein was found in emission of HTPs, the conclusions are likely to be transferable to HTPs.

**Conclusion:**

*When looking at platelets there is no difference between the impact of HTP and conventional cigarettes.*

- **Emission of particulate matter from HTPs and impact on cardiovascular disease**

HTPs emit significant amounts of particulate matter inhaled by the users. The direct connection of particulate matter and cardiovascular diseases, including heart failure, ischemic heart disease, and stroke, is well known.\textsuperscript{49} This can be explained as a consequence of increased blood pressure caused by particulate matter and the effect worsens in obese patients.\textsuperscript{50} Particulate matter is associated with malign ventricular arrhythmias.\textsuperscript{51} This could be interpreted as the result of structural remodeling of the heart and cardiac inflammation, which were associated with particulate matter in a preclinical trial.\textsuperscript{52}

**Conclusion**

*The use of HTPs leads to particulate matter emissions, which have a devastating effect on CVD.*

- **Other toxins and their impact on CVD**

Harmful and potential harmful compounds (non-nicotine toxins) in emissions produced by HTPs include tar, particulate matter, carbon monoxide, reactive oxygen species, benzene, acrolein, carbonyl compounds, acetol, and tobacco-specific nitrosamines (carcinogenic byproducts of tobacco
Although the majority of harmful and potentially harmful compounds emitted by HTPs are reduced when compared to CCs, HTPs expose users to high levels of toxins and the emissions still represent a significant CVD risk for consumers. Furthermore, harmful compounds associated with negative cardiovascular impact were generated by heating tobacco stick mouthpieces. This produces acrolein, which is associated with vascular endothelial dysfunction and oxidative stress.

### Conclusion

The consumption of HTPs leads to inhalation of high levels of toxins which have a devastating effect on CVD.

- **Compensatory puffing**

A manufacturer-funded randomised controlled trial with a follow-up of 5 days reported for the HTPs (compared to CCs) no differences in consumed cigarettes per day, no difference in nicotine or cotinine levels, but more frequent and longer puffs with higher volumes. This effect of compensatory puffing is well known i.e. from “light cigarettes” or e-cigarettes with reduced nicotine content. Compensatory puffing was detected in three manufacturer-based studies too, while subjective smoking satisfaction was rated by subjects as lower compared to conventional cigarettes.

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67. Lüdicke F, Picavet P, Baker G, Haziza C, Poux V, Lama N, Weitkunat R. Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label,
Conclusion

Potential consequences of compensatory puffing include more consumption or more intense smoking to gain equal doses of nicotine, which can be associated with intake of higher levels of non-nicotine toxins, leading to increased tobacco-associated diseases such as cardiovascular disease.

Conclusions on the impact of HTP and the cardiovascular system

- Emissions from HTPs contain the same toxin profile as CCs, and intake of these harmful or potentially harmful compounds will cause tobacco-associated diseases. Nevertheless, clinical trials comparing HTP users with non-smokers are needed to assess the full spectrum of health consequences. Results of machine-generated smoke cannot be transferred to real-life smoking of HTPs or other tobacco products.67
- As the harmful characteristics of tobacco are triggered by the innumerably harmful or potentially harmful toxins, the currently characterised compounds of HTPs are associated with increased cardiovascular risk, altered lipid metabolism, arterial stiffness, and decreased pulmonary function.68,69,70,71,72,73
- The use of HTPs leads to heart failure, ischemic heart disease, and stroke, and thus contributes to the burden of cardiovascular disease. HTP users suffer from intake of substances associated with cardiovascular disease.

Use and awareness of heated tobacco products:

Use of Heated tobacco products

There is not much information about the prevalence of HTP use and less about its trends. In 2017–2018, HTP use was still limited in Europe among the general population. In Italy, 1.4% of the population aged ≥ 15 years tried IQOS in 2017. Overall, 1.0% of never-smokers, 0.8% of ex-smokers and 3.1% of current cigarette smokers had tried IQOS74. In Germany, 0.3% of current smokers and
recent ex-smokers aged 14 years or more currently used HTPs in 2017. In Great Britain, 1.7% of adults had tried or were using HTPs in 2017, but only 13% of them had been using it daily.

However, the dual use of these products, their popularity and higher use among younger generations, and the interest of non-smokers in these products are worrying and indicate the need for close monitoring in terms of prevalence and the characteristics of users.

### Awareness of Heated tobacco products

Many HTP users consider HTPs as safe and non-addictive. A study among Polish medical students for example (with a respective use of 13.2% of CCs and 2.8% of HTPs) shows that among HTP users, 43.2% considered HTPs as safe and not addictive, and disagreed with a public ban on HTPs use.

Other studies show similar results.

Out of 10,839 European citizens interviewed in 2017 to 2018, 27.8% of subjects were aware of HTPs, and 1.8% had at least once used HTPs (ranging from 0.6% in Spain to 8.3% in Greece). Another European survey found an increase of awareness of HTPs from 8% in 2016 to 17% in 2018. Ever use of HTPs was significantly higher in subjects who tried to quit smoking CCs in the last year.

### Conclusion:

Awareness of addictiveness and toxicity of HTPs among users is low and needs to be improved.
Gateway into smoking and HTPs as a quit aid

Gateway into smoking

The National Youth Tobacco Surveys conducted in 2020 in the USA reported the use of HTPs in 1.3% (95% CI 0.9 to 1.8%) of middle school pupils (grades 6-8) during the past 30 days. As young users of e-cigarettes were more vulnerable to HTPs advertising, vaping is a potential gateway to future HTPs use.

Research in Italy also showed that in total, 45% of Italian HTP users have never smoked cigarettes. Potential susceptibility of youth trying HTPs was also represented among youth in England (n=3,970), where 41.8% of subjects reported interest in trying HTPs and 23.2% of non-smoking subjects reported interest in trying HTPs.

Conclusion

From the above information, it can be concluded that HTPs are a gateway into smoking.

HTPs as quit aid

The World Health Organisation does not recommend HTPs as a nicotine replacement product.

Analysing publicity data, the tobacco industry failed to provide evidence that the young generation, non-HTP users and ex users will not find HTPs appealing, will not initiate the use of HTPs and will not perceive these products as risk-free.

An Italian study investigated the development of smoking habits in users who had ever used HTPs. Out of these ever HTP users, 19.1% started or re-started smoking CCs, and only 14.6% were able to quit smoking after HTPs use. Current smokers reported in 55.1% of cases the use of HTPs because HTPs might help them to quit smoking, and 52.0% of current smokers used HTPs to replace some of the cigarettes to avoid giving up smoking altogether. Data from Osaka, Japan, reported significantly lower prevalence ratios for quitting smoking in subjects who changed from CCs to HTPs during the

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86 Czoli CD, White CM, Reid JL, O'Conner RJ, Hammond D. Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. Tob Control 2020;29:89–95
COVID-19 pandemic (PR 0.15, 95% 0.04-0.58). Exclusive HTPs smokers were 40% less likely to quit HTPs than users of CCs.

**Conclusion:**

*HTPs cannot be considered as a nicotine replacement product or a quit aid. Quite the opposite, it should be considered as a gateway into smoking.*

**HTP and Secondhand smoke**

HTPs produce relevant amounts of side stream and secondhand emissions containing harmful and potentially harmful substances, although the quantity of emission is lower when compared to CCs.

A Japanese survey reported frequent indoor, public use of HTPs (80.1%). The tobacco industry tries to circumvent smoking bans with abstracting the definition of smoke and with ambiguously worded laws.

Relevant differences in independent and manufacturer-funded publications exist, as independent trials found both particulate matter and acrolein in HTP secondhand emissions, while manufacturer-funded studies did not detect these.
Increased concentrations of particulate matter and acrolein were reported after smoking HTPs indoors.\textsuperscript{107,108} HTPs generated one-fourth of particulate matter of CCs, and the emitted particulate matter was sufficiently small to result in alveolar deposition.\textsuperscript{109} Furthermore, these particulates can enter the systemic circulation, causing disorders in hemostasis and end organ damage.\textsuperscript{110} Particulate matter emitted by HTPs may be especially detrimental to populations at risk (in particular children and young people). Particle dosimetry modeling of secondhand emissions reported an inverse relationship of age and dose, resulting in the highest doses in 3-Month-old infants.\textsuperscript{111}

HTP use inside cars resulted in relevant amounts of particulate matter and nicotine in the air of cars.\textsuperscript{112,113}

Outdoor smoking of HTPs affects indoor air quality, persisting also after the end of smoking sessions.\textsuperscript{114}

Asthma attacks and chest pain accompanied exposure to secondhand smoke of HTPs.\textsuperscript{115}

**Conclusion:** HTPs are a harmful source of secondhand smoke even if smoked outdoor, resulting in relevant health consequences. For these reasons alone, the same legislative measures on smoke free places should apply to HTPs as with conventional cigarettes.

**Conclusions and recommendations**

Although Heated tobacco products may expose users to lower levels of some toxicants than conventional cigarettes, they also expose users to higher levels of other toxicants which have a devastating effect on the cardiovascular system.

Although use and uptake of Heated Tobacco Products is not very high yet compared to use of conventional cigarettes, the emerging HTPs, are expected to capture a significant market share, particularly among the younger population.

\textsuperscript{2016;80}:91–101.


\textsuperscript{110} Sun Q, Hong X, Wold LE. Cardiovascular Effects of Ambient Particulate Air Pollution Exposure. *Circulation* 2010;121:2755–2765.


The dual use of HTPs (use along with CCs), their popularity and higher use among younger generations, and the interest of non-smokers in these products are worrying trends and indicate the necessity for close monitoring in terms of prevalence and the characteristics of users.

**EHN therefore has the following recommendations:**

- A clear definition of HTPs is imperative.
- Users of HTPs suffer from similar, devastating effects on cardiovascular health as conventional cigarettes. They can therefore not be recommended as safe alternatives, nicotine replacement therapies or quit aids.
- HTPs produce second-hand smoke, both indoors and outdoors, and can therefore not be considered safe for non-users.
- Considering the similarities in CVD outcome in users of HTPs and conventional cigarettes, both should be subject to the full effect of the Tobacco Products Directive. In countries where the TPD does not apply, HTPs should be subject to the same smoke free legislation.
- Considering the similarities in CVD outcome in users of HTPs and conventional cigarettes, taxes and excise duties on HTPs should be at the same level as for conventional cigarettes.