fighting heart disease and stroke
european heart network

Heated tobacco products and cardiovascular disease – a position paper from the European Heart Network

September 2021

Acknowledgement

The European Heart Network would like to thank contributing expert Dr. Martin Riesenhuber from the Medical University of Vienna, Department of Internal Medicine II, Division of Cardiology, for his invaluable input in this report.

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]

[1] Wilkins, E. *et al*. European Cardiovascular Disease Statistics 2017. *European Heart Network* (2017)
[2] Wilkins, E. *et al*. European Cardiovascular Disease Statistics 2017. *European Heart Network* (2017)
[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 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.

---

[4] Jankowski M, Brożek G, Lawson J, Skoczyński S, Majek P, Zejda J. New ideas, old problems? Heated tobacco products – a systematic review. *Int J Occup Med Environ Health* 2019;**32**:595–634.
[5] Dautzenberg B, Dautzenberg M-D. Le tabac chauffé : revue systématique de la littérature. *Revue des Maladies Respiratoires* 2019;**36**:82–103.
[6] McKelvey K, Popova L, Kim M, Chaffee BW, Vijayaraghavan M, Ling P, Halpern-Felsher B. Heated tobacco products likely appeal to adolescents and young adults. *Tob Control* 2018;**27**:s41–s47.
[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
[8] Simonavicius E, McNeill A, Shahab L, Brose LS. Heat-not-burn tobacco products: a systematic literature review. *Tob Control* 2019;**28**:582–594.
[9] Drovandi A, Salem S, Barker D, Booth D, Kairuz T. Human Biomarker Exposure From Cigarettes Versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis. *Nicotine & Tobacco Research* 2020;**22**:1077–1085.
[10] Akiyama Y, Sherwood N. Systematic review of biomarker findings from clinical studies of electronic cigarettes and heated tobacco products. *Toxicology Reports* 2021;**8**:282–294.
[11] Lüdicke F, Ansari SM, Lama N, Blanc N, Bosilkovska M, Donelli A, Picavet P, Baker G, Haziza C, Peitsch M, Weitkunat R. Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically Relevant Biomarkers to Assess a Candidate Modified Risk Tobacco Product: A Randomized Trial. *Cancer Epidemiol Biomarkers Prev* 2019;**28**:1934–1943
[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.
[13] Yudkin JS, Lipska KJ, Montori VM. The idolatry of the surrogate. BMJ. 2011 Dec 28;343:d7995. doi: 10.1136/bmj.d7995. PMID: 22205706.
[14] Institute of Medicine (US) Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease; Editors Micheel CM and Ball JR. National Academies Press, Washington, DC. 2010. Available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0079490/ (Accessed on July 10, 2021).

In its document 'Heated Tobacco Products – A brief[15]', 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[16] of tobacco at temperatures of around 350°C, although in some products it may reach up to 550 ºC.[17] 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]

[15] Heated tobacco products: a brief (2020) – WHO, 2020.
[16] Davis B, Williams M, Talbot P. iQOS: evidence of pyrolysis and release of a toxicant from plastic. Tob Control 2019;28:34–41. doi:10.1136/tobaccocontrol-2017-054104.
[17] Jiang Z, Ding X, Fang T, Huang H, Zhou W, Sun Q. Study on heat transfer process of a heat not burn tobacco product flow field. J Phys Conf Ser. 2018;1064:012011. doi:10.1088/1742-6596/1064/1/012011.
[18] Fried ND, Gardner JD. Heat-not-burn tobacco products: an emerging threat to cardiovascular health. *American Journal of Physiology-Heart and Circulatory Physiology* 2020;**319**:H1234–H1239.
[19] Ioakeimidis N, Emmanouil E, Terentes-Printzios D, Dima I, Aznaouridis K, Tousoulis D, Vlachopoulos C. Acute effect of heat-not-burn versus standard cigarette smoking on arterial stiffness and wave reflections in young smokers. *European Journal of Preventive Cardiology* 2020;2047487320918365.
[20] Franzen KF, Belkin S, Goldmann T, Reppel M, Watz H, Mortensen K, Droemann D. The impact of heated tobacco products on arterial stiffness. *Vasc Med* 2020;**25**:572–574.

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.[21,22] Cardiac dysfunction, cardiotoxicity and fibrosis was reported in preclinical trials.[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.[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[31] indicating that HTPs are more harmful than is commonly assumed.[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*

[21] Arastoo S, Haptonstall KP, Choroomi Y, Moheimani R, Nguyen K, Tran E, Gornbein J, Middlekauff HR. Acute and chronic sympathomimetic effects of e-cigarette and tobacco cigarette smoking: role of nicotine and non-nicotine constituents. *American Journal of Physiology-Heart and Circulatory Physiology* 2020;**319**:H262–H270.

[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;**75**:1305–1314

[23] Jia G, Meng Z, Liu C, Ma X, Gao J, Liu J, Guo R, Yan Z, Christopher T, Lopez B, Liu W, Dai H, Lau WB, Jiao X, Zhao J, Wang Z-X, Cao J, Wang Y. Nicotine induces cardiac toxicity through blocking mitophagic clearance in young adult rat. *Life Sciences* 2020;**257**:118084.

[24] Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J, Berthet A. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. *JAMA Intern Med* 2017;**177**:1050.

[25] Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K. Nicotine Delivery to the Aerosol of a Heat-Not-Burn Tobacco Product: Comparison With a Tobacco Cigarette and E-Cigarettes. *Nicotine & Tobacco Research* 2018;**20**:1004–1009.

[26] Bekki K, Inaba Y, Uchiyama S, Kunugita N. Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes. *J UOEH* 2017;**39**:201–207.

[27] Schaller J-P, Keller D, Poget L, Pratte P, Kaelin E, McHugh D, Cudazzo G, Smart D, Tricker AR, Gautier L, Yerly M, Reis Pires R, Le Bouhellec S, Ghosh D, Hofer I, Garcia E, Vanscheeuwijck P, Maeder S. Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. *Regul Toxicol Pharmacol* 2016;**81 Suppl 2**:S27–S47.

[28] Schaller J-P, Pijnenburg JPM, Ajithkumar A, Tricker AR. Evaluation of the Tobacco Heating System 2.2. Part 3: Influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the Tobacco Heating System 2.2 aerosol. *Regul Toxicol Pharmacol* 2016;**81 Suppl 2**:S48–S58.

[29] Jaccard G, Tafin Djoko D, Moennikes O, Jeannet C, Kondylis A, Belushkin M. Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes. *Regulatory Toxicology and Pharmacology* 2017;**90**:1–8.

[30] Forster M, McAughey J, Prasad K, Mavropoulou E, Proctor C. Assessment of tobacco heating product THP1.0. Part 4: Characterisation of indoor air quality and odour. *Regul Toxicol Pharmacol* 2018;**93**:34–51

[31] Chavarrio Cañas JE, Monge-Palacios M, Grajales-González E, Sarathy SM. Early Chemistry of Nicotine Degradation in Heat-Not-Burn Smoking Devices and Conventional Cigarettes: Implications for Users and Second- and Third-Hand Smokers. *J Phys Chem A* 2021;**125**:3177–3188.

[32] Chavarrio Cañas JE, Monge-Palacios M, Grajales-González E, Sarathy SM. Early Chemistry of Nicotine Degradation in Heat-Not-Burn Smoking Devices and Conventional Cigarettes: Implications for Users and Second- and Third-Hand Smokers. J Phys Chem A. 2021 Apr 22;125(15):3177-3188. doi: 10.1021/acs.jpca.1c01650. Epub 2021 Apr 9. PMID: 33834773.

Vascular-endothelial dysfunction was measurable by ultrasound after consuming HTPs, and participants suffered from oxidative stress and dysfunction of platelet aggregation.[33, 34,35, 36] 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.[37]

Conclusion

Vascular endothelial dysfunction and oxidative stress is evident in HTPs and can be explained by the emitted acrolein and other toxins.[38,39,40] There is hardly any difference between the impact of HTPs and conventional cigarettes.

- *Platelets*

The negative impact of HTPs on platelet function could be demonstrated in biomarker studies.[41,42] 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.[43,44] The

[33] Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violi F, Loffredo L, Pignatelli P, Perri L, Peruzzi M, Marullo AGM, De Falco E, Chimenti I, Cammisotto V, Valenti V, Coluzzi F, Cavarretta E, Carrizzo A, Prati F, Carnevale R, Frati G. Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 2 Randomized Trial. *JAHA* 2019;**8**.

[34] Frati G, Carnevale R, Nocella C, Peruzzi M, Marullo AGM, De Falco E, Chimenti I, Cammisotto V, Valenti V, Cavarretta E, Carrizzo A, Versaci F, Vitali M, Protano C, Roever L, Giordano A, Sciarretta S, Biondi-Zoccai G. Profiling the Acute Effects of Modified Risk Products: Evidence from the SUR-VAPES (Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking) Cluster Study. *Curr Atheroscler Rep* 2020;**22**:8.

[35] Wang L, Liu X, Chen L, Liu D, Yu T, Bai R, Yan L, Zhou J. Harmful chemicals of heat not burn product and its induced oxidative stress of macrophages at air-liquid interface: Comparison with ultra-light cigarette. *Toxicology Letters* 2020;**331**:200–207.

[36] Nabavizadeh P, Liu J, Havel CM, Ibrahim S, Derakhshandeh R, Jacob III P, Springer ML. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. *Tob Control* 2018;**27**:s13–s19.

[37] Abplanalp W, DeJarnett N, Riggs DW, Conklin DJ, McCracken JP, Srivastava S, Xie Z, Rai S, Bhatnagar A, O'Toole TE. Benzene exposure is associated with cardiovascular disease risk. PLoS One 12: e0183602, 2017. doi:10.1371/journal.pone.0183602

[38] Cancelada L, Sleiman M, Tang X, Russell ML, Montesinos VN, Litter MI, Gundel LA, Destaillats H. Heated Tobacco Products: Volatile Emissions and Their Predicted Impact on Indoor Air Quality. *Environ Sci Technol* 2019;**53**:7866–7876.

[39] Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violi F, Loffredo L, Pignatelli P, Perri L, Peruzzi M, Marullo AGM, De Falco E, Chimenti I, Cammisotto V, Valenti V, Coluzzi F, Cavarretta E, Carrizzo A, Prati F, Carnevale R, Frati G. Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 2 Randomized Trial. *JAHA* 2019;**8**

[40] Kuntic M, Oelze M, Steven S, Kröller-Schön S, Stamm P, Kalinovic S, Frenis K, Vujacic-Mirski K, Bayo Jimenez MT, Kvandova M, Filippou K, Al Zuabi A, Brückl V, Hahad O, Daub S, Varveri F, Gori T, Huesmann R, Hoffmann T, Schmidt FP, Keaney JF, Daiber A, Münzel T. Short-term e-cigarette vapour exposure causes vascular oxidative stress and dysfunction: evidence for a close connection to brain damage and a key role of the phagocytic NADPH oxidase (NOX-2). *European Heart Journal* 2020;**41**:2472–2483.

[41] Frati G, Carnevale R, Nocella C, Peruzzi M, Marullo AGM, De Falco E, Chimenti I, Cammisotto V, Valenti V, Cavarretta E, Carrizzo A, Versaci F, Vitali M, Protano C, Roever L, Giordano A, Sciarretta S, Biondi-Zoccai G. Profiling the acute effects of modified risk products: evidence from the SUR-VAPES (Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking) Cluster Study. Curr Atheroscler Rep 22: 8, 2020. doi:10.1007/s11883-020-0824-4.

[42] Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violi F, Loffredo L, Pignatelli P, Perri L, Peruzzi M, Marullo AGM, De Falco E, Chimenti I, Cammisotto V, Valenti V, Coluzzi F, Cavarretta E, Carrizzo A, Prati F, Carnevale R, Frati G. Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR - VAPES) 2 Randomized Trial. J Am Heart Assoc. 2019 Mar 19;8(6):e010455. doi: 10.1161/JAHA.118.010455. PMID: 30879375; PMCID: PMC6475061.

[43] Haziza C, de La Bourdonnaye G, Donelli A, Skiada D, Poux V, Weitkunat R, Baker G, Picavet P, Lüdicke F. Favorable Changes in Biomarkers of Potential Harm to Reduce the Adverse Health Effects of Smoking in Smokers Switching to the Menthol Tobacco Heating System 2.2 for 3 Months (Part 2). Nicotine Tob Res. 2020 Apr 17;22(4):549-559. doi: 10.1093/ntr/ntz084. PMID: 31125079; PMCID: PMC7164580.

[44] Lüdicke F, Picavet P, Baker G, Haziza C, Poux 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.[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.[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.[49] This can be explained as a consequence of increased blood pressure caused by particulate matter and the effect worsens in obese patients.[50] Particulate matter is associated with malign ventricular arrhythmias.[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.[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

Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 2). Nicotine Tob Res. 2018 Jan 5;20(2):173-182. doi: 10.1093/ntr/ntx028. PMID: 28177498; PMCID: PMC5896432.

[45] Conklin DJ. Cardiovascular inury induced by tobacco products: assessment of risk factors and biomarkers of harm. A Tobacco Centers of Regulatory Science compilation. Am J Physiol Heart Circ Physiol. 2019;316(4):H801-H827. DOI: 10.1152/ajpheart.00591.2018

[46] Srivastava S. Oral exposure to acrolein exacerbates atherosclerosis in apoE-null mice. Atherosclerosis. 2011 Apr; 215(2):301-8.

[47] Sithu SD. Exposure to acrolein by inhalation causes platelet activation. Toxicol Appl Pharmacol. 2010 Oct 15; 248(2):100-10.

[48] DeJarnett N. Acrolein exposure is associated with increased cardiovasclar disease risk. J Am Heart Assoc. 2014 Aug 6; 3(4)

[49] Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC, Whitsel L, Kaufman JD. Particulate Matter Air Pollution and Cardiovascular Disease: An Update to the Scientific Statement From the American Heart Association. *Circulation* 2010;**121**:2331–2378.

[50] Prabhakaran D, Mandal S, Krishna B, Magsumbol M, Singh K, Tandon N, Venkat Narayan KM, Shivashankar R, Kondal D, Ali MK, Srinath Reddy K, Schwartz JD, GeoHealth Hub Study investigators, COE-CARRS Study investigators. Exposure to Particulate Matter Is Associated With Elevated Blood Pressure and Incident Hypertension in Urban India. *Hypertension* 2020;**76**:1289–1298.

[51] Peralta AA, Link MS, Schwartz J, Luttmann-Gibson H, Dockery DW, Blomberg A, Wei Y, Mittleman MA, Gold DR, Laden F, Coull BA, Koutrakis P. Exposure to Air Pollution and Particle Radioactivity With the Risk of Ventricular Arrhythmias. *Circulation* 2020;**142**:858–867.

[52] Grimmer JA, Tanwar V, Youtz DJ, Adelstein JM, Baine SH, Carnes CA, Baer LA, Stanford KI, Wold LE. Exercise does not ameliorate cardiac dysfunction in obese mice exposed to fine particulate matter. *Life Sciences* 2019;**239**:116885.

curing).[53,54, 55, 56,57,58,59] 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.[60]

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.[61] This effect of compensatory puffing is well known i.e. from "light cigarettes" or e-cigarettes with reduced nicotine content.[62,63] Compensatory puffing was detected in three manufacturer-based studies too, while subjective smoking satisfaction was rated by subjects as lower compared to conventional cigarettes.[64,65,66]

---

[53] Schaller J-P, Pijnenburg JPM, Ajithkumar A, Tricker AR. Evaluation of the Tobacco Heating System 2.2. Part 3: Influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the Tobacco Heating System 2.2 aerosol. *Regul Toxicol Pharmacol* 2016;**81 Suppl 2**:S48–S58

[54] Jankowski M, Brożek G, Lawson J, Skoczyński S, Majek P, Zejda J. New ideas, old problems? Heated tobacco products – a systematic review. *Int J Occup Med Environ Health* 2019;**32**:595–634.

[55] Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J, Berthet A. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. *JAMA Intern Med* 2017;**177**:1050.

[56] Bekki K, Inaba Y, Uchiyama S, Kunugita N. Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes. *J UOEH* 2017;**39**:201–207. .

[57] Schaller J-P, Keller D, Poget L, Pratte P, Kaelin E, McHugh D, Cudazzo G, Smart D, Tricker AR, Gautier L, Yerly M, Reis Pires R, Le Bouhellec S, Ghosh D, Hofer I, Garcia E, Vanscheeuwijck P, Maeder S. Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. *Regul Toxicol Pharmacol* 2016;**81 Suppl 2**:S27–S47.

[58] Jaccard G, Tafin Djoko D, Moennikes O, Jeannet C, Kondylis A, Belushkin M. Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes. *Regulatory Toxicology and Pharmacology* 2017;**90**:1–8

[59] Forster M, McAughey J, Prasad K, Mavropoulou E, Proctor C. Assessment of tobacco heating product THP1.0. Part 4: Characterisation of indoor air quality and odour. *Regul Toxicol Pharmacol* 2018;**93**:34–51

[60] Kim Y-H, An Y-J, Shin J-W. Carbonyl Compounds Containing Formaldehyde Produced from the Heated Mouthpiece of Tobacco Sticks for Heated Tobacco Products. *Molecules* 2020;**25**:5612.

[61] Lüdicke F, Haziza C, Weitkunat R, Magnette J. Evaluation of Biomarkers of Exposure in Smokers Switching to a Carbon-Heated Tobacco Product: A Controlled, Randomized, Open-Label 5-Day Exposure Study. *NICTOB* 2016;**18**:1606–1613.

[62] Benowitz NL, Donny EC, Hatsukami DK. Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game: Editorial. *Addiction* 2017;**112**:6–7.

[63] Morean ME, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Nicotine concentration of e-cigarettes used by adolescents. *Drug and Alcohol Dependence* 2016;**167**:224–227

[64] Haziza C, La Bourdonnaye G de, Merlet S, Benzimra M, Ancerewicz J, Donelli A, Baker G, Picavet P, Lüdicke F. Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: A randomized controlled study in confinement. *Regulatory Toxicology and Pharmacology* 2016;**81**:489–499.

[65] Haziza C, La Bourdonnaye G de, Skiada D, Ancerewicz J, Baker G, Picavet P, Lüdicke F. Evaluation of the Tobacco Heating System 2.2. Part 8: 5-Day randomized reduced exposure clinical study in Poland. *Regulatory Toxicology and Pharmacology* 2016;**81**:S139–S150.

[66] 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 IQOS[74]. In Germany, 0.3% of current smokers and

---

Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 1). *Nicotine & Tobacco Research* 2018;**20**:161–172.

[67] Hammond D, Wiebel F, Kozlowski LT, Borland R, Cummings KM, O'Connor RJ, McNeill A, Connolly GN, Arnott D, Fong GT. Revising the machine smoking regime for cigarette emissions: implications for tobacco control policy. *Tobacco Control* 2007;**16**:8–14.

[68] Bentley MC, Almstetter M, Arndt D, Knorr A, Martin E, Pospisil P, Maeder S. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. *Anal Bioanal Chem* 2020;**412**:2675–2685.

[69] Abplanalp W, DeJarnett N, Riggs DW, Conklin DJ, McCracken JP, Srivastava S, Xie Z, Rai S, Bhatnagar A, O'Toole TE. Benzene exposure is associated with cardiovascular disease risk. Ariga H, ed. *PLoS ONE* 2017;**12**:e0183602.

[70] Moazed F, Chun L, Matthay MA, Calfee CS, Gotts J. Assessment of industry data on pulmonary and immunosuppressive effects of IQOS. *Tob Control* 2018;**27**:s20–s25

[71] Davis B, To V, Talbot P. Comparison of cytotoxicity of IQOS aerosols to smoke from Marlboro Red and 3R4F reference cigarettes. *Toxicology in Vitro* 2019;**61**:104652

[72] Leigh NJ, Tran PL, O'Connor RJ, Goniewicz ML. Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells. *Tob Control* 2018;**27**:s26–s29

[73] Pataka A, Kotoulas S, Chatzopoulos E, Grigoriou I, Sapalidis K, Kosmidis C, Vagionas A, Perdikouri E-I, Drevelegas K, Zarogoulidis P, Argyropoulou P. Acute Effects of a Heat-Not-Burn Tbacco Product on Pulmonary Function. *Medicina* 2020;**56**:292.

[74] Liu X, Lugo A, Spizzichino L, Tabuchi T, Pacifici R, Gallus S. Heat-not-burn tobacco products: concerns from the Italian experience. Tob Control 2018;tobaccocontrol-2017-054054. doi:10.1136/tobaccocontrol-2017-054054.

recent ex-smokers aged 14 years or more currently used HTPs in 2017.[75] 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.[76]

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.[77]

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.[78] Other studies show similar results.[79,80]

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).[81] 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.[82]

Conclusion:

Awareness of addictiveness and toxicity of HTPs among users is low and needs to be improved.

[75] Kotz D, Kastaun S. E-Zigaretten und Tabakerhitzer: repräsentative Daten zu Konsumverhalten und assoziierten Faktoren in der deutschen Bevölkerung (die DEBRA-Studie) [E-cigarettes and tobacco heaters: representative data on consumer behaviour and associated factors in the German population (the DEBRA study)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2018;61(11):1407–14. doi:10.1007/s00103-018-2827-7 [in German]

[76] Brose L, Simonavicius E, Cheeseman H. Awareness and use of "heat-not-burn" tobacco products in Great Britain. Tob Regul Sci. 2018;4(2):44–50. doi:10.18001/trs.4.2.4.

[77] Use and Awareness of Heated Tobacco Products in Europe: Gallus et al. 2021, Journal of Epidemiology https://www.jstage.jst.go.jp/article/jea/advpub/0/advpub_JE20200248/_article.

[78] Majek P, Jankowski M, Nowak B, Macherski M, Nowak M, Gil A, Nakiela P, Lewicka B, Lawson JA, Zejda JE, Brożek GM. The Frequency of Use and Harm Perception of Heated Tobacco Products (HTPs): The 2019 Cross-Sectional Survey among Medical Students from Poland. *IJERPH* 2021;**18**:3381.

[79] Maria Lotrean L, Trofor A, Radu-Loghin C, Eremia M, Mihaltan F, Driezen P, Kyriakos CN, Mons U, Demjén T, Fernández E, Katsaounou PA, Przewoźniak K, Filippidis FT, Gravely S, Fong GT, Vardavas CI, the EUREST-PLUS Consortium, Vardavas CI, Glahn A, Kyriakos CN, Nguyen D, Nikitara K, Radu-Loghin C, Starchenko P, Tsatsakis A, Girvalaki C, Igoumenaki C, Papadakis S, Papathanasaki A, Tzatzarakis M, et al. Awareness and use of heated tobacco products among adult smokers in six European countries: findings from the EUREST-PLUS ITC Europe Surveys. *European Journal of Public Health* 2020;**30**:iii78–iii83.

[80] Zhu S-H, Ong J, Wong S, Cole A, Zhuang Y-L, Shi Y. Early adoption of heated tobacco products resembles that of e-cigarettes. *Tob Control* 2021;tobaccocontrol-2020-056089.

[81] Gallus S, Lugo A, Liu X, Borroni E, Clancy L, Gorini G, Lopez MJ, Odone A, Przewozniak K, Tigova O, Van Den Brandt P, Vardavas C, Fernandez E, the TackSHS Project Investigators. USE AND AWARENESS OF HEATED TOBACCO PRODUCTS IN EUROPE. *Journal of Epidemiology* 2021;

[82] Maria Lotrean L, Trofor A, Radu-Loghin C, Eremia M, Mihaltan F, Driezen P, Kyriakos CN, Mons U, Demjén T, Fernández E, Katsaounou PA, Przewoźniak K, Filippidis FT, Gravely S, Fong GT, Vardavas CI, the EUREST-PLUS Consortium, Vardavas CI, Glahn A, Kyriakos CN, Nguyen D, Nikitara K, Radu-Loghin C, Starchenko P, Tsatsakis A, Girvalaki C, Igoumenaki C, Papadakis S, Papathanasaki A, Tzatzarakis M, et al. Awareness and use of heated tobacco products among adult smokers in six European countries: findings from the EUREST-PLUS ITC Europe Surveys. *European Journal of Public Health* 2020;**30**:iii78–iii83.

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.[83] As young users of e-cigarettes were more vulnerable to HTPs advertising, vaping is a potential gateway to future HTPs use.[84]

Research in Italy also showed that in total, 45% of Italian HTP users have never smoked cigarettes.[85]

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.[86]

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.[87,88]

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.[89]

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.[90] 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.[91] Data from Osaka, Japan, reported significantly lower prevalence ratios for quitting smoking in subjects who changed from CCs to HTPs during the

---

[83] Gentzke AS, Wang TW, Jamal A, Park-Lee E, Ren C, Cullen KA, Neff L. Tobacco Product Use Among Middle and High School Students — United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:1881–1888.
[84] Liu J, Phua J, Krugman D, Xu L, Nowak G, Popova L. Do Young Adults Attend to Health Warnings in the First IQOS Advertisement in the U.S.? An Eye-Tracking Approach. *Nicotine & Tobacco Research* 2020;ntaa243
[85] Fried ND, Gardner JD. Heat-not-burn tobacco products: an emerging threat to cardiovascular health. *American Journal of Physiology-Heart and Circulatory Physiology* 2020;**319**:H1234–H1239.
[86] Czoli CD, White CM, Reid JL, OConnor 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
[87] World Health Organisation. WHO study group on tobacco product regulation: report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. 2019. https://apps.who.int/iris/handle/10665/329445
[88] World Health Organisation. WHO Statement on Heated Tobacco Products and the US FDA Decision Regarding IQOS. 2020. https://www.who.int/news/item/27-07-2020-who-statement-on-heated-tobacco-products-and-the-us-fda-decision-regarding-iqos (3 May 2021)
[89] McKelvey K, Popova L, Kim M, Chaffee BW, Vijayaraghavan M, Ling P, Halpern-Felsher B. Heated tobacco products likely appeal to adolescents and young adults. *Tob Control* 2018;**27**:s41–s47.
[90] Gallus S, Borroni E, Odone A, Brandt PA van den, Gorini G, Spizzichino L, Pacifici R, Lugo A. The Role of Novel (Tobacco) Products on Tobacco Control in Italy. *IJERPH* 2021;**18**:1895.
[91] Xu SS, Meng G, Yan M, Gravely S, Quah ACK, Ouimet J, O'Connor RJ, Sutanto E, Yoshimi I, Mochizuki Y, Tabuchi T, Fong GT. Reasons for Regularly Using Heated Tobacco Products among Adult Current and Former Smokers in Japan: Finding from 2018 ITC Japan Survey. *IJERPH* 2020;**17**:8030.

COVID-19 pandemic (PR 0.15, 95% 0.04-0.58).[92] Exclusive HTPs smokers were 40% less likely to quit HTPs than users of CCs.[93]

***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.[94,95,96,97,98,99,100,101,102.]

A Japanese survey reported frequent indoor, public use of HTPs (80.1%).[103] The tobacco industry tries to circumvent smoking bans with abstracting the definition of smoke and with ambiguously worded laws.[104]

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.[105,106.]

---

[92] Koyama S, Tabuchi T, Okawa S, Kadobayashi T, Shirai H, Nakatani T, Miyashiro I. Changes in Smoking Behavior Since the Declaration of the COVID-19 State of Emergency in Japan: A Cross-sectional Study From the Osaka Health App. *Journal of Epidemiology* 2021;

[93] Lee CM, Kim C-Y, Lee K, Kim S. Are Heated Tobacco Product Users Less Likely to Quit than Cigarette Smokers? Findings from THINK (Tobacco and Health IN Korea) Study. *IJERPH* 2020;**17**:8622.

[94] Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K. Nicotine Delivery to the Aerosol of a Heat-Not-Burn Tobacco Product: Comparison With a Tobacco Cigarette and E-Cigarettes. *Nicotine & Tobacco Research* 2018;**20**:1004–1009.

[95] Forster M, McAughey J, Prasad K, Mavropoulou E, Proctor C. Assessment of tobacco heating product THP1.0. Part 4: Characterisation of indoor air quality and odour. *Regul Toxicol Pharmacol* 2018;**93**:34–51

[96] Pratte P, Cosandey S, Goujon Ginglinger C. Investigation of solid particles in the mainstream aerosol of the Tobacco Heating System THS2.2 and mainstream smoke of a 3R4F reference cigarette. *Hum Exp Toxicol* 2017;**36**:1115–1120.

[97] Protano C, Manigrasso M, Avino p. Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system. *Annali di Igiene: Medicina Preventiva e di Comunità* 2016;109–112.

[98] Protano C, Manigrasso M, Avino P, Vitali M. Second-hand smoke generated by combustion and electronic smoking devices used in real scenarios: Ultrafine particle pollution and age-related dose assessment. *Environment International* 2017;**107**:190–195.

[99] Ruprecht AA, De Marco C, Saffari A, Pozzi P, Mazza R, Veronese C, Angellotti G, Munarini E, Ogliari AC, Westerdahl D, Hasheminassab S, Shafer MM, Schauer JJ, Repace J, Sioutas C, Boffi R. Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products, and conventional cigarettes. *Aerosol Science and Technology* 2017;**51**:674–684

[100] Mitova MI, Campelos PB, Goujon-Ginglinger CG, Maeder S, Mottier N, Rouget EGR, Tharin M, Tricker AR. Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality. *Regulatory Toxicology and Pharmacology* 2016;**80**:91–101

[101] Cancelada L, Sleiman M, Tang X, Russell ML, Montesinos VN, Litter MI, Gundel LA, Destaillats H. Heated Tobacco Products: Volatile Emissions and Their Predicted Impact on Indoor Air Quality. *Environ Sci Technol* 2019;**53**:7866–7876

[102] Leigh NJ, Palumbo MN, Marino AM, O'Connor RJ, Goniewicz ML. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. *Tob Control* 2018;**27**:s37–s38

[103] Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J, Berthet A. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. *JAMA Intern Med* 2017;**177**:1050.

[104] Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J, Berthet A. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. *JAMA Intern Med* 2017;**177**:1050.

[105] Protano C, Manigrasso M, Avino p. Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system. *Annali di Igiene: Medicina Preventiva e di Comunità* 2016;109–112.

[106] Mitova MI, Campelos PB, Goujon-Ginglinger CG, Maeder S, Mottier N, Rouget EGR, Tharin M, Tricker AR. Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality. *Regulatory Toxicology and Pharmacology*

Increased concentrations of particulate matter and acrolein were reported after smoking HTPs indoors.[107,108] HTPs generated one-fourth of particulate matter of CCs, and the emitted particulate matter was sufficiently small to result in alveolar deposition.[109] Furthermore, these particulates can enter the systemic circulation, causing disorders in hemostasis and end organ damage.[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.[111]

HTP use inside cars resulted in relevant amounts of particulate matter and nicotine in the air of cars.[112,113]

Outdoor smoking of HTPs affects indoor air quality, persisting also after the end of smoking sessions.[114]

Asthma attacks and chest pain accompanied exposure to secondhand smoke of HTPs.[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.

2016;**80**:91–101.

[107] Cancelada L, Sleiman M, Tang X, Russell ML, Montesinos VN, Litter MI, Gundel LA, Destaillats H. Heated Tobacco Products: Volatile Emissions and Their Predicted Impact on Indoor Air Quality. *Environ Sci Technol* 2019;**53**:7866–7876

[108] Protano C, Manigrasso M, Cammalleri V, Biondi Zoccai G, Frati G, Avino P, Vitali M. Impact of Electronic Alternatives to Tobacco Cigarettes on Indoor Air Particular Matter Levels. *IJERPH* 2020;**17**:2947.

[109] Protano C, Manigrasso M, Avino p. Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system. *Annali di Igiene: Medicina Preventiva e di Comunità* 2016;109–112.

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

[111] Protano C, Manigrasso M, Avino P, Vitali M. Second-hand smoke generated by combustion and electronic smoking devices used in real scenarios: Ultrafine particle pollution and age-related dose assessment. *Environment International* 2017;**107**:190–195.

[112] Savdie J, Canha N, Buitrago N, Almeida SM. Passive Exposure to Pollutants from a New Generation of Cigarettes in Real Life Scenarios. *IJERPH* 2020;**17**:3455.

[113] Schober W, Fembacher L, Frenzen A, Fromme H. Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (IQOS, e-cigarette) in passenger cars. *International Journal of Hygiene and Envlronmental Health* 2019;**222**:486–493

[114] Cammalleri V, Marotta D, Protano C, Vitali M, Villari P, Cattaruzza M, on behalf of the Smoke-free Department Working Group. How Do Combustion and Non-Combustion Products Used Outdoors Affect Outdoor and Indoor Particulate Matter Levels? A Field Evaluation Near the Entrance of an Italian University Library. *IJERPH* 2020;**17**:5200.

[115] Imura Y, Tabuchi T. Exposure to Secondhand Heated-Tobacco-Product Aerosol May Cause Similar Incidence of Asthma Attack and Chest Pain to Secondhand Cigarette Exposure: The JASTIS 2019 Study. *IJERPH* 2021;**18**:1766.

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.