WHO Technical Report Series

1029

WHO study group on tobacco product regulation

Report on the scientific basis of tobacco product regulation: eighth report of a WHO study group

World Health Organization

WHO was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective, reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These publications are closely tied to the Organization's priorities, which are to prevent and control disease and ensure equitable health systems based on primary health care and health promotion for individuals and communities. This includes strengthening implementation of the WHO Framework Convention on Tobacco Control (to meet Sustainable Development Goal 3a), thereby contributing to WHO's priority of improving the lives of one billion individuals through enjoyment of better health and well-being. Progress towards better health for all requires global dissemination and exchange of information based on the knowledge and experience of all WHO's Member States and on collaboration among world leaders in public health and the biomedical sciences.

To ensure the widest possible availability of authoritative information and guidance on health matters, WHO ensures broad international distribution of its publications and encourages their translation and adaptation. By helping to promote and protect health and prevent and control disease throughout the world, WHO's publications contribute to achieving the Organization's principal objective – the attainment by all people of the highest possible level of health.

The WHO Technical Report Series makes available the findings of international groups of experts who provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration, in their personal capacities rather than as representatives of governments or other bodies; their views do not necessarily reflect the decisions or the stated policy of WHO.

For further information, please contact WHO Press, World Health Organization; 1211 Geneva 27, Switzerland; www.who.int/bookorders; tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int.

WHO Technical Report Series
1029

WHO study group on tobacco product regulation

Report on the scientific basis of tobacco product regulation: eighth report of a WHO study group

World Health Organization

WHO study group on tobacco product regulation.
Report on the scientific basis of tobacco product regulation: eighth report of a WHO study group

(WHO Technical Report Series, No. 1029)
ISBN 978-92-4-002272-0 (electronic version)
ISBN 978-92-4-002273-7 (print version)
ISSN 0512-3054

Suggested citation. WHO study group on tobacco product regulation. Report on the scientific basis of tobacco product regulation: eighth report of a WHO study group. Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1029). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Contents

Participants in the 10th meeting of the WHO study group on tobacco product regulation

Virtual meeting, 28 September–2 October 2020

Members

Dr D.L. Ashley, Rear-Admiral (retired), Public Health Service; Research Professor, Department of Population Health Sciences, Georgia State University, Atlanta (GA), United States of America (USA)

Professor O.A. Ayo-Yusuf, Acting Vice-Chancellor, Postgraduate Studies and Innovation, Sefako Makgatho Health Sciences University, Pretoria, South Africa

Professor A.R. Boobis, Emeritus Professor, National Heart and Lung Institute, Imperial College London, London, United Kingdom of Great Britain and Northern Ireland

Professor Mike Daube AO, Emeritus Professor, Faculty of Health Sciences, Curtin University, Perth, Western Australia, Australia

Dr P. Gupta, Director, Healis Sekhsaria Institute for Public Health, Mumbai, India

Professor S. Katharine Hammond, Professor, Environmental Health Sciences; Director, Industrial Hygiene Program; Associate Dean, Academic Affairs, School of Public Health, University of California, Berkeley (CA), USA

Dr D.K. Hatsukami, Professor of Psychiatry, University of Minnesota, Minneapolis (MN), USA

Dr A. Opperhuizen, Director, Office for Risk Assessment and Research, Food and Consumer Product Safety Authority, Utrecht, Netherlands

Dr G. Zaatari (Chair), Professor and Chairman, Department of Pathology and Laboratory Medicine, American University of Beirut, Beirut, Lebanon

Chair of the WHO Tobacco Laboratory Network

Dr Nuan Ping Cheah, Director, Pharmaceutical, Cosmetics and Cigarette Testing Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore

WHO regional offices[1]

Dr Nivo Ramanandraibe, Acting Team Lead, Tobacco and Reduction of Other NCD Risk Factors, WHO Regional Office for Africa, Brazzaville, Congo

Dr Francisco Armada, Adviser, Tobacco Control, WHO Regional Office for the Americas, Washington (DC), USA

1 Apologies: Ms Kristina Mauer-Stender, Programme Manager, WHO Regional Office for Europe, UN City, Marmorvej, Copenhagen, Denmark

Ms Rosa Sandoval Correa de Kroeger, Adviser, Tobacco Control, WHO Regional Office for the Americas, Washington (DC), USA

Dr Jagdish Kaur, Regional Adviser, Health Risk Factors, Health Promotion, WHO Regional Office for South-East Asia, New Delhi, India

Dr Angela Ciobanu, Technical Officer, WHO Regional Office for Europe, UN City, Marmorvej, Copenhagen, Denmark

Dr Fatimah El-Awa, Regional Adviser, Tobacco Free Initiative, WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt

Ms Joung-eun Lee, Tobacco Free Initiative, WHO Regional Office for the Western Pacific, Manila, Philippines

Presenters

Dr Ranti Fayokun, No Tobacco Unit (Tobacco Free Initiative), Department of Health Promotion, Division of Universal Health Coverage and Healthier Populations, World Health Organization, Geneva, Switzerland

Dr Maciej Goniewicz, Associate Professor of Oncology, Nicotine and Tobacco Product Assessment Resource, Department of Health Behavior, Division of Cancer Prevention and Population Studies, Roswell Park Comprehensive Cancer Center, Buffalo (NY), USA

Dr Anne Havermans, Centre for Health Protection, National Institute for Public Health and the Environment, Bilthoven, Netherlands

Dr Ryan David Kennedy, Associate Professor, Institute for Global Tobacco Control, Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore (MD), USA

Dr Farrah Kheradmand, Co-Director, Clinical Scientist Training Program, Graduate School of Biomedical Sciences, Baylor College of Medicine, Houston (TX), USA

Professor Suchitra Krishnan-Sarin, Department of Psychiatry, Vice-Chair, Human Investigations Committee, Yale School of Medicine, New Haven (CT), USA

Professor Richard O'Connor, Professor of Oncology, Department of Health Behavior, Division of Cancer Prevention and Population Studies, Roswell Park Comprehensive Cancer Center, Buffalo (NY), USA

Dr Vinayak Prasad, Unit Head, No Tobacco (Tobacco Free Initiative), Department of Health Promotion, Division of Universal Health Coverage and Healthier Populations, World Health Organization, Geneva, Switzerland

Professor Najat A. Saliba, Professor of Chemistry, Faculty of Arts and Sciences, American University of Beirut, Beirut, Lebanon

Dr Yvonne Staal, Centre for Health Protection, National Institute for Public Health and the Environment, Bilthoven, Netherlands

Dr Irina Stepanov, Associate Professor, Division of Environmental Health Sciences and the Masonic Cancer Center, University of Minnesota, Minneapolis (MN), USA

Dr Reinskje Talhout, Senior Scientist, Centre for Health Protection, National Institute for Public Health and the Environment, Bilthoven, Netherlands

Co-authors[1]

Dr Nuan Ping Cheah, Director, Pharmaceutical, Cosmetics and Cigarette Testing Laboratory, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore

Mr Caleb Clawson, Research Assistant, Department of Health Behavior and Society, Institute for Global Tobacco Control, Johns Hopkins Bloomberg School of Public Health, Baltimore (MD), USA

Dr Laura E. Crotty Alexander, Associate Professor of Medicine, Division of Pulmonary Critical Care and Sleep, University of California at San Diego; Section Chief, Veterans Administration San Diego Healthcare System, San Diego (CA), USA

Dr Danielle R. Davis, Postdoctoral Fellow, Department of Psychiatry, Yale School of Medicine, New Haven (CT), USA

Dr Enrico Davoli, Head, Laboratory of Mass Spectrometry, Environmental Health Sciences Department, Mario Negri Institute for Pharmacological Research, Milan, Italy

Dr Thomas Eissenberg, Professor of Psychology and Co-director, Center for the Study of Tobacco Products, Virginia Commonwealth University, Richmond (VA), USA

Dr Ahmad El-Hellani, American University of Beirut, Department of Chemistry, Faculty of Arts and Sciences, Beirut, Lebanon

Dr Ranti Fayokun, No Tobacco Unit (Tobacco Free Initiative), Department of Health Promotion, Division of Universal Health Coverage and Healthier Populations, World Health Organization, Geneva, Switzerland

Dr Frank Henkler-Stephani, Department of Chemical and Product Safety, Federal Institute for Risk Assessment, Berlin, Germany

Ms Federica Mattioli, Mass Spectrometry Laboratory, Environmental Health Sciences Department, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Ms Marine Perraudin, Technical Officer, No Tobacco Unit (Tobacco Free Initiative), Department of Health Promotion, Division of Universal Health Coverage and Healthier Populations, World Health Organization, Geneva, Switzerland

Dr Armando Peruga, Researcher, Tobacco Control Group, Bellvitge Biomedical Research Institute, Barcelona, Spain; Centre for Epidemiology and Health Policy, School of Medicine Clínica Alemana, Universidad del Desarrollo, Santiago, Chile

1 Apologies: Dr Andrew Barnes, Virginia Commonwealth University, Richmond (VA), USA

Ms Meagan Robichaud, PhD student, Department of Health Behavior and Society, Institute for Global Tobacco Control, Johns Hopkins Bloomberg School of Public Health, Baltimore (MD), USA

Ms Moira Sy, Consultant, No Tobacco Unit (Tobacco Free Initiative), Department of Health Promotion, World Health Organization, Geneva, Switzerland

European Union and selected countries

Dr Matus Ferech, Policy Officer, Tobacco Control Team, Directorate-General for Health and Food Safety, Unit B2 - Cross-border Healthcare and Tobacco Control, European Commission, Brussels, Belgium

Dr Andre Luiz Oliveira da Silva, Health Regulation and Surveillance Specialist, Coordination of Tobacco Derived or Non-tobacco Control Processes, General Manager of Registration and Inspection of Tobacco Derived or Non-tobacco Products, Health Regulatory Agency, Rio de Janeiro, Brazil

Mr Denis Chonière, Director, Tobacco Products Regulatory Office, Controlled Substances and Tobacco Directorate, Health Canada, Ottawa, Ontario, Canada

Dr Peyman Altan, Tobacco Control Department, Ministry of Health, Ankara, Turkey

Secretariat of the WHO Framework Convention on Tobacco Control, Geneva, Switzerland

Dr Adriana Blanco, Head, Convention Secretariat

Secretariat of the No Tobacco Unit, Tobacco Free Initiative, Department of Health Promotion, WHO, Geneva, Switzerland

Dr Jennifer Brown, Consultant

Dr Ranti Fayokun, Scientist

Dr Ruediger Krech, Director

Dr Vinayak Prasad, Unit Head, No Tobacco, Tobacco Free Initiative

Ms Anne Sikanda, Assistant to Unit Head

Ms Simone St Claire, Consultant

Ms Moira Sy, Consultant

Acknowledgements

The WHO study group on tobacco product regulation (TobReg) expresses its gratitude to the authors of the background papers used as the basis for this report. Production of the report was coordinated by Dr Ranti Fayokun, with the supervision and support of Dr Vinayak Prasad, Unit Head, No Tobacco Unit, Department of Health Promotion, and Dr Ruediger Krech, Director of the WHO Department of Health Promotion.

Administrative support was provided by the following WHO personnel: Ms Miriamjoy Aryee-Quansah, Ms Anne Sikanda, Mr Gareth Burns, Ms Moira Sy, Ms Simone St Claire and Dr Jennifer Brown.

TobReg expresses its gratitude to Germany for providing the funds to support the preparation of the background papers for the 10th meeting of TobReg and acknowledges all authors of the background papers, as listed, for their expertise and contribution to the development of the report.

Our thanks go to Ms Elisabeth Heseltine for editing the report, Ms Teresa Lander for proofreading and Ms Ana Sabino for typesetting the report.

The Study Group also thanks the Secretariat of the WHO Framework Convention on Tobacco Control (WHO FCTC) for facilitating drafting of the requests of the Conference of the Parties to the WHO FCTC, which served as a basis for some of the background papers.

Abbreviations and acronyms

BAT	British American Tobacco
CC	conventional cigarette
CC16	club cell 16-kDa protein
CI	confidence interval
CO	carbon monoxide
COP	Conference of the Parties
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
COVID-19	coronavirus disease
ENDS	electronic nicotine delivery system
ENNDS	electronic non-nicotine delivery system
EVALI	e-cigarette- or vaping product use-associated lung injury
FDA	United States Food and Drug Administration
HCI	Health Canada method for the testing of tobacco products "Intense puffing regime"
HTP	heated tobacco product
ISO	International Organization for Standardization
JTI	Japan Tobacco International
KT&G	Korea Tobacco and Ginseng Corporation
MRTP	modified risk tobacco product
NAT	N′-nitrosoanatabine
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N′-nitrosonornicotine
PAH	polycyclic aromatic hydrocarbons
PATH	Population Assessment of Tobacco and Health
PM	particulate matter
PM2.5	particulate matter < 2.5 µm
PMI	Philip Morris International
SD	standard deviation
THC	Δ^9-tetrahydrocannabinol
THP	tobacco heating product
THS	tobacco heating system
TSNA	tobacco-specific nitrosamines
TTC	threshold of toxicological concern
USA	United States of America
US CDC	United States Centers for Disease Control and Prevention
WHO FCTC	WHO Framework Convention on Tobacco Control

1. Introduction

Effective tobacco product regulation is an essential component of a comprehensive tobacco control programme. It includes regulation of contents and emissions by mandated testing, disclosure of test results, setting limits as appropriate, disclosure of product information and imposing standards for product packaging and labelling. Tobacco product regulation is covered under Articles 9, 10 and 11 of the WHO Framework Convention on Tobacco Control (WHO FCTC) *(1)* and in the partial guidelines on implementation of Articles 9 and 10 of the WHO FCTC *(2)*. Other WHO resources, including the basic handbook on tobacco product regulation *(3)*, the handbook on building laboratory testing capacity *(4)* and the online modular courses based on the handbooks, which were published in 2018 *(5)*, support Member States in this respect.

The WHO Study Group on Tobacco Product Regulation (TobReg) was formally constituted by the WHO Director-General in 2003 to address gaps in the regulation of tobacco products. Its mandate is to provide evidence-based recommendations on policy for tobacco product regulation to the Director-General. TobReg is composed of national and international scientific experts on product regulation, treatment of tobacco dependence, toxicology and laboratory analyses of tobacco product ingredients and emissions. The experts are from countries in all six WHO regions *(6)*. As a formal entity of WHO, TobReg submits technical reports that provide the scientific basis for tobacco product regulation to the WHO Executive Board, through the Director-General, to draw the attention of Member States to WHO's work in this field. The reports, in the WHO Technical Report Series, include previously unpublished background papers that synthesize published scientific literature and have been discussed, evaluated and reviewed by TobReg. In accordance with Articles 9 and 10 of the WHO FCTC, relevant decisions of the Conference of the Parties (COP) to the WHO FCTC and relevant WHO reports submitted to the COP, the TobReg reports identify evidence-based approaches to regulating all forms of nicotine and tobacco products, including new and emerging products such as electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENNDS), heated tobacco products (HTPs) and nicotine pouches. These reports, now considered to be WHO global public health goods, respond to World Health Assembly resolutions WHA54.18 (2001), WHA53.17 (2000) and WHA53.8 (2000). "Global public health goods" are initiatives developed or undertaken by WHO that are of benefit either globally or to many countries in many regions *(7)*. This designation presents a unique opportunity for TobReg to speak directly to Member States and influence national, regional and global policy.

The 10th meeting of TobReg took place virtually on 28 September–2 October 2020, coordinated from WHO headquarters in Geneva. Over 50 participants, including the members of TobReg, discussed the scientific literature

on the attractiveness, toxicity, appeal, variation, marketing, health effects and regulation of novel and emerging nicotine and tobacco products, with a focus on HTPs. These products, which have a long history but have attracted increased international interest in the past decade, present various regulatory challenges, as there is a lack of capacity to regulate them, they distract from evidence-based interventions, conflation of product categories, unsubstantiated health claims and opposition to and interference with effective tobacco control policies and marketing and promotional activities that target children and adolescents by tobacco and related industries. The meeting provided a platform for discussing nine background papers:

- toxicants in heated tobacco products, exposure, health effects and claims of reduced risk (section 2);
- the attractiveness and addictive potential of heated tobacco products: effects on perception and use and associated effects (section 3);
- variations among heated tobacco products, considerations and implications (section 4);
- use of heated tobacco products: product switching and dual or poly product use (section 5);
- regulations on HTPs, ENDS and ENNDS, with country approaches, barriers to regulation and regulatory considerations (section 6);
- estimation of exposure to nicotine from use of electronic nicotine delivery systems and from conventional cigarettes (section 7);
- exploration of methods for quantifying individual risks associated with electronic nicotine and non-nicotine delivery systems and heated tobacco products: impact on population health and implications for regulation (section 8).
- flavours in novel and emerging nicotine and tobacco products (section 9);
- global marketing and promotion of novel and emerging nicotine and tobacco products and their impacts (section 10);

TobReg also discussed two supplementary "horizon scanning" papers, on:

- forms of nicotine in tobacco plants, chemical modifications and implications for electronic nicotine delivery systems products (section 11); and
- EVALI: "e-cigarette or vaping product use-associated lung injury" (section 12).

The background papers and the horizon scanning papers were prepared by subject matter experts according to the terms of reference or outline drawn up by the WHO Secretariat for each paper and were reviewed and revised by expert reviewers and members of the Study Group. The horizon scanning papers, which are new additions to the report, are short papers on emerging issues in product regulation for members to decide whether further work on these topics is warranted, such as a full background paper for a future meeting of the Study Group. The papers on HTPs and novel and emerging tobacco products addressed the request in paragraph 2a of decision FCTC/COP8(22) *(8)* at the eighth session of the COP (COP8):

> 2. REQUESTS the Convention Secretariat to invite WHO and, as appropriate, the WHO Tobacco Laboratory Network (TobLabNet):
>
> (a) to prepare a comprehensive report, with scientists and experts, independent from the tobacco industry, and competent national authorities, to be submitted to the Ninth session of the COP on research and evidence on novel and emerging tobacco products, in particular heated tobacco products, regarding their health impacts including on non-users, their addictive potential, perception and use, attractiveness, potential role in initiating and quitting smoking, marketing including promotional strategies and impacts, claims of reduced harm, variability of products, regulatory experience and monitoring of Parties, impact on tobacco control efforts and research gaps, and to subsequently propose potential policy options to achieve the objectives and measures outlined in paragraph 5 of the present decision.

The request made to WHO via the Convention Secretariat on novel and emerging tobacco products was examined by WHO and was the basis for deciding the topics of the papers, with other emerging issues in nicotine and tobacco product regulation, including requests for technical assistance to WHO from Member States. The Secretariat, in consultation with the Study Group, invited experts who not only contributed to discussions but also provided the most recent empirical scientific evidence and regulations on nicotine and tobacco products in their background papers. The period of the literature search is indicated in each paper; for most, it was the second quarter of 2020. The papers were subject to several rounds of review before and after the meeting by independent technical experts, the WHO Secretariat, people in other relevant WHO departments, regional colleagues and members of the Study Group before compilation into the technical report. This eighth report of TobReg on the scientific basis of tobacco product regulation is designed to guide Member States in finding the most effective, evidence-based means to bridge regulatory gaps and address challenges in tobacco control and should lead to development of coordinated regulatory

frameworks for nicotine and tobacco products. All experts and other participants in the meeting, including members of the Study Group, were required to complete a declaration of interests, which was evaluated by WHO to ensure independence from tobacco and related industries.

This report includes five papers on HTPs (sections 2–6), two on ENDS (sections 7 and 8) and two general reviews on novel and emerging nicotine and tobacco products, on the use of flavours in these products (section 9) and global marketing and promotion (section 10). It also includes two supplementary sections (11 and 12) that scan the horizon of studies on forms of nicotine in tobacco plants and on e-cigarette or vaping product use-associated lung injury (EVALI) and concludes with a section of overall recommendations, summarizing the recommendations in each section. The recommendations, which represent syntheses of complex research and evidence, promote international coordination of regulation and adoption of best practices in product regulation, strengthen capacity-building for product regulation in all WHO regions, represent a ready resource for Member States based on sound science and support implementation of the WHO FCTC by its States Parties.

This eighth report of the Study Group addresses ENDS, ENNDS and HTPs; however, it does not cover all aspects of these products, because many of the papers were written to meet the request of COP8, which was to review understanding on novel and emerging tobacco products (FCTC/COP8(22)). Continued research is necessary on these products; the Study Group will cover other products of interest (including traditional products, such as waterpipes, cigarettes and smokeless tobacco) in its next report, guided by countries' regulatory requirements and pertinent issues in tobacco product regulation. This will ensure continued, timely technical support to all countries and address all products, recognizing that their availability depends on the jurisdiction.

In summary, the outcomes of TobReg's deliberations and its recommendations will improve Member States' understanding of the evidence on ENDS, ENNDS and HTPs, contribute to the body of knowledge on product regulation, inform WHO's work, especially in providing technical support to Member States and keep Member States, regulators, civil society, research institutions and other interested parties up to date on product regulation through various platforms. States Parties to the WHO FCTC will be updated by a comprehensive report to be submitted to COP9, via the Convention Secretariat, on novel and emerging tobacco products, in line with decision FCTC/COP8(22), which will include the messages and recommendations in this report. Thus, the Study Group's activities will contribute to meeting target 3.a of the Sustainable Development Goals: strengthening implementation of the WHO FCTC *(9)*.

References

1. WHO Framework Convention on Tobacco Control. Geneva: World Health Organization; 2003 (http://www.who.int/fctc/en/, accessed 10 January 2021).
2. Partial guidelines on implementation of Articles 9 and 10. Geneva: World Health Organization; 2012 (https://www.who.int/fctc/guidelines/Guideliness_Articles_9_10_rev_240613.pdf, accessed January 2019).
3. Tobacco product regulation: basic handbook. Geneva: World Health Organization; 2018 (https://www.who.int/tobacco/publications/prod_regulation/basic-handbook/en/, accessed 10 January 2021).
4. Tobacco product regulation: building laboratory testing capacity. Geneva: World Health Organization; 2018 (https://www.who.int/tobacco/publications/prod_regulation/building-laboratory-testing-capacity/en/, accessed 14 January 2019).
5. Tobacco product regulation courses. Geneva: World Health Organization (https://openwho.org/courses/TPRS-building-laboratory-testing-capacity/items/3S11LKUFGyoTksZ5RSZblD; https://openwho.org/courses/TPRS-tobacco-product-regulation-handbook/items/7zq-7S1jxAtpbUWiZdfH98l).
6. TobReg members. In: World Health Organization [website]. Geneva: World Health Organization (https://www.who.int/groups/who-study-group-on-tobacco-product-regulation/about, accessed 10 January 2021).
7. Feacham RGA, Sachs JD. Global public goods for health. The report of working group 2 of the Commission on Macroeconomics and Health. Geneva: World Health Organization; 2002 (https://apps.who.int/iris/bitstream/handle/10665/42518/9241590106.pdf?sequence=1, accessed 10 January 2021).
8. Decision FCTC/COP8(22). Novel and emerging tobacco products. Decision of the Conference of the Parties to the WHO Framework Convention on Tobacco Control, Eighth session. Geneva: World Health Organization; 2018 (https://www.who.int/fctc/cop/sessions/cop8/FCTC__COP8(22).pdf, accessed 7 November 2020).
9. Sustainable development goals. Geneva: World Health Organization (https://www.who.int/health-topics/sustainable-development-goals#tab=tab_2, accessed 10 January 2021).

2. Toxicants in heated tobacco products, exposure, health effects and claims of reduced risk

Irina Stepanov, Professor, Division of Environmental Health Sciences and Masonic Cancer Center, University of Minnesota, Minneapolis (MN), USA

Federica Mattioli, Mass Spectrometry Laboratory, Environmental Health Sciences Department, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Enrico Davoli, Head, Mass Spectrometry Laboratory, Environmental Health Sciences Department, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Contents

Abstract

Increased marketing and the increasing popularity of novel and emerging heated tobacco products (HTPs) calls for urgent assessment of their potential impact on public health. In this report, we evaluate the published literature on the chemical composition of HTPs, exposure to these products and their effects in model

toxicological systems (in vitro and in experimental animals) and in humans. Such evaluation is the key initial step in characterizing the addictive, toxic and carcinogenic potential of HTPs and comparing them with other tobacco products on the market. The data indicate that the chemical profile of HTP aerosols is substantially different from that of conventional cigarettes or e-cigarettes. In the absence of standard analytical methods, however, these findings should be interpreted with caution. Studies also suggests that nicotine intake from some HTPs may be similar to or greater than that from conventional cigarettes. Studies of exposure in vitro and in experimental animals and humans generally confirm reduced exposure to some combustion-derived toxicants; however, some studies raise concern about potential cardiopulmonary toxicity and hepatotoxicity in users and harm from second-hand exposure in non-users. The report highlights the paucity of independent, non-industry research and recommends research and regulatory priorities.

2.1 Background

Heated tobacco products (HTPs), also referred to by manufacturers and some regulators as "heat-not-burn" or tobacco heating products, produce aerosols by heating tobacco at lower temperatures than in conventional tobacco-burning cigarettes (generally < 600 °C) in battery-powered heating systems. Early versions of HTPs, such as the cigarettes Eclipse and Accord, were poorly accepted by smokers or did not gain a meaningful market share; however, the versions of HTPs introduced during the past decade have started to gain popularity in some parts of the world. As combustion of conventional cigarettes results in many harmful emissions, including numerous toxicants and carcinogens, the purported aim of the new HTPs is to offer smokers a "less harmful alternative" to conventional cigarettes. HTPs are thus marketed with claims of "reduced risk products", "cleaner alternatives to conventional cigarettes" and "smoke-free alternatives". Examples of currently marketed HTPs are IQOS (Philip Morris International, PMI), glo and iFuse (British American Tobacco, BAT) and Ploom TECH (Japan Tobacco). Although they all heat tobacco, they differ in their construction and composition and in the mechanisms for heating tobacco and generating aerosol. For example, IQOS and glo generate aerosol containing nicotine by heating cigarette-like tobacco sticks at 240–350 °C, while Ploom TECH and iFuse produce aerosols by heating a mixture of glycerol and propylene glycol, which is then passed through a capsule containing tobacco material.

There are several major challenges to assessing user and non-user exposure to emitted chemical constituents, many of which are important toxicants and carcinogens, and the effects associated with the currently marketed HTPs. The first is that products such as IQOS were introduced relatively recently, in 2015, and were initially available only on limited markets. The second is the diversity of

HTPs, outlined above, as the chemical composition of the aerosols produced by these devices may differ. While the concentrations of many combustion-associated chemicals in HTP aerosols may be lower than in conventional cigarettes, some are higher, and HTPs may emit unique harmful chemicals because of their distinctive characteristics and how they are used. A third issue is that some of the tobacco sticks manufactured for one device can be used with other devices and can be reused; the interchangeability and misuse of products make it difficult to determine the toxic emissions to which the user is exposed. Fourthly, most of the scientific data on currently marketed HTPs were generated and published by the tobacco industry or funded by affiliates of the industry, and there is a critical lack of independent academic literature on HTPs. Given the history of misleading marketing and misinterpretation of research data by some tobacco product manufacturers, their publications must be interpreted with caution and after rigorous review of the raw data and methods. Unpublished data reported to regulators by manufacturers should be reviewed in a similarly rigorous way.

This report was commissioned by WHO in response to the request made by the Conference of the Parties to the WHO Framework Convention on Tobacco Control at its eighth session (Geneva, Switzerland, 1–6 October 2018) to the Convention Secretariat to invite WHO to prepare a comprehensive report of research and evidence on novel and emerging tobacco products, in particular HTPs, and to propose policy options to achieve the objectives and measures outlined in the relevant decision (FCTC/COP8(22)). This report partly addresses that request. It covers a broad range of aspects of the health impacts of HTPs, including in non-users, their addictive potential, perception and use, attractiveness, potential role in initiating and quitting smoking, marketing, including promotional strategies and impacts, claims of reduced harm, variation among products, regulatory experience and monitoring by Parties, impact on tobacco control and research gaps.

In this paper, we review the current literature on the toxicity of and exposure to HTP emissions and associated health effects and evaluate claims that HTPs reduce risk. In particular, we cover:

- toxicants in HTP emissions and in other tobacco products;
- exposure to HTP emissions and their effects in model systems (in vitro and in experimental animals) and in humans and the implications for health;
- assessment of the basis of the claims that HTPs reduce risk or harm;
- implications for public health;
- research gaps and priorities; and
- relevant policy recommendations.

The literature search was based primarily on the PubMed database and the SciFinder search tool, which retrieves data from the Medline and CAplus databases. Relevant articles cited in publications obtained in the search were also included. In addition, we consulted manufacturers' websites and the websites of the US Centers for Disease Control and Prevention, the United States Food and Drug Administration (FDA) and other relevant organizations that provide information on the chemistry and health effects of HTPs.

2.2 Toxicants in heated tobacco product emissions

2.2.1 Laboratory methods for measuring toxicants

As outlined above, the HTP devices on the market vary in design, the main differences among them being how the tobacco is heated and the temperatures reached in the devices. The effect of temperature on the formation of harmful constituents in emissions of tobacco products, including conventional and e-cigarettes, is well documented. HTP devices produced by third parties are also available, mainly online, usually without product specifications. (A simple Google or Amazon Internet search with "IQOS sticks compatible" as keywords indicates a number of brands, like Uwoo, Luckten, Kacig, Hotcig, Uwell, Vaptio, G-taste and Smok Nord.) Reliable, analytically validated testing procedures are necessary to draw reliable inferences from assessments of the levels of harmful emissions from HTPs and to compare them with emissions from other products, such as conventional and e-cigarettes.

Most of the methods for analysing HTP emissions used to date by both the industry and independent research groups are adapted from methods used to analyse conventional cigarettes, mainly for determining common emissions and other parameters (e.g. nicotine and some other tobacco-derived constituents) *(1,2)*. To analyse compounds that may be specific to HTPs, some laboratories used complex analytical approaches, such as multidimensional gas chromatography coupled with mass spectrometry or liquid chromatography–tandem mass spectrometry *(1,3)*. In 2019, the Tobacco and Tobacco Products Technical Committee, TC126, of the International Organization for Standardization (ISO) created a working group on HTP, but they have not yet published HTP-specific methods.

While, in principle, methods used to analyse conventional cigarettes could be adapted for analysing HTPs, there are key differences between the two products. First, the tobacco material in HTPs may contain more humectant and water than that of conventional cigarettes *(4)*, which may have implications for analysis of emissions. At a minimum, studies should be conducted to determine the efficiency of the usual glass-fibre Cambridge filter pads in capturing toxicants found in both cigarette smoke and HTP-specific constituents derived mainly from thermal degradation of glycerol, propylene glycol and additives. Secondly, it

is uncertain what puffing regimens (standardized puffing volume and frequency) should be used in the analysis of HTPs, as information on human topography in use of HTPs is lacking. The puffing parameters of HTPs are limited by HTP firmware and differ by device; manufacturers provide only specifications for "proper" product use and operation. As a result, use of different devices with different suggested puffing regimes *(5)* might result in large differences in desorption temperature and in toxicant emissions among studies. In addition, the higher intensity of HTP puffing may change the emission profile, because the kinetics of pyrolysis product generation is different from the kinetics of constituent desorption from tobacco material *(6)*. For example, increasing puffing intensity to generate more nicotine in the smoke, and thus the temperature at which the tobacco material is heated, is likely to increase the emissions of toxic pyrolysis products significantly. Finally, reference materials are not yet available, for either HTP devices or tobacco filler, obviating adequate analytical quality control.

In the absence of standard reference materials, analytical methods and puffing topography, accurate comparisons of HTPs and with other tobacco products cannot yet be made. For these reasons, generic statements of relative risk for users of these products are still preliminary and should be used carefully and cited only with recognition of this context.

2.2.2 Nicotine

As both conventional cigarettes and HTPs contain tobacco, both emit nicotine during use. Nicotine is the main known addictive constituent in tobacco products *(7)*; therefore, its levels in HTP emissions are of great importance. Table 2.1 lists the reported nicotine contents and emissions in two HTPs, IQOS and glo. Overall, the results of the analyses are consistent in both industry-supported and independent academic research. The corresponding nicotine values in reference cigarettes, which represent popular "full-flavour" (3R4F and CM6) and ventilated, formerly referred to as "light" (1R5F), filtered conventional cigarettes, are also shown in Table 2.1. The reported levels in the tobacco material (contents) of regular and menthol IQOS sticks were comparable to those of conventional cigarettes *(8,9)*; however, because HTP sticks are shorter and thinner than conventional cigarettes, they contain less tobacco material and, as a consequence, less total nicotine content per stick than a conventional cigarette. For example, Liu et al. *(10)* reported a nicotine content ranging from 1.9 to 4.6 mg per stick in three different HTPs.

Table 2.1. Representative reported nicotine contents and emissions in IQOS and glo HTPs

Product brand and variety	Range of reported average nicotine levels			References
	Contents (tobacco material) (mg/g)	Emissions		
		By ISO regimen[a]	By HCI regimen[a]	
IQOS				
Regular	15.2–15.7	0.4–0.77 mg/stick 0.3 mg/14 puffs[b]	1.1–1.5 mg/stick 1.1–1.4 mg/12 puffs	*1,6,8,9,11–13*
Menthol	15.6–17.1	0.43 mg/stick	1.2 mg/stick 1.38 mg/12 puffs	*6,8,9*
Mint	NR	0.32 mg/stick	1.2 mg/stick	*6*
Essence	NR	NR	1.14 mg/stick	*4*
Glo				
Regular	NR	0.07 mg/stick	0.27 mg/stick	*6*
Bright tobacco	NR	0.09–0.15 mg/stick	0.31–0.57 mg/stick	*1,4,6*
Fresh mix	NR	0.14 mg/stick	0.51 mg/stick	*6*
Intensely fresh	NR	0.13–0.15 mg/stick	0.36–0.51 mg/stick	*1,4,6*
Coolar green	NR	0.068 mg/stick	0.17 mg/stick	*6*
Coolar purple	NR	0.06 mg/stick	0.25 mg/stick	*6*
Reference conventional cigarettes				
3R4F	15.9–19.7 mg/g	0.73–0.76 mg/ cigarette	1.4–2.1 mg/cigarette	*1,6,12,14–16*
1R5F	15.9–17.2 mg/g	0.12 mg/ cigarette	1.0–1.1 mg/cigarette	*6,8,15,16*
CM6	18.7 mg/g	1.2 ± 0.13 mg/ cigarette	2.6–2.73 mg/cigarette	*6,15,16*

NR: not reported.

[a] Smoking machine regimes used to puff HTPs for emission analyses: ISO, International Organization for Standardization (ISO) method; HCI, Health Canada method for testing tobacco products "Intense puffing regime".

[b] Some studies reported data based on the number of puffs taken to consume one HTP stick by using the corresponding machine-smoking regimen.

Data on HTP emissions also show significant differences among brands. For example, the nicotine levels in the aerosol of IQOS puffed under ISO or intense smoking conditions are comparable to those found in conventional cigarettes (Table 2.1). This suggests that the efficiency of nicotine desorption or transfer from the tobacco material to aerosol or smoke is much higher for IQOS than for conventional cigarettes. In contrast, the nicotine levels in the aerosol of glo were reported to be about 40% of those reported for IQOS and 23% of those for reference cigarettes *(17)*. Other studies show similar differences between the two products (Table 2.1). These observations indicate the importance of systematic surveillance and reporting of nicotine content and emissions in HTPs. Research should be conducted on the implications of these differences for the abuse liability and toxicity of the products.

2.2.3 Other toxicants

HTP emissions generally contain lower concentrations of toxic chemicals than conventional cigarettes because of the lower temperature at which they operate, which is the main source of many toxicants in the smoke of conventional cigarettes. The levels of most of the harmful and potentially harmful constituents measured in HTP aerosol are lower than those in reference cigarette smoke *(1,2,18–22)*, with the exception of glycidol, which is found at higher levels *(23)*. Nevertheless, both independent and manufacturer-funded studies show that, even if the temperatures reached by HTPs are not sufficient for combustion, they are still sufficient for the formation of harmful chemicals. Davis et al. *(24)* reported that IQOS tobacco filler appears to char without ignition and that charring increased when the IQOS is not cleaned after each use. Some signs of combustion were also identified in another study *(3)*. Auer et al. *(11)* found that the aerosol released by IQOS contains elements from pyrolysis and thermogenic degradation that are the same harmful constituents of conventional cigarette smoke.

A study by BAT researchers showed that nicotine and some cigarette smoke compounds were released at between 100 °C and 200 °C as a result of evaporative transfer or initial thermal decomposition from the tobacco blend. It is important to note that tobacco heated to 200 °C can generate emissions for a substantially longer time than a burning cigarette. With increments of temperature, the levels of some analytes increase gradually: between 180 °C and 200 °C, the amounts of carbon monoxide (CO), those of crotonaldehyde and methyl ethyl ketone double, and that of formaldehyde triples; between 120 °C and 200 °C, that of acetaldehyde increases 15 times; between 160 °C and 200 °C, that of acetone doubles and that of propionaldehyde triples; and between 140 °C and 200 °C, that of butyraldehyde doubles. These chemicals can be formed by pyrolytic decomposition of carbohydrates and tobacco structural polymers. Tobacco-specific nitrosamines (TSNAs) were quantifiable, but there was no consistent difference at different temperatures *(25)*.

Humectants contribute mainly to the total particulate matter of aerosols generated by HTPs. Much higher levels of humectants (e.g. glycerol) were found in HTP aerosol than in conventional cigarette smoke *(4)*. Independent studies found that the content of glycerol generated from HTPs in the HCI regimen was approximately 360 µg/stick for IQOS, 520 µg/stick for glo and 5900 µg/stick for Ploom TECH, as compared with 18 µg/cigarette from conventional cigarettes. HTPs generated fewer chemical compounds than conventional cigarettes, except for water, propylene glycol, glycerol and acetol *(5)*. The total particulate matter of a prototype HTP, THS 2.2, was composed mainly of glycerine (56.3%) and propylene glycol.

Although glycerine and propylene glycol may be safe for humans, they were found to produce harmful products when heated, including acrolein

(a strong airway irritant) and glycidol (a carcinogen), in studies of IQOS and e-cigarette emissions. These carbonyls have been reported as by-products of propylene glycol and glycerine thermal decomposition in e-cigarettes. As the HTP stick contains a large amount of glycerine, its degradation by-products were present in IQOS emissions *(26)*.

Carbon monoxide

CO was found as a product of incomplete combustion in in HTPs emissions in both independent and tobacco industry studies.

Industry research

Forster et al. *(1)* reported that CO yields were below the reporting limits at temperatures < 180 °C, representing a reduction of > 99% from those in conventional cigarette emissions. Above this temperature (to 200 °C), the CO level increased with increasing temperature. The CO yield from an HTP was below the limit of detection, whereas that from a conventional cigarette was 31.2 mg/cigarette *(2)*. No correlation was found between the presence of flavours and CO levels: both the flavoured and unflavoured HTPs generated ≤ 0.22 mg/stick, while conventional cigarettes generated 32.8 mg/cigarette *(23)*.

Academic research

CO was found in IQOS aerosol *(11)*, even though the temperature was only 330 °C, as compared with 684 °C in smoke from a conventional cigarette, but at lower levels than in mainstream smoke of conventional cigarettes. The concentration of CO emitted by IQOS, measured with the official WHO TobLabNet method, was approximately one hundredth of that emitted by conventional cigarettes *(8)*. Similar results were found with the ISO and HCI regimes, THS 2.2 releasing 90% less CO than conventional cigarettes *(3)*.

Tobacco-specific nitrosamines

Manufacturers of HTPs claim that the levels of tobacco-specific nitrosamines (TSNA) are lower in HTPs. Several studies reported considerably lower levels of TSNA in e-liquids and in HTPs than in conventional cigarettes *(29)*. Independent studies reported less tar and more TSNA than the manufacturers did *(17)*.

Industry research

PMI and BAT reported a mean reduction of 90% in the levels of TSNAs in HTP aerosols as compared with mainstream smoke of conventional cigarettes. They claimed that the reduction is due to lower evaporating transfer and a lower working temperature, which reduce pyrosynthesis and pyrorelease *(27)*. TSNA

emissions from a prototype HTP, THP1.0, were reported to be reduced by 80–98% from those in the smoke of conventional cigarettes *(1)*.

Academic research

Studies by non-industry researchers have also demonstrated lower levels of TSNA in the aerosol of HTPs than in smoke from conventional cigarettes *(30,31)*, the reductions of individual TSNA ranging from 8–22 times per puff in the HTP aerosol as compared with cigarette smoke; the reduction in HTP HeatStick aerosol was 7–17 times. TSNA yields per puff in IQOS aerosol were an order of magnitude lower than those in the smoke of conventional cigarettes but an order of magnitude higher than those in the aerosol of e-cigarettes *(32,33)*. Other independent studies confirmed that the levels of TSNA in tobacco material and mainstream smoke of IQOS were significantly lower than those of conventional cigarettes, although the transfer rates of *N*′-nitrosonornicotine (NNN), *N*′nitrosoanatabine (NAT) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in IQOS were slightly higher than those in conventional cigarettes *(8,13)*. Ratajczak et al. *(28)* reported that the concentration of TSNAs was one fifth that of conventional cigarettes. Li et al. *(3)* found that > 92% less NNN, NNK and NAT was released than from conventional cigarettes under both the ISO and the HCI regimen, and 72% less *N*'-nitrosoanabasine than 3R4F was released under both regimens.

Carbonyl compounds

HTPs emit toxic carbonyl compounds generated from thermal decomposition, and their levels increase gradually with temperature rising from 160 °C or 180 °C to 200 °C *(8,25)*. Formaldehyde, acetaldehyde, acrolein and other aldehydes form during heating of mixtures of glycerol and propylene glycol in e-cigarettes *(34,35)*. As these humectants are also present in HTPs, aldehydes may be derived from them *(36)*. In most cases, however, the levels are lower than in conventional cigarette smoke, according to both manufacturer-funded and independent studies.

Industry research

Aldehydes accounted for 41% of the total estimated concentration of constituents in THP1.0 emissions *(37)*. Crooks et al. *(23)* measured the levels of some aldehydes in aerosol from flavoured and unflavoured HTPs and in conventional cigarette smoke. They found formaldehyde at 1.52 µg/stick in aerosols from flavoured and 1.79 µg/stick in those from unflavoured HTPs and at 66.67 µg/stick in smoke from conventional cigarettes; and acetaldehyde at 35.48 µg/stick in aerosols from flavoured and 35.54 µg/stick in those from unflavoured HTPs and at 2164.73 µg/stick in smoke from conventional cigarettes. The reduction in formaldehyde in HTP aerosols as compared with smoke from conventional

cigarettes was reported to be 90% *(2,18)*. The concentrations of formaldehyde (16.3 μg/m^3) and acetaldehyde (12.4 μg/m^3) fell within the range of the mean concentrations observed in residential and public environments *(19)*.

Academic research

Studies by non-industry researchers confirm the lower carbonyl production by IQOS than by conventional cigarettes, although it was higher than that from e-cigarettes *(26)*. The level of formaldehyde in HTP aerosols was 91.6% lower than in smoke from conventional cigarettes, and reductions of 84.9% were seen for acetaldehyde, 90.6% for acrolein, 89% for propionaldehyde and 95.3% for crotonaldehyde. At more intense puffing regimens, minimal differences in carbonyl emissions were observed between IQOS and conventional products, except that formaldehyde levels were increased three to four times over those with the HCI puffing regimen, from 6.4 to 17.1 μg/stick for regular IQOS. Carbonyl levels were higher in aerosols from HTPs than those from e-cigarettes *(38)*. Similar results were obtained by Ruprecht et al. *(39)*, who observed that the levels of aldehydes formed by use of IQOS were 2% higher than with conventional cigarettes for acrolein, 6% higher for acetaldehyde and 7% higher for formaldehyde; e-cigarettes generated only 1% of the amount of aldehydes generated by conventional cigarettes. Other authors observed that the yields of carbonyls were 80–96% lower than those from conventional cigarettes *(12,13,30,40,43)*.

Uchiyama et al. *(5)* compared acetaldehyde production by different HTP types under the HCI regimen and found that IQOS generated 210 μg/stick, glo™ generated 250 μg/stick and Ploom TECH 0.45 μg/stick, while conventional cigarettes generated 1300 μg/cigarette. Salman et al. *(41)* estimated reductions of 70% and 65% in the daily intake of formaldehyde and acetaldehyde, respectively, with use of IQOS instead of conventional cigarettes. Li et al. *(3)* observed reductions of 55.80% and 77.34% in formaldehyde and acetaldehyde, respectively, under the ISO regime.

Cyanidric formaldehyde can be formed from pyrolysis of the polymer filter in HTPs *(42)*. This thin plastic sheet melts during IQOS use, releasing formaldehyde cyanohydrin *(24)*.

Benzo[*a*]pyrene and other polycyclic aromatic hydrocarbons

Benzo[*a*]pyrene and other polycyclic aromatic hydrocarbons (PAH) are typical products of incomplete combustion. Their determination is important, as they are carcinogens *(13)*.

Industry research

Manufacturer-funded studies reported lower levels of PAH, including benzo[*a*]pyrene, in HTPs than in conventional cigarettes. The formation of PAH, aromatic amines, phenols and aldehydes was reduced by > 75% *(22)*, and acyclic, alicyclic and monocyclic aromatic hydrocarbons in HTP aerosol accounted for < 4%, as compared with 64% in mainstream smoke of conventional cigarettes *(37)*. Benzo[*a*]pyrene levels were very low in the aerosols of all products, in contrast to the yields found in the mainstream smoke of conventional cigarettes *(18)*.

Takahashi et al. *(2)* found < 0.531 ng benzo[*a*]pyrene in an HTP aerosol and 12.9 ng in conventional cigarette smoke, while Crooks et al. *(23)* found 0.44 ng/stick benzo[*a*]pyrene in the aerosol of flavoured HTPs, 0.41 ng/stick in that from unflavoured HTPs and 12.76 ng/stick in smoke from conventional cigarettes, indicating that the levels were not associated with the presence of flavours.

Pyrolysed menthol could be a precursor of benzo[*a*]pyrene in the smoke of a mentholated cigarette product, although no significant contribution of menthol to the yield of benzo[*a*]pyrene was observed in THS2.2 *(20)*.

Academic research

Auer et al. *(11)* found 0.8 ng/stick benzo[*a*]pyrene in HTP emissions and 20 ng/cigarette in smoke from conventional cigarettes; these levels are higher than those found in manufacturer-funded studies. HTP released higher levels of acenaphthene than conventional cigarettes. St Helen et al. *(12)* found levels similar to those in tobacco industry studies, with 0.736 ng/stick benzo[*a*]pyrene in HTP aerosols and 13.3 ng/stick in smoke from conventional cigarettes, indicating a reduction of 94%.

Other toxic chemicals

Most of the chemical constituents of the particulate phase of HTP aerosol and conventional cigarette smoke were oxygenated compounds, comprising 39% and 70% of the total estimated concentration of analytes in cigarette and HTP particulate phase, respectively. The levels of oxygenated compounds are higher in the HTP particulate phase probably because of the large amount of glycerine and other humectants *(43)*.

Industry research

Nitrogen-containing compounds. The levels of these compounds were 12% lower in HTP aerosols than in smoke from conventional cigarettes, accounting for 58% and 29% of the total estimated concentration of analytes in the cigarette and the HTP particulate phase, respectively *(43)*. The level of nitrogen oxide increased with time in conventional cigarette smoke but remained constant in HTP aerosol.

The levels found in HTP aerosol were 5.5–7.3% those of smoke from conventional cigarettes *(21)*.

Manufacturer-funded studies reported reductions of 25–50% in the levels of ammonia and some other toxicants in HTPs *(20)*. Ammonia was found at a level 88% lower than in conventional cigarette smoke in HTP emissions *(1)*. Crooks et al. *(23)* reported that the levels of ammonia, nitrogen oxides and *o*-cresol were higher in aerosol from flavoured than in that from unflavoured Neostik.

Metals. In one study, the level of mercury in HTP emissions was 69% lower than in cigarette mainstream smoke, while others reported reductions of 25–50% *(1,20)*. The levels of chromium, nickel and selenium were below the limits of detection in reference cigarette smoke *(2)*.

Volatile organic compounds. In some studies, the levels of certain volatile hydrocarbons in HTP emissions were 97–99% lower than in smoke from conventional cigarettes *(13,40)*. Industry researchers reported that the concentrations of Hoffmann list volatile compounds were significantly lower in the aerosol of prototype HTP product THP1.0 than in smoke from conventional cigarettes, with the level of toluene was reduced by 99% and that of 2-propanone by 91% *(37)*. After HTP use, the level of benzene in the aerosol was 0.93 μg/m^3, and that after e-cigarette use was lower. Toluene was not detectable in HTP aerosol but was present at 151.1 μg/m^3 after conventional cigarette use *(36)*.

Other chemicals. The levels of many constituents of HTP emissions were below the level of quantification or detection, except for formaldehyde, acetone and ammonia *(2)*. Aldehydes, ketones and heterocyclic compounds accounted for 41%, 32% and 10% of the total concentration of analytes, respectively. The level of 2-propanone was higher in the mainstream smoke of conventional cigarettes (152 μg/cigarette) than in HTP aerosol (13.3 μg/stick), whereas the levels of pyridine and dimethyl trisulfide in HTP aerosols were marginally higher *(37)*. Forster et al. *(1)* calculated a reduction of 96–99% in the levels of phenols (except for resorcinol, *p*-cresol and caffeic acid) and a 99% reduction in the levels of ethylene oxide and propylene oxide; however, acetoin and methylglyoxal were present at higher levels in HTP emissions than in conventional cigarette smoke.

Particulate matter. Manufacturer-funded studies found that the levels of particulate matter < 2.5 μm (PM2.5) in HTP emissions were 28 times lower than in conventional cigarette smoke *(19)*. The yield of total particulate matter from HTPs was approximately twice that of conventional cigarettes. The levels of water and humectants in total particulate matter were higher in HTPs than in conventional cigarettes: 90% (w/w) in HTP and 37% in conventional cigarettes *(2)*. PMI studies showed that the respirable fraction of particles is 90% lower in HTP aerosols than in conventional cigarette smoke *(44),* equivalent to the concentration in background air; however, the limits were below the lower working range of the methods *(45)*.

Academic research

Reactive oxygen species. Independent studies reported that the level of total reactive oxygen species was 85% lower in HTP emissions than in those of conventional cigarettes *(41)*. Emission of reactive oxygen species during use of IQOS can be harmful *(46)*.

Metals. Independent studies found lower levels of metals in HTP emissions than in cigarette smoke *(13,42)*. Ruprecht et al. *(39)* observed that use of mentholated IQOS is associated with higher metal concentrations than use of IQOS without menthol. They found metals such as aluminium, titanium, strontium, molybdenum, tin and antimony in IQOS that are not present in conventional cigarettes, and metals such as nickel, copper, zinc, lanthanum and lead in conventional cigarettes that are not detected in IQOS. One article reported an unusual case of criminal mercury poisoning with use of HTPs; its addition to a tobacco stick caused the victim to inhale vaporized mercury *(47)*.

Volatile organic compounds. More than 70 volatile compounds were detected in mainstream emissions of IQOS, including isoprene, acrylonitrile, cresols, benzene, phenol, naphthalene, acetaldehyde, propanal, acrolein, formaldehyde, 2-butanone, acetone, crotonaldehyde and quinoline *(26)*. All these compounds are considered potentially harmful by the FDA. Some studies, however, found that the levels of some volatile hydrocarbons were 97–99% lower in HTP aerosols than in smoke from conventional cigarettes *(13,40)*. No PAHs were found in IQOS side-stream aerosol *(42)*. Heated tobacco materials contained more types of volatile compounds than conventional cigarette emissions *(48)*.

Black carbon. Ruprecht et al. *(39)* found the highest black carbon concentrations in conventional cigarettes, with 78 μg/m^3 for organic compounds and 2.3 μg/m^3 for elemental carbon. Elemental carbon was not detectable during puffing of IQOS, while the levels of organic compounds were 2.81–3.89% of those in conventional cigarettes.

Other chemicals. Results similar to those of manufacturer-funded studies were obtained in an independent study, with 90% lower levels of most toxicants, except for carbonyls, ammonia and *N*'-nitrosoanabasine. The level of ammonia, in particular, was 63.4% lower with the HCI regimen than in conventional cigarette smoke *(3)*.

Particulate matter. The concentration of particles in the mainstream aerosol of IQOS was lower than that in emissions from e-cigarettes and conventional cigarettes *(49)*, and use of HTPs resulted in the lowest levels of fine particulate matter *(36)*. The concentrations of PM>0.1 and PM>0.3 were significant in aerosol from conventional cigarettes and that from IQOS (for PM>0.3) but were trivial in aerosol from e-cigarettes as compared with conventional cigarettes *(39)*. Other studies found that the level of particulates in emissions from e-cigarettes and HTPs was about 25% that in cigarette smoke. The diameter of most particles in IQOS

aerosol is < 1000 nm, which is considered safer than a lower mass. The respirable fraction of particles is higher in glo and conventional cigarette smoke *(50)*.

As these results show that the composition of IQOS HeatSticks is different from that of conventional cigarettes, including flavourings and additives, IQOS aerosol may contain other chemical constituents not present in tobacco smoke, which have not yet been investigated in untargeted analyses *(12)*.

2.3 Exposure and effects of HTPs in vitro and in laboratory animals

2.3.1 In-vitro studies

Industry research

Research groups at PMI and BAT have published several reports on the results of in-vitro toxicological studies with prototype HTPs that differed in the device and tobacco characteristics. Most reported substantially lower cytotoxicity of HTP aerosol than of the smoke of reference cigarettes.

PMI research. PMI published a series of papers on the cytotoxicity (measured in the neutral red uptake assay) and mutagenicity (*Salmonella* reverse mutation assay) of a prototype electrically heated cigarette smoking system puffed under ISO smoking conditions and one alternative puffing condition *(51–53)*. They reported that the aerosol from these devices was up to 40% less cytotoxic and up to 90% less mutagenic than the smoke of a reference 1R4F cigarette (comparisons based on total particulate matter yield). In a study published in 2012, PMI reported toxicological evaluation of the same prototype system with 25 additional smoking regimens that reflect human puffing behaviour *(54)*. While the overall biological activity of the HTPs tested was lower than that of a reference cigarette, increased smoking intensity led to substantial increases in cytotoxicity and nearly 36 times more bacterial mutagenicity than with HTP aerosols generated under low-intensity ISO conditions. They concluded that the increases were probably due to changes in the emissions of harmful constituents, suggesting that the results of ISO-based testing are not informative in terms of potential effects in humans.

PMI also reported on the biological effects of the aerosol from another HTP prototype, THS2.2. In one study, the ability of THS2.2 aerosol to inhibit monoamine oxidase activity was investigated, to assess the potential abuse liability of this product *(55)*. The authors reported significant inhibitory activity of a 3R4F reference cigarette aerosol but not by THS2.2. In another study, histology, cytotoxicity, secreted cytokines and chemokines, ciliary beating and genome-wide mRNA/miRNA profiles were assessed in human organotypic bronchial epithelial cultures at various times after exposure to THS2.2 aerosol or reference 3R4F cigarette smoke, with similar nicotine concentrations *(56)*. Cell fate, cell

proliferation, cell stress and inflammatory network models 4 h after exposure to THS2.2 aerosol were only 7.6% of those observed after exposure to 3R4F smoke. No morphological changes were reported after exposure to THS2.2 aerosol, even at a nicotine concentration three times that in 3R4F smoke. Similar studies were conducted with another HTP prototype, CHTP1.2, in human organotypic cultures derived from buccal and gingival epithelia *(57)*, small airway and nasal epithelial cells *(58)* and endothelial cells *(59)*. Cells were exposed acutely (28 min) or repeatedly (28 min/day for 3 days) to CHTP1.2 aerosol or to 3R4F smoke. The authors reported lack of cytotoxicity, fewer pathophysiological alterations and less change in toxicological and inflammatory biomarkers after exposure to CHTP1.2 than after exposure to 3R4F smoke. Alterations in mRNA expression were, however, detected in small airway and nasal epithelial cultures exposed to CHTP1.2 aerosol.

BAT research. BAT researchers assessed nicotine delivery and cytotoxicity in H292 human bronchial epithelial cells of aerosols from IQOS and glo in comparison with tobacco smoke from 3R4F cigarettes; all products were smoked under HCI *(60)*. The authors reported more nicotine delivery but less cytotoxicity of HTPs than 3R4F cigarettes. They concluded that there was no difference between the HTPs; however, the figures in the report suggest that IQOS was more cytotoxic than the glo product. In another study, RNA sequencing was used to compare transcriptomic perturbations after acute exposure of 3D airway tissue to the aerosols of the same products *(61)*. Differential expression of 115 RNAs was reported with IQOS and of two RNAs with the glo product as compared with air, while 2809 RNAs were differentially expressed in response to 3R4F. Examination of the data and charts in the report suggests that the results depended on the thresholds set for data analyses (i.e. *P* values and fold change in expression) and that inflammatory and xenobiotic metabolizing gene expression may be affected by the HTPs tested. A subsequent study was conducted to complement these two assessments and to determine the effect of flavours on in-vitro responses to Neostik *(62)*. The authors concluded that the addition of flavours does not change the in-vitro baseline responses to unflavoured Neostik.

Academic research

Leigh et al. *(63)* used an in-vitro model of an air–liquid interface with human bronchial epithelial cells (H292) to investigate the toxic effects of inhaling emissions from IQOS and from e-cigarettes and conventional cigarettes. The number of puffs of each product was adjusted to achieve similar nicotine delivery to the cells, and cytotoxicity was measured in the neutral red uptake and trypan blue assays. The cytotoxicity of IQOS in the neutral red assay, but not in the trypan blue assay, was higher than that in air controls and lower than that with conventional cigarette smoke. In another study, the cytotoxicity of

IQOS aerosols was compared with that of smoke from Marlboro Red and 3R4F reference cigarettes *(64)* in three assays with eight different cell types. The results with transformed mouse NIH/3T3 fibroblasts were similar to those previously reported by PMI *(51–53)*; but assessments in other types of cells and with higher concentrations of aerosols showed comparable depression of mitochondrial and lysosomal activity by IOQS and cigarette smoke solutions. No adjustment was made in this study, however, for the levels of nicotine in the different products, and the puffing regimen used was described in insufficient detail.

In another study, the effect of exposure of culture medium to IQOS aerosol, e-cigarette aerosol and conventional cigarette smoke was studied on the viability and differentiation of 3T3-L1 pre-adipocytes to beige adipocytes *(65)*. The authors concluded that exposure to IQOS had limited or no effect as compared with air. Examination of the data in this report shows that expression of the adipogenic markers Ppar-γ and Resistin was statistically significantly decreased in IQOS-treated cells at the end of differentiation (10 days), an effect similar to that observed in cigarette smoke-treated cells. It was noted that the authors of this report have a history of industry-linked research funding.

2.3.2 Studies in laboratory animals

Industry research

Most reports on the effects of HTPs in laboratory animals have been published by tobacco industry research groups, namely PMI and Japan Tobacco, which generally report substantially less toxicity and carcinogenicity with HTP aerosols than with the smoke of reference tobacco cigarettes.

Japan Tobacco research. Two studies have been published on the effects of a prototype "heated" cigarette on dermal tumorigenicity and inhalation toxicity in mouse models. In the first study, the effect of HTP on dermal tumour promotion in female SENCAR mice was studied after topical application of 7,12-dimethylbenz[*a*]anthracene as a tumour initiator *(66)*. Condensates of HTP aerosol or cigarette smoke (3R4F cigarettes) generated under the modified HCI smoking regimen were applied repeatedly for 30 weeks at five doses up to 30 mg tar/application. At ≤ 15 mg tar, animals treated with HTP aerosol developed neoplasms with a longer latency and lower incidence and multiplicity and lower incidences of inflammation and squamous epithelial hyperplasia than animals treated with cigarette smoke. At the end of treatment, however, these effects were more prevalent than in untreated animals. At doses ≥ 22.5 mg of tar, the differences between HTP aerosol and 3R4F condensate were less clear.

In the second study, the same HTP was investigated in nose-only 5-week and 13-week inhalation studies *(67)*. Lesser histopathological changes were found in the respiratory tracts of HTP-treated animals (respiratory epithelial hyperplasia in the nasal cavity and accumulation of pigmented macrophages

in alveoli) and less pulmonary inflammation (as measured by the percentage of neutrophils and activity of γ-glutamyl transpeptidase, alkaline phosphatase and lactic dehydrogenase in bronchoalveolar lavage fluids) than in cigarette smoke-treated animals. HTP treatment nevertheless had significant effects on the histopathological outcomes as compared with air treatment, as HTP-treated animals showed a 100% incidence of hyperplasia and hyperkeratosis in the larynx and epiglottis at all doses tested in both treatment regimens and substantial dose-related increases (≤ 100%) in the incidence of alterations in nasal epithelium, ventral pouch and lung tissues.

PMI research. In a 90-day study in rats exposed by inhalation through the nose only to the same or twice the nicotine concentration in the inhalation zone, CHTP1.2 aerosol resulted in significantly less exposure to harmful constituents and induced less respiratory tract irritation and systemic and pathological effects than 3R4F cigarettes *(68)*. The toxicology arm of this study, which included transcriptomics, proteomics and lipidomics analyses *(69)*, showed much weaker inflammatory and cellular stress responses in the respiratory nasal epithelium and lungs with CHTP1.2 aerosol than with 3R4F smoke. Many of these effects showed dose–response relations. CHTP1.2 aerosol also induced lower lipid concentrations in the serum of exposed animals.

PMI researchers also conducted 6-month exposure studies in the ApoE-/- mouse model to investigate the effects of THS 2.2 and CHTP1.2 on the cardiorespiratory system. One report, a systems toxicology approach with a combination of physiology, histology and molecular measurements, demonstrated a lower impact of 3R4F on the cardiorespiratory system, including little to no lung inflammation or emphysematous changes and reduced atherosclerotic plaque formation *(70)*. In another study, cardiovascular effects were investigated in echocardiographic, histopathological, immunohistochemical and transcriptomics analyses. The authors reported that continuous exposure to HTP aerosols did not affect atherosclerosis progression, heart function, left ventricular structure or the cardiovascular transcriptome *(71)*. Review of the data in these publications reveals, however, consistent increases in many of the outcome measures in animals treated with HTPs as compared with sham controls, although the increases did not reach statistical significance.

Academic research

In a study to investigate whether exposure to IQOS aerosol affects vascular endothelial function, which is known to be impaired by conventional cigarette smoke *(72)*, rats were exposed acutely through the nose only to IQOS aerosol generated by single HeatSticks, to mainstream smoke from single Marlboro Red cigarettes or to clean air. Arterial flow-mediated dilation, a measure of vascular endothelial function, was measured before and after exposure. The authors

reported that flow-mediated dilation was impaired to comparable degrees by exposure to IQOS aerosol and to conventional cigarette smoke, and no effect was observed with clean air. Serum nicotine and cotinine levels were approximately 4.5 times higher in rats exposed to IQOS than in those exposed to cigarettes, even though the IQOS aerosol contained less nicotine than cigarette smoke. Brief exposure regimens that resulted in similar serum nicotine levels in groups exposed to IQOS and to cigarettes induced comparably impaired flow-mediated dilation. The authors concluded that IQOS use does not necessarily avoid the adverse cardiovascular effects of smoking cigarettes.

2.4 Exposure of humans to toxicants in HTPs and implications for health

2.4.1 Product use and topography

Davis et al. *(24)* evaluated the performance of IQOS under five conditions with two different protocols for cleaning devices. HeatSticks were inspected before and after use to determine any signs of tobacco material pyrolysis (charring) and melting of the polymer-film filter and to assess the effects of cleaning on charring. The results showed charring of the tobacco material after use, and gas chromatography–mass spectrometry headspace analysis of the polymer-film filter showed release of highly toxic formaldehyde cyanohydrin at 90 °C (a lower temperature than during normal IQOS usage). Increases in charring and formaldehyde cyanohydrin emissions were observed when the device was not cleaned between consecutive uses of HeatSticks. The authors concluded that limitations of the device (i.e. short tobacco sticks and shutting of the device after a certain number of puffs) may contribute to decreases in inter-puff intervals, potentially increasing users' intake of nicotine and other harmful chemicals.

Some industry research acknowledges the potential modifying effects of use topography and device characteristics on the exposure of human users. For example, researchers at BAT investigated the impact of puffing parameters on the volume of emissions *(73)* and found that the choice of puffing parameters affects the volume, with significant differences among types of HTP. They suggested that detailed real-world HTP puffing topography should be studied in order to identify the most appropriate puffing parameters for laboratory testing. In another study, PMI researchers presented a modelling approach, named "nicotine bridging", to estimate human exposure to HTP emissions *(74)*. The approach involves determination of harmful constituents and in-vitro toxicity parameter-to-nicotine regressions for multiple machine-smoking protocols; the distribution of nicotine uptake is determined from 24-h excretion of nicotine metabolites in a clinical study. The approach was illustrated with data for a prototype HTP *(54)* that showed less exposure of HTP users than conventional cigarette smokers,

with little or no overlap between the distribution curves. The authors proposed that the method could be used to extrapolate exposure distributions to smoke constituents for which there are no specific biomarkers. As this method relies on machine-smoking protocols that are not representative of human exposure, extrapolation may not be justified, and additional independent research is required.

2.4.2 Biomarkers of exposure and effect

Industry research

As for the studies with cell cultures and animal models, many of the reports on biomarkers are provided by industry, particularly PMI and BAT.

PMI research. PMI researchers reported on biomarkers of exposure and effect in smokers who switched to prototype HTPs, some of which have been tested in vitro and in laboratory animals, as summarized above. Prototype HTPs were developed and tested by PMI for more than a decade before the release of IQOS and are apparently precursors of contemporary HTPs *(75)*. A series of publications in 2012 reported on randomized, controlled, open-label, parallel-group, single-centre studies on the use of type-K prototype HTPs (EHCSS-K3 and EHCSS-K6). In a study in the United Kingdom, biomarkers of exposure to nine cigarette smoke constituents and urinary mutagenicity were measured in 160 male and female smokers of Marlboro cigarettes who switched to EHCSS-K3 or EHCSS-K6 for 8 days *(76)*. Statistically significant mean decreases between baseline and day 8 ($P \leq 0.05$) were found for all biomarker measures, with reductions in urinary mutagenicity in smokers assigned to both HTPs. In a similar study in the Republic of Korea, biomarkers of exposure to 12 selected constituents and urinary mutagenicity were measured in 72 male and female subjects who smoked low-yield Lark One cigarettes at baseline and switched to EHCSS-K3 for 8 days *(77)*. Statistically significant reductions in urinary mutagenicity and in 10 of 12 constituent biomarkers were found between baseline and day 8 for the EHCSS-K3 group. In a study in Japan, the same measurements were made in 128 male and female participants who smoked Marlboro cigarettes at baseline and switched to EHCSS-K3 or EHCSS-K6 for 8 days *(78)*. The mean decreases in all constituents and in urinary mutagenicity between baseline and day 8 were statistically significant for participants who switched to HTPs ($P \leq 0.05$). An additional report on Japanese smokers presented data on biomarkers of exposure to 12 constituents, urinary mutagenicity and serum club cell 16-kDa protein (CC16) in 102 male and female subjects who smoked Marlboro Ultra Light menthol cigarettes at baseline and switched to the menthol version of the HTP prototype EHCSS-K6(M) for 6 days *(79)*. Statistically significant decreases in exposure to 10 of the 12 cigarette smoke constituents and in urinary mutagenicity were found, as in the previous studies; however, serum CC16, an indicator of lung

epithelial injury, was unchanged in all groups, including that assigned to use no product. Despite the reductions in exposure measures after switching to HTPs, the levels of biomarkers in all these studies remained substantially higher than in the group assigned to stop smoking and not to use any product (Table 2.2). Another PMI study, in Polish smokers, included measurement of a broad panel of biomarkers associated with cardiovascular risk, in addition to biomarkers of exposure *(80)*. In this study, 316 male and female smokers were randomized to continue smoking conventional cigarettes or to switch to smoking the EHCSS-K6 prototype HTP for 1 month. Most of the cardiovascular biomarkers did not change after use of the HTP device, although the biomarkers of exposure decreased, as in the previous studies. A substantial mean increase was seen in high-density lipoprotein cholesterol, from a baseline median of 36.7 ng/mL (95% CI 2.1, 3410) to 59.0 ng/mL (95% CI 2.1, 4535), after 1 month of using EHCSS-K6; however, reductions in red blood cell count, haemoglobin and haematocrit were observed in the EHCSS-K6 group.

Table 2.2. Reported levels of biomarkers of exposure in smokers who switched to HTPs and in smokers assigned to continuous smoking or abstinence from all tobacco products

Biomarker of exposure [source]	HTP prototype (duration of use)	Mean ± SD level after switching to HTP	Comparison (↑, higher, or ↓, lower) with biomarker levels in participants assigned to other conditions		Reference
			HTP vs continuous smoking	HTP vs abstinence	
SPMA, µg/24 h [benzene]	EHCSS-K3 (8 days)	1.26 ± 1.26	↓80%	↑473%	*66*
	EHCSS-K3 (8 days)	1.63 ± 0.55	↓66%	↑19%	*77*
	EHCSS-K3 (8 days)	0.48 ± 0.28	↓78%	↑41%	*68*
	EHCSS-K6 (8 days)	0.86 ± 0.81	↓86%	↑291%	*66*
	EHCSS-K6 (8 days)	0.57 ± 0.57	↓75%	↑68%	*68*
	EHCSS-K6^{M} (6 days)	0.35 ± 0.13	↓85%	↓34%	*69*
MHBMA, µg/24 h [1,3-butadiene]	EHCSS-K3 (8 days)	2.63 ± 2.78	↓49%	↑874%	*66*
	EHCSS-K3 (8 days)	0.59 ± 0.58	↓75%	↑111%	*67*
	EHCSS-K3 (8 days)	0.66 ± 0.69	↓57%	↑50%	*68*
	EHCSS-K6 (8 days)	1.54 ± 1.52	↓70%	↑470%	*66*
	EHCSS-K6 (8 days)	0.74 ± 0.56	↓51%	↑68%	*68*
	EHCSS-K6^{M} (6 days)	0.61 ± 1.06	↓58%	↑69%	*69*
3-HPMA, mg/24 h [acrolein]	EHCSS-K3 (8 days)	1.15 ± 0.74	↓37%	↑140%	*66*
	EHCSS-K3 (8 days)	2.41 ± 0.67	↓18%	↑44%	*67*
	EHCSS-K3 (8 days)	1.01 ± 0.36	↓26%	↑110%	*68*
	EHCSS-K6 (8 days)	1.28 ± 0.87	↓30%	↑167%	*66*
	EHCSS-K6 (8 days)	1.09 ± 0.51	↓20%	↓127%	*68*
	EHCSS-K6^{M} (6 days)	0.83 ± 0.32	↓30%	↑110%	*69*
3-HMPMA, mg/24 h [crotonaldehyde]	EHCSS-K3 (8 days)	2.59 ± 1.90	↓50%	↑49%	*66*
	EHCSS-K3 (8 days)	1.99 ± 1.07	↓18%	↑20%	*67*
	EHCSS-K3 (8 days)	0.61 ± 0.17	↓52%	↑30%	*68*
	EHCSS-K6 (8 days)	2.62 ± 1.29	↓49%	↑51%	*66*
	EHCSS-K6 (8 days)	0.63 ± 0.15	↓51%	↑34%	*68*
	EHCSS-K6^{M} (6 days)	0.19 ± 0.08	↓85%	↓60%	*69*

Biomarker of exposure [source]	HTP prototype (duration of use)	Mean ± SD level after switching to HTP	Comparison (↑, higher, or ↓, lower) with biomarker levels in participants assigned to other conditions		Reference
			HTP vs continuous smoking	HTP vs abstinence	
Total NNAL, ng/24 h [NNK]	EHCSS-K3 (8 days)	104.3 ± 55.3	↓65%	↑76%	*66*
	EHCSS-K3 (8 days)	80.4 ± 59.3	↓59%	↑78%	*67*
	EHCSS-K3 (8 days)	102 ± 48	↓53%	↑23%	*68*
	EHCSS-K6 (8 days)	100.6 ± 68.8	↓66%	↑70%	*66*
	EHCSS-K6 (8 days)	100 ± 65	↓54%	↑20%	*68*
	EHCSS-K6^{M} (6 days)	95 ± 53	↓49%	↑19%	*69*
1-HOP, ng/24 h [pyrene, PAH]	EHCSS-K3 (8 days)	73.1 ± 30.4	↓60%	↓3%	*66*
	EHCSS-K3 (8 days)	143.62 ± 76.08	↓40%	↑13%	*67*
	EHCSS-K3 (8 days)	59.0 ± 35.3	↓56%	↑40%	*68*
	EHCSS-K6 (8 days)	71.9 ± 38.8	↓60%	↓4%	*66*
	EHCSS-K6 (8 days)	56.0 ± 28.4	↓59%	↑33%	*68*
	EHCSS-K6^{M} (6 days)	38.4 ± 22.7	↓64%	↑2%	*69*

1-HOP: 1-hydroxypyrene; 3-HPMA: 3-hydroxypropyl mercapturic acid; MHBMA: monohydroxybutenyl mercapturic acid; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; SPMA: S-phenylmercapturic acid.

PMI published a separate series of reports on studies in Polish smokers who switched to prototype HTPs. In one study, harmful exposures were assessed in 112 male and female adult smokers who switched to a prototype carbon-heated tobacco product, MD2-E7, for 5 days, continued smoking or abstained *(81)*. Puffing topography during HTP use was also studied. Smoking intensity and nicotine intake increased after the switch to the test HTP; however, despite the more intense puffing topography, switching to the prototype HTP decreased all the measured biomarkers of exposure and urinary mutagenicity, consistent with the previous reports. In a study of smokers who switched to the THS 2.1 prototype for 5 days, puff duration and frequency increased over the baseline patterns of smoking conventional cigarettes, and use of HTP tobacco sticks increased by 27% during the study period *(82)*. The total puff volume returned to baseline at the end of the study, however, and the mean exposure to nicotine was comparable to that at baseline. Increased product consumption and total puff volume were also observed in a larger study of the THS 2.2 prototype *(83)*. The average puff duration was about 32% longer, the total puff duration was about 37% longer, and puff frequency was about 32% higher on day 4 than smoking patterns for conventional cigarettes at baseline. While the authors claimed that there was no change in nicotine intake, review of the data reveals an approximately 23% increase in nicotine biomarkers (total nicotine equivalents) between baseline and day 4. Although reductions in exposure to harmful constituents were observed consistently in these studies, the higher-intensity HTP puffing topography indicates that additional, longer studies are necessary to accurately assess reductions in the exposure to toxicants of smokers who switch to HTPs.

A longer study of 984 adult smokers in the USA has been reported *(84)*. The participants were randomized to switch to a THS2.2 device or to continue

smoking for 6 months, and changes in a panel of biomarkers of exposure and effect were assessed. Reductions in biomarkers of exposure and in four biomarkers of effect (high-density lipoprotein cholesterol, white blood cell count, forced expiratory volume in 1 s as percentage predicted and carboxyhaemoglobin) were reported in smokers who switched as compared with those who continued smoking. Approximately 30% of smokers assigned to the HTP became dual users of conventional cigarettes and HTPs. In the group who predominantly used HTPs (average use, 16.5 sticks and two conventional cigarettes per day), the reductions in biomarkers of exposure ranged from 16% to 49% of the baseline smoking level, which were not as substantial as in previous, shorter switching studies. While some differences in the study procedures could have contributed to the lesser impact of HTP switching, longitudinal adaptations in HTP puffing topography could have played a role. The report did not provide information on product consumption or intensity of use of the test HTP.

BAT research. BAT researchers reported the results of a randomized, controlled study in Japan on switching to two commercial HTPs, glo and IQOS, for 5 days *(85)*. The 180 Japanese smokers were randomized to either continue smoking conventional cigarettes, switch to glo (mentholated or non-mentholated), switch to a non-mentholated IQOS or abstinence. As in the PMI studies, switching to HTPs resulted in significant decreases in urinary biomarkers of exposure and exhaled CO, as compared with baseline smoking. The reductions were similar for the two HTPs. An increase in HTP consumption was observed during the study; however, a similar increase was seen in consumption of tobacco cigarettes, which the authors attributed to the typical escalating product use seen in confinement studies.

BAT has been conducting another long-term randomized, multi-centre, controlled clinical switching study since March 2018 *(86)*. Up to 280 smokers were randomized to switching to a commercially available HTP for 1 year or to continuing smoking. In addition, up to 190 participants who wished to quit smoking were enrolled in a smoking cessation arm, and 40 never smokers served as a control group. Biomarkers of exposure and effect to toxicants are being assessed, and the changes will be compared with those in the smoking cessation and never smoker cohorts.

Japan Tobacco. In 2014, Japan Tobacco researchers reported on a controlled, semi-randomized, open-label, residential clinical study of changes in levels of biomarkers of exposure to tobacco constituents in healthy Japanese male smokers who switched to a prototype HTP *(87)*. A total of 70 smokers were enrolled and randomized to either an HTP or continued smoking for four consecutive weeks. As in the studies by PMI and BAT researchers, measured urinary biomarkers of exposure and urinary mutagenicity were significantly reduced in the HTP group.

Academic research

Little independent research on the exposure of HTP users has been published. A randomized, cross-over laboratory behavioural trial of use of IQOS was conducted in Belgium *(88)*, in which 30 participants were randomized to use of conventional cigarettes, e-cigarettes or IQOS for 5 min. Using an IQOS resulted in a small but reproducible increase in exhaled CO (0.3 ppm), although the level was lower than that observed after smoking a conventional cigarette (4.7 ppm). A similar randomized cross-over study was conducted in Italy by academic researchers with a history of tobacco industry-related funding *(30)*. A total of 12 healthy smokers were recruited, who used IQOS in the clinic (10 puffs, two sessions separated by 5 min) and provided exhaled CO samples at several times after the first puff of the first puffing session. No increase in exhaled CO was reported after use of IQOS. In a study in the USA, nicotine delivery and exhaled CO were measured in smokers of IQOS, JUUL e-cigarettes and conventional cigarettes *(89)*. The researchers recruited 18 smokers with no experience of IQOS or JUUL to complete a within-subject, laboratory study of controlled (10 puffs, ~30-s inter-puff interval) and ad-libitum (90 min) use of the test products or their own brand of conventional cigarettes. The amount of exhaled CO did not increase after use of IQOS, while the mean plasma nicotine increased significantly, from 2.1 (0.2) ng/mL to 12.7 (6.2) ng/mL after 10 puffs and to 11.3 (8.0) ng/mL after use ad libitum. The increase in plasma nicotine was about half that after smoking conventional cigarettes.

2.4.3 Passive exposure

Non-industry researchers have conducted studies of the potential impact of passive exposure to HTP emissions. In a study of particle size distribution, the profiles of exposure to submicron particles (5.6–560 nm) in conventional cigarettes and in IQOS were evaluated to estimate their potential deposition in the human respiratory system *(90)*. IQOS aerosol contained approximately four times lower amounts of such particles than the smoke of conventional cigarettes, and the particles in the IQOS aerosol dissipated rapidly; however, approximately half of such particles are small enough to reach the alveolar region upon inhalation. In a follow-up modelling study, the same group estimated the deposition of ultrafine particles from IQOS, e-cigarettes and conventional cigarettes in the respiratory tract of people of different ages in a multiple-path particle dosimetry model *(91)*. IQOS delivered significantly lower doses of second-hand particles than conventional cigarettes, but the doses were 50–110% higher than those from e-cigarettes, suggesting that non-users may have meaningful second-hand exposure. In the same study, 60–80% of the particles deposited in the head region of a 3-month-old infant measured < 100 nm, suggesting that they could be translocated to the brain via the olfactory bulb. In another study,

the concentrations of aerosol particles, carbonyl and nicotine were analysed in a model chamber during use of an unidentified HTP *(19)*. Use of the HTP resulted in statistically significant increases in the amounts of several analytes, including nicotine, acetaldehyde and PM2.5, and in particle number as compared with background measurements. As in the previous study, the authors reported that HTP particles dissipated or evaporated within seconds and that the levels of particles and individual constituents were significantly lower than in smoke from conventional cigarettes under the same conditions. The authors concluded that intensive use of HTPs in a confined space with limited ventilation can substantially increase the exposure of bystanders to second-hand aerosol emissions.

In a study in Germany, particle size and concentrations were also measured to compare potential passive exposure due to use of IQOS, e-cigarettes and conventional tobacco cigarettes in cars *(92)*. The results showed that use of an IQOS had almost no effect on the mean concentration of fine particles (> 300 nm) or on the PM2.5 concentration in the interior of the car, but the concentration of smaller particles (25–300 nm) increased in all vehicles. The nicotine concentrations obtained from IQOS and e-cigarette use were comparable and were both lower than those from conventional cigarette smoking. In a more comprehensive chemical analysis of IQOS emissions in the context of second-hand exposures, the HCI smoking regimen was used to generate IQOS aerosol in an environmental chamber, and 33 volatile organic compounds were analysed, including aldehydes and nitrogenated aromatic species, in mainstream and side-stream emissions *(26)*. As in the studies described above, the yields from IQOS were substantially lower than those from conventional cigarettes and sometimes higher than those from e-cigarettes. Acrolein at > 0.35 μg/m^3 was identified as an exposure of potential concern.

Passive exposure from HTP use has also been studied in population-based research in Japan. In one study, the weighted prevalence of HTP use in indoor public spaces was estimated from nationally representative data in the International Tobacco Control Japan Survey (February–March 2018) *(93)*. It was found that 15.6% of current tobacco users in Japan reported using HTPs in indoor public spaces. In a survey of perceived symptoms due to exposure to second-hand HTP aerosol *(94)*, 8240 individuals aged 15–69 years were followed up between 2015 and 2017 in a longitudinal Internet survey. Of the respondents who reported having been exposed to second-hand HTP aerosol, 37% reported having experienced at least one symptom as a result. The most common symptoms were generally feeling ill, eye discomfort and sore throat. Nearly half of never smokers who had been exposed to second-hand HTP aerosol reported at least one symptom.

In an industry study of second-hand emissions from a prototype HTP in simulated "office" and "hospitality" environments with different baseline indoor

air quality *(47)*, smoking an HTP under ISO conditions gave significantly lower yields of many constituents than smoking a Marlboro cigarette: the levels of 24 of 29 smoke constituents were reduced by a mean of > 90%, and the concentrations of five smoke constituents were reduced by a mean of 80–90%. Nicotine emissions were on average 97% lower from HTPs than from smoking Marlboro cigarettes, and the total number of respirable suspended particles was reduced by 90%. These results are generally consistent with those of non-industry research, which show that HTPs are a weaker source of indoor pollution than conventional cigarettes. Their impact on indoor air quality and on passive exposures is, however, not negligible and is not well understood.

2.4.4 Impact on health outcomes

Little research has been conducted on exposure to and effects of HTPs in toxicological models or human participants, partly because extensive marketing and use of these products is relatively recent. Assessment of the health implications of HTP use is therefore limited, and the available data should be interpreted with caution.

The apparent reduction in exposure of smokers who switch to HTPs to various emissions of traditional smoked products is an important but not sufficient factor in assessing the health effects of HTP use. Highly efficient nicotine intake from HTPs is an emerging concern, and particular attention should be paid to the potential effects in vulnerable populations, such as individuals with pre-existing conditions, pregnant women and young people.

Nicotine intake. Nicotine is a powerful, addictive chemical and the main driver of users' exposure to the toxic and carcinogenic constituents present in tobacco products. Emerging indications from studies in vitro and in laboratory animals and humans that more nicotine may be absorbed from HTPs than from cigarette smoke raise concern about the potentially high abuse liability of these products. In addition, nicotine is an important reproductive and neurobehavioural toxicant and contributes to mortality from cardiovascular diseases. Such effects are expected to be seen in HTP users.

Cardiovascular disease. The evidence that many cardiovascular biomarkers are not reduced in smokers who switch to HTPs *(80,95)* suggests that HTPs may represent a similar risk for cardiovascular disease as smoking. While the reasons are not clear at this time, elevated levels of certain chemical constituents in HTPs could play a role. These observations suggest that switching to HTPs is not likely to reduce the risk of cardiovascular morbidity and mortality associated with tobacco use.

Chronic respiratory disease. Although some research suggests relief of respiratory symptoms in smokers with chronic obstructive pulmonary disease who switch to HTPs *(96)*, other studies and expert groups have raised concern about the association between e-cigarette use and respiratory diseases *(97–99)*.

HTPs contain higher levels of volatile respiratory toxicants than e-cigarettes (Table 2.2). Furthermore, data from studies in laboratory animals suggest an impact of HTP exposure on respiratory organs *(67)* and the expression of RNAs associated with pulmonary response to injury *(61)*. An industry trial showed no reduction in the levels of a biomarker of lung epithelial injury (CC16) in smokers who switched to HTPs *(78)*. Thus, addicted adult smokers who switch to HTPs may not reduce their risk of chronic respiratory disease associated with tobacco use, and the use of these products by non-smokers may increase their risk of pulmonary disorder, particularly if they have other health conditions.

Pregnant women and children. Given the adverse effect of nicotine on development in utero and on birth outcomes, such as impaired cardiorespiratory and pulmonary function in infants, and the negative cognitive and neurobehavioural effects of exposure to nicotine during adolescence, use of HTPs by pregnant women and children is of particular concern.

The above considerations are based on knowledge of the effects associated with specific constituents reported to be present in HTPs and indirect evidence from in-vitro, in-vivo and biomarker studies on HTPs. There are virtually no studies in which the association between HTPs and health outcomes was studied directly. The few relevant studies are summarized below.

Health effects in young people. A large survey was conducted in the Republic of Korea to evaluate the effects of cigarettes, HTPs and e-cigarettes on the prevalence of asthma and allergic rhinitis among 60 040 middle- and high-school students *(100)*. "Ever HTP use" was significantly associated with current asthma and allergic rhinitis in adjusted models, although the association was weaker than that with current use of conventional cigarettes. The odds ratio for current asthma was particularly increased in those who were dual users of HTP and/or e-cigarettes with conventional cigarettes. In an earlier study *(101)*, the association between use of tobacco products and the risk of allergic diseases was assessed from cross-sectional data on 58 336 students aged 12–18 years from the 2018 Korea Youth Risk Behavior Survey. Use of conventional cigarettes, HTPs and e-cigarettes was each significantly associated with increased risks of asthma, allergic rhinitis and atopic dermatitis.

Health effects in adults. A study is being conducted in Kazakhstan to evaluate the health outcomes in men and women aged 40–59 who use IQOS with HeatSticks, as compared with smokers of conventional cigarettes *(102)*. In this 5-year, single-centre cohort observational study, data on the frequency of exacerbated respiratory symptoms, intolerance of physical exercise, abnormal lung function and other parameters and comorbid conditions are analysed. The study also includes comprehensive clinical assessments at baseline and annually, continuous monitoring of chronic obstructive pulmonary disease and registration of exacerbation of acute respiratory conditions. The clinical assessments

include spirometry, chest computed tomography, electrocardiography, physical examinations, laboratory testing of serum for biomarkers of inflammation and metabolic syndrome, anthropometry and the 6-min walk test. Recruitment began in December 2017; results were not available as of July 2020. Similar studies should be conducted in other countries in which IQOS and other HTPs are marketed, for early identification of the potential health risks associated with these products.

2.5 Review of the evidence for reduced risk or harm with use of HTPs

2.5.1 Harm reduction in the context of tobacco products

The health consequences of smoking conventional cigarettes are well documented – and devastating. Nicotine is a powerful addictive substance, however, and quitting smoking is very difficult. The concept of reducing the harm of tobacco, as described by some in the tobacco control community, is based on the idea that cigarette smokers who are unwilling or unable to quit nicotine intake should have a less harmful alternative to conventional combusted cigarettes *(103,104)*. Over the past two decades, novel products claimed to reduce exposure and risk have been introduced continuously, including smokeless tobacco products, e-cigarettes and now HTPs. As these novel and emerging products generally evolve rapidly and are sometimes limited to a few markets, it has been difficult to generate timely research, independent of the tobacco industry, on their potential to reduce harm. This is particularly true for HTPs, and most of the available research on these products has been conducted by their manufacturers. Analysis of the data and the claims made on the basis of those data is essential to inform the research agenda and regulatory considerations.

2.5.2 Claims of reduced risk

Industry claims

All the studies conducted by the industry are based on a similar strategy for generating evidence to support claims of "reduced risk" associated with HTPs. The model is based on standard in-vitro assays, toxicological modelling, studies in laboratory animals and measurement of human biomarkers of exposure and potential harm. Importantly, the conclusions of all the published reports are based on comparisons of HTPs with conventional cigarettes.

To support its claim of "reduced risk" associated with use of HTPs, PMI modelled the population health impact of introducing IQOS *(105)*. Using the PMI assessment method, the authors conducted various simulations to estimate the population health impact of introducing a "reduced-risk tobacco product" in Japan and modelled different situations over a 20-year period from 1990. They

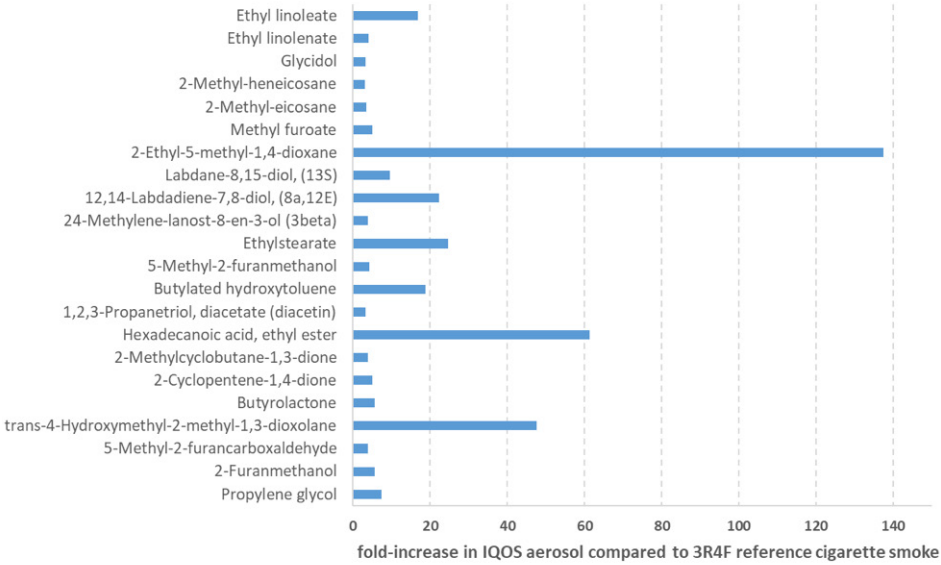
estimated that, if tobacco use was stopped completely at baseline, the overall reduction in tobacco-attributable deaths from lung cancer, ischaemic heart disease, stroke and chronic obstructive pulmonary disease for men and women combined would be 269 916 deaths; if smoking was completely replaced by the reduced-risk tobacco product at baseline, they estimated 167 041–232 519 fewer deaths; and, if the product was introduced at baseline, with uptake rates consistent with the known uptake of IQOS, the estimated reduction in the number of deaths was 65 126–86 885.

Analysis of claims

While industry-sponsored publications fully disclose experimental data, their interpretation and the conclusions often omit important observations or present the findings inadequately. Therefore, careful analysis of industry claims and data is critical.

Analysis of specific claims and concerns about their accuracy. Several independent studies have examined the claims and conclusions of industry-published research reports. For example, St Helen et al. *(12)* examined sections on aerosol chemistry and human exposure assessment in the PMI application to the United States Food and Drug Administration (FDA) for authorization of a "modified risk tobacco product" (MRTP) to assess the validity of the claims of reduced exposure and risk. The authors of the analysis noted that PMI reported the levels in IQOS aerosol of only 40 of the 93 harmful and potentially harmful constituents on the FDA list. They also noted that, while the levels of all 58 constituents on the PMI list were lower in IQOS aerosol than in 3R4F cigarette smoke, the levels of 56 other constituents (not on either the PMI or the FDA list) were higher in IQOS emissions. The levels of some of these constituents were strikingly increased: 22 were > 200% higher and seven were > 1000% higher in IQOS aerosol than in 3R4F smoke (Fig. 2.1). The full list of constituents reported is available on the FDA website (https://www.fda.gov/media/110668/download). The impact of these constituents at the levels found in IQOS emissions on the overall toxicity or harm of this product should be assessed independently, as they may increase the overall risk for disease due to use of IQOS.

Fig. 2.1. Constituents reported by PMI to be at levels at least 200% higher in IQOS aerosol than in the smoke of 3R4F cigarettes



Data and chemical compound names as listed by PMI in its application to the FDA (https://www.fda.gov/media/110668/download, accessed 10 January 2021).

Data on the toxicity of IQOS in vitro and in vivo included by PMI in its MRTP application have also been evaluated. Moazed et al. *(106)* reviewed the pulmonary and immune toxicity of IQOS in studies in laboratory animals and humans. The data in the MRTP application provide evidence of pulmonary inflammation and immunomodulation after use of IQOS and no evidence of improvement in pulmonary inflammation or pulmonary function in cigarette smokers who switched to IQOS. Another group assessed the possible hepatotoxicity of IQOS *(107)* in PMI preclinical studies *(108)* and in studies of human IQOS use in PMI's MRTP application. They found that exposure to HTP increased liver weights, serum alanine aminotransferase activity and hepatocellular vacuolization in experimental animals, whereas these effects were not seen after exposure to conventional cigarettes. Clinical data showed increased alanine aminotransferase activity and plasma bilirubin in smokers who switched to IQOS, indicating hepatocellular injury. The potential impact of passive exposure to IQOS aerosol in non-users has not been considered.

Reduced exposure vs reduced risk. Assessment of the published studies on biomarkers after HTP use tend to support the claims that these products reduce exposure to many harmful constituents. For example, Drovandi et al. *(109)* conducted a meta-analysis of trials published between 2010 and 2019 to compare

the levels of biomarkers of exposure with use of conventional combusted cigarettes and various HTP devices. The authors identified 10 non-blinded, randomized controlled trials involving a total of 1766 participants, all conducted by industry researchers. The analysis showed that the levels of 12 biomarkers of exposure to toxicants were significantly lower in participants assigned to an HTP than in those who smoked conventional cigarettes. In comparison with abstinence from smoking, the levels of eight biomarkers were similar and those of four biomarkers were significantly elevated in people who switched to HTPs. An analysis of the results for 24 biomarkers of potential harm in PMI studies of smokers who switched to IQOS or prototype HTPs *(95)* found no statistically detectable difference between users of IQOS and conventional cigarettes for the majority of the biomarkers, suggesting that reductions in exposure to tobacco constituents do not necessarily result in proportional reductions in risk for disease.

Analysis of the strategies used by the industry to support their claims of reduced risk. The overall approach of the industry to assessing the public health impact of HTPs, particularly PMI's modelling with regard to IQOS, has also been analysed. Max et al. *(110)* reviewed the "population health impact model" used by PMI in its application to the FDA to market IQOS as an MRTP and compared it with the FDA guidelines for MRTP applications; more general criteria for evaluating reduced-risk tobacco products were also considered. They found that the model addressed the impact of IQOS on mortality from four tobacco-attributable diseases but not morbidity, that it underestimates mortality rates, does not apply to tobacco products other than cigarettes, does not include FDA-recommended impacts on non-users and underestimates the impact on other population groups. Thus, the industry model underestimates the health impact of IQOS. Although even an improved model will have to rely on industry data and on a number of assumptions, the health outcomes and/or surrogate measures of health effects associated with HTP use must be assessed by independent researchers to provide regulatory agencies with information on the impact of HTPs on public health.

A review was reported of previously secret internal PMI documents on Accord, a precursor product similar to IQOS, with regard to public communications and the application for IQOS as an MRTP *(111)*. Like IQOS, Accord was marketed as a product that reduced users' exposure to harmful tobacco constituents; however, PMI consistently emphasized that such reductions did not render Accord safer. The review concluded that claims that use of IQOS reduces risks to health are not supported, given the similarity of the two products and the absence of consistent reductions in toxic emissions from IQOS aerosols as compared with Accord.

Even when there is no claim of reduced risk, however, a claim of reduced exposure may suggest the safety of currently marketed HTPs. A review *(112)*

was conducted of PMI's qualitative and quantitative studies of perceptions of the claims of reduced risk submitted to the FDA in the MRTP application, which found that adult consumers perceived claims of reduced exposure as claims of reduced risk.

2.6 Summary and implications for public health

Although HTPs are not a new concept, the active marketing and uptake by users of the newer generation of these products around the world is relatively recent. Most of the information on HTP contents and emissions and the exposure and effects in HTP users was generated and published by the industry, although some more recent studies have been published by independent research groups. The current literature shows some agreement and some inconsistencies among publications. The industry-published reports tend to be biased towards favourable conclusions about the benefits of switching to HTPs, even when they contain clear data in tables and figures that do not fully support those conclusions.

2.6.1 Summary of data

The main conclusions from this review of publications on HTP toxicant emissions, exposures and effects in model systems and humans, and implications for health are outlined below.

Toxicant emissions and comparison with other tobacco products: The machine puffing regimens that have been used to test HTP emissions are based mainly on those used for conventional cigarettes, such as ISO and HCI. There may, however be important differences in how HTPs and conventional cigarettes are puffed by human users, which adds complexity to the known limitations of interpreting data generated by smoking machines. Nevertheless, in the absence of other data, approximate comparisons can be made of the emissions of HTPs and of conventional and e-cigarettes. Most publications, including non-industry studies, show that the levels of nicotine in HTPs and conventional cigarettes (on per-stick basis) are comparable. The levels of many harmful constituents that derive from the combustion process are consistently reported to be significantly lower in HTP aerosol than in conventional cigarette smoke. These include CO, PAH, some carbonyl compounds (formaldehyde, acetaldehyde) and other volatile toxicants, as well as components such as black carbon, nitrogen oxide and ammonia. The levels of TSNAs are also lower in HTP aerosols than in cigarette smoke. Some reports, however, indicate that the levels of other constituents, such as pyridine, dimethyl trisulfide, acetoin and methylglyoxal, may be comparable to or higher than those in the smoke of conventional cigarettes, and the levels of toxicants such as TSNA, CO, benzo[*a*]pyrene and carbonyls are higher in emissions of HTPs than in e-cigarettes.

Effects of HTPs in vitro: Studies in cell cultures can provide important mechanistic insights into any acute or chronic harmful effects associated with HTP use. Industry-published studies generally claim reduced cytotoxicity and mutagenicity and lower levels of a range of toxicological and inflammatory biomarkers after exposure in vitro to HTP aerosols as compared with conventional cigarette smoke. Increasing smoking intensity, however, results in substantial increases in these effects. Furthermore, more nicotine is delivered into cells exposed to HTPs than into those exposed to smoke from reference cigarettes. Both industry and independent publications show that cytotoxicity, mutagenicity and expression of certain RNAs are higher after exposure to HTP aerosol than after exposure to air. Differences in outcome measures have also been seen among HTPs, such as between IQOS and glo™.

Effects of HTPs in experimental animals: Industry studies of dermal tumorigenicity and acute and chronic inhalation toxicity in rodents reported that animals treated with HTP aerosol had lower tumour incidence and multiplicity, fewer inflammatory and cellular stress responses and fewer histological changes than animals treated with conventional cigarette smoke. Analysis of these publications, however, reveals dose–response relations for many of these effects and consistently greater responses in animals treated with HTPs than in air controls. Limited data suggest that exposure to HTPs delivers more nicotine than conventional cigarette smoke, consistent with the in-vitro results.

Exposure and effects in smokers who switch to HTPs and comparison with use of e-cigarettes or abstinence from tobacco: Industry publications report reductions in biomarkers of exposure to certain constituents, less urinary mutagenicity and reduction in some biomarkers of effect in smokers who switch to HTPs. Examination of the publications, however, shows substantially higher levels of biomarkers of exposure than in groups assigned to stop smoking and not use any product (Table 2.2). In addition, the levels of biomarkers of many cardiovascular and other diseases did not decrease and in some cases increased (CC16, alanine aminotransferase activity, plasma bilirubin) after a switch to HTPs over baseline levels. This suggests that HTPs have similar or greater cardiovascular toxicity than conventional cigarettes. Lastly, HTP consumption and nicotine intake clearly increased over time in the switching studies, suggesting increasing exposures to other aerosol constituents.

Passive exposure to HTPs and comparison with other tobacco products or clean air: Research on passive exposure to HTP aerosol has been limited. The results to date suggest that use of HTPs may expose bystanders to certain constituents at levels lower than with passive exposure to conventional cigarette smoke but at higher levels than exposure to clean air or e-cigarette aerosol.

2.6.2 Implications for public health

Real-world exposure and its effects on HTP users are not well characterized, and it is impossible at this time to accurately evaluate the long-term health outcomes in users who switch completely to HTPs or use them in combination with conventional cigarettes, e-cigarettes or other tobacco- or nicotine-containing products. Careful analysis of data from industry and academic studies calls attention to the following potential public health consequences of HTP use.

- **Addictive potential**. HTPs may be more efficient in delivering nicotine to users than other tobacco products, including conventional cigarettes. Therefore, in the absence of clear understanding of the health consequences of HTP use, the potential for addiction and subsequent long-term use of these products by various population subgroups, including young people and adults with comorbid conditions, HTPs are a public health concern.
- **Significant differences in exposure of users to toxicants**. Increasing the intensity of HTP puffing dramatically increases the yields of toxicants and the cytotoxic and mutagenic effects of HTP emissions in a dose–response manner. There could therefore be significant variation in toxic exposures and subsequent risks among individuals who use the same HTP, depending on the product type and use topography.
- **No reduction in the chronic disease burden among smokers who switch to HTPs**. Some smokers may choose to switch to HTPs to reduce harmful exposure without quitting tobacco use. As summarized above, the data indicate no improvement in several pulmonary and cardiovascular indicators and a high prevalence of dual use (with smoking) in participants in switching studies. Therefore, uptake of HTPs by smokers may not significantly reduce the prevalence of smoking-associated chronic diseases.
- **Increased risk of chronic diseases in non-smokers who initiate HTP use**. Studies conducted to date consistently show higher exposure and more effects with HTPs than with no exposure (such as sham controls in experimental studies and smoking abstinence in human trials). Uptake of HTPs by non-users of any tobacco product will therefore increase their risk for adverse outcomes such as respiratory, cardiovascular and potentially other diseases.
- **Unknown or unique toxic effects of HTPs**. Most research on HTP aerosols has been limited to analyses of key combustion and tobacco-specific constituents and comparisons with conventional cigarette smoke. HTP aerosols may contain unique harmful constituents that have not yet been identified or well characterized, as suggested by

indications of hepatocellular injury in response to HTPs but not to conventional cigarettes in experimental and clinical trials.

- **Second-hand exposure of non-users**. Exposure to particulates, nicotine and other components of HTP aerosols may pose risks to non-users.
- **Perceptions of safety among users**. Claims of reduced exposure from HTPs may be perceived by users and non-users of other tobacco products as claims of reduced risk, which may lead to uptake of HTPs by individuals who would otherwise quit smoking or not initiate tobacco use.

Lastly, there is sufficient variation among HTP brands to suggest that the technologies used in HTPs will continue to evolve. This may include changes in the chemical composition of aerosols produced by HTPs and in subsequent exposure and effects in users. Therefore, the limited data available on currently marketed HTPs, much of which was generated by industry, may not be directly applicable in the future.

2.7 Research gaps and priorities

This review of the toxicants in HTPs and reports on in vitro and in vivo toxicity and levels of exposure and effects in humans indicates the following areas for research:

- sound, more rigorous, innovative laboratory assessment of HTP emissions, such as non-targeted analyses to identify toxicants that may be responsible for the lack of improvement in biomarkers of potential harm to smokers who switch to HTPs;
- better characterization of human topography to understand how HTPs are used in the real world (as opposed to clinical confinement trials), including potential increases in product consumption over time and how they affect addictiveness, harmful exposures and health outcomes;
- better characterization of nicotine uptake by HTP users and the potential impact on abuse liability;
- use of toxicological models (e.g. cells or laboratory animals) to better understand nicotine absorption in cells and tissues and to predict unique or unknown toxicity of HTPs;
- identification of biomarkers of exposure and effect that are specific to HTPs to facilitate research on the amount of HTP use, associated exposure and potential health effects;

- the impact of dual or poly use of HTPs with other tobacco products, particularly conventional cigarettes;
- the effects of second-hand exposure on non-users, particularly vulnerable populations (those with pre-existing medical conditions, children, pregnant women); and
- monitoring of health outcomes in longitudinal population-based cohorts of HTP users and exposed non-users in various countries and comparison with non-users of any tobacco product.

2.8 Policy recommendations

The following recommendations are proposed for consideration by policy-makers, researchers and the public health community, as appropriate.

- Thoroughly examine industry research data on HTPs to ensure accurate interpretation.
- Prioritize and support independent research of the public health impact of HTPs.
- Develop standards for HTP surveillance and research, such as product-related terminology, standard testing procedures for HTP emissions, including puffing regimens, and HTP-specific reference products that could be used as quality controls.
- Conduct surveillance of the prevalence of use of the available HTPs and the potential associations with health outcomes, by country.
- Until further, independent evidence on the public health impact of HTPs is available, prohibit all manufacturers and associated groups from making claims about reduced harm as compared with other products, including advertisements and modifications to health warnings, and from portraying HTPs as appropriate for cessation of use of any tobacco product; and prohibit use of HTPs in public spaces, as they are tobacco products.
- Policy-makers should clearly communicate to the public that there is currently no evidence that HTPs reduce the risks associated with tobacco products.

2.9 References

1. Forster M, Fiebelkorn S, Yurteri C, Mariner D, Liu C, Wright C et al. Assessment of novel tobacco heating product THP1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. Regul Toxicol Pharmacol. 2018;93:14–33.
2. Takahashi Y, Kanemaru Y, Fukushima T, Eguchi K, Yoshida S, Miller-Holt J et al. Chemical analysis

and in vitro toxicological evaluation of aerosol from a novel tobacco vapor product: A comparison with cigarette smoke. Regul Toxicol Pharmacol. 2018;92:94–103.
3. Li X, Luo Y, Jiang X, Zhang H, Zhu F, Hu S et al. Chemical analysis and simulated pyrolysis of tobacco heating system 2.2 compared to conventional cigarettes. Nicotine Tob Res. 2019;21(1):111–8.
4. Gasparyan H, Mariner D, Wright C, Nicol J, Murphy J, Liu C et al. Accurate measurement of main aerosol constituents from heated tobacco products (HTPs): Implications for a fundamentally different aerosol. Regul Toxicol Pharmacol. 2018;99:131–41.
5. Uchiyama S, Noguchi M, Takagi N, Hayashida H, Inaba Y, Ogura H et al. Simple determination of gaseous and particulate compounds generated from heated tobacco products. Chem Res Toxicol. 2018;31(7):585–93.
6. Uchiyama S, Noguchi M, Sato A, Ishitsuka M, Inaba Y, Kunugita N. Determination of thermal decomposition products generated from e-cigarettes. Chem Res Toxicol. 2020;33(2):576–83.
7. Hukkanen J, Jacob P III, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev. 2005;57(1):79–115.
8. 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(3):201–7.
9. 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 Tob Res. 2018;20(8):1004–9.
10. Liu S, Li J, Zhu L, Liu W. Quantitative determination and puff-by-puff analysis on the release pattern of nicotine and menthol in heat-not-burn tobacco material and emissions. Paris: Cooperation Centre for Scientific Research Relative to Tobacco; 2020.
11. 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(7):1050–2.
12. St Helen G, Jacob P III, Nardone N, Benowitz NL. IQOS: examination of Philip Morris International's claim of reduced exposure. Tob Control. 2018;27(Suppl 1):s30–6.
13. Mallock N, Pieper E, Hutzler C, Henkler-Stephani F, Luch A. Heated tobacco products: a review of current knowledge and initial assessments. Front Public Health. 2019;7:287.
14. Counts ME, Morton MJ, Laffoon SW, Cox RH, Lipowicz PJ. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. Regul Toxicol Pharmacol. 2005;41(3):185–227.
15. Standard operating procedure for determination of nicotine and carbon monoxide in mainstream cigarette smoke under intense smoking conditions, WHO TobLabNet SOP10. Geneva: World Health Organization; 2016.
16. Standard operating procedure for determination of nicotine in cigarette tobacco filler, TobLabNet SOP 4. Geneva: World Health Organization; 2014.
17. Simonavicius E, McNeill A, Shahab L, Brose LS. Heat-not-burn tobacco products: a systematic literature review. Tob Control. 2019;28(5):582–94.
18. 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. Regul Toxicol Pharmacol. 2017;90:1–8.
19. Meišutovič-Akhtarieva M, Prasauskas T, Čiužas D, Krugly E, Keratayté K, Martuzevičius D et al. Impacts of exhaled aerosol from the usage of the tobacco heating system to indoor air quality: A chamber study. Chemosphere. 2019;223:474–82.
20. Schaller JP, Keller D, Poget L, Pratte P, Kaelin E, McHugh D et al. 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):S27–47.
21. Shein M, Jeschke G. Comparison of free radical levels in the aerosol from conventional ci-

garettes, electronic cigarettes, and heat-not-burn tobacco products. Chem Res Toxicol. 2019;32(6):1289–98.
22. Smith MR, Clark B, Lüdicke F, Schaller JP, Vanscheeuwijck P, Hoeing J et al. Evaluation of the tobacco heating system 2.2. Part 1: Description of the system and the scientific assessment program. Regul Toxicol Pharmacol. 2016;81(Suppl 2):S17–26.
23. Crooks I, Neilson L, Scott K, Reynolds L, Oke T, Meredith C et al. Evaluation of flavourings potentially used in a heated tobacco product: Chemical analysis, in vitro mutagenicity, genotoxicity, cytotoxicity and in vitro tumour promoting activity. Food Chem Toxicol. 2018;118:940–52.
24. Davis B, Williams M, Talbot P. iQOS: evidence of pyrolysis and release of a toxicant from plastic. Tob Control. 2019;28(1):34–41.
25. Forster M, Liu C, Duke MG, McAdam KG, Proctor CJ. An experimental method to study emissions from heated tobacco between 100–200°C. Chem Cent J. 2015;9:20.
26. Cancelada L, Sleiman M, Tang X, Russell ML, Montesinos VN, Litter MI et al. Heated tobacco products: volatile emissions and their predicted impact on indoor air quality. Environ Sci Technol. 2019;53(13):7866–76.
27. Jaccard G, Kondylis A, Gunduz I, Pijnenburg J, Belushkin M. Investigation and comparison of the transfer of TSNA from tobacco to cigarette mainstream smoke and to the aerosol of a heated tobacco product, THS2.2. Regul Toxicol Pharmacol. 2018;97:103–9.
28. Ratajczak A, Jankowski P, Strus P, Feleszko W. Heat not burn tobacco product – a new global trend: Impact of heat-not-burn tobacco products on public health, a systematic review. Int J Environ Res Public Health. 2020;17(2):409.
29. Konstantinou E, Fotopoulou F, Drosos A, Dimakopoulou N, Zagoriti Z, Niarchos A et al. Tobacco-specific nitrosamines: A literature review. Food Chem Toxicol. 2018;118:198–203.
30. Caponnetto P, Maglia M, Prosperini G, Busà B, Polosa R. Carbon monoxide levels after inhalation from new generation heated tobacco products. Respir Res. 2018;19(1):164.
31. Ishizaki A, Kataoka H. A sensitive method for the determination of tobacco-specific nitrosamines in mainstream and sidestream smokes of combustion cigarettes and heated tobacco products by online in-tube solid-phase microextraction coupled with liquid chromatography-tandem mass spectrometry. Anal Chim Acta. 2019;1075:98–105.
32. Glantz SA. Heated tobacco products: the example of IQOS. Tob Control. 2018;27(Suppl 1):s1–6.
33. Leigh NJ, Palumbo MN, Marino AM, O'Connor RJ, Goniewicz ML. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. Tob Control. 2018;27(Suppl 1):s37–8.
34. Ogunwale MA, Li M, Ramakrishnam Raju MV, Chen Y, Nantz MN, Conklin DJ et al. Aldehyde detection in electronic cigarette aerosols. ACS Omega. 2017;2(3):1207–14.
35. Conklin DJ, Ogunwale MA, Chen Y, Theis WS, Nantz MH, Fu XA et al. Electronic cigarette-generated aldehydes: The contribution of e-liquid components to their formation and the use of urinary aldehyde metabolites as biomarkers of exposure. Aerosol Sci Technol. 2018;52(11):1219–32.
36. Kaunelienė V, Meišutovič-Akhtarieva M, Martuzevičius D. A review of the impacts of tobacco heating system on indoor air quality versus conventional pollution sources. Chemosphere. 2018;206:568–78.
37. Savareear B, Escobar-Arnanz J, Brokl M, Saxton MJ, Wright C, Liu C et al. Comprehensive comparative compositional study of the vapour phase of cigarette mainstream tobacco smoke and tobacco heating product aerosol. J Chromatogr A. 2018;1581–2.
38. Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K, Leischow SJ. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. Addiction. 2018;113(11):2099–106.
39. Ruprecht AA, Marco CD, Saffari A, Pozzi P, Mazza R, Veronese C et al. Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products, and conventional cigarettes. Aerosol Sci Technol. 2017;51(6):674–84.

40. Mallock N, Böss L, Burk R, Danziger M, Welsch T, Hahn H et al. Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. Arch Toxicol. 2018;92(6):2145–9.
41. Salman R, Talih S, El-Hage R, Haddad C, Karaoghlanian N, El-Hellani A et al. Free-base and total nicotine, reactive oxygen species, and carbonyl emissions From IQOS, a heated tobacco product. Nicotine Tob Res. 2019;21(9):1285–8.
42. De Marco C, Borgini A, Ruprecht AA, Veronese C, Mazza R, Bertoldi M et al. La formaldeide nelle sigarette elettroniche e nei riscaldatori di tabacco (HnB): facciamo il punto. [Formaldehyde in electronic cigarettes and in heat-not-burn products (HnB): let's make the point]. Epidemiol Prev. 2018;42(5–6):351–5.
43. Savareear B, Escobar-Arnanz J, Brokl M, Saxton MJ, Wright C, Liu C et al. Non-targeted analysis of the particulate phase of heated tobacco product aerosol and cigarette mainstream tobacco smoke by thermal desorption comprehensive two-dimensional gas chromatography with dual flame ionisation and mass spectrometric detection. J Chromatogr A. 2019;1603:327–37.
44. Tricker AR, Schorp MK, Urban HJ, Leyden D, Hagedorn HW, Engl J et al. Comparison of environmental tobacco smoke (ETS) concentrations generated by an electrically heated cigarette smoking system and a conventional cigarette. Inhal Toxicol. 2009;21(1):62–77.
45. Mitova MI, Campelos PB, Goujon-Ginglinger CG, Maeder S, Mottier N, Rouget EJR et al. Comparison of the impact of the tobacco heating system 2.2 and a cigarette on indoor air quality. Regul Toxicol Pharmacol. 2016;80:91–101.
46. Jankowski M, Brożek GM, Lawson J, Skoczyński S, Majek P, Zejda JE. New ideas, old problems? Heated tobacco products – a systematic review. Int J Occup Med Environ Health. 2019;32(5):595–634.
47. Hitosugi M, Tojo M, Kane M, Shiomi N, Shimizu T, Nomiyama T. Criminal mercury vapor poisoning using heated tobacco product. Int J Legal Med. 2019;133(2):479–81.
48. A study on production and delivery of volatile aroma substances from heat-not-burn products' tobacco material to emissions. Paris: Cooperation Centre for Scientific Research Relative to Tobacco; 2020.
49. Pacitto A, Stabile L, Scungio M, Rizza V, Buonanno G. Characterization of airborne particles emitted by an electrically heated tobacco smoking system. Environ Pollut. 2018;240:248–54.
50. Górski P. e-Cigarettes or heat-not-burn tobacco products – advantages or disadvantages for the lungs of smokers. Adv Resp Med. 2019;87(2):123–34.
51. Roemer E, Stabbert R, Veltel D, Müller BP, Meisgen TJ, Schramke H et al. Reduced toxicological activity of cigarette smoke by the addition of ammonium magnesium phosphate to the paper of an electrically heated cigarette: smoke chemistry and in vitro cytotoxicity and genotoxicity. Toxicol In Vitro. 2008;22(3):671–81.
52. Tewes FJ, Meisgen TJ, Veltel DJ, Roemer E, Patskan G. Toxicological evaluation of an electrically heated cigarette. Part 3: Genotoxicity and cytotoxicity of mainstream smoke. J Appl Toxicol. 2003;23(5):341–8.
53. Werley MS, Freelin SA, Wrenn SE, Gerstenberg B, Roemer E, Schramke H et al. Smoke chemistry, in vitro and in vivo toxicology evaluations of the electrically heated cigarette smoking system series K. Regul Toxicol Pharmacol. 2008;52(2):122–39.
54. Zenzen V, Diekmann J, Gerstenberg B, Weber S, Wittke S, Schorp MK. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 2: Smoke chemistry and in vitro toxicological evaluation using smoking regimens reflecting human puffing behavior. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S11–34.
55. van der Toorn M, Koshibu K, Schlage WK, Majeed S, Pospisil P, Hoeng J et al. Comparison of monoamine oxidase inhibition by cigarettes and modified risk tobacco products. Toxicol Rep. 2019;6:1206–15.

56. Iskandar AR, Mathis C, Schlage WK, Frentzel S, Leroy P, Xiang Y et al. A systems toxicology approach for comparative assessment: Biological impact of an aerosol from a candidate modified risk tobacco product and cigarette smoke on human organotypic bronchial epithelial cultures. Toxicol In Vitro. 2017;39:29–51.
57. Zanetti F, Sewer A, Scotti E, Titz B, Schlage WK, Leroy P et al. Assessment of the impact of aerosol from a potential modified risk tobacco product compared with cigarette smoke on human organotypic oral epithelial cultures under different exposure regimens. Food Chem Toxicol. 2018;115:148–69.
58. Iskandar AR, Martin F, Leroy P, Schlage WK, Mathis C, Titz B et al. Comparative biological impacts of an aerosol from carbon-heated tobacco and smoke from cigarettes on human respiratory epithelial cultures: A systems toxicology assessment. Food Chem Toxicol. 2018;115:109–26.
59. Poussin C, Laurent A, Kondylis A, Marescotti D, van der Toorn M, Guedj E et al. In vitro systems toxicology-based assessment of the potential modified risk tobacco product CHTP 1.2 for vascular inflammation- and cytotoxicity-associated mechanisms promoting adhesion of monocytic cells to human coronary arterial endothelial cells. Food Chem Toxicol. 2018;120:390–406.
60. Jaunky T, Adamson J, Santopietro S, Terry A, Thorne D, Breheny D et al. Assessment of tobacco heating product THP1.0. Part 5: In vitro dosimetric and cytotoxic assessment. Regul Toxicol Pharmacol. 2018;93:52–61.
61. Haswell LE, Corke S, Verrastro I, Baxter A, Banerjee A, Adamson J et al. In vitro RNA-seq-based toxicogenomics assessment shows reduced biological effect of tobacco heating products when compared to cigarette smoke. Sci Rep. 2018;8(1):1145.
62. Godec TL, Crooks I, Scott K, Meredith C. In vitro mutagenicity of gas-vapour phase extracts from flavoured and unflavoured heated tobacco products. Toxicol Rep. 2019;6:1155–63.
63. 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(Suppl 1):s26–9.
64. Davis B, To V, Talbot P. Comparison of cytotoxicity of IQOS aerosols to smoke from Marlboro Red and 3R4F reference cigarettes. Toxicol In Vitro. 2019;61:104652.
65. Zagoriti Z, El Mubarak MA, Farsalinos K, Topouzis S. Effects of exposure to tobacco cigarette, electronic cigarette and heated tobacco product on adipocyte survival and differentiation in vitro. Toxics. 2020;8(1):9.
66. Tsuji H, Okubo C, Fujimoto H, Fukuda I, Nishino T, Lee KM et al. Comparison of dermal tumor promotion activity of cigarette smoke condensate from prototype (heated) cigarette and reference (combusted) cigarette in SENCAR mice. Food Chem Toxicol. 2014;72:187–94.
67. Fujimoto H, Tsuji H, Okubo C, Fukuda I, Nishino T, Lee KM et al. Biological responses in rats exposed to mainstream smoke from a heated cigarette compared to a conventional reference cigarette. Inhal Toxicol. 2015;27(4):224–36.
68. Phillips BW, Schlage WK, Titz B, Kogel U, Sciuscio D, Martin F et al. A 90-day OECD TG 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of the aerosol from the carbon heated tobacco product version 1.2 (CHTP1.2) compared with cigarette smoke. I. Inhalation exposure, clinical pathology and histopathology. Food Chem Toxicol. 2018;116(Pt B):388–413.
69. Titz B, Kogel U, Martin F, Kogel U, Sciuscio D, Martin F et al. A 90-day OECD TG 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of the aerosol from the carbon heated tobacco product version 1.2 (CHTP1.2) compared with cigarette smoke. II. Systems toxicology assessment. Food Chem Toxicol. 2018;115:284–301.
70. Phillips B, Szostak J, Titz B, Schlage WK, Guedj E, Leroy P et al. A six-month systems toxicology inhalation/cessation study in ApoE-/- mice to investigate cardiovascular and respiratory exposure effects of modified risk tobacco products, CHTP 1.2 and THS 2.2, compared with conventional cigarettes. Food Chem Toxicol. 2019;126:113–41.

71. Szostak J, Titz B, Schlage WK, Guedj E, Sewer A, Phillips B et al. Structural, functional, and molecular impact on the cardiovascular system in ApoE-/- mice exposed to aerosol from candidate modified risk tobacco products, carbon heated tobacco product 1.2 and tobacco heating system 2.2, compared with cigarette smoke. Chem Biol Interact. 2020;315:108887.
72. Nabavizadeh P, Liu J, Havel CM, Ibrahim S, Derakhshandeh R, Jacob P III et al. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. Tob Control. 2018;27(Suppl 1):s13–9.
73. McAdam K, Davis P, Ashmore L, Eaton D, Jakaj B, Eldridge A et al. Influence of machine-based puffing parameters on aerosol and smoke emissions from next generation nicotine inhalation products. Regul Toxicol Pharmacol. 2019;101:156–65.
74. Urban HJ, Tricker AR, Leyden DE, Forte N, Zenzen V, Fueursenger A et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 8: Nicotine bridging – estimating smoke constituent exposure by their relationships to both nicotine levels in mainstream cigarette smoke and in smokers. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S85–97.
75. Patskan G, Reininghaus W. Toxicological evaluation of an electrically heated cigarette. Part 1: Overview of technical concepts and summary of findings. J Appl Toxicol. 2003;23(5):323–8.
76. Tricker AR, Stewart AJ, Martin Leroy C, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 3: Eight-day randomized clinical trial in the UK. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S35–44.
77. Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 4: Eight-day randomized clinical trial in Korea. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S45–53.
78. Tricker AR, Kanada S, Takada K, Martin Leroy C, Lindner D, Schorp MK et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 5: 8-Day randomized clinical trial in Japan. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S54–63.
79. Tricker AR, Kanada S, Takada K, Martin Leroy C, Lindner D, Schorp MK et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 6: 6-Day randomized clinical trial of a menthol cigarette in Japan. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S64–73.
80. Martin Leroy C, Jarus-Dziedzic K, Ancerewicz J, Lindner D, Kulesza A, Magnette J. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 7: A one-month, randomized, ambulatory, controlled clinical study in Poland. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S74–84.
81. 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. Nicotine Tob Res. 2016;18(7):1606–13.
82. Lüdicke F, Baker G, Magnette J, Picavet P, Weitkunat R. Reduced exposure to harmful and potentially harmful smoke constituents with the tobacco heating system 2.1. Nicotine Tob Res. 2017;19(2):168–75.
83. Haziza C, de La Bourdonnaye G, Skiada D, Ancerewicz J, Baker G, Picavet P et al. Evaluation of the tobacco heating system 2.2. Part 8: 5-Day randomized reduced exposure clinical study in Poland. Regul Toxicol Pharmacol. 2016;81 Suppl 2:S139–50.
84. Lüdicke F, Ansari SM, Lama N, Blanc N, Bosilskova M, Donelli A et al. 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(11):1934–43.
85. Gale N, McEwan M, Eldridge AC, Fearon IM, Sherwood N, Bowen E et al. Changes in biomarkers of exposure on switching from a conventional cigarette to tobacco heating products: a randomized, controlled study in healthy Japanese subjects. Nicotine Tob Res. 2019;21(9):1220–7.
86. Newland N, Lowe FJ, Camacho OM, McEwan M, Gale N, Ebajemito J et al. Evaluating the effects

of switching from cigarette smoking to using a heated tobacco product on health effect indicators in healthy subjects: study protocol for a randomized controlled trial. Intern Emerg Med. 2019;14(6):885–98.
87. Sakaguchi C, Kakehi A, Minami N, Kikuchi A, Futamura Y. Exposure evaluation of adult male Japanese smokers switched to a heated cigarette in a controlled clinical setting. Regul Toxicol Pharmacol. 2014;69(3):338–47.
88. Adriaens K, Gucht DV, Baeyens F. IQOSTM vs. e-cigarette vs. tobacco cigarette: A direct comparison of short-term effects after overnight-abstinence. Int J Environ Res Public Health. 2018;15(12):2902.
89. Maloney S, Eversole A, Crabtree M, Soule E, Eissenberg T, Breland A. Acute effects of JUUL and IQOS in cigarette smokers. Tob Control. 2020: doi: 10.1136/tobaccocontrol-2019-055475.
90. Protano C, Manigrasso M, Avino P, Sernia S, Vitali M. Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system. Ann Ig. 2016;28(2):109–12.
91. 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. Environ Int. 2017;107:190–5.
92. 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. Int J Hyg Environ Health. 2019;222(3):486–93.
93. Sutanto E, Smith DM, Miller C, O'Connor RJ, Hyland A, Tabuchi T et al. Use of heated tobacco products within indoor spaces: Findings from the 2018 ITC Japan survey. Int J Environ Res Public Health. 2019;16(23):4862.
94. Tabuchi T, Gallus S, Shinozaki T, Nakaya T, Kunugita N, Colwell B. Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to second-hand heat-not-burn tobacco aerosol. Tob Control. 2018;27(e1):e25–33.
95. Glantz SA. PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes. Tob Control. 2018;27(Suppl 1):s9–12.
96. Polosa R, Morjaria JB, Caponnetto P, Prosperini U, Russo C, Pennisi A et al. Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. Respir Res. 2016;17(1):166.
97. Bhatta DN, Glantz SA. Association of e-cigarette use with respiratory disease among adults: A longitudinal analysis. Am J Prev Med. 2020;58(2):182–90.
98. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Iftekhar Uddin SM, Benjamin EJ et al. Association between e-cigarette use and chronic obstructive pulmonary disease by smoking status: behavioral risk factor surveillance system 2016 and 2017. Am J Prev Med. 2019;58(3):336–42.
99. Wills TA, Pagano I, Williams RJ, Tam EK. e-Cigarette use and respiratory disorder in an adult sample. Drug Alcohol Depend. 2019;194:363–70.
100. Chung SJ, Kim BK, Oh JH, Shim JS, Chang YS, Cho SH et al. Novel tobacco products including electronic cigarette and heated tobacco products increase risk of allergic rhinitis and asthma in adolescents: Analysis of Korean youth survey. Allergy. 2020;75(7):1640–8.
101. Lee A, Lee SY, Lee KS. The use of heated tobacco products is associated with asthma, allergic rhinitis, and atopic dermatitis in Korean adolescents. Sci Rep. 2019;9(1):17699.
102. Sharman A, Zhussupov B, Sharman D, Kim I, Yerenchina E. Lung function in users of a smoke-free electronic device with HeatSticks (iQOS) versus smokers of conventional cigarettes: Protocol for a longitudinal cohort observational study. JMIR Res Protoc. 2018;7(11):e10006.
103. Hatsukami DK, Slade J, Benowitz NL, Giovino GA, Gritz ER, Leischow S et al. Reducing tobacco harm: research challenges and issues. Nicotine Tob Res. 2002;4 Suppl 2:S89–101.
104. Warner KE. Tobacco harm reduction: promise and perils. Nicotine Tob Res. 2002;4(Suppl 2):S61–71.

105. Lee PN, Djurdjevic S, Weitkunat R, Baker G. Estimating the population health impact of introducing a reduced-risk tobacco product into Japan. The effect of differing assumptions, and some comparisons with the US. Regul Toxicol Pharmacol. 2018;100:92–104.
106. 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(Suppl 1):s20–5.
107. Chun L, Moazed F, Matthay M, Calfee C, Gotts J. Possible hepatotoxicity of IQOS. Tob Control. 2018;27(Suppl 1):s39–40.
108. Wong ET, Kogel U, Veljkovic E, Martin F, Xiang Y, Boue S et al. Evaluation of the tobacco heating system 2.2. Part 4: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects compared with cigarette smoke. Regul Toxicol Pharmacol. 2016;81(Suppl 2):S59–81.
109. 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 Tob Res. 2020;22(7):1077–85.
110. Max WB, Sung HY, Lightwood J, Wang Y, Yao T. Modelling the impact of a new tobacco product: review of Philip Morris International's population health impact model as applied to the IQOS heated tobacco product. Tob Control. 2018;27(Suppl 1):s82–6.
111. Elias J, Dutra LM, St Helen G, Ling PM. Revolution or redux? Assessing IQOS through a precursor product. Tob Control. 2018;27(Suppl 1):s102–10.
112. Popova L, Lempert LK, Glantz SA. Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims. Tob Control. 2018;27(Suppl 1):s87–95.

3. The attractiveness and addictive potential of heated tobacco products: effects on perception and use and associated effects

Reinskje Talhout, National Institute for Public Health and the Environment, Centre for Health Protection, Bilthoven, Netherlands

Richard J. O'Connor, Department of Health Behavior, Roswell Park Comprehensive Cancer Center, Buffalo (NY), USA

Contents

Abstract

Decision FCTC/COP8(22) requests a report on several aspects of novel and emerging tobacco products, in particular heated tobacco products (HTPs). This paper addresses the aspect of addictive potential, perception and use, attractiveness, potential role in initiating and quitting smoking, marketing including promotional strategies and impacts, and claims of "reduced harm". We reviewed the attractive and addictive features of HTPs and the effects of those features on

consumer perception and use. The available literature on HTPs was complemented by information from the wider body of knowledge on e-cigarettes.

We searched the bibliographic database PubMed, with no restriction on time, up to January 2020. Studies on toxicity in users (i.e. toxicants in emissions, in-vitro studies, biomarkers of exposure) and environmental smoke and studies in a language other than English were excluded. We also included studies in the application of Philip Morris International (PMI) to the United States Food and Drug Administration (FDA) for their IQOS modified risk tobacco product (MRTP) were also used.

With regard to features that increase attractiveness, information was found on sensory attributes, ease of use, cost, reputation and image, and assumed risks and benefit. Little is known about how these different features affect consumer perception and use; a recent study reported that six important factors were health, cost, enjoyment and satisfaction, ease of use, use practices and social aspects. With regard to addictiveness, currently marketed HTPs deliver significant levels of nicotine in aerosol, and their pharmacokinetics and physiological and subjective effects are similar to those of contemporary ENDS products, suggesting comparable abuse liability.

HTPs have become popular in some markets, probably due to factors such as marketing as a "clean", modern, elegant, "reduced harm" product. Their sensory properties and ease of use are generally rated lower than those of conventional cigarettes but are directly correlated with their attractiveness, perceived risk and appeal, thus determining their uptake. The history of e-cigarettes shows that any new tobacco and related product that comes onto the market can quickly become popular. Knowledge of e-cigarettes indicates that the factors of concern for HTPs, and therefore potential regulatory targets, are nicotine levels and "throat hit", flavour variety, design of the device, marketing and perception of reduced harm.

Common regulatory principles for e-cigarettes include minimizing product appeal and thus potential uptake by young people, increasing product safety and minimizing false beliefs about health effects. A similar strategy could be followed for HTPs. Policy-makers are advised to monitor the HTP market, communicate the risks to the general public, limit marketing, consider regulating flavours and stimulate research, especially on perceptions and use.

3.1 Background

Since the 1980s, tobacco companies have tried to promote HTPs on the market as "healthier" than conventional cigarettes. Until recently, they failed *(1)*, but HTPs are now increasingly marketed as an alternative to smoking combustible products, primarily cigarettes, although controversy has surrounded the public health context of their marketing and use *(2)*. Since 2014, various new products have been introduced – including Philip Morris International (PMI)'s IQOS,

and industry analysts predict that HTPs will absorb 30% of the regular cigarette market in the USA by 2025 *(3)*. Other examples are Ploom TECH from Japan Tobacco International, glo from British American Tobacco and PAX from PAX Labs *(4)*. Production of HTPs is expected to grow quickly *(5)*.

Like e-cigarettes, HTPs are rechargeable battery-powered devices that heat the product; however, the product consumed is tobacco *(6,7)*. According to WHO *(4)*, HTPs

> … produce aerosols containing nicotine and toxic chemicals when tobacco is heated or when a device containing tobacco is activated. These aerosols are inhaled by users during a process of sucking or smoking involving a device. They contain the highly addictive substance nicotine as well as non-tobacco additives and are often flavoured. The tobacco may be in the form of specially designed cigarettes (e.g. "heat sticks" and "Neo sticks") or pods or plugs.

In decision FCTC/COP8(22) on novel and emerging tobacco products *(8)*, the Conference of the Parties to the WHO FCTC at its eighth session noted the evolution of HTPs, their marketing as "harm reduction" products and the resulting regulatory challenges, with "limited guidance to guide Parties on the classification and regulation of heated tobacco products". Hence, they requested a report to be submitted to the ninth session

> on novel and emerging tobacco products, in particular heated tobacco products, regarding their health impacts including on non-users, *their addictive potential, perception and use, attractiveness, potential role in initiating and quitting smoking, marketing including promotional strategies and impacts, claims of reduced harm* [italics added], variability of products, regulatory experience and monitoring of Parties, impact on tobacco control efforts and research gaps, and to subsequently propose potential policy options ….

The objectives of this paper address the italicized part of the request, as below, by reviewing current literature on:

- the attractive features of HTPs, in light of WHO's definition of attractiveness (section 3.2), including filling gaps in the available literature with expectations from studies on e-cigarettes, for which there is a larger body of information;
- the addictive features of HTPs, including nicotine delivery (section 3.3), also complemented by data on e-cigarettes and with an assessment of the overall abuse potential of HTPs; and
- the effects of attractiveness and addictiveness on the perception and

> use of consumers (section 3.4), including the following, related constructs: awareness, attitude, knowledge, intention, reasons for use and risk perception. Consumer use includes prevalence, user behaviour (such as frequency, intensity and duration and place of use), user profiles, initiation, switching, complementing and quitting conventional tobacco products. Again, lessons learnt from e-cigarettes are used to hypothesize factors that could play a role.

The behavioural implications of different patterns of use among different groups and the implications for public health are covered in the discussion. We conclude with recommendations for research and policy.

A search was conducted of the bibliographic database PubMed, with no restrictions on time, up to January 2020, with the following (combinations of) keywords: heated tobacco products, heat-not-burn tobacco products, HTP, heat sticks and heatsticks and heets, tobacco sticks and IQOS. Studies on toxicity (toxicants in emissions, in-vitro data, biomarkers of exposure) and environmental smoke and studies in a language other than English were excluded. We also used data sent in 2016 by Philip Morris International (PMI) to the US Food and Drug Administration (FDA) seeking authorization to market its IQOS HTP system and flavoured "HeatSticks" in the USA as a modified risk tobacco product (MRTP), and the resulting files of the FDA assessment *(9–12)*.

3.2 Attractiveness of HTPs

3.2.1 Definition of attractiveness in the context of Articles 9 and 10 of the WHO FCTC

"Attractiveness" has been defined by WHO *(13)* as

> factors such as taste, smell and other sensory attributes, ease of use, flexibility of the dosing system, cost, reputation or image, assumed risks and benefits, and other characteristics of a product designed to stimulate use.

Data on all of these aspects are reviewed below. We will also cover marketing, including promotional strategies, and claims of reduced harm.

3.2.2 Attractive features of HTPs

Taste, smell and other sensory attributes

Few studies are available on the taste, smell and other sensory attributes of HTPs in humans. Three PMI studies *(14–16)*, report that smoking IQOS suppressed the urge to smoke to the same extent as smoking cigarettes but was consistently rated as providing less sensory and psychological satisfaction than cigarettes *(17)*. An independent study similarly showed that the HTP PAX was considered

significantly less satisfying, good tasting and calming than own-brand cigarettes but showed no significant effect of PAX on the urge to smoke *(17,18)*. Participants in focus groups in Japan and Switzerland also reported less satisfaction with the IQOS than with combustible cigarettes, a strange or unpleasant taste and smell, milder taste and reduced sensory cues, but less throat discomfort *(19)*.

Information on the availability and variability of flavours in HTPs is also important, as it is known that a variety of available flavours plays an important role in liking tobacco and related products such as e-cigarettes *(20)*. For example, in the Republic of Korea, IQOS HeatSticks (HEETS) are available in tobacco, menthol, bubble gum and lime flavours and glo Dunhill Neosticks in tobacco, menthol and lemon ginger, cherry and grape flavours *(7)*. KT&G "lil" sticks (Fiit) contain novel flavour capsules (menthol, mint, apple mint, bubble gum and apricot flavours) *(7,21)*. Like capsule cigarettes, capsule sticks contain menthol and other flavours that can mask the harshness of tobacco and may appeal to female and young non-smokers *(7)*. Perhaps in reaction to this novelty, British American Tobacco introduced Dunhill Neosticks containing capsules (strong menthol and tobacco/menthol), and PMI introduced Sienna Caps ("Sienna selection with a menthol capsule"). These flavoured HTPs are marketed only in countries outside the USA, where HEETS are considered a cigarette product, for which characterizing flavours are not allowed[1] *(22)*, and only menthol and tobacco may be sold *(11)*.

Ease of use

Focus group participants in Japan and Switzerland reported using IQOS indoors instead of combustible cigarettes, "because it creates no ash or odour" *(19)*. Many participants in both countries commented that the product felt unfamiliar and complicated to use and that using IQOS was cumbersome, as the charger and HeatSticks may be bulky, and the IQOS must be charged and cleaned. In the newer generation IQOS, the holder is integrated with the charger and the product can be used up to 10 times before recharging *(23)*. This could make use easier and thus increase its appeal.

Flexibility of the dosing system

Nicotine dosing is described in the sections on addictiveness, under the broader heading of abuse liability. No other information was found.

1 A cigarette or any of its component parts (including the tobacco, filter or paper) shall not contain, as a constituent (including a smoke constituent) or additive, an artificial or natural flavour (other than tobacco or menthol) or a herb or spice, including strawberry, grape, orange, clove, cinnamon, pineapple, vanilla, coconut, liquorice, cocoa, chocolate, cherry or coffee, that is a characterizing flavour of the tobacco product or tobacco smoke.

Cost

Unlike combustible cigarettes, which can be used directly from the package, use of an HTP generally requires the purchase of an external device. The price of such devices can far exceed the price of the consumables, for example, about 25 times the price of a pack of HEETS in the Republic of Korea *(3)*. While the excise tax on HTPs is generally lower than that on combustible cigarettes, HTPs were less expensive to use than combustible cigarettes in fewer than half the countries studied *(21,24)*. In Israel in 2018, HEETS were sold at prices on average 9.5% higher than those of cigarettes *(25)*. In Japan, younger non-users participating in a focus group commented that price could be a potential barrier, but overall, the price contributed to the cachet of the product as luxurious and prestigious *(19)*.

Reputation or image: marketing at point of sale, package and device

Advertising and promotion of HTPs are not always banned in the countries in which they are on the market *(6)*. A systematic Internet search for new tobacco and related products showed that common terms used in marketing or promoting HTPs include "reduced risk", "alternative", "clean", "smoke-free" and "innovative" *(26)*. Expert interviews and IQOS packaging and marketing analyses in Japan and Switzerland also showed that the product is marketed as a clean, chic, pure product *(19)*. In Israel, PMI promoted IQOS as part of its "Smoke-free Israel vision", focusing on "harm reduction" and stressing that the product was clean with less smell and no ash *(27)*. Retailers described the IQOS products as less harmful, a cessation device and not producing smoke *(25)*.

IQOS shops are situated prominently and strategically in selected cities as a core component of marketing. When HTPs were released in futuristic IQOS flagship stores across Italy, Japan and Switzerland, awareness and use of these products increased dramatically *(28)*. In Italy, the "IQOS embassy" and "IQOS boutique" are fancy concept stores where IQOS is promoted as a status symbol and people can try it for free *(6)*. Similarly, in Canada, IQOS was marketed in many tobacco retail outlets (1029 in Ontario) *(29)*. In IQOS boutiques, promotion activities include exchanging a pack of cigarettes or a lighter for an IQOS device, launch parties, "meet and greet" lunches and after-hours events. Promotional elements outside the shops are IQOS signs, sandwich-board signs reading "Building a smoke-free future" and sales representatives regularly smoking IQOS. In Ontario. however, the IQOS signage had to be taken down to comply with national and provincial laws on display and advertising *(30)*. In the Republic of Korea, IQOS flagship shops are located at prime locations in Seoul, again with shop design and product display giving a clean, refined look and feel to IQOS *(3)*. In the USA, IQOS was launched in Atlanta, Georgia, and IQOS shops are located in shopping malls in affluent areas *(31)*.

The IQOS name, device, packaging and shops resemble those of popular cell phones that attract children and adolescents; in combination with the purchasing process, this positions IQOS as a high-demand, upscale product for tech-savvy users, rather different from regular cigarettes *(3)*. Focus group participants in Japan and Switzerland found the product packaging appealing, and even non-users were intrigued, indicating that the product's sleek appearance compared well with that of tech devices *(19)*.

For stick packaging, in Israel, displays of HEETS packages were prominently placed close to consumers, in most cases near youth-oriented merchandise and pack colours indicating tobacco flavourings and strength *(25)*. While cigarette packs in many countries are required to feature graphic warning labels showing various negative consequences of smoking, with explicit colour pictures, to the best of our knowledge this is not required for HTPs in any country as yet. In the Republic of Korea, for example, HEETS packs have only a black-and-white warning label about nicotine addiction *(3)*. The visual design of tobacco products can influence consumers by implying product characteristics. Tests with three IQOS packages that decreasingly linked the product to the Marlboro brand but that were similarly noticeable showed that the packaging appeal, uniqueness and brand equity was significantly lower for the HEETS package than for the Marlboro package *(32)*; however, perceived safety of the Marlboro pack was lower than for the other two packs.

Assumed risks and benefits

HTPs are part of a long tradition in tobacco companies of developing and marketing products that they claim to be less dangerous than conventional cigarettes, beginning with so-called "safer cigarettes" in the 1960s *(33)*. Marketing and media accounts of HTPs explicitly or implicitly claim that they are safer than cigarettes, and some HTPs are claimed by the tobacco industry to help smokers to quit *(5,33)*. HTPs are often claimed to be less harmful than cigarettes because they expose users to lower levels of some toxicants *(33)*. While IQOS may contain lower levels of some toxicants, the data in the PMI application to the FDA for IQOS as an MRTP do not support claims of reduced risk *(34)*. The data do demonstrate, however, that adult consumers in the USA perceive claims of reduced exposure as claims of reduced risk *(35)*, as confirmed in an independent study of adults and adolescents in the USA *(36)*. Analysis of the first nine waves of a survey of the population aged ≥ 14 years in Germany also showed that the majority of 61 HTP users perceived HTPs as somewhat (41.0%) or much (14.8%) less harmful, and 37.7% perceived them as harmful as tobacco cigarettes *(37)*. In Italy, the pilot results of a questionnaire administered to 60 high-school students showed that 40 considered HTPs to be harmful to health, while 24 students said they would accept one of these products if offered by a friend *(38)*.

Several perceived benefits of IQOS use have been identified by focus group participants in Japan and Switzerland, including less throat discomfort, appealing packaging, cleanliness, lack of ash and smoke and greater social acceptability, but only few reported any health benefits of use as compared with combustible tobacco products *(19)*. Use in smoking cessation might be another perceived benefit. In Italy, 19 of 60 high-school students said they would recommend HTPs to a person who wished to stop smoking *(38)*.

Two interesting study protocols have been published, but, unfortunately, neither is independent of industry. PMI cross-sectional surveys are under way in Germany, Italy and the United Kingdom (Greater London) to estimate the prevalence and use patterns of IQOS and other tobacco- and nicotine-containing products *(39)*. The questionnaire also contains items on potential benefits (self-reported improvement in teeth colouring, breath smell, exercise capacity and skin appearance), use experience, perceived risk and experienced reinforcing effects, such as satisfaction, psychological rewards, aversion, enjoyment of respiratory tract sensations and reduced craving. The other protocol *(40)* is for a prospective study to compare changes in cigarette consumption and adoption rates among smokers randomized to HTPs or electronic cigarettes. Product acceptability, tolerability and their harm reduction potential will also be compared. There is, however a potential conflict of interest, as the research is supported by an Investigator-initiated Study award by Philip Morris Products SA, although the authors state that PMI "had no role in the design of the study protocol and will not have any role during its execution, analysis, data interpretation or writing of the manuscript". Further, some of the authors have undeclared conflicts of interest related to tobacco companies, both directly and through funding from tobacco industry front groups.

3.2.3 What we can learn from studies on ENDS and ENNDS and relevance to HTPs

The history of e-cigarettes should make us cautious about any new tobacco or related product coming onto the market, as e-cigarettes have attracted young people who may then proceed to cigarette use *(33)*. As many features of e-cigarettes are also found in HTP, knowledge about their attractiveness may be useful. For example, a study of e-cigarette users showed that the attractive characteristics were the variety of e-liquid flavours (69%), e-cigarette design (44%), ability to adjust e-liquid nicotine levels (31%), ability to adjust settings of device (25%), variety of e-cigarette design (21%), ability to do "cloud chasing" (16%) and price (13%) *(41)*. Fewer dual users, smokers and non-users found these product characteristics attractive, but in the same order. Similarly, analysis of self-reported data showed the importance of the following factors in the choice of an e-cigarette: flavour (39%), price (39%), amount of nicotine (27%),

type of e-cigarette (22%), health claims (12%), design (10%), brand (9.4%) and packaging (3.7%) *(20)*.

With regard to sensory properties, users reported that they were dissatisfied with some aspects of e-cigarettes as compared with cigarettes, because many do not deliver nicotine into the bloodstream as quickly as cigarettes and lack the "throat hit" of cigarettes *(1)*. Although this observation was made before nicotine salt-containing e-liquids with a stronger nicotine hit came on the market, this may be one reason why smokers try HTPs instead of e-cigarettes. The sensory studies on HTPs described above show that smokers rate the taste, smell and throat hit are lower than for cigarettes. Flavours and flavour variety are considered the most attractive features of e-cigarettes *(20,41)*. Therefore, banning or restricting available HTP flavours might be helpful in decreasing their popularity among never users.

Although the ease of use of e-cigarettes and HTPs appears to be similar, e-cigarettes are much cheaper to use. Cost has been mentioned as a reason for using e-cigarettes *(20,41)* and could be a barrier for use of HTPs by some groups, especially children and adolescents.

Many e-cigarette users have accepted the marketing claim that non-combustible devices are safer than conventional cigarettes and may see HTPs as a means of enjoying an authentic tobacco taste with lower perceived risk *(1)*. Moreover, like e-cigarette users, HTP consumers may not understand that they must completely quit smoking cigarettes to achieve the claimed health benefits of HTPs and probably also wrongly believe that unsubstantiated claims of reduced risk by the tobacco industry mean that HTPs are risk-free *(33)*.

3.3 Addictiveness of HTPs

Addictiveness is a summary indicator of the abuse liability or abuse potential of a drug and its delivery system. In one model *(42)*, the abuse liability of tobacco products is considered to comprise the likelihood of repeated use (summarized as pharmacokinetics, drug effects and reinforcement) and the consequences of use (effects on functioning, physical dependence, adverse effects).

3.3.1 Addictiveness

The nicotine emissions under machine-smoking conditions from the three types of HTP for which there are the most published data can be summarized as follows (in µg/cigarette): Eclipse under ISO conditions, 0.18 *(43)*; an electrically heated cigarette smoking system under ISO conditions, 0.313 *(44)*; tobacco heating system (THS) 2.2 (IQOS) under Health Canada Intense (HCI) conditions, 1.32 *(45)*; and tobacco heating product (THP) 1.0 under HCI conditions, 0.462 *(46)*, keeping in mind that the data were published by the manufacturers. In general, the nicotine levels are lower than those in a comparison reference cigarette, 1R6F,

which has certified values for many of the emissions of concern *(47)*, for which the values are 0.721 µg/per cigarette under ISO conditions and 1.90 µg/cigarette under HCI conditions. The levels for the HTPs have been largely replicated by studies inside *(48)* and outside *(49,50)* the industry. Note in particular the lower levels of nicotine for Eclipse and the electrically heated cigarette smoking system. At the meeting of the Society for Research on Nicotine and Tobacco in 2017, British American Tobacco presented two posters on its HTP (THP 1.0) *(46,51)* and in late 2017 published eight studies in a supplement to a journal *(52–60)*. The studies generally report lower nicotine emissions from HTP than from cigarettes smoked under standard machine conditions.

Bekki et al. *(50)* showed that the rate of transfer of nicotine from tobacco filler to aerosol in IQOS was comparable or slightly higher than in conventional cigarettes. Salman and colleagues *(61,62)* showed that IQOS and traditional cigarettes delivered similar quantities of total nicotine in aerosol under ISO conditions (0.77 and 0.80 mg/cigarette) and slightly less under HCI conditions (1.5 and 1.8 mg/cigarette). They also showed levels of 13% free nicotine in IQOS aerosol under ISO and 5.7% under HCI conditions. Meehan-Atrash and colleagues, using nuclear magnetic resonance, found a level of 0.53 mg/cigarette free nicotine *(63)*. Uchiyama et al. *(64)*, in an extensive investigation of the aerosols emitted by IQOS, glo and PloomTECH (Table 3.1), found that IQOS delivered by far the most nicotine in aerosol and also had more than three times the amount of nicotine in the rod than glo (5.2 mg vs 1.7 mg), although the transfer rates were comparable (23% for IQOS, 30% for glo).

Table 3.1. Nicotine concentrations emitted by IQOS, glo and PloomTECH with various flavours

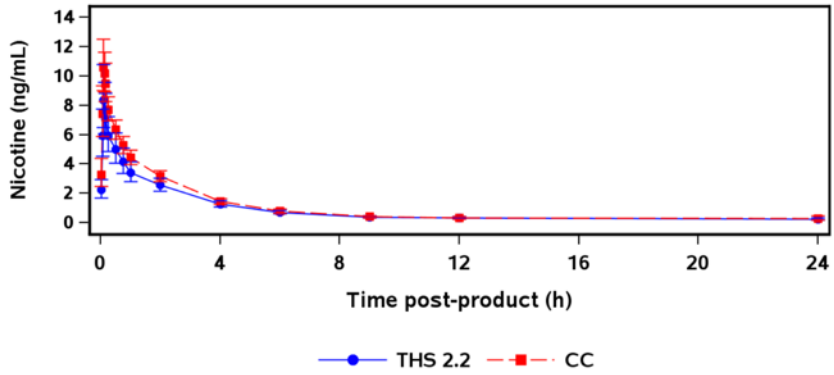
HTP and flavour	ISO (µg/cig)	HCI (µg/cig)
IQOS tobacco	400	1200
IQOS menthol	430	1200
IQOS mint	320	1200
glo bright tobacco	150	570
glo fresh mix	140	510
glo intensely fresh	150	440
PloomTECH regular	70	270
PloomTECH green	68	170
PloomTECH purple	60	250

Source: reference *64*.

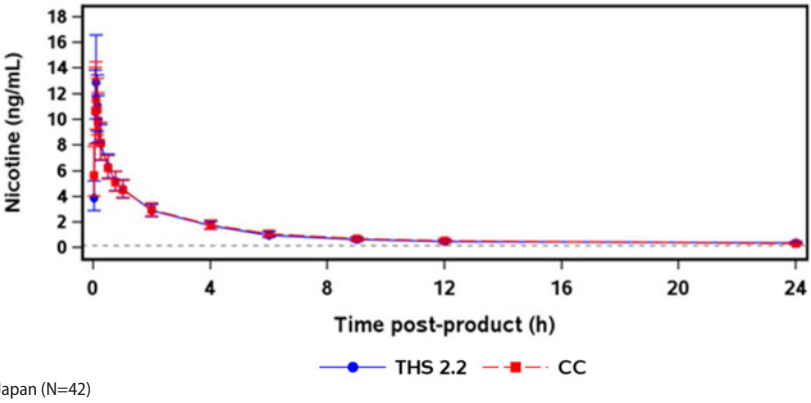
The FDA concluded from the data submitted by PMI that "nicotine pharmacokinetics (PK) in smokers who switched [to IQOS]… is similar to those who continued to smoke CC [conventional smoke, RT]" and that "IQOS is

addictive and has nicotine delivery, addiction potential, and abuse liability similar to combustible cigarettes"; however, no comparisons with other substitutes, such as e-cigarettes, were available. The FDA concluded *(11)* that IQOS "provides nicotine at a high enough level to satisfy the withdrawal and craving symptoms of current smokers", but with no comparisons with ENDS. Fig. 3.1 shows the pharmacokinetics of nicotine delivery from IQOS and cigarettes in four studies conducted by PMI. The average C_{max} of IQOS in smokers in the USA was substantially lower than that in smokers in the other countries, although the C_{max} of cigarettes was remarkably consistent. No differences among products were found that explain this finding. Maloney et al. *(65)* found in a laboratory study that IQOS increased mean plasma nicotine significantly, from 2.1 to 12.7 ng/mL after 10 puffs and to 11.3 ng/mL after ad-libitum use, comparable to the rate with JUUL and somewhat lower than that with own-brand cigarettes.

Fig. 3.1. Pharmacokinetics of nicotine in four PMI studies of IQOS

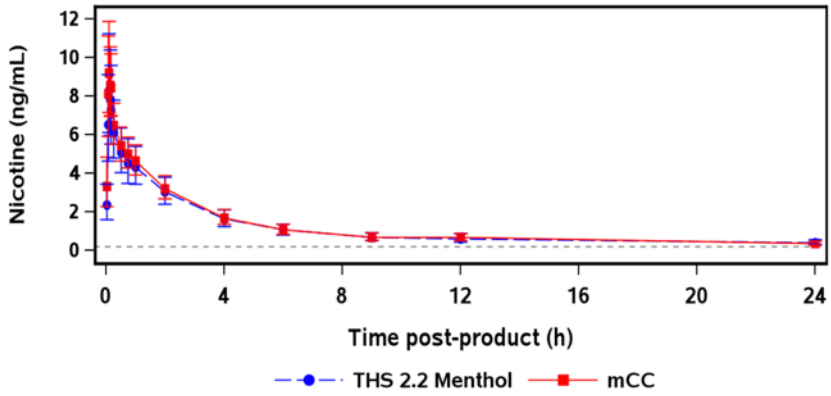


United Kingdom (Northern Ireland) (N=42)
Tmax = 6 min
Cmax = 9.6 ng/mL (THS), 12.4 ng/mL (CC)

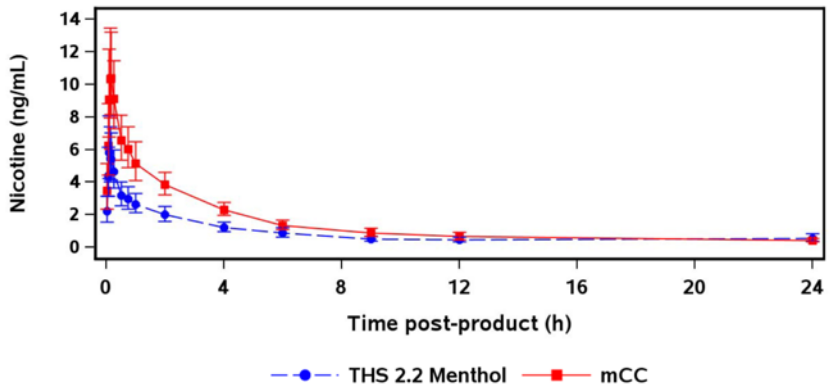


Japan (N=42)
Tmax = 6 min
Cmax = 14.3 ng/mL (THS), 13.8 ng/mL (CC)

Fig. 3.1. Pharmacokinetics of nicotine in four PMI studies of IQOS (continued)



Japan (N=43)
Tmax = 6 min
Cmax = 10.7 ng/mL (THS), 12.1 ng/mL (CC)



USA (N=41)
Tmax = 7 min (THS), 10 min (CC)
Cmax = 7.4 ng/mL (THS), 13.1 ng/mL (CC)

Source: reference *11*.
THS 2.2, IQOS precursor or prototype; CC, conventional cigarette
Limit of quantification in all studies, 0.2 ng/mL

British American Tobacco has published one study on use patterns of its glo product *(58)*. Three groups took glo menthol, glo tobacco and glo + IQOS home for up to 14 days, with up to four laboratory visits. A fourth group used glo in the laboratory only. Laboratory measures included puffing topography, mouth level exposure and depth of mouth insertion. Participants who took the products home completed daily diaries of product use. Overall, the puff volume was about 60 mL with the glo product, with an average of 10–12 puffs per session, a duration of 1.8–2.0 s and a mean interval of 8.8 s. The volume per puff and total volume were

significantly higher than with comparison cigarettes but comparable to those with the IQOS product. Participants reported using 12–15 cigarettes per day at baseline and used 8–12 units per day of the glo/IQOS products during the 4 days at home. The mouth level exposure per product used was lower for glo than for cigarettes, especially to nicotine.

In a longer (90 days) study of HTP use *(16)*, total nicotine equivalents in urine were comparable in people who used tobacco heating systems and those who smoked cigarettes (7 vs 6 mg/g creatinine).

There is a dearth of published independent research on exposure to nicotine, puffing topography and other metrics of abuse liability for currently marketed HTPs; however, this is an area of active research, and new results are published frequently, so that peer-reviewed literature should be monitored continuously. There is emerging evidence that IQOS has the hallmarks of a product liable to abuse. Detailed information on other HTPs is not yet available. Two conclusions can be reached.

- Mainstream aerosol from IQOS delivers about 70% of the nicotine in the smoke of cigarettes. Relative nicotine delivery by IQOS is between 57% and 103%, with a median of 64.7% as compared with a reference cigarette. The median in studies funded by the tobacco industry is not statistically significantly different from the median in independent studies.
- Other HTPs analysed appear to be less efficient than IQOS in delivering a proportion of nicotine in their mainstream smoke.

3.3.2 What we can learn from ENDS and ENNDS and relevance to HTPs

A number of studies of the abuse liability of e-cigarettes have been published, which indicate broadly that the design features that affect nicotine delivery should be considered in evaluating the abuse potential of ENDS *(66–69)*. As at least one HTP delivers nicotine and suppresses craving in the same way as an ENDS *(65)*, it is reasonable to hypothesize that the usage patterns observed for ENDS could be generalized to HTPs. Both HTP and ENDS are, however, broad classes of products, and the findings for one product might not be generalizable to others. More studies of direct comparisons of the use of leading HTPs and leading ENDS could clarify this issue.

3.3.3 Overall abuse liability of HTPs

As noted earlier, abuse liability comprises the likelihood of repeated use (summarized as pharmacokinetics), drug effects, reinforcement (rewarding effects that support future use) and consequences of use (effects on functioning, physical dependence, adverse effects). HTPs appear to deliver nicotine at least as

well as cigarettes and suppress withdrawal and craving for nicotine. HTP users also show signs of nicotine dependence *(16,58,65)*. Thus, the abuse liability of at least some HTPs for which data are available is likely to be comparable to that of conventional cigarette. The liability may differ by HTP brand and type according to factors such as nicotine delivery, sensory properties and ease of use.

3.4 Effects of the attractiveness and addictiveness of ENDS, ENNDS and HTPs on perceptions of risk and harm and use

3.4.1 Contributions of attractiveness and addictiveness to initiation, switching, complementing and quitting conventional tobacco products

Few studies were found on awareness, use, user profile, initiation, switching, complementing or quitting conventional tobacco products in relation to the attractive aspects of the product. A few addressed perception and reasons for using HTPs. One study implied a direct link between marketing and initiation of IQOS. Google search query data showed that, in Japan, the largest Internet search volume for IQOS was in the week after a popular national television show introduced IQOS *(70)*. Furthermore, the prevalence of use of IQOS increased from 0.3% in January–February 2015 to 0.6% in January–February 2016 and up to 3.6% in January–February 2017, while the estimated rates of use of other HTP remained low in 2017. Respondents who had seen the TV programme in 2016 were more likely to have used IQOS than those who had not seen it (10.3% vs 2.7%).

An online survey of 228 young adults, including current, ever and non-users, in the Republic of Korea indicated that the reasons for using IQOS were a belief that they are less harmful or useful for stopping smoking *(71)*. A PMI premarket observational study showed that the main predictors of adoption were liking the smell, taste, aftertaste and ease of use *(72)*. Adoption was higher among participants who used both regular and menthol THS than among those who used only one variant. In wave 1 of the International Tobacco Control survey in Japan of 4684 adult participants, menthol was the most common flavour reported (41.5%) *(73)*. It has been reported[1] that the levels of menthol in IQOS vary markedly in different markets.

In an exploratory study among adults in London, United Kingdom *(74)*, with 22 current and eight ex-users of IQOS, the six main factors that influenced initiation and use of IQOS were health (wanting to reduce or quit smoking and perceptions of reduced harm), cost (high start-up cost but cheaper continuous cost than smoking), enjoyment and satisfaction (e.g. discretion, cleanliness, less smell, tactile qualities comparable to combustible cigarettes), ease of use (accessibility, shortcomings of maintenance or operation limited continuous use but increased use in smoke-free places), use practices (similar to smoking but new practices developed to charge and clean, new technology) and social aspects

1 Goniewicz ML, unpublished data. See Annex 3.1.

(improved social interactions with use of IQOS rather than smoking, but fewer shared social experiences for some).

Studies published by PMI on IQOS precursors *(75,76)* include information on subjective responses to the product, which are often important for understanding why it is used and how effective it might be as a substitute. The cigarette evaluation questionnaire consisted of 12 items in five categories *(77)*: smoking satisfaction, aversion, reduced craving, enjoyment of respiratory tract sensation and psychological reward. The questionnaire on smoking urges consisted of 10 items, with a single score on a seven-point scale *(78)*.

In a laboratory study of THS in Japan *(14)*, the mean satisfaction scores during the study decreased more for THS than for conventional cigarettes. In a similar study in Poland *(15)*, the observed differences in evaluation scales between THS and cigarettes were large and statistically significant. Broadly, cigarettes were rated more highly on satisfaction, craving reduction, sensation and reward and lower on aversion. An earlier study of THS 2.1 showed a similar pattern of results, with satisfaction scores on day 5 an average of 1.4 points lower for THS than for conventional cigarettes ($P < 0.001$) *(79)*. Significant differences were also seen on the reward, sensation and craving subscales, THS scoring lower than cigarettes in all cases. Adriaens and colleagues *(80)* conducted a small study of subjective responses to IQOS and to a tank-style ENDS in comparison with own-brand cigarettes. They found that IQOS and ENDS were equivalent in reducing craving for a cigarette but that both were less effective in suppressing craving than the own-brand cigarette. A study on longer-term use in Japan *(16)* suggested that the difference between cigarettes and HTP with regard to satisfaction fades with continued use over 90 days. These studies show that scores on questionnaires on smoking urges increase for THS over time, as do scores for withdrawal (as measured on the Minnesota nicotine withdrawal scale *(81)*), which may suggest some dissatisfaction with the product as a longer-term substitute for smoking.

3.4.2 Learning from ENDS and ENNDS and application to HTPs

As summarized above, few data are available on the effects of attractiveness and addictiveness on perceptions and reasons for using HTP and on initiation, switching, complementing and quitting conventional tobacco products. Below we summarize the available evidence on those factors in relation to the attractiveness and addictiveness of ENDS.

A review of reasons for e-cigarette use reported by e-cigarette users, cigarette smokers, dual users and non-users among both adults and young people showed that adults' perceptions and reasons for e-cigarette use are often related to smoking cessation, while the young like the novelty of the product *(82)*. Young non-users perceived e-cigarettes as a cool, fashionable product that mimics the smoking routine and is safe to use. In general, the perceived benefits included

avoidance of smoking restrictions, the product being cool and fashionable, having health benefits, lower cost than cigarettes, positive experiences (mimics smoking routine, enjoyable taste, throat hit, weight control, increases concentration), safe to use, smoking cessation or reduction, social acceptability and perceived benefits for bystanders. Another review of studies in young adults *(83)* showed that their reasons for using e-cigarettes are more varied than only smoking cessation. Independently of smoking status, curiosity was the most frequently reported reason for initiating use of e-cigarettes. Continued use of e-cigarettes could be due to either replication of smoking habits or a different, personalized use of nicotine by inhalation. In Europe *(84)*, the most frequently mentioned reason (61%) for taking up e-cigarettes was to stop or reduce tobacco consumption. Other reasons included a perception of e-cigarettes as less harmful (31%) and lower cost (25%). Reducing tobacco consumption and being less harmful were cited more often by participants aged > 40 (76–78%) than those aged 15–24 (59%).

Flavours attract both young people and adults to e-cigarettes *(85)*. Flavours decrease the perception of harm and increase willingness to try and initiate use of e-cigarettes. Among adults, e-cigarette flavours increase product appeal and are a primary reason for using the product. "Pod mod" devices have become popular, especially among adolescents, due to their design, user-friendliness, less aversive vaping experiences, desirable flavours and discretion in places where smoking is forbidden *(86)*. Currently marketed HTPs share several of these characteristics, suggesting some generalizability of the ENDS experience.

3.5 Discussion

3.5.1 Behavioural implications of different patterns of use in different groups

Few studies are available on the perception and reasons for using HTPs among users, ex-users, smokers, dual users and never users of tobacco and related products (section 3.1). While the role of attractive or addictive aspects of HTPs is little known, studies are available on awareness, use, user profile, initiation, switching, complementing and quitting conventional tobacco products. Information on the patterns and prevalence of use in several groups is important for regulators, as the risk profile of smokers is different from that of never smokers.

An important question is whether HTPs are used primarily by smokers, or whether non-smokers also use the product. It would appear that, currently, most HTP users are smokers. For example, in Japan, virtually all HTP users were current (67.8%) or former smokers (25.0%), and only 1.0% were never smokers *(73)*. According to the premarket review by the FDA *(5)*,

> … although the data for IQOS uptake by never smokers, former smokers, and youth is limited, there are some data from countries where IQOS is

> marketed – Italy and Japan – which show low uptake by youth and current non-smokers. In these countries, the likelihood of uptake is slightly higher in former smokers, but still low.

While most HTP users may be smokers, most are dual users of both HTPs and conventional cigarettes and are therefore exposed to emissions from both. PMI studies showed that most people who use IQOS, concurrently use cigarettes *(33)*. Studies in the Republic of Korea showing that 96% of current HTP users (2% of the study population) were dual users and that dual use with conventional cigarettes was not associated with an intention to quit cigarette smoking *(87)*. A survey of adolescents aged 12–18 years showed that 75.5% of the ever HTP users (2.8%) were current cigarette users, 45.6% were current e-cigarette users and 40.3% were concurrent users of cigarettes and e-cigarettes *(88)*. No difference in cigarette quit attempts was found with ever use of HTPs.

PMI and independent data suggest that IQOS will attract adolescent and young adult non-users to initiate tobacco use *(3)*. In Italy, marketing led to an increase in IQOS use, with an intent to use IQOS among non-smokers and long-term former smokers *(6,89)*. According to the FDA *(5)*,

> Certainly, the potential for rapid uptake of a novel tobacco product among youth exists. In the decade since e-cigarettes were introduced to the U.S. market, youth use rose rapidly but the limited flavour choices may reduce IQOS' appeal to youth. The limited options in terms of flavour choice and the price of the IQOS device may reduce the appeal to youth.

Evidence from Japan indicates that younger (< 30 years), wealthier people adopt IQOS *(90)*, and emerging evidence from Canada, United Kingdom (England) and the USA suggests that HTP have at least some appeal for young adults, including non-smokers *(91,92)*.

3.5.2 Implications for public health

HTPs have probably become popular in some markets because of factors such as their marketing as a "clean", modern, elegant, reduced-harm product. Factors that enhance their attractiveness appear to be sensory attributes, ease of use, cost, reputation and image and perceived risks and benefits. While HTPs suppress the urge to smoke, they are generally considered less satisfactory than cigarettes; however, different flavours are available, and this is known to be an attractive feature of tobacco and related products. Users find the fact that they create less ash and smell appealing and may use them indoors for that reason. Other attractive features include their marketing as an exclusive, modern and less harmful product suitable for smoking cessation. The product is, however, often considered to be less easy to use than cigarettes, and cost may be a barrier.

With regard to addictiveness, currently marketed HTPs deliver significant levels of nicotine in aerosol, and their pharmacokinetics, drug and subjective effects are similar to those of contemporary ENDS products, suggesting comparable abuse liability. Little information is available on how these features affect consumer perception and use, including initiation, switching, complementing and quitting conventional tobacco products. Industry studies show that the main predictors of adoption are liking of the smell, taste, aftertaste and ease of use. The only independent study that explored reasons for use and continuation and discontinuation of IQOS among smokers and ex-smokers found that the six important factors were: health, cost, enjoyment and satisfaction, ease of use, use practices and social aspects.

As described above, the vast majority of current IQOS users are current or ex-smokers, and most are dual users of HTPs and conventional cigarettes, with no intention to quit smoking cigarettes. Hence, the expected reduction in exposure to smoking-related toxicants will be much smaller than if they switch completely, and the reduction in risk, if any, will probably be much lower. For dual users, any risk reduction would be smaller than for people who switched completely, and reduced risk has not been proven even for complete switchers. Although few users of HTPs are never users or ex-users of cigarettes, their potential interest in HTPs is still a risk at population level, especially for never users. The history of e-cigarettes shows that any new tobacco or related product coming onto the market quickly becomes popular. Knowledge of e-cigarettes indicates that the factors of concern with regard to HTPs, and therefore potential regulation, are nicotine levels and "throat hit", flavour variety, marketing and perception of reduced harm. Furthermore, like e-cigarettes *(85)*, HTPs could be a gateway towards cigarette smoking.

3.5.3 Research gaps, priorities and questions

- There is almost no information on perceptions and reasons for using HTPs among users, ex-users, smokers, dual users and never users of tobacco and related products. Only one independent study addressed the reasons for use, continuation and discontinuation of IQOS among smokers and ex-smokers.
- There is also little information on how the attractiveness of HTPs affects consumer perception and use, including initiation, switching, complementing and quitting conventional tobacco products.
- There is no information on whether HTPs could be a gateway to use of combustible tobacco.

Most independent studies on HTPs have focused on emissions and toxicity rather than attractiveness and addictiveness. Instead of trying to reproduce PMI emission data and claims of assessing reduced harm, researchers should study the actual trajectory of smokers, never smokers and ex-smokers to initiating use of HTPs and the role of appealing product characteristics.

Additional independent research should be conducted on all the features that enhance the attractiveness and addictiveness of HTPs described in this paper. The studies should include:

- sensory studies, including the roles of flavourings and flavours and other attractiveness-enhancing content and additives, such as sugars and humectants, in the use of HTPs;
- behavioural studies, both qualitative and quantitative, on knowledge, attitude and risk perceptions, including health messages;
- studies on all the features that enhance attractiveness and addictiveness in relation to consumer perception and use, with, preferably, groups of smokers, dual users, HTP users and never users, ideally in longitudinal quantitative studies that include use of other types of tobacco and related products to establish the impact of several features of perception of different types of tobacco products and to study transitions from e.g. current or never smoking to HTP use or even to combustible tobacco products; and
- studies on the pharmacokinetics of use of HTPs other than IQOS, to establish patterns of use and nicotine delivery under real conditions.

3.5.4 Policy recommendations

Policy-makers might consider adopting regulatory principles that have been applied successfully to tobacco and related products in many jurisdictions in order to minimize product appeal and uptake among young people, increase product safety and minimize false beliefs about health with regard to HTPs. They should thus consider the following measures, with a focus on protecting young people and non-users.

- Ban sale to minors, price promotions, flavours that appeal to young people and flavour capsules; limit marketing at points of sale and elsewhere; and introduce plain packaging to minimize the appeal of HTPs and their uptake by young people.
- Ensure that the public is not misled by their appeal and by claims from the manufacturers but is well informed about the risks of HTPs, including the risk of dual use with cigarettes and use during

pregnancy; correct false perceptions, counter misinformation, and clarify that reduced exposure does not necessarily mean reduced harm.

- Monitor the prevalence of use and user profiles; establish or extend surveillance of the product and users, including demographics, use of other tobacco and related products, devices, brands, types and flavours used.

3.6 Conclusions

HTPs have become popular in some markets probably because of a combination of factors, including their marketing as a "reduced risk", "clean", modern, elegant product. Their sensory properties and ease of use are generally rated lower than those of conventional cigarettes but are important dimensions of their attractiveness, thus determining their uptake. Little is known about how these features affect consumer perceptions and use. Factors such as packaging, labelling, risk communication, price and smoke-free policies appear to influence initiation and use.

Currently marketed HTPs deliver significant levels of nicotine in aerosol, and their pharmacokinetics and drug and subjective effects are similar to those of contemporary ENDS products, suggesting comparable abuse liability. The history of e-cigarettes has shown that any new tobacco or related product coming onto the market may quickly become popular. Knowledge about e-cigarettes indicate that the factors of concern with regard to HTPs – and therefore potential aims of regulation – are nicotine levels and "throat hit", variety of flavours, design of the devices, marketing and a perception of reduced harm.

3.7 References

1. Caputi TL. Industry watch: heat-not-burn tobacco products are about to reach their boiling point. Tob Control. 2016;26(5):609–10.
2. Ratajczak A, Jankowski P, Strus P, Feleszko W. Heat not burn tobacco product – A new global trend: impact of heat-not-burn tobacco products on public health, a systematic review. Int J Environ Res Public Health. 2020;17(2):409.
3. Kim M. Philip Morris International introduces new heat-not-burn product, IQOS, in South Korea. Tob Control. 2018;27(e1):e76–8.
4. Heated tobacco products information sheet. Second edition. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/bitstream/handle/10665/331297/WHO-HEP-HPR-2020.2-eng.pdf?sequence=1&isAllowed=y, accessed 10 January 2021).
5. Bialous SA, Glantz SA. Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control. Tob Control. 2018;27(Suppl 1):s111–7.
6. Liu X, Lugo A, Spizzichino L, Tabuchi T, Gorini G, Gallus S. Heat-not-burn tobacco products are getting hot in Italy. J Epidemiol. 2018;28(5):274–5.
7. Cho YJ, Thrasher JF. Flavour capsule heat-sticks for heated tobacco products. Tob Control. 2019;28(e2):e158–9.

8. Decision FCTC/COP8(22). Novel and emerging tobacco products. Geneva: World Health Organization; 2018 (https://www.who.int/fctc/cop/sessions/cop8/FCTC__COP8(22).pdf?ua=1, accessed 10 January 2021).
9. Philip Morris Products S.A. modified risk tobacco product (MRTP) applications. Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications, accessed 10 January 2021).
10. Marketing order. FDA submission tracking numbers (STNs): PM0000424-PM0000426, PM0000479. Silver Spring (MD): Food and Drug Administration; 2019 (https://www.fda.gov/media/124248/download, accessed 10 January 2021).
11. PMTA. Silver Spring (MD): Food and Drug Administration; 2019 (https://www.fda.gov/media/124247/download, accessed 10 January 2021).
12. The public health rationale for recommended restrictions on new tobacco product labeling, advertising, marketing, and promotion. Silver Spring (MD): Food and Drug Administration; 2019 (https://www.fda.gov/media/124174/download, accessed 10 January 2021).
13. Partial guidelines for implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control. Regulation of the contents of tobacco products and of tobacco product disclosures (FCTC/COP4(10)). Geneva: World Health Organization; 2012 (https://www.who.int/fctc/guidelines/Guideliness_Articles_9_10_rev_240613.pdf?ua=1, accessed 10 January 2021).
14. Haziza C, de la Bourdonnaye G, Merlet S, Benzimra M, Ancerewicz J, Donelli A et al. 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. Regul Toxicol Pharmacol. 2016;81:489–99.
15. Haziza C, de la Bourdonnaye G, Skiada D, Ancerewicz J, Baker G, Picavet P et al. Evaluation of the tobacco heating system 2.2. Part 8: 5-day randomized reduced exposure clinical study in Poland. Regul Toxicol Pharmacol. 2016;81(Suppl 2):S139–50.
16. Lüdicke F, Picavet P, Baker G, Haziza C, Poux V, Lama N et al. 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, multicenter study in sequential confinement and ambulatory settings (Part 1). Nicotine Tob Res. 2018;20(2):161–72.
17. Simonavicius E, McNeill A, Shahab L, Brose LS. Heat-not-burn tobacco products: a systematic literature review. Tob Control. 2019;28(5):582–94.
18. Lopez AA, Hiler M, Maloney S, Eissenberg T, Breland A. Expanding clinical laboratory tobacco product evaluation methods to loose-leaf tobacco vaporizers. Drug Alcohol Depend. 2016;169:33–40.
19. Hair EC, Bennett M, Sheen E, Cantrell J, Briggs J, Fenn Z et al. Examining perceptions about IQOS heated tobacco product: consumer studies in Japan and Switzerland. Tob Control. 2018;27(Suppl 1):s70–3.
20. Laverty AA, Vardavas CI, Filippidis FT. Design and marketing features influencing choice of e-cigarettes and tobacco in the EU. Eur J Public Health. 2016;26(5):838–41.
21. Lee J, Lee S. Korean-made heated tobacco product, "lil". Tob Control. 2019;28(e2):e156–7.
22. Reversing the Youth Tobacco Epidemic Act of 2019. 116th Congress, 1st session. H.R. 2339. Washington (DC): United States Government; 2019 (https://www.congress.gov/116/bills/hr2339/BILLS-116hr2339ih.xml, accessed 10 January 2021).
23. Our tobacco heating system. IQOS. Tobacco meets technology. Lausanne: Philip Morris International; 2020 (https://www.pmi.com/smoke-free-products/iqos-our-tobacco-heating-system, accessed 10 January 2021).
24. Liber AC. Heated tobacco products and combusted cigarettes: comparing global prices and

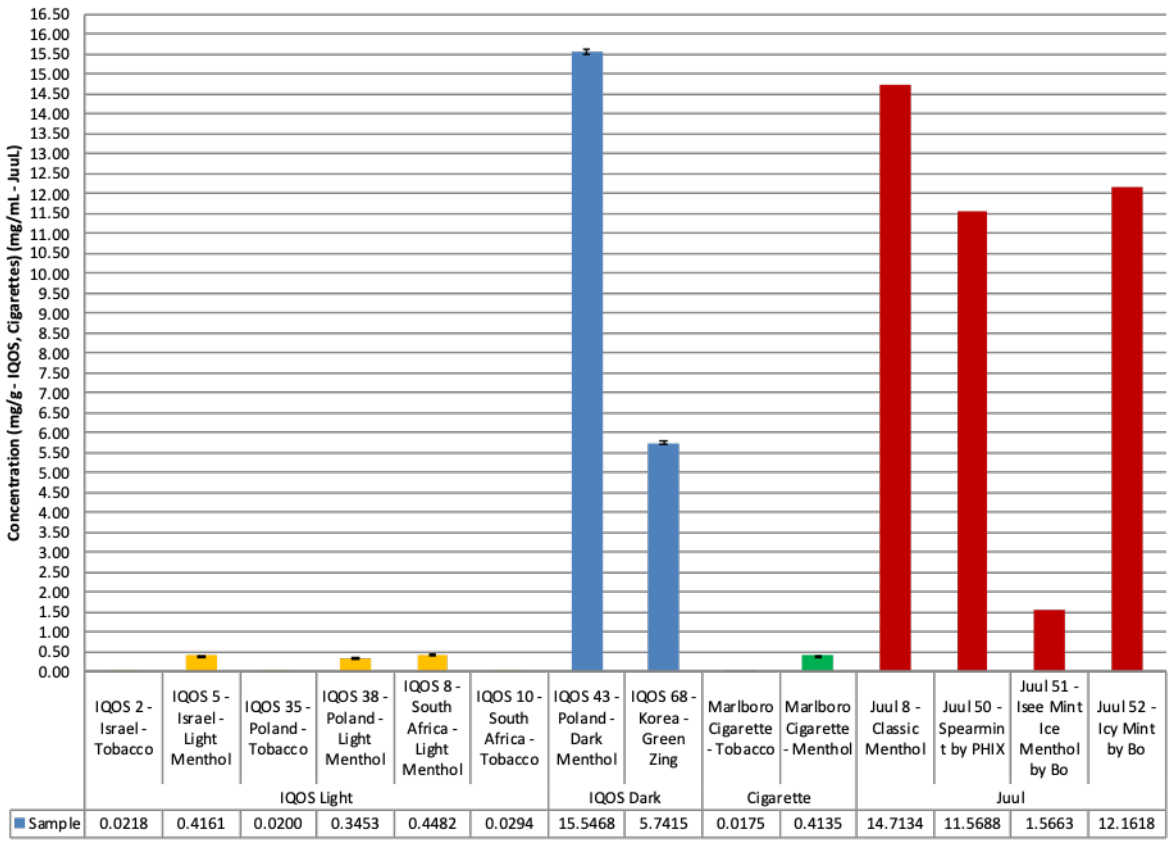
taxes. Tob Control. 2019;28(6):689–91.
25. Bar-Zeev Y, Levine H, Rubinstein G, Khateb I, Berg CJ. IQOS point-of-sale marketing strategies in Israel: a pilot study. Isr J Health Policy Res. 2019;8(1):11.
26. Staal YC, van de Nobelen S, Havermans A, Talhout R. New tobacco and tobacco-related products: early detection of product development, marketing strategies, and consumer interest. JMIR Public Health Surveill. 2018;4(2):e55.
27. Rosen LJ, Kislev S. IQOS campaign in Israel. Tob Control. 2018;27(Suppl 1):s78–81.
28. Tabuchi T, Kiyohara K, Hoshino T, Bekki K, Inaba Y, Kunugita N. Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan. Addiction. 2016;111(4):706–13.
29. Mathers A, Schwartz R, O'Connor S, Fung M, Diemert L. Marketing IQOS in a dark market. Tob Control. 2019;28(2):237–8.
30. Yuen J. Health Canada orders IQOS tobacco storefront to remove its signs. Toronto Sun, 1 November 2018 (https://torontosun.com/news/local-news/health-canada-orders-iqos-tobacco-storefront-to-remove-its-signs, accessed 10 January 2021).
31. Churchill V, Weaver SR, Spears CA, Huang J, Massey ZB, Fairman RT et al. IQOS debut in the USA: Philip Morris International's heated tobacco device introduced in Atlanta, Georgia. Tob Control. 2020:doi: 10.1136/tobaccocontrol-2019-055488.
32. Lee JGL, Blanchflower TM, O'Brien KF, Averett PE, Cofie LE, Gregory KR. Evolving IQOS packaging designs change perceptions of product appeal, uniqueness, quality and safety: a randomised experiment, 2018, USA. Tob Control. 2019;28(e1):e52–5.
33. Glantz SA. Heated tobacco products: the example of IQOS. Tob Control. 2018;27(Suppl 1):s1–6.
34. Lempert LK, Glantz SA. Heated tobacco product regulation under US law and the FCTC. Tob Control. 2018;27(Suppl 1):s118–25.
35. Popova L, Lempert LK, Glantz SA. Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims. Tob Control. 2018;27(Suppl 1):s87–95.
36. El-Toukhy S, Baig SA, Jeong M, Byron MJ, Ribisi KM, Brewer NT. Impact of modified risk tobacco product claims on beliefs of US adults and adolescents. Tob Control. 2018;27(Suppl 1):s62–9.
37. 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 heat-not-burn products: representative data on consumer behaviour and associated factors in the German population (the DEBRA study)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2018;61(11):1407–14.
38. La Torre G, Dorelli B, Ricciardi M, Grassi M, Mannocci A. Smoking E-CigaRette and HEat-no-T-burn products: validation of the SECRHET questionnaire. Clin Ter. 2019;170(4):e247–51.
39. Sponsiello-Wang Z, Langer P, Prieto L, Dobrynina M, Skiada D, Camille N et al. Household surveys in the general population and web-based surveys in IQOS users registered at the Philip Morris International IQOS user database: protocols on the use of tobacco- and nicotine-containing products in Germany, Italy, and the United Kingdom (Greater London), 2018–2020. JMIR Res Protoc. 2019;8(5):e12061.
40. Caponnetto P, Caruso M, Maglia M, Emma R, Saitta D, Busà B et al. Non-inferiority trial comparing cigarette consumption, adoption rates, acceptability, tolerability, and tobacco harm reduction potential in smokers switching to heated tobacco products or electronic cigarettes: Study protocol for a randomized controlled trial. Contemp Clin Trials Commun. 2020;17:100518.
41. Romijnders KA, Krüsemann EJ, Boesveldt S, Graaf K, de Vries H, Talhout R. e-Liquid flavor preferences and individual factors related to vaping: A survey among Dutch never-users, smokers, dual users, and exclusive vapers. Int J Environ Res Public Health. 2019;16:4661–76.
42. Carter LP, Stitzer ML, Henningfield JE, O'Connor RJ, Cummings KM, Hatsukami DK. Abuse liability assessment of tobacco products including potential reduced exposure products. Cancer

Epidemiol Biomarkers Prev. 2009;18(12):3241–62.
43. Slade J, Connolly GN, Lymperis D. Eclipse: does it live up to its health claims? Tob Control. 2002;11(Suppl 2):ii64–70.
44. Werley MS, Freelin SA, Wrenn SE, Gerstenberg B, Roemer E, Schramke H et al. Smoke chemistry, in vitro and in vivo toxicology evaluations of the electrically heated cigarette smoking system series K. Regul Toxicol Pharmacol. 2008;52(2):122–39.
45. Schaller JP, Keller D, Poget L, Pratte P, Kaelin E, McHugh D et al. 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):S27–47.
46. Jakaj B, Eaton D, Forster M, Nicol T, Liu C, McAdam K et al. Characterizing key thermophysical processes in a novel tobacco heating product THP1.0(T). Poster. Society for Research on Nicotine and Tobacco, 7–11 March 2017, Florence, Italy; 2017.
47. Certificate of Analysis. 1R6F certified reference cigarette. Lexington (KY): University of Kentucky; 2016 (https://www.ecigstats.org/docs/research/CoA_1R6F.pdf, accessed 10 January 2021).
48. Li X, Luo Y, Jiang X, Zhang H, Zhu F, Hu S et al. Chemical analysis and simulated pyrolysis of tobacco heating system 2.2 compared to conventional cigarettes. Nicotine Tob Res. 2018;21(1):111–8.
49. 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 Tob Res. 2018;20(8):1004–9.
50. Bekki K, Inaba Y, Uchuyama S, Kunugita N. Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. J UOEH. 2017;39(3):201–7.
51. Scott JK, Poynton S, Margham J, Forster M, Eaton D, Davis P et al. Controlled aerosol release to heat tobacco: product operation and aerosol chemistry assessment. Poster. Society for Research on Nicotine and Tobacco. 2–5 March 2016, Chicago, Illinois (http://www.researchgate.net/publication/298793405_Controlled_aerosol_release_to_heat_tobacco_product_operation_and_aerosol_chemistry_assessment, accessed 10 January 2021).
52. Eaton D, Jakaj B, Forster M, Nicol J, Mavropoulou E, Scott K et al. Assessment of tobacco heating product THP1.0. Part 2: Product design, operation and thermophysical characterisation. Regul Toxicol Pharmacol. 2018;93:4–13.
53. Forster M, Fiebelkorn S, Yurteri C, Mariner D, Liu C, Wright C et al. Assessment of novel tobacco heating product THP1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. Regul Toxicol Pharmacol. 2018;93:14–33.
54. Murphy J, Liu C, McAdam K, Gaça M, Prasad K, Camacho O et al. Assessment of tobacco heating product THP1.0. Part 9: The placement of a range of next-generation products on an emissions continuum relative to cigarettes via pre-clinical assessment studies. Regul Toxicol Pharmacol. 2018;93:92–104.
55. Taylor M, Thorne D, Carr T, Breheny D, Walker P, Proctor C et al. Assessment of novel tobacco heating product THP1.0. Part 6: A comparative in vitro study using contemporary screening approaches. Regul Toxicol Pharmacol. 2018;93:62–70.
56. Thorne D, Breheny D, Proctor C, Gaça M. Assessment of novel tobacco heating product THP1.0. Part 7: Comparative in vitro toxicological evaluation. Regul Toxicol Pharmacol. 2018;93:71–83.
57. 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.
58. Gee J, Prasad K, Slayford S, Gray A, Nother K, Cunningham A et al. Assessment of tobacco heating product THP1.0. Part 8: Study to determine puffing topography, mouth level exposure and consumption among Japanese users. Regul Toxicol Pharmacol. 2018;93:84–91.
59. Jaunky T, Adamson J, Santopietro S, Terry A, Thorne D, Breheny D et al. Assessment of tobacco

heating product THP1.0. Part 5: In vitro dosimetric and cytotoxic assessment. Regul Toxicol Pharmacol. 2018;93:52–61.
60. Proctor C. Assessment of tobacco heating product THP1.0. Part 1: Series introduction. Regulatory toxicology and pharmacology : RTP 2017 doi: 10.1016/j.yrtph.2017.09.010 [published Online First: 2017/10/11]
61. Salman R, Talih S, El-Hage R, Haddad C, Karaoghlanian N, El-Hellani A et al. Free-base and total nicotine, reactive oxygen species, and carbonyl emissions from IQOS, a heated tobacco product. Nicotine Tob Res. 2019;21(9):1285–8.
62. Albert RE, Peterson HT Jr, Bohning DE, Lippmann M. Short-term effects of cigarette smoking on bronchial clearance in humans. Arch Environ Health. 1975;30(7):361–7.
63. Meehan-Atrash J, Duell AK, McWhirter KJ, Luo W, Peyton DH, Strongin RM. Free-base nicotine is nearly absent in aerosol from IQOS heat-not-burn devices, as determined by (1)H NMR spectroscopy. Chem Res Toxicol. 2019;32(6):974–6.
64. Uchiyama S, Noguchi M, Takagi N, Hayashida H, Inaba Y, Ogura H et al. Simple determination of gaseous and particulate compounds generated from heated tobacco products. Chem Res Toxicol. 2018;31(7):585–93.
65. Maloney S, Eversole A, Crabtree M, Soule E, Eissenberg T, Breland A. Acute effects of JUUL and IQOS in cigarette smokers. Tob Control. 2020:doi: 10.1136/tobaccocontrol-2019-055475.
66. Wagener TL, Floyd EL, Stepanov I, Driskill LM, Frank SG, Meier E et al. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. Tob Control. 2017;26(e1):e23–8.
67. Fearon IM, Eldridge AC, Gale N, McEwan M, Stiles MF, Round EK. Nicotine pharmacokinetics of electronic cigarettes: A review of the literature. Regul Toxicol Pharmacol. 2018;100:25–34.
68. Voos N, Goniewicz ML, Eissenberg T. What is the nicotine delivery profile of electronic cigarettes? Expert Opin Drug Deliv. 2019;16(11):1193–203.
69. Yingst JM, Foulds J, Veldheer S, Hrabovsky S, Trushin N, Eissenberg TT et al. Nicotine absorption during electronic cigarette use among regular users. PLoS One/ 2019;14(7):e0220300.
70. Tabuchi T, Gallus S, Shinozaki T, Nakaya T, Kunugita N, Colwell B. Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to second-hand heat-not-burn tobacco aerosol. Tob Control. 2018;27(e1):e25–33.
71. Kim J, Yu H, Lee S, Paek YJ. Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults. Tob Control. 2018;27(Suppl 1):s74–7.
72. Roulet S, Chrea C, Kanitscheider C, Kallischnigg G, Magnani P, Weitkunat R. Potential predictors of adoption of the tobacco heating system by US adult smokers: An actual use study. F1000Res. 2019;8:214.
73. Sutanto E, Miller C, Smith DM, O'Connor RJ, Quah ACK, Cummings KM et al. Prevalence, use behaviors, and preferences among users of heated tobacco products: Findings from the 2018 ITC Japan survey. Int J Environ Res Public Health. 2019;16(23):4630.
74. Tompkins CNE, Burnley A, McNeill A, Hitchman SC. Factors that influence smokers' and ex-smokers' use of IQOS: a qualitative study of IQOS users and ex-users in the UK. Tob Control. 2020:doi: 10.1136/tobaccocontrol-2019-055306.
75. Hanson K, O'Connor R, Hatsukami D. Measures for assessing subjective effects of potential reduced-exposure products. Cancer Epidemiol Biomarkers Prev. 2009;18(12):3209–24.
76. Rees VW, Kreslake JM, Cummings KM, O'Connor RJ, Hatsukami DK, Parascandola M et al. Assessing consumer responses to potential reduced-exposure tobacco products: a review of tobacco industry and independent research methods. Cancer Epidemiol Biomarkers Prev. 2009;18(12):3225–40.
77. Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict Behav.

2007;32(5):912–23.
78. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob Res. 2001;3(1):7–16.
79. Lüdicke F, Baker G, Magnette J, Picavet P, Weitkunat R. Reduced exposure to harmful and potentially harmful smoke constituents with the tobacco heating system 2.1. Nicotine Tob Res. 2017;19(2):168–75.
80. Adriaens K, Gucht DV, Baeyens F. IQOS(TM) vs. e-cigarette vs. tobacco cigarette: A direct comparison of short-term effects after overnight-abstinence. Int J Environ Res Public Health. 2018;15(12):2902.
81. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry. 1986;43(3):289–94.
82. Romijnders K, van Osch L, de Vries H, Talhout R. Perceptions and reasons regarding e-cigarette use among users and non-users: A narrative literature review. Int J Environ Res Public Health. 2018;15(6):1190.
83. Kinouani S, Leflot C, Vanderkam P, Auriacombe M, Langlois E, Tzourio C. Motivations for using electronic cigarettes in young adults: A systematic review. Subst Abus. 2020;41(3):315–22.
84. Attitudes of Europeans towards tobacco and electronic cigarettes (Special Eurobarometer 458, wave EB87.1). Brussels: European Commission; 2017
85. Fadus MC, Smith TT, Squeglia LM. The rise of e-cigarettes, pod mod devices, and JUUL among youth: Factors influencing use, health implications, and downstream effects. Drug Alcohol Depend. 2019;201:85–93.
86. Meernik C, Baker HM, Kowitt SD, Ranney LM, Goldstein AO. Impact of non-menthol flavours in e-cigarettes on perceptions and use: an updated systematic review. BMJ Open. 2019;9(10):e031598.
87. Hwang JH, Ryu DH, Park SW. Heated tobacco products: Cigarette complements, not substitutes. Drug Alcohol Depend. 2019;204:107576.
88. Kang H, Cho SI. Heated tobacco product use among Korean adolescents. Tob Control. 2020;29(4):466–8.
89. Liu X, Lugo A, Spizzichino L, Tabuchi T, Pacifici R, Gallus S. Heat-not-burn tobacco products: concerns from the Italian experience. Tob Control. 2019;28(1):113–4.
90. Igarashi A, Aida J, Kusama T, Osaka K. Heated tobacco products have reached younger or more affluent people in Japan. J Epidemiol. 2020:doi: 10.2188/jea.JE20190260.
91. Czoli CD, White CM, Reid JL, O'Connor RJ, Hammond D. Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. Tob Control. 2020;29(1):89–95.
92. Dunbar MS, Seelam R, Tucker JS, Rodriguez A, Shih RA, D'Amico EJ. Correlates of awareness and use of heated tobacco products in a sample of US young adults in 2018–2019. Nicotine Tob Res. 2020:doi: 10.1093/ntr/ntaa007.

Annex 3.1. Menthol concentrations in IQOS, cigarettes and JUUL products



Source: Goniewicz ML, unpublished data, 2019.

4. Variations among heated tobacco products: considerations and implications

Maciej L. Goniewicz, Associate Professor of Oncology, Nicotine and Tobacco Product Assessment Resource, Department of Health Behavior, Division of Cancer Prevention and Population Studies, Roswell Park Comprehensive Cancer Center, Buffalo (NY), USA

Contents

Abstract

Heated tobacco products (HTPs) have attracted interest in the past few years and are now available on approximately 50 markets. The interest is attributed to factors that include aggressive marketing by manufacturers, users' perception that HTPs represent a "safer alternative" to other smoked products, their capacity to deliver nicotine to users, the variety of flavours, including tobacco

and menthol, technological advances and the variety of products and product features from which users can choose. The wide variation among the products, devices and their features result in the delivery of different levels of nicotine and toxicants, which has important regulatory implications. It is therefore important to understand how HTPs differ and how the differences affect the emissions of nicotine and other toxicants in order to formulate effective regulatory strategies and policies. The aim of this paper is thus to describe variations among the HTPs on the market in their characteristics and design features and how those features influence product toxicity, appeal and implications for regulations.

4.1 Background

4.1.1 Overview

HTPs are an emerging class of "potentially reduced exposure products" promoted by manufacturers as associated with "reduced risk", as "cleaner alternatives" and as "smoke-free" products. The concept of these products proceeds from the principle that most of the harm associated with tobacco smoking is from the combustion process. In a conventional tobacco cigarette, the temperature of the burning cone can reach up to 900 °C, with a median temperature across the rod of 600 °C *(1)*. This leads to myriad thermal reactions, including combustion, pyrolysis and pyrosynthesis, that result in the > 7000 compounds identified in tobacco smoke *(1)*. As burning tobacco is ultimately unnecessary to aerosolize nicotine (although it is efficient), alternative means for liberating nicotine from tobacco in an inhalable form have been explored; these might modify the toxicological risk associated with conventional tobacco cigarettes and influence consumer acceptability, which the earlier generation of these products failed to do.

4.1.2 Decision FCTC/COP8(22) of the Conference of the Parties

This paper was commissioned by WHO to address a component of the request to the Convention Secretariat in paragraph 2 of decision FCTC/COP8(22) by the Conference of the Parties to the WHO Framework Convention on Tobacco Control (WHO FCTC) at its eighth session, on novel and emerging tobacco products to address key topics related to those products and to submit a comprehensive report.

4.1.3 Scope and objectives

This report contains reviews of research on variations among novel and emerging HTPs and examination of the findings in the context of relevant aspects of the request. To the extent possible, the paper includes descriptions of the characteristics and design features of different types of HTPs, their contents and emissions, product diversity, market distribution and manufacturers and

discussion of the evidence for implications for users, non-users and regulators. Research gaps and priorities, some key questions and some recommendations for policy-makers are identified.

4.2 Variations among products on the market

4.2.1 Overview of product categories and types

HTPs have a different operating system from those of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (Table 4.1). HTPs contain a source of heat, which heats tobacco and vaporizes the tobacco constituents into an inhalable nicotine-containing aerosol, which contains other toxicants. Although HTPs contain tobacco material (as opposed to liquid in ENDS), they differ from conventional tobacco cigarettes, which must be combusted to create and deliver an aerosol to the user. HTPs do not achieve high temperatures during combustion and therefore aerosolize the nicotine from tobacco at a lower temperature (contemporary HTPs operate at < 350 °C) than conventional tobacco cigarettes (800 °C) *(2,3)*. Like ENDS, they are products that are purported to emit smaller amounts of toxicants than in the smoke from conventional cigarettes.

Table 4.1. Product performance characteristics and primary ingredients of heated tobacco products (HTPs), tobacco cigarettes and electronic nicotine delivery systems (ENDS)

Characteristic	Tobacco cigarettes	HTPs	ENDS
Nicotine	Yes	Yes	Yes[a]
Tobacco	Yes	Yes	No (nicotine derived mainly from tobacco)
Combustion	Yes	No (potential risk of incomplete combustion)	No (risk of thermal degradation of ingredients in the nicotine solution)
Temperature	Yes (very high during puffs)	Yes (generally lower than in tobacco cigarettes; may be overheated)	Yes (generally lower than in tobacco cigarettes; may be overheated)
Electronic system	No	Yes	Yes
Example of product			

[a] Electronic non-nicotine delivery systems (ENNDS) do not contain nicotine.

HTP systems have three common components: an insert (such as a stick, capsule or pod) that contains processed tobacco; a means for heating the tobacco (battery, carbon tip or aerosol); and a charger for electrically heated devices. Manufacturers have used four basic design approaches to HTPs that could serve as a useful basis for product classification. They differ in how the tobacco material is heated and whether it is separated from the heating element (Table 4.2).

Table 4.2. Classification of heated tobacco products according to the tobacco heating mechanism

Key characteristics	Examples of products
Integrated heating element	Premier, Eclipse, PMI "Platform 2" (TEEPS)
External heating element with specialized "cigarettes"	Accord, Heatbar, IQOS, glo
Hybrid devices: "vapour" plus tobacco; indirect heating	iFuse, PloomTECH
Heating chamber for loose tobacco material	PAX

The first and arguably the oldest type is a cigarette-like device with an embedded heat source that can be used to aerosolize nicotine (HTP type 1). The second approach is use of an external heat source to aerosolize nicotine from specially designed cigarettes (HTP type 2). This is the basic design of the Philip Morris International (PMI) IQOS (and its progenitors Accord and Heatbar) and the British American Tobacco (BAT) glo. For regulatory purposes, these represent two classes, one based on the heating device and the other on tobacco-containing sticks. Sticks generally meet the World Customs Organization classification of a cigarette (roll of tobacco in paper; harmonized system 2402.20). In the USA, the IQOS device is regulated as an accessory by the Food and Drug Administration (FDA) (much like ENDS, ENNDS and waterpipes), while the HeatSticks meet the statutory definition of cigarettes *(4)*. A third approach is to use ENDS technology to derive nicotine and tobacco flavour from small amounts of tobacco (HTP type 3). BAT's iFuse product appears to be a hybrid ENDS–tobacco product, in which the aerosol is passed over tobacco before reaching the user. Japan Tobacco International's (JTI) PloomTECH operates similarly, except that the solution from which the aerosol is created appears not to contain nicotine. A fourth approach is use of a heated sealed chamber to aerosolize nicotine directly from loose tobacco (HTP type 4). This class is represented by personal dry-herb vaporizers such as PAX, which have been marketed mainly for use with cannabis but can also aerosolize nicotine from tobacco. In the USA, since at least the 1970s, tobacco companies have been interested in marijuana and its legalization as both a potential and a rival product. Heating devices such as HTPs could be used with inserts containing marijuana and marketed for use with cannabis.

4.2.2 Variations among heated tobacco products

The concept of heating rather than burning tobacco emerged in the 1980s from the tobacco companies Philip Morris and RJ Reynolds in the USA, with Accord and Premier, respectively. These products and conceptually similar ones have continued to evolve and may now be poised to capture a significant market share. The introduction, aggressive marketing and growing popularity of ENDS may have set the conditions for these products to succeed, in part by changing social norms and perceptions of cigarette smoking and of devices that deliver nicotine. Strategies similar to those for promoting ENDS and ENNDS have been used for aggressive promotion and marketing of HTPs, and these products are now available in about 50 countries with plans for expansion to other markets.

4.2.3 Market distribution of product types and categories

Owing to declining sales of cigarettes, increased awareness of the health risk of smoked tobacco, increasing implementation of the WHO FCTC and the recent commercial success of ENDS and ENNDS, tobacco companies have reintroduced HTPs on the global market. Even as their usefulness for public health remains unclear, the marketing strategies of PMI, BAT and JTI are based on claims that the products reduce harm. Each of those companies has launched new-generation HTP brands in several countries since 2014 *(5)*. The international HTP market was valued at US$ 6.3 billion in 2018 *(6)*, with substantial market growth forecast over the next few years *(7)*. HTPs have attained a significant share of the tobacco market, particularly in Japan. Reports from market analysts indicate that Japan has the best-developed HTP market in the world, accounting for 85% of HTP sales in 2018 *(6)*, and tobacco inserts for PMI's primary HTP brand (IQOS) comprised 17% of all tobacco sales in July–September 2019 *(8)*. Table 4.3 shows product and pricing information for the three main HTPs in Japan. In the Republic of Korea, IQOS and domestic HTPs (KT&G, lil®) were launched simultaneously in 2017 *(9)*. HTPs are also gaining popularity elsewhere. BAT reported that its HTP brand, glo, had at least a 5% share of national tobacco markets in Poland, Romania and Serbia in June 2019 *(10)*. IQOS has been retailed online and in selected metropolitan shops in the United Kingdom (England) since December 2016 and in Canada since April 2017, while BAT launched glo in Vancouver, Canada, in May 2017. Early data suggest that, in both countries, awareness of HTPs was limited and uptake negligible 3–6 months after entry of HTPs to the market, and BAT halted glo sales in Canada in September 2019 *(11)*. Nevertheless, since 2018–2019, PMI has reported revenue increases of 92.5% in the United Kingdom (England) and 44.2% in Canada in their so-called "reduced risk" product line (including IQOS) *(7)*, suggesting that demand for HTPs is growing. In stark contrast, the sale of HTPs is effectively barred in Australia *(12)*, banned in a few other countries, including India, Saudi Arabia and Singapore, and,

until recently, the USA prohibited sales of IQOS, glo and other contemporary HTPs. In April 2019, however, IQOS and three varieties of "HeatSticks" were authorized for sale as tobacco products *(13)*, with other HTP brands expected to follow suit. On 7 July 2020, the FDA authorized IQOS as a "modified risk tobacco product" after an assessment of scientific studies that indicated that switching completely from conventional cigarettes to the IQOS system significantly reduced exposure to harmful or potentially harmful chemicals *(14)*.

Table 4.3. Product and pricing information for the three most popular heated tobacco products in Japan

	IQOS	**glo**	**Ploom TECH**
Device image			
Manufacturer	Philip Morris International	British American Tobacco	Japan Tobacco International
Launched	November 2014	December 2016	March 2016
Type of tobacco insert	Stick	Stick	Capsule
Device generations	1st: IQOS 2nd: IQOS 2.4 3rd: IQOS 3 and IQOS 3 Multi	1st: glo 2nd: glo Series 2 and glo Series 2 Mini	1st: Ploom TECH 2nd: Ploom TECH+ and Ploom S[a]
Brand name of insert	Marlboro Heatsticks	Kent Neostick	Mevius for Ploom TECH
Flavours of inserts	Balanced Regular, Menthol, Mint, Purple Menthol, Smooth Regular	Bright Tobacco, Citrus Fresh, Dark Fresh, Fresh Mix, Intense Fresh, Refreshing Menthol, Regular, Rich Tobacco, Smooth Fresh, Spark Fresh, Strong Menthol	Brown Aroma, Cooler Green, Cooler Purple, Red Cooler, Regular
Price[b]	IQOS 2.4: ¥ 7980 (~US$ 76) IQOS 3 Multi: ¥ 8980 (~US$ 85) Marlboro Heatsticks: ¥ 500 (~US$ 4.73)	glo: ¥ 2980 (~US$ 28) glo Series 2: ¥ 2980 (~US$ 28) glo Series 2 Mini: ¥ 3980 (~US$ 38) Kent Neostick: ¥ 420 (~US$ 3.97)	Ploom TECH: ¥ 2980 (~US$ 28) Ploom TECH+: ¥ 4980 (~US$ 47) Ploom S: ¥ 7980 (~US$ 76) Mevius for Ploom TECH: ¥ 490 (~US$ 4.64)

Source: reference 15.

[a] Has a stick instead of a capsule.

[b] In comparison, the price of a pack of conventional cigarettes is approximately ¥ 500 (about US$ 4.73).

4.3 Characteristics and design features of products

4.3.1 Temperature profiles of products and operational capabilities

In PMI's IQOS, the tobacco stick ("HeatStick") is heated by a blade inserted into the end, so that the heat dissipates through the tobacco plug on a puff *(2)*. The aerosol then passes through a hollow acetate tube and a polymer-film filter on the way to the mouth. The product is designed not to exceed 350 °C, at which point the energy supplied to the blade is cut off. BAT describes its glo product as a heating tube consisting of two separately controlled chambers, which are activated by the user by a button on the device, and reach an operating temperature of 240 °C, within 30-40 s *(3)*. BAT's iFuse product appears to be a hybrid HTP, which has a liquid component but also contains tobacco; it passes the aerosol generated from the liquid over tobacco before it reaches the user. One study indicated a small heat loss in the aerosol when it is passed over the tobacco chamber (from 35 °C to 32 °C), implying some tobacco heating *(16)*. The delivery of toxicants under machine-smoking conditions without the tobacco chamber is reported to be nearly identical to that from an ENDS, implying a minimal contribution of the tobacco. JTI's PloomTECH operates in a similar manner, except that the solution used to create the aerosol appears not to contain nicotine.

4.3.2 Battery characteristics

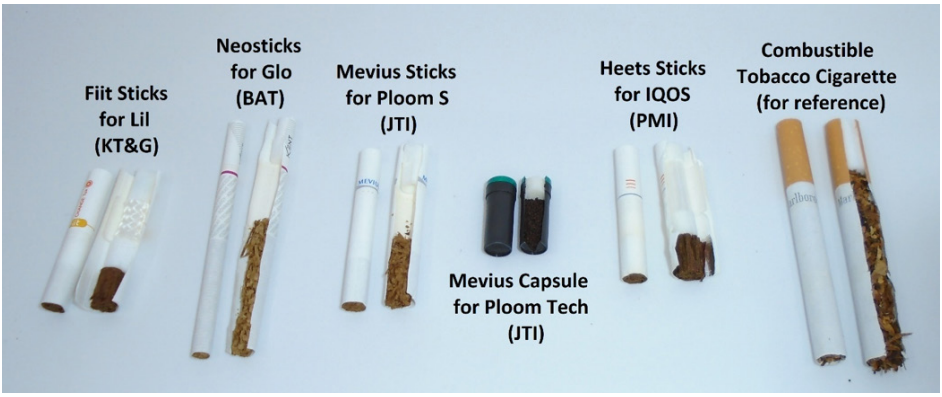
Different sources of heat are used in different HTP devices, including electric energy from a battery and carbon tip that is lit with a match or lighter. Most HTPs have lithium ion batteries, which are rechargeable and are used in many products, such as laptops, mobile phones and electric cars. All lithium ion batteries operate in the same way: the ions flow, in a solvent, between two oppositely charged poles separated by a permeable thin sheet. The direction of the flow depends on whether the battery is charging or discharging. Generally, lithium ion batteries are considered safe, however, if the separator between the poles is breached, the poles short-circuit, causing an increase in temperature, which in turn causes the highly flammable electrolyte solvent to combust, with an explosion.

4.3.3 Properties of tobacco inserts, sticks and capsules

The sticks for PMI's IQOS (45 mm long, 7 mm diameter) contain approximately 320 mg of tobacco material, whereas a conventional cigarette is 84–100 mm long, 7.5–8.0 mm in diameter and contains about 700 mg of tobacco material *(17)*. The tobacco in IQOS appears not to be typical tobacco cut-filler but rather a reinforced web of cast-leaf tobacco (a type of reconstituted tobacco), which contains 5–30% by weight of aerosol-forming components such as polyols, glycol esters and fatty acids *(17)*. This composition is advantageous as an aerosol-forming substrate for use with a heating system. A tobacco insert for BAT's glo product is an 82-mm

long, 5-mm diameter stick inserted into the heating chamber. The stick consists of a tobacco rod, a tubular cooling section, a filter and a mouthpiece. It contains approximately 260 mg of reconstituted sheet tobacco with 14.5% glycerol as the aerosolizing agent *(3)*. BAT's iFuse product appears to be a hybrid, with a cartridge containing nicotine solution at a concentration of 1.86 mg/mL, with machine delivery of 20–40 µg/puff *(16)*, and tobacco. It is, however, difficult to estimate the contribution, if any, of the tobacco in the iFuse device to the delivery of aerosolized nicotine, which the user inhales. JTI's PloomTECH operates in a similar manner, except that the liquid ENDS-like component appears not to contain nicotine (Fig. 4.1).

Fig. 4.1. Tobacco sticks and capsules in different heated tobacco products

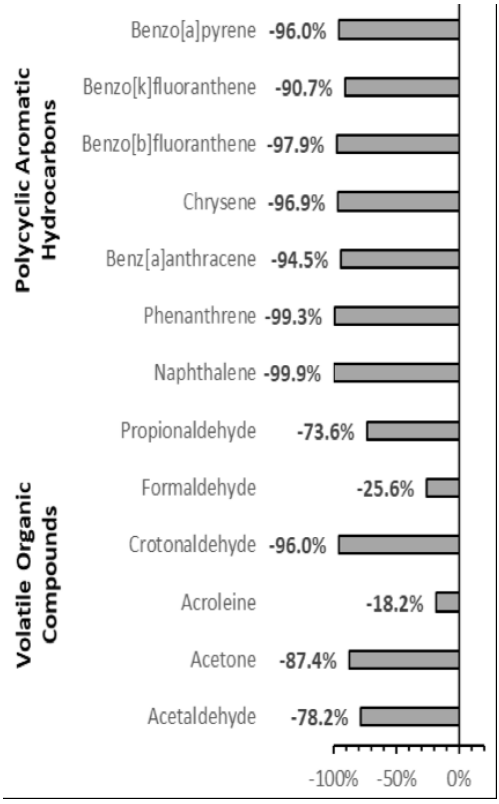


4.4 Content, emissions and general design of products

4.4.1 Content and emissions

Little is currently known about the individual ingredients and the emissions of HTPs products, and the health effects of many aerosolized constituents from tobacco and the other contents of the products, including humectants and additives, should be investigated to determine their effects on the health of users and non-users. HTP tobacco inserts often contain and emit toxicants, including cancer-causing chemicals, respiratory irritants and cardiovascular toxicants such as tobacco-specific nitrosamines, metals, volatile organic compounds, phenolic compounds, polycyclic aromatic hydrocarbons and minor tobacco alkaloids and organic solvents *(18–21)*. Many of those chemicals are classified as carcinogens and as harmful and potentially harmful when inhaled. These toxicants are present in HTPs in various amounts, although typically at levels lower than those found in conventional cigarettes (Fig. 4.2).

Fig. 4.2. Percentage decrease in yields of selected harmful chemicals in emissions from IQOS from those in smoke from conventional cigarettes



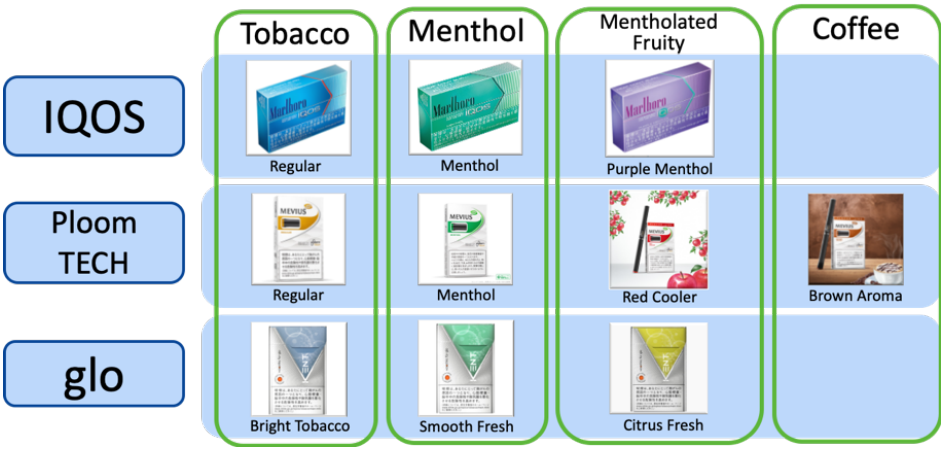
Source: reference *18.*

A toxicological review by the FDA found lower levels of some harmful and potentially harmful constituents in IQOS aerosol than in smoke from 3R4F standard reference research cigarettes and commercially available conventional tobacco cigarettes; however, the FDA also found that 80 chemicals in HeatStick aerosols, including four that are possibly carcinogenic, are unique to IQOS or present at higher levels than in 3R4F smoke. Additionally, IQOS aerosol contains 15 other chemicals that are possibly genotoxic and 20 more compounds generally recognized as safe for ingestion that have potential adverse health effects *(22,23)*. The FDA Technical Project Lead Review concluded that "although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of harmful and potentially harmful chemicals found in conventional cigarettes" and that the presence of these chemicals does "not raise significant concerns from a public health perspective" *(24)*.

The risks associated with inhaling large doses of the humectants used in HTPs, e.g. propylene glycol and vegetable glycerine, are not well characterized, although they have been approved for use for other purposes. For example, propylene glycol is commonly used as an additive in foods and cosmetics, a solvent in pharmaceuticals, an antifreeze and as an ingredient of theatrical mist or fog. Studies of the health effects in theatre staff exposed to such mists concluded that massive, prolonged exposure results in irritation of the airways *(25,26)*. Vegetable glycerine, although widely used in the food and chemical industry as a non-toxic additive, may pose risks as used in HTPs because they can generate toxic aldehydes (including formaldehyde, acetaldehyde, acrolein and acetone) at high temperatures, some of which are classified as carcinogens.

Some HTPs contain flavouring agents, including menthol and fruit (Fig. 4.3). (See also section 6.) Although most of the flavourings are also commonly used in foods and indoor fragrances, little is known about their health effects when inhaled. Use of flavours in HTPs is widespread and is often cited as the main reason for using each product *(15)*. Flavours also reportedly play an important role in shaping consumer perceptions of emerging tobacco products, as their use is associated with experimentation or initiation of use *(27)*. A wide range of flavours is available on the market, which include tobacco, menthol, fruity and coffee. Certain chemicals (e.g. vanillin, limonene, isoamyl alcohol) and classes of chemicals that are used to provide the taste and odour of these flavours have been associated with respiratory toxicity *(28)*. Few studies have addressed the role of flavours in use of HTPs. There is also little information on whether smokers who initiate use of flavoured HTPs do so to substitute completely for conventional cigarette use or whether the same association is seen in countries with different regulatory environments for HTPs.

Fig. 4.3. Varieties of flavoured tobacco inserts, cartridges and capsules for heated tobacco products



HTPs, as a product class, are exceptionally heterogeneous, with differences in the source of heat, heating elements and heating temperature. Each of these characteristics can influence the emissions of nicotine and non-nicotine toxicants and their delivery to users. Heating temperature in particular affects emissions of respiratory toxicants (including carbonyl compounds like formaldehyde, acetaldehyde and acrolein) that are generated by thermal degradation of humectants. Some HTPs may generate high levels of toxic chemicals.

4.4.2 Nicotine delivery

In most HTPs, nicotine is released from tobacco by heating the tobacco to a temperature that aerosolizes nicotine but may not achieve complete combustion of the plant material. In some hybrid HTPs, nicotine is present in the solution used to create inhalable aerosols. Volatilized nicotine that is not derived from combustion would, in principle, produce a less complex aerosol, with fewer toxic constituents than that from conventional tobacco cigarettes. Nicotine is not efficiently delivered as a gas; to deliver nicotine to a user's lungs, an aerosol-forming agent must be added to suspend nicotine on aerosol particles.

Nicotine is present in HTP aerosol in one of two forms: an unprotonated free base and a protonated salt. Nicotine is a weak base, and the fraction of any one form can be increased or decreased by altering the pH of the liquid. Free-base nicotine is volatile, is absorbed more readily than the monoprotonated form, produces enhanced electrophysiological and subjective responses in humans and may therefore be more addictive *(29)*. Free-base nicotine is, however, harsher on the throat than protonated nicotine when inhaled *(29)*. Laboratory studies have shown that nicotine in IQOS aerosol is present primarily in a protonated salt form *(20,30)*.

Nicotine is a pharmacologically active compound with a wide range of health effects. Although it can be used safely under controlled conditions in adults, it has been associated with various adverse health outcomes for the developing fetus, including fetal growth restriction, risk of preterm delivery and stillbirth, and may have effects on brain development during adolescence *(31–33)*. In addition, evidence suggests that nicotine poses a risk of acute toxicity or poisoning after ingestion of high doses *(34,35)*.

4.4.3 Risk profiles

As HTPs have appeared on the tobacco marketplace only recently, scientific evidence of their toxicity and possible harm reduction potential, both biochemical and behavioural, is still accumulating. Industry-funded sources have reported reduced concentrations of toxicants in serum and urine after a complete switch from conventional cigarettes to HTPs *(36–43)*, while independent studies have reported less cytotoxicity *(44)* and lower levels of tobacco-specific nitrosamines

after use of HTPs than after smoking conventional cigarettes, although the levels are higher than with ENDS *(21)*. Unlike ENDS, HTPs contain tobacco and, therefore, if there is no combustion, are expected to expose users to numerous chemicals present in the tobacco material. Moreover, some tobacco constituents that would be completely burnt and decomposed during combustion may be present in emissions from HTPs. Thus, HTPs may deliver a unique chemical mixture with a distinct toxicity profile, and the potential benefits of reductions in exposure to selected toxicants might be replaced by new health risks. Side-stream emissions and second-hand exposure are also a concern with HTPs. Some tobacco manufacturers claim that certain HTPs result in minimal side-stream exposure, whereas other studies show more substantial levels *(45)*. This may depend in part on the design of each product.

In the studies of human exposure currently available (all conducted by manufacturers), IQOS appears to deliver fewer toxicants than cigarettes and may serve as an effective short-term substitute for cigarettes, as assessed by nicotine delivery and subjective effects. Published data on BAT's HTPs are limited, although a study protocol for a randomized trial was published recently, suggesting work in this area by BAT. No published studies are available on JTI's Ploom product. Recent studies have, however, suggested a high prevalence of concurrent use of HTPs with conventional cigarettes and/or ENDS *(46–48)*. Studies on concurrent use of ENDS and conventional cigarettes did not generally show any significant reduction in exposure to tobacco-specific toxicants *(49–51)*. Thus, it is unlikely that the exposure of dual users of HTPs and conventional cigarettes to toxicants is significantly decreased.

4.4.4 Regulatory implications of the contents of heated tobacco products

Introduction of HTPs into the current landscape of nicotine and tobacco products presents a regulatory challenge (see also section 3), as it is currently impossible to determine whether these products could play a role in reducing risk or harm to smokers. The variation in regulations on new and emerging nicotine and tobacco products among countries will probably affect nicotine content and emission, use of devices, uptake by non-smokers and substitution for conventional cigarettes among smokers. The differences in regulatory environments could also influence overall use and consumer behaviour by affecting the availability of these products. Thus, it is important to understand the nature of the emerging tobacco product market, including the diversity of HTPs and how they are used, to fully appreciate the impact of the regulatory environment, the potential implications of different types of devices on use and their potential harm.

HTPs are often not subject to mandatory manufacturing standards, resulting in minimal oversight to prevent inaccurate labelling of ingredients or the presence of toxic components. Although the commercial sensitivity of flavour

recipes may limit disclosure of constituents, especially for ingredients of natural origin, governments and health authorities should require reporting of HTP constituents to appropriate government agencies. Several constituencies have enacted policies to regulate both the manufacture and marketing of flavoured tobacco products, including HTPs, to reduce their public appeal and health impact; these include the European Union, Canada, Ethiopia and the Republic of Moldova *(52)*. Some countries consider HTPs to be tobacco products, and the provisions that apply to other tobacco products apply also to HTPs. Various product standards may be imposed on HTPs by a regulatory body, such as maximum nicotine content and yields and thresholds for tobacco-related toxicants, heavy metals, pesticides, residual solvents, mould, yeast, mycotoxins and other chemical and biological impurities. Product standards for HTPs may also specify chemicals that are prohibited, including certain flavourings, colouring agents and sweeteners.

Regulators should also be alert to changes in the design and composition of a product. In a presentation to the Consumer Analyst Group of New York *(53)*, PMI claimed that IQOS had been modified from the original Japanese design in 2014–2017 in its aesthetics, blade self-cleaning technology, improved user interface, faster charging, Bluetooth connectivity, an accompanying mobile application and use of colours to increase the appeal of the device. Thus, a product may change after its introduction, as seen in the tobacco industry's practice of making minor adjustments to their cigarette products over time and among markets, such that a 2017 Marlboro is not necessarily identical to a 2010 Marlboro, and a Marlboro sold in France is not necessarily the same as one sold in the USA. In addition, research on a product may be done not with the product currently available to consumers but with a prototype (or even a series of different prototypes). While this practice is not in itself nefarious, any differences in design, function or presentation between the studied and the marketed product should be established and if and how such differences might affect consumer use. In the USA, the FDA follows a marketing authorization pathway in which changes to a product must be reported and can be monitored, with greater scrutiny and requirements for changes that impinge on public health (e.g. changes to delivery of harmful constituents; substantial design changes). European Union Member States, in the Tobacco Products Directive, have similar provisions. Regulators in other countries should consider a similar requirement for notification and justification of changes to products.

4.4.5 Regulatory implications of emissions

Given that HTPs have been found to contain various toxicants, product testing and constituent analysis can indicate the potential exposure of consumers to chemicals of concern for health. New tobacco products could be tested at

independent laboratory facilities licensed for analytical testing. It is unclear whether the toxicants potentially emitted by HTPs differ among markets. For example, whether these products are covered by smoke-free legislation depends on the specific wording *(53,54)*. The precautionary principle would support their inclusion in such regulations.

An additional concern with respect to emissions from HTPs is variation in the results reported by laboratories, which may result from use of differences in the analytical methods, the products tested and the puffing regimens used. For example, the puff duration for sampling aerosols may differ among laboratories, which will influence the toxicants emitted, as increasing the puff duration increases the mass of aerosol inhaled and exposes users to higher levels of toxicants. Other aspect of puffing protocols that may influence emissions include the number of puffs, flow rate and inter-puff intervals. Use of a standard puffing protocol designed for conventional cigarettes, such as those of the International Organization for Standardization or Health Canada (intense), could limit differences in results for emissions. A standardized puffing regimen may not, however, always be applicable, as the design of some products may limit it. For example, IQOS is designed to ensure the same puff duration and number of puffs as a cigarette, i.e. up to 14 puffs or 6 min of use. The puffing protocol may therefore be dictated by the device tested. This aspect of HTPs raises an additional challenge for designing regulations.

While the major ENDS and HTP companies sell their products worldwide, some smaller companies sell entire devices and device parts. For example, some tobacco inserts that are not manufactured by PMI can be used in IQOS devices *(55,56)*. Tobacco sticks manufactured by Imperial Brands Plc in the United Kingdom for their Pulze HTP system also fit the IQOS device. Such combinations might yield toxicants different from those from the original product, due to changes in features such as electrical power. In general, combinations of products should be considered in designing regulations.

4.5 Variations among products, manufacturers and selling points

4.5.1 Manufacturers and selling points

Most current HTPs are manufactured and marketed by major transnational tobacco companies. While the distribution of HTPs is markedly unique, the inserts for HTPs are commonly sold at conventional retail outlets, and the devices are sold in specialty shops and online. The specialty shops therefore rely on a single product, and sales representatives explain the device, provide free cleaning of customers' devices and propose a free trial of the product (Fig. 4.4). HTP specialty shops usually have clean, sleek, modern designs (like the aesthetic of an Apple outlet).

Fig. 4.4. HTP shops in Japan and the Republic of Korea (2019)

4.5.2 Implications for customer pulling power

Cigarette smoking remains one of the leading causes of preventable morbidity and mortality worldwide, even as the prevalence of smoking continues to decrease in many countries. The main driver of the health consequences of tobacco smoking is inhalation of combustion by-products during use. Newer nicotine and tobacco products might therefore reduce health risks if smokers switch to exclusive use of products, with modified chemical and physical properties. The potential usefulness of HTPs for reducing harm has been examined. Industry data suggest that HTPs can serve as a long-term substitute in highly controlled settings *(36–41)*. As noted elsewhere in this report, however, the issues should be addressed by independent research. There is also concern that "real-world" concurrent use of cigarettes and HTPs might prolong smoking behaviour, whereby smokers initiate HTPs according to the situation, rather than switching from smoking completely *(57)*. Additionally, population studies in several Asian countries have found substantial use of other tobacco products with HTPs, raising concern about whether the products can replace conventional tobacco smoking or are rather used as complementary products *(15,46–48,58)*. Large tobacco companies use a

variety of marketing strategies to promote HTPs to different sociodemographic groups, and differentiated marketing of cigarettes has disproportionately appealed to population subgroups such as adolescents and young adults, women, minorities and health-concerned smokers. (See section 10.)

Some concern has been raised about HTP users' privacy and security and how their personal information is collected and handled by HTP devices and by tobacco companies. HTPs are the first tobacco products that can harvest personal data on users' tobacco habits. PMI is already building a database of IQOS customers who register with the company *(59)*. Some HTP devices, including PMI's IQOS, are equipped with microcontroller chips that can store usage information and potentially transmit the information to the producer. The data could include details such as the number of puffs taken and how many times the user smoked the device in each day. The acquired data could potentially be used by tobacco industry in marketing. According to a statement by a PMI representative, the company extracts data from the device when investigating a malfunction *(59)*.

4.6 Discussion

HTPs are battery-operated devices that deliver nicotine aerosolized from tobacco, as well as other toxicants, to users. They are an emerging class of "potentially reduced exposure products" promoted by manufacturers as "reduced risk", "cleaner alternatives" and/or "smoke-free" products. HTPs have been marketed around the world with claims that they are less harmful than conventional cigarettes because they expose users to lower levels of some toxicants. There is, however, little evidence from independent studies on the chemistry of the aerosol produced by various types and brands of HTPs, the toxicology, effects on clinical measures, perceptions of the product and its packaging and behavioural factors.

HTPs present numerous regulatory challenges. The amounts of nicotine and non-nicotine toxicants depend on product features such as the composition of the tobacco insert, the temperature to which the heating element can rise and device design and characteristics. Understanding how these features influence important product characteristics such as temperature and emissions of nicotine and non-nicotine toxicants is essential for designing effective regulations and limiting the toxicity of these products. There is currently wide variation among the devices on the market, and users can control many of the devices' features that affect emissions, including those of numerous harmful chemicals, such as aldehydes, metals, volatile organic compounds and reactive oxygen species. As HTPs may emit chemicals that are not present in conventional cigarettes, chemical assessment of emissions from HTPs should go beyond those found in cigarette smoke. Additionally, the technology of HTPs is evolving rapidly, with new, more advanced devices constantly entering the market. These devices may

have new features that could increase the levels of toxicants in emissions. Keeping track of the HTPs on the market and of any new features they may have will allow assessment of how the new features affect the emissions of aerosol toxicants and therefore users' health.

An important concern is that HTPs could increase concomitant use of other tobacco products. Although industry data suggest that HTPs could be used as a long-term substitute in highly controlled settings, there is concern that "real-world" concurrent use of cigarettes and HTPs might prolong smoking behaviour, whereby smokers initiate HTPs for use according to the situation rather than switching completely from smoking. Current smokers may not understand that "switching completely" means that they would have to quit conventional cigarettes to achieve any claimed health benefits of HTPs. According to WHO, however, "quitting" is complete cessation of tobacco use for at least 6 months with no use of cessation aids. As HTPs are tobacco products, conversion from use of conventional cigarettes to HTPs would not constitute cessation *(60)*. Currently, there is no information on how HTPs affect smokers' intentions to quit smoking.

4.7 Conclusions

- HTPs are an emerging class of "potentially reduced exposure products" promoted by manufacturers as "reduced risk", "cleaner alternatives" and/or "smoke-free" products.
- HTPs, as a product class, are exceptionally heterogeneous, differing in materials, configuration, content of tobacco inserts and temperature to which the heating element can rise. Each of these characteristics can influence emissions of nicotine and non-nicotine toxicants.
- HTPs contain and emit nicotine.
- HTPs emit numerous toxic chemicals, including tobacco-specific nitrosamines, aldehydes and metals, although exclusive users of those products appear to be exposed to lower levels of toxicants than cigarette smokers.
- Unlike ENDS, HTPs contain tobacco and are therefore expected to expose users to numerous chemicals present in the tobacco material.
- HTPs may emit chemicals that are not present in conventional cigarettes.
- While HTPs may expose users to lower levels of some toxicants than cigarettes, they might expose them to higher levels of other toxicants.
- As these products have been introduced recently into the tobacco marketplace, scientific evidence on their toxicity and long-term health effects is still accumulating.

- Although the public health utility of these new tobacco products remains unclear, tobacco companies are extensively using marketing strategies based on potential harm reduction.
- Although industry data suggest that HTPs could be used as a long-term substitute in highly controlled settings, independent population-based studies have raised concern that "real-world" concurrent use of cigarettes and HTPs might prolong smoking behaviour.

4.8 Research gaps, priorities and questions

Research conducted independently of the industry is required to inform product users, public health professionals and regulatory agencies about the potential public health impact of HTPs. As the tobacco marketplace continues to evolve in various regulatory environments, it is vital to assess trends in awareness and use of HTPs.

The chemical profile and toxicity of all emerging tobacco products, including HTPs, must be thoroughly investigated. It is important to understand where these products are positioned along the continuum of risk relative to conventional cigarettes, ENDS and other smoked tobacco products.

Studies of the prevalence of use and of substitution for tobacco cigarettes are limited. Many of these products were test-marketed in a single country or small geographical region. Thus, it can be difficult to predict the uptake of novel products, particularly among young people. The characteristics of current and potential users of new tobacco products should be considered in assessing their potential public health impact. The concept of a continuum of harm is often based on the toxicity profile of a product as compared with cigarette smoke, with less attention to the characteristics of users and other important factors.

It is important to understand whether HTPs could play a role in reducing the risks to smokers by reducing their exposure to certain toxic chemicals as compared with conventional tobacco smoke. They might either reduce the risk of smokers or impose serious risks to health. How this balance is viewed depends on the context.

4.9 Policy recommendations

Key recommendations

- Tobacco companies should be required to investigate the chemical profile and toxicity of all HTPs. HTP manufacturers should disclose the findings of product testing and provide detailed descriptions of the testing methods used to the appropriate regulatory agencies. The effects of the combination of factors in the product should be investigated.

- Policy-makers should continuously monitor the market to identify new HTPs and similar products and changed features of products and emissions. Changes to an existing product must be reported to regulatory agencies so they can be monitored, with greater scrutiny and requirements for changes that affect public health (e.g. changes to the delivery of harmful constituents; substantial design changes).
- New or modified products should be subjected to premarket review by appropriate regulatory agencies before marketing. All HTP components should be regulated as stringently as other tobacco products, including restrictions on labelling, advertising, sales to minors, price and taxation policies and smoke-free measures.

Other recommendations

- Research independent of the tobacco industry should be conducted to inform product users, public health professionals and regulatory agencies of the potential public health impact of HTPs and to assess trends in awareness and use of HTPs.
- The chemical profile and toxicity of all emerging tobacco products, including HTPs, should be established.
- Studies of the prevalence of use and of substitution for tobacco cigarettes should be conducted in several marketplaces, with consideration of the characteristics of current and potential users of newer tobacco products and assessment of the potential public health impact of the products.
- Carefully designed, independent studies should be conducted to understand the toxicity profile of the chemicals emitted from HTPs in order to assess the risks of smokers relative to those of non-smokers and smokers of conventional cigarettes. Such evaluations should address differences in prevalence, user behaviour and the population risk of other tobacco products.
- The privacy and security of HTP users should be protected. The collection and handling of personal information on HTP devices and by tobacco companies should be regulated.

4.10 References

1. Stedman RL. Chemical composition of tobacco and tobacco smoke. Chem Rev. 1968;68(2):153–207.
2. Smith MR, Clark B, Lüdicke F, Schaller JP, Vanscheeuwijck P, Hoeing J et al. Evaluation of the tobacco heating system 2.2. Part 1: Description of the system and the scientific assessment program. Regul Toxicol Pharmacol. 2016;81(Suppl 2):S17–26.
3. Eaton D, Jakaj B, Forster M, Nicol J, Mavropoulou E, Scott K et al. Assessment of tobacco heating product THP1.0. Part 2: Product design, operation and thermophysical characterisation. Regul Toxicol Pharmacol. 2018;93:4–13.
4. US Code: Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–392 (Suppl 3 1934). Washington (DC): US Congress; 1934 (https://www.loc.gov/item/uscode1934-005021009).
5. Bialous SA, Glantz SA. Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control. Tob Control. 2018;27(Suppl 1):s111–7.
6. Uranaka T, Ando R. Philip Morris aims to revive Japan sales with cheaper heat-not-burn tobacco. Reuters, 23 October 2018 (https://www.reuters.com/article/us-pmi-japan/philip-morris-aims-to-revive-japan-sales-with-cheaper-heat-not-burn-tobacco-idUSKCN1MX06E, accessed 29 August 2019).
7. Heat-not-burn tobacco products market by product and geography – Forecast and analysis 2020–2024. Toronto: Technavio; 2020.
8. Third-quarter results 2019. Lausanne: Philip Morris International; 2019 (https://www.pmi.com/investor-relations/reports-filings, accessed 10 January 2021).
9. Lee MH. KT&G's heat-not-burn cigar overcomes downsides of competitors. The Korea Times, 22 December 2017 (http://www.koreatimes.co.kr/www/tech/2017/12/133_241123.html, accessed 20 February 2019).
10. Half-year report for the six months to 30 June 2019. London: British American Tobacco; 2019 (https://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOBELLYE, accessed 10 January 2021).
11. glo is being discontinued. British American Tobacco (glo.ca).
12. Greenhalgh EC. Heated tobacco ("heat-not-burn") products. In: Tobacco in Australia: Facts and issues. Melbourne: Cancer Council Victoria; 2018.
13. FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway. Silver Spring (MD): Food and Drug Administration; 2019.
14. FDA authorizes marketing of IQOS Tobacco Heating System with "reduced exposure" information. Press release; Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/news-events/press-announcements/fda-authorizesmarketing-IQOS-tobacco-heating-system-reduced-exposure-information, accessed 10 January 2021).
15. Sutanto E, Miller C, Smith DM, O'Connor RJ, Quah ACK, Cummings KM et al. Prevalence, use behaviors, and preferences among users of heated tobacco products: Findings from the 2018 ITC Japan survey. Int J Environ Res Public Health. 2019;16(23):4630.
16. Poynton S, Margham J, Forster M et al. Controlled aerosol release to heat tobacco: product operation and aerosol chemistry assessment. In: Society for Research on Nicotine and Tobacco, 2–5 March 2016, Chicago (IL) (https://cdn.ymaws.com/www.srnt.org/resource/resmgr/Conferences/2016_Annual_Meeting/Program/FINAL_SRNT_Abstract_WEB02171.pdf).
17. Batista RNM. Reinforced web of reconstituted tobacco. Neuchatel: Philip Morris Products SA; 2017.
18. 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(7):1050–2.
19. Davis B, Williams M, Talbot P. IQOS: evidence of pyrolysis and release of a toxicant from plastic.

Tob Control 2018;28(1).
20. Salman R, Talih S, El-Hage R, Karaoghlanian N, El-Hellani A, Saliba NA et al. Free-base and total nicotine, reactive oxygen species, and carbonyl emissions from IQOS, a heated tobacco product. Nicotine Tob Res. 2019;21(9):1285–8.
21. Leigh NJ, Palumbo MN, Marino AM, O'Connor RJ, Goniewicz ML. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. Tob Control. 2018;27(Suppl 1):s37–8.
22. Lempert LK, Glantz S. Analysis of FDA's IQOS marketing authorisation and its policy impacts. Tob Control. 2020. doi: 10.1136/tobaccocontrol-2019-055585.
23. St. Helen G, Jacob III P, Nardone N, Benowitz NL. IQOS: examination of Philip Morris International's claim of reduced exposure. Tob Control. 2018;27:s30–6.
24. PMTA coversheet: Technical Project Lead Review (TPL), 29 April 2019. Silver Spring (MD): Food and Drug Administration; 2019 (https://www.fda.gov/media/124247/download, accessed 10 March 2020).
25. Varughese S, Teschke K, Brauer M, Chow Y, van Netten C, Kennedy SM. Effects of theatrical smokes and fogs on respiratory health in the entertainment industry. Am J Ind Med. 2005;47:411–8.
26. Teschke K, Chow Y, van Netten C, Varughese S, Kennedy SM, Brauer M. Exposures to atmospheric effects in the entertainment industry. J Occup Environ Hyg. 2005;2(5):277–84.
27. Meernik C, Baker HM, Kowitt SD, Ranney LM, Goldstein AO. Impact of non-menthol flavours in e-cigarettes on perceptions and use: an updated systematic review. BMJ Open. 2019;9(10):e031598.
28. Leigh NJ, Lawton RI, Hershberger PA, Goniewicz ML. Flavourings significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ENDS). Tob Control. 2016;25(Suppl 2):ii81–7.
29. Voos N, Goniewicz ML, Eissenberg T. What is the nicotine delivery profile of electronic cigarettes? Exp Opinion Drug Deliv. 2019:1–11.
30. Meehan-Atrash J, Duell AK, McWhirter KJ, Luo W, Peyton DH, Strongin RM. Free-base nicotine is nearly absent in aerosol from IQOS heat-not-burn devices, as determined by 1H NMR spectroscopy. Chem Res Toxicol. 2019;32(6):974–6.
31. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol. 2009;49:57–71.
32. Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. Drug Saf. 2001;24(4):277–322.
33. Benowitz NL. Toxicity of nicotine: implications with regard to nicotine replacement therapy. Prog Clin Biol Res. 1988;261:187–217.
34. Appleton S. Frequency and outcomes of accidental ingestion of tobacco products in young children. Regul Toxicol Pharmacol. 2011;61(2):210–4.
35. Solarino B, Rosenbaum F, Riesselmann B, Buschmann CT, Tsokos M. Death due to ingestion of nicotine-containing solution: case report and review of the literature. Forensic Sci Int. 2010;195(1–3):e19–22.
36. Martin Leroy C, Jarus-Dziedzic K, Ancerewicz J, Lindner D, Kulesza A, Magnette J. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 7: A one-month, randomized, ambulatory, controlled clinical study in Poland. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S74–84.
37. Tricker AR, Kanada S, Takada K, Martin Leroy C, Lindner D, Schorp MK et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 6: 6-Day randomized clinical trial of a menthol cigarette in Japan. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S64–73.
38. Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 4: Eight-day randomized clinical trial in Korea. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S45–53.

39. Urban HJ, Tricker AR, Leyden DE, Forte N, Zenzen V, Feuersenger A et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 8: Nicotine bridging – estimating smoke constituent exposure by their relationships to both nicotine levels in mainstream cigarette smoke and in smokers. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S85–97. Erratum in: Regul Toxicol Pharmacol. 2015;71(2):185.
40. Tricker AR, Kanada S, Takada K, Leroy CM, Lindner D, Schorp MK et al. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 5: 8-Day randomized clinical trial in Japan. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S54–63.
41. Tricker AR, Stewart AJ, Leroy CM, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 3: Eight-day randomized clinical trial in the UK. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S35–44.
42. Schorp MK, Tricker AR, Dempsey R. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 1: Non-clinical and clinical insights. Regul Toxicol Pharmacol. 2012;64(2 Suppl):S1–10.
43. Gale N, McEwan M, Eldridge AC, Sherwood N, Bowen E, McDermott S et al. A randomised, controlled, two-centre open-label study in healthy Japanese subjects to evaluate the effect on biomarkers of exposure of switching from a conventional cigarette to a tobacco heating product. BMC Public Health. 2017;17(1):67.
44. 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(Suppl 1):s26–9.
45. Cancelada L, Sleiman M, Tang X, Russell ML, Montesinos VN, Litter Mi et al. Heated tobacco products: volatile emissions and their predicted impact on indoor air quality. Environ Sci Technol. 2019;53(13):7866–76.
46. Sutanto E, Miller C, Smith DM, Borland R, Hyland A, Cummings KM et al. Concurrent daily and non-daily use of heated tobacco products with combustible cigarettes: Findings from the 2018 ITC Japan Survey. Int J Environ Res Public Health. 2020;17(6):2098.
47. Hwang JH, Ryu DH, Park SW. Heated tobacco products: Cigarette complements, not substitutes. Drug Alcohol Depend. 2019;204:107576.
48. Kim J, Yu H, Lee S, Paek YJ. Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults. Tob Control. 2018;27(Suppl 1):s74–7.
49. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Udeni Alwis K et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: A cross-sectional study. Ann Intern Med. 2017;166(6):390–400.
50. Goniewicz ML, Smith DM, Edwards KC, Blount BC, Caldwell KL, Feng J et al. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. JAMA Netw Open. 2018;1(8):e185937.
51. Czoli CD, Fong GT, Goniewicz ML, Hammond D. Biomarkers of exposure among "dual users" of tobacco cigarettes and electronic cigarettes in Canada. Nicotine Tob Res. 2019;21(9):1259–66.
52. How other countries regulate flavored tobacco products. Saint Paul (MN): Tobacco Control Legal Consortium; 2020 (https://www.publichealthlawcenter.org/sites/default/files/resources/tclc-fs-global-flavored-regs-2015.pdf, accessed 12 August 2020).
53. Event details. Philip Morris International Inc. presents at the Consumer Analyst Group of New York (CAGNY) conference. Philip Morris International, 19 February 2020 (http://www.pmi.com/2020cagny).
54. Sutanto E, Smith DM, Miller C, O'Connor RJ, Hyland A, Tabuchi T et al. Use of heated tobacco products within indoor spaces: Findings from the 2018 ITC Japan Survey. Int J Environ Res Public Health. 2019;16(23):4862.
55. Gretler C. Philip Morris has a Nespresso problem. Bloomberg, 21 June 2019 (https://www.bloomberg.com/news/articles/2019-06-20/philip-morris-arms-itself-to-battle-emerging-

iqos-knockoffs, accessed 12 August 2020).
56. Asun. IQOS sets to launch "cartridge recognition" technology to counter Imperial Tobacco. VapeBiz, 2 July 2019 (https://vapebiz.net/iqos-sets-to-launch-cartridge-recognition-technology-to-counter-imperial-tobacco/, accessed 12 August 2020).
57. Miller CR, Sutanto E, Smith DM, Hitchman SC, Gravely S, Yong HH et al. Awareness, trial, and use of heated tobacco products among adult cigarette smokers and ecigarettes users: Findings from the 2018 ITC Four Country Smoking & Vaping Survey. Tob Control. 2020. [In press.]
58. Kim SH, Kang SY, Cho HJ. Beliefs about the harmfulness of heated tobacco products compared with combustible cigarettes and their effectiveness for smoking cessation among Korean adults. Int J Environ Res Public Health. 2020;17(15):E5591.
59. Lasseter T, Wilson D, Wilson T, Bansal P. Every puff you take. Part 5. Philip Morris device knows a lot about your smoking habit. Reuters, 15 May 2018 (https://www.reuters.com/investigates/special-report/tobacco-iqos-device, accessed 12 August 2020).
60. WHO report on the global tobacco epidemic, 2019. Geneva: World Health Organization, 2019 (https://www.who.int/teams/health-promotion/tobacco-control/who-report-on-the-global-tobacco-epidemic-2019#:~:text=The%20%22WHO%20report%20on%20the,bans%20to%20no%20smoking%20areas, accessed 10 January 2021).

5. Use of heated tobacco products: product switching and dual or poly product use

Richard O'Connor, Department of Health Behavior, Roswell Park Comprehensive Cancer Center, Buffalo (NY), USA

Armando Peruga, Tobacco Control Group, Bellvitge Biomedical Research Institute, Barcelona, Spain; Centre for Epidemiology and Health Policy, School of Medicine Clínica Alemana, Universidad del Desarrollo, Santiago, Chile

Contents

Abstract

New-generation heated tobacco products (HTPs) are claimed by their manufacturers to assist smokers of conventional tobacco products to quit and switch completely to HTPs as a "safer alternative" source of nicotine. Concurrent use of two or more nicotine or tobacco products (poly use) consists of various types of behaviour, with heterogeneous frequencies of product use and different health risks, influenced by user characteristics. The capacity of newer-generation HTPs to substitute completely for conventional cigarette use is likely to depend on product features and on the characteristics of smokers, including experience, preparedness to switch to and use HTPs for a long time and perhaps the tobacco control regulatory environment. We reviewed literature on HTP use in both the laboratory and real-world contexts. Contemporary HTPs appear to deliver

nicotine in pharmacologically meaningful doses in a similar manner to cigarettes or ENDS. Emerging independent studies indicate that poly use of cigarettes and HTPs is more common than implied by initial industry-sponsored studies. Little information is available on transitioning from cigarette smoking to HTPs, but the evidence suggests that smokers who use HTPs are more nicotine-dependent. Research is required on awareness about HTPs and the use behaviour in countries in which they have been introduced, including national surveys in the countries in which the products are available. Where their sale is permitted and the distinction is legally meaningful, HTPs should be considered as cigarettes rather than ENDS for the purposes of smoke-free laws, taxation, marketing and purchase.

5.1 Introduction

New-generation heated tobacco products (HTPs) are claimed by their manufacturers to assist smokers of conventional tobacco products to quit and switch to HTPs as a "safer, alternative" source of nicotine. This paper was commissioned by WHO to explore the potential role of HTPs in transitioning from conventional cigarettes (CCs) and other tobacco products. In particular, we addressed whether, as with use of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS), the marketing of HTPs leads to significant concurrent use of HTPs and CCs or additional tobacco products and if dual or poly use with HTPs helps or prevents smokers of conventional tobacco products in switching completely to HTPs. As regulators are pressured by industry to apply more lenient regulations to HTPs than to other tobacco products, claims that these products are "reduced risk" or can help "smokers" to switch to other products must be carefully evaluated.

The difficulty in responding to these questions is due to the paucity of information on the use of HTPs at population level, whether the use is mainly dual or poly use and the health effects of such use. Data on exposure from exclusive or poly use are limited. Secondly, we found no empirical studies on whether HTPs can transition cigarette smokers completely from smoking (smoking cessation) or nicotine use (nicotine cessation); therefore, it is not possible to explore the relation between cigarette smoking cessation with HTPs among exclusive HTP users or poly users. Finally, no studies have been reported on cessation of HTPs per se.

5.2 Information on HTP use at population level

Table 5.1 summarizes the 13 studies found on the prevalence of HTP use *(1–13)*, half of which describe experience of use of these products in Japan. Studies are available from only six countries between 2015 and 2019. All the data are from studies conducted at one time, except for one study in United Kingdom and one

in Japan. Therefore, except for the United Kingdom, it is difficult to establish any trends in the use of HTPs in the general population. According to the most recent studies, in 2018 and 2019, about 3% of the adult population in Japan currently uses HTPs, with far lower numbers in the United Kingdom (England) and Poland. The studies do not provide any real sense of the frequency of dual use of HTPs and cigarettes or other smoking products (cigars, *bidis*, hookahs).

Table 5.1. Prevalence of HTP use (2015 – 2019): studies by country and year of data collection

Year	Germany	Italy	Japan	Poland	Republic of Korea	United Kingdom
2015			Adults aged 15-69[a] IQOS, current use, 0.3% Ploom, current use, 0.3%			
			Adults aged 16-69[b] HTP, ever use, 0.5% HTP, never smokers, 0.1% HTP, former smokers, 1.0% HTP, current smokers, 1.8%			
			Adult patients with NCDs aged 40–69[c] HTP, ever use, ♂1.7% ♀ 0.6% HTP, current HTP use, ♂ 0.8% ♀ 0%			
2016			Adults aged 15–69[a] IQOS, current use, 0.6% Ploom, current use, 0.3%			
2017	Current smokers and recent ex-smokers aged ≥ 14[d] Current HTP use, 0.3%	Adults aged ≥ 15[e] Ever tried IQOS, 1.4%	Adults aged 15–69[a] IQOS, current use[c] 3.6% Ploom, current use, 1.2% glo, current use, 0.8%		Young adults aged 19–24[g] IQOS, current use, 3.5%	Adults[h] HTP, ever use, 1.7%
			Adults[f] Current IQOS use, 1.8%			English adults[i] Current HTP use • Quarter 1, 0.1% • Quarter 2, 0.1% • Quarter 3, 0.1% • Quarter 4, 0.1%

Year	Germany	Italy	Japan	Poland	Republic of Korea	United Kingdom
2018			Adults[f] Current IQOS use, 3.2% Adult population ≥ 15[j] Current HTP use, 2.7% Daily HTP use, 1.7%		Secondary school students[k] HTP, ever use, ♂ 4.4% ♀1.2%	English adults[i] Current HTP use • Quarter 1, 0.1% • Quarter 2, 0.1% • Quarter 3, 0.1% • Quarter 4, 0.1%
2019				Adults aged ≥ 15[i] Current HTP use, 0.4%		English adults[i] Current HTP use • Quarter 1, 0% • Quarter 2. 0.1% • Quarter 3, 0.1% • Quarter 4, 0.2%

HTP: heated tobacco product; NCD: noncommunicable disease.

[a] Prevalence of current HTP use (i.e. use in the previous 30 days) was calculated from a longitudinal internet survey of a nationally representative sample of 8240 Japanese individuals (15-69 years old in 2015) followed up to 2017 *(1,2)*.

[b] Internet survey conducted between 31 January and 17 February 2015 among 7338 respondents aged 18–69 from a panel by Rakuten Research *(3)*.

[c] Among 4432 Japanese patients with chronic diseases aged 40–69 years from an Internet survey in 2015 *(4)*.

[d] Among 18 415 Germans over the age of 14 in a representative sample of people participating in a household survey between June 2016 and November 2017; 0.3% (95% CI = 0.09–0.64) of current tobacco smokers and new ex-tobacco smokers (< 12 months smoke-free) currently used HTPs. Use of HTPs increased with increasing education and income *(5)*.

[e] Among a sample of 3086 people selected by multistage sampling to be representative of the general Italian population aged ≥ 15 years and interviewed face-to-face *(6)*.

[f] Of 4878 Japanese adults in 2017, 1.8% used IQOS. Of 2394 Japanese adults in the first half of 2018, 3.2% used IQOS. Of "platform 1" registered users, 1.3% and 1.6% in 2017 and 2018, respectively, were never smokers, and 98% in 2016 and 98.6% in 2017 were dual users with tobacco *(7)*.

[g] Online survey in 2017 of 228 general young adults aged 19–24 years *(8)*.

[h] Among a nationally representative sample of 12 696 adults aged ≥ 17 interviewed by the market research company YouGov Plc in Great Britain in February–March 2017 *(9)*.

[i] From the Smoking Toolkit Study, a monthly household survey with a new representative sample of ~1800 English respondents aged > 15 each month. The fieldwork is conducted by the British Market Research Bureau. Cigarette smokers and recent ex-smokers (who smoked in the previous year) who agreed to be re-contacted are followed up 3 and 6 months later by postal questionnaire. The data on HTPs cover 63 499 adults since January 2017 *(10)*.

[j] Among 4684 Japanese adult participants in a nationally representative Internet survey conducted in February–March 2018; 2.7% used HTPs at least once a month and 1.7% daily. Among current smokers, 1.8% used HTPs at least once a month and about 50% daily. Among never smokers, 0.02% used HTPs at least once a month, all of them daily *(11)*.

[k] Among 60 040 adolescents attending secondary schools in the Republic of Korea as of April 2018, 4.4% of males and 1.2% of females ever used HTPs. About 6% were current smokers. Of these, 32.4% had ever used HTPs. Of the 86% never smokers, only 0.3% had ever used HTPs *(12)*.

[l] Among a representative nationwide sample of 1011 people aged ≥ 15 in Poland in September 2019; 0.4% used HTPs, all of whom were current smokers, representing 1.9% of current smokers *(13)*.

5.3 Dynamics of switching from conventional cigarettes to HTPs: Is dual or poly use a transitional or permanent state?

Concurrent use of two or more nicotine or tobacco products (poly use) comprises many types of behaviour and heterogeneous frequencies of product use and health risks, influenced by user characteristics. In the USA, poly users of tobacco tended to be male, use other drugs and be more nicotine-dependent *(14–23)*. Use of several tobacco products tends to be unstable over time *(24–27)*. Table 5.2 outlines some common definitions of poly use drawn from the published literature on ENDS and ENNDS.

Table 5.2. Types of poly use described in studies on tobacco and nicotine

Type of use	Reported use	Pros	Cons
Lifetime poly use	Ever use of two products or more in a lifetime	Broadest measure; captures a number of potential use patterns	Captures use that may have occurred years before or minimal experimentation that may have little impact on current behaviour or disease risk
Recent poly use	Use of two or more products in past 30 days	Captures contemporary use	Does not account for quantity or frequency of use; one use of two products is considered equivalent to daily use of each product
Predominantly poly user	Use of two or more products in past 30 days, used one of the products more than the other, daily or nearly daily	More comprehensive assessment of use pattern	Requires more questioning. Potentially subject to recall bias, particularly for the less frequently used product
Balanced poly user	Use of two or more products in past 30 days, in equivalent amounts, daily or nearly daily	More comprehensive assessment of use pattern	Requires more questioning. Potentially subject to recall bias, particularly for the less frequently used product
Intermittent poly user	Use of two or more products in past 30 days on at least some days, but no consistent pattern of use of any product	More comprehensive assessment of use pattern	Requires more questioning. Potentially subject to recall bias, particularly for the less frequently used product

While few studies are available on HTP poly use per se, studies of ENDS may be instructive. Borland and colleagues *(28)* analysed survey data from Australia, Canada, the United Kingdom (England) and the USA and described four subgroups of concurrent use of cigarettes and ENDS who differed in nicotine dependence, quitting behaviour and perceptions *(28)*: 1) dual daily users, 2) predominantly smokers (who used cigarette daily and ENDS less than daily), 3) predominantly vapers (who used ENDS daily and cigarette less than daily); and 4) concurrent non-daily users (who used both cigarette and ENDS less than daily). While many concurrent cigarette–ENDS users report trying to reduce smoking *(29,30)*, this claim tends not to be reflected in biomarkers of exposure *(31,32)*, and reductions in cigarettes per day may not meaningfully reduce the risk of mortality

from smoking *(33–36)*. A study by Baig and Giovenco *(37)* on dual use of ENDS and cigarettes suggests some probable transition pathways for different dual use behaviour. Broadly, dual users who had higher education or income were more likely to completely switch to e-cigarettes or to quit tobacco use over two years.

Currently, there is insufficient evidence to conclude that HTPs are less harmful than CCs. In fact, there is concern that, while they may expose users to lower levels of some toxicants than CCs, they expose users to higher levels of other toxicants *(38–40)*. Studies indicate that up to 65% of HTP users in Japan and nearly all (96.2%) users in the Republic of Korea also smoked cigarettes *(2,11,41–43)*. Sutanto and colleagues *(44)* analysed subgroups of poly users in Japan and found the overall distribution shown in Table 5.3.

Table 5.3. Proportions in four subgroups of concurrent users of HTPs in Japan, 2018

Weighted percentages (95% confidence interval)		
	Daily HTP user (n=594)	Non-daily HTP user (n=265)
	51.5 (46.7–56.3)[a]	48.5 (43.7–53.3)[a]
Daily smoker (n=3686)	Dual daily user	Predominantly smoker
94.4 (91.9–96.2)[b]	51.0 (46.2–55.7)	43.4 (38.6–48.4)
Non-daily smoker (n=213)	Predominantly HTP user	Concurrent non-daily user
5.6 (3.8–8.1)[b]	0.5 (0.2–1.3)	5.1 (3.4–7.6)

Source: reference 44.
[a] Values shown are the sum of the overall column.
[b] Values shown are the sum of the overall row.

In 2018, most HTP users in Japan concurrently smoked cigarettes, and most used both products every day *(44)*. While there was no difference between exclusive daily smokers and dual daily users in the number of cigarettes per day, predominant smokers reported smoking more cigarettes per day than exclusive daily smokers, and predominant smokers used fewer tobacco-containing inserts per day than dual daily users; exclusive HTP users used more tobacco-containing inserts per day than dual daily users. Apart from greater frequency of use, this suggests that HTPs may not effectively substitute for cigarettes, consistent with the data from the Republic of Korea *(41)*. Cigarette–HTP users were younger than exclusive smokers, while a study of actual use in the USA found greater interest among middle-aged smokers *(45)*. Novel and emerging tobacco products often appeal to younger users for various reasons, including a perception of lower risk, marketing messaging and imagery and product appearance *(29,46–49)*. Only about 10% of concurrent cigarette–HTP users planned to quit smoking in the next six months. This finding is in contrast to that of Borland et al. *(28)* that 50% of concurrent cigarette–ENDS users planned to quit but consistent with the findings of Baig et al. *(37)*.

British American Tobacco (BAT) reported one study on use of its glo product *(50)*. Three groups took glo menthol, glo tobacco, glo and IQOS home for up to 14 days (with up to four laboratory visits). Participants reported using 12–15 cigarettes per day at baseline and used 8–12 units per day of the glo and IQOS products.

An application by Philip Morris International (PMI) to the US Food and Drug Administration for registration of IQOS as a "modified risk tobacco product" included a series of observational studies conducted by PMI on product switching in Germany, Italy, Japan, the Republic of Korea, Switzerland and the USA *(51)*. The study in the USA comprised 1106 current daily smokers who, after a 1-week baseline, were given access to IQOS (for free) for four weeks. The amount of product used (cigarettes and HeatSticks) was recorded in a diary. For this study, "switching" to IQOS was defined as using > 70% of total consumption as HeatSticks. About 15% of the participants met this definition by the end of the study, whereas 22% were dual users (30–70% of consumption as HeatSticks) and 63% were primarily smokers. In a second study, the product and its associated marketing were offered to 2089 daily smokers in Germany, Japan, Poland, the Republic of Korea and the USA. The prevalence of complete switching to a tobacco heating system (THS) ranged from 10% in Germany to 37% in the Republic of Korea, while dual use ranged from 32% in Japan to 39% in the Republic of Korea at the end of the 4-week trial. A 90-day use study on IQOS was conducted in the USA in 2013–2014, in which 88 of the 160 enrolled completed the study. It is noted that compliance with abstinence was substantially less in this study than in a similarly designed study in Japan, suggesting that experiences in one context cannot be generalized to others.

Limited post-market data are presented in the PMI application for IQOS. Those that are available are primarily from Japan, drawing on PMI's register of IQOS purchasers *(51)*. The proportion of exclusive IQOS use (> 95% of total consumption) increased from 52% to 65% between January and July 2016. Markov modelling of the transition in two cohorts of IQOS purchasers in Japan (in September 2015 and May 2016) suggested that those who transitioned to exclusive IQOS use are unlikely to transition back to exclusive cigarette use.

The Tobacco Products Scientific Advisory Committee of the US Food and Drug Administration expressed concern about some of the evidence on IQOS, and particularly the definition of "complete switching" and limitations of studies of consumer understanding of the claim of modified risk. The Committee offered qualified support only for a claim of exposure modification and expressed concern that the claims as worded would not be effective in communicating risk *(52)*.

In December 2017, the Committees on Toxicity, Carcinogenicity and Mutagenicity of Chemical Products in Food, Consumer Products and the Environment in the United Kingdom evaluated two HTPs on the market and concluded *(53)* that

> … while there is a likely reduction in risk for smokers switching to "heat-not-burn" tobacco products, there will be a residual risk and it would be more beneficial for smokers to quit smoking entirely. This should form part of any long-term strategy to minimize risk from tobacco use.

As few studies are available specifically on exposure to and the health effects of contemporary HTP poly use and are short-term, studies on older HTPs were evaluated. A study of an early-generation HTP (Accord) *(54)* analysed concurrent use with use of subjects' own-brand cigarettes. After 6 weeks of use, Accord appeared to reduce cigarette smoking and exposure to carbon monoxide dose-dependently, i.e. more use of Accord was associated with fewer cigarettes smoked, and participants did not appear to increased their puff intensity when they reduced the number of cigarettes per day. A study of an early-generation HTP, Eclipse, was reported by Fagerstrom and colleagues *(55)*. After an initial 4-week randomized study, participants self-selected to use Eclipse (n=10), a nicotine inhaler (n=13) or cigarettes (n=13) for an additional eight weeks. At baseline, those who chose Eclipse smoked fewer cigarettes per day (18.0) on average than the other groups (20.4 for inhaler, 21.3 for cigarette). Over the 8 weeks, 30–60% of participants reported smoking no cigarettes at all, and an average of 2.6 cigarettes were smoked per day, with little change over time. Overall, the older literature suggests incomplete substitution of HTPs for cigarettes, which is generally not associated with a meaningfully lower health risk *(56–58)*, rather than the complete switching on which HTP's promotion of harm reduction is predicated.

5.4 Potential role of HTPs as a substitute for conventional cigarettes

PMI stated in January 2018 that "more than 3.7 million smokers outside the US have switched exclusively to IQOS in only two years. At the same time, non-smokers and former smokers show very little interest in the product" *(59)*. We were unable, however, to find any empirical study to substantiate this claim or any other with regards to use of new-generation HTPs to transition cigarette smokers from smoking. Some surveillance was conducted in the United Kingdom (England), where 0–1.4% of 4155 adults who smoked and tried to stop or who had stopped in the 12 months before the survey mentioned HTPs as a method for switching after 2016, depending on the quarter, with a median quarter prevalence of 0.4% *(10)*.

The capacity of the newer-generation HTPs to substitute for use of CCs probably depends on product features, the characteristics of smokers, including their experience and their preparedness to switch to HTPs for a prolonged period, and perhaps the characteristics of the tobacco control regulatory environment. In the absence of direct empirical evidence of the potential efficacy and effectiveness

of HTPs in aiding switching, we used information on product features, such as their desirability and whether they deliver nicotine at a sufficient dose to reduce craving or withdrawal symptoms from CCs. The published studies of nicotine pharmacokinetics and evidence of the appeal of HTPs to smokers are described below, on the assumption that greater nicotine delivery and greater appeal might lead to greater substitution for cigarettes.

5.5 Exposure to nicotine and potential health risks among poly users

In this section, we compare use of HTPs with CCs among current smokers with regard to total nicotine delivered in mainstream emissions and key pharmacokinetics in plasma and urine.

Table 5.4 describes the 12 papers from 11 studies that we found up to January 2020 *(60–71)*, of which five were carried out or funded by the tobacco industry. The table updates and expands on that of Simonavicius et al. *(72)*. Comparison of the nicotine delivery in the aerosol of HTPs and the mainstream smoke of CCs is complicated by the variety of products and the methods used. The HTPs studied were IQOS (PMI), glo (BAT), iFuse (BAT) and a tobacco vaporizer. The reference products differed among studies. They included those developed for research, 3R4F 1R5F and 1R6F (most used 3R4F) and commercially available cigarettes, in which the yield of nicotine differs by brand, country and year. Mainstream emissions were obtained under the Health Canada Intense (HCI) regimen in most studies but with the International Standards Organization (ISO) regimen in others. It should be borne in mind that no machine-smoking regimen corresponds to human smoking and exposure, and their relevance to HTP use has not been validated. With these caveats, two conclusions can be reached from the studies.

- IQOS delivers about 70% of the nicotine contained in the smoke of CC. The relative nicotine delivery of IQOS is 40.7–102.8% (median 76.9%) when the reference is a commercial cigarette and 57–103% (median 64.7%) when the reference CC is one developed for research. The median in studies funded by the tobacco industry is not statistically significantly different from that in independent studies.
- The other HTPs studies appear to be less efficient (< 50%) than IQOS in delivering nicotine as compared with CC.

Table 5.4. Nicotine delivery in mainstream HTP aerosol and in mainstream smoke of conventional cigarettes

Reference			***69***	***66***	***65***	***67***	***63***	***62***	***60***	***61***	***68***	***64***	***70***	***71***
Year of publication			2019	2018	2018	2018	2018	2017	2017	2017	2017	2017	2016	2016
Tobacco industry affiliation or funding			No	No	No	No	Yes, BAT	No	No	No	Yes, BAT	Yes, PMI	Yes, PMI	Yes, PMI
Smoking	machine		Custom-built	LM4E	SM450 linear	NR	LM	Custom-built	Custom-built	NR	NR	LM set to 12 puffs (1/30s)	LM SM405XR SM405RH LM20X	NR
	regime		ISO, 6 puffs HCI, 12 puffs	HCI, 12 puffs	ISO, HCI		HCI	HCI, 12 puffs	ISO 14 puffs	HCI 9–11 puffs	HCI for CC CORESTA 3-s puff duration for HTP	HCI	HCI, ISO and five others based on observed HTP user puffing	NR
Product														
Conventional cigarettes	Type		Marlboro Red	48 commercial PM + 1R4F ISO, MDPH and HC smoking regimes[a]	3R4F	Marlboro Red, 1R6F	3R4F, 1R6F	Marlboro Regular	Lucky Strike Blue Lights	1R5F 3R4F	3R4F	3R4F	3R4F	3R4F
	Nicotine mg/ stick	Total	ISO, 0.8; HCI, 1.8	Min. 1.07; max. 2.7	ISO, 0.71; HCI 1.9	MR: 1.07 1R6F: 0.65	1.86	1.99 mg/ stick	0.361 mg/ stick	1.0–1.7 mg/ stick	1.8 mg/stick	1.86 mg/ stick	1.89 mg/ stick	1.88 mg/ stick
		FB	0.12–0.10	–	–			–	–	–				

Reference			*69*	*66*	*65*	*67*	*63*	*62*	*60*	*61*	*68*	*64*	*70*	*71*
Heated tobacco product	Nicotine	Type	IQOS	IQOS	IQOS	IQOS	THS (IQOS) THP1.0 (glo)	IQOS	IQOS	IQOS	Disposable neopod (iFuse)	IQOS THS2.2 regular	IQOS THS2.2 regular and menthol	IQOS THS2.2 with 43 different tobacco blends
		Unit[b]	mg/stick	mg/stick	mg/stick	mg/stick		mg/12 puffs	mg/stick	mg/stick			mg/stick	Mean mg/stick
		Total	0.77–1.5	1.1	0.50–1.35	0.67	IQOS:1.16 glo: 0.462	1.4	0.301	1.1 (regular) 1.2 (menthol)	Average mg per puff of first 100 puffs 2.56	1.14	1.3 (regular) 1.2 (menthol)	Reference blend, 1.38 Range of 43 blends, 1.6–6
		FB	0.10–0.09											
	Relative to CC		83.3–96.3% 81.9–90.3%	40.7–102.8%[c]	70.4–71.1%	MR: 63% 1R6F: 103%	IQOS: 57% glo: 23%	70.4%	83.4%	64.7%	14.5%[d]	61%	70% (regular)[d] 64% (menthol)	Reference blend 73% Range of 43 blends: 87–33%

BAT: British American Tobacco; CC: conventional cigarette; CORESTA: Cooperation Centre for Scientific Research Relative to Tobacco; FB: Free-base; HCI: Health Canada Intensive; ISO: International Standards Organization; NR: not reported; PMI: Philip Morris International; THC: tobacco heating system

[a] As estimated in 2005 in a separate study *(73)*.

[b] In comparison with the maximum and minimum nicotine yield of reference cigarettes. The authors report inconsistent nicotine delivery: the nicotine levels were initially < 50% of those found in the middle of the smoking procedure and therefore represent only 10–12% of the total nicotine yield. They argue that such inconsistency may influence consumer satisfaction, nicotine blood levels and adaptations of smoking behaviour.

[c] 14.5% is the authors' calculation; however, if the concentration in 14 puffs is the same as in other studies (2.56 * 0.14 = 0.358), the concentration is 19%.

[d] The authors reported a lower percentage in simulated Mediterranean, tropical and desert climate conditions, but did not report the exact figure.

5.6 Pharmacokinetics in animals

We found only one study in experimental animals. In this independent research, Nabavizadeh et al. *(67)* exposed three groups of eight rats each to IQOS aerosol from a single HeatStick, mainstream smoke from a single Marlboro Red cigarette or clean air. Exposure was for 1.5–5 min in a series of consecutive 30-s cycles, each cycle consisting of 5 or 15 s of exposure. After exposure, serum nicotine was about 4.5 times higher in rats exposed to IQOS than in those exposed to cigarettes, even though the IQOS aerosol contained about 63% the amount of the nicotine measured in smoke. When exposure to IQO emissions was shorter, the serum nicotine was similar in rats exposed to IQOS and cigarette emissions.

5.7 Pharmacokinetics in people

In most of these studies, values for biomarkers were reported after use of HTPs, ENDS and CCs. We report only the pharmacokinetics of nicotine after use of HTPs and CCs. The methods are summarized in Table 5.5.

Table 5.5. Methods used in studies on the pharmacokinetics of nicotine from HTPs and CCs in humans

Reference	Tobacco industry affiliation	Participants			Product		Exposure	
		Country	n	Design	HTPs	CCs		Biomarker of exposure
74	PMI	Poland	160	Healthy white smokers aged 21–65 years with 3-year smoking history and smoked ≥ 10 CCs in past 4 weeks	Controlled, three-arm parallel, single-centre study in confinement with participants randomized to exclusive use of HTP, CC or abstinence	IQOS THS2.2	Own brand	Daily ad-libitum use of assigned product for 5 days	Urine NEQ
75	PMI	Japan	160	Healthy smokers aged 23–65 years with 3-year smoking history and ≥ 10 CCs in past 4 weeks	Controlled, three-arm parallel, single-centre study in confinement with participants randomized to exclusive use of HTP, CC or abstinence	IQOS THS2.2	Own brand	Daily ad-libitum of assigned product for 5 days	Urine NEQ
76	PMI	Japan	62	Healthy smokers aged 23–65 years with 3-year smoking history and ≥ 10 CCs in past 4 weeks	Open-label, cross-over study with participants randomized to exclusive use of HTP, CC or NRT gum	IQOS THS2.2 regular and menthol	Own-brand, regular and menthol	1 unit/day of assigned product (CC: 1 cigarette, HTTP: 1 stick used for 14 puffs or ≈ 6 min, Gum: 1 chewed for 35 ± 5 min) in sequences after 1-day washout. 1: THS-CC; 2: CC-THS; 3: THS-Gum; 4: Gum-THS	Plasma nicotine
77	PMI	United Kingdom	28	Healthy white cigarette smokers aged 23–65 years with 3-year smoking history and ≥ 10 non-menthol CCs in past 4 weeks. Excluded if used other tobacco products, ENDS or ENNDS	Open-label, randomized, two-period, two-sequence cross-over study with participants randomized 1:1 to exclusive use of HTP or CC	IQOS THS2.1	Own brand	HTTP: 1 stick and ad-libitum use daily in sequence of 1 day abstinence, 1 day single stick, 1 day ad libitum of one product; sequence repeated with the other product	Plasma nicotine
78, 79	PMI	Japan	160	Healthy smokers aged 23–65 years with BMI 18.5–32 kg/m^2, smoked ≥ 10/day menthol CCs in the past 4 weeks and reported smoking menthol CCs for ≥ 3 years	Controlled, three-arm parallel, single-centre study in confinement with participants randomized to exclusive use of HTP, CC or abstinence	IQOS THS2.2 menthol	Menthol own-brand	Limited ad-libitum use of assigned product for 5 days	Urine NEQ
80	PMI	Poland	112	Healthy white smokers with BMI 18.5–27.5kg/m^2, aged 23–55 years, smoke 10–30 cigarettes per day, smoking for at least 5 consecutive years	Controlled, open-label, three-arm parallel group, single-centre confinement study with participants randomized 2:1:1 to exclusive use of HTP, CC or abstinence	CHTP prototype MD2-E7	Own brand	Ad-libitum use of assigned product for 5 days	Urine NEQ, cotinine
81	PMI	Poland	40	Healthy smokers who reported smoking for past 3 consecutive years and had smoked 10 commercially available non-menthol CCs daily for at least 4 weeks before the start of the study.	Controlled, open-label, two-arm parallel-group, single-centre confinement study with participants randomized 1:1 to exclusive use of HTP or CC	IQOS THS 2.1	Own brand	Ad-libitum use of assigned product for 5 days	Plasma nicotine, cotinine and urine NEQ

Reference	Tobacco industry affiliation	Participants			Design	Product		Exposure	Biomarker of exposure
		Country	n			HTPs	CCs		
82	PMI	USA	160	Healthy smokers of at least 22 years of age who had a BMI 18.5–35 kg/m^2 and reported smoking for past three consecutive years and had smoked 10 commercially available non-menthol CCs daily for at least 4 weeks before the start of the study (verified on a urinary cotinine test). The subject did not plan to quit smoking within the next six months.	Subjects randomized (day 0) in a 2:1:1 ratio to the menthol THS, menthol CC, and abstention groups. Randomization was stratified by sex and daily mCC consumption quotas. The 5-day confinement period was followed by an 86-day ambulatory period and an additional 28-day safety follow-up period.	IQOS THS 2.2	Own brand	Ad-libitum use of assigned product for 5 days	Plasma nicotine, cotinine and urine NEQ
83	BAT	Japan	180	Healthy verified daily smokers of 10–30 cigarettes/day with a ≥ 3-year history of smoking; exclusion of regular users of other nicotine and tobacco products in the previous 2 weeks or planning to quit in the next 12 months	Randomized, controlled, parallel-group open-label, clinical 5-day confinement study	IQOS, glo, THP1.0 non-menthol and menthol	Own brand	Limited ad-libitum use of assigned product for 5 days	Urine NEQ
84	JTI	Japan		Healthy smokers aged 21–65 years who smoked an average of ≥ 11 manufactured cigarettes/day at screening and had smoked for ≥ 12 months before trial	Open-label, two-sequence, two-period, randomized cross-over, confinement study	Prototype tobacco vapour product	Commercial CC	HTP: 10 puffs for 3 min at approximately 20-s intervals CC: 10 puffs for 3 min at approximately 20s intervals Each product was used alone for 1 day and the other product the following day	Plasma nicotine
85	No	Italy	20	Healthy smokers	Cross-over randomized trial	IQOS THS2.2	Marlboro Gold	Used assigned product during six 1-day cycles, each rotating the assigned product with an inter-cycle washout of 1 week. The product used in each cycle was: CC: 1 cigarette with mean nicotine content of 0.60 mg ENDS: 9 puffs from a tobacco-flavoured e-liquid with a mean nicotine content of 16 mg, thus yielding 0.58 mg of nicotine content in 9 puffs HTP: 1 stick with a mean nicotine content of 0.50 mg per stick	Plasma cotinine
86	No	USA	15	Healthy smokers aged 18–55 years of ≥ 10 cigarettes per day. Had not used marijuana in past 30 days, had used ENDS ≤ 20 times and LLTV ≤ 4 times in lifetime		LLTV HTP (PAX) prefilled with 1 g LLT	Own brand	Three sessions of two daily bouts of 10 puffs per product with a 30-s inter-puff interval and an inter-bout period of 60 min, with ≥ 48 h intersession intervals with pre-session ≥ 2-h abstinence	Plasma nicotine

BAT: British American Tobacco; BMI: body mass index; CC: conventional cigarette; CHTP: carbon-heated tobacco product; END: electronic nicotine delivery; ENND: electronic non-nicotine delivery; HTP: heated tobacco product; JTI: Japan Tobacco International; LLTV: loose-leaf tobacco vaporizer; NEQ: nicotine equivalents; NRT: nicotine replacement therapy; PMI: Philip Morris International; THS: tobacco heating system.

Independent studies

Two independent studies were found, one conducted with IQOS and the other with a loose-leaf tobacco vaporizer from PAX. Biondi-Zoccai et al. *(85)* performed a randomized, cross-over trial to compare the effects on smokers of using one stick of IQOS, ENDS and one CC. Exposure to nicotine was evaluated by measuring serum cotinine before use, after a 1-week washout from any tobacco or nicotine product, and immediately after product use. Use of CC and IQOS increased cotinine plasma levels significantly: for CC, from 34.4 ng/mL (SD±19.3) before using a CC to 65.5 ng/mL (SD±10.2), afterwards, and, for IQOS, from 30.4 ±12.0 ng/mL to 61.0 ±16.7 ng/mL. In each case, the difference was statistically significant at $P < 0.001$, but no significant difference was found between products.

Lopez et al. *(86)* compared plasma nicotine in current smokers before and after use of a loose-leaf tobacco vaporizer HTP from PAX (Ploom), an ENDS and the participant's own brand of CC. Mean plasma nicotine concentration increased significantly immediately after each of two bouts of scheduled product use, from baseline (all $P < 0.025$) to 24.4 (SD±12.6) ng/mL after use of CC and 14.3 (±8.1) ng/mL after use of HTP in bout 1, and 23.7 (SD±14.5) ng/mL after use of CC and 16.4 (SD±11.3) ng/mL after use of an HTP in bout 2. The level of plasma nicotine attained immediately after each bout was higher with CCs than with HTPs; however, only the difference between nicotine levels in CCs and HTPs immediately after bout 1 was statistically significant (all $P < 0.017$). The mean plasma nicotine concentrations after use of CC were significantly higher than those after use of HTPs from the beginning to the end of experimental use.

Tobacco industry studies

Ten studies conducted by the tobacco industry were found: nine papers derived from eight studies by PMI *(74– 82)*, one by BAT *(83)* and one by Japan Tobacco International (JTI) *(84)* (see Table 5.5). All the PMI studies are randomized trials with allocation to use mainly of IQOS (a carbon-tip HTP was used in one study), the participant's regular brand of CC or, in five studies, abstinence or nicotine replacement therapy. Exposure was usually for about 5 days of ad-libitum use of the assigned product. The studies of BAT and JTI were randomized trials with participants assigned to use of an HTP (IQOS or glo in the case of BAT and Tobacco Vaporizer in the case of JTI) or a commercial CC. Participants were exposed to 5 days of ad-libitum use of the assigned product in the BAT trial and to use of one stick for 2 days in the JTI trial.

Levels of biomarkers in plasma

Three studies *(76,77,84)* compared pharmacokinetics after use of the products (Table 5.6), as the area under the plasma concentration versus time curve from

time 0 to the last quantifiable concentration (AUC_{0-last}), an indicator of total exposure to nicotine on the assumption of equal clearance of the drug in all participants; the maximum observed plasma concentration attained (C_{max}), an indicator of the uptake of nicotine; the time to reach C_{max} (t_{max}), an indicator of the speed at which C_{max} is attained; and the half-life ($t_{1/2}$), an indicator of the duration of significant pharmacological effects. The values for IQOS THS2.2 were similar to those for CCs, with a t_{max} of 6 min. IQOS THS2.1 appeared to be less effective than CCs and IQOS THS2.2 in the uptake of nicotine and in providing the same maximal concentration. However, it presented a very similar t_{max} to CCs (8 min) and a slightly longer half-life than CCs. The tobacco vaporizer tested by Yuki et al. *(84)* reaching the t_{max} at the same time as CCs (3.8 min) but reached less than half of the C_{max} of CCs and generated < 70% of the nicotine taken up from CCs. Three studies in which IQOS, THS2.1 and THS2.2 were compared with CCs reported mean levels of nicotine and cotinine in plasma after 5 days of ad-libitum use of the HTP of about 85% for THS 2.1 and 100% for THS 2.2 of the levels reached after use of CCs.

Table 5.6. Pharmacokinetics of plasma nicotine after single use of IQOS and conventional cigarettes

Reference	***76***	***76***	***77***	***84***
Year of publication	2017	2017	2016	2017
Industry affiliation or funding	Yes	Yes	Yes	Yes
Reference CC	Own non-menthol brand	Own menthol brand	Own brand	CC1
HTP	THS2.2 IQOS	THS2.2 menthol IQOS	THS2.1	PNTV
HTP (single use) t to C_{max} (min)	6	6	8	3.8
AUC_{0-last} (ng*h/mL) Ratio of geometric LS means	96.3% 85.1–109.7%	98.1% 80.6–119.5%	77.4% 70.5–85.0[a]	68.3% 54.3–85.9%
C_{max} ng/mL Ratio of geometric least-squares means	103.5% 84.9–126.1%	88.5% 68.6–114%	70.3% 60.0–82.2%	45.7% 34.1–61.4%
t C_{max} (min) Median difference	0.04 -1.0–1.05	1.0 0.0–2.5	0.1 -1.0–2.0	-0.5 -1.1–0.03
$t_{1/2}$ (h) Ratio of geometric least-squares means	93.1% 84.6–102.4%	102.3% 85.3–122.7%	110.9% 101.7–120.9%	89.1% 78.2–102%

PNTV: prototype novel tobacco vapour. [a] 90% confidence interval.

Levels of biomarkers in urine

Six studies presented the value for nicotine equivalents in 24-h urine. The total with THS 2.2 and a carbon-tip HTP was ≥ 100% of that after use of CCs. For THS 2.1, the total was 87% of that of CCs. Use of glo resulted in urinary nicotine equivalents that were 57% and 74% of those of the comparable CCs, depending on whether they had menthol.

5.8 Subjective effects of use of HTPs and conventional cigarettes

We identified 10 studies in which the subjective effects of HTPs and CCs were compared *(74–77,79,81,82,86-88)*. IQOS was the HTP tested in all but one. The psychometric instruments most often used to assess the subjective impacts of HTPs and CCs were the brief questionnaire on smoking urges (QSU-brief) *(89)* and the modified cigarette evaluation questionnaire (mCEQ) *(90)*. The QSU-brief is a 10-item questionnaire, usually presented before use of the assigned product and then at the end of use to measure craving. The score may be reported as the total scale for its two components, desire to smoke with anticipation of pleasure from smoking and relief from nicotine withdrawal or negative affect with an urgent and overwhelming desire to smoke. The mCEQ assesses the reinforcing effects of product use, with three multidimensional domains, "smoking satisfaction", "psychological reward" and "aversion", and two single-item domains, "enjoyment of respiratory tract sensations" and "craving reduction".

The QSU-brief was used in eight studies, two independent *(86,88)* and six linked to industry *(74–77,79,82)*. All found, as expected, that the score for craving was high in all groups immediately before the start of the intervention. The score fell significantly immediately after use of IQOS or CC; however, the only independent study of IQOS reported that smoking resulted in lower craving scores than after use of IQOS (all $P < 0.001$) *(88)*, but the six industry studies did not. The least-squares mean differences between the IQOS and CC groups in the total QSU-brief scores in the industry studies, covering all times from the beginning to the end of use of the products, were generally small and none was statistically significant. The two independent studies *(86,88)*, which reported scores as the two-factor composition of the QSU-brief scale, found similar results over time. The study *(77)* that reported the QSU-brief scores for single-use and ad-libitum use found no difference in the mean total score (least square mean difference, 1.4 (95% CI: −1.0, 3.7) ad-libitum vs 0.2 (95% CI: −2.9, 5.3) for single use). This study, in which a loose-leaf tobacco vaporizer was compared with CCs, found that craving decreased significantly more after use of CC than after use of the vaporizer.

The mCEQ was used in seven studies *(74,75,77,79,81,82,88)*. In all the studies, the questionnaire was administered at the end of exposure, sometimes immediately. The only independent study *(88)* found that use of both products, IQOS and CCs, had a reinforcing effect on all subscales; however, CCs had a more substantial subjective effect than IQOS in terms of satisfaction, psychological reward, enjoyment of respiratory tract sensations and reduced craving. The industry studies tended to report significantly less reinforcing effect of IQOS use than of CC use on all or some of the mCEQ subscale scores, except aversion. Two studies *(75,79)* reported significant differences in all subscales at the beginning and one at the end of the exposure period, with the greatest difference for

satisfaction and craving reduction. Another study *(81)* found that CC smokers had greater smoking satisfaction than IQOS users highlighted on the last day of exposure as compared with baseline. In another study *(82)*, the average results on the mCEQ for the entire 5-day exposure period were significantly lower for participants who switched to IQOS use than for participants who continued to smoke CC, after adjustment for baseline, smoking satisfaction, craving reduction, enjoyment of respiratory tract sensation and psychological reward. One study *(77)* indicated that the differences between the two products for smoking satisfaction, psychological reward, craving reduction and enjoyment of respiratory tract sensations were more significant after ad-libitum use. In an independent study, Biondi-Zoccai et al. *(85)* used neither the QSU-brief nor the mCEQ but a seven-question product satisfaction questionnaire *(91)*, which was administered after each session of product use. Satisfaction scores were higher for CCs than HTPs.

This limited body of research shows that HTPs overall deliver nicotine at a lower dose and more slowly than CCs. Of the HTPs analysed, only IQOS THS2.2 reaches the nicotine delivery of CCs. IQOS can reduce craving for smoking, perhaps to a lesser degree than CCs. Industry-linked studies showed little difference, and the one independent study showed significantly less reduction in craving than CCs. The sole study on other HTPs showed that a loose-leaf tobacco vaporizer was less able to quench smoking craving than CCs; however, IQOS and the vaporizer were perceived as less satisfying than CCs.

5.9 Discussion and implications

Little published information is available on use of HTPs at population level or whether the use is part of a poly use pattern or associated with cessation of use of CCs or nicotine. While research in this area is increasing and HTP use is being assessed in a number of surveys (e.g. International Tobacco Control, Japan Society and New Tobacco Internet Survey), publication will take months to years *(44,92–107)*. Independent studies do indicate that dual use of cigarettes and HTPs is more common than implied by initial industry-sponsored studies *(44,98,100)*. More information is required, however, on usage patterns in view of sociodemographic confounders *(95,99,106)*. There is little empirical support for the suggestion that new-generation HTPs overall help to transition smokers from CCs, and no studies on nicotine cessation have been published. Most of the available studies are industry-linked, and most studied IQOS. Laboratory studies suggested that only one of the HTPs analysed could deliver nicotine at a dose comparable to that of cigarettes *(76,77,84)*; however, other factors, including attractiveness and appeal, are often important in substitution behaviour. HTPs appear to reduce smoking craving subjectively, although perhaps not as significantly as CCs. It is, however, clear that HTPs are not as satisfying to smokers as CCs.

5.10 Research gaps

- Independent data on population-level usage patterns other than ever use. The key metrics include use with other products, amount used, daily or non-daily use and flavour preferences (where applicable) to determine the validity of claims of reduced risk.
- Studies on lil (KT&G), an HTP available in the Republic of Korea and now being marketed elsewhere by PMI, for which no published data were found.
- Independent studies of the pharmacokinetics of nicotine in HTPs other than IQOS, preferably between subjects to allow direct comparisons.
- Studies of the pharmacokinetics of nicotine delivery by HTPs, of leading ENDS products and/or of nicotine replacement therapy to compare the potential abuse liability of HTPs with that of products used to stop smoking.
- Independent studies of smoking cessation and use behaviour after adoption of HTPs expressly to cease smoking of conventional products.
- Studies of cessation of HTP use.

5.11 Policy recommendations

Policy-makers should consider the following recommendations for policy on the potential role of HTPs in cessation of smoking conventional tobacco products, particularly in the context of poly use of tobacco products.

5.11.1 Cessation policy

There is insufficient evidence that HTPs aid a switch from smoking. Therefore, claims should not be made to that effect. Even if future evidence supported HTPs as effective switching aids (i.e. substituting one tobacco product for another), they should never be considered as treatment for smoking cessation, which includes quitting nicotine use.

5.11.2 Surveillance policy

Surveillance of the prevalence and patterns of use of HTPs in various sociodemographic groups over time is rarely conducted at country level and should urgently be implemented. Understanding patterns of use among vulnerable populations (e.g. young people, racial and ethnic minorities, pregnant women) is of particular importance. The variables surveyed should include frequency of use (daily

or non-daily use), amount used, concurrent use of other tobacco and nicotine products (poly use) and flavours used (where applicable). Surveillance systems might also include making it mandatory to record tobacco use, including HTPs, in medical notes.

5.11.3 Research policy

Studies should be conducted of consumers' use of HTPs to substitute completely for conventional cigarettes. Policy-makers are encouraged to prioritize funded research on ways to increase the reach, demand, quality, dissemination, implementation and sustainability of evidence-based smoking treatments.

5.11.4 Cooperation and partnership policy

Given the rapid dissemination of use of HTPs in the absence of the necessary scientific evidence of their effectiveness as aids for switching to conventional tobacco smoking, policy-makers are urged to share national experiences and to collaborate in developing an appropriate regulatory framework for HTPs.

5.12 References

1. Tabuchi T, Gallus S, Shinozaki T, Nakaya T, Kunugita N, Colwell B. Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. Tob Control. 2017;27(e1):e25–33.
2. Tabuchi T, Kiyohara K, Hoshino T, Bekki K, Inaba Y, Kunugita N. Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan. Addiction. 2016;111(4):706–13.
3. Miyazaki Y, Tabuchi T. Educational gradients in the use of electronic cigarettes and heat-not-burn tobacco products in Japan. PloS One. 2018;13(1):e0191008.
4. Kioi Y, Tabuchi T. Electronic, heat-not-burn, and combustible cigarette use among chronic disease patients in Japan: A cross-sectional study. Tob Induc Dis. 2018;16:41.
5. 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 heat-not-burn products: representative data on consumer behaviour and associated factors in the German population (the DEBRA study)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2018;61(11):1407–14.
6. Liu X, Lugo A, Spizzichino L, Tabuchi T, Pacifici R, Gallus S. Heat-not-burn tobacco products: concerns from the Italian experience. Tob Control. 2019;28(1):113–4.
7. Langer P, Prieto L, Rousseau C. Tobacco product use after the launch of a heat-not-burn alternative in Japan: results of two cross-sectional surveys. Poster. Global Forum on Nicotine, 2019 (https://www.pmiscience.com/resources/docs/default-source/posters2019/langer-2019-tobacco-product-use-after-the-launch-of-a-heat-not-burn-alternative-in-japan.pdf?sfvrsn=460ed806_4, accessed 10 January 2021).
8. Kim J, Yu H, Lee S, Paek YJ. Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults. Tob Control. 2018;27(Suppl 1):s74–7.
9. Brose LS, Simonavicius E, Cheeseman H. Awareness and use of "Heat-not-burn" tobacco products in Great Britain. Tob Reg Sci. 2018;4(2):44–50.
10. West R, Beard E, Brown J. Trends in electronic cigarette use in England. Smoking Toolkit Study,

2020 (http://www.smokinginengland.info/sts-documents/, accessed 10 January 2021).
11. Sutanto E, Miller C, Smith DM, O'Connor RJ, Quah ACK, Cummings KM et al. Prevalence, use behaviors, and preferences among users of heated tobacco products: Findings from the 2018 ITC Japan survey. Int J Environ Res Public Health. 2019;16(23):4630.
12. Lee Y, Lee KS. Association of alcohol and drug use with use of electronic cigarettes and heat-not-burn tobacco products among Korean adolescents. PloS One. 2019;14(7):e0220241.
13. Pinkas J, Kaleta D, Zgliczynski WS, Lusawa A, Iwona Wrześniewska-Wal, Wierzba W et al. The prevalence of tobacco and e-cigarette use in Poland: A 2019 nationwide cross-sectional survey. Int J Environ Res Public Health. 2019;16(23):4820.
14. Berg CJ, Haardorfer R, Schauer G, Getachew B, Masters M, McDonald B et al. Reasons for polytobacco use among young adults: Scale development and validation. Tob Prev Cessation. 2016;2:69.
15. Bombard JM, Pederson LL, Koval JJ et al. How are lifetime polytobacco users different than current cigarette-only users? Results from a Canadian young adult population. Addictive behaviors 2009;34(12):1069-72. doi: 10.1016/j.addbeh.2009.06.009 [published Online First: 2009/08/04]
16. Bombard JM, Pederson LL, Nelson DE, Malarcher AM. Are smokers only using cigarettes? Exploring current polytobacco use among an adult population. Addict Behav. 2007;32(10):2411–9.
17. Fix BV, O'Connor RJ, Vogl L, Smith D, Bansal-Travers M, Conway KP et al. Patterns and correlates of polytobacco use in the United States over a decade: NSDUH 2002–2011. Addict Behav. 2014;39(4):768–81.
18. Horn K, Pearson JL, Villanti AC. Polytobacco use and the "customization generation" – new perspectives for tobacco control. J Drug Educ. 2016;46(3–4):51–63.
19. Lee YO, Hebert CJ, Nonnemaker JM, Kim AE. Multiple tobacco product use among adults in the United States: cigarettes, cigars, electronic cigarettes, hookah, smokeless tobacco, and snus. Prev Med. 2014;62:14–9.
20. Martinasek MP, Bowersock A, Wheldon CW. Patterns, perception and behavior of electronic nicotine delivery systems use and multiple product use among young adults. Respir Care. 2018;63(7):913–9.
21. Sung HY, Wang Y, Yao T et al. Polytobacco use of cigarettes, cigars, chewing tobacco, and snuff among US adults. Nicotine Tob Res. 2016;18(5):817-26. doi: 10.1093/ntr/ntv147 [published Online First: 2015/07/03].
22. Sung HY, Wang Y, Yao T, Lightwood J, Max W. Polytobacco use and nicotine dependence symptoms among US adults, 2012–2014. Nicotine Tob Res. 2018;20(Suppl 1):S88–98.
23. Wong EC, Haardorfer R, Windle M, Berg CJ. Distinct motives for use among polytobacco versus cigarette only users and among single tobacco product users. Nicotine Tob Res. 2017;20(1):117–23.
24. Hinton A, Nagaraja HN, Cooper S,Wewers ME. Tobacco product transition patterns in rural and urban cohorts: Where do dual users go? Prev Med Rep. 2018;12:241–4.
25. Miller CR, Smith DM, Goniewicz ML. Changes in nicotine product use among dual users of tobacco and electronic cigarettes: Findings from the Population Assessment of Tobacco and Health (PATH) study, 2013–2015. Subst Use Misuse. 2020:1–5. doi: 10.1080/10826084.2019.1710211.
26. Niaura R, Rich I, Johnson AL, Villanti AC, Romberg AR, Hair EC et al. Young adult tobacco and e-cigarette use transitions: Examining stability using multi-state modeling. Nicotine Tob Res. 2020;22(5):647–54.
27. Piper ME, Baker TB, Benowitz NL, Jorenby DE. Changes in use patterns over one year among smokers and dual users of combustible and electronic cigarettes. Nicotine Tob Res. 2020;22(5):672–80.
28. Borland R, Murray K, Gravely S, Fong GT, Thompson ME, McNeill A et al. A new classificati-

on system for describing concurrent use of nicotine vaping products alongside cigarettes (so-called "dual use"): findings from the ITC-4 Country Smoking and Vaping wave 1 survey. Addiction. 2019;114(Suppl 1):24–34.

29. Bhatnagar A, Whitsel LP, Blaha MJ, Huffman MD, Krishan-Sarin S, Maa J et al. New and emerging tobacco products and the nicotine endgame: The role of robust regulation and comprehensive tobacco control and prevention: A Presidential Advisory from the American Heart Association. Circulation. 2019;139(19):e937–58.
30. Farsalinos KE, Romagna G, Voudris V. Factors associated with dual use of tobacco and electronic cigarettes: A case control study. Int J Drug Policy. 2015;26(6):595–600.
31. Goniewicz ML, Smith DM, Edwards KC, Blount BC, Caldwell KL, Feng J et al. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. JAMA Netw Open. 2018;1(8):e185937.
32. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. Ann Intern Med. 2017;166(6):390–400.
33. Bjartveit K, Tverdal A. Health consequences of smoking 1–4 cigarettes per day. Tob Control. 2005;14(5):315–20.
34. Gerber Y, Myers V, Goldbourt U. Smoking reduction at midlife and lifetime mortality risk in men: a prospective cohort study. Am J Epidemiol. 2012;175(10):1006–12.
35. Hart C, Gruer L, Bauld L. Does smoking reduction in midlife reduce mortality risk? Results of 2 long-term prospective cohort studies of men and women in Scotland. Am J Epidemiol. 2013;178(5):770–9.
36. Tverdal A, Bjartveit K. Health consequences of reduced daily cigarette consumption. Tob Control. 2006;15(6):472–80.
37. Baig SA, Giovenco DP. Behavioral heterogeneity among cigarette and e-cigarette dual-users and associations with future tobacco use: Findings from the Population Assessment of Tobacco and Health study. Addict Behav. 2020;104:106263.
38. 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 Tob Res. 2018;20(8):1004–9.
39. Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K, Leischow SJ. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. Addiction. 2018;113(11):2099–106.
40. Leigh NJ, Palumbo MN, Marino AM, O'Connor RJ, Goniewicz ML. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. Tob Control. 2018;27(Suppl 1):s37–8.
41. Hwang JH, Ryu DH, Park SW. Heated tobacco products: Cigarette complements, not substitutes. Drug Alcohol Depend. 2019;204:107576.
42. Tabuchi T, Gallus S, Shinozaki T, Nakaya T, Kunugita N, Colwell B. Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. Tob Control. 2018;27(e1):e25–33.
43. Tabuchi T, Shinozaki T, Kunugita N, Nakamura M, Tsuji I. Study profile: The Japan "Society and New Tobacco" Internet Survey (JASTIS): A longitudinal Internet cohort study of heat-not-burn tobacco products, electronic cigarettes, and conventional tobacco products in Japan. J Epidemiol. 2019;29(11):444–50.
44. Sutanto E, Miller C, Smith DM, Borland R, Hyland A, Cummings KM et al. Concurrent daily and non-daily use of heated tobacco products with combustible cigarettes: Findings from the 2018 ITC Japan survey. Int J Environ Res Public Health. 2020;17(6):2098.
45. Roulet S, Chrea C, Kanitscheider C, Kallischnigg G, Magnani P, Weitkunat R. Potential predictors of adoption of the tobacco heating system by US adult smokers: An actual use study.

F1000Res. 2019;8:214.
46. Hair EC, Bennett M, Sheen E, Cantrell J, Briggs J, Fenn Z et al. Examining perceptions about IQOS heated tobacco product: consumer studies in Japan and Switzerland. Tob Control. 2018;27(Suppl 1):s70–3.
47. Mays D, Arrazola RA, Tworek C, Rolle IV, Neff LJ, Portnoy DB. Openness to using non-cigarette tobacco products among US young adults. Am J Prev Med. 2016;50(4):528–34.
48. McKelvey K, Popova L, Kim M, Chaffee BW, Vijayaraghavan M, Ling P et al. Heated tobacco products likely appeal to adolescents and young adults. Tob Control. 2018;27(Suppl 1):s41–7.
49. Soneji S, Sargent JD, Tanski SE, Primack BA. Associations between initial water pipe tobacco smoking and snus use and subsequent cigarette smoking: Results from a longitudinal study of US adolescents and young adults. JAMA Pediatr. 2015;169(2):129–36.
50. Gee J, Prasad K, Slayford S, Gray A, Nother K, Cunningham A et al. Assessment of tobacco heating product THP1.0. Part 8: Study to determine puffing topography, mouth level exposure and consumption among Japanese users. Regul Toxicol Pharmacol. 2018;93:84–81.
51. Philip Morris Products S.A. modified risk tobacco product (MRTP) applications. Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications, accessed 10 January 2021).
52. Tobacco Products Scientific Advisory Committee, 25 January 2018. Silver Spring (MD): Food and Drug Administration; 2018 (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM599235.pdf, accessed 10 January 2021).
53. Committees on Toxicity, Carcinogenicity and Mutagenicity of Chemical Products In Food, Consumer Products And The Environment (COT, COC and COM). Statement on the toxicological evaluation of novel heat-not-burn tobacco products. London: Food Standards Agency; 2017 (https://cot.food.gov.uk/sites/default/files/heat_not_burn_tobacco_statement.pdf, accessed 10 January 2021).
54. Hughes JR, Keely JP. The effect of a novel smoking system – Accord – on ongoing smoking and toxin exposure. Nicotine Tob Res. 2004;6(6):1021–7.
55. Fagerstrom KO, Hughes JR, Callas PW. Long-term effects of the Eclipse cigarette substitute and the nicotine inhaler in smokers not interested in quitting. Nicotine Tob Res. 2002;4(Suppl 2):S141–5.
56. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenković M. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. 2018;360:j5855.
57. Inoue-Choi M, Christensen CH, Rostron BL, Cosgrove CM, Reyes-Guzman C, Apelberg B et al. Dose–response association of low-intensity and nondaily smoking with mortality in the United States. JAMA Netw Open. 2020;3(6):e206436.
58. Inoue-Choi M, Hartge P, Liao LM, Caporaso N, Freedman ND. Association between long-term low-intensity cigarette smoking and incidence of smoking-related cancer in the National Institutes of Health–AARP cohort. Int J Cancer. 2018;142(2):271–80.
59. Gilchrist M. Presentation by Moira Gilchrist, PhD, Vice President Scientific and Public Communications, Philip Morris International, before the Tobacco Products Scientific Advisory Committee (TPSAC). Lausanne: Philip Morris International; 2018 (https://tobacco.ucsf.edu/sites/g/files/tkssra4661/f/wysiwyg/PMI-24Jan-TPSAC-Presentation.pdf).
60. 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(7):1050–2.
61. Bekki K, Inaba Y, Uchuyama S, Kunugita N. Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. J UOEH. 2017;39(3):201–7.

62. 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 Tob Res. 2018;20(8):1004–9.
63. Forster M, Fiebelkorn S, Yurteri C, Mariner D, Liu C, Wright C et al. Assessment of novel tobacco heating product THP1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. Regul Toxicol Pharmacol. 2018;93:14–33.
64. 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. Regul Toxicol Pharmacol. 2017;90:1–8.
65. Li X, Luo Y, Jiang X, Zhang H, Zhu F, Hus S et al. Chemical analysis and simulated pyrolysis of tobacco heating system 2.2 compared to conventional cigarettes. Nicotine Tob Res. 2019;21(1):111–8.
66. Mallock N, Boss L, Burk R, Dabziger M, Welsch T, Hahn H et al. Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. Arch Toxicol. 2018;92(6):2145–9.
67. Nabavizadeh P, Liu J, Havel CM, Ibrahim S, Derakhshandeh R, Jacon P III et al. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. Tob Control. 2018;27(Suppl 1):s13–9.
68. Poynton S, Sutton J, Goodall S, Margham J, Forster M, Scott K et al. A novel hybrid tobacco product that delivers a tobacco flavour note with vapour aerosol (Part 1): Product operation and preliminary aerosol chemistry assessment. Food Chem Toxicol. 2017;106(Pt A):522–32.
69. Salman R, Talih S, El-Hage R, Haddad C, Karaoghlanian N, El-Hellani A et al. Free-base and total nicotine, reactive oxygen species, and carbonyl emissions from IQOS, a heated tobacco product. Nicotine Tob Res. 2019;21(9):1285–8.
70. Schaller JP, Keller D, Poget L, Pratte P, Kaelin E, McHugh D et al. 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):S27–47.
71. Schaller JP, Pijnenburg JP, 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):S48–58.
72. Simonavicius E, McNeill A, Shahab L, Brose LS. Heat-not-burn tobacco products: a systematic literature review. Tob Control. 2019;28(5):582–94.
73. Counts M, Morton M, Laffoon S, Cox R, Lipowicz P. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. Regul Toxicol Pharmacol. 2005;41(3):185–227.
74. Haziza C, de la Bourdonnaye G, Skiada D, Ancerewicz J, Baker G, Picavet P et al. Evaluation of the tobacco heating system 2.2. Part 8: 5-day randomized reduced exposure clinical study in Poland. Regul Toxicol Pharmacol. 2016;81(Suppl 2):S139–50.
75. Haziza C, de la Bourdonnaye G, Merlet S, Benzimra M, Ancerewicz J, Donelli A et al. 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. Regul Toxicol Pharmacol. 2016;81:489–99.
76. Brossard P, Weitkunat R, Poux V, Lama N, Haziza C, Picavet P et al. Nicotine pharmacokinetic profiles of the tobacco heating system 2.2, cigarettes and nicotine gum in Japanese smokers. Regul Toxicol Pharmacol. 2017;89:193–9.
77. Picavet P, Haziza C, Lama N, Weitkunat R, Lüdicke F. Comparison of the pharmacokinetics of nicotine following single and ad libitum use of a tobacco heating system or combustible

cigarettes. Nicotine Tob Res. 2016;18(5):557–63.
78. Lüdicke F, Picavet P, Baker G, Haziza C, Poux V, Lama N et al. 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, open-label, multicenter study in sequential confinement and ambulatory settings (Part 2). Nicotine Tob Res. 2018;20(2):173–82.
79. Lüdicke F, Picavet P, Baker G, Haziza C, Poux V, Lama N et al. 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, multicenter study in sequential confinement and ambulatory settings (Part 1). Nicotine Tob Res. 2018;20(2):161–72.
80. Lüdicke F, Haziza C, Weitkunat R et al. Evaluation of biomarkers of exposure in smokers switching to a carbon-heated tobacco product: a controlled, randomized, open-label 5-day exposure study. Nicotine Tob Res. 2016;18:1606–13. doi:10.1093/ntr/ntw022.
81. Lüdicke F, Baker G, Magnette J et al. Reduced exposure to harmful and potentially harmful smoke constituents with the tobacco heating system 2.1. Nicotine Tob Res. 2016;19:168-175. doi:10.1093/ntr/ntw164.
82. Haziza C, de la Bourdonnaye G, Donelli A, Poux V, Skiada D, Weitkunat R et al. Reduction in exposure to selected harmful and potentially harmful constituents approaching those observed upon smoking abstinence in smokers switching to the menthol tobacco heating system 2.2 for 3 months (Part 1). Nicotine Tob Res. 2020;22(4):539–48.
83. Gale N, McEwan M, Eldridge A, Fearon IM, Sherwood N, Bowen E et al. Changes in biomarkers of exposure on switching from a conventional cigarette to tobacco heating products: A randomized, controlled study in healthy Japanese subjects. Nicotine Tob Res. 2018;21:122–7.
84. Yuki D, Sakaguchi C, Kikuchi A, Futamura Y. Pharmacokinetics of nicotine following the controlled use of a prototype novel tobacco vapor product. Regul Toxicol Pharmacol. 2017;87:30–5.
85. Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violo F, Loffredo L et al. 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;8(6):e010455.
86. Lopez AA, Hiler M, Maloney S, Eissenberg T, Breland A. Expanding clinical laboratory tobacco product evaluation methods to loose-leaf tobacco vaporizers. Drug Alcohol Depend. 2016;169:33–40.
87. Newland N, Lowe FJ, Camacho OM, McEwan M, Gale N, Ebajemito J et al. Evaluating the effects of switching from cigarette smoking to using a heated tobacco product on health effect indicators in healthy subjects: study protocol for a randomized controlled trial. Intern Emergency Med. 2019;14(6):885–98.
88. Adriaens K, Gucht DV, Baeyens F. IQOS(TM) vs. e-cigarette vs. tobacco cigarette: A direct comparison of short-term effects after overnight-abstinence. Int J Environ Res Public Health. 2018;15(12):2902.
89. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine Tob Res. 2001;3(1):7–16.
90. Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addict Behav. 2007;32(5):912–23.
91. Shiffman S, Terhorst L. Intermittent and daily smokers' subjective responses to smoking. Psychopharmacology (Berl). 2017;234(19):2911–7.
92. Cruz-Jiménez L, Barrientos-Gutiérrez I, Coutiño-Escamilla L, Gallegos-Carrillo K, Arillo-Santillán E, Thrasher JF. Adult smokers' awareness and interest in trying heated tobacco products: perspectives from Mexico, where HTPs and e-cigarettes are banned. Int J Environ Res Public Health. 2020;17(7):2173.

93. Czoli CD, White CM, Reid JL, O'Connor RJ, Hammond D. Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. Tob Control. 2020;29(1):89–95.
94. Dunbar MS, Seelam R, Tucker JS, Rodriguez A, Shih RA, D'Amico EJ. Correlates of awareness and use of heated tobacco products in a sample of US young adults in 2018–2019. Nicotine Tob Res. 2020:doi: 10.1093/ntr/ntaa007.
95. Gravely S, Fong GT, Sutanto E, Loewen R, Ouimet J, Xu SS, et al. Perceptions of harmfulness of heated tobacco products compared to combustible cigarettes among adult smokers in Japan: Findings from the 2018 ITC Japan Survey. Int J Environ Res Public Health.2020;17(7):2394.
96. Hori A, Tabuchi T, Kunugita N. Rapid increase in heated tobacco product (HTP) use from 2015 to 2019: from the Japan "Society and New Tobacco" Internet Survey (JASTIS). Tob Control. 2020;5(5):652.
97. Igarashi A, Aida J, Kusama T, Tabuchi T, Tsuboya T, Sugiyama K et al. Heated tobacco products have reached younger or more affluent people in Japan. J Epidemiol. 2020:doi: 10.2188/jea.JE20190260.
98. Kang H, Cho SI. Heated tobacco product use among Korean adolescents. Tob Control. 2020;29(4):466–8.
99. Kim K, Kim J, Cho HJ. Gendered factors for heated tobacco product use: Focus group interviews with Korean adults. Tob Induc Dis. 2020;18:43.
100. Kim SH, Cho HJ. Prevalence and correlates of current use of heated tobacco products among a nationally representative sample of Korean adults: Results from a cross-sectional study. Tob Induc Dis. 2020;18:66.
101. Kim SH, Kang SY, Cho HJ. Beliefs about the harmfulness of heated tobacco products compared with combustible cigarettes and their effectiveness for smoking cessation among Korean adults. Int J Environ Res Public Health. 2020;17(15):5591.
102. Okawa S, Tabuchi T, Miyashiro I. Who uses e-cigarettes and why? e-Cigarette use among older adolescents and young adults in Japan: JASTIS Study. J Psychoactive Drugs. 2020;52(1):37–45.
103. Ratajczak A, Jankowski P, Strus P, Feleszko W. Heat not burn tobacco product – A new global trend: Impact of heat-not-burn tobacco products on public health, a systematic review. Int J Environ Res Public Health. 2020;17(2):0409.
104. Siripongvutikorn Y, Tabuchi T, Okawa S. Workplace smoke-free policies that allow heated tobacco products and electronic cigarettes use are associated with use of both these products and conventional tobacco smoking: the 2018 JASTIS study. Tob Control. 2020;doi: 10.1136/tobaccocontrol-2019-055465.
105. Sugiyama T, Tabuchi T. Use of multiple tobacco and tobacco-like products including heated tobacco and e-cigarettes in Japan: A cross-sectional assessment of the 2017 JASTIS study. Int J Environ Res Public Health. 2020;17(6):2161.
106. Tompkins CNE, Burnley A, McNeill A, Hitchman SC. Factors that influence smokers' and ex-smokers' use of IQOS: a qualitative study of IQOS users and ex-users in the UK. Tob Control. 2020:doi: 10.1136/tobaccocontrol-2019-055306.
107. Wu YS, Wang MP, Ho SY, Li HCW, Cheung YTD, Tabuchi T, et al. Heated tobacco products use in Chinese adults in Hong Kong: a population-based cross-sectional study. Tob Control. 2020;29(3):277–81.

6. Regulations on heated tobacco products, electronic nicotine delivery systems and electronic non-nicotine delivery systems, with country approaches, barriers to regulation and regulatory considerations

Ranti Fayokun, Moira Sy, Marine Perraudin and Vinayak Prasad
No Tobacco Unit (Tobacco Free Initiative), Department of Health Promotion, Division of Universal Health Coverage and Healthier Populations, World Health Organization, Geneva, Switzerland

Contents

Abstract

Heated tobacco products (HTPs) are increasingly marketed by the tobacco industry as part of a newer portfolio of products that are claimed to pose fewer risks to users and non-users than conventional tobacco products. These products have gained a considerable market share since they became available and are now found on about 50 markets worldwide. The new generation of HTPs, owing to their novelty, their unconventional technology and industry claims that they pose fewer risks to health than conventional tobacco products, are classified in various ways by different countries. The classifications have filtered through to the mechanisms adopted by countries to regulate these products, resulting in inconsistencies among countries, including the extent to which they

apply the provisions of the WHO Framework Convention on Tobacco Control (WHO FCTC). This paper reviews the markets on which HTPs are available, the common classifications of these products and how the classifications affect regulatory outcomes. Further, we describe commonly used regulatory frameworks, barriers to regulation, considerations for regulations and unforeseen consequences. We also present guidance from WHO and the WHO FCTC to countries in formulating regulatory strategies for HTPs according to their national laws and ensuring strong protection of human health.

6.1 Background

6.1.1 Introduction and the request of the Conference of the Parties (FCTC/COP8(22))

HTPs produce aerosols containing nicotine and toxic chemicals when their tobacco material is heated or when a device containing tobacco is activated *(1)*. The tobacco may be in the form of specially designed cigarettes (e.g. "heat sticks" and "neo sticks"), pods or plugs. The resulting aerosols are inhaled by users after heating of tobacco in a device specifically designed for that purpose *(1)*. HTPs are aggressively marketed and promoted by the tobacco industry in a number of ways, including as "smoke-free", "cleaner alternatives", "safer alternatives" and "reduced risk" products relative to conventional cigarettes. They were available for sale legally in over 50 markets in all six WHO regions as of July 2020 *(2)*, examples of which are given in Table 6.1.

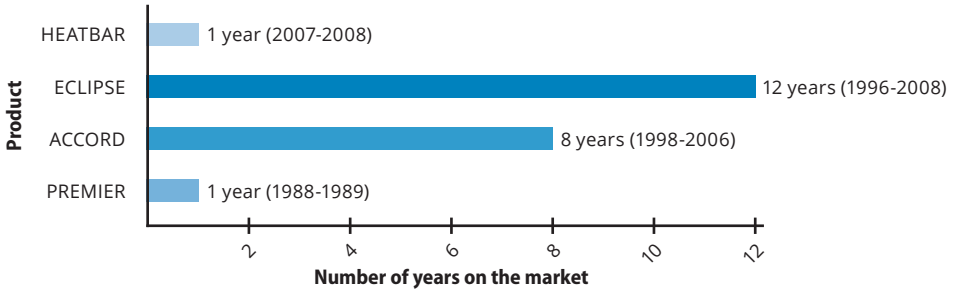
Table 6.1. Examples of markets on which HTPs are available

Device	Company	Markets
IQOS	Philip Morris International	Andorra, Albania, Armenia, Belarus, Bosnia and Herzegovina, Bulgaria, Canada, Colombia, Croatia, Cyprus, Czechia, Denmark, Dominican Republic, France (including La Réunion), Germany, Greece, Guatemala, Hungary, Israel, Italy, Japan, Kazakhstan, Latvia, Lithuania, Malaysia, Mexico, Monaco, Netherlands (including Curaçao), New Zealand, Poland, Portugal, Republic of Korea, Republic of Moldova, Romania, Russian Federation, Serbia, Slovakia, Slovenia, South Africa, Spain (including the Canary Islands), Sweden, Switzerland, Ukraine, United Arab Emirates, United Kingdom, USA and occupied Palestinian territory, including east Jerusalem
iFuse, glo	British American Tobacco	Canada, Italy, Japan, Republic of Korea, Romania, Russian Federation and Switzerland
Lil	KT&G	Japan, Republic of Korea, Russian Federation and Ukraine
Ploom	Japan Tobacco International	Italy, Japan, Republic of Korea, Russian Federation, Switzerland and United Kingdom

HTPs are one of the three broad categories of products, with electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS), that have become popular in several jurisdictions, especially in Japan and the Republic of Korea. While the technology for HTPs has been available since the

1980s, earlier attempts to introduce these products were unsuccessful, and the newer generations of these products became popular only in the past seven years (Fig. 6.1; see also sections 3 and 5).

Fig. 6.1. Dates of launch and withdrawal from the market of early-generation heated tobacco products



Source: adapted from reference *3*.

HTPs pose significant challenges to tobacco regulation, specifically because of their novel operating mechanisms and inadequate knowledge about their effects on health. The tobacco industry has exploited these challenges by using marketing tactics especially for "harm reduction" or "reduced risk" to facilitate their entry onto the market and have argued that HTPs should be categorized differently from tobacco products and specifically conventional cigarettes. The lack of an internationally agreed approach for assessing the risks of their use, because of insufficient knowledge, further complicates tobacco control. Novelty, misinformation and industry manipulation have resulted in disparate approaches to their classification and their regulation.

Decision FCTC/COP8(22) of the eighth session of the Conference of the Parties (COP) to the WHO FCTC on novel and emerging tobacco products) *(4)* requests the Convention Secretariat to invite WHO to prepare a comprehensive report on these products, covering several areas of research. WHO is expected to report to the ninth session of the COP on the regulatory experience and monitoring of Parties, effects on tobacco control and research gaps and to subsequently propose policy options for achieving the objectives and measures outlined in paragraph 5 of the decision. The aim of this paper is to map regulation of HTPs, review the regulatory experiences of WHO Member States with regard to HTPs, consider the impact of HTPs on tobacco control and identify research gaps.

6.1.2 Scope and objectives

We describe the regulatory experience of countries with HTPs after explaining common classifications for these products that may dictate specific regulatory pathways. For instance, classification in a certain category may result in a

complete ban on HTPs, although the regulatory implications of a category differ by country and the classifications in a country determine the degree of application of tobacco control laws. An HTP classified as an "e-cigarette" product may result in a ban in one country and in regulation in another.

The common regulatory frameworks that follow from classifications with respect to product bans; advertising, promotion and sponsorship; smoke-free places; sales restrictions; packaging and labelling; and product design are described. Because of limitations and interpretation of the available data, we do not provide an authoritative list of policies implemented to date but provide information about the types of approaches adopted by regulators with respect to HTPs and examples of such regulation. We also describe the barriers to regulation and inconsistent application of conventional tobacco control measures to use of these products.

6.1.3 Sources

The summaries of legislation and policy were drawn from data collected by WHO in 2019–2020, the legislative database managed by the Campaign for Tobacco Free Kids *(5)*, desk research on specific countries and internal WHO correspondence with country regulators. The data are, however, limited, because they may depend on interpretation of domestic legislation to application of general tobacco control measures to these newer products.

6.2 Regulatory mapping of novel and emerging nicotine and tobacco products

6.2.1 Availability of HTPs

HTPs are currently available on over 50 markets *(2)* (see Table 6.1). The number is, however, increasing rapidly, as 15 markets have been added in only the past two years. The availability of these products has increased recently in some countries where HTPs are gaining a market share from conventional tobacco products, mainly cigarettes, although HTP sales revenue represents a small fraction of what the industry earns from cigarettes *(6)*. The tobacco industry plans to expand the market share and to increase the availability, visibility and access to these products globally *(7)*, in particular by maintaining their availability on the market and avoiding strict tobacco control measures resulting from Parties' obligations to the WHO FCTC. Regulatory exception would advance the tobacco industry's long-term objective of increasing the acceptability of a wide range of its newer tobacco products, undermining the WHO FCTC.

HTPs are not only sold legally in countries but are also traded illegally in some countries where they are banned and in countries where the products have not met regulatory requirements or have not had premarketing authorization.

6.2.2 Product classification

According to WHO guidance, HTPs should be classified as tobacco products *(8)*. At its eighth session, the COP to the WHO FCTC recognized these products as tobacco products and reminded Parties of their obligation to do so under the WHO FCTC. Some regulators have, however, classified HTPs into categories distinct from conventional cigarettes or tobacco products because of their unconventional characteristics. These distinct categories result mainly from industry arguments for weaker or no regulation of so-called "reduced-risk" products and insufficient knowledge about the products. To date, countries have classified HTPs into categories, including:

- tobacco products
- HTPs
- smokeless tobacco products
- novel, emerging, new or next-generation tobacco products and
- e-cigarettes *(9)*.

Table 6.2 lists examples of countries in which these categories are used.

Table 6.2. Examples of regulatory classification of HTPs

Classification	**Example of countries** (non-exhaustive lists)
Tobacco products	Republic of Korea, United Arab Emirates More than 110 other countries, where HTPs are classified as tobacco products by definition
ENDS	Brazil, India, Russian Federation, Saudi Arabia
Novel tobacco products	European Union countries, United Kingdom
Emerging and imitation tobacco products	Singapore
Smokeless tobacco products	New Zealand

ENDS: electronic nicotine delivery systems; HTPs: heated tobacco products.

HTPs may also fall into hybrid or exempt categories *(9)*, often resulting in more favourable treatment of HTPs than of conventional cigarettes. The nature of the device may also affect its classification: sticks (which contain tobacco) may be classified as tobacco products, while a heating device into which the sticks are inserted may be classified differently *(9)*.

The definitions of products are closely linked to their classification or categorization, as the definition of "tobacco products" under domestic law differs from one jurisdiction to another. Some countries define "tobacco products" as all tobacco-derived materials, including nicotine, as well as the way in which the product is consumed (e.g. sucked, smoked, chewed), and some may extend the definition to the way in which the products are presented or how the nicotine is

derived. Some may include all nicotine-containing products. The way in which tobacco products are defined determines the extent to which existing tobacco control regulations and legislation are applicable to HTPs in that country, unless exceptions are specifically made for HTPs or specific laws that apply to HTPs.

Tobacco products

Many national laws and regulations in all regions of WHO define tobacco products broadly enough to include HTPs. If the tobacco control law includes no specific regulation, HTPs can be regulated through other applicable regulations, such as consumer protection or poisons laws. For example, Australia's Poison Standards Act classifies nicotine as a Schedule 7 poison, so that its sale and possession are largely illegal, although, in some states, a 3-month supply may be imported under the Therapeutic Goods Administration "personal importation scheme" with a medical prescription. Not surprisingly, this restrictive approach has been challenged by the tobacco industry. Philip Morris filed a regulatory application to the Advisory Committee on Chemicals and Poisons of the Therapeutic Goods Administration to seek an exemption from the poisons standard to allow legal sale of the nicotine in tobacco prepared and packed for "heating". The proposed amendment was rejected by the Therapeutic Goods Administration in June 2020 *(10)*.

e-Cigarettes

Some countries have classified HTPs as "e-cigarettes" or "electronic smoking devices" on the basis of legislative definitions. This may result in regulation similar to that for e-cigarettes or, in other countries, in a ban on the sale or importation of the entire category of products. For instance, in the Republic of Korea, although HTPs are primarily classified as tobacco products, under the law, tobacco products in which electronic devices are used to consume tobacco (e.g. by heating) are sub-categorized as e-cigarettes. This subcategory is thus applicable to HTPs, as they contain electronic devices, which heat the tobacco. In the country's regulatory context, this means that most tobacco product regulations, including on smoke-free areas, taxation, advertising, health warnings and labels, and prohibition of sale to minors, apply to HTPs; however, only 90% of the cigarette tax rate applies to HTPs. Depending on national legislation, classification of HTPs as e-cigarettes or electronic smoking devices could result in a range of measures, from a ban (Brazil) to regulation.

Novel tobacco products

In the European Union, HTPs are regulated as novel tobacco products according to the European Union Tobacco Product Directive 2014/40/EU *(11)*. "Novel tobacco products" are defined as tobacco products that are required to comply

with the provisions of the Directive, including a ban on misleading elements foreseen by Article 13 and, notably, any suggestion that a particular tobacco product is less harmful than others *(12)*.

In line with Article 19 of the Directive on notification of novel tobacco products, tobacco manufacturers and importers are required to provide information and supporting documentation for all products that they intend to place on the national market and that fall into the category of novel tobacco products. Specifically, manufacturers and importers of these products are required to notify the competent authorities of Member States, in electronic form, 6 months before the products are placed on the market, accompanied by information about the products' ingredients and emissions.

Manufacturers and importers are also required to provide the competent authorities with:

> (a) available scientific studies on toxicity, addictiveness and attractiveness of the novel tobacco product, in particular as regards its ingredients and emissions; (b) available studies, executive summaries thereof and market research on the preferences of various consumer groups, including young people and current smokers; and (c) other available and relevant information, including a risk/benefit analysis of the product, its expected effects on cessation of tobacco consumption, its expected effects on initiation of tobacco consumption and predicted consumer perception.

Additionally, they are required to submit to their competent authorities any new or updated information on the studies, research and other information referred to in a–c above and conduct additional tests or submit additional information as required by the competent authority in question. In addition to notification of these products to the relevant national authorities, Member States may introduce an authorization process, if deemed appropriate, and may charge manufacturers and importers proportional fees for authorization.

Countries including Poland (Article 11a of the Act of 9 November 1995 on the Protection of Health against Consequences of Consumption of Tobacco and Tobacco Products) and Spain (Royal Decree 579/2017) classify HTPs as novel tobacco products. France regulates HTPs as tobacco products under the French Public Health Code, Article L3512-1, 1° and as a novel tobacco product under Article L3512-1, 2°. French law does not establish an authorization system for products but includes a system for reporting product information (notification). HTP manufacturers are required to report the names, quantities and associated health effects of the ingredients to the national authorities. Use of HTPs in public places is banned under French Public Health Code Article L3512-8. Use of health claims, sale of HTPs to people under 18 and advertising, promotion and sponsorship of HTPs are also prohibited. Warning labels are required.

Emerging and imitation tobacco products

In Singapore, HTPs are treated in the same way as e-cigarettes that contain nicotine and electronic nicotine delivery systems, as both are considered to be emerging imitation tobacco products. Products that fall into this category include any device or article that:

- resembles, or is designed to resemble, a tobacco product;
- can be smoked;
- may be used in such a way as to mimic the act of smoking; or
- the packaging of which resembles, or is designed to resemble, the packaging commonly associated with tobacco products *(13)*.

It is prohibited to import, distribute, sell, purchase use or possess such products under the Tobacco (Control of Advertisement and Sale) Act, amended in 2011 *(13)*.

Smokeless tobacco

Article 2 of the European Union Tobacco Product Directive defines smokeless tobacco as "a tobacco product not involving a combustion process, including chewing tobacco, nasal tobacco and tobacco for oral use". Consequently, a number of countries in the European Union, such as Czechia (Section 2 (1) t) of Act No. 110/1997 Coll) and Portugal (Law 109/2015), classify HTPs as smokeless tobacco products.

In the Netherlands, HTPs are also regulated as smokeless tobacco under the Dutch Tobacco Act *(14)*, which is enforced by the Netherlands Food and Consumer Products Safety Authority. In line with the requirements of the European Union Directive for notification, the Dutch National Institute for Public Health and the Environment (RIVM) analyses and processes premarketing notification documents *(15)*. Requirements for HTPs include: warning labels similar to those for smokeless tobacco, a ban on health claims, a ban on sales to persons under the age of 18 and a ban on promotion and marketing, with few exceptions. HTPs are taxed at € 99.25/kg, like other smoked tobacco products. According to the Dutch Government, categorization of HTPs as smokeless tobacco could be changed if new evidence or information about their use becomes available. RIVM is currently analysing and conducting research on the contents and emissions of different IQOS HeatStick flavours and other HTPs for the Ministry of Health.

Next-generation products

In Italy, HTPs are regulated as next-generation products. Because of alleged belief that HTPs can reduce harm, these HTPs are exempt from the fiscal regimes of tobacco products. Rather, they are taxed under the category "inhalation product

without combustion" under a specific excise structure *(16)*. Thus, these products enjoy the same tax reduction as electronic cigarettes, which is half the excise tax applied to conventional cigarettes *(17)*. Although the sale of HTPs to minors is banned (Decree n°6/2016 Chapter II Art. 24,3), enforcement of tobacco control regulations is only minimal for HTPs. Health warnings are required to cover only 30% of HTP packages (instead of 65% for conventional cigarettes), and they are not required to have pictorial images *(18)*. Comprehensive regulations prohibiting smoking in all public places and workplaces do not apply to HTPs. In addition, advertising and promotion of HTPs are not banned, and "IQOS embassies" and "IQOS boutiques", fancy concept stores in which people can try the products for free, are present in several strategic Italian cities. Therefore, for HTPs, the country has weakened the best-recognized tobacco control policies, i.e. price and tax increases, smoking bans, advertising bans and health warnings.

International approaches to the classification of HTPs

Discrepancies in national approaches to the classification of HTPs and legal challenges by the tobacco industry have raised concern about the lack of international standards for classifying HTPs. WHO is collaborating with experts and researchers on a classification tree for tobacco products, which will include HTPs, and will publish its findings once the project is finalized. A report will also be made to the next COP to the WHO FCTC, in November 2021, on appropriate classification of HTPs in accordance with paragraph 3(b) of decision FCTC/COP8(22), in which the COP requested the Convention Secretariat to advise on adequate classification of novel and emerging tobacco products such as HTPs *(19)*. The World Customs Organization is facilitating a revision of the "harmonized system code" to introduce new, specific customs codes for HTPs. The annex to the International Convention on the Harmonized Commodity Description and Coding System currently states that:

- heated tobacco units do not have a specific customs code and fall under the subheading of "other" (2403.99) in Chapter 24 of the International Convention on the Harmonized Commodity Description and Coding System, which addresses tobacco products; and
- devices used to heat tobacco units (i.e. HTPs) do not have a specific customs code and fall under the subheading of "other machines and apparatus" (8543.70) in Chapter 85, which concerns electrical machinery.

Mandatory changes have been made for 2022, to standardize these headings so that the products fall under heading 24.4:

> Products containing tobacco, reconstituted tobacco, nicotine, or tobacco or nicotine substitutes, intended for inhalation without combustion; other nicotine-containing products intended for the intake of nicotine into the human body *(20)*.

Countries will be obliged to amend their domestic customs codes in 2020. The World Customs Organization will determine how disposable devices are to be classified later in the year.

The Harmonized System Code is not intended to affect domestic regulation of HTPs, but, as described in a WHO FCTC Secretariat information note *(21)*, in practice, these codes affect the entry and exit of goods at borders for the purposes of levying excise taxes and classification in domestic legislation. Such measures could be used by the tobacco industry to lobby for more favourable treatment of HTPs.

6.2.3 Regulatory frameworks and measures to reduce tobacco demand

As noted above, the classification of a tobacco product determines the regulations that are applicable. This in turn affects the availability and use of these products, as well as regulations on taxation, restrictions on advertising, promotion and sponsorship, use of the products in smoke-free places and packaging and labelling requirements. Some countries choose to ban the importation, sale or use of HTPs entirely, through a ban on an entire category of products, such as e-cigarettes or emerging and imitation tobacco products. For example, if a country has banned e-cigarettes and then makes a regulatory decision to classify HTPs as e-cigarettes, the classification will ensure that the HTPs do not enter the market (e.g. India). Nevertheless, the same product classification (i.e. "e-cigarettes") may result in a ban in one country and regulatory restrictions in another.

Various mechanisms have been adopted by WHO Member States to regulate HTPs. While many countries have used existing tobacco control laws, some have formulated specific provisions. Information held by WHO indicates the following common mechanisms.

Existing laws

HTPs could be defined in the same way as products that are already covered by law, such as in South Africa, where HTPs are considered tobacco products. As noted above (section 6.2.1), in Australia, HTPs are regulated under the Standard for the Uniform Scheduling of Poisons, with products containing nicotine categorized under Schedule 7, "dangerous poison". The Therapeutic Goods Administration recently refused to amend the Poisons Standard to allow sales of HTPs *(11)*.

Amendment of existing laws

Existing legislation can be amended to include HTPs if the definitions do not clearly cover these products. In Malaysia, an amendment to the Control of Tobacco Product Regulations 2004 changed the definition of "smoking" in 2015 to include use of HTPs *(22)*.

New legislation and other mechanisms

New legislation and other mechanisms may be used to regulate HTPs or to include them explicitly in existing legislation. The United Arab Emirates enacted an Electronic Nicotine Products (Equivalents of Traditional Tobacco Products) standard *(23)*, which regulates e-cigarettes, e-liquids with and without nicotine and HTPs, with a requirement to specify their production, import, retail and display. Consequently, these products now fall within the same regulatory framework as tobacco products, provided by Federal Law 15/2009. In the Philippines, the President issued an executive order in February 2020 regulating the commercialization and use of electronic cigarettes, HTPs and other novel tobacco products *(24)*. The executive order excludes HTPs from the definition of tobacco products but includes them in the definition of smoking.

As noted earlier, HTPs were recognized as tobacco products at COP8 (decision FCTC/COP8(22)) *(19)*. This decision reminded Parties of their commitments under the WHO FCTC when addressing the challenges of novel and emerging tobacco products such as HTPs and devices designed for consuming such products, to consider prioritizing specified tobacco control measures in accordance with the WHO FCTC and national law. These, listed in paragraph 5 of the decision, are:

(a) to prevent the initiation of novel and emerging tobacco products;

(b) to protect people from exposure to their emissions and to explicitly extend the scope of smoke-free legislation to these products in accordance with Article 8 of the WHO FCTC;

(c) to prevent health claims from being made about novel and emerging tobacco products;

(d) to apply measures regarding advertising, promotion and sponsorship of novel and emerging tobacco products in accordance with Article 13 of the WHO FCTC;

(e) to regulate the contents and the disclosure of the contents of novel and emerging tobacco products in accordance with Articles 9 and 10 of the WHO FCTC;

(f) to protect tobacco-control policies and activities from all commercial and other vested interests related to novel and emerging tobacco

products, including interests of the tobacco industry, in accordance with Article 5.3 of the WHO FCTC;

(g) to regulate, including restrict, or prohibit, as appropriate, the manufacture, importation, distribution, presentation, sale and use of novel and emerging tobacco products, as appropriate to their national laws, taking into account a high level of protection for human health; and

(h) to apply, where appropriate, the above measures to the devices designed for consuming such products.

Advertising, promotion and sponsorship (Article 13)

Article 1 of the WHO FCTC provides a comprehensive definition of tobacco advertising, promotion and sponsorship. Tobacco advertising and promotion are defined as "any form of commercial communication, recommendation or action with the aim, effect or likely effect of promoting a tobacco product or tobacco use either directly or indirectly" and sponsorship as "any form of contribution to any event, activity or individual with the aim, effect or likely effect of promoting a tobacco product or tobacco use either directly or indirectly" *(25)*.

Although most countries do not specifically regulate the advertising, promotion and sponsorship of HTPs, the products should be covered by the bans on advertising, promotion and sponsorship applied to conventional tobacco products, in accordance with the guidance of WHO and the COP. If a distinction is made between HTP sticks and devices and if the definition of tobacco product covers only the sticks, advertising of the device may not be banned.

A comprehensive ban on tobacco advertising, promotion and sponsorship covers not only traditional forms of advertising such as television, radio and print but also "brand stretching", displays of products at points of sale and tobacco-industry-sponsored corporate social responsibility programmes, among others. Nevertheless, the fast-changing media landscape creates regulatory loopholes that allow tobacco product advertising in social media campaigns and by influencers, often targeting young people. For example, the tobacco industry engages in public relations and corporate social responsibility-related activities, sponsors events and uses social media and online platforms to promote HTPs, all of which have contributed to the proliferation of the products around the world. Early in 2020, the State Council in the Republic of Korea passed an amendment to the country's National Health Promotion Act banning any direct or indirect promotional activity by tobacco manufacturers to consumers. The Ministry of Health and Welfare plans to ban practices such as discounts on ENDS and HTPs and free distribution of these products, including the devices, during promotional events *(26)*.

Smoke-free spaces (Article 8)

HTPs are commonly referred to by some as "heat-not-burn" products, a term coined by the industry, which has positive connotations. Manufacturers suggest that the products are "ash-free", "smoke-free" and "cleaner alternatives" to conventional cigarettes, which may create confusion about their categorization. To reduce the confusion created by this terminology, especially in regulations on the application of smoke-free laws, WHO introduced the term "heated tobacco products". Philip Morris has tried to distinguish IQOS from conventional smoking by creating partnerships with hundreds of "IQOS-friendly" restaurants and bars in countries such as Romania and Ukraine *(27)*, which may ban cigarettes but allow use of IQOS, undermining prohibitions on indoor smoking. Romania does not classify HTPs as "tobacco products for smoking" with regard to smoke-free policies on the grounds that these products do not generate smoke *(28)*.

Packaging and labelling (Article 11)

Article 11 of the WHO FCTC states that regulators should ensure that tobacco product packaging and labelling

> do not promote a tobacco product by any means that are false, misleading, deceptive or likely to create an erroneous impression about its characteristics, health effects, hazards or emissions, including any term, descriptor, trademark, figurative or any other sign that directly or indirectly creates the false impression that a particular tobacco product is less harmful than other tobacco products. These may include terms such as "low tar", "light", "ultra-light" or "mild".

The aim of these prohibitions is to avoid misleading consumers into thinking that one tobacco product is healthier than another, an especially important aim with respect to HTPs. Currently, however, health warning requirements for HTPs tend to be less onerous than for those for conventional cigarettes. Even where health warnings are imposed, in some countries (Japan and Netherlands), they apply only to inserts and not to the devices.

Articles 9–12 of the European Union Tobacco Product Directive address health warnings and their dimensions. For novel tobacco products considered to be "smokeless tobacco", text (but not pictorial) health warnings must cover 30% of each of the two largest surface areas; for novel tobacco products intended for smoking, combined health warnings (graphic and text) must cover 65% of the two largest surfaces. Categorization as smokeless tobacco is therefore preferable for the tobacco industry. Article 13 of the Directive on product presentation prohibits labelling or packaging with any element or feature that creates an erroneous impression about the characteristics, health effects, risks or emissions

of the product. Labelling or packaging may not include any information about the nicotine, tar or carbon monoxide content of the tobacco product; suggest that a particular tobacco product is less harmful than others, reduces the effects of any harmful components of smoke or has vitalizing, energizing, healing, rejuvenating, natural or organic properties or other health or lifestyle benefits; or refer to taste, smell, any flavourings or other additives or the absence thereof.

In the USA, the Food and Drug Administration (FDA) requires that all HTP package labels and advertisements include an additional warning about the addictiveness of nicotine, as well as the other warnings required for cigarettes. The aim of this requirement is to correct a misperception among users that IQOS pose a lower risk of addiction than conventional cigarettes. An application for designation as a modified risk tobacco product may be submitted to the FDA to allow a product to be marketed with a claim of reduced risk *(29)*, i.e. "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products". In 2016, Philip Morris Products S.A. sought authorization to market IQOS with the claims that the product "can reduce the risks of tobacco-related diseases", "significantly reduce[s] your body's exposure to harmful or potentially harmful chemicals" and "presents less risk of harm than continuing to smoke cigarettes". The FDA concluded, however, that the company had not provided sufficient evidence that consumers would not be misled by those claims, and Philip Morris were consequently not allowed to market HTPs with a claim of reduced risk *(30)*. Under US law, the FDA may issue two types of order for a modified risk tobacco product: a "risk modification order" or an "exposure modification order". Philip Morris Products S.A. had requested both types of order. Although the FDA determined that the evidence did not support issuance of the first type, the evidence supported issuance of an exposure modification order for the IQOS device and the tobacco HeatSticks. The exposure modification order authorizes Philip Morris to make claims about how tobacco is heated and about the production of harmful and potentially harmful chemicals and exposure to those chemicals in advertising and marketing of the products. On 7 July 2020, the FDA authorized the marketing of an "IQOS tobacco heating system", which includes the IQOS device, Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks and Marlboro Fresh Menthol Heatsticks, as a modified risk tobacco product *(31)*. The FDA stressed that this authorization does not indicate that the products are safe or approved by the FDA, and it rejected claims that the company had adequately demonstrated that use of the products is less harmful than use of another tobacco product or reduces risks to health *(32)*. Philip Morris hailed the exposure authorization as a milestone for public health and cited it as "an important example of how governments and public health organizations can regulate smoke-free alternatives to differentiate them from cigarettes in order to promote the public health".

The Republic of Korea, which primarily regulates HTPs as tobacco products, requires graphic health warnings on HTP packages. The move by the Ministry of Health and Welfare to mandate use of graphic images of the consequences of tobacco use, such as cancer-ridden organs, and more concise written warnings with specific risk figures was part of a set of measures to deter smoking implemented in late 2018. The strengthened measures followed a one-year deliberation by a 13-member special committee comprising Government officials and private experts and a survey of 1500 smokers and non-smokers to gauge public opinion *(33)*. All the regulations that apply to tobacco products, such as taxation, smoke-free areas, advertising, package warnings and labels, also apply to HTPs *(1)*, in line with WHO recommendations that HTPs be subject to the same policy and regulatory measures as applied to all other tobacco products *(34)*.

In Canada, the Tobacco Products Regulations (Plain and Standardized Appearance), which came into force on 9 November 2019, apply to tobacco products, including devices necessary for the use of a product made in whole or in part of tobacco, such as HTPs, as they are defined as "tobacco products" under the Act *(35)*. Israel and New Zealand also require plain packaging for HTPs.

Sales restrictions

In most countries, the sales restrictions imposed on tobacco products are also applicable to HTPs. These include prohibition of certain methods of sale (e.g. from vending machines or the Internet), restricted locations, age restriction for purchasers and licensing or requirements for retailers. For example, Cyprus prohibits the sale of HTPs from automatic tobacco vending machines, sales to minors and free distribution of HTPs *(36)*. In Slovenia, the premises for the sale of tobacco, tobacco products and related products, including HTPs, must be registered under Article 35(1) of the Restriction of the Use of Tobacco Products Act 2017 *(37)*. The Act prohibits sales to minors and sale of HTPs at temporary and mobile points of sale, via the Internet, telecommunications or any other developing technology or cross-border distance sales and in single units, except in the manufacturer's original packaging (Article 30). The law in Saudi Arabia prohibits the sale of HTP sticks in packages of more than 20 sticks *(38)*.

All countries that ban the sale of tobacco products to minors implicitly extend the ban to HTPs; however, some countries apply different age limits. Japan for instance applies a sales ban to persons under 20 *(39)*, while Austria and Belgium prohibit HTP sales only to children under 16 *(40)*. Federal systems, such as those of Canada, Switzerland and the USA, may have different subnational limits. In Switzerland, an age restriction of either 16 or 18 years applies to the purchase of HTPs, depending on the canton, while, in Canada, the age restriction is between 18 and 19 years. In December 2019, the USA enacted a ban on sales of all tobacco products, including HTPs, to any person under the age of 21 years.

Contents and emissions (Articles 9 and 10)

Most countries in the European Union require manufacturers to report the names, quantities and health effects of ingredients, including flavours. Under the European Union Tobacco Product Directive, tobacco products with a characterizing flavour are prohibited. A "characterizing flavour" is defined in Article 1(25) of the Directive as:

> a clearly noticeable smell or taste other than one of tobacco, resulting from an additive or a combination of additives, including, but not limited to, fruit, spice, herbs, alcohol, candy, menthol or vanilla, which is noticeable before or during the consumption of the tobacco product.

The prohibition on characterizing flavours currently applies only to cigarettes and roll-your-own tobacco and not to HTPs. Article 7(2) notes, however, that the Commission may determine that a particular tobacco product is subject to this ban, either on the initiative of the European Commission or at the request of a Member State. Characterizing flavours in HTPs may therefore be banned in the European Union in the future.

Education, communication, training and public awareness (Article 12)

The tobacco industry, with its new portfolio of products, uses marketing and promotion mainly as "reduced harm", "reduced risk" and alternatives to conventional cigarette as a strategy to manipulate governments to open their markets to HTPs. These claims are, however, unsubstantiated, as these products have not been proven to be different from conventional cigarettes in terms of tobacco-related risk, and the claims have distracted attention from evidence-based tobacco control policy measures to reduce tobacco use and protect public health. Article 12 of the WHO FCTC states:

> Parties shall promote and strengthen public awareness of tobacco control issues, using all available communication tools, as appropriate, and adopt and implement effective legislative, executive, administrative or other measures to promote the following:
>
> (a) broad access to effective and comprehensive educational and public awareness programmes on the health risks including the addictive characteristics of tobacco consumption and exposure to tobacco smoke;
>
> (b) public awareness about the health risks of tobacco consumption and exposure to tobacco smoke, and about the benefits of the cessation of tobacco use and tobacco-free lifestyles as specified in Article 14.2;

(c) public access, in accordance with national law, to a wide range of information on the tobacco industry as relevant to the objective of this Convention;

(d) effective and appropriate training or sensitization and awareness programmes on tobacco control addressed to persons such as health workers, community workers, social workers, media professionals, educators, decision-makers, administrators and other concerned persons;

(e) awareness and participation of public and private agencies and non-governmental organizations not affiliated with the tobacco industry in developing and implementing intersectoral programmes and strategies for tobacco control; and

(f) public awareness of and access to information regarding the adverse health, economic, and environmental consequences of tobacco production and consumption.

These are evidence-based measures for sensitizing the public and raising awareness about the ill-effects of use of tobacco products. All countries, and not just Parties to the WHO FCTC, should consider prioritizing these measures to protect public health.

6.3 Considerations and barriers to regulation, implementation and enforcement of policies

6.3.1 Regulatory considerations in implementing policies

HTPs may be considered differently from conventional cigarettes because of insufficient knowledge about the products, tobacco industry lobbying, regulatory classification of smokeless products based on arguments that these products are "smoke-free", "ash-free" or "cleaner alternatives" than conventional cigarettes, and differential approaches to the devices and the inserts. The tobacco industry has aggressively marketed these products, lobbied governments for more lenient regulations and exerted substantial pressure on regulatory decisions concerning HTPs. This has resulted in only partial application of comprehensive tobacco control regulatory measures to HTPs, which will ultimately undermine existing tobacco control.

The authors of a study *(41)* on an IQOS campaign in Israel described ways in which the industry attempts to define a new product as part of a category not covered by existing tobacco laws, in this case by using the term "smoking" in the argument. When IQOS was launched in Israel in December 2016, Philip Morris International organized high-level meetings and other direct communications with the Israeli Ministries of Health and Finance to put pressure

on the Government to exempt IQOS from existing tobacco regulations, which were reversed after three petitions to the Supreme Court. The authors warned that, in the absence of requirements for specific health warnings for HTPs, the industry may voluntarily place warnings on newer products, such as "research suggests that cigarettes cause addiction", which may introduce doubt about well accepted evidence regarding cigarettes.

The industry categorizes HTPs in the way that ensures the most favourable treatment under applicable national law. In New Zealand, HTPs were banned as a "smokeless product", but the ban was successfully challenged in court by Philip Morris International on the basis that HTPs are not "smokeless". New Zealand now applies all tobacco control laws for smoked products to HTPs, including plain packaging. In Romania, regulation of HTPs as smoked products was challenged in an industry submission on the basis of arguments of reduced harm, no combustion and therefore no smoke.

In determining the most appropriate approach to regulation of HTPs, countries should consider factors such as:

- the absolute and relative health risks to users and non-users;
- whether HTPs can be regulated continuously as scientific knowledge is gained on these products;
- the risk that tobacco use and smoking will be "renormalized";
- the risk of initiation by non-users of tobacco products, particularly young people;
- the possibility that smokers who have quit tobacco use, thereby improving their health, might switch to HTPs, although these are tobacco products and have not been proven to reduce tobacco-related risk;
- use with other nicotine and tobacco products, so that users are exposed to the emissions of two or more products; and
- capacity to assess industry claims regarding the relative harm of HTPs relative to conventional cigarettes and to prevent claims that could mislead consumers.

As noted previously, Parties to the WHO FCTC could go beyond its provisions in accordance with Article 2.1 of the Convention, which states that:

> In order to better protect human health, Parties are encouraged to implement measures beyond those required by this Convention and its protocols, and nothing in these instruments shall prevent a Party from imposing stricter requirements that are consistent with their provisions and are in accordance with international law.

6.3.2 Barriers to implementing and enforcing policies

In addition to lobbying, industry litigation threatens the passage, implementation and enforcement of policies. In New Zealand, a district court decision in 2018 (Philip Morris vs Ministry of Health) *(42)* overturned the previous classification of HTPs as "any tobacco product labelled or otherwise described as suitable for chewing, or for any other oral use (other than smoking)", which are banned under Section 29(2) of the Smokefree Environments Act 1990 *(43)*. Philip Morris Ltd was charged with violating the law by selling "Heets", the HTP inserts for IQOS. The holding found that, because the law was originally intended to control the sales of chewing tobacco and other tobacco products consumed orally, it should not apply to tobacco inserts for HTPs. Therefore, the district court ruled in favour of Philip Morris, and HTPs may be legally imported, sold, packed and distributed in New Zealand under the Act. Consequently, the Smokefree Environments Act regulations, including the ban on sales to minors and restrictions on advertising, apply to HTPs. This case highlights the challenges of regulating these products and the importance of legislation that can be adapted to the changing tobacco product landscape.

Much of the litigation is based on claims of combustion or non-combustion, whichever determines the most favourable treatment for the industry. As described earlier, regulation of HTPs as smoked products may be challenged by the industry on the basis of no combustion, while their regulation as smokeless products may be challenged on the basis that these products are not "smokeless".

6.3.3 Other considerations and unintended consequences

When countries regulate HTPs as smoked tobacco products, the health warnings for other smoked tobacco products apply. The same principle applies when HTPs are regulated as smokeless tobacco products. Many countries may be under the impression that these products require specific provisions, whereas they are already covered by their current tobacco control law. The Pan American Health Organization has made recommendations to countries in the Region of the Americas on regulation of HTPs under existing regulations for tobacco products. As the way in which tobacco products are defined in some regulations may make application of tobacco control laws difficult, regulations should be broadened to encompass novel and emerging nicotine and tobacco products. This would limit exploitation of regulatory loopholes by the tobacco industry. The WHO report on the global tobacco epidemic, 2019 *(44)* provides useful information and recommendations for countries.

- HTPs contain tobacco and should be regulated in the same way as tobacco products.

- HTPs produce toxic emissions, many of which are similar to those found in cigarette smoke.
- HTP users are exposed to toxic emissions from the products, and bystanders could also be exposed to toxic second-hand emissions.
- Although the levels of several toxicants in HTPs are generally lower than those in conventional cigarettes, the levels of others are higher. A lower level of a toxicant does not necessarily indicate a lower health risk.
- HTPs contain nicotine. Nicotine is highly addictive and is linked to harm, particularly in children, pregnant women and adolescents.
- The long-term health effects of HTP use and exposure to their emissions remain unknown. There is currently insufficient independent evidence on the relative and absolute risks. Independent studies should be conducted to determine the health risks they pose to users and bystanders.

This information includes important considerations for HTPs, as their availability on the market could have unintended consequences for public health, which should be considered in formulating policies and determining a regulatory path for HTPs.

6.4 Discussion

HTPs are tobacco products, defined in the WHO FCTC as "products entirely or partly made of the leaf tobacco as raw material which are manufactured to be used for smoking, sucking, chewing or snuffing". These products have gained a considerable market share in some countries and are now available on over 50 markets worldwide. Their unique characteristics, intensive industry lobbying, lack of clarity about their health risks and the absence of international approaches all pose challenges to regulators.

While limited data are available, as regulations depend on national interpretations of laws, which cannot be assessed independently, different countries clearly regulate HTPs in different ways, on the spectrum from bans to no regulation. Some countries consider HTPs to be in the same category as conventional tobacco products. Many countries already have domestic legislation and regulations with respect to basic tobacco control measures, including advertising, promotion and sponsorship, smoke-free spaces and packaging and labelling. A misconception is that regulating HTPs would be a new, resource-intensive initiative, when, in fact, these products are already covered by current tobacco control law.

The marketing of HTPs is, however, strategic, and its regulation presents challenges. The fact that devices and inserts are sold separately may exempt the devices (which do not contain tobacco) from, for instance, restrictions on advertising, promotion and sponsorship and even on sale to minors. The tobacco industry claims that there is no combustion in HTPs, and many European Union countries classify them as novel smokeless tobacco products, such that requirements for warnings and restrictions such as smoke-free areas may differ from those for conventional cigarettes. This paper poses a number of considerations for addressing regulation of these products.

6.5 Conclusions

In the past several years, the industry has significantly expanded its "reduced risk" portfolio with newer generation tobacco products, such as HTPs. The innovative technologies, design, marketing and health claims associated with these products have weakened tobacco control measures in some countries where there were relatively strong laws to regulate conventional cigarettes and attempts by the tobacco industry to reposition itself as a public health partner. Regulators were largely unprepared for these new products, especially their claims of "no combustion", "no smoke" and "no ash", which the industry has used to lobby governments for favourable regulatory treatment and in particular to circumvent smoke-free laws. As a result, the current regulations on HTPs are specific to each country. HTPs generate aerosols that contain toxicants, many at levels lower than those in conventional cigarette smoke, but in some cases higher. A lower level of a toxicant does not, however, necessarily mean lower risk. As the long-term effects on health of the use of and exposure to emissions from these products remain unknown and there is currently insufficient independent evidence on the relative and absolute risks, they should be fully subject to the provisions of the WHO FCTC, including a ban on their use in indoor spaces. The aim of this paper was to increase awareness about the inconsistent approaches used to regulate HTPs and to prepare regulators should a case be made by the industry to introduce HTPs and other novel and emerging tobacco products onto their markets.

Countries that are examining their legislative options can learn from regulatory successes and challenges in other countries. New tobacco control laws should anticipate not only HTPs but other emerging products, with definitions that are broad enough to encompass all innovative developments. Tobacco industry interference, including lobbying and misinformation, should be monitored and subjected to protection under WHO FCTC Article 5.3.

6.6 Research gaps

- Global surveillance of HTP products and their use to understand industry marketing strategies.
- Systematic monitoring of industry mechanisms to limit application of the WHO FCTC to HTPs and to undermine tobacco control.
- Comprehensive mapping of legislation on HTPs to identify regulatory loopholes that could be exploited by the industry and the level of implementation of existing policies, in order to improve it and to provide evidence on the regulatory approaches that promote maximum protection for public health.
- Effective surveillance for better understanding of the availability, marketing and use of HTPs.

6.7 Policy recommendations

As HTPs evolve and their availability spreads, regulators must address questions about these products in the face of industry pressure and scientific uncertainty. The varied approaches used by governments to classify and regulate these products reflect the absence of internationally agreed approaches. One thing is clear: HTPs are tobacco products. Therefore, policy-makers are urged to consider the following recommendations.

- Classify HTPs as tobacco products, except in countries where such classification would result in the more lenient regulations, undermine existing tobacco control provisions or allow market entry when similar products have been banned.
- Apply all the regulatory measures of the WHO FCTC to HTPs and especially those in Articles 5.3, 6, 8, 9 and 10, 11, 12, 13, 14 and 20. These include protecting tobacco control activities from all commercial and other vested interests, application of excise tax on these products, requiring reporting and disclosure of product information, requiring combined health warnings on HTPs and covering HTPs under smoke-free laws and bans and restrictions on tobacco advertising, promotion and sponsorship.
- In line with Article 13.4(a), prohibit "all forms of tobacco advertising, promotion and sponsorship that promote a tobacco product by any means that are false, misleading or deceptive or likely to create an erroneous impression about its characteristics, health effects, hazards or emissions".

- Use existing regulations for tobacco products to regulate HTPs, and broaden the scope of those regulations to ensure that regulatory loopholes cannot be exploited by the industry, even in countries in which these products are not currently (legally) on the market.
- Include HTPs in surveillance to understand their use and availability through existing channels, to inform regulation of these products and to ensure maximum protection of public health.
- Put the burden of proof on manufacturers to support claims about the products, and prohibit unsubstantiated claims about the relative risk or harmfulness of HTPs relative to other tobacco products.
- Monitor misinformation with respect to HTPs and claims about the risk or harm of these products relative to other products, and take appropriate regulatory action to curb such practices.
- Require premarket notification of novel and emerging tobacco products to enable the government to assess whether to authorize their sale.
- Define and classify these products to ensure that public health objectives are protected and to avoid regulatory loopholes. Given the variety of products on the market and under development, legal definitions must cover all product designs and be adaptable to product innovations.
- Closely monitor the products and their markets in the country, and institute effective measures to enforce adherence to relevant policies and regulations.
- Make clear regulatory distinctions among products and categories of products, and clearly define products and their components to ensure effective regulation.

6.8 References

1. Heated tobacco products: information sheet, 2nd edition. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/WHO-HEP-HPR-2020.2, accessed 10 January 2021).
2. Our tobacco heating system. IQOS. Lausanne: Philip Morris International; 2020 (https://www.pmi.com/smoke-free-products/iqos-our-tobacco-heating-system, accessed 10 January 2021).
3. Heated tobacco products (HTPs). Market monitoring information sheet (WHO/NMH/PND/18.7). Geneva: World Health Organization; 2018 (https://apps.who.int/iris/bitstream/handle/10665/273459/WHO-NMH-PND-18.7-eng.pdf, accessed 10 January 2021).
4. Novel and emerging tobacco products (FCTC/COP/8/22). Geneva: World Health Organization; 2018 (https://www.who.int/fctc/cop/sessions/cop8/FCTC__COP8(22).pdf?ua=1, accessed 28 December 2019).
5. Tobacco control laws. Washington (DC): Campaign for Tobacco-Free Kids; 2020 (https://www.tobaccocontrollaws.org/, accessed 10 January 2021).

6. Warner J. Vaping or cannabis: Where's the growth for Big Tobacco? IG, 17 February 2020 (https://www.ig.com/uk/news-and-trade-ideas/vaping-or-cannabis--wheres-the-growth-for-big-tobacco--200217, accessed 10 January 2021).
7. Bialous SA, Glantz SA. Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control. Tob Control. 2018;27:s111–7.
8. Preamble. Novel and emerging tobacco products (FCTC/COP/8/22). Geneva: World Health Organization; 2018 (https://www.who.int/fctc/cop/sessions/cop8/FCTC__COP8(22).pdf?ua=1, accessed 28 December 2019).
9. HTP information sheet. Geneva: World Health Organization; 2019 (https://www.who.int/tobacco/publications/prod_regulation/heated-tobacco-products/en/, accessed 10 January 2021).
10. Notice of final decisions to amend (or not amend) the current Poisons Standard 24 August 2020. Canberra: Department of Health, Therapeutic Goods Administration; 2020 (https://www.tga.gov.au/sites/default/files/public-notice-final-decisions-acms29-accs27-joint-acms-accs24-march-2020.pdf, accessed 10 January 2021).
11. Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products. Strasbourg: European Parliament; 2014 (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ%3AJOL_2014_127_R_0001, accessed 10 January 2021).
12. Parliamentary questions (P-009191/2016(ASW). Strasbourg: European Parliament; 2017 (https://www.europarl.europa.eu/doceo/document/P-8-2016-009191-ASW_ES.html).
13. Tobacco (Control of Advertisements and Sale) Act (as amended), Arts. 16(1)-(2). Singapore; 2011 (https://www.tobaccocontrollaws.org/.../Singapore%20- %20Control%20of%20Ads%20%26%20Sale%20-%20national.pdf, accessed 10 January 2021).
14. Act of April 26, 2016 Amending the Tobacco Act to Implement Directive 2014/40/EU on the Manufacture, Presentation and Sale of Tobacco and Related Products. The Hague: Staatsblad van het Koninkrijk der Nederlanden; 2016 (https://www.tobaccocontrollaws.org/files/live/Netherlands/Netherlands%20-%20Act of April 26%2C 2016%20-%20national.pdf, accessed 10 January 2021).
15. Information for suppliers. Bilthoven: National Institute for Public Health and the Environment; 2017 (https://www.rivm.nl/en/tobacco/information-for-suppliers, accessed 10 January 2021).
16. Gambaccini P. Blog. How should heated tobacco be taxed? Lausanne: Vapor Products Tax, 12 July 2017 (https://vaporproductstax.com/how-should-heated-tobacco-be-taxed/, accessed 10 January 2021).
17. Decreto legislativo, 15 dicembre 2014, n. 188. Disposizioni in materia di tassazione dei tabacchi lavorati, dei loro succedanei, nonche' di fiammiferi, a norma dell'articolo 13 della legge 11 marzo 2014, n. 23. Rome: Government of Italy; 2014 (http://www.governo.it/sites/governo.it/files/77443-9913.pdf, accessed 10 January 2021).
18. Legislative decree. Implementation of Directive 2014/40/EU on streamlining the legislative, regulatory and administrative provisions of the member states regarding the processing, presentation and sale of tobacco products and related products, which replaces directive 2001/37/EC. Rome: Government of Italy; 2016 (https://www.tobaccocontrollaws.org/.../Italy%20-%20Leg.%20Decree%20No. %206%20of%20Jan.%2012%2C%202016.pdf, accessed 10 January 2021).
19. Conference of the Parties to the WHO Framework Convention on Tobacco Control (eighth session), Decision FCTC/COP8(22). Novel and emerging tobacco products. Geneva: World Health Organization; 2018 (https://www.who.int/fctc/cop/sessions/cop8/FCTC__COP8(22).pdf?ua=1, accessed 10 January 2021).

20. International Convention on the Harmonized Commodity Description and Coding System (Brussels, 14 June 1983). Amendments to the nomenclature as an annex to the Convention accepted pursuant to the recommendation of 28 June 2019 of the Cistoms Co-operation Council (NG0262B1). Brussels: World Customs Organization; 2019:19 (http://www.wcoomd.org/-/media/wco/public/global/pdf/topics/nomenclature/instruments-and-tools/hs-nomenclature-2022/ng0262b1.pdf?db=web, accessed 10 January 2021).
21. Information note on classification of novel and emerging tobacco products. Geneva: World Health Organization; 2019 (https://untobaccocontrol.org/impldb/wp-content/uploads/Info-Note_Novel-Classification_EN.pdf, accessed 10 January 2021).
22. Federal Government Gazette. 28 December 2015. Control of Tobacco Product (Amendment) (No. 2) Regulations 2015. Kuala Lumpur: Federal Government; 2015 (https://www.tobaccocontrollaws.org/legislation/country/malaysia/laws, accessed 10 January 2021).
23. Notification detail. Draft of the UAE GCC Technical Regulation "Electronic nicotine products (equivalents of traditional tobacco products)" (G/TBTN/ARE/482). Brussels: European Commission; 2020 (https://ec.europa.eu/growth/tools-databases/tbt/en/search/?tbtaction=search.detail&num=482&Country_ID=ARE&dspLang=EN&BASDATEDEB=&basdatedeb=&basdatefin=&baspays=ARE&basnotifnum=482&basnotifnum2=482&bastypepays=ARE&baskeywords=, accessed 10 January 2021).
24. Executive order No. 106. Prohibiting the manufacture, distribution, marketing and sale of unregistered and/or adulterated electronic nicotine/non-nicotine delivery systems, heated tobacco products and other novel tobacco products, amending Executive Order No. 26 (S. 2017) and for other purposes. Manila: Malacañan Palace; 2020 (https://perma.cc/B7UY-BMR8, accessed 10 January 2021).
25. Guidelines for implementation of Article 13 of the WHO Framework Convention on Tobacco Control (Tobacco advertising, promotion and sponsorship). Geneva: World Health Organization; 2008 (https://www.who.int/fctc/guidelines/article_13.pdf?ua=1, accessed 10 January 2021).
26. Indirect promotional activities such as providing discount vouchers for electronic cigarette devices are prohibited. Sejong City: Health promotion Division; 2020 (http://www.mohw.go.kr/react/al/sal0301vw.jsp?PAR_MENU_ID=04&MENU_ID=0403&CONT_SEQ=352444, accessed 10 January 2021).
27. Jackler RK, Ramamurthi D, Axelrod AK, Jung JK, Louis-Ferdinand NG, Reidel JE et al. Global marketing of IQOS. The Philip Morris campaign to popularize "heat not burn" tobacco. Stanford (CA): Stanford Research into the Impact of Tobacco Advertising; 2020 (http://tobacco.stanford.edu/tobacco_main/publications/IQOS_Paper_2-21-2020F.pdf, accessed 10 January 2021).
28. Law No. 349 of June 6, 2002. On preventing the consumption of tobacco products and combating its effects. Bucharest: Government of Romania; 2002 (https://www.tobaccocontrollaws.org/files/live/Romania/Romania%20-%20Law%20No.%20349.pdf, accessed 10 January 2021).
29. Section 911 of the Federal Food, Drug, and Cosmetic Act – Modified Risk Tobacco Products. Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/section-911-federal-food-drug-and-cosmetic-act-modified-risk-tobacco-products accessed 10 January 2021).
30. McKelvey K, Popova L, Kim M, Kass Lempert L, Chaffee BW, Vijayaraghavan M et al. IQOS labelling will mislead consumers. Tob Control. 2018;27:s48–54.
31. Modified risk tobacco orders. FDA authorizes marketing of IQOS tobacco heating system with "reduced exposure" information. Press release, 7 July 2020. Silver Spring (MD): US Food and Drug Administration; 2020 (https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information,

accessed 10 January 2021).
32. WHO statement on heated tobacco products and the US FDA decision regarding IQOS. Geneva: World Health Organization; 2020 (https://www.who.int/news-room/detail/27-07-2020-who-statement-on-heated-tobacco-products-and-the-us-fda-decision-regarding-iqos, accessed 10 January 2021).
33. Lee KM. Gov't to mandate graphic warnings on heated tobacco products. The Korea Times, 2020 (https://www.koreatimes.co.kr/www/nation/2018/05/119_248951.html, accessed 10 January 2021).
34. Enforcement Decree of the National Health Promotion Act. Seoul: Ministry of Government Legislation; 2016 (https://www.tobaccocontrollaws.org/files/live/South%20Korea/South%20Korea%20-%20Enf.%20Decree%20of%20Nat'l%20Health%20Promotion%20Act.pdf, accessed 10 January 2021).
35. Tobacco product regulations: plain and standardized appearance. Ottawa: Government of Canada; 2020 (https://www.canada.ca/en/health-canada/services/health-concerns/tobacco/legislation/federal-regulations/products-regulations-plain-standardized-appearance.html, accessed 10 January 2021).
36. Law that provides for measures for the reduction of smoking. Nicosia: Government of Cyprus; 2002 (https://www.tobaccocontrollaws.org/files/live/Cyprus/Cyprus – Reduction of Smoking.pdf, accessed 10 January 2021).
37. The Restriction of the Use of Tobacco Products Act (Zoutpi). Ljubljana: National Assembly; 2017 (https://www.tobaccocontrollaws.org/.../Slovenia%20- %20TC%20Act%202017.pdf, accessed 10 January 2021).
38. Controls and requirements for electronic smoking devices. Version No. 1 (18/9/1440 AH). Riyadh: Saudi Food and Drug Authority; 2018 (https://www.tobaccocontrollaws.org/files/live/Saudi%20Arabia/Saudi%20Arabia%20-%20SFDA%20E-Cig%20Requirements.pdf, accessed 10 January 2021).
39. Act Prohibiting Smoking by Minors Act No. 33 on March 7, 1900. Last revision: Act No. 152 on December 12, 2001. Tokyo: Government of Japan; 2001 (https://www.tobaccocontrollaws.org/files/live/Japan/Japan%20-%20Act%20Prohibiting%20Smoking%20by%20Minors.pdf, accessed 10 January 2021).
40. Purchasing and consuming tobacco. Vienna: European Union Agency for Fundamental Rights; 2018 (https://fra.europa.eu/en/publication/2017/mapping-minimum-age-requirements/purchase-consumption-tobacco, accessed 10 January 2021).
41. Rosen L, Kislev S. The IQOS campaign in Israel. Tob Control 2018;27(Suppl1):s78–81.
42. Tobacco Control Laws. Litigation by country. New Zealand MOH v. PMI. Washington (DC: Campaign for Tobacco-Free Kids; 2020 (https://www.tobaccocontrollaws.org/litigation/decisions/nz-20180312-new-zealand-moh-v.-pmi, accessed 10 January 2021).
43. Smokefree Environments and Regulated Products Act 1990. Auckland: Ministry of Health; 1990 (https://www.tobaccocontrollaws.org/files/live/New%20Zealand/New%20Zealand%20-%20SF%20Act%201990%20-%20national.pdf, accessed 10 January 2021).
44. WHO report on the global tobacco epidemic, 2019. Geneva: World Health Organization; 2019.

7. Estimation of exposure to nicotine from use of electronic nicotine delivery systems and from conventional cigarettes

Anne Havermans, Centre for Health Protection, National Institute for Public Health and the Environment, Antonie van Leeuwenhoeklaan 9, 3721 MA Bilthoven, Netherlands

Thomas Eissenberg, Center for the Study of Tobacco Products, Department of Psychology, Virginia Commonwealth University, Richmond (VA), USA

Contents

Abstract

Electronic nicotine delivery systems (ENDS) are a diverse class of products intended to deliver aerosolized nicotine. ENDS comprise a rapidly evolving range of technologies and a wide variety of types, from the first-generation "cig-a-like" devices to the currently popular "pod"-based devices. Factors such as device design, liquid ingredients and user behaviour all affect the content of nicotine and non-nicotine toxicants in ENDS aerosol. Although some evidence suggests that ENDS may help some smokers to replace conventional cigarettes, dual use of ENDS with combustible cigarettes and the increasingly common initiation of ENDS use among previously nicotine-naïve individuals raise clear public health

concern. We reviewed the literature on nicotine emissions and delivery from ENDS and explored the factors that influence ENDS users' exposure to nicotine and non-nicotine toxicants. The review revealed that: ENDS are a heterogeneous product class that is evolving at a rate that outpaces regulation; flavoured ENDS liquids contribute to initiation and maintenance of their use by previously nicotine-naïve individuals; under certain circumstances, ENDS that deliver nicotine effectively might help some smokers to quit smoking combustible cigarettes; most ENDS users do not quit combustible smoking; regulation of ENDS nicotine emissions would be difficult because of the numerous inputs that control the emissions; and a regulatory focus on the rate of nicotine emission (e.g. nicotine "flux") might be useful, which would involve a requirement that only "closed-system" ENDS be marketed. In this context, future research needs and policy recommendations are proposed.

7.1 Background

Electronic nicotine delivery systems (ENDS) are a diverse class of products intended to deliver aerosolized nicotine to their users. They contain a battery-powered heating element known as a "coil" or "atomizer", which heats a liquid solution that contains nicotine, carrier liquids (e.g. propylene glycol, vegetable glycerine) and, usually, flavouring chemicals. The user inhales the resulting aerosol, which contains certain concentrations of nicotine and other toxicants. ENDS are a rapidly evolving class of products and include a wide variety of types, ranging from the first-generation "cig-a-like" devices to the currently popular "pod"-based devices in which a disposable cartridge holds the liquid *(1)*. Product design features and characteristics (such as wattage and coil dimensions), liquid constituents (such as carriers and nicotine concentration) and use behaviour (such as puff volume and duration) may be combined in numerous ways to affect the content (yield) of nicotine and other toxicants in the aerosol that the user inhales *(2)*.

Use of ENDS has risen substantially in some places during the past decade *(3,4)*. Use by children and adolescents has increased particularly rapidly in some countries, particularly in Europe, Canada and the USA, to the point that ENDS are now the most commonly used tobacco products in these age groups in the USA *(5,6)*. This raises concern, as ENDS emissions contain toxic chemicals that may be harmful to health *(7)* and also the dependence-producing drug nicotine. Nicotine is the primary addictive component of all tobacco products (e.g. combustible cigarettes, smokeless tobacco, heated tobacco) and in ENDS. In addition to causing dependence, nicotine can also have negative effects on health *(8)*. Children, adolescents and young adults are especially susceptible to the long-term neurocognitive effects of nicotine, as brain maturation continues into the early 20s *(9)*. It has been hypothesized that adolescents experience enhanced

nicotine reward and reduced withdrawal via enhanced excitation and reduced inhibition of dopaminergic striatal cells, making them more vulnerable to long-term nicotine dependence than adults *(10)*. In addition, ENDS may serve as a "gateway" to smoking; several studies have found that their use is associated with an increased risk of initiating cigarette smoking among adolescents and young adults *(11)*.

Although some ENDS may help some smokers to replace cigarettes by providing nicotine in a similar amount and form (i.e. protonated state) *(12)*, initiation of ENDS use by young non-smokers raises clear concern *(11)*. Regulators might have to characterize and control the factors that influence nicotine delivery to users from ENDS in order to minimize their abuse liability and health impact while maximizing any opportunities to reduce the risk for cigarette smokers. As nicotine delivery is a combined result of product design, liquid composition and user behaviour *(2)*, however, it might be difficult for regulation to account for all these factors together. As nicotine delivery from ENDS is a function of so many variables (e.g. device characteristics and liquid constituents), it has been suggested that regulation focus on the rate at which ENDS emit nicotine and other toxicants, which would account simultaneously for all the device, liquid and user factors that control the emission rate. Nicotine flux – the rate at which ENDS emit nicotine – has thus been suggested as a regulatory target (e.g. *13*). As described in more detail below, regulation of ENDS nicotine flux (and also potentially the rate at which other toxicants are emitted) would have the advantage of directly controlling the factors that affect public health, rather than proxy factors (e.g. liquid nicotine concentration), which, when regulated individually, may not achieve public health goals.

This background paper provides a narrative review of the literature (as of March 2020) on emission and delivery of nicotine from ENDS and explores factors that influence users' exposure to nicotine and non-nicotine toxicants in ENDS emissions. We searched PubMed for relevant publications in the past five years using the search terms "ENDS" OR "E-cigarette" OR "electronic cigarette" AND "Nicotine" AND "exposure" OR "emission" OR "yield" OR "delivery". To find relevant literature about use patterns, an additional search was performed with the search terms "ENDS" OR "E-cigarette" OR "electronic cigarette" AND "topography" OR "behavior". Additional searches were performed for information about specific user groups, with the search terms "ENDS" OR "E-cigarette" OR "electronic cigarette" combined with terms related to specific hypothesized user groups, such as "race", "ethnicity", "gender", "male", "female" and "dual use". Relevant articles cited in publications obtained through the database search were also included (i.e. snowball method). As the aim of this document is to provide a narrative review, no formal selection criteria were applied to the results of these searches.

7.2 Exposure to nicotine from ENDS

7.2.1 ENDS nicotine emission

"Nicotine emission" can be defined as the amount of nicotine in the ENDS aerosol that leaves the device, in other words the nicotine yield. The nicotine yield can be analysed in the aerosol from a smoking machine with a predetermined puffing regime. The aerosol can be trapped on filter pads and extracted with suitable solvents, and the extract is analysed by chromatographic methods *(2)*. Studies with these methods and a variety of puffing regimes have shown various amounts of nicotine in ENDS aerosol, some showing yields below those generally obtained from combustible cigarettes and others showing yields equal to or exceeding that of combustible cigarettes (i.e. 1.76–2.20 mg/cigarette) *(2,14,15)*. Importantly, if machine puffing regimes do not mimic human puffing behaviour, they are not valid measures of human exposure. Arbitrarily chosen machine puffing regimens, however, allow valid comparisons when the regimen is applied equally to all products under study.

7.2.2 Influence of ENDS electrical power on nicotine emission

The amount of nicotine per puff in the aerosol is influenced by factors that include the electrical power flowing through the device, the nicotine concentration in the liquid aerosolized by the device and the puffing behaviour of the user *(2)*. Electrical power (W) is a function of battery voltage (V) and coil resistance (Ω), such that $W=V^2/\Omega$. The power of ENDS ranges from ≤ 10 W in early models to ≥ 250 W in currently marketed models *(16)*. Higher power is often achieved by integrating low resistance coils (i.e. < 1 Ω) into the device, colloquially referred to as "sub-ohm vaping" *(17)*. The voltage of the battery and default power settings differ widely among ENDS models, and more advanced devices often allow the user to adjust the power settings. Devices that cannot be adjusted in this manner, "closed-system" ENDS, often have lower power because they are smaller and more closely resemble combustible cigarettes, whereas "open-system" ENDS are larger and can thus contain larger batteries and lower-resistance heating elements *(1,18)*. An ENDS that is truly a "closed system" does not allow the user to alter any of the elements of the device or liquid that influence nicotine yield, e.g. battery voltage, coil resistance and liquid nicotine concentration; it may also limit user puffing behaviour (e.g. puff duration *(19)*).

Increasing the power flowing through the heating element that vaporizes the liquid can increase the amount of aerosol produced and may also lead the element to overheat, which can cause thermal degradation of the liquid, with resulting toxicant formation. The impact of electrical power on aerosol nicotine yield has not been studied extensively, but one study found that increasing the power output from 3 to 7.5 W increased the nicotine yield by four or five times *(2)*. Increased power can also increase the emissions of non-nicotine toxicants *(20)*.

7.2.3 Contribution of the concentrations of nicotine and other compounds in ENDS liquids to nicotine emissions

The nicotine-containing liquids used in ENDS come in refill bottles or prefilled cartridges or pods, with a wide range of nicotine concentrations, usually reported on the label in mg/mL or as a percentage of total volume. The maximum nicotine concentration may differ from country to country according to differences in regulations. For instance, the European Tobacco Products Directive states that liquids should not contain nicotine concentrations exceeding 20 mg/mL *(21)*. The rationale for this regulation, as described in the Directive, is that this concentration would allow delivery of nicotine at a concentration comparable to the permitted dose of nicotine from a standard cigarette during the time required to smoke the cigarette. The relation between the nicotine concentration in liquid and nicotine delivery to the ENDS user is not, however, straightforward, because of the interplay of factors in the device (e.g. electrical power), the composition of the liquid and user behaviour.

In the USA, up to about 2017, the nicotine concentration in commonly available liquids was usually 0–36 mg/mL *(1,22–25)*. Some newer products, however, contain nicotine at levels up to 67 mg/mL *(26,27)*, and there is concern that innovations in ENDS liquid formulations are spurring a "nicotine arms race" *(28)*. Furthermore, the nicotine concentrations in ENDS liquid often do not match the labelled content, with deviations of up to 52% *(15)*, and several studies have demonstrated measurable amounts of nicotine in some liquids labelled as not containing nicotine *(24,25,29)*.

Some studies have shown that the nicotine concentration in ENDS liquids directly influences nicotine yield, that is, higher liquid nicotine concentrations result in higher emissions of nicotine in the aerosol *(2,14)*. Power settings also play a role, as increasing the device power increases nicotine yields *(14,30)*. Furthermore, users of ENDS liquids with low nicotine strength can obtain the same amount of nicotine per puff as high-nicotine ENDS users by adjusting their puffing behaviour *(2,31)*. In this way, they may also be exposed to higher amounts of toxicants (see next section). Other chemicals in ENDS liquids also influence the nicotine yield in ENDS aerosols. For instance, liquids usually contain the solvents propylene glycol and/or vegetable glycerine in various ratios; higher levels of propylene glycol than vegetable glycerine result in higher nicotine yields at low device power settings *(30)*. This might be a consequence of the greater volatility of propylene glycol at relatively low temperatures, resulting in greater vaporization. As vegetable glycerine becomes more volatile at higher temperatures, the putative difference is thought to become less pronounced at higher power settings *(30)*.

7.3 Overview of exposure to accompanying substances

In addition to nicotine, ENDS emissions contain other toxicants, which are either present in the liquid or are formed by thermal breakdown of the liquid's ingredients. The toxicants present in liquids include propylene glycol, vegetable glycerine and various flavouring chemicals *(32,33)*. In addition, because the nicotine in ENDS is derived from tobacco plants, the liquid may contain tobacco-related toxicants such as tobacco-specific nitrosamines *(1)*. The flavouring agents used in ENDS liquids are "generally recognized as safe" when added to food, but their risk profiles when heated and inhaled are unknown *(34)*. Some flavouring chemicals such as diacetyl (buttery flavour) *(35,36)*, benzaldehyde (fruity flavour) *(37,38)* and cinnamaldehyde (cinnamon flavour) *(36,38–40)* are known to be toxic when inhaled *(41,42)*. Moreover, findings from the Population Assessment of Tobacco and Health study indicate that users of fruit-flavoured ENDS have significantly higher concentrations of the biomarker for the carcinogen acrylonitrile than users of other flavours *(43)*. Toxicants present after heating ENDS liquid include carbonyls, volatile organic compounds and polycyclic aromatic hydrocarbons, which are also present in tobacco smoke. Toxicant production from ENDS is affected by factors such as user behaviour and the type and power settings of the device *(2,44)*. For instance, more intensive puffing patterns can increase the production of carbonyls such as formaldehyde, acetaldehyde and acetone *(14,44)*, which have been correlated with pulmonary disease in smokers *(45)*.

ENDS emissions may also contain substances that potentiate the addictive effects of nicotine. For example, menthol is a common component of both ENDS and combustible cigarettes, and it is present in many ENDS liquids even when they are not labelled as containing menthol or mint flavour *(46)*. Menthol can enhance the reinforcing properties of nicotine in various ways, e.g. by facilitating inhalation and by acting on relevant nicotinic acetylcholine receptor subtypes in the brain *(46)*. Other examples are the popular ENDS flavouring agents vanillin and ethyl vanillin, which have been found to act as monoamine oxidase inhibitors and reinforce the brain's response to nicotine *(47)*. The green apple flavouring chemical farnesene can cause reward-related behaviour by stimulating nicotinic acetylcholine receptors and the potency of nicotine for activating those receptors *(48)*. Other compounds that may potentiate the effects of nicotine and affect its metabolism are alcohol and the minor tobacco alkaloid nicotyrine. The interaction of alcohol and nicotine in ENDS emissions has not been studied, but one study has shown that high levels of alcohol in ENDS liquid can acutely impact psychomotor function *(49)*. In addition, alcohol and tobacco are commonly used together *(50)*, and alcohol drinking can increase smoking *(46)*. Nicotyrine is a thermal reaction product of nicotine and is present in ENDS emissions at levels 2–63 times higher per unit of nicotine than in emissions from tobacco cigarettes *(51)*. It inhibits nicotine metabolism in vivo and may thereby increase nicotine delivery from ENDS *(1,46,51)*.

7.4 Nicotine delivery from ENDS

ENDS vary in their ability to deliver nicotine to users' blood and brain. Evaluation of the nicotine delivery profile of ENDS is important, as ENDS that deliver nicotine as effectively as a combustible cigarette are probably more effective substitutes for combustible cigarettes *(52)*. The nicotine delivery profile of ENDS is also influenced by the combination of device type and power, the composition of the liquid and user behaviour *(15,17,53)*. For instance, higher-wattage ENDS models deliver nicotine more effectively than lower-wattage models *(16,54,55),* higher liquid nicotine concentrations deliver more nicotine, especially in experienced users *(17,56)*, and liquids with a higher propylene glycol than vegetable glycerine content increase nicotine delivery (probably due to the lower threshold of propylene glycol for evaporation and/or smaller particles that are more likely to reach users' lungs) *(57)*.

One study showed that cherry and menthol flavours increase nicotine delivery (i.e. maximum concentration of nicotine in the blood) as compared with tobacco flavour *(58)*. Another showed that more nicotine is delivered from a strawberry-flavoured liquid than from a tobacco-flavoured one, even though similar amounts of nicotine are inhaled, which may be related to differences in the pH of the liquids *(59)*. Overall, substantial variation is seen in the nicotine delivery from different devices and liquids, some not increasing plasma nicotine concentrations and others delivering nicotine at a level approaching that of a tobacco cigarette (i.e. 10–30 ng/mL) *(15,16,58,60–65)*.

Nicotine delivery to ENDS users may also depend on the bioavailability of nicotine in the liquid or aerosol. Thus, at a higher pH, a larger proportion of nicotine is in unprotonated form (free-base), which causes more irritation and increases the unpleasant taste of nicotine *(28,66)*. At lower pH, more nicotine is present in protonated form, which reduces absorption in the upper respiratory tract and also reduces harshness and unpleasant taste, allowing users to inhale more deeply without experiencing discomfort, so that a larger portion of the aerosol reaches the lower lungs with enhanced absorption of nicotine. Originally, with very few exceptions, ENDS liquids contained only free-base nicotine. New liquids have been introduced onto the market, however, to which acids are added to increase the proportion of protonated nicotine (i.e. nicotine salts) *(67)*. Liquids with a high nicotine concentration and small proportion of free-base nicotine are thought to be more likely to provide effective "cigarette-like" delivery of nicotine *(66)*. In line with this notion, one study showed that the concentrations of urinary cotinine (a major metabolite of nicotine) in adolescents using "pod"-system ENDS containing nicotine salts were higher than those of adolescents who regularly smoked conventional tobacco cigarettes *(26)*. The pH of ENDS liquids also varies widely, not only with brand and nicotine concentration but also within the same brand and nicotine concentration *(68)*. ENDS liquids that have the same nicotine concentration and the same device characteristics, including electrical power but

that differ in pH may have differing nicotine delivery profiles as well as differing sensory effects when the aerosols are inhaled. All other things being equal, protonated nicotine aerosol would be less harsh; however, this notion has not yet been tested empirically, as no studies have yet been reported in which liquid pH was manipulated systematically when all other variables were held constant.

7.5 Behavioural patterns of exposure according to use

7.5.1 Definition of user groups and user patterns

An important factor in exposure to nicotine is user behaviour, or puff topography. User puff topography includes variables such as the number, duration and volume of puffs and inter-puff interval and is highly individual. Various factors influence the way ENDS are used, such as the experience of the user and the composition of the liquid. Exposure to nicotine may also be affected by individual characteristics, and various user groups might be distinguished by the way in which they use ENDS. For example, experienced ENDS users typically take longer, larger puffs than ENDS-naïve users, resulting in higher nicotine delivery *(15,56,69)*. A study of "naturalistic" puffing topography identified three types of users: one that almost exclusively had "light" sessions (i.e. low puff volume (59.9 mL), flow rate (28.7 mL/s) and puff duration (2 s)), one with mainly "heavy" sessions (i.e. high puff volume (290.9 mL), flow rate (71.5 mL/s) and puff duration (4.4 s)) and a third with mainly "light" sessions (75%) and some "heavy" sessions (25%) *(70)*.

While some people use only ENDS, many ENDS users use tobacco cigarettes concurrently. In the USA, almost 70% of adult ENDS users also currently smoke cigarettes *(71)*, while the percentage of dual users among young people is lower, at 33% *(72)*. One study showed that cigarette smokers had longer puff duration and larger puff volume when using ENDS than non-smoking ENDS users *(73)*. Two other studies in users of both ENDS and tobacco cigarettes showed lower plasma nicotine concentrations after short-term ENDS use than after cigarette smoking in standardized laboratory settings *(55,74)*; however, the values were not compared in the same study to those for exclusive ENDS users. Other individual characteristics, such as gender and race, have been shown to affect exposure to nicotine from cigarette smoking *(75–77)* but have not been investigated for ENDS.

7.5.2 Factors that influence behavioural patterns

Various lifestyle and social factors also encourage or discourage ENDS use, potentially influencing exposure to nicotine. (See also section 3.) For example, local or national policies or regulations may prohibit the use of ENDS in certain enclosed public spaces (e.g. prohibition under smoke-free laws), and companies and institutions may ban ENDS use on their property, so that users have to restrict their use to home or outdoors. As smoke-free policies have reduced the

social acceptability of smoking *(78)* and smoking *(79,80)*, a similar effect might be seen on ENDS use if it was included in such policies.

Advertisements and other information to which people are exposed through public channels may also influence their perception and use of ENDS *(81)*. Several studies have shown that e-cigarette advertising can increase interest in, purchase of and use of e-cigarettes *(82–84)*. Policy measures such as health warnings and public education campaigns may discourage people, especially children and adolescents, from initiating use of these products. For example, in the USA, an education campaign called "The real cost" has been highly successful in preventing young people from initiating smoking and has been extended to ENDS *(85)*. Such information may influence non-users' and users' knowledge and beliefs about the risks and benefits of ENDS use and thereby the likelihood of sustained use among users and uptake by non-users.

The social networks of ENDS users also play a role in uptake of the product *(86–91)*. Especially among young users, ENDS use tends to take place in the presence of peers *(92–94)*.

Design and characteristics of ENDS devices

Other factors that influence ENDS use and exposure to nicotine are the design and characteristics of the ENDS device. For example, several newer ENDS models are similar in appearance to a USB stick, which facilitates concealed use in schools and other public places *(95,96)*. They are also "smart"-looking and hence appeal to the e-generation. Other ENDS models are highly customizable, so that users can change power settings and use liquids with different nicotine concentrations and flavours, factors that are known to influence use. For example, power settings influence puff behaviour, such that higher power reduces the puff number and duration *(97)*. This change in response to device power may reflect users' attempt to titrate nicotine and/or the sensory effects of the inhaled aerosol. Use patterns also are correlated with the nicotine concentration in the liquid, such that lower concentrations of nicotine are associated with larger, longer puffs *(17,98)*. The first use of nicotine-containing ENDS may increase exposure to nicotine throughout life, as one study showed that adolescents who initially used an ENDS with nicotine tended to use ENDS on more days during the first year of high school than adolescents who initially used an ENDS without nicotine *(99)*.

Solvents (propylene glycol and vegetable glycerine)

Higher ratios of propylene glycol to vegetable glycerine in ENDS liquid have been related to reduced puff duration and size but increased nicotine delivery *(57)*. Liquids with higher propylene glycol ratios were also rated as less "pleasant" and less "satisfying" by participants in the same study. This may be because pure propylene glycol liquids produce little to no visible exhaled aerosol, which is

usually considered a positive aspect by users and may be a conditioned reinforcer for nicotine. Another study showed that liquids with more vegetable glycerine were preferred to those with more propylene glycol and that "good taste" was the most important consideration when using and purchasing liquids *(100)*.

Flavours (See also section 6.)

ENDS liquid flavours have also been shown to affect puffing behaviour. For instance, one study showed that smokers took significantly longer puffs from flavoured ENDS (vanilla, cherry, menthol, espresso or tobacco flavours) than from tobacco cigarettes and tended to puff less frequently on vanilla- than on tobacco-flavoured ENDS *(58)*. In another study, experienced ENDS users took longer puffs from a strawberry-flavoured liquid than from a tobacco-flavoured one; however, they took even larger and more puffs when using their usual brand of ENDS liquid *(101)*. A third study found that ENDS liquid flavours influenced puff flow rate and puff volume but not puff duration *(102)*, although the direction of the effect was unclear. Flavours not only affect use behaviour but are also an important reason for initiating and continuing ENDS use, particularly for adolescents and young adults *(99,103,104)*.

7.6 Passive exposure to nicotine and other toxicants (See also section 8.)

ENDS users are exposed directly to nicotine and other toxicants by inhaling the aerosol emitted by their device. Non-users may be exposed to nicotine and other toxicants by "second-hand" exposure (also known as environmental exposure) or "third-hand" exposure to emissions that have settled onto surfaces, from skin contact or by ingestion of nicotine-containing liquid *(46)*. A growing body of literature suggests that ENDS use has a negative effect on indoor air quality *(105–109)*, supporting the idea that non-users may be exposed to toxicants exhaled by ENDS users when they share the same indoor space. Several studies have reported effective methods for assessing second- and third-hand exposure *(110)*. One study showed delivery of various levels of nicotine to non-users after acute second-hand exposure to ENDS aerosol in a real social setting *(100)*. Another, of exhaled breath of ENDS users, concluded that bystanders may experience systemic effects of nicotine, including increased heart rate and higher systolic blood pressure *(111)*. A further study confirmed that 30 min of second-hand exposure to ENDS aerosol caused sensory irritation and respiratory symptoms, which were related to the concentration of volatile organic compounds in the emissions *(112)*.

In pregnant women, nicotine readily crosses the placenta *(113)* and binds to nicotine acetylcholine receptors in the fetal brain, which play a critical role in brain development *(114)*. Early activation and desensitization of these

receptors by nicotine can disrupt development, with long-term consequences *(9)*. Although there are no published studies on how ENDS use affects pregnancy outcomes or fetal development, nicotine is considered to contribute substantially to a range of adverse effects of maternal smoking, and CO is thought to be a cause of low birthweight. Neonates exposed prenatally to nicotine and tobacco have a lower birthweight and earlier gestational age, have a higher risk of lung and cardiorespiratory problems and are more prone to asthma and allergy in childhood *(9,115)*. They are also at higher risk of neurocognitive effects that can lead to poor academic performance and significant behavioural problems throughout life, including attention deficit hyperactivity disorder, aggressive behaviour and future substance abuse *(116)*. Although it is difficult to conclude that these effects are caused specifically by nicotine or by other components of tobacco smoke, nicotine is considered to be the substance mainly responsible for most of the adverse effects on fetuses from maternal smoking *(9,116)*. Studies of pregnant women who use smokeless nicotine-containing products have also found associations with preterm birth, stillbirth and orofacial cleft defects *(117–120)*. Use of nicotine replacement therapy during pregnancy is associated with lower exposure to nicotine *(121)* and a lower risk of preterm delivery and low birth weight than with smoking *(122)*. As some ENDS deliver nicotine in amounts comparable to those in combustible cigarettes, some of the adverse effects of maternal smoking also may occur after exposure to nicotine from maternal ENDS use. It should be noted that ENDS emissions contain other possibly harmful compounds, with effects on fetal development that have not been thoroughly studied. For example, one study showed that flavouring agents in ENDS refill solutions are cytotoxic to human embryonic stem cells *(123)*.

7.7 Nicotine flux

ENDS nicotine "flux" is the rate at which an ENDS device emits nicotine, or the ENDS nicotine yield per unit time (e.g. μg/s). The rate of drug delivery has long been a relevant metric for understanding drug abuse, as faster drug delivery leads to greater abuse potential *(124,125)*. When nicotine was delivered to cigarette smokers intravenously at different rates, faster delivery was considered to give more rewarding positive effects *(126)*. Combustible cigarettes are used by millions of people worldwide, and, generally, they emit nicotine at approximately 100 μg/s (calculated from data obtained by Djordjevic et al. *(127)*) and deliver nicotine to blood and brain very quickly *(128,129)*. While combustible cigarette nicotine flux is generally stable for all combustible cigarette brands, similar stability is not seen for ENDS, mainly because of the heterogeneity of the product class. When all possible combinations of device power, construction, liquid and nicotine and other ingredients are accounted for, ENDS fluxes may range from 0 μg/s (i.e. no nicotine emission) to > 100 μg/s. This vast range of nicotine flux

explains the considerable variation in ENDS nicotine delivery profiles, with low-power devices and liquids with a low nicotine concentration delivering little or no nicotine and higher-power devices and liquids with higher concentrations delivering as much as or more nicotine than a combustible cigarette in the same number of puffs *(1)*. Importantly, nicotine flux is independent of user behaviour (e.g. longer puff durations do not alter flux), but flux and behaviour combined determine nicotine yield and exposure and the amount of drug delivered to the blood and brain. For example, a flux of 100 μg/s and a 1-s puff duration yields 100 μg nicotine, but a 4-s puff yields 400 μg nicotine. This explains why longer puffs result in greater nicotine delivery even when flux is controlled *(56)*. Longer puffs deliver a larger inhaled nicotine dose to the user.

While the heterogeneity of ENDS devices and liquids makes it difficult to measure flux in all possible combinations, ENDS flux can be predicted mathematically in a physics-based model *(130)*. As described elsewhere *(131)*, the model accounts for the time it takes for a coil to heat up after electricity begins to flow, cooling of the coil between puffs and the various ways in which heat can be transferred from the coil. Inputs to the model include the length, diameter, electrical resistance and thermal capacitance of the coil, the composition and thermodynamic properties of the liquid (including nicotine concentration), the ambient temperature and user behaviour (puff velocity and duration, inter-puff interval). In a validation study, model predictions were generated, and actual nicotine flux was measured in 100 conditions, in which power, device type, liquid composition and user behaviour were varied. The model accounted for 72% of the variation in nicotine flux under the conditions tested. This model could be used to predict the nicotine flux of any ENDS on the market today (open or closed system) as well as of ENDS that are being designed. Thus, mathematical modelling of nicotine flux presents a potential tool for policy-makers who wish to regulate ENDS nicotine emissions.

As has been noted *(18)*, if the goal of regulation is to decrease the likelihood that ENDS will be abused by a population such as non-smoking young people, an effective way may be to decrease ENDS nicotine flux. As the nicotine flux is a result of all of the ENDS characteristics (construction, wattage, liquid nicotine content), regulators can focus on a single product performance target – nicotine emission rate (i.e. nicotine flux), and manufacturers can choose the device and liquid characteristics that fall safely within that range. The flux target is not necessarily a single value but a range of allowable nicotine flux conditions (a nicotine emission rate no less than X and no greater than Y), allowing for a range of products designed to minimize abuse and maximize any potential benefit for smokers seeking to quit smoking combustible cigarettes and an eventual end to nicotine dependence, if ENDS can be demonstrated to provide such a therapeutic benefit. In sum, a mathematical model of nicotine flux allows regulators to examine an array of products efficiently to determine whether they meet or fall

outside a specified nicotine flux range. Unfortunately, such a regulatory approach cannot succeed if users have control over key parameters such as device power and liquid nicotine concentration. Therefore, policy-makers also may wish to consider the extent to which "open-system" devices are amenable to effective regulation *(18)*.

7.8 Discussion

ENDS are a diverse, evolving product class with growing global popularity, particularly among children, adolescents and young adults. Some ENDS users were former cigarette smokers who used ENDS to quit smoking combustible cigarettes, and there is some empirical evidence from randomized clinical trials that ENDS assist smoking cessation, although results are inconsistent. Many ENDS users are dual users, who continue to use ENDS with other tobacco products, in particular conventional cigarettes. Others were nicotine-naïve before using ENDS and may be at risk for subsequent initiation of conventional cigarette smoking. The myriad flavours of ENDS liquids available on the market may help some smokers to quit smoking, may encourage dual or poly use and almost certainly encourage nicotine-naïve young people to initiate ENDS use. The proportion of naïve ENDS users who were potential smokers and of those who would have remained non-smokers is a potential confounder in such analyses.

Some ENDS can deliver as much or more nicotine than a combustible cigarette in the same number of puffs. Some ENDS also deliver much less nicotine than a combustible cigarette. The extent to which ENDS deliver or do not deliver nicotine depends on a variety of device characteristics (e.g. electrical power, coil dimensions), liquid constituents (e.g. nicotine concentration, ratio of propylene glycol to vegetable glycerine) and user behaviour (e.g. puff duration). These same factors influence the extent to which ENDS emit non-nicotine toxicants that may be injurious to users' health. A recent influence on ENDS nicotine delivery is the marketing of liquids that contain protonated nicotine (nicotine salts). The aerosol formed from a protonated liquid is less harsh to inhale than aerosol formed from free-base nicotine, so that manufacturers can increase the nicotine concentration of the liquid without making the resulting aerosol unpalatable.

In view of all the factors that influence nicotine and non-nicotine emissions from ENDS, regulation of this product class may be difficult. There is a temptation to focus on single factors when regulating ENDS nicotine delivery, such as liquid nicotine concentration; however, such an approach may drive users to obtain more nicotine by manipulating unregulated factors such as using higher-powered devices and/or increasing puff duration. Such behaviour could reduce the effectiveness of regulation, such that nicotine delivery remains higher than intended by the regulators, while also exposing users to more aerosol that may be more toxic than if they used lower-powered devices and/or took shorter puffs.

Thus, it has been suggested that regulators focus on the rate at which nicotine is emitted from ENDS, the nicotine flux, as a regulatory target. This focus would also require that ENDS products not allow users to access many of the device, liquid and user behaviour characteristics that influence nicotine flux, such as "closed-system" ENDS with built-in limits on puff duration. These devices exist in some markets and are therefore clearly feasible. Exactly which nicotine flux parameters are conducive to promoting smoking cessation by current cigarette smokers while limiting abuse liability in nicotine-naïve young people are yet to be determined.

7.9 Conclusions

The data reviewed lead to the following conclusions.

- ENDS are a heterogeneous product class that continues to evolve at a speed that outpaces current regulatory efforts.
- ENDS performance characteristics are also heterogeneous, some users being exposed to very low levels of nicotine and other toxicants and others being exposed to much higher levels.
- ENDS use by previously nicotine-naïve individuals is inconsistent with public health goals.
- Flavoured ENDS liquids contribute to initiation and maintenance of ENDS use among previously nicotine-naïve individuals. They may also be attractive for smokers who want to quit cigarettes.
- Under certain circumstances, such as in the context of intensive behavioural counselling, ENDS that deliver nicotine effectively might help some smokers to quit combustible smoking, with positive public health effects. Most of these individuals, however, continue to use ENDS, with uncertain individual health consequences and thus an uncertain public health impact.
- Most ENDS users do not quit smoking combustible cigarettes but rather use both ENDS and combustible cigarettes, which, at the least, maintains the substantial health risks associated with cigarette smoking and may increase their health risks.
- Regulation of the emissions of nicotine and other toxicants from ENDS is complicated by the numerous inputs to emissions.
- Regulation of the emissions of nicotine and non-nicotine toxicants from ENDS may be necessary. This would require that marketed ENDS be constructed so that users cannot alter important characteristics such as device power and liquid constituents.

- The profile of nicotine emission and delivery from ENDS that would be most likely to achieve cessation of conventional smoking, ideally while also reducing the abuse liability of ENDS among nicotine-naïve individuals, is not known. Identification of that profile, if it exists, will require careful empirical work similar to that conducted for other pharmacological compounds that are used therapeutically even though, in some forms or via some routes, they can also be abused (e.g. opioids).

7.10 Research gaps, priorities and questions

The data reviewed here raise many research questions, including those listed below.

- Studies to determine the range of nicotine flux, if any, that will reduce the abuse liability of ENDS products and limit initiation by young people while helping smokers to eliminate their use of cigarettes and other smoked products with ENDS.
- Studies to compare fetal exposure to nicotine and other toxicants from ENDS with that from maternal cigarette smoking.
- Which way of achieving a given ENDS nicotine flux poses the least risk for users? Many different combinations of device power and liquid nicotine concentration can achieve the same flux, and some may lead to more non-nicotine toxicants than others.
- To what extent are flavoured ENDS liquids required for ENDS-facilitated cigarette cessation? Could unflavoured ENDS liquids, made only of nicotine, propylene glycol and vegetable glycerine, when paired with a device that emits nicotine as effectively as a combustible cigarette, facilitate cigarette smoking cessation in a current smoker?
- To what extent is intensive behavioural counselling a requirement for ENDS-facilitated cigarette smoking cessation?
- Which smokers are most likely to achieve smoking cessation with an ENDS product that delivers nicotine effectively? Is cessation more likely to be facilitated by ENDS in some smokers than others?
- Given the diversity of regulatory approaches to ENDS (i.e. different countries have different approaches), which policies are most effective in protecting public health with respect to ENDS use?
- To what extent does the availability of ENDS at numerous retail outlets facilitate initiation among nicotine-naïve individuals? Would restricting ENDS sales to regulated venues (perhaps where individu-

alized smoking cessation counselling is available) be more consistent with public health goals?

- What is the effect of increased levels of protonated nicotine in ENDS liquids on toxicity (additional acid ingredients) and abuse liability (by making inhalation of high doses of nicotine less harsh)?

7.11 Policy recommendations

The data reviewed here support the following three recommendations.

- Regulators should not permit ENDS in which users can control device features and liquid ingredients (i.e. open-system ENDS) and should ensure that the ENDS that are permitted do not appeal to young people.
- Regulators should focus on nicotine emission rate or flux (i.e. outcome) as a regulatory target, instead of any single input variable (e.g. liquid nicotine concentration or device power).
- ENDS should not have a higher abuse liability than combustible cigarettes. Thus, the ENDS nicotine emission rate or flux should not be higher than the emission rate of combustible cigarettes.

7.12 References

1. Breland A, Soule E, Lopez A, Romôa C, El-Hellani A, Eissenberg T. Electronic cigarettes: what are they and what do they do? Ann NY Acad Sci. 2017;1394(1): 5–30.
2. Talih S, Balhas Z, Eissenberg T, Salman R, Karaoghlanian N, El-Hellani A et al. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. Nicotine Tob Res. 2015;17(2):150–7.
3. Filippidis FT, Laverty AA, Gerovasili V, Vardavas CI. Two-year trends and predictors of e-cigarette use in 27 European Union member states. Tob Control. 2017;26(1):98.
4. McMillen RC, Gottlieb MA, Whitmore Schaefer RM, Winickoff JP, Klein JD. Trends in electronic cigarette use among US adults: Use is increasing in both smokers and nonsmokers. Nicotine Tob Res. 2015;17(10):1195–202.
5. Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM et al. Tobacco use among middle and high school students – United States, 2011–2016. Morbid Mortal Wkly Rep. 2016;66:597–603.
6. Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the field: Use of electronic cigarettes and any tobacco product among middle and high school students – United States, 2011–2018. Morbid Mortal Wkly Rep. 2018;67:1276–7.
7. Hutzler C, Paschke M, Kruschinski S, Henkler F, Hahn J, Luch A. Chemical hazards present in liquids and vapors of electronic cigarettes. Arch Toxicol. 2014;88(7):1295–308.
8. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends Cardiovasc Med. 2016;26(6):515–23.
9. England LJ, Bunnell RE, Pechacek TE, Tong VT, McAfee TA. Nicotine and the developing human: a neglected element in the electronic cigarette debate. Am J Prev Med. 2015;49(2):286–93.

10. O'Dell LE. A psychobiological framework of the substrates that mediate nicotine use during adolescence. Neuropharmacology. 2009;56(Suppl 1):263–78.
11. Soneji S, Barrington-Trimis JL, Wills TA, Levanthal AM, Unger JB, Gibson LA et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. JAMA Pediatrics. 2017;171(8):788–97.
12. Rahman MA, Hann N, Wilson A, Mnatzaganian G, Worrall-Carter L. e-Cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. PLoS One. 2015;10(3):e0122544.
13. Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. Nicotine Tob Res. 2015;17(2):158–62.
14. El-Hellani A, Salman R, El-Hage R, Talih S, Malek N, Baalbaki R et al. Nicotine and carbonyl emissions from popular electronic cigarette products: Correlation to liquid composition and design characteristics. Nicotine Tob Res. 2018;20(2):215–23.
15. Voos N, Goniewicz ML, Eissenberg T. What is the nicotine delivery profile of electronic cigarettes? Expert Opin Drug Deliv. 2019;16(11):1193–203.
16. Wagener TL, Floyd EL, Stepanov I, Driskill LM, Frank SG, Meier E et al. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. Tob Control. 2017;26(e1):e23–8.
17. Hiler M, Karaoghlanian N, Talih S, Maloney S, Breland A, Shihadeh A et al. Effects of electronic cigarette heating coil resistance and liquid nicotine concentration on user nicotine delivery, heart rate, subjective effects, puff topography, and liquid consumption. Exp Clin Psychopharmacol, 2020;28(5):527–39.
18. Eissenberg T et al. "Open-system" electronic cigarettes cannot be regulated effectively. Tob Control, 2020 (in press).
19. Talih S, Salman R, El-Hage R, Karam E, Karaoghlanian N, El-Hellani A et al. Characteristics and toxicant emissions of JUUL electronic cigarettes. Tob Control. 2019;28(6):678.
20. Talih S, Salman R, El-Hage R, Karam EE, Karaoghlanian N, El-Hellani A et al. Might limiting liquid nicotine concentration result in more toxic electronic cigarette aerosols? Tob Control. 2020:10.1136/tobaccocontrol-2019-055523.
21. The European Parliament and the Council of the European Union, Directive 2014/40/EU on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC. Off J Eur Union. 2014;L127/1:127.
22. Nicotine salts e-liquid overview. Singapore: Wingle Group Electronics Ltd; 2018 (https://vape.hk/wp-content/uploads/2019/05/NICOTINE_SALTS_E-LIQUID.pdf, accessed 10 January 2021).
23. El-Hellani A, El-Hage R, Baalbaki R, Salman R, Talih S, Shihadeh A et al. Free-base and protonated nicotine in electronic cigarette liquids and aerosols. Chem Res Toxicol. 2015;28(8):1532–7.
24. Goniewicz ML, Gupta R, Lee YH, Reinhardt S, Kim S, Kim B et al. Nicotine levels in electronic cigarette refill solutions: A comparative analysis of products from the US, Korea, and Poland. Int J Drug Policy. 2015;26(6):583–8.
25. Raymond BH, Collette-Merrill K, Harrison RG, Jarvis S, Rasmussen RJ. The nicotine content of a sample of e-cigarette liquid manufactured in the United States. J Addict Med. 2018;12(2):127–31.
26. Goniewicz ML, Boykan R, Messina CR, Eliscu A, Tolentino J. High exposure to nicotine among adolescents who use Juul and other vape pod systems ("pods"). Tob Control. 2019;28(6):676–7.
27. Omaiye EE, McWhirter KJ, Luo W, Pankow JF, Talbot P. High-nicotine electronic cigarette products: toxicity of JUUL fluids and aerosols correlates strongly with nicotine and some flavor chemical concentrations. Chem Res Toxicol. 2019;32(6):1058–69.
28. Jackler RK, Ramamurthi D. Nicotine arms race: JUUL and the high-nicotine product market.

Tob Control, 2019;28(6):623–8.
29. Omaiye EE, Cordova I, Davis B, Talbot P. Counterfeit electronic cigarette products with mislabeled nicotine concentrations. Tob Regul Sci. 2017;3(3):347–57.
30. Kosmider L, Spindle TR, Gawron M, Sobczak A, Goniewicz ML. Nicotine emissions from electronic cigarettes: Individual and interactive effects of propylene glycol to vegetable glycerin composition and device power output. Food Chem Toxicol. 2018;115:302–5.
31. Robinson RJ, Hensel EC. Behavior-based yield for electronic cigarette users of different strength eliquids based on natural environment topography. Inhal Toxicol. 2019;31(13–14):484–91.
32. Madison MC, Landers CT, Gu BH, Chang CY, Yung HY, You R et al., Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine. J Clin Invest. 2020;129(10):4290–304.
33. Chaumont M, Bernard A, Pochet S, Mélot C, El Khattabi C, Ree F et al. High-wattage e-cigarettes induce tissue hypoxia and lower airway injury: a randomized clinical trial. Am J Resp Critical Care Med. 2018;198(1):123–6.
34. Safety assessment and regulatory authority to use flavors – Focus on electronic nicotine delivery systems and flavored tobacco products. Washington (DC): Flavor and Extract Manufacturers Association of the United States; 2018.
35. Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins. Nicotine Tob Res. 2015;17(2):168–74.
36. Muthumalage T, Prinz M, Ansah KO, Gerloff J, Sundar IK, Rahman I. Inflammatory and oxidative responses induced by exposure to commonly used e-cigarette flavoring chemicals and flavored e-liquids without nicotine. Front Physiol. 2017;8:1130.
37. Kosmider L, Sobczak A, Prokopowicz A, Kurek J, Zaciera M, Knysak J et al. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. Thorax. 2016;71(4):376–7.
38. Hickman E, Herrera CA, Jaspers I. Common e-cigarette flavoring chemicals impair neutrophil phagocytosis and oxidative burst. Chem Res Toxicol. 2019;32(6):982–5.
39. Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. Toxicol In Vitro. 2014;28(2):198–208.
40. Clapp PW, Lavrich KL, van Heusden CA, Lazarowski ER, Carson JL, Jaspers I. Cinnamaldehyde in flavored e-cigarette liquids temporarily suppresses bronchial epithelial cell ciliary motility by dysregulation of mitochondrial function. Am J Physiol Lung Cell Mol Physiol. 2019;316(3):L470–86.
41. Barrington-Trimis JL, Samet JM, McConnell R. Flavorings in electronic cigarettes: An unrecognized respiratory health hazard? JAMA. 2014;312(23):2493–4.
42. Tierney PA, Karpinski CD, Brown JE, Luo W, Pankow JF. Flavour chemicals in electronic cigarette fluids. Tob Control. 2016;25(e1):e10–5.
43. Smith DM, Schneller LM, O'Connor RJ, Goniewicz ML. Are e-cigarette flavors associated with exposure to nicotine and toxicants? Findings from wave 2 of the Population Assessment of Tobacco and Health (PATH) study. Int J Environ Res Public Health. 2019;16(24):5055.
44. Kosmider L, Kimber CF, Kurek J, Corcoran O, Dawkins LE. Compensatory puffing with lower nicotine concentration e-liquids increases carbonyl exposure in e-cigarette aerosols. Nicotine Tob Res. 2017;20(8):998–1003.
45. Talhout R, Schulz T, Florek E, van Benthern J, Wester P, Opperhuizen A. Hazardous compounds in tobacco smoke. Int J Environ Res Public Health. 2011;8(2):613–28.
46. DeVito EE, Krishnan-Sarin S. e-Cigarettes: Impact of e-liquid components and device characteristics on nicotine exposure. Curr Neuropharmacol. 2018;16(4):438–59.
47. Truman P, Stanfill S, Heydari A, Silver E, Fowles J. Monoamine oxidase inhibitory activity of

flavoured e-cigarette liquids. NeuroToxicology. 2019;75:123–8.
48. Cooper SY, Akers AT, Henderson BJ. Green apple e-cigarette flavorant farnesene triggers reward-related behavior by promoting high-sensitivity nAChRs in the ventral tegmental area. eNeuro. 2020;7(4):0172.
49. Valentine GW, Jatlow PI, Coffman M, Nadim H, Gueorgiueva R, Sofuoglu M. The effects of alcohol-containing e-cigarettes on young adult smokers. Drug Alcohol Depend; 2016;159:272–6.
50. Van Skike CE, Maggio SE, Reynolds AR, Casey EM, Bardo MT, Dwoskin LP et al. Critical needs in drug discovery for cessation of alcohol and nicotine polysubstance abuse. Prog Neuropsychopharmacol Biol Psychiatry. 2016;65:269–87.
51. Son Y, Wackowski O, Weisel C, Schwander S, Mainelis G, Delnevo et al. Evaluation of e-vapor nicotine and nicotyrine concentrations under various e-liquid compositions, device settings, and vaping topographies. Chem Res Toxicol. 2018;31(9):861–8.
52. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiol Biomarkers Prev. 201019(8):1945–53.
53. Blank MD, Pearson J, Cobb CO, Felicione NJ, Hiler MM, Spindle TR et al. What factors reliably predict electronic cigarette nicotine delivery? Tob Control. 2019;29(6):644–51.
54. Yingst JM, Foulds J, Veldheer S, Hrabovsky S, Trushin N, Eissenberg T et al. Nicotine absorption during electronic cigarette use among regular users. PLoS One; 2019;14(7):e0220300.
55. Hajek P, Przulj D, Phillips A, Anderson R, McRobbie H. Nicotine delivery to users from cigarettes and from different types of e-cigarettes. Psychopharmacology. 2017;234(5):773–9.
56. Hiler M, Breland A, Spindle T, Maloney S, Lipato T, Karaoghlanian N et al. Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience. Exp Clin Psychopharmacol. 2017;25(5):380–92.
57. Spindle TR, Talih S, Hiler MM, Karaoghlanian N, Halquist MS, Breland AB et al. Effects of electronic cigarette liquid solvents propylene glycol and vegetable glycerin on user nicotine delivery, heart rate, subjective effects, and puff topography. Drug Alcohol Depend. 2018;188:193–9.
58. Voos N, Smith D, Kaiser L, Mahoney MC, Bradizza CM, Kozlowski LT et al. Effect of e-cigarette flavors on nicotine delivery and puffing topography: results from a randomized clinical trial of daily smokers. Psychopharmacology (Berl). 2020;237(2):491–502.
59. St Helen G, Dempsey DA, Havel CM, Jacob P III, Benowitz NL. Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. Drug Alcohol Depend. 2017;178:391–8.
60. St Helen G, Havel C, Dempsey DA, Jacob P III, Benowitz NL. Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes. Addiction. 2016;111(3):535–44.
61. Lopez AA, Hiler MM, Soule EK, Ramôa CP, Karaoghlanian N, Lipato T et al. Effects of electronic cigarette liquid nicotine concentration on plasma nicotine and puff topography in tobacco cigarette smokers: a preliminary report. Nicotine Tob Res. 2016;18(5):720–3.
62. Ramôa CP, Hiler MM, Spindle TR, Lopez AA, Karaoghlanian N, Lipato T et al. Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: a preliminary report. Tob Control. 2016;25(e1):e6–9.
63. Marsot A, Simon N. Nicotine and cotinine levels with electronic cigarette: a review. Int J Toxicol. 2016;35(2):179–85.
64. Hajek P, Pittaccio K, Pesola F, Myers Smith K, Phillips-Waller A et al. Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. Addiction. 2020;115(6).
65. Voos N, Kaiser L, Mahoney MC, Bradizza CM, Kozlowski LT, Benowitz NL et al. Randomized within-subject trial to evaluate smokers' initial perceptions, subjective effects and nicotine delivery across six vaporized nicotine products. Addiction. 2019;114(7):1236–48.

66. Duell AK, Pankow JF, Peyton DH. Nicotine in tobacco product aerosols: "It's déjà vu all over again". Tob Control, 2019;29(6):656–62.
67. Duell AK, Pankow JF, Peyton DH. Free-base nicotine determination in electronic cigarette liquids by 1H NMR spectroscopy. Chem Res Toxicol. 2018;31(6):431–4.
68. Stepanov I, Fujioka N. Bringing attention to e-cigarette pH as an important element for research and regulation. Tob Control. 2015;24(4):413.
69. Farsalinos KE, Spyrou A, Stefopoulos C, Tsimopoulou K, Kourkoveli P, Tsiapras D et al. Corrigendum: Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naive users (smokers). Sci Rep. 2015;5:13506.
70. Lee YO, Morgan-Lopez AA, Nonnemaker JM, Pepper JK, Hensel EC, Robinson RJ. Latent class analysis of e-cigarette use sessions in their natural environments. Nicotine Tob Res. 2018;21(10):1408–13.
71. Coleman BN, Rostron B, Johnson SE, Ambrose BK, Pearson J, Stanton CA et al. Electronic cigarette use among US adults in the Population Assessment of Tobacco and Health (PATH) study, 2013–2014. Tob Control. 2017;26(e2):e117–26.
72. Vogel EA, Cho J, McConnell RS, Barrington-Trimis JL, Leventhal AM. Prevalence of electronic cigarette dependence among youth and its association with future use. JAMA Netw Open. 2020;3(2):e1921513.
73. Lee YO, Nonnemaker JM, Bradfield B, Hensel EC, Robinson RJ. Examining daily electronic cigarette puff topography among established and nonestablished cigarette smokers in their natural environment. Nicotine Tob Res. 2017;20(10):1283–8.
74. St. Helen G, Nardone N, Addo N, Dempsey D, Havel C, Jacob P III et al. Differences in nicotine intake and effects from electronic and combustible cigarettes among dual users. Addiction. 2019;115(4):757–67.
75. Chen A, Krebs NM, Zhu J, Muscat JE. Nicotine metabolite ratio predicts smoking topography: The Pennsylvania Adult Smoking Study. Drug Alcohol Depend. 2018;190:89–93.
76. Holford TR, Levy DT, Meza R. Comparison of smoking history patterns among African American and white cohorts in the United States born 1890 to 1990. Nicotine Tob Res. 2016;18(suppl 1):S16–29.
77. Ross KC, Gubner NR, Tyndale RF, Hawk LW Jr, Lerman C, George TP et al. Racial differences in the relationship between rate of nicotine metabolism and nicotine intake from cigarette smoking. Pharmacol Biochem Behav. 2016;148:1–7.
78. Preventing tobacco use among youth and young adults: a report of the Surgeon General. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention; 2012.
79. Hoffman SJ, Tan C. Overview of systematic reviews on the health-related effects of government tobacco control policies. BMC Public Health. 2015;15:744.
80. Hopkins DP, Razi S, Leeks KD, Kalra GP, Chattopadhyay SK, Soler RE et al. Smokefree policies to reduce tobacco use: a systematic review. Am J Prev Med. 2010;38(2):S275–89.
81. Alcalá HE, Shimoga SV. It is about trust: Trust in sources of tobacco health information, perceptions of harm, and use of e-cigarettes. Nicotine Tob Res. 2020;22(5):822–6.
82. Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: an experimental study. Tob Control. 2016;25(e2):e107–12.
83. Farrelly MC, Duke JC, Crankshaw EC, Eggers ME, Lee YO, Nonnemaker JM et al. A randomized trial of the effect of e-cigarette TV advertisements on intentions to use e-cigarettes. Am J Prev Med. 2015;49(5):686–93.
84. Camenga D, Gutierrez KM, Kong G, Cavallo D, Simon P, Krishnan-Sarin S. e-Cigarette advertising exposure in e-cigarette naïve adolescents and subsequent e-cigarette use: A longitudi-

nal cohort study. Addict Behav. 2018;81:78–83.
85. Zeller M. Evolving "The real cost" campaign to address the rising epidemic of youth e-cigarette use. Am J Prev Med. 2019;56(2 Suppl 1):S76–8.
86. Leavens ELS, Stevens EM, Brett EI, Hébert ET, Villanti AC, Pearson JL et al. JUUL electronic cigarette use patterns, other tobacco product use, and reasons for use among ever users: Results from a convenience sample. Addict Behav. 2019;95:178–83.
87. Ickes M, Hester JW, Wiggins AT, Rayens MK, Hahn EJ, Kavuluru R. Prevalence and reasons for Juul use among college students. J Am Coll Health. 2019;68(5):1–5.
88. Kong G, Bold KW, Morean ME, Bhatti H, Camenga DR, Jackson A et al. Appeal of JUUL among adolescents. Drug Alcohol Depend. 2019;205:107691.
89. Leavens ELS, Stevens EM, Brett EI, Leffingwell TR, Wagener TL. JUUL in school: JUUL electronic cigarette use patterns, reasons for use, and social normative perceptions among college student ever users. Addict Behav. 2019;99:106047.
90. Nardone N, St Helen G, Addo N, Meighan S, Benowitz NL. JUUL electronic cigarettes: Nicotine exposure and the user experience. Drug Alcohol Depend. 2019;203:83–7.
91. Patel M, Cuccia AF, Willett J, Zhou Y, Kierstead EC, Czaplicki L et al. JUUL use and reasons for initiation among adult tobacco users. Tob Control. 2019;28(6):681–4.
92. Keamy-Minor E, McQuoid J, Ling PM. Young adult perceptions of JUUL and other pod electronic cigarette devices in California: a qualitative study. BMJ Open. 2019;9(4):e026306.
93. Hrywna M, Bover Manderski MT, Delnevo CD. Prevalence of electronic cigarette use among adolescents in New Jersey and association with social factors. JAMA Netw Open. 2020;3(2):e1920961.
94. McKelvey K. Halpern-Felsher B. How and why California young adults are using different brands of pod-type electronic cigarettes in 2019: Implications for researchers and regulators. J Adolesc Health. 2020;67(1):46–52.
95. Kavuluru R, Han S, Hahn EJ. On the popularity of the USB flash drive-shaped electronic cigarette Juul. Tob Control. 2019;28(1):110–2.
96. Ramamurthi D, Chau C, Jackler RK. JUUL and other stealth vaporisers: hiding the habit from parents and teachers. Tob Control. 2018;28(6):610–6.
97. Farsalinos K, Poulas K, Voudris V. Changes in puffing topography and nicotine consumption depending on the power setting of electronic cigarettes. Nicotine Tob Res. 2017;20(8):993–7.
98. Dawkins L, Cox S, Goniewicz M, McRobbie H, Kimber C, Doig M et al. "Real-world" compensatory behaviour with low nicotine concentration e-liquid: subjective effects and nicotine, acrolein and formaldehyde exposure. Addiction. 2018;113(10):1874–82.
99. Audrain-McGovern J, Rodriguez D, Pianin S, Alexander E. Initial e-cigarette flavoring and nicotine exposure and e-cigarette uptake among adolescents. Drug Alcohol Depend. 2019;202:149–55.
100. Melstrom P, Sosnoff C, Koszowski B, King BA, Bunnell R, Le G et al. Systemic absorption of nicotine following acute secondhand exposure to electronic cigarette aerosol in a realistic social setting. Int J Hyg Environ Health. 2018;221(5):816–22.
101. St Helen G, Shahid M, Chu S, Benowitz NL. Impact of e-liquid flavors on e-cigarette vaping behavior. Drug Alcohol Depend. 2018;189:42–8.
102. Robinson RJ, Hensel EC, al-Olayan AA, Nonnemaker JM, Lee YO. Effect of e-liquid flavor on electronic cigarette topography and consumption behavior in a 2-week natural environment switching study. PLoS One. 2018;13(5):e0196640.
103. Schneller LM, Bansal-Travers M, Goniewicz ML, McIntosh S, Ossip D, O'Connor RJ. Use of flavored electronic cigarette refill liquids among adults and youth in the US – Results from wave 2 of the Population Assessment of Tobacco and Health Study (2014–2015). PLoS One. 2018;13(8):e0202744.

104. Villanti AC, Johnson AL, Ambrose BK, Cummings KM, Stanton CA, Rose SW et al. Flavored tobacco product use in youth and adults: Findings from the first wave of the PATH study (2013–2014). Am J Prev Med. 2017;53(2):139–51.
105. Chen R, Ahererra A, Isichei C, Olmedo P, Jarmul S, Cohen JE et al. Assessment of indoor air quality at an electronic cigarette (vaping) convention. J Expo Sci Environ Epidemiol. 2018;28(6):522–9.
106. Melstrom P, Koszowski B, Thanner MH, Hoh E, King B, Bunnell R et al. Measuring PM2.5, ultrafine particles, nicotine air and wipe samples following the use of electronic cigarettes. Nicotine Tob Res. 2017;19(9):1055–61.
107. 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. Int J Hyg Environ Health. 2019;222(3):486–93.
108. Soule EK, Maloney SF, Spindle TR, Rudy AK, Hiler MM, Cobb CO. Electronic cigarette use and indoor air quality in a natural setting. Tob Control. 2017;26(1):109–12.
109. Volesky KD, Maki A, Scherf C, Watson L, Van Ryswyck K, Fraser B et al. The influence of three e-cigarette models on indoor fine and ultrafine particulate matter concentrations under real-world conditions. Environ Pollut. 2018;243(Pt B):882–9.
110. Quintana PJE, Hoh E, Dodder NG, Matt GE, Zakarian JM, Anderson KA et al. Nicotine levels in silicone wristband samplers worn by children exposed to secondhand smoke and electronic cigarette vapor are highly correlated with child's urinary cotinine. J Expo Sci Environ Epidemiol. 2019;29(6):733–41.
111. Visser FW, Klerx WN, Cremers HWJM, Ramlal R, Schwillens PL, Talhout R. The health risks of electronic cigarette use to bystanders. Int J Environ Res Public Health. 2019;16(9):1525.
112. Tzortzi A, Teloniatis S, Matiampa G, Bakelas G, Tzavara C, Vyzikidou VK et al. Passive exposure of non-smokers to e-cigarette aerosols: Sensory irritation, timing and association with volatile organic compounds. Environ Res. 2020;182:108963.
113. Luck W, Nau H, Hansen R, Steldinger R. Extent of nicotine and cotinine transfer to the human fetus, placenta and amniotic fluid of smoking mothers. Dev Pharmacol Ther. 1985;8:384–95.
114. Cairns NJ, Wonnacott S. (3H)(-)Nicotine binding sites in fetal human brain. Brain Res. 1988;475(1):1–7.
115. Suter MA, Aagaard KM. The impact of tobacco chemicals and nicotine on placental development. Prenatal Diagn. 2020;40(9): 10.1002/pd.5660.
116. Holbrook BD. The effects of nicotine on human fetal development. Birth Defects Res C: Embryo Today Rev. 2016;108(2):181–92.
117. Wikström AK, Cnattingius S, Stephansson O. Maternal use of Swedish snuff (snus) and risk of stillbirth. Epidemiology. 2010;21(6):772–8.
118. Gupta PC, Sreevidya S. Smokeless tobacco use, birth weight, and gestational age: population based, prospective cohort study of 1217 women in Mumbai, India. Br Med J. 2004;328(7455):1538.
119. Gupta PC, Subramoney S. Smokeless tobacco use and risk of stillbirth: a cohort study in Mumbai, India. Epidemiology. 2006;17(1):47–51.
120. Steyn K, De Wet T, Salojee Y, Nel H, Yach D. The influence of maternal cigarette smoking, snuff use and passive smoking on pregnancy outcomes: the Birth To Ten Study. Paediatric Perinatal Epidemiol. 2006;20(2):90–9.
121. Hickson C, Lewis S, Campbell KA, Cooper S, Berlin I, Claire R et al. Comparison of nicotine exposure during pregnancy when smoking and abstinent with nicotine replacement therapy: systematic review and meta-analysis. Addiction. 2019;114(3):406–24.
122. Forinash AB, Pitlick JM, Clark K, Alstat V. Nicotine replacement therapy effect on pregnancy outcomes. Ann Pharmacother. 2010;44(11):1817–21.

123. Bahl V, Lin S, Xu N, Davis B, Wang Y, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. Reprod Toxicol. 2012;34(4):529–37.
124. Balster RL, Schuster CR. Fixed-interval schedule of cocaine reinforcement: effect of dose and infusion duration. J Exp Anal Behav. 1973;20(1):119–29.
125. Carter LP, Stitzer ML, Henningfield JE, O'Connor RJ, Cummings KM, Hatsukami DK. Abuse liability assessment of tobacco products including potential reduced exposure products. Cancer Epidemiol Biomarkers Prev. 2009;18(12):3241–62.
126. Jensen KP, Valentine G, Gueorguieva R, Sofuoglu M. Differential effects of nicotine delivery rate on subjective drug effects, urges to smoke, heart rate and blood pressure in tobacco smokers. Psychopharmacology (Berl), 2020;237(5):1359–69.
127. Djordjevic MV, Fan J, Ferguson S, Hoffmann D. Self-regulation of smoking intensity. Smoke yields of the low-nicotine, low-"tar" cigarettes. Carcinogenesis. 1995;16(9):2015–21.
128. Henningfield JE, London ED, Benowitz NL. Arterial–venous differences in plasma concentrations of nicotine after cigarette smoking. J Am Med Assoc. 1990;263(15):2049–50.
129. Henningfield JE, Stapleton JM, Benowitz NL, Grayson RF, London ED. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. Drug Alcohol Depend. 1993;33(1):23–9.
130. Talih S, Balhas Z, Salman R, El-Hage R, Karaoghlanian N, El-Hellani A et al. Transport phenomena governing nicotine emissions from electronic cigarettes: model formulation and experimental investigation. Aerosol Sci Technol. 2017;51(1):1–11.
131. Breland A, Balster RL, Cobb C, Fagan P, Foulds J, Koch JR et al. Answering questions about electronic cigarettes using a multidisciplinary model. Am Psychol. 2019;74(3):368–79.

8. Exploration of methods for quantifying individual risks associated with electronic nicotine and non-nicotine delivery systems and heated tobacco products: impact on population health and implications for regulation

Frank Henkler-Stephani, German Federal Institute for Risk Assessment, Department of Chemicals and Product Safety, Berlin, Germany

Yvonne Staal, National Institute for Public Health and the Environment, Centre for Health Protection, Bilthoven, Netherlands

Contents

Abstract

e-Cigarettes heat and aerosolize e-liquids for inhalation. Many of the liquids contain nicotine (electronic nicotine delivery systems, ENDS), while others do not (electronic non-nicotine delivery systems, ENNDS). Although the basic design of ENDS or ENNDS is similar or the same, the devices that are used to heat liquids vary widely in details of their use, operation temperature or performance standards. The health risk depends not only on the properties of the device but also on the composition of the e-liquids, of which several thousand flavour varieties are commercially available or could be prepared at home.

Initial assessments suggest that the toxicological risks of individual ENDS depend on the devices and e-liquids, but the risk associated with high-powered devices may be relatively high. In this paper, we summarize methods that can be used to quantify the health risks associated with the use of ENDS, ENNDS and heated tobacco products (HTPs), due to either the individual compounds or the mixture in emissions. Most methods require substantial data on both emissions and hazards, only some of which are available. Currently, quantitative risk assessment methods cannot be used in regulation, although the most promising approaches are based on the relative potency of the compounds in emissions. Because of the diversity of ENDS and ENNDS, risk assessments remain a challenge, and the results cannot be generalized to the entire spectrum of devices. The wide variety of both liquids and devices indicates that different health risk assessments should be conducted for different combinations of liquid and device and for individual products. Relevant indicators of high risk could be characterized, such as specific ingredients or specific device settings.

8.1 Background

Tobacco use is the major cause of premature death worldwide. Each year, about 8 million people die from tobacco-related diseases, including an estimated 1.2 million non-smokers who were exposed to second-hand smoke *(1)*. Although cigarettes are the most common tobacco product, especially in developed countries, other tobacco products and replacement products also pose serious health risks. In India, more than 350 000 deaths are attributed to use of chewing and oral tobacco each year *(2)*.

While addiction is the driving force for maintenance of this hazardous behaviour, nicotine does not trigger the major toxic effects associated with the high mortality rate associated with tobacco consumption, which is due to carcinogenic and otherwise hazardous combustion products and tobacco constituents. The contributions of individual compounds to the carcinogenicity of tobacco use have been estimated *(3,4)*, leading to identification of the major carcinogens and ranking of smoke constituents by their potency in inducing tumours. Similar approaches have been used for cardiovascular and other health risks.

Strategies have been proposed to reduce the exposure of smokers to toxicants, including mandatory limits on the most relevant toxicants in cigarette smoke *(5–7)*. Attempts to restrict toxicant levels in conventional cigarettes have not, however, been successful because of technical limits to reducing combustion and combustion products *(8)*. HTPs contain electrical heating and other exothermic processes for generating an aerosol from tobacco material that consists of humectants, nicotine and other tobacco constituents and pyrolysis products. Aerosols from HTPs have generally been found to contain fewer hazardous and

potentially hazardous compounds than cigarette smoke *(9)*; however, it is not yet known whether reduced exposure to toxicants markedly reduces health risks.

e-Cigarettes are the most common form of ENDS, and the two terms are often used synonymously. In contrast to HTPs, ENDS no longer link nicotine consumption to tobacco use. While ENDS are clearly defined as nicotine delivery systems, the name "electronic non-nicotine delivery systems" (ENNDS) refers only to the absence of nicotine. According to current understanding *(10)*, ENDS and ENNDS are similar products, except for nicotine. Glycerol and/or propylene glycol are usually the major components of the liquids that form the aerosol. Liquids also contain various flavours and other ingredients to increase the palatability and attractiveness of the aerosol *(11–13)*. First-generation e-cigarettes are shaped like conventional cigarettes and consist of a battery, a liquid reservoir and an aerosolizing chamber containing a filament for heating liquid through wicks made of various materials *(14)*. The generated aerosol is directed to the mouthpiece and can be inhaled. Liquids are also provided in cartridges, either designed for single use or refillable. The initial devices were not very efficient at delivering nicotine to the user; however, this basic function has been gradually improved. Open systems have emerged, which are sophisticated devices that can be refilled and reused. Other improvements include increased battery capacity, variable electrical power, removal of tin solder joints and coiled filaments. Recent developments include sub-ohm-atomizing units that can be operated at higher variable voltages because of low electrical resistance *(14)*. Modern atomizers can evaporate a much higher volume of liquid per puff than the original cigarette-like devices *(15)*. These systems are highly adaptable. For example, users can build their own coils or customize performance parameters such as wattage, airflow and, indirectly, nicotine delivery. The operation of advanced systems is, however, also increasingly complicated, and products have been developed that are easier to use, with modules that contain prefilled liquid reservoirs and atomizers designed for single use *(16)*. (See also section 6.) These products have been termed "pod" systems, possibly as an analogy to coffee capsules. A nicotine-containing pod may be attached to a stick- or pen-shaped device containing a low-powered battery and a mouthpiece. A popular example is JUUL, which has become a leading e-cigarette brand in the USA *(16,17)*. Although pod systems lack the flexibility of advanced refillable e-cigarettes, their nicotine delivery and addictiveness are comparable to those of combustible cigarettes *(18)* due to very high nicotine concentrations in the liquid, which can reach 60 mg/mL, as in the US version of JUUL. This is three times higher than the upper limit of nicotine allowed in European products. Most pod systems contain nicotine salts, such as nicotine benzoate or salicylate, to limit the harshness of alkaline nicotine.

Until recently, e-cigarettes were considered mainly as devices for delivering nicotine, with no consideration of the harm they impose. ENNDS

were regarded by some as an acceptable nicotine-free version of combustible cigarettes. This may have been a limited perspective. Many novel technologies initially retain their original applications, while more applications are explored over time. Use of modified e-cigarettes to consume cannabis and other illicit compounds *(19)* may well be seen as an early indicator of an initially unintended use of these products. Recently, use of cannabidiol has emerged as a commercially relevant novel application that shows little relation to nicotine or tobacco use. Cannabidiol has defined pharmacological properties *(20)* and is claimed to have many beneficial effects. Some commercial products have been reported to contain other cannabinoids *(21)*. It is therefore misleading to describe cannabidiol liquids as consumables for ENNDS because they do not contain nicotine, and terms such as "electronic cannabidiol inhalation system" or "electronic inhalation system" might be more appropriate. A growing number of electronic delivery products are now beyond the traditional reach of nicotine and tobacco control, and their increasing, often unregulated use in some countries is a cause of concern.

8.1.1 Challenges to quantifying risk

From the perspective of risk assessment, the important distinction between ENDS and combustible cigarettes is that the adverse health effects of e-cigarettes depend on factors such as the system itself, the way it is used, manipulation and the e-liquid. The technical developments described above were not, however, made primarily for health considerations. The aim of the manufacturers was to improve the delivery of nicotine and the palatability and other properties of the products that determine consumer acceptance and use. This aim is a double-edged sword. Acceptance of e-cigarettes is a prerequisite for potential use of these systems in smoking cessation, but their attractiveness, especially to children and adolescents, increases the risk of use by people who would otherwise not have done so.

It is increasingly difficult to assess the toxicological risks of the properties of ENDS, because they are diversifying so rapidly. Initial assessments of early products postulated a temperature range up to 100 °C. Novel high-powered systems can reach temperatures up to 250 °C, which could facilitate chemical degradation of some ingredients; however, other technical features, such as overheating control or replacement of parts containing tin or other metals, might have decreased the exposure of users to toxicants *(14)*. The ambiguous role of technical features in modifying risk is also illustrated by pod systems, such as JUUL, with unique systems that influence their toxicological profiles. For example, closed systems are difficult to manipulate, prevent incidental dermal or oral contact with the liquids and form only minimal amounts of heat-dependent toxicants because of the low wattage. Pod systems pose a higher risk for young people, however, because of their addictiveness and attractiveness and the high nicotine content, especially in products sold in the USA *(16,18)*.

Further risks related to the ingredients and constituents of e-liquids are discussed below. Again, however, rapid product diversity makes it difficult to generalize, except for categories such as pod systems or sub-ohm devices, with very different properties. The rapid diversification also results in an information lag, in that, by the time studies are published, the market has moved on. An increasing challenge for both risk assessment and risk communication is distinguishing those products intended primarily to provide another means of delivering nicotine from those of unconventional liquids containing illicit or recreational drugs or other physiologically active compounds. Although it might be difficult to make this distinction for some products, it would, for example, be misleading to attribute any adverse effects of Δ^9-tetrahydrocannabinol (THC) or synthetic cannabinoids to ENDS or ENNDS per se, even when they are delivered by electronic inhalation systems. Restrictions should be considered on use of ENDS to combine nicotine with other pharmacologically or physiologically active compounds. ENNDS and their liquids should be defined specifically, as the absence of nicotine is insufficient as a criterion for defining this emerging product group. Alternative assessment frameworks are required for products that contain cannabidiol, THC or other drugs. In principle, consideration should be given to whether products that are intended for the delivery of physiologically active compounds or drugs other than nicotine are within the scope of tobacco control.

Individual and population-based risk assessments also depend on e-cigarette use and smoking behaviour, including the prevalence of dual or poly use (i.e. parallel use with tobacco cigarettes or other tobacco products). (See also section 5.) In the USA, dual use is common, although the prevalence of smoking has decreased among adults who currently use e-cigarettes, from 56.9% in 2015 to 40.8% in 2018 *(22)*. Although ENDS can reduce exposure to toxicants, any putative health benefits will be limited if users continue to smoke cigarettes. Even when heavy smokers (> 15 cigarettes per day) reduced their smoking by > 50%, the incidence of lung cancer decreased by only 27%, and their lung cancer risk remained more than seven times higher than that of non-smokers *(23)*. Gradual substitution of tobacco cigarettes with ENDS is of only limited value, as the risks associated with tobacco use remain. Unfortunately, epidemiological studies of the health effects of consistent, exclusive e-cigarette use are difficult to conduct because of limited data. In addition, the prevalence of e-cigarette smoking is highest among cigarette smokers and ex-smokers *(22)*, and it is difficult to separate diseases putatively associated with e-cigarette use from continuing effects of previous tobacco consumption.

8.2 Risk assessment and quantification of risks associated with use of ENDS and ENNDS

Quantitative risk assessment is a powerful tool for assessing the impact of cigarettes, ENDS, ENNDS or HTPs on human health. For example, modelling of tumour potency *(4)* allows estimates of the carcinogenic risk associated with individual constituents of cigarette smoke or the entire smoke, as described below. Modelling and risk quantification have confirmed the exceptionally high adverse effects of tobacco cigarettes in relation to ENDS, ENNDS and HTP *(24)*. Although modelling might also be conducted for ENDS and ENNDS, it would be difficult to cover the entire product spectrum. Nevertheless, relevant hazards can be identified that substantially increase health risks. Regulators should be aware of the growing differences among types and categories of ENDS. Therefore, regulation should address the ingredients, emissions and technical features that have the strongest effects on risk.

In general, ENDS emit fewer toxicants than conventional cigarettes, with two notable exceptions. The first is nicotine, a highly toxic compound added to e-liquids at concentrations up to 60 mg/mL, depending on the jurisdiction, or even higher in so-called "nicotine shots". Intake of 10 mL of a liquid that complies with European regulations corresponds to a dose of 2.8 mg/kg body weight for an adult (70 kg) or 20 mg/kg body weight for a small child (10 kg); the minimum potentially lethal dosage is estimated to be 6.5–13 mg/kg body weight *(25)*, and the lethal dose for infants and small children can be < 5 mg/kg body weight *(26)*. As refill containers may contain several hundred milligrams, the risk of accidental or intentional poisoning is high. Users of open systems and refill containers are at risk of dermal exposure, and incidental oral poisoning can occur, although oral absorption of nicotine is often limited by its emetic effects. A number of weak or moderate cases of intoxication were reported in 2018 (*27*), but fatal poisonings are very rare *(28)*. The second exception to emission of fewer toxicants than conventional cigarettes is contaminants and intentionally added compounds, including essential oils, herbal extracts and certain flavours such as diacetyl and acetyl propionyl, which can cause serious (acute) lung injury.

Commercial products that comply with regulations in Europe, the USA and other countries should not pose such risks. Single cases of lipid pneumonia have been reported, probably caused by glycerol contaminated with fatty oils *(29)*. Many users prepare their own e-liquids and sometimes make their own ingredients, perhaps because they are not aware of the risks. Such risks are avoidable and should not apply to commercial products if appropriately regulated. In the worst case, however, use of irregular, manipulated or faulty products could have acute and fatal toxic effects, while smoking-associated diseases take years to develop. Typical hazards of e-cigarettes are discussed below.

8.2.1 Health risks associated with specific ingredients or unintentionally added substances

The health effects that could occur from direct or indirect exposure to harmful and potentially harmful constituents of ENDS or ENNDS aerosols when inhaled by children or adolescents are summarized below. The actual occurrence of effects would depend on the quantity of the compound that is inhaled.

Nicotine

Tobacco smoking increases the risks for arteriosclerosis, myocardial infarction, stroke and other cardiovascular diseases. These are due not only to nicotine but also to other compounds, such as carbon monoxide, nitrogen oxides, metals and particulate matter. The pathogenesis is usually associated with inflammation *(30,31)*. Some effects of nicotine, such as increased blood pressure and decreased perfusion of coronary vessels, can contribute to cardiovascular injuries. Limited data are available, however, on the cardiovascular effects of nicotine in ENDS. The cardiovascular toxicity of nicotine is lower without combustion products than in cigarette smoke *(30)*, as indicated by studies on use of smokeless tobacco. For example, Swedish snus did not increase the risks of stroke or infarction *(32)*, despite efficient nicotine absorption, although this requires further study *(33)*. A meta-analysis of 11 studies in Sweden and the USA indicated that smokeless tobacco users had increased risks for myocardial infarction and stroke *(34)*. Increased odds for myocardial infarction with smokeless tobacco use were also reported in the INTERHEART study of data on 27 089 participants in 52 countries *(35)*.

Modern e-cigarettes can be optimized to deliver nicotine at levels comparable to those in combustible cigarettes *(15)*. In open systems, nicotine levels can usually also be adjusted with the power setting and increase with the amount of aerosolized liquid per puff. On inhalation, aerosolized nicotine might contribute to inflammation and vascular injuries *(36)*; however, pathogenesis also depends on inflammatory co-factors *(31)* such as reactive oxygen species, and it is not known whether these factors are generated by e-cigarettes. Smoking during pregnancy can affect embryonic development, reduce birth weight and increase the risk for complications, such as premature delivery, stillbirth or sudden infant death. Further, both lung function and development can be impaired by maternal smoking. It is again, however, difficult to distinguish the adverse effects of smoke and combustion products from those of nicotine. Nicotine has been reported to limit the availability of oxygen to the fetus by constricting blood vessels in the umbilical cord and uterus *(37)*. Prenatal exposure to nicotine interferes with development of the brain *(38)* and is associated with neurobehavioural impairment, including hyperactivity, anxiety and impaired cognitive function. Nicotine was confirmed as teratogenic to the nervous system in a study in rats

(39), and other experimental studies have suggested that developmental exposure to nicotine has long-term adverse effects such as impaired fertility, hypertension, obesity and respiratory dysfunction *(40)*.

Nicotine may induce other adverse effects, such as insulin resistance, thus increasing the risk for diabetes type 2 *(41)*, although the question should to be addressed in additional studies. One suggested that nicotine can inhibit mucociliary clearance in the lung *(42)*, which could increase exposure to toxicants.

Hazardous constituents and emissions of ENDS and ENNDS

Glycerol and propylene glycol. Glycerol and propylene glycol are the most commonly used solvents for aerosolization and are the major constituent of e-liquids. Although mild adverse effects such as irritation have been described after inhalation *(43,44)*, both compounds are considered relatively safe. The amount of evaporated liquid per puff varies, however, and is extremely high in sub-ohm devices *(45)*. No comparison has yet been reported of the toxic properties of e-cigarette aerosols according to the density of the aerosol or the total mass of inhaled material, particularly in the long term. Other solvents, such as ethylene glycol, have been used *(12)*, which have higher toxicological risks *(46)*; however, it is not clear whether ENDS containing other nebulizing agents as major components are currently on the market.

Flavours and other ingredients. Some flavours, including diacetyl, are of concern, as they can cause bronchiolitis obliterans, a rare but serious lung disease. Diacetyl was detected in a large proportion of liquids tested *(11)*, albeit 5 years ago, before the ban on its use in e-cigarettes in many jurisdictions. The sweetener sucralose, a halogenated disaccharide, can be degraded in e-liquids when devices reach temperatures > 200 °C, which can generate potentially harmful organochlorines *(47)*. Other compounds in regular e-liquids include sensitizers. For example, limonene oxide, found in lemon-flavoured concentrates *(13)*, is considered an important contact allergen *(48)*. Rare cases of hypersensitivity pneumonitis have been reported that might be related to use of ENDS and ENNDS; however, no specific allergen has yet been identified in e-liquids *(49)*. In 2019, a further case of hypersensitivity pneumonitis was reported in the United Kingdom *(50)*. This case was not related to e-cigarette- and vaping-associated lung injury (EVALI) (see HSP2) but indicates that inhalation of e-cigarette aerosol can induce allergic responses, although rarely. The etiology of these cases should therefore be elucidated, with monitoring of future developments. The increasing variety of e-liquids should be regarded as a potential hazard, as many of the constituents can generate thermal degradation products and undergo chemical conversions. Indeterminate chemical reactions are facilitated by coil temperatures of ≥ 250 °C *(51)*.

Carbonyls and thermal degradation products. Carbonyl compounds, including formaldehyde, acetaldehyde and acrolein, are considered the most relevant toxic emissions from commercial ENDS. They originate from degradation of glycerol and propylene glycol, depending on the device temperature. In low-powered devices, carbonyls occur mainly under dry-puff conditions due to overheating of the wire in the absence of liquid *(12,52)*. In high-wattage devices, carbonyls are formed according to the applied power. Talih et al. *(45)* demonstrated enhanced carbonyl formation in high-power single-coil conventional ENDS and sub-ohm devices that varied with the coil surface and the amount of liquid consumed. The study showed total aldehyde emissions of ≤ 400 µg per 15 puffs. The carbonyl content of the aerosol can approach that of conventional cigarettes but is highly variable. For example, it may be strongly enhanced by flavours *(53)*, and puffing topography can account for variations in formaldehyde levels from 20 to 255 ng/puff *(45)*. In general, carbonyls in ENDS and ENNDS occur at levels from hardly detectable to several micrograms per puff. Acetaldehyde not only has carcinogenic and other hazardous properties but also increases the addictiveness of nicotine *(54)* by inhibiting monoamine oxidase. Moderate levels of carbonyls might therefore increase consumer satisfaction by making products more attractive.

Adult smokers are less likely than non-smoking adolescents to use JUUL as an alternative to cigarettes, although this device delivers high levels of nicotine *()*. The trend to increasing the wattage to variable, higher levels may be partly to increase user satisfaction, as higher levels of carbonyls can enhance the effects of nicotine and possibly its addictiveness. Toxicological assessments should be conducted of various groups of ENDS and ENNDS products. A special category might be considered for ENDS that operate at ≥ 15 W, as these devices produce dense aerosols and markedly higher levels of toxicants than low-power devices. It has been reported that high-power ENDS and ENNDS increase the risk for lung injuries, including transient inflammation, and disturb gas exchange *(56)*. Regulators should be aware that it would be difficult to impose upper limits on the levels of ingredients in high-capacity open-system ENDS and ENNDS, as they could be compensated by switching to a higher power *(57)*. For example, the intake of nicotine per puff can be increased when a higher volume of liquid is aerosolized, increasing the risk to health.

Metals. Metals that occur in the aerosols of ENDS and ENNDS usually originate from the devices themselves *(58)*. The levels remain below the limits of toxicological concern *(59,60)* but can be increased at high-power settings *(61)*. As redox-active metals might increase the levels of reactive oxygen species, cardiovascular risk might be increased, especially in the presence of a high level of nicotine. Haddad et al. *(62)* showed that high-wattage ENDS can generate levels of reactive oxygen species that are comparable to those from combustible cigarettes.

In summary, hazard analysis has confirmed that nicotine, carbonyls and metals are relevant risk factors, implying that e-cigarette use could enhance the risks for cardiovascular diseases. The high nicotine content, application of high wattages and low-quality standards also affect the levels of metals in emissions. As aerosols may contain irritants, the risks of respiratory diseases should also be assessed. ENDS generate levels of carcinogens that are lower than those typical for tobacco smoke, except those of carbonyls *(63,64)*. This finding was recently confirmed for sub-ohm and high-wattage devices in an industry-sponsored study (*65)* but should be confirmed in independent research.

8.2.2 Potential health effects of ENDS and ENNDS

Smoking can increase the risks for arteriosclerosis, myocardial infarction, stroke and other cardiovascular diseases. The risk factors include a number of chemical species, such as carbon monoxide, nitrogen oxides, metals and particulate matter. Pathogenesis is usually linked to inflammation, and some nicotine-related effects, such as increased blood pressure and decreased perfusion of coronary vessels, can exacerbate cardiovascular injuries *(30,31)*. There is still, however, some debate about whether e-cigarette use also increases cardiovascular risk. A systematic review of studies on the use of e-cigarettes and cardiovascular disease indicated potentially increased risks for thrombosis and atherosclerosis *(66)*.

Short-term exposure to e-cigarette emissions can trigger vascular oxidative stress and dysfunction *(67)*. e-Cigarettes can have an effect even after a single use and even without nicotine, with a transient effect on endothelial function *(68)*. In a meta-analysis, Skotsimara et al. *(69)* found associations between e-cigarette use and endothelial damage, arterial stiffness and a long-term risk for coronary events; however, these findings were made in single studies and were not confirmed in others. Short-term effects on vascular function do not necessarily progress to clinically relevant disease. Analysis of data collected in the Behavioral Risk Factor Surveillance System in 2016 showed substantially increased risks for stroke, myocardial infarction and coronary artery disease among 70 000 respondents who reported use of e-cigarettes *(70,71)*. Further, analysis of National Health Interview Surveys (2014–2016) confirmed a higher risk for myocardial infarction after adjustment for cigarette smoking and other risk factors *(72)*. Analysis of pooled Behavioral Risk Factor Surveillance System data collected in 2016 and 2017 did not confirm an increased cardiovascular risk for e-cigarette users who never smoked cigarettes *(73)*. No specific data are yet available on devices that might enhance such risks. A comprehensive review of preclinical findings and epidemiological evidence on the effects of e-cigarettes on cardiovascular and general health was inconclusive, and more data are needed. The authors concluded that, while it is reasonable to consider e-cigarettes less hazardous than combustible tobacco products, no smoke is better than electronic

smoke *(70)*. One report showed that smokers who switched to e-cigarettes had significantly improved endothelial function and vascular health *(74)*.

Other health effects include irritation of the respiratory tract, mainly the upper airways *(75)*. Effects on lung function have also been reported, with decreased lung function capacity among e-cigarette users than non-users and possibly increased lung resistance *(76,77)*. Furthermore, e-cigarette users may have a reduced response to infections *(78)*. An analysis of the data in the Behavioral Risk Factor Surveillance System for 2016–2017 indicated that e-cigarettes enhance pulmonary toxicity. Increased risks of respiratory diseases have also been confirmed by others *(79)*. Another study suggested that the health of patients with chronic obstructive pulmonary disease who smoked tobacco improved after they switched completely to e-cigarettes, including better outcomes and reversal of some of the harm caused by smoking *(80)*. This illustrates the different perspectives of smokers and non-smokers on the health risks of e-cigarettes. A link between e-cigarette use and asthma has been reported; however, the high prevalence of e-cigarette use by adults with asthma could be related to quit attempts in this group *(73)*.

In the summer of 2019, a series of cases of serious lung injury associated with use of vaping or e-cigarette product use was reported in the USA. (See also section 12.) The number of incident cases related to e-cigarette use increased, and fatalities with no history of lung disease were reported *(81)*. The disease, named "E-cigarette- and Vaping-Associated Lung Injury" (EVALI), was restricted mainly to the USA. By 18 February 2020, 2807 hospitalized cases had been reported, including 68 EVALI-associated deaths *(82,83)*. The patients presented similar clinical characteristics, such as dyspnoea and cough, and were hypoxaemic, with bilateral airspace opacities on chest imaging *(84)*. As these symptoms are similar to those of other respiratory diseases, these cases were not immediately linked to use of specific types of e-cigarettes *(85)*. Many, but not all, patients had used THC-containing e-liquids, and further research indicated that vitamin E acetate, which is added to THC-containing e-liquids as a thickener, was the probable cause of the respiratory injuries *(86–88)*. The patients with respiratory disease were found to have used e-liquids containing THC more often than non-patients and, perhaps more importantly, reported more frequently obtaining products from informal sources *(89)*. Cases also occurred, however, in patients who did not use THC-containing liquids. Patients showed respiratory effects within a few days to several weeks of inhaling vitamin E acetate, which allowed identification of the cause of the disease; however, an association is much more difficult to establish with long-term health effects. In one study that confirmed the association *(88)*, exceptionally high levels of vitamin E acetate were found in products collected from EVALI patients. The reported concentrations were 31–88%, while the THC content was often lower than that advertised *(90)*. It should be noted that these

products have little in common with typical e-cigarettes. Both risk assessment and public education are necessary to respond to the increasing proliferation of unconventional, often illicit uses of e-cigarettes to deliver drugs other than nicotine. Risk assessment would benefit from a clear distinction between these products and regular ENDS, which would be difficult to achieve in practice.

8.2.3 Risks for bystanders

Bystanders may be exposed to emissions of ENDS, ENNDS or HTP exhaled by users. Their actual exposure will depend largely on the size and ventilation of the room. Bystanders could experience irritation of the respiratory tract as a result of exposure to propylene glycol and glycerol. Systemic effects of nicotine might also be expected if nicotine-containing e-liquid is used, including heart palpitations and raised systolic blood pressure. Because tobacco-specific nitrosamines are present in some e-liquids, bystanders might be at increased risk of tumours in a worst-case scenario *(91)*. Another study concluded that the health of bystanders was unlikely to be at risk due to e-cigarette use *(92)*. Studies of bystander exposure to e-cigarettes and to tobacco cigarettes have shown that the health risk associated with second-hand e-cigarette aerosol was lower than that associated with second-hand smoke *(93,94)*. Other studies have shown that the concentration of nicotine in the air is much lower when e-cigarettes are used than with tobacco cigarettes *(95)*, although bystanders can take up nicotine from second-hand smoke *(96)*. Use of HTPs is considered to result in higher exposure of bystanders than use of e-cigarettes *(97)*. Whether exposure of bystanders to second-hand HTP or e-cigarette emissions could have adverse effects is largely unknown. One study suggested an association between second-hand exposure to e-cigarettes and reported asthma attacks in the past 12 months *(98)*. This indicates that some population groups, such as patients with airway disease and young children, are more vulnerable to adverse effects on exposure to second-hand emissions.

8.3 Methods for quantifying risk

Tobacco products differ not only in type but also in emissions and use, resulting in different health risks. Even products within a class, like ENDS and ENNDS, have different effects on health. Smokers of tobacco cigarettes who wish to switch to a potentially less harmful product require information on the relative risks of such products. A product that is potentially less harmful for a smoker is more harmful for a non-smoker. Quantitative hazard characterization, which includes a dose–or concentration–response relation, can be used to determine the potential health effects at population level when information is available on the number of users and their use pattern. Generalization of the health risk of a tobacco product is, however, not scientifically appropriate in view of the differences among products in a class and among users *(99)*. Risk assessment for ENDS and ENNDS should

therefore be conducted separately for groups of devices or even for individual devices and liquids. A wide range of e-cigarette use parameters must also be considered in estimating human exposure.

Quantification of the risks of chemical mixtures is inherently difficult, and the appearance of novel nicotine and tobacco products adds to the challenges of the wide variety of products, compositions and diversity of use. Differences among products make quantification of both exposure and hazard uncertain. To measure exposure, information is necessary on the topography of e-cigarette use, the emissions inhaled and, depending on the method used, particle size and particle size distribution, which determines deposition in the respiratory tract and therefore local exposure and effects *(100,101)*. Information on the chemical composition of the emissions is also necessary to identify the compounds to which users are exposed. The emissions from tobacco products contain many different compounds, which depend on the topography of e-cigarette use and device settings such as temperature and power *(62,102)*. The compounds in emissions must be characterized and quantified in order to assess the risk of these products *(9)*. Unfortunately, information on ingredients (contents) alone is insufficient, as they may degrade or burn during aerosolization or may originate from the device.

Information on hazard can be derived from toxicological studies of compounds, preferably administered by inhalation, the most relevant route of exposure for ENDS, ENNDS and tobacco products. Information on hazard is not available for all the compounds in each of these products. e-Liquids commonly contain flavours that have been tested for toxicity by oral administration for use in foods, and no information on toxicity resulting from inhalation of these compounds is available. Such information is necessary, as, in toxicity studies, some compounds, like diacetyl and cinnamaldehyde, can have local effects on the respiratory tract when inhaled *(103,104)*. Furthermore, users of ENDS, ENNDS and HTP products are exposed to mixtures of compounds that may or may not interact biologically.

The risk associated with mixtures can be quantified by combining data on the hazard of individual compounds with the quantities present in the emissions of products. Alternatively, the risks of ENDS, ENNDS or HTP could be quantified case by case in toxicity studies; however, studies in experimental animals may not provide meaningful results for assessing the risks that tobacco products pose to humans. In addition, exposure in experimental studies is generally for 6 h/day, 5 days/week, which is not comparable to use of ENDS, ENNDS or HTP, which result in irregular peak exposure for 7 days/week. The development and use of alternative models, such as cell models, are increasing rapidly, but this has not yet allowed hazard characterization of mixtures.

Some work has been conducted on the toxicological effects of mixtures *(105)*. In a project by the European Union *(106)*, EuroMix (https://www.euromix project.eu/), which ended in 2019, compounds were classified according to

their target organ and their mechanism of action. Compounds with similar and dissimilar modes of action were assessed in assays specific for a target organ to determine whether the effect of the mixture was different from those of the individual compounds. The project resulted in a toolbox for exposure scenarios and testing strategies outlined in a handbook of practical guidance. As in the EuroMix project, most studies of the toxicity of mixtures have addressed binary combinations; however, no reliable method is available even for these relatively simple mixtures to predict quantitatively the effects of any combination of the two compounds in the mixture without the input of at least some experimental data. It is difficult to predict whether the compounds in a mixture will interact, and this may be obscured by variations in the biological response. Binary mixtures often have an additive effect, such that the potency-adjusted doses of the individual compounds can be summed to predict their combined effect. Mathematical models are available to determine whether the toxicity of a mixture is due to interaction between the compounds. The two commonly used mathematical models used are the dose–concentration addition model and the independent action–response addition model *(107–109)*. The dose–concentration addition model is based on the assumption that all compounds have a similar mode of action but may have different potency to induce an effect. Once the potency of one compound is determined relative to that of another, the concentrations of both compounds can be expressed relative to that of one of the compounds as a reference. When the concentrations are summed, they can be used to determine the effect of the binary mixture on the dose–response curve of the reference compound *(110)*. In the concentration addition model, a similar mode of action is assumed, whereas the independent action model can be used to determine the effects of compounds that are due to different mechanisms or modes of action *(111)*. Mathematical models can be used to determine whether compounds interact, which is the case in synergism or antagonism. These models cannot be used to predict the effects of complex mixtures such as tobacco smoke.

Risk assessment of the complex emissions of tobacco products, ENDS and ENNDS is even more complicated and is similar to the assessment of other complex mixtures, such as petroleum-derived and cement-like products. Generally, the approach to assessing the risks of such products is to assess the toxicity of a representative sample of the mixture as a whole, primarily in experimental animals. A similar approach may be used to assess the hazard of ENDS and ENNDS, while differentiating classes of products. Although studies in experimental animals are ethically debatable, various (tobacco) products have been tested; however, translating the results into human effects and assessing different products within a class remains a challenge.

8.3.1 Threshold of toxicological concern

One approach to assessing exposure to complex mixtures is the threshold of toxicological concern (TTC) *(112)*. In this approach, originally developed for assessing carcinogenicity, the compounds of greatest toxicological concern in a mixture are identified from structure–activity relations and read-across. TTC values (in µg/person or µg/kg body weight per day) have been defined for three classes (Cramer classes I–III) according to structural elements, but only after oral exposure. Cramer class III indicates the highest carcinogenic risk and consequently the lowest TTC value *(113)*. The risk of a mixture is then assessed by comparing exposure to these compounds, either alone or summed, with the appropriate TTC value. This approach has been applied to complex mixtures such as botanical extracts *(114)*, flavour complexes *(115)* and inhaled toxicants *(116,117)*. This method does not indicate a risk to health but indicates that further testing is required if a compound exceeds the TTC threshold; otherwise, the probability of a health risk is low. This method might be used when no hazard data are available. As it is already known that tobacco products have adverse health effects, the TTC approach for risk assessment cannot be used to quantify health effects. For ENDS and ENNDS, however, it might be used to identify compounds that pose a health risk and to prioritize them for further testing.

8.3.2 Risk assessment based on individual compounds

Information on exposure to and the hazard of individual components could be used to assess the risk of a product as a whole. For cigarettes, compounds could be selected for their hazardous potential *(6,118,119)*. For ENDS, the number of compounds in emissions is limited, and they do not necessarily overlap with known tobacco toxicants. Compounds that are generated by thermal degradation, such as aldehydes, should also be considered for ENDS and ENNDS. This method has been applied to assess the toxicity of e-cigarettes for users and bystanders *(91)*. The data on hazards used in this approach are derived from studies for setting a safe level of exposure. In emissions from tobacco products, and in some cases also from ENDS and ENNDS, the concentrations are often above the safe level of exposure, so that the information can be used as an indicator of potential concern but not for quantifying risk. The effect seen in experimental animals may not directly reflect a similar effect at a similar exposure level in humans, as the exposure regime in experimental studies differs from human exposure patterns. Addition of the risks of individual compounds in order to estimate the risk of a complex mixture probably results in underestimates of health risks, as interactive effects among compounds in the mixture are ignored. Risk assessment based on individual compounds does not allow comparison of the risks of different (tobacco) products because of the design of many experimental studies. To compare the severity of effects, detailed information is necessary on the relations between exposure and health effects and how they can be extrapolated to effects in humans.

8.3.3 Relative risk approaches

Studies have also been conducted to estimate the carcinogenic potency of a tobacco product as a whole and relative to a (reference) tobacco cigarette *(3,24)*. In this approach, data from carcinogenicity studies in rodents are used to determine the carcinogenic potency of a compound, by using a modelled linear relation between exposure level and the number of tumours induced. For example, benchmark dose methods can be used to determine a lower confidence bound (usually 95%) of the effective dose that results in a tumour incidence of 10%. Quantitative data on carcinogenic potential can be used to calculate the relative carcinogenic potency of each compound according to technical guidance documents, such as that published by the Office of Environmental Health Hazard Assessment in California, USA *(120)*. The total relative carcinogenic potency of mixtures or aerosols can then be calculated by adding the values for individual compounds. In this approach, it is assumed that relative potency factors are equal over the entire dose range and the mechanisms are comparable. Although the mechanisms of action differ among carcinogens, the outcomes may give an indication of carcinogenic risk and allow comparison of carcinogenic risk among products. The validity of the assumptions is assessed during validation of the method.

This relative risk approach depends on the availability of data on both emissions and carcinogenicity. Data on the emissions of as many compounds as possible is required, as the inclusion of more compounds improves the calculation of relative risk. The methods used to analyse emissions should be similar for both products, and information on variations in the emissions must be available to determine the uncertainty in the relative risk. Information on carcinogenic potency should be derived from studies in rodents; alternatively, data from other sources can be used that are indicators of carcinogenic potency, if data on dose and response are available. This approach currently appears to be the best for quantifying the (relative) risk of products; however, for systematic application, more data should be available on emissions and on hazard level. A similar method might be applicable to other health effects, such as cardiovascular disease or chronic obstructive pulmonary disease.

8.3.4 Margin-of-exposure approach

The margin-of-exposure approach is based on the ratio of the exposure level and the dose at which no effects occur or the dose at which a predefined adverse effect occurs (e.g. a benchmark dose level). The larger the margin of exposure of a compound, the higher the risk may be. This approach has been applied to compounds in tobacco products *(121,122)* and can be used to prioritize compounds that should be reduced in tobacco smoke emissions and to assess individual compounds in the emissions of ENDS and ENNDS. A margin of exposure is calculated for each compound from data on inhaled emissions and information on hazard and depends on the quality of the data. The approach does

not result in a quantitative risk characterization. Its main goal is to determine whether a specific exposure is of concern. The magnitude of the margin of exposure is not a measure of risk.

8.3.5 Non-carcinogenic effects

Many methods address risk evaluation of carcinogenic effects, which are easier to model than non-carcinogenic effects, as the end-point (cancer) is easier to compare and the dose–response curves for carcinogens are comparable. Inherently, non-carcinogenic effects are diverse. Local effects should be differentiated from systemic effects; different compounds have effects on different organs and, even if compounds have an effect on the same organ, their mechanism and result may be different. Quantification of non-carcinogenic effects might have to be conducted at the level of the mechanism of action *(106)*; however, this approach requires dose–response data on the mechanism of action of compounds, which is limited. Non-cancer risk indices have, however, been generated for the cardiovascular and respiratory effects of cigarette smoke *(4)*.

Alternatively, toxicological assays of emissions may be used to characterize the risk of a product. As mentioned above, bioassays in experimental animals may not be preferable, and the results of cellular assays are difficult to translate into effects in humans. In addition, not only should the effects (read-out parameters) be extrapolated to human effects, but the exposure should resemble human exposure. This includes smoking topography and, in the case of a lung model, deposition in the airways. This field is evolving, but in vitro assays for characterizing non-carcinogenic effects of ENDS, ENNDS and HTPs remain in the future.

8.3.6 Evaluation frameworks

Assessment of the health effects of ENDS and ENNDS could be based on an appropriate evaluation framework. In this approach, expert judgement is used to score aspects of a product in order to identify the most important risks of, for example, drugs *(123)*. The Netherlands National Institute for Public Health and the Environment has developed an evaluation framework for tobacco products that summarizes all the factors that may influence the attractiveness, addictiveness and toxicity of a product and can be used to identify knowledge gaps or prioritize research on a specific product *(124)*. These models allow evaluation of a product even when limited data are available. Evaluation improves with increasing knowledge about a product, but this approach is limited to qualitative results based on expert judgement.

The methods described above can be used to compare the hazards of different products. Table 8.1 summarizes the methods, their data requirements and their application. The feasibility of applying the methods is determined by the

information available and not by the product itself. The information necessary for full risk characterization is currently not available. In some methods, a weight-of-evidence approach can be used for data of different quality. Many methods for risk quantification also require data on emissions, an indicator of human exposure. Tobacco smoke and emissions from ENDS and ENNDS are dynamic. Emissions cool as they pass from a heating element to the exit of the device, resulting in condensation of volatile compounds and agglomeration of particles. In addition, the inhaled air, which includes the emission, is humidified in the upper airways. These processes occur simultaneously and determine local deposition in the airways, which can result in high doses at specific locations in the airways, which could have site-specific adverse effects. Modelling of airway deposition of tobacco smoke and ENDS or ENNDS emissions is under way *(100,125)*. The outcome of a qualitative risk assessment depends on the quality of dosimetry, which is limited.

Table 8.2 summarizes the limitations and advantages of the methods described in this paper. It should be noted that all the methods are intended for assessment of risk to users. Similar methods could be used to assess the risk of bystanders, provided that information is available on their exposure.

Table 8.1. Summary of methods for quantitative risk assessment of ENDS and ENNDS according to individual compounds or their mixture (1), the data required (2 and 3) and their application (4–7)

Method	1. Individual compounds or mixture?	2. Dependent on emission characterization?	3. Dependent on available hazard data?	4. Allows quantification of risk of single compounds?	5. Allows quantification of risk of the product as a whole?	6. Allows quantification of risk of the product as a whole for vulnerable groups?	7. Data required for a modified product
Threshold of toxicological concern	Individual	Yes	No	No, allows identification of potential hazardous compounds	No	No	Emission data
Risk assessment based on individual compounds	Individual	Yes	Yes	Yes	Yes, but only if data for all compounds are available	Yes, but only if data for all compounds and specific hazard data on vulnerable groups are available	Emission data
Relative risk approaches	Mixture	Yes	Yes	Yes	Yes, but only if data for all compounds are available	Yes, but only if data for all compounds and specific hazard data on vulnerable groups are available	Emission data

Method	1. Individual compounds or mixture?	2. Dependent on emission characterization?	3. Dependent on available hazard data?	4. Allows quantification of risk of single compounds?	5. Allows quantification of risk of the product as a whole?	6. Allows quantification of risk of the product as a whole for vulnerable groups?	7. Data required for a modified product
Margin-of-exposure approach	Individual	Yes	Yes	No	No	No	Emission data
Bioassays for non-carcinogenic effects	Mixture	No	No	No	Yes	Yes, but only if specific data on hazards for vulnerable groups are available	Toxicity bioassays
Evaluation frameworks	Mixture	No	Yes	No	No, only non-quantitative risk	No, only non-quantitative risk if data are available on vulnerable groups	Re-evaluation of e.g. emission data

Column 1: Applicability of the output of the method to individual compounds or to the emission as a mixture
Column 2: Requirement for quantitative data on (ideally) all compounds in the emission
Column 3: Requirement for data on dose–response related hazard
Column 4: Applicability of the method to quantify the risk of exposure to one of the compounds in the emission
Column 5: Applicability of the method to quantify the risk of exposure to the product
Column 6: Applicability of the method to quantify the risk of exposure to the product pf vulnerable groups, such as infants
Column 7: Data required to quantify the risk of a slightly changed product, such as a new flavour in an e-liquid or technical adaptation of the device

Table 8.2. Limitations and advantages of each method for quantifying the health risk of ENDS and ENNDS

Method	Main limitations	Main advantages	Potential application for ENDS, ENNDS and HTPs
Threshold of toxicological concern	Cannot assess risk of complete product No quantification of risk	Information on possible risk from exposure	Prioritization of compounds for further testing
Risk assessment of individual compounds	Cannot assess risk of complete product	Identification of compounds with highest health risk	Health risk assessment based on available data
Relative risk approaches	Currently only for carcinogens	Allows comparison of risks between products	Health risk assessment based on available data and allows comparison of products
Margin-of-exposure approach	Cannot assess risk of complete product	Information on exposure in relation to health concern	Prioritization of compounds for further testing
Bioassays for non-carcinogenic effects	Extensive testing required and extrapolation of exposure and results to humans	Does not require data on emissions or hazard	Health risk assessment based on available bioassays
Evaluation frameworks	Most subjective method	Requires limited data; more data will improve outcomes	Non-quantitative health risk assessment, can be used for setting priorities

8.4 Heated tobacco products

Methods used to assess the risks of ENDS and ENNDS can in principle be applied to HTPs. HTPs currently vary less than the e-systems, and some reliable, independent data are available on the composition of the aerosol *(9)*. Industry data must be verified independently before it can be used for risk assessment. Previous investigations addressed the toxicants that typically occur in cigarette smoke, and further independent research is required for a comprehensive analysis of emissions and health risks. The methods used to analyse cigarette smoke and standardization of inhalation topography must still be adapted to obtain user-representative measurements. Further, some toxicants might not be relevant in cigarette smoke but could occur preferentially in the aerosol of HTPs. This question has been addressed with untargeted screening methods *(126–128)*, which have also been used by industry scientists *(129)*. Some components of concern, including glycidol (classified in 2A by a working group at the International Agency for Research on Cancer) and furfuryl alcohol (classified in 2B) have been identified in HTP aerosol, and data for specified HTPs would allow risk modelling and comparative or quantitative assessment. Stephens *(24)* modelled the carcinogenic potency of aerosols from cigarettes, ENDS and an HTP device, and comparative modelling approaches have since been refined *(3)* to determine the relative cancer potency of individual compounds and product emissions, with confidence intervals. The ratio or change in cumulative exposure can then be calculated with a probabilistic approach for two products. For HTPs, the change in cumulative exposure to selected compounds was 10–25 times lower than from smoking cigarettes. With relevant information on human dose responses, the change in cumulative exposure can be translated into an associated health impact for each device. This approach was initially used for eight carcinogens that occur in the aerosol of HTP and in cigarette smoke but should be extended to compounds that are found at higher levels in HTP aerosols than in cigarette smoke.

These calculations illustrate the differences in the composition of HTP aerosol and that of tobacco smoke, which may affect the health risks. As HTPs continue to evolve, standards of performance and upper limits for key toxicants should be considered the most useful, feasible options for regulation. The methods for quantitative risk assessment of ENDS and ENNDS described above are based on data on emissions and hazards and can therefore be applied to HTPs as well, if the data are available.

8.5 Implications for regulation

Current methods for quantifying the health risk of ENDS, ENNDS and tobacco products are not yet adequate for use in regulation. Some approaches can be used, however, to obtain an indication of the absolute health risk of a

product. These methods are based on the risk associated with specific or unique compounds in emissions, which depends on the availability of data. Compounds in emissions should be identified and quantified, ideally in user-representative settings. In addition, (human) toxicological data on these compounds is required to quantify health risk; however, data are lacking for both these parameters. The risk assessment approaches described in this paper could be considered for use in regulation; however, currently, because of lack of data, this stage has not been reached, as the model is only as good as the quality of the data.

Quantified health risks could be used in models for estimating health risks at a population level. Although this has not yet been done, the feasibility of modelling population health effects has been explored *(130)*. The health impact of ENDS, ENNDS or HTPs in smokers, non-smokers and former smokers can be estimated when monitoring their popularity and use and used as a reason for legislative measures to limit use of the product or as a basis for public education. The outcomes depend strongly on the input data, which, in this case, will also include epidemiological data. The observation that epidemiological data on product use and switching between products is inconsistent should be considered when applying population modelling.

Modelling has indicated that switching from cigarettes to HTPs can affect human health; however, the effect depends on the compliance of devices with substantially lower levels of previously documented toxicants in the emissions. Regulators should consider setting mandatory upper limits for carbonyls, carbon monoxide and other key toxicants to ensure that devices meet technical and performance standards.

Effective regulation of ENDS and ENNDS and their characteristics could also contribute to limiting their health risks. Priority should be given to closed systems, like pods or sealed cartridges that cannot be easily manipulated by consumers. Problematic ingredients and constituents (diacetyl, sucralose, essential oils and all carcinogenic, mutagenic and teratogenic compounds) should be prohibited, and upper limits for nicotine in the emissions of closed-system ENDS might also be considered. Although prohibitions of hazardous compounds should apply to liquids in general, the emissions of flexible, usually high-powered open systems are difficult to regulate. The focus might therefore be shifted to technical features, such as overheating controls, maximum wattage or temperature. Further regulation would require detailed assessment of ENDS and ENNDS subcategories, especially of high-powered products, including aerosol chemistry, toxicology and the design and performance of devices.

The ambiguous terminology and definition of ENNDS are also matters of concern. For example, nicotine-free devices can be used to inhale compounds such as cannabidiol, for which some health benefits have been claimed. The impression that certain ENNDS might be beneficial for health, however, might distract from and confuse current assessments and should be avoided. Use of

ENDS to combine nicotine with other pharmacologically or physiologically active compounds should be prohibited, as this could increase the attractiveness of nicotine consumption. The terminology and definition of ENNDS should be specified, to identify them as products that are the same as ENDS products but without nicotine. This should be applied to both devices and consumables. The term "ENNDS" would still cover conventional e-liquids offered as nicotine-free versions. The regulatory framework for ENDS and ENNDS might still include other electronic inhalation systems as related products, thus defining all devices equally. A clear separation of nicotine and tobacco substitutes from other electronic inhalation products would, however, be beneficial, for several reasons. First, specific rules could be adopted for ENDS, ENNDS and other electronic inhalation systems used to inhale other substances or materials. Second, the clarification would require specific risk communication, thus preventing a misleading generalization, as observed early in the EVALI episode. Third, regulators might gain more flexibility for dealing with any novel inhalation systems developed in the future.

It should be noted that quantification of health risks is not a static outcome but remains an estimation based on the available knowledge. Information on ENDS and ENNDS is increasing, as is, probably even more important for ENDS and ENNDS, the wide variety of devices, user settings and e-liquids, which will influence health risks. Providing public information on the health effects of ENDS and ENNDS is a challenge. It is difficult to convey to the general public the changing (relative) risks over time due to differences in devices or information. Furthermore, information on health risks could be used by the industry to promote alternative products inappropriately.

Several of the methods described in this paper are promising for assessing the risks of ENDS, ENNDS and HTPs, although probably more than one model will be required for a full assessment. At this time, not enough scientific data are available to make definitive assessments. As many of the methods require a substantial amount of data on hazards and exposure, we could prepare for the future by collecting those data and conducting standardized assays so that the results are suitable for feeding into a database for future use. Non-targeted screening can be used to identify product-specific compounds, and their hazard could be derived from the database. Information on the relation between actual human exposure and the occurrence of adverse effects is necessary for risk characterization. Development of risk assessment models should continue, and, at some point, they should be validated with human data. Models of airway deposition should also be developed for application in risk assessment, as this is a crucial step between emission quantification and hazard characterization. Ultimately, this would require only chemical analysis of a novel product, which, combined with models of deposition and risk assessment, would allow determination of the health effects.

8.6 Discussion

A causal relation between ENDS or ENNDS use and acute effects (short-term health risk) is generally easier to identify, as the time between exposure and effect is short. In many cases, when users stop using the product the adverse effects are reversed. Assessment of the health risk of ENDS and ENNDS would benefit from data on health effects in long-time e-cigarette users; unfortunately, such data are not yet available, as e-cigarettes have not been available for the time necessary to develop chronic health effects such as cancer. In addition, current ENDS and ENNDS users are often former smokers. Thus, if an ENDS or ENNDS user develops disease, it may be a delayed effect of smoking and not necessarily related to ENDS and ENNDS use. The most robust data for assessing health risk would be for ENDS or ENNDS users who are not former smokers. The wide variety of devices and e-liquids, which continue to evolve rapidly, and the lack of information on the products in current use obviate conclusions on the risk posed by the group of ENDS and ENNDS as a whole. The lack of long-term data and of information on non-smokers may change over time as the products remain on the market for longer and if more non-smokers start using ENDS and ENNDS. The variation in products is not expected to stop; on the contrary, more and more products are entering the market. On the Dutch market, as in other countries, more than 20 000 different e-liquids are already available. A pragmatic approach would be to identify compounds in e-liquids or device settings that adversely affect health, as mentioned previously. The health risks of individual compounds could indicate the health risk of the product as a whole, and such information could inform policy on permissible constituents, device design features and the levels of certain constituents.

Risk modelling, epidemiological studies and assessments of individual compounds have resulted in consensus among some experts that unadulterated ENDS are less harmful than conventional cigarettes *(131)*. Nevertheless, a number of health risks remain, as acknowledged and summarized by WHO *(10)*. Although quantitative assessments remain difficult *(70)*, ENDS use results in a substantial decrease in carcinogenic risk, as confirmed by modelling *(24)*. ENDS are, however, associated with a high risk of nicotine addiction and increased risks for respiratory diseases and other adverse health effects that are especially relevant for children, adolescents and people who have never smoked. The rapid increase in use of pod systems in the USA is a concern *(16)*; however, the potential benefits for established smokers who use ENDS as a substitute for cigarettes should also be considered. For example, patients with chronic obstructive pulmonary disease who switched to ENDS showed improvement *(80)*. There is some evidence that ENDS are useful for smoking cessation *(132)*; however, a general conclusion is not scientifically justified, as ENDS and ENNDS are a heterogeneous, changing group of products *(99)*. Communication of health risks should avoid imprecise generalizations, especially because of the diversity of the products and their possible effects.

ENDS and ENNDS are often still considered as a single group of products in terms of risk assessment and legislation. Regulators and ENDS users should, however, be aware of the highly variable risks, which might range from very low to levels comparable to those for HTPs with devices that reach ≥ 250 °C. The health risks even of individual compounds are highly variable, depending on the device and performance settings. Major subgroups of ENDS (i.e. pod, sub-ohm) should therefore be categorized separately to ensure more specific terms of reference for both risk assessment and regulation.

Hazardous ingredients or device settings that lead to formation of (more) hazardous compounds could also be regulated. Although this would be beneficial from a health perspective, toxicological information on exposure to e-liquid ingredients by inhalation is very limited. Regulation or prohibition of specific ingredients on the basis of toxicological information might be a useful option. As noted above, flexible strategies will be required to cover different product groups and open and closed systems. Importantly, restrictions only on liquids should not imply that other ingredients are safe, as their risks especially in the context of inhalation are not yet known.

Furthermore, ENDS and ENNDS should be distinguished from inhalation devices used to deliver cannabidiol and other substances for their pharmacological or physiological effects and responses. Health risks and injuries caused, for example, by unconventional liquid constituents and modified devices that can aerosolize oils and waxes or are used to inhale illicit drugs must not be considered to be adverse outcomes related to vaping or e-cigarette use. Combination of nicotine with other physiologically or pharmacologically active compounds in ENDS should be prohibited, as this could increase the attractiveness of nicotine consumption. Tobacco control should include definition and specification of the framework for assessing ENDS and ENNDS according to these new challenges.

8.7 Recommendations

Risk assessment of mixtures is of great interest, not only for ENDS and ENNDS but also for tobacco products. Several models are available that can be used to assess the risk of mixtures, although most address carcinogenic effects. Implementation is limited by lack of data, which also implies that the models cannot yet be validated with data on human use. A few recommendations based on the findings of this review are listed below.

- Data should be collected on the emissions, toxicity, use and effects of ENDS, ENNDS and HTPs on exposed populations for application of quantitative methods of risk assessment.
- Characterization of toxicants should include non-targeted screening approaches to identify product-specific compounds that are not usually measured in tobacco smoke.

- Appropriate studies in experimental animals and epidemiological studies should be conducted on long-term adverse effects and of product switching.
- The models used to justify any claim of a positive health impact of HTPs and in their marketing should be verified.

Each product and change in product may result in a change in risk. In addition, users can flexibly adapt the systems to their requirements, which may alter their exposure from that used in risk assessments and change their health risk. Other recommendations for consideration by regulators are listed below.

- Limit product variations.
- Regulators should define subcategories or classes and terminology for ENDS and ENNDS as a basis for differentiated risk assessments. Different product groups, such as "single-use" products, open, refillable and highly powered systems, might warrant specified technical standards or regulatory approaches to minimize health risks and addictiveness.
- Neither ENDS nor ENNDS should contain any compound that might mediate drug-related effects or potentially lead to health effects, except for nicotine in ENDS.
- The term "ENNDS" should not be applied to electronic "vaping" products that contain pharmacologically active ingredients such as cannabidiol or hemp oils.

8.8 Conclusions

ENDS and ENNDS are highly variable categories of products, although they share many features. The variation in e-liquids and devices makes it impossible to assess the health risks of this group of products. Risks should therefore be assessed for each individual device, liquid and use. Alternatively, indicators of risk could be highlighted, such as specific ingredients or specific settings of a device, that could be applied to many products.

Several approaches have been used to quantify the health risk of tobacco products, either the absolute risk or that relative to a tobacco cigarette. Currently, the most promising approaches are those based on the relative potency of compounds in the emissions. Their applicability depends, however, on the availability of data, which are often limited. None of the methods is ready to be used in regulation, although this may be possible in due time, and care should be used in communicating health risks to the general public to ensure that the message is clear.

8.9 References

1. Tobacco. Geneva: World Health Organization; 2019 (https://www.who.int/news-room/fact-sheets/detail/tobacco, accessed 10 January 2021).
2. Sinha DN, Palipudi KM, Gupta PC, Singhal S, Ramasundarahettige C, Jha P et al. Smokeless tobacco use: a meta-analysis of risk and attributable mortality estimates for India. Indian J Cancer. 2014;51(Suppl 1):S73–7.
3. Slob W, Soeteman-Hernández LG, Bil W, Staal YCM, Stephens WE, Talhout R. A method for comparing the impact on carcinogenicity of tobacco products: a case study on heated tobacco versus cigarettes. Risk Anal. 2020;40(7):1355–66.
4. Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tob Control. 2003;12(4):424–30.
5. The scientific basis of tobacco product regulation. Second report of a WHO study group (WHO Technical Report Series, No. 951). Geneva: World Health Organization; 2008:277 (https://www.who.int/tobacco/global_interaction/tobreg/publications/9789241209519.pdf?ua=1, accessed 10 January 2021).
6. Burns DM, Dybing E, Gray N, Hecht S, Anderson C, Sanner T et al. Mandated lowering of toxicants in cigarette smoke: a description of the World Health Organization TobReg proposal. Tob Control. 2008;17(2):132–41.
7. Work in progress in relation to Articles 9 and 10 of the WHO FCTC. Geneva: World Health Organization; 2014:21 (https://apps.who.int/gb/fctc/PDF/cop4/FCTC_COP4_ID2-en.pdf, accessed 10 January 2021).
8. Hoffmann D, Hoffmann I, El-Bayoumy K. The less harmful cigarette: a controversial issue. a tribute to Ernst L. Wynder. Chem Res Toxicol. 2001;14(7):767–90.
9. Mallock N, Pieper E, Hutzler C, Henkler-Stephani F, Luch A. Heated tobacco products: A review of current knowledge and initial assessments. Front Public Health. 2019;7:287.
10. Electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS and ENNDS). Geneva: World Health Organization; 2016.
11. Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P, Stewart JH et al. Flavoring chemicals in e-cigarettes: Diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. Environ Health Perspect. 2016;124(6):733–9.
12. Hutzler C, Paschke M, Kruschinski S, Henkler F, Hahn J, Luch A. Chemical hazards present in liquids and vapors of electronic cigarettes. Arch Toxicol. 2014;88(7):1295–308.
13. Noel JC, Rainer D, Gstir R, Rainer M, Bonn G. Quantification of selected aroma compounds in e-cigarette products and toxicity evaluation in HUVEC/Tert2 cells. Biomed Chromatogr. 2020;34(3):e4761.
14. Williams M, Talbot P. Design features in multiple generations of electronic cigarette atomizers. Int J Environ Res Public Health. 2019;16(16):e2904.
15. Yingst J, Foulds J, Zurlo J, Steinberg MB, Eissenberg T, Du P. Acceptability of electronic nicotine delivery systems (ENDS) among HIV positive smokers. AIDS Care. 2020;32(10):1224–8.
16. Fadus MC, Smith TT, Squeglia LM. The rise of e-cigarettes, pod mod devices, and JUUL among youth: Factors influencing use, health implications, and downstream effects. Drug Alcohol Depend. 2019;201:85–93.
17. Walley SC, Wilson KM, Winickoff JP, Groner J. A public health crisis: Electronic cigarettes, vape, and JUUL. Pediatrics. 2019;143(6):e20182741.
18. Goniewicz ML, Boykan R, Messina CR, Eliscu A, Tolentino J. High exposure to nicotine among adolescents who use Juul and other vape pod systems ("pods"). Tob Control. 2019;28(6):676–7.
19. Giroud C, de Cesare M, Berthet A, Varlet V, Concha-Lozano N, Favrat B. e-Cigarettes: A review of new trends in cannabis use. Int J Environ Res Public Health. 2015;12(8):9988–10008.

20. Pisanti S, Malfitano AM, Ciaglia E, Lamberti A, Ranieri R, Cuomo G et al. Cannabidiol: State of the art and new challenges for therapeutic applications. Pharmacol Ther. 2017;175:133–50.
21. Poklis JL, Mulder HA, Peace MR. The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids. Forensic Sci Int. 2019;294:e25–7.
22. Owusu D, Huang J, Weaver SR, Pasch KE, Perry CL. Patterns and trends of dual use of e-cigarettes and cigarettes among US adults, 2015–2018. Prev Med Rep. 2019;16:101009.
23. Godtfredsen NS, Prescott E, Osler M. Effect of smoking reduction on lung cancer risk. JAMA. 2005;294(12):1505–10.
24. Stephens WE. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tob Control. 2018;27(1):10–7.
25. Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol. 2014;88(1):5–7.
26. Seo AD, Kim DC, Yu HJ, Paulus MC, van Heel DAM, Bomers BHA et al. Accidental ingestion of e-cigarette liquid nicotine in a 15-month-old child: an infant mortality case of nicotine intoxication. Korean J Pediatr. 2016;59(12):490–3.
27. Wang B, Liu S, Persoskie A. Poisoning exposure cases involving e-cigarettes and e-liquid in the United States, 2010–2018. Clin Toxicol. 2020;58(6):488–94.
28. Morley S, Slaughter J, Smith PR. Death from ingestion of e-liquid. J Emerg Med. 2017;53(6):862–4.
29. Viswam D, Trotter S, Burge PS, Walters GI. Respiratory failure caused by lipoid pneumonia from vaping e-cigarettes. BMJ Case Rep. 2018;2018:bcr2018224350.
30. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends Cardiovasc Med. 2016;26(6):515–23.
31. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol. 2014;34(3):509–15.
32. Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L et al. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. Eur J Epidemiol. 2012;27(10):771–9.
33. MacDonald A, Middlekauff HR. Electronic cigarettes and cardiovascular health: What do we know so far? Vasc Health Risk Manag. 2019;15:159–74.
34. Boffetta P, Straif K. Use of smokeless tobacco and risk of myocardial infarction and stroke: Systematic review with meta-analysis. BMJ. 2009;339:b3060.
35. Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case–control study. Lancet. 2006;368:647–58.
36. Babic M, Schuchardt M, Tölle M, van der Giet M. In times of tobacco-free nicotine consumption: The influence of nicotine on vascular calcification. Eur J Clin Invest. 2019;49(4):e13077.
37. The 2004 United States Surgeon General's report: The health consequences of smoking. New S Wales Public Health Bull. 2004;15(5–6):107.
38. Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. Pharmacol Ther. 2009;122(2):125–39.
39. Joschko MA, Dreosti IE, Tulsi RS. The teratogenic effects of nicotine in vitro in rats: A light and electron microscope study. Neurotoxicol Teratol. 1991;13(3):307–16.
40. Bruin JE, Gerstein HC, Holloway AC. Long-term consequences of fetal and neonatal nicotine exposure: a critical review. Toxicol Sci. 2010;116(2):364–74.
41. Bergman BC, Perreault L, Hunerdosse D, Kerege A, Playdon M, Samek AM et al. Novel and reversible mechanisms of smoking-induced insulin resistance in humans. Diabetes. 2012;61(12):3156–66.
42. Hess R, Bartels MJ, Pottenger LH. Ethylene glycol: an estimate of tolerable levels of exposure

based on a review of animal and human data. Arch Toxicol. 2004;78(12):671–80.
43. Chung S, Baumlin N, Dennis JS, Moore R, Salathe SF, Whitney PL et al. Electronic cigarette vapor with nicotine causes airway mucociliary dysfunction preferentially via TRPA1 receptors. Am J Respir Crit Care Med. 2019;200(9):1134–45.
44. Pisinger C, Døssing M. A systematic review of health effects of electronic cigarettes. Prev Med. 2014;69:248–60.
45. Wieslander G, Norbäck D, Lindgren T. Experimental exposure to propylene glycol mist in aviation emergency training: Acute ocular and respiratory effects. Occup Environ Med. 2001;58(10):649–55.
46. Talih S, Salman R, Karaoghlanian N, El-Hellani A, Saliba N, Eissenberg T et al. "Juice monsters": sub-ohm vaping and toxic volatile aldehyde emissions. Chem Res Toxicol. 2017;30(10):1791–3.
47. Duell AK, McWhirter KJ, Korzun T, Strongin RM, Peyton DH. Sucralose-enhanced degradation of electronic cigarette liquids during vaping. Chem Res Toxicol. 2019;32(6):1241–9.
48. Matura M, Goossens A, Bordalo O, Garcia-Bravo B, Magnusson K, Wrangsjö A et al. Oxidized citrus oil (R-limonene): a frequent skin sensitizer in Europe. J Am Acad Dermatol. 2002;47(5):709–14.
49. Sommerfeld CG, Weiner DJ, Nowalk A, Larkin A. Hypersensitivity pneumonitis and acute respiratory distress syndrome from e-cigarette use. Pediatrics. 2018;141(6):e20163927.
50. Gallagher J. Vaping nearly killed me, says British teenager. BBC News, 12 November 2019 (https://www.bbc.com/news/health-50377256).
51. Chen W, Wang P, Ito K, Fowles J, Shusterman D, Jaques PA et al. Measurement of heating coil temperature for e-cigarettes with a "top-coil" clearomizer. PLoS One. 2018;13(4):e0195925.
52. Farsalinos KE, Voudris V, Spyrou A, Poulas K. e-Cigarettes emit very high formaldehyde levels only in conditions that are aversive to users: A replication study under verified realistic use conditions. Food Chem Toxicol. 2017;109(1):90–4.
53. Gillman IG, Pennington ASC, Humphries KE, Oldham MJ. Determining the impact of flavored e-liquids on aldehyde production during vaping. Regul Toxicol Pharmacol. 2020;112:104588.
54. Talhout R, Opperhuizen A, van Amsterdam JG. Role of acetaldehyde in tobacco smoke addiction. Eur Neuropsychopharmacol. 2007;17(10):627–36.
55. Patel M, Cuccia A, Willett J, Zhou Y, Kierstead EC, Czaplicki L et al. JUUL use and reasons for initiation among adult tobacco users. Tob Control. 2019;28(6):681–4.
56. Chaumont M, van de Borne P, Bernard A, Van Muylem A, Deprez G, Ullmo J et al. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: results from two randomized clinical trials. Am J Physiol Lung Cell Mol Physiol. 2019;316(5):L705–19.
57. Gotts JE. High-power vaping injures the human lung. Am J Physiol Lung Cell Mol Physiol. 2019;316(5):L703–4.
58. Gray N, Halstead M, Gonzalez-Jimenez N, Valentin-Blasisni L, Watson C, Pappas RS. Analysis of toxic metals in liquid from electronic cigarettes. Int J Environ Res Public Health. 2019;16(22):4450.
59. Farsalinos KE, Rodu B. Metal emissions from e-cigarettes: A risk assessment analysis of a recently-published study. Inhal Toxicol. 2018;30(7–8):321–6.
60. Olmedo P, Goessler W, Tanda S, Grau-Perez M, Jarmul S, Aherrera A et al. Metal concentrations in e-cigarette liquid and aerosol samples: The contribution of metallic coils. Environ Health Perspect. 2018;126(2):027010.
61. Zhao D, Navas-Acien A, Ilievski V, Slavkovich V, Olmedo P, Adria-Mora B et al. Metal concentrations in electronic cigarette aerosol: Effect of open-system and closed-system devices and power settings. Environ Res. 2019;174:125–34.
62. Haddad C, Salman R, El-Hellani A, Talih S, Shihadeh A, Saliba NA. Reactive oxygen species emissions from supra- and sub-ohm electronic cigarettes. J Anal Toxicol. 2019;43(1):45–50.

63. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 2014;23(2):133–9.
64. Goniewicz ML, Smith DM, Edwards KC, Blount BC, Caldwell KL, Feng J et al. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. JAMA Netw Open. 2018;1(8):e185937.
65. Belushkin M, Tafin Djoko D, Esposito M, Korneliou A, Jeannet C, Lazzerini M et al. Selected harmful and potentially harmful constituents levels in commercial e-cigarettes. Chem Res Toxicol. 2020: doi:10.1021/acs.chemrestox.9b00470.
66. Kennedy CD, van Schalkwyk MCI, McKee M, Pisinger C. The cardiovascular effects of electronic cigarettes: A systematic review of experimental studies. Prev Med. 2019;127:105770.
67. Kuntic M, Oelze M, Steven S, Kröller-Schön S, Stamm P, Kalinovic S et al. 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). Eur Heart J. 2019;41(26):2472–83.
68. Caporale A, Langham MC, Guo W, Johncola A, Chatterjee S, Wehrli SW. Acute effects of electronic cigarette aerosol inhalation on vascular function detected at quantitative MRI. Radiology. 2019;293(1):97–106.
69. Skotsimara G, Antonopoulos AS, Oikonomou E, Siasos G, Ioakeimidis N, Tsalamandris S et al. Cardiovascular effects of electronic cigarettes: A systematic review and meta-analysis. Eur J Prev Cardiol. 2019;26(11):1219–28.
70. D'Amario D, Migliaro S, Borovac JA, Vergallo R, Galli M, Restivo A et al. Electronic cigarettes and cardiovascular risk: Caution waiting for evidence. Eur Cardiol. 2019;14(3):151–8.
71. Ndunda PM, Muutu TM. Electronic cigarette use is associated with a higher risk of stroke. Stroke. 2019;50(Suppl 1):A9.
72. Alzahrani T, Pena I, Temesgen N, Glantz SA. Association between electronic cigarette use and myocardial infarction. Am J Prev Med. 2018;55(4):455–61.
73. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Iftekhar Uddin SM, Dardari ZA et al. The association between e-cigarette use and asthma among never combustible cigarette smokers: Behavioral risk factor surveillance system (BRFSS) 2016 & 2017. BMC Pulmon Med. 2019;19(1):180.
74. George J, Hussain M, Vadiveloo T, Ireland S, Hopkinson P, Struthers AD et al. Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. J Am Coll Cardiol. 2019;74(25):3112–20.
75. Jordt SE, Jabba S, Ghoreshi K, Smith GJ, Morris JB. Propylene glycol and glycerin in e-cigarettes elicit respiratory irritation responses and modulate human sensory irritant receptor function. Am J Respir Crit Care Med. 2019;201:A4169.
76. Meo SA, Ansary MA, Barayan FR, Almusallam AS, Almehaid AM, Alarifi NS et al. Electronic cigarettes: Impact on lung function and fractional exhaled nitric oxide among healthy adults. Am J Mens Health. 2019;13(1):1557988318806073.
77. Stockley J, Sapey E, Gompertz S, Edgar R, Cooper B. Pilot data of the short-term effects of e-cigarette vaping on lung function. Eur Respir J. 2018;52(Suppl 62):PA2420.
78. Rebuli ME, Glista-Baker E, Speen AM, Hoffmann JR, Duffney PF, Pawlak E et al. Nasal mucosal immune response to infection with live-attenuated influenza virus (LAIV) is altered with exposure to e-cigarettes and cigarettes. Am J Respir Crit Care Med. 2019;199(9):A4170.
79. Wills TA, Pagano I, Williams RJ, Tam EK. e-Cigarette use and respiratory disorder in an adult sample. Drug Alcohol Depend. 2019;194:363–70.
80. Polosa R, Morjaria JB, Prosperini U, Russo C, Pennisi A, Puleo R et al. Health effects in COPD smokers who switch to electronic cigarettes: A retrospective-prospective 3-year follow-up. Int J Chron Obstruct Pulmon Dis. 2018;13:2533–42.
81. Layden JE, Ghinai I, Pray I, Kimball A, Layer M, Tenforde MW et al. Pulmonary illness related to

e-cigarette use in Illinois and Wisconsin – Preliminary report. N Engl J Med. 2020;382(10):903–16.
82. Moritz ED, Zapata LB, Lekiachvili A, Glidden E, Annor FB, Werner AK et al. Update: Characteristics of patients in a national outbreak of e-cigarette, or vaping, product use-associated lung injuries – United States, October 2019. Morb Mortal Wkly Rep. 2019;68(43):985–9.
83. Outbreak of lung injury associated with e-cigarette use, or vaping. Atlanta (GA): Centers for Disease Control and Prevention; 2020 (https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html).
84. Kalininskiy A, Bach CT, Nacca NE, Ginsberg G, Marraffa J, Navarette KA et al. e-Cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. Lancet Respir Med. 2019;7(12):1017–26.
85. Blagev DP, Harris D, Dunn AC, Guidry DW, Grissom CK, Lanspa MJ. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: A prospective observational cohort study. Lancet. 2019;394(10214):2073–83.
86. Blount BC, Karwowski MP, Morel-Espinosa M, Rees J, Sosnoff C, Cowan E et al. Evaluation of bronchoalveolar lavage fluid from patients in an outbreak of e-cigarette, or vaping, product use-associated lung injury – 10 states, August–October 2019. Morb Mortal Wkly Rep. 2019;68(45):1040–1.
87. Boudi FB, Patel S, Boudi A, Chan C. Vitamin E acetate as a plausible cause of acute vaping-related illness. Cureus. 2019;11(12):e6350.
88. Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. N Engl J Med. 2020;382(8):697–705.
89. Navon L, Jones CM, Ghinai I, King BA, Briss PA, Hacker KA et al. Risk factors for e-cigarette, or vaping, product use-associated lung injury (EVALI) among adults who use e-cigarette, or vaping, products – Illinois, July–October 2019. Morb Mortal Wkly Rep. 2019;68(45):1034–9.
90. Lewis N, McCaffrey K, Sage K, Cheng CJ, Green J, Goldstein L et al. e-Cigarette use, or vaping, practices and characteristics among persons with associated lung injury – Utah, April–October 2019. Morb Mortal Wkly Rep. 2019;68(42):953–6.
91. Visser WF, Klerx WN, Cremers HWJM, Ramlal R, Schwillens PL, Talhout R. The health risks of electronic cigarette use to bystanders. Int J Environ Res Public Health. 2019;16(9):1525.
92. McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. Inhal Toxicol. 2012;24(12):850–7.
93. Avino P, Scungio M, Stabile L, Cortelessa G, Buonnano G, Manigrasso M. Second-hand aerosol from tobacco and electronic cigarettes: Evaluation of the smoker emission rates and doses and lung cancer risk of passive smokers and vapers. Sci Total Environ. 2018;642:137–47.
94. Hess IM, Lachireddy K, Capon A. A systematic review of the health risks from passive exposure to electronic cigarette vapour. Public Health Res Pract. 2016;26(2):e2621617.
95. Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. Nicotine Tob Res. 2014;16(6):655–62.
96. Ballbe M, Martínez-Sánchez JM, Sureda X, Fu M, Pérez-Ortuña R, Pascual JA et al. Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. Environ Res. 2014;135:76–80.
97. 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. Environ Int. 2017;107:190–5.
98. Bayly JE, Bernat D, Porter L, Choi K. Secondhand exposure to aerosols from electronic nicotine delivery systems and asthma exacerbations among youth with asthma. Chest. 2019;155(1):88–93.
99. Smoking cessation: A report of the Surgeon General. Rockville (MD): Department of Health and Human Services; 2020 (https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-re-

port.pdf).
100. Kane DB, Asgharian B, Price OT, Rostami A, Oldham M. Effect of smoking parameters on the particle size distribution and predicted airway deposition of mainstream cigarette smoke. Inhal Toxicol. 2010;22(3):199–209.
101. Son Y, Mainelis G, Delnevo C, Wackowski OA, Schwander S, Meng Q. Investigating e-cigarette particle emissions and human airway depositions under various e-cigarette-use conditions. Chem Res Toxicol. 2020;33(2):343–52.
102. Beauval N, Verriele M, Garat A, Fronval I, Dusautoir R, Anthérieu S et al. Influence of puffing conditions on the carbonyl composition of e-cigarette aerosols. Int J Hyg Environ Health. 2019;222(1):136–46.
103. Hubbs AF, Kreiss K, Cummings KJ, Fluharty KL, O'Connell R, Cole A et al. Flavorings-related lung disease: A brief review and new mechanistic data. Toxicol Pathol. 2019;47(8):1012–6.
104. Clapp PW, Lavrich KS, van Heusden CA, Lazarowski ER, Carson JL, Jaspers I. Cinnamaldehyde in flavored e-cigarette liquid temporarily suppresses bronchial epithelial cell ciliary motility by dysregulation of mitochondrial function. Am J Physiol Lung Cell Mol Physiol. 2019;316(3):L470–86.
105. Bopp SK, Barouki R, Brack W, Dalla Costa S, Dorne JCM, Drakvik PE et al. Current EU research activities on combined exposure to multiple chemicals. Environ Int. 2018;120:544–62.
106. EFSA Scientific Committee, More SJ, Bampidis V, Benford D, Bennekou SH, Bragard C et al. Guidance on harmonised methodologies for human health, animal health and ecotoxicological risk assessment of combined exposure to multiple chemicals. EFSA J. 2019;17(3):5634.
107. Ukić S, Sigurnjak M, Cvetnić M, Markić M, Novak Stankov M et al. Toxicity of pharmaceuticals in binary mixtures: Assessment by additive and non-additive toxicity models. Ecotoxicol Environ Saf. 2019;185:109696.
108. Gao Y, Feng J, Kang L, Xu X, Zhu L. Concentration addition and independent action model: Which is better in predicting the toxicity for metal mixtures on zebrafish larvae. Sci Total Environ. 2018;610-611:442–50.
109. Jonker MJ, Svendsen C, Bedaux JJ, Bongers M, Kammenga JE. Significance testing of synergistic/antagonistic, dose level-dependent, or dose ratio-dependent effects in mixture dose-response analysis. Environ Toxicol Chem. 2005;24(10):2701–13.
110. Altenburger R, Backhaus T, Boedeker W, Faust M, Scholze M, Grimme LH. Predictability of the toxicity of multiple chemical mixtures to Vibrio fischeri: Mixtures composed of similarly acting chemicals. Environ Toxicol Chem. 2000;19(9):2341–7.
111. Baas J, Van Houte BP, Van Gestel CA, Kooijman SALM. Modeling the effects of binary mixtures on survival in time. Environ Toxicol Chem. 2007;26(6):1320–7.
112. Leeman WR, Krul L, Houben GF. Complex mixtures: Relevance of combined exposure to substances at low dose levels. Food Chem Toxicol. 2013;58:141–8.
113. EFSA Scientific Committee. Scientific opinion on exploring options for providing advice about possible human health risks based on the concept of threshold of toxicological concern (TTC). EFSA J. 2012;10(7).
114. Kawamoto T, Fuchs A, Fautz R, Morita O. Threshold of toxicological concern (TTC) for botanical extracts (botanical-TTC) derived from a meta-analysis of repeated-dose toxicity studies. Toxicol Lett. 2019;316:1–9.
115. Rietjens I, Cohen SM, Eisenbrand G, Fukushima S, Gooderham NJ, Guengerich FP et al. FEMA GRAS assessment of natural flavor complexes: Cinnamomum and Myroxylon-derived flavoring ingredients. Food Chem Toxicol. 2020;135:110949.
116. Tluczkiewicz I, Kühne R, Ebert RU, Batke M, Schüürmann G, Mangelsdorf I et al. Inhalation TTC values: A new integrative grouping approach considering structural, toxicological and mechanistic features. Regul Toxicol Pharmacol. 2016;78:8–23.
117. Schüürmann G, Ebert RU, Tluczkiewicz I, Escher SE, Kühne R. Inhalation threshold of toxico-

logical concern (TTC) – Structural alerts discriminate high from low repeated-dose inhalation toxicity. Environ Int. 2016;88:123–32.

118. The scientific basis of tobacco product regulation. Report of a WHO Study Group (WHO Technical Report Series, No. 945). Geneva: World Health Organization; 2007 (https://www.who.int/tobacco/global_interaction/tobreg/who_tsr.pdf, accessed 10 January 2021).
119. Wagner KA, Flora JW, Melvin MS, Avery KC, Ballentine RM, Brown AP et al. An evaluation of electronic cigarette formulations and aerosols for harmful and potentially harmful constituents (HPHCs) typically derived from combustion. Regul Toxicol Pharmacol. 2018;95:153–60.
120. Air Toxics Hot Spots Program risk assessment guidelines. Part II. Technical support document for cancer potency factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. Sacramento (CA): California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Air Toxicology and Epidemiology Branch; 2008 (https://oehha.ca.gov/media/downloads/crnr/tsd062008.pdf).
121. Cunningham FH, Fiebelkorn S, Johnson M, Meredith C. A novel application of the margin of exposure approach: segregation of tobacco smoke toxicants. Food Chem Toxicol. 2011;49(11):2921–33.
122. Soeteman-Hernández LG, Bos PM, Talhout R. Tobacco smoke-related health effects induced by 1,3-butadiene and strategies for risk reduction. Toxicol Sci. 2013;136(2):566–80.
123. Risicobeoordeling lachgas [Risk assessment on nitrous oxide]. Bilthoven: Coördinatiepunt Assessment en Monitoring nieuwe drugs; 2019 (https://www.vvgn.nl/wp-content/uploads/2019/12/risicobeoordelingsrapport-lachgas-20191209-beveiligd.pdf).
124. Staal YCM, Havermans A, van Nierop L et al. Evaluation framework to qualitatively assess the health effects of new tobacco and related products [submitted 2020].
125. Sosnowski TR, Kramek-Romanowska K. Predicted deposition of e-cigarette aerosol in the human lungs. J Aerosol Med Pulm Drug Deliv. 2016;29(3):299–309.
126. Savareear B, Escobar-Arnanz J, Brokl M, Saxton MJ, Wright C, Liu C et al. Non-targeted analysis of the particulate phase of heated tobacco product aerosol and cigarette mainstream tobacco smoke by thermal desorption comprehensive two-dimensional gas chromatography with dual flame ionisation and mass spectrometric detection. J Chromatogr A. 2019;1603:327–37.
127. Salman R, Talih S, El-Hage R, Haddad C, Karaoghlanian N, El-Hellani A et al. Free-base and total nicotine, reactive oxygen species, and carbonyl emissions from IQOS, a heated tobacco product. Nicotine Tob Res. 2019;21(9):1285–8.
128. Cancelada L, Sleiman M, Tang X, Russell ML, Montesinos VN, Litter MI et al. Heated tobacco products: Volatile emissions and their predicted impact on indoor air quality. Environ Sci Technol. 2019;53(13):7866–76.
129. Bentley MC, Almstetter M, Arndt D, Knorr A, Martin E, Pospisil P et al. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. Anal Bioanal Chem. 2020;412(11):2675–85.
130. Apelberg BJ, Feirman SP, Salazar E, Corey CG, Ambrose BK, Paredes A et al. Potential public health effects of reducing nicotine levels in cigarettes in the United States. N Engl J Med. 2018;378(18):1725–33.
131. Chen J, Bullen C, Dirks K. A comparative health risk assessment of electronic cigarettes and conventional cigarettes. Int J Environ Res Public Health. 2017;14(4):382.
132. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. 2019;380(7):629–37.

9. Flavours in novel and emerging nicotine and tobacco products

Ahmad El-Hellani, Department of Chemistry, Faculty of Arts and Sciences, American University of Beirut, Beirut, Lebanon; Center for the Study of Tobacco Products, Virginia Commonwealth University, Richmond (VA), USA

Danielle Davis, Department of Psychiatry, Yale School of Medicine, Yale University, New Haven (CT), USA

Suchitra Krishnan-Sarin, Department of Psychiatry, Yale School of Medicine, Yale University, New Haven (CT), USA

Contents

Abstract

Nicotine and tobacco products contain characterizing flavours that mask their harshness, ease their use and increase their acceptability. Recent estimates indicate that flavour use is common, and thousands of flavours are now available

for electronic nicotine delivery systems. Non-traditional flavours, like fruit and confectionery, are particularly appealing to young people, and use of these flavours is also increasing among adults, especially among adult smokers who are trying to quit smoking. Flavours in all nicotine and tobacco products have been shown not only to increase the appeal and first use of the products but may also contribute to extent of use, progression from experimental to regular use and dependence. Another concern is that chemicals in flavours may contribute to the toxicity of these products. Flavours are not regulated uniformly in nicotine and tobacco products or among countries. Some countries ban all flavours in all products, others have bans on only some flavours (e.g. excluding menthol), while others include only certain products (e.g. traditional products, such as cigarettes and smokeless tobacco) in regulations. This report on flavours in nicotine and tobacco products calls for adoption of common terminology for flavours in nicotine and tobacco products and consideration of policy for reducing the availability of flavoured nicotine and tobacco products on the market to those for which there is clear evidence of benefit in assisting smokers in quitting use of traditional smoked tobacco products.

9.1 Background and introduction

Addition of flavours to tobacco products dates back to the nineteenth century, when fruity flavours were added to smokeless tobacco products *(1)*. Now, almost all nicotine and tobacco products, including traditional smoked tobacco products such as cigarettes and cigars, newer products such as snuff and snus, heated tobacco products (HTPs) and electronic nicotine delivery systems (ENDS) are available with a variety of flavours, which contributes to their increased appeal, the prevalence of use and the perception of reduced harm *(2,3)*. Flavourings mask the harshness of nicotine and tobacco, ease their use and also reduce second-hand exposure to harsh odours, thus increasing their acceptability and potentially leading to progression and maintenance of dependence on these products. Flavourings also enhance the appeal of nicotine and tobacco products to novice users and vulnerable populations, thus increasing initiation and progression in the use of these products *(4)*. The dual role that flavours play in enticing novice users, especially young people, to initiate nicotine and tobacco product use and in prolonging use by current users should be addressed by health authorities and public health communities to ensure the best regulations to address the inclusion of flavours in nicotine and tobacco products *(5–8)*.

Flavoured nicotine and tobacco products are used all over the world. There is limited systematic evidence about their availability and use globally, and preferences for such products are often specific to countries and regions. For example, traditional cigarettes that contain cloves and oils (*kretek*) are highly popular in Indonesia, and spiced smokeless tobacco containing tobacco mixed

with spices, oils, flavouring, betel nut and other ingredients (*pan masala*, *gutka*) is widely used in India. Hookah smoking, which involves heating heavily flavoured, sweetened tobacco, originated in India and the Middle East but has become increasingly popular among young people in Europe and North America.

Restrictions on the use of flavours in nicotine and tobacco products differ by country. Some countries, such as Brazil, Chile, Ethiopia, the Republic of Moldova, and some Canadian provinces restrict all flavours in nicotine and tobacco products, including menthol, although flavours that impart a port, wine, rum or whisky flavour are allowed in Canada *(9)*. In May 2020, the European Union, with 28 Member States, implemented a ban on menthol cigarettes and roll-your-own tobacco *(10)*. Brazil, Canada, Chile and Ethiopia include non-cigarette smoked products, such as little cigars and cigarillos, in flavour restrictions, while others, including those in the European Union, the Republic of Moldova and Turkey, do not extend the restrictions to products other than cigarettes and roll-your-own tobacco *(11)*. There is also variation in whether menthol is included in restrictions; for example, while Brazil has banned all characterizing flavours (defined as flavours with a taste or aroma, apart from tobacco, distinguishable before, during or after tobacco consumption *(12)*), including menthol, in all tobacco products, in the USA, characterizing flavours except menthol are banned only in cigarettes and roll-your-own tobacco in most jurisdictions *(13)*, although some localities (e.g. San Francisco, California) have banned all characterizing flavours, including menthol *(14)* in tobacco products. In the European Union, as in the Republic of Moldova, Turkey and the USA, this ruling does not extend to other tobacco products, such as cigars, cigarillos, little cigars and smokeless tobacco products *(15)*.

ENDS may be regulated differently from tobacco products, as they do not contain tobacco. While WHO does not consider them to be tobacco products *(16)*, some countries include these products under existing tobacco product laws, while others consider these products separately from tobacco products.

The sale of these products is banned in 30 countries, and several countries have regulations to restrict the availability of flavours *(17)* and limit the maximal nicotine concentration. Restrictions on the addition of flavours to pod-based ENDS were instituted in the USA in late 2019, but many states have local restrictions on sales of flavoured nicotine and tobacco products *(18)*. The sale of nicotine-containing e-cigarettes is banned in some countries, including Australia and Japan *(19)*. e-Cigarettes that do not contain nicotine are referred to as electronic non-nicotine delivery systems (ENNDS) and, depending on regulations, are still available with flavours. In countries in which ENDS are available, the rate of ENNDS use is reported to be low *(20)*; as a result, they are often included with ENDS in evaluations of flavoured electronic systems. In this review, we have distinguished the two where possible in descriptions of the patterns of ENDS use.

Since the introduction of ENDS onto the global market in 2003, there has been renewed interest in the role of flavours. The popularity of ENDS has grown globally, but they are arguably most popular in Canada, Europe and the USA *(21)*. ENDS are available in an ever-growing range of customizable e-liquid flavours. A study of the online ENDS marketplace in 2013–2014 found 7764 unique e-liquid flavours *(22)*, and a follow-up in 2018 showed that the figure had doubled, to 15 586 flavours *(23)*. The availability of ENDS has led to debate in the public health field about use of these devices to reduce harm by helping smokers quit use of more harmful traditional smoked tobacco products. The debate has carried over into one on the risk versus benefit of flavours in ENDS. Some researchers and advocates argue that addition of flavours to ENDS products is beneficial, as it may potentially help smokers to quit smoking *(24–26)*, while others argue that the presence of flavours only enhances the appeal of these devices to young people and leads to increased use and dependence *(26–29)*.

ENDS are not the only relatively new product on the market. Heated tobacco products (HTPs), which have unique characteristics but are tobacco products, emerged in their current iteration in 2013. These products do not have the variety of ENDS flavours but are marketed similarly, in that they are advertised as potential alternatives to traditional tobacco products.

Given the relatively recent appearance of HTPs on the market and the fact that they may be marketed as a lower-risk product, it is important to understand how flavours contribute to their appeal and use, especially among non-users and young people *(30)*.

This report is an update to that in the seventh report of the WHO Study Group on Tobacco Product Regulation *(31)*. We describe the epidemiology of flavoured products, the impact of flavours on appeal, experimentation and continual use of nicotine and tobacco products, the most commonly used flavours, their health effects and current regulation of flavours in these products.

9.2 Epidemiology of flavoured products (frequency, patterns and reasons for use by sociodemographic variables)

Although flavoured nicotine and tobacco products are used globally, there is limited systematic information on their use. Most of the information is for the USA, where surveys indicate high rates of use. The National Adult Tobacco Survey in 2013–2014 indicates that an estimated 10.2 million ENDS users (68.2%), 6.1 million hookah users (82.3%), 4.1 million cigar smokers (36.2%) and 4.0 million smokeless tobacco users (50.6%) had used flavoured products in the past 30 days *(32)*. In the same survey, among cigarette smokers, the use of cigarettes flavoured with menthol (the only characterizing flavour in cigarettes in the USA at the time of the survey) was relatively high, comprising 39% of cigarettes used *(33)*. Similar results were reported from a population-based survey in 2014–2015,

which showed that 41.4% of nicotine and tobacco users reported use of flavoured products, ranging by product from 28.3% of cigar smokers to 87.2% of hookah users *(34)*.

Limited data exist on global use of flavoured nicotine and tobacco products and are sorely needed to evaluate the scope of flavour use worldwide. Information should be generated on use of flavoured nicotine and tobacco products elsewhere in the world. Although data for the USA provide a reasonable estimate, the types of flavoured nicotine and tobacco products used and regulation of these products differ by country, which may affect the use of different flavours. The patterns of use of flavoured tobacco products may differ according to their availability and popularity. Nevertheless, there is a higher prevalence of use among adolescents and young adults than among older adults. Evidence on the epidemiology of flavour use in different tobacco products is described below.

9.2.1 Electronic nicotine and non-nicotine delivery systems

Flavours are increasingly available for use in ENDS, because of both the dynamic growth in the number of flavours available *(23)* and their popularity among adolescents and young adults *(8)*. The Population Assessment of Tobacco and Health (PATH), a longitudinal national survey conducted in the USA, indicated that use of flavoured ENDS by current vapers was most prevalent among adolescents aged 12–17 (97%), followed by young adults aged 18–24 (97%) and adults aged ≥ 25 years (81%). A similar pattern was observed in initiation of ENDS products, 93% of adolescents, 84% of young adults and 55% of adults reporting initiation of ENDS with a flavoured product *(35)*. These patterns of use of flavoured ENDS are confirmed by other studies *(36–38)* and recent reviews *(39,40)*, which suggest that use of flavoured ENDS use is more prevalent among adolescents and young adults than among older adults. A report from the National Youth Tobacco Survey in the USA on tobacco product use by middle- and high-school students in 2019 indicated that use of flavours by current ENDS users was most prevalent among non-Hispanic white adolescents (77%) and similar among males (71%) and females (69%) *(41)*.

Use of non-traditional flavours (i.e. other than tobacco or menthol flavours) is more prevalent among adolescents and young adults; however, a shift in flavour preferences towards non-traditional flavours appears to be occurring in all age groups. Wave 2 of the PATH study suggested that fruit flavours were the category most commonly reported by adolescents, and menthol or mint, a flavour traditionally found in tobacco products, was most commonly reported by adults *(42)*. A follow-up study of wave 3 showed that fruit flavours were those most commonly used by both young and adult users and that dessert or confectionery was also highly popular among young and adult users *(29)*. These findings are consistent with other recent work; specifically, evidence that fruit flavours are

the most highly endorsed flavour category across age groups, including youth, young adults and adults *(36,43,44)*. A study of long-term use of flavours in ENDS in the USA found that a preference for tobacco and menthol or mint flavours decreased over time, preference for fruit flavours remained stable, and preference for dessert and sweet flavours increased *(45)*.

Research has also been conducted on the flavour preferences of ENDS users who are current or former users of other tobacco products (i.e. cigarettes). This is important because, particularly in Europe and the USA, there is debate about whether and how flavours reduce the appeal of ENDS for young people or enhance their appeal for users of tobacco products, such as cigarette smokers, who wish to switch to ENDS. Fruit flavours appear to be popular regardless of the type of tobacco use. A global Internet survey of former and current adult cigarette smokers found that, while fruit and sweet flavours were the most popular (69% and 61%, respectively), current cigarette smokers were more likely to report use of tobacco flavours and less likely to report use of fruit and sweet flavours than former cigarette smokers *(24)*. In a study in New Zealand, fruit flavour was preferred by exclusive ENDS users, former cigarette smokers and current cigarette smokers *(46)*. Even as flavour preferences appear to be shifting to non-traditional flavours in all age groups, it is important to note that the prevalence of use of non-traditional flavours in ENDS products appears still to be the highest among young people *(47)*.

Many users of flavoured ENDS report that they use several flavours (e.g. fruit, dessert or confectionery, menthol or mint). A study of ENDS users in the USA suggested that multiple flavour use is more prevalent among adolescents (46%) than adults (32%) *(29)*. In India, adult ENDS users reported a relatively high rate (65%) of use of several flavours *(48)*. The global Internet survey of current and former adult cigarette smokers who used ENDS *(24)* indicated that switching between flavours was common; 68% reported switching at least daily, 16% weekly and 10% less than weekly.

Although there is limited evidence on use of flavoured ENNDS, a study among adolescents and young adults (18–29 years) in Japan, where these products are banned, indicated use by 4.3% of the group. Although flavour use was not directly studied, the main reason reported for using the product use was fruit flavours, suggesting that flavours are a reason for using ENNDS *(49)*.

9.2.2 Traditional smoked and smokeless tobacco products

Although ENDS offer by far the most flavours of all nicotine and tobacco products, flavours are also used in other nicotine and tobacco products, both smokeless and smoked. As for ENDS, use of flavoured tobacco products is more prevalent among adolescents and young adults than adults. In a nationally representative sample of Canadian young people who used tobacco products

(cigarettes, pipes, cigars, cigarillos, *bidis*, smokeless tobacco, hookah, blunts, roll-your-own cigarettes), 52% reported using flavoured products *(50)*. Similarly, a national survey in Poland showed that younger smokers were more likely to use flavoured cigarettes *(51)*. In the PATH study in the USA, about half of users of all ages who reported current use of cigarillos and filtered cigars said that they used a flavoured product, while relatively low proportions of current cigar smokers reported use of flavoured products, from 24% of adults, 27% of adolescents to 36% of young adults. In the same study, the proportions of those who reported that their first tobacco product had been flavoured were 68% of adolescents, 63% of young adults and 42% of adults for cigarillos; and 56% of adolescents, 54% of young adults and 40% of adults for filtered cigars. Among traditional cigar users, the overall prevalence was lower, but the graded effect of age was still evident, with 39% of adolescents, 35% of young adults and 22% adults reporting that their first product had been flavoured *(35)*.

The types of flavours used in more traditional tobacco products were shown in 2013–2014 in the National Adult Tobacco Survey in the USA to be menthol or mint in smokeless tobacco (77%), fruit in hookah tobacco (74%); fruit (52%), confectionery, chocolate and other sweet flavours (22%) and alcohol (14%) in cigars, cigarillos and filtered little cigars; and fruit (57%), confectionery, chocolate and other sweet flavours (26%) and menthol or mint (25%) in pipe tobacco *(32)*.

Capsules have been inserted in cigarettes to incorporate flavours other than traditional tobacco and menthol, and capsule cigarettes appear to be capturing a growing portion of the global market *(52)*. The flavours range from menthol to green tea and whisky and others. Capsule cigarettes are popular among adolescents and young adult smokers. Over half of adolescent cigarette smokers in Australia reported capsule use *(53)*, and young adults in the United Kingdom and the USA expressed a preference for these products *(53,54)*. This may change, as flavour capsules have been banned in Brazil and the European Union since spring 2020 *(55)*.

9.2.3 Heated tobacco products

HTPs have been developed since the 1960s in the USA and globally since the 1980s; however, the early products were unsuccessful. A new generation of HTPs has been marketed since 2013 *(30)*, and they are currently available in about 50 countries, including Canada, Israel, Italy, Japan, the Republic of Korea and, most recently, the USA *(56,57)*. HTPs contain flavours, which may increase their appeal and use *(58)*. These devices produce aerosols containing nicotine and toxic chemicals when tobacco is heated or when a device containing tobacco is activated, and users inhale the aerosol by sucking or smoking. The products have been marketed as a safer alternative to combustible cigarettes *(59)*. They

have fewer flavour options than ENDS, the main choices being either tobacco or menthol; other flavour options include "mentholated-fruity" and coffee.

Japan has been a recent test markets for these products. Data from wave 1 of the International Tobacco Control Japan Survey, collected in 2018, indicated that the prevalence of HTP use was only 2.7%. The popularity of flavours appeared to be similar among exclusive HTP users and HTP users who used other products, menthol flavour being the most popular, followed by tobacco and mentholated-fruity flavour *(60)*. Given the evidence that flavours increase the appeal of other nicotine and tobacco products, particularly for adolescents and young adults who do not use tobacco, the alarm has been sounded that these products might appeal as a function of their flavours *(58)*. Comprehensive research should be conducted on the use of flavours in these products as the market for HTPs is extended to other countries.

9.3 Effects of flavours on appeal, experimentation, uptake and sustained use (See also section 3.)

9.3.1 Adolescents and young adults

Appeal

As adolescent and young adult tobacco product users appear to use flavoured products and ENDS at greater rates than adults *(36,51)*, it is important to understand the appeal of these products to adolescents and how it may differ from that to adult users. Comparisons of smoked product use by age show that flavoured cigars, cigarettes and hookahs are more appealing to young than to adult users *(61,62)*. Young people have reported that flavours are the main reason for both initiation and continued use of ENDS *(63,64)*, and sweet and fruit-flavoured e-liquid solutions were more appealing to adolescents and young adults than non-sweet (e.g. tobacco-flavoured) e-liquids *(65,66)*. Similarly, young people reported that flavours were the main reason for cigarillo use *(67)*.

Notably, appeal for flavoured tobacco products may begin even before using the flavour. ENDS. Flavours in both smoked tobacco products and ENDS may appeal not only because of a positive experience associated with flavours *(68–70)* but also because they reduce the perceived risk of the harm of these products *(71–75)*. ENDS are not only provided in non-traditional tobacco flavours but are also advertised with colourful images and appealing descriptions of the flavours. Functional magnetic resonance imaging showed that, in young adults susceptible to using ENDS, just viewing advertisements showing fruit, mint and sweet flavours for ENDS products increased activity in the nucleus acumens to a greater extent than advertisements for tobacco flavours. Heightened activity was also seen when participants viewed advertisements for non-ENDS fruit, mint and sweet flavours, indicating that the appeal of non-traditional flavours may begin before an ENDS is sampled and the advertisements may lead to initiation *(76)*.

Experimentation, uptake and sustained use

Flavours may play an important role in initiation of ENDS use and progression by adolescents and young adults. Thus, initial use of flavoured ENDS was associated not only with continued use but also with more days of use, suggesting heavier use with time *(77)*. In another study, preference for specific flavours and the total number of flavours used were associated with more days of ENDS use by young people and not by adult users *(28)*, indicating that flavour preferences play a different role in adolescent use from that of adults. Sweet non-traditional flavours, in particular, appeal to young people and may contribute to the uptake and use of ENDS *(28,37,63,78,79)*. In a study in young people, use of flavoured ENDS was associated with non-traditional flavours (i.e. not tobacco, mint or menthol) and continuation but not with the number of days of ENDS use over time, suggesting that use of non-traditional flavours may sustain use *(37)*. This may be due in part to perceived sensory effects of non-traditional flavours. In a laboratory study of ENDS with six commercially available flavours, fruit flavours were considered the sweetest and tobacco flavour the most bitter. When flavours were rated for coolness and harshness, sweetness and coolness were positively correlated and harshness and bitterness negatively correlated with liking *(80)*.

Flavours in nicotine and tobacco products may increase their addictive potential, which will sustain their use *(81)*. It has been reported that green apple tobacco flavour in ENDS alters smoking behaviour, which may be associated with upregulation of nicotinic acetylcholine receptors *(82)*, as suggested by a study of the biological mechanisms by which menthol alters tobacco smoking behaviour, including reinforcing sensory cues associated with nicotine, upregulating nicotinic acetylcholine receptors and altering nicotine metabolism to increase its bioavailability *(83)*.

Initiation with flavoured ENDS results in continued, heavier use by young people, and this pattern may also occur with other tobacco products and in older age groups. Longitudinal results from the PATH study indicated that first use of a flavoured (i.e. menthol) cigarette was associated with continued cigarette use in adolescents, young adults and adult smokers, and, in young adults and adults, this pattern extended to other tobacco products. Thus, first use of a flavoured ENDS, cigar, cigarillo, filtered cigar, hookah or any smokeless tobacco was associated with continued use of the product *(38)*.

9.3.2 Adults

Appeal

In adults, flavours also appear to contribute to the appeal of tobacco products. As in young people, flavoured ENDS products in particular appear to be highly appealing. In studies of ENDS users in the Netherlands, New Zealand and the USA, ENDS were rated as appealing as a function of the availability of flavours

(46,84). A study of university students (from undergraduates to doctoral candidates) in the Asian–Pacific rim found that 34% of e-cigarettes users used the products because of the flavours offered *(85)*. Flavours may contribute to the appeal in adults by raising positive expectancy about the product *(86)* and an overall positive perception among both users and non-users *(87)*.

Experimentation, uptake and sustained use

Flavours play a role in uptake not only among adolescents and young adults but also among older adults. In a sample of adults (≥ 25 years), regular current use of flavoured cigarettes, cigars, cigarillos, filtered cigars, hookah, smokeless tobacco and e-cigarettes was associated with flavoured products but not with first use of a non-flavoured product, as among adolescents and younger adults *(38)*. Smokeless tobacco users had a similar pattern of flavour use, whereby those who started with an unflavoured product were likely to switch to a flavoured product, while those who started with a flavoured product were likely to continue using it *(88)*.

There is evidence in adults that the use of flavoured tobacco products leads to greater dependence, which contributes to sustained use. Two markers of dependence on tobacco products, daily use and time to first use in the morning, were associated with use of flavoured products in a survey in the USA in 2014–2015. The same study indicated that use of flavoured ENDS was more likely to be daily than use of unflavoured products. More users of flavoured cigars (large cigars, cigarillos and little cigars) than of unflavoured cigars reported first use in the morning within 30 min of waking *(89)*.

Flavoured products may sustain use because they influence the reward and reduce the aversiveness of nicotine, the dependence-producing constituent in these products *(90)*. There is extensive literature on the interaction of nicotine and menthol in combustible cigarettes, which suggests that menthol serves as a cue for the sensory effects of nicotine *(91)* and enhances both the reward from nicotine *(92)* and the withdrawal symptoms *(93)*. This finding may indicate why menthol cigarette use is growing among smokers of combustible cigarettes even as overall use decreases *(94)* and why smokers of menthol cigarettes have more difficulty in quitting smoking *(95)*. Fruit flavours in ENDS have been shown to enhance the reward and reinforcing effects of nicotine *(78,96)* and to suppress its aversive effects *(97)*. Menthol flavours improve the taste of e-liquids in ENDS and make higher nicotine concentrations less aversive and more rewarding *(96–98)*. Similar patterns have been observed for combustible products. Tobacco industry documents suggest that flavoured cigar products increase their appeal to naïve users by reducing throat irritation and making emissions easier to inhale *(99)*.

Another mechanism that may sustain use is the perception that, in general, flavoured tobacco products, including ENDS, are less harmful than unflavoured tobacco products. Flavours in ENDS give a false perception of safety not only to

users but also to bystanders *(100)*. This attitude is, however, changing, as more voices rise for the inclusion of use of ENDS in designated smoke-free indoor areas, as second-hand aerosols from flavoured ENDS can leave pungent odours *(101)*. Chemical and toxicological assessment of second-hand aerosols from flavoured ENDS is lagging behind their excessive use indoors and in public spaces *(102,103)*.

Questions remain about the role of flavours in switching from conventional smoked products to other products, such as ENDS or HTPs. No studies have yet been reported on the relation between HTPs, flavours and switching behaviour. The flavours in ENDS may appeal to users of smoked products, and use of flavoured ENDS may be associated with a greater likelihood of short and longer attempts to quit use of smoked tobacco products *(104,105)*. There have been no experimental investigations of the specific role ENDS flavours play in switching from traditional smoked products, although many describe the abuse liability of ENDS in adolescents and young adults and in users of non-combustible products. Proof is required to determine the role flavours in ENDS play in product switching.

9.4 Common flavours, properties, health effects and implications for public health

9.4.1 Common flavours in electronic nicotine delivery systems and tobacco products

The National Institute for Public Health and the Environment in The Netherlands has published a "flavour library" of flavours added to tobacco cigarettes and roll-your-own products *(106)*. The flavours are listed in eight main categories: fruit, spice, herb, alcohol, menthol, sweet, floral and miscellaneous. A year later, a similar report was issued in which the authors classified flavours in ENDS into 13 categories: tobacco, menthol, fruit, dessert, alcohol, nut, spices, confectionery, coffee/tea, beverages, sweet-like flavours, unspecified and unflavoured *(107)*. As noted above, the number of unique ENDS flavours on the market has increased dramatically in recent years, from 7764 in 2013–2014 to 15 586 in 2016–2017 *(22,23)*. Unique to ENDS products, users commonly mix and match flavours in refillable ENDS *(108)*, and "do-it-yourself" is common practice, sometimes with the addition of illicit substances *(109)*, and researchers should also consider the impact of such additives on ENDS use.

9.4.2 Chemical and physical properties of common flavours in flavoured products

Flavour ingredients in tobacco cigarettes

The above-mentioned flavour library *(106)* includes chemical analyses of flavours in tobacco cigarettes and roll-your-own products. This complements analyses of

the total tobacco matrix in cigarette filler. Identification of flavour ingredients in tobacco cigarettes and studies to assess their fate after pyrolysis have been reported *(110)*.

Flavour additives in ENDS

Several studies have reported chemical profiling of flavoured ENDS liquids *(111,112)*, indicating the complexity that flavours add to the ENDS matrix *(113)*. Although no comprehensive study is available of the thousands of possible flavours, analysis of commercial flavours showed that some chemicals are commonly used in more than one flavour *(114)*. A meta-analysis of the reported literature *(115–117)* was recently published by one of the authors of this report of the recurrence of certain chemicals, which indicates the frequency of chemicals such as ethyl maltol (47%), vanillin (37%), menthol (29%), ethyl vanillin (23%), linalool (23%), benzaldehyde (22%), benzyl alcohol (21%), maltol (20%), cinnamaldehyde (20%), ethyl butanoate (19%) and hydroxyacetone (16%). The work also describes the possible contributions of these flavouring additives to the toxicity of the aerosols generated by ENDS activation *(115)*. Flavours are either distilled intact into the aerosol (their contribution to toxicity depends on their properties and emission levels) *(118)*, react with ENDS carriers (propylene glycol and glycerol) to form acetal compounds with unique toxicological properties *(119)* or undergo thermal degradation to toxicants such as carbonyls *(120)*, reactive oxygen species *(121)* and volatile organic compounds *(122)*. The gas–particle-phase partitioning coefficients of several flavour ingredients have been determined; they are relevant to assessment of toxicity as they may determine the site of absorption of these chemicals into the body *(123)*.

Flavours added to ENDS not only impart a specific flavour but also increase sweetness (e.g. sucrose) *(124)*, as observed in other products, including smokeless products *(125)* and cigars *(126)*. Sweeteners, including artificial ones (e.g. sucralose), can increase the appeal of nicotine and tobacco products *(65)*, although there is limited evidence for direct effects of sweeteners *(127)*.

Flavours in other tobacco products

Flavour additives in smokeless tobacco products have been addressed in two studies *(128,129)*. Flavour compounds have also been identified and quantified in *bidis (130),* clove cigarettes *(131)* and flavoured waterpipe tobacco *(132)*.

9.4.3 Toxicity of flavours

Flavours in ENDS can strongly increase the general toxicity of the aerosols *(133)*. Several targeted analyses of ENDS liquids included quantification of diacetyl in nutty-flavoured ENDS liquids *(134)* and found that emission of this chemical and

its inhalation by ENDS users increased their risk of bronchiolitis obliterans or "popcorn lung" disease *(135)*. Some cherry-flavoured ENDS liquids expose users to benzaldehyde, albeit at low levels *(136)*. To assess disease risk, the levels of these toxicants in ENDS aerosols are usually compared with workspace exposure limits. Toxicological assessment of flavours in ENDS liquids and aerosols, in cell lines and in animals, showed that flavours increase the toxicity of ENDS aerosols in various ways *(121,137)*. One report showed that adducts of flavours with ENDS carriers are more cytotoxic than their parent flavour compounds *(119)*.

Flavours may also increase the toxicity of ENDS aerosols by adding to toxicant emissions. For example, flavours in liquids increase emissions of carbonyl compounds and other compounds that are known or possible human carcinogens *(120)*. Flavours also increase toxicity by disturbing the oxidative balance in the body, as they increase the presence of radicals and reactive oxygen species in ENDS aerosols over that produced by plain liquids composed only of carriers *(138)*. This type of contribution to the toxicity of aerosols depends on the device operating parameters, such as power input and liquid composition *(139)*, as higher power increases the temperature of the heating coil, resulting in greater degradation of flavour compounds.

At present, the net effect of flavours on the toxicity of emissions from tobacco and nicotine products cannot be determined for products other than ENDS.

9.5 Regulation of flavoured products

9.5.1 Global regulation of flavoured ENDS

The contentious issue of the impact of flavours on the acceptability of ENDS and satisfaction among smokers who are seeking cessation and on the appeal of ENDS for experimentation and continued use by young people is highly polarized and intense *(81,140,141)*. This controversy is reflected in the different approaches used to tackle the ENDS use epidemic by public health authorities in different countries: flavours are banned, restricted or allowed (Table 9.1), depending on the authorities' assessment of the available information and view of the arguments on both sides of the debate *(142,143)*. Currently, about 100 countries regulate use of ENDS with new regulations or, mainly, by adapting regulations for other tobacco products *(144)*. About 30 countries ban the marketing and sale of ENDS *(145,146)*. A search in June 2020 on the website of the Institute for Global Tobacco Control at the Johns Hopkins Bloomberg School of Public Health in Baltimore (USA) indicated that the policies of 35 countries on ENDS referred to ingredients or flavours *(147)*. Most focus on labelling and ensuring that high-quality ingredients are used, and only five, Canada, Finland, Luxembourg, Saudi Arabia and the USA, had specific regulations on flavours in ENDS *(142)*. Finland bans characterizing flavours (e.g. fruity, confectionery) in all ENDS; Luxembourg's policy prohibits

additives that influence the perceptions of ENDS users with regard to health; Saudi Arabia allows fruit flavours and menthol but prohibits other characterizing flavours (e.g. cocoa, vanilla, coffee, tea, spices, confectionery, chewing-gum, cola and alcohol) *(149)*, while the US Food and Drug Administration (FDA) has issued a policy banning all flavoured cartridge ENDS (except tobacco- and menthol-flavoured products) on the basis of evidence that flavours strongly influence young people's use of ENDS, especially the extremely popular cartridge products (e.g. JUUL) *(150)*. It also exempts the flavoured liquids used in open-system ENDS *(150,151)*. Canada restricts marketing flavours that may appeal to young people, and, recently, the province of Nova Scotia banned flavoured ENDS; other provinces are considering doing the same *(152,153)*.

Table 9.1. Country regulatory approaches to flavoured e-cigarettes (as of June 2020)

Country	Regulation
Argentina, Australia, Azerbaijan, Bahrain, Barbados, Brazil, Brunei Darussalam, Cambodia, Chile, Colombia, Costa Rica, Ecuador, Egypt, El Salvador, Fiji, Gambia, Georgia, Honduras, Hungary, Iceland, India, Indonesia, Iran (Islamic Republic of), Israel, Jamaica, Japan, Jordan, Kuwait, Lao People's Democratic Republic, Lebanon, Malaysia, Maldives, Mauritius, Mexico, Nepal, New Zealand, Nicaragua, Norway, Oman, Palau, Panama, Paraguay, Philippines, Qatar, Republic of Korea, Republic of Moldova, Seychelles, Singapore, South Africa, Sri Lanka, Suriname, Switzerland, Syrian Arab Republic, Tajikistan, Thailand, Timor-Leste, Togo, Turkey, Turkmenistan, Uganda, Ukraine, United Arab Emirates, Uruguay, Venezuela (Bolivarian Republic of), Viet Nam	No specific regulation
Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom (England, Northern Ireland, Wales)	e-Liquid should not contain certain additives (not specified). High-quality ingredients should be used in e-cigarette manufacture. Only ingredients that do not pose a risk to human health in heated or unheated form can be used.
Canada	Marketing and sale of e-cigarettes that contain certain additives is prohibited (not specified). Restrictions on the marketing of flavours that may appeal to young people (including flavour suggestions, confectionery, dessert, cannabis, soft drink and energy drink).
Finland	e-Liquid should not contain certain additives and characterizing flavours (such as confectionery or fruit flavours). High-quality ingredients should be used in e-cigarette manufacture. Only ingredients that do not pose a risk to human health in heated or unheated form can be used.
Saudi Arabia	Flavours in e-cigarette liquids are partially prohibited. Fruit flavours and menthol are allowed, but cocoa, vanilla, coffee, tea, spices, confectionery, chewing-gum, cola and alcohol flavours are banned.
USA	All flavoured cartridge-based ENDS except tobacco- and menthol-flavoured products are banned. Flavoured liquids used in open-system ENDS are exempted.

Country	Regulation
Luxembourg	Additives that may create the impression that an e-cigarette product has a health benefit or presents a reduced health risk are prohibited (e.g. vitamins). Caffeine, taurine and other stimulants associated with energy or vitality are prohibited. Any additives that add colour, alter the properties of emissions or facilitate inhalation or nicotine uptake are prohibited. Only ingredients that do not pose a risk to human health in heated or unheated form can be used. Additives that have carcinogenic, mutagenic or reproductive toxic properties in their unburnt form are also prohibited. High-quality ingredients should be used in e-cigarette manufacture.

9.5.2 Global regulation of flavoured tobacco products

As for ENDS, regulation of other flavoured tobacco products also differs among countries. Table 9.2 lists countries and territories with different regulatory approaches from an analysis of regulations by the Campaign for Tobacco-Free Kids *(154)*. These can be summarized as no regulations, partial bans on specific categories of flavours (with or without menthol) and full bans on all characterizing flavours (the definition may differ by jurisdiction), which may include menthol.

Table 9.2. Countries and territories approaches to regulation of the contents of tobacco products, including flavours (As of June 2020)

Countries and Territories	Regulation
Afghanistan, Argentina, Azerbaijan, Bangladesh, Belarus, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cabo Verde, Chad, China, Colombia, Comoros, Congo, Côte d'Ivoire, Djibouti, Egypt, El Salvador, Eritrea, Eswatini, Fiji, France, Gabon, Germany, Ghana, Guinea, Iceland, India, Iran (Islamic Republic of), Israel, Jamaica, Japan, Jordan, Kazakhstan, Lao People's Democratic Republic, Latvia, Lebanon, Liberia, Madagascar, Malawi, Malaysia, Maldives, Mali, Mauritius, Mexico, Myanmar, Namibia, Nepal, New Zealand, Norway, Oman, Pakistan, Panama, Peru, Philippines, Poland, Qatar, Saudi Arabia, Seychelles, Singapore, Solomon Islands, South Africa, Spain, Suriname, Sweden, Syrian Arab Republic, Timor-Leste, Togo, Turkmenistan, United Arab Emirates, Venezuela (Bolivarian Republic of), Viet Nam, occupied Palestinian territory, including east Jerusalem	The law does not grant authority to regulate the contents of cigarettes.
Algeria, Brunei Darussalam, Chile, Costa Rica, Democratic Republic of the Congo, Ecuador, Gambia, Georgia, Guatemala, Guyana, Honduras, Indonesia, Iraq, Kenya, Rwanda, Thailand, Ukraine, United Republic of Tanzania, Uruguay	The law grants authority to regulate the contents of cigarettes; however, no regulations have been issued.
Australia	The contents and ingredients of cigarettes are not regulated at national level; however, fruit- and confectionery-flavoured cigarettes are banned in all states and territories. Mint is banned in at least one state.
Armenia, Russian Federation	The law regulates specified contents of cigarettes, including banning mint and some herbs, and other, unspecified flavourings.

Country	Regulation
Brazil, Canada,[a] Ireland,[a] Italy, Mauritania, Republic of Moldova, Niger,[b] Romania,[a] Senegal, Slovenia,[a] Sri Lanka, Turkey, Uganda, United Kingdom (England, Northern Ireland, Wales) [a]	The law regulates specified contents of cigarettes, including banning of sugars and sweeteners, characterizing flavours, menthol, mint and spearmint, spices and herbs, ingredients that facilitate nicotine uptake, ingredients that create the impression of health benefits, other flavourings, ingredients associated with energy and vitality and colouring agents.
Ethiopia, Nigeria	The law regulates specified contents of cigarettes, including banning characterizing flavours, ingredients that create the impression of health benefits and ingredients associated with energy and vitality.

[a] Menthol as a characterizing flavour was banned as of 20 May 2020.
[b] Menthol is not prohibited.

In 2009, the FDA banned all characterizing flavours in cigarettes except for menthol *(13)*. In 2014, the European Union followed suit, with a series of policies banning flavours other than menthol in cigarettes and roll-your-own tobacco *(28,155)*, and the Tobacco Products Directive banned menthol in cigarettes and roll-your-own tobacco in May 2020 *(156,157)*, although the regulations do not apply to other tobacco products *(28)*. Other countries have banned flavours in tobacco products *(158)*, including cigarettes; however, the regulations are either still at legislative level, as in Brazil *(159)* and Uganda *(160)*, or were recently implemented, as in Turkey *(161)*. In 2014, Singapore prohibited fruit flavours in waterpipe tobacco *(63)*. In 2010, Canada prohibited the sale of all flavoured cigarettes and little cigars but exempted menthol cigarettes, and banned all flavours in other tobacco products, including waterpipe, smokeless tobacco and *bidis*. In 2017, the provinces of Alberta and Ontario banned the sale of menthol cigarettes *(161)*.

In a study of the response to regulations, quitting behaviour was observed in Canadians who reported daily, some or "never" (i.e. users of non-menthol cigarettes) use of menthol cigarettes after the menthol product ban and found that more daily and occasional users than non-menthol product users had attempted to or had quit cigarette use *(162)*. In a study of residents of San Francisco, USA, menthol product and e-cigarette use decreased among young (18–24 years) and older adults (25–34 years) after a ban on menthol flavour, but cigarette smoking increased among young adults, and 65% of participants did not believe that the ban was enforced uniformly across the city *(14)*. Ethiopia provides an ideal example of a strict tobacco control strategy, with a ban on the sale and distribution of all flavoured tobacco products, including those with menthol, and all ENDS are banned in a comprehensive approach to protect public health *(163)*. Use of tobacco products in the country is lower than in other countries with a low human development index *(164)*.

9.5.3 Pros and cons of common approaches

Flavours in tobacco products increase their appeal and the perceptions of users and bystanders of their safety *(100,165–166)*. National regulatory offices have therefore attempted to reduce the effect of use of these products on public health. As noted above, only a few countries ban characterizing flavours in nicotine and tobacco products, either to respond to their obligations under the WHO Framework Convention on Tobacco Control or to protect young people and public health *(158)*.

The different approaches to regulating flavours globally present a mosaic of policies that could be weighed according to their estimated benefit to public health. Some do not mention flavours, tobacco ingredients or content in general. Such lack of specificity could leave loopholes through which the tobacco industry could address young people. Partial banning of some flavours or banning of flavours in some nicotine and tobacco products also leaves a wide margin for the tobacco industry to advertise other flavours or alternative flavoured nicotine and tobacco products and thus challenge the work of regulators. A full ban on all flavours in all nicotine and tobacco products would appear to be a strong approach to curbing young people's use of tobacco products, although regulators should consider the potential argument that flavours might be tools to accommodate switching from use of traditional smoked products to other products which could be substitutes. Regulators should make sure that customizable products that can be used to deliver nicotine in products such as open-system ENDS are removed from the market; otherwise, users will add unorthodox and illicit additives to their products *(167)*. There have also been several calls for the removal of flavours from ENDS, as the associated risks outweigh their potential public health benefit *(168,169)*. Both the supply and demand should be addressed in all regulations through widespread advocacy and awareness campaigns to seek support from the public to enforce implementation *(170–172)*.

9.5.4 Impact of regulation of specific flavoured nicotine products

As most regulations on flavoured tobacco products were introduced recently, limited information about their impact is available *(173–175)*. Lessons can nevertheless be learnt of the effects of policies to restrict flavours in tobacco products on their consumption *(176–178)*. For example, assessment of the effect of restrictions of the sale of flavoured cigars (< 1.4 g) in Canada on the sale of other cigars showed an overall decrease. Furthermore, after the ban on mentholated combustible products, more menthol cigarette smokers quit and made quit attempts than smokers of non-mentholated products *(162)*, although the authors noted that the exemption of certain flavours and product types might have reduced the effectiveness of the policy *(179)*. Similarly, evaluation of the effect of the ban on flavoured tobacco products (e.g. cigars, little cigars, roll-your-own)

in New York City, USA, showed a significant decrease (28%) in the odds of adolescents using any tobacco product *(180)*, although evaluation of the effect of the ban on menthol in San Francisco, USA, indicated a decrease in e-cigarette use but not cigarette use among younger people *(14)*. Another report suggested that making flavoured tobacco products less accessible and less affordable could help reduce the use of all tobacco products *(181)*.

As there are no or only relatively new regulations on flavouring in ENDS, there are no longitudinal data on their use in ENDS or other tobacco products *(182)*. Impact analysis and modelling have been used to estimate the possible effect of a regulation on use of flavours in ENDS *(143,183,184)*, including the net effect on use of all tobacco products *(185)*. One report showed that restrictive regulations on ENDS flavours could increase the intention of young adults to use cigarettes and both ENDS and combustible cigarettes *(183)*, although re-evaluation of the data showed that the net effect of regulation of both products is favourable to public health *(185)*. Estimation of the impact of a ban on all flavours in ENDS, menthol in cigarettes or all flavours in cigarettes showed that the measure that would reduce both smoking and vaping rates would be a ban on all flavours in both products, although use of cigarettes would still be 2.7% higher than the status quo *(169)*. As HTPs are considered to be tobacco products and are included with ENDS in some policies, there are no specific regulations on flavours in these products *(186)*. We have demonstrated that flavours in ENDS increase the abuse liability of these products, specifically among adolescents and young adults, and we have no evidence that specific flavours in ENDS would help cigarette smokers to quit. In considering regulatory measures, it might be important to consider whether unflavoured ENDS have an effect similar to flavoured ENDS in supporting attempts to quit combustible cigarette use and reducing the abuse liability of these products.

9.5.5 Future regulation of flavours

Flavours increase the appeal, continued use, extent of use, dependence and toxicity of nicotine and tobacco products and increase the risk of new generations of nicotine and tobacco addicts. Addiction to nicotine and exposure to the other toxicants emitted place a significant burden on public health *(187)*. The only way in which flavours could benefit public health would be in tobacco products proven to be less toxic, less risky and that support reduced use of combustible tobacco *(81)*. Even so, users of such alternative flavoured tobacco products should be encouraged to stop using them in order to withdraw from nicotine addiction and to avoid any lapse or relapse to use of tobacco or nicotine products.

The section in the seventh report of the WHO Study Group on Tobacco Product Regulation *(31)* on flavours in tobacco and nicotine products noted that the research priorities were systematic monitoring of the global epidemiology

of flavoured conventional, traditional, new and emerging tobacco products, identification of how flavours contribute to the appeal of these products and identification of flavour chemicals, their toxicity and their health effects. This report confirms that flavours are still widely prevalent in all nicotine and tobacco products, that the popularity of ENDS products has increased, that, while there are regulations on the availability of flavours in nicotine and tobacco products, they vary widely by country and that the global epidemiology of flavoured nicotine and tobacco product use should be monitored systematically.

This report also raises concern about the appeal of flavoured products to adolescents and young adults. ENDS are the most commonly used nicotine and tobacco products in these groups, and they have the highest use of flavours of all age groups. Flavours in ENDS may therefore be uniquely appealing to adolescents and young adults. One explanation may be the wide availability of non-traditional flavours *(23)*, which are more popular in these groups than among older adults *(47)*. It has been shown that fruit flavours in ENDS enhance the reward and reinforcing effects of nicotine delivered to the user *(24,91)*.

To better understand the impact of ENDS flavours on use, they have been grouped into categories, similar to those for combustible tobacco *(107)*. For example, flavours such as blueberry and green apple are considered fruit flavours, while muffin and cupcake flavours are categorized as "dessert". This grouping is useful for interpreting results for products with a wide, growing variety of flavour options.

Use of flavoured products is associated with a greater likelihood of use of other tobacco products *(188)*, especially among young people *(189)*. Policies to reduce all tobacco use must therefore be based on actual use patterns *(190)*. The effect of flavours on the appeal and use of ENDS is controversial from a regulatory perspective, as there is hot debate about whether the availability of many flavours assists in switching from combustible products to ENDS or increases the uptake of ENDS by naïve young people. It has been shown that the availability of flavours in ENDS is an important consideration for acceptance of these products by cigarette smokers *(24,191,192)*.

Flavours in nicotine and tobacco products, especially ENDS, are marketed by vivid descriptions of the taste and sensory experiences associated with them *(193)*. Perhaps not surprisingly, the overwhelming majority of ENDS users – adolescents, young adults and adults – endorsed "Come in flavours I like" as a reason for using ENDS *(35),* and ENDS users ranked a choice of flavours and unique flavours as two of the most important factors in choosing between competing vape shops *(157)*. The availability of many flavours may make it more likely that users will find a product that appeals to them and may explain why flavours are used to a greater extent in ENDS products than in other tobacco and nicotine products. Flavours are still prevalent in other products with demonstrated

appeal and sustained use, such as smokeless and combustible products and newer tobacco products such as HTPs. As tobacco regulations globally increasingly focus on ENDS, regulatory agencies should continue to monitor use of other nicotine and tobacco products in order to reduce their use.

Regulation of ENDS began some time after the major tobacco companies began their production *(194)*. Some advocacy groups have criticized the FDA for not acting fast enough to prevent young people from using ENDS, which may have contributed to the high rates of use by young people in the USA, and health organizations won a lawsuit that obliged the FDA to bring forward the deadline for submission of studies on the safety of ingredients in premarketing applications for ENDS products from 2022 to 12 May 2020 *(196–198)*. Regulation of flavours in other tobacco products, including cigarettes, also lagged behind their spread in the population *(37)*. Flavours were introduced in smokeless tobacco in the nineteenth century, while flavouring of cigarettes flourished only a few decades ago *(1,4,199)*. Flavours are used extensively in other tobacco products such as waterpipes and *bidis (2,32)*, and the wide choice of flavours contributes to their popularity, especially among young people *(27,61)*. Flavours not only increase the addictiveness of tobacco products but also increase their toxic emissions exponentially. Regulation of flavours is therefore at the intersection of harm reduction and a precautionary approach in tobacco regulation *(200)*. The best regulatory approach to stop the tobacco epidemic is to develop complementary policies on all flavoured tobacco products that will eventually bring this epidemic to an end *(201,202)*.

9.6 Discussion

The use of flavours in nicotine and tobacco products is controversial, as they have been clearly shown to contribute to the use and appeal of these products, particularly among young people. ENDS products continue to be a major concern, as their popularity is growing. A major feature of their appeal is the wide variety of flavours, which promote experimentation and prolonged use. Additionally, emerging evidence suggests that flavours may contribute to the toxicity of newer products such as ENDS in unique ways. Increased use of tobacco and nicotine due to flavours increases the burden on public health; however, flavours might be used to reduce the burden, as some adult smokers have reported that the flavours in products like ENDS contribute to their efforts to stop or reduce cigarette use. Policy-makers should consider this aspect when regulating flavours in tobacco products. Regulation of flavouring in tobacco products should be a priority in all regulatory approaches to limit the spread and progression of nicotine and tobacco use and to reduce use of combustible tobacco products.

9.7 Research gaps, priorities and questions

Research is necessary on the following aspects of flavoured nicotine and tobacco products, especially ENDS:

- surveillance studies on the global epidemiology of use of flavoured nicotine and tobacco products;
- longitudinal studies of ENDS use characteristics, reasons for uptake, flavour use over time and continued use;
- scientific classification to provide a means to categorize flavoured tobacco products and their chemical constituents;
- consensus on a current definition of a "characterizing flavour";
- impact analyses of regulations, restrictions and bans on flavours in new and emerging nicotine and tobacco products, especially ENDS, including modelling of responses to flavour-related policies in hypothetical scenarios and tasks;
- biomedical and behavioural studies on the impact of flavour on the experience of reward with use of nicotine and tobacco products, by age group and tobacco use status; and
- the toxicity of individual flavour ingredients and of chemicals in nicotine and tobacco products and of newly formed combined moieties.

Global priorities are to:

- build evidence of the impact of flavours on use of nicotine and tobacco products by age group and on use of different products in different countries;
- determine the impact of flavours in nicotine and tobacco products on the decades-long effort to reduce nicotine and tobacco use in the population; and
- exchange experience among countries in the regulation of flavours in tobacco products.

Questions to policy-makers and international organizations such as WHO include:

- How can concerns about the use of flavours in nicotine and tobacco products be addressed rapidly to prevent a new generation of users from becoming dependent on nicotine and tobacco?
- What can be done to outpace industry manoeuvres to use flavours to enhance the appeal and use of their products?
- Can a robust, self-developing, sustainable regulatory model be built to address similar concerns for any new or modified risk tobacco product?

9.8 Policy recommendations

A piecemeal approach to regulating flavoured nicotine and tobacco products will not turn the tide of the tobacco epidemic. A multi-pronged combination of various policy tools with a panoramic view of all nicotine and tobacco product use will help health agencies to address the issue of flavoured products *(203,204)*. ENDS could be used as an opportunity to increase the regulation of all tobacco products *(205)* to achieve the ultimate objective of nicotine- and tobacco-free future generations *(206)*. Policies on flavours in novel and emerging nicotine and tobacco products should include the following.

- Where flavours are not banned, their regulation in nicotine and tobacco products should be consistent globally; i.e. the availability of flavours should be regulated similarly for all nicotine and tobacco products rather than for each product.
- Research should be conducted on the possible role of characterizing flavours in products like ENDS or HTPs in helping smokers to quit.

9.9 References

1. Kostygina G, Ling PM. Tobacco industry use of flavourings to promote smokeless tobacco products. Tob Control. 2016;25(Suppl 2):ii40–9.
2. Ben Taleb Z, Breland A, Bahelah R, Kalan ME, Vargas-Rivera M, Jaber R et al. Flavored versus nonflavored waterpipe tobacco: A comparison of toxicant exposure, puff topography, subjective experiences, and harm perceptions. Nicotine Tob Res. 2018;21(9):1213–9.
3. Meernik C, Baker HM, Kowitt SD, Ranney LM, Goldstein AO. Impact of non-menthol flavours in e-cigarettes on perceptions and use: an updated systematic review. BMJ Open. 2019;9(10):e031598.
4. Carpenter CM, Wayne GF, Pauly JL, Koh HK, Connolly GN. New cigarette brands with flavors that appeal to youth: tobacco marketing strategies. Health Aff (Millwood). 2005;24(6):1601–10.
5. Gendall P, Hoek J. Role of flavours in vaping uptake and cessation among New Zealand smokers and non-smokers: a cross-sectional study. Tob Control. 2020: 055469.
6. Yao T, Jiang N, Grana R, Ling PM, Glantz SA. A content analysis of electronic cigarette manufacturer websites in China. Tob Control. 2016;25(2):188–94.
7. He G, Lin X, Ju G, Chen Y. Mapping public concerns of electronic cigarettes in China. J Psychoactive Drugs. 2019:52(1):1–7.
8. Cullen KA, Gentzke AS, Sawdey MD, Chang JT, Anic GM, Wang TW et al. e-Cigarette use among youth in the United States, 2019. JAMA. 2019;322(21):2095–2103.
9. Prohibited additives. In: Tobacco and Vaping Products Act (S.C. 1997, c. 13). Ottawa: Department of Justice; 1997 (https://laws.justice.gc.ca/eng/acts/T-11.5/page-12.html).
10. Hiscock R, Silver K, Zatoński M, Gilmore AB. Tobacco industry tactics to circumvent and undermine the menthol cigarette ban in the UK. Tob Control. 2020; 055769.
11. Farrelly MC, Loomis BR, Kuiper N, Han B, Gfroerer J, Caraballo RS et al. Are tobacco control policies effective in reducing young adult smoking? J Adolesc Health. 2014;54(4):481–6.
12. Talhout R, van de Nobelen S, Kienhuis AS. An inventory of methods suitable to assess additi-

ve-induced characterising flavours of tobacco products. Drug Alcohol Depend. 2016;161:9–14.
13. Food and Drug Administration. Enforcement of general tobacco standard special rule for cigarettes. Fed Reg. 2009;E9:23144 (https://www.federalregister.gov/documents/2009/09/25/E9-23144/enforcement-of-general-tobacco-standard-special-rule-for-cigarettes, accessed 18 February 2020).
14. Yang Y, Lindblom EN, Salloum RG, Ward KD. The impact of a comprehensive tobacco product flavor ban in San Francisco among young adults. Addict Behav Rep. 2020;11:100273.
15. Family Smoking Prevention and Tobacco Control. Division A. Public Law. 22 June 2009;111-31 (https://www.govinfo.gov/content/pkg/PLAW-111publ31/pdf/PLAW-111publ31.pdf, accessed 30 November 2020).
16. Tobacco. Geneva: World Health Organization; 2020 (https://www.who.int/news-room/fact-sheets/detail/tobacco, accessed 18 August 2020).
17. Kennedy RD, Awopegba A, De León E, Cohen JE. Global approaches to regulating electronic cigarettes. Tob Control. 2017;26(4):440–5.
18. FDA finalizes enforcement policy on unauthorized flavored cartridge-based e-cigarettes that appeal to children, including fruit and mint. Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/news-events/press-announcements/fda-finalizes-enforcement-policy-unauthorized-flavored-cartridge-based-e-cigarettes-appeal-children, accessed 23 June 2020).
19. Drope J, Schulger NW, editors. The Tobacco Atlas, sixth edition. Atlanta (GA): American Cancer Society; 2018.
20. Dawkins L, Turner J, Roberts A, Soar K. "Vaping" profiles and preferences: an online survey of electronic cigarette users. Addiction. 2013;108(6):1115–25.
21. WHO global report on trends in prevalence of tobacco smoking 2015. Geneva: World Health Organization; 2015.
22. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob Control. 2014;23(suppl 3):iii3–9.
23. Hsu G, Sun JY, Zhu SH. Evolution of electronic cigarette brands from 2013–2014 to 2016–2017: Analysis of brand websites. J Med Internet Res. 2018;20(3):e80.
24. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. Int J Environ Res Public Health. 2013;10(12):7272–82.
25. Jones DM, Ashley DL, Weaver SR, Eriksen MP. Flavored ENDS use among adults who have used cigarettes and ENDS, 2016–2017. Tob Regul Sci. 2019;5(6):518–31.
26. Bold KW, Krishnan-Sarin S. e-Cigarettes: Tobacco policy and regulation. Curr Addict Rep. 2019;6(2):75–85.
27. Ambrose BK, Day HR, Rostron B, Conway KP, Borek N, Hyland A et al. Flavored tobacco product use among US youth aged 12–17 years, 2013–2014. JAMA. 2015;314(17):1871–3.
28. Morean ME, Butler ER, Bold KW, Kong G, Camenga DR, Simon P et al. Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. PLoS One. 2018;13(1):e0189015.
29. Schneller LM, Bansal-Travers M, Goniewicz ML, McIntosh S, Ossip D, O'Connor RJ. Use of flavored e-cigarettes and the type of e-cigarette devices used among adults and youth in the US – Results from wave 3 of the Population Assessment of Tobacco and Health Study (2015–2016). Int J Environ Res Public Health. 2019;16(16):2991.
30. Heated tobacco products (HTPs) market monitoring information sheet 2018. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/bitstream/handle/10665/273459/WHO-NMH-PND-18.7-eng.pdf?ua=1, accessed 18 August 2020).

31. Krishnan-Sarin S, Green BG, Jordt SE, O'Malley SS. The science of flavour in tobacco products. In: WHO Study Group on Tobacco Product Regulation, Seventh report (WHO Technical Report Series No. 1015). Geneva: World Health Organization; 2019.
32. Bonhomme MG, Holder-Hayes E, Ambrose BK, Tworek C, Feirman SP, King BA et al. Flavoured non-cigarette tobacco product use among US adults: 2013–2014. Tob Control. 2016;25(Suppl 2):ii4–13.
33. Villanti AC, Mowery PD, Delnevo CD, Niaura RS, Abrams DB, Giovino GA. Changes in the prevalence and correlates of menthol cigarette use in the USA, 2004-2014. Tob Control. 2016;25(Suppl 2):ii14–20.
34. Odani S, Armour B, Agaku IT. Flavored tobacco product use and its association with indicators of tobacco dependence among US adults, 2014–2015. Nicotine Tob Res. 2020;22(6):1004–15.
35. Rostron BL, Cheng YC, Gardner LD, Ambrose BK. Prevalence and reasons for use of flavored cigars and ENDS among US youth and adults: Estimates from wave 4 of the PATH study, 2016–2017. Am J Health Behav. 2020;44(1):76–81.
36. Harrell MB, Weaver SR, Loukas A, Creamer M, Marti CN, Jackson CD et al. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. Prev Med Rep. 2017;5:33–40.
37. Leventhal AM, Goldenson NI, Cho J, Kirkpatrick MG, McConnell RS, Stone MD et al. Flavored e-cigarette use and progression of vaping in adolescents. Pediatrics. 2019;144(5):e20190789.
38. Villanti AC, Johnson AL, Glasser AM, Rose SW, Ambrose BK, Conway KP et al. Association of flavored tobacco use with tobacco initiation and subsequent use among US youth and adults, 2013–2015. JAMA Netw Open. 2019;2(10):e1913804.
39. Goldenson NI, Leventhal AM, Simpson KA, Barrington-Trimis JL. A review of the use and appeal of flavored electronic cigarettes. Curr Addict Rep. 2019;6(2):98–113.
40. Zare S, Nemati M, Zheng Y. A systematic review of consumer preference for e-cigarette attributes: Flavor, nicotine strength, and type. PLoS One. 2018;13(3):e0194145.
41. Wang TW, Gentzke AS, Creamer MR, Cullen KA, Holder-Hayes E, Sawdey MD et al. Tobacco product use and associated factors among middle and high school students – United States, 2019. Morbid Mortal Wkly Rep. 2019;68(12):1–22.
42. Schneller LM, Bansal-Travers M, Goniewicz ML, McIntosh S, Ossip D, O'Connor RJ. Use of flavored electronic cigarette refill liquids among adults and youth in the US – Results from wave 2 of the Population Assessment of Tobacco and Health Study (2014–2015). PLoS One. 2018;13(8):e0202744.
43. Russell C, McKeganey N, Dickson T, Nides M. Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. Harm Reduct J. 2018;15(1):33.
44. Berg CJ. Preferred flavors and reasons for e-cigarette use and discontinued use among never, current, and former smokers. Int J Public Health. 2016;61(2):225–36.
45. Du P, Bascom R, Fan T, Sinharoy A, Yingst J, Mondal P et al. Changes in flavor preference in a cohort of long-term electronic cigarette users. Ann Am Thorac Soc. 2020;17(5):573–81.
46. Gendall P, Hoek J. Role of flavours in vaping uptake and cessation among New Zealand smokers and non-smokers: a cross-sectional study. Tob Control. 2020; doi.org/10.1136/tobaccocontrol-2019-055469.
47. Soneji SS, Knutzen KE, Villanti AC. Use of flavored e-cigarettes among adolescents, young adults, and older adults: Findings from the Population Assessment for Tobacco and Health Study. Public Health Rep. 2019;134(3):282–92.
48. Sharan RN, Chanu TM, Chakrabarty TK, Farsalinos K. Patterns of tobacco and e-cigarette use status in India: a cross-sectional survey of 3000 vapers in eight Indian cities. Harm Reduct J. 2020;17(1):21.
49. Okawa S, Tabuchi T, Miyashiro I. Who uses e-cigarettes and why? e-Cigarette use among older

adolescents and young adults in Japan: JASTIS study. J Psychoactive Drugs. 2020;52(1):37–45.
50. Minaker LM, Ahmed R, Hammond D, Manske S. Flavored tobacco use among Canadian students in grades 9 through 12: prevalence and patterns from the 2010–2011 youth smoking survey. Prev Chronic Dis. 2014;11:E102.
51. Kaleta D, Usidame B, Szosland-Faltyn A, Makowiec-Dabrowska T. Use of flavoured cigarettes in Poland: data from the global adult tobacco survey (2009–2010). BMC Public Health. 2014;14:127.
52. Moodie C, Thrasher JF, Cho YJ, Barnoya J, Chaloupka FJ. Flavour capsule cigarettes continue to experience strong global growth. Tob Control. 2019;28(5):595–6.
53. White V, Williams T. Australian secondary school students' use of tobacco in 2014. Victoria: Centre for Behavioural Research in Cancer, Cancer Council Victoria; 2014.
54. Emond JA, Soneji S, Brunette MF, Sargent JD. Flavour capsule cigarette use among US adult cigarette smokers. Tob Control. 2018;27(6):650–5.
55. Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC. Offic J Eur Union. 2014; L127:1–38.
56. Kim M. Philip Morris International introduces new heat-not-burn product, IQOS, in South Korea. Tob Control. 2018;27(e1):e76–8.
57. Valinsky J. A new non-vaping, non-smoking way to get nicotine has come to America. CNN Business, 4 October 2019.
58. McKelvey K, Popova L, Kim M, Chaffee BW, Vijayaraghaven M, Ling P et al. Heated tobacco products likely appeal to adolescents and young adults. Tob Control. 2018;27(Suppl 1):s41–7.
59. Sustainability. Lausanne: Philip Morris International; 2017 (https://www.pmi.com/sustainability, accessed 1 November 2017).
60. Sutanto E, Miller C, Smith DM, O'Connor RJ, Quah ACK, Cummings KM et al. Prevalence, use behaviors, and preferences among users of heated tobacco products: Findings from the 2018 ITC Japan survey. Int J Environ Res Public Health. 2019;16(23):10.3390.
61. Klein SM, Giovino GA, Barker DC, Tworek C, Cummings KM, O'Connor RJ. Use of flavored cigarettes among older adolescent and adult smokers: United States, 2004–2005. Nicotine Tob Res. 2008;10(7):1209–14.
62. King BA, Tynan MA, Dube SR, Arrazola R. Flavored-little-cigar and flavored-cigarette use among US middle and high school students. J Adolesc Health. 2014;54(1):40–6.
63. Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. Nicotine Tob Res. 2015;17(7):847–54.
64. Kong G, Bold KW, Morean ME, Bhatti H, Camenga DR, Jackson A et al. Appeal of JUUL among adolescents. Drug Alcohol Depend. 2019;205:107691.
65. Goldenson NI, Kirkpatrick MG, Barrington-Trimis JL, Pang RD, McBeth JF, Pentz MA et al. Effects of sweet flavorings and nicotine on the appeal and sensory properties of e-cigarettes among young adult vapers: Application of a novel methodology. Drug Alcohol Depend. 2016;168:176–80.
66. Jackson A, Green B, Erythropel HC, Kong G, Cavallo DA, Eid T et al. Influence of menthol and green apple e-liquids containing different nicotine concentrations among youth e-cigarette users. Exp Clin Psychopharmacol. 2020:10.1037.
67. Kong G, Bold KW, Simon P, Camenga DR, Cavallo DA, Krishnan-Sarin S. Reasons for cigarillo initiation and cigarillo manipulation methods among adolescents. Tob Regul Sci. 2017;3(2 Suppl 1):S48–58.
68. Sharma E, Clark PI, Sharp KE. Understanding psychosocial aspects of waterpipe smoking

among college students. Am J Health Behav. 2014;38(3):440–7.
69. Choi K, Fabian L, Mottey N, Corbett A, Forster J. Young adults' favorable perceptions of snus, dissolvable tobacco products, and electronic cigarettes: findings from a focus group study. Am J Public Health. 2012;102(11):2088–93.
70. Moodie C, Ford A, Mackintosh A, Purves R. Are all cigarettes just the same? Female's perceptions of slim, coloured, aromatized and capsule cigarettes. Health Educ Res. 2015;30(1):1–12.
71. Griffiths MA, Harmon TR, Gilly MC. Hubble bubble trouble: The need for education about and regulation of hookah smoking. J Public Policy Marketing. 2011;30(1):119–32.
72. Roskin J, Aveyard P. Canadian and English students' beliefs about waterpipe smoking: A qualitative study. BMC Public Health. 2009;9:10.
73. Hammal F, Wild TC, Nykiforuk C, Abdullahi K, Mussie D, Finegan BA. Waterpipe (hookah) smoking among youth and women in Canada is new, not traditional. Nicotine Tob Res. 2016;18(5):757–62.
74. Kowitt SD, Meernik C, Baker HM, Osman A, Huang LL, Goldstein AO. Perceptions and experiences with flavored non-menthol tobacco products: A systematic review of qualitative studies. Int J Environ Res Public Health. 2017;14(4):338.
75. Sterling KL, Fryer CS, Fagan P. The most natural tobacco used: A qualitative investigation of young adult smokers' risk perceptions of flavored little cigars and cigarillos. Nicotine Tob Res. 2016;18(5):827–33.
76. Garrison KA, O'Malley SS, Gueorguieva R, Krishnan-Sarin S. A fMRI study on the impact of advertising for flavored e-cigarettes on susceptible young adults. Drug Alcohol Depend. 2018;186:233–41.
77. Audrain-McGovern J, Rodriguez D, Pianin S, Alexander E. Initial e-cigarette flavoring and nicotine exposure and e-cigarette uptake among adolescents. Drug Alcohol Depend. 2019;202:149–55.
78. Audrain-McGovern J, Strasser AA, Wileyto EP. The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers. Drug Alcohol Depend. 2016;166:263–7.
79. Krishnan-Sarin S, Morean ME, Camenga DR, Cavallo DA, Kong G. e-Cigarette use among high school and middle-school adolescents in Connecticut. Nicotine Tob Res. 2015;17(7):810–8.
80. Kim H, Lim J, Buehler SS, Brinkman MC, Johnson NM, Wilson L et al. Role of sweet and other flavours in liking and disliking of electronic cigarettes. Tob Control. 2016;25(Suppl 2):ii55–61.
81. Landry RL, Groom AL, Vu THT, Stokes AC, Berry KM, Kesh A et al. The role of flavors in vaping initiation and satisfaction among US adults. Addict Behav. 2019;99:106077.
82. Avelar AJ, Akers AT, Baumgard ZJ, Cooper SY, Casinelli GP, Henderson BJ. Why flavored vape products may be attractive: Green apple tobacco flavor elicits reward-related behavior, upregulates nAChRs on VTA dopamine neurons, and alters midbrain dopamine and GABA neuron function. Neuropharmacology. 2019;158:107729.
83. Wickham RJ. How menthol alters tobacco-smoking behavior: A biological perspective. Yale J Biol Med. 2015;88(3):279–87.
84. Romijnders KA, Krüsemann EJ, Boesveldt S, Graaf K, Vries H, Talhout R. e-Liquid flavor preferences and individual factors related to vaping: A survey among Dutch never-users, smokers, dual users, and exclusive vapers. Int J Environ Res Public Health. 2019;16(23):4661.
85. Wipfli H, Bhuiyan MR, Qin X, Gainullina Y, Palaganas E, Jimba M et al. Tobacco use and e-cigarette regulation: Perspectives of university students in the Asia-Pacific. Addict Behav. 2020;107:106420.
86. Ashare RL, Hawk LW Jr, Cummings KM, O'Connor RJ, Fix BV, Schmidt WC. Smoking expectancies for flavored and non-flavored cigarettes among college students. Addict Behav. 2007;32(6):1252–61.

87. Feirman SP, Lock D, Cohen JE, Holtgrave DR, Li T. Flavored tobacco products in the United States: A systematic review assessing use and attitudes. Nicotine Tob Res. 2016;18(5):739–49.
88. Oliver AJ, Jensen JA, Vogel RI, Anderson AJ, Hatsukami DK. Flavored and nonflavored smokeless tobacco products: rate, pattern of use, and effects. Nicotine Tob Res. 2013;15(1):88–92.
89. Odani S, Armour B, Agaku IT. Flavored tobacco product use and its association with indicators of tobacco dependence among US adults, 2014–2015. Nicotine Tob Res. 2020;22(6):1004–15.
90. Lynn WR, Davis RM, Novotny TE, editors. The health consequences of smoking: Nicotine addiction: A report of the Surgeon General. Atlanta (GA): Center for Health Promotion and Education, Office on Smoking and Health; 1988.
91. DeVito EE, Valentine GW, Herman AI, Jensen KP, Sofuoglu M. Effect of menthol-preferring status on response to intravenous nicotine. Tob Regul Sci. 2016;2(4):317–28.
92. Henderson BJ, Wall TR, Henley BM, Kim CH, McKinney S, Lester HA. Menthol enhances nicotine reward-related behavior by potentiating nicotine-induced changes in nAChR function, nAChR upregulation, and DA neuron excitability. Neuropsychopharmacology. 2017;42(12):2285–91.
93. Alsharari SD, King JR, Nordman JC, Muldoon PP, Jackson A, Zhu AZX et al. Effects of menthol on nicotine pharmacokinetic, pharmacology and dependence in mice. PLoS One. 2015;10(9):e0137070.
94. Villanti AC, Johnson AL, Ambrose BK, Cummings KM, Stanton CA, Rose SW et al. Flavored tobacco product use in youth and adults: Findings from the first wave of the PATH study (2013–2014). Am J Prev Med. 2017;53(2):139–51.
95. Ahijevych K, Garrett BE. The role of menthol in cigarettes as a reinforcer of smoking behavior. Nicotine Tob Res. 2010;12(Suppl 2):S110–6.
96. DeVito EE, Jensen KP, O'Malley SS, Gueorguieva R, Krishnan-Sarin S, Valentine G et al. Modulation of "protective" nicotine perception and use profile by flavorants: Preliminary findings in e-cigarettes. Nicotine Tob Res. 2020;22(5):771–81.
97. Leventhal AM, Goldenson NI, Barrington-Trimis JL, Pang RD, Kirkpatrick MG. Effects of non-tobacco flavors and nicotine on e-cigarette product appeal among young adult never, former, and current smokers. Drug Alcohol Depend. 2019;203:99–106.
98. Krishnan-Sarin S, Green BG, Kong G, Cavallo DA, Jatlow P, Gueorguieva R et al. Studying the interactive effects of menthol and nicotine among youth: An examination using e-cigarettes. Drug Alcohol Depend. 2017;180:193–9.
99. Kostygina G, Glantz SA, Ling PM. Tobacco industry use of flavours to recruit new users of little cigars and cigarillos. Tob Control. 2016;25(1):66–74.
100. Romijnders KAGJ, van Osch L, de Vries H, Talhout R. Perceptions and reasons regarding e-cigarette use among users and non-users: A narrative literature review. Int J Environ Res Public Health. 2018;15(6):1190.
101. Wilson N, Hoek J, Thomson G, Edwards R. Should e-cigarette use be included in indoor smoking bans? Bull World Health Organ. 2017;95(7):540–1.
102. Shearston J, Lee L, Eazor J, Meherally S, Park SH, Vilcassim MR et al. Effects of exposure to direct and secondhand hookah and e-cigarette aerosols on ambient air quality and cardiopulmonary health in adults and children: protocol for a panel study. BMJ Open. 2019;9(6):e029490.
103. Visser WF, Klerx WN, Cremers HWJM, Ramlal R, Schwillens PL, Talhout R. The health risks of electronic cgarette use to bystanders. Int J Environ Res Public Health. 2019;16(9):1525.
104. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. 2019;380(7):629–37.
105. Glasser A, Vojjala M, Cantrell J, Levy DT, Giovenco DP, Abrams D et al. Patterns of e-cigarette use and subsequent cigarette smoking cessation over two years (2013/2014 to 2015/2016) in the Population Assessment of Tobacco and Health (PATH) study. Nicotine Tob Res. 2020: doi: 10.1093/ntr/ntaa182.

106. Krüsemann EJ, Visser WF, Cremers JW, Pennings JL, Talhout R. Identification of flavour additives in tobacco products to develop a flavour library. Tob Control. 2018;27(1):105–11.
107. Krüsemann EJZ, Boesveldt S, de Graaf K, Talhout R. An e-liquid flavor wheel: A shared vocabulary based on systematically reviewing e-liquid flavor classifications in literature. Nicotine Tob Res. 2019;21(10):1310–9.
108. Cooper M, Harrell MB, Perry CL. A qualitative approach to understanding real-world electronic cigarette use: Implications for measurement and regulation. Prev Chronic Dis. 2016;13:E07.
109. Cox S, Leigh NJ, Vanderbush TS, Choo E, Goniewicz ML, Dawkins L. An exploration into "do-it-yourself" (DIY) e-liquid mixing: Users' motivations, practices and product laboratory analysis. Addict Behav Rep. 2019;9:100151.
110. Baker RR, Bishop LJ. The pyrolysis of tobacco ingredients. J Anal Appl Pyrolysis. 2004;71(1): 223–311.
111. Aszyk J, Kubica P, Kot-Wasik A, Namieśnik J, Wasik A. Comprehensive determination of flavouring additives and nicotine in e-cigarette refill solutions. Part I: Liquid chromatography–tandem mass spectrometry analysis. J Chromatogr A. 2017;1519:45–54.
112. Aszyk J, Woźniak MK, Kubica P, Kot-Wasik A, Namieśnik J, Wasik A. Comprehensive determination of flavouring additives and nicotine in e-cigarette refill solutions. Part II: Gas-chromatography–mass spectrometry analysis. J Chromatogr A. 2017;1517:156–64.
113. Aszyk J, Kubica P, Woźniak MK, Namieśnik J, Wasik A, Kot-Wasik A. Evaluation of flavour profiles in e-cigarette refill solutions using gas chromatography–tandem mass spectrometry. J Chromatogr A. 2018;1547:86–98.
114. Krüsemann EJZ, Havermans A, Pennings JLA, de Graaf K, Boesveldt S, Talhout R. Comprehensive overview of common e-liquid ingredients and how they can be used to predict an e-liquid's flavour category. Tob Control. 2020:055447.
115. Hua M, Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P. Identification of cytotoxic flavor chemicals in top-selling electronic cigarette refill fluids. Sci Rep. 2019;9(1):2782.
116. Omaiye EE, McWhirter KJ, Luo W, Tierney PA, Pankow JF, Talbot P. High concentrations of flavor chemicals are present in electronic cigarette refill fluids. Sci Rep. 2019;9(1):2468.
117. Salam S, Saliba NA, Shihadeh A, Eissenberg T, El-Hellani A. Flavor–toxicant correlation in e-cigarette: A meta-analysis. Chem Res Toxicol. 2020.
118. El-Hage R, El-Hellani A, Salman R, Talih S, Shihadeh A, Saliba NA. Fate of pyrazines in the flavored liquids of e-cigarettes. Aerosol Sci Technol. 2018;52(4):377–84.
119. Erythropel HC, Jabba SV, DeWinter TM, Mendizabal M, Anastas PT, Jordt SE et al. Formation of flavorant–propylene glycol adducts with novel toxicological properties in chemically unstable e-cigarette liquids. Nicotine Tob Res. 2019;21(9):1248–58.
120. Khlystov A, Samburova V. Flavoring compounds dominate toxic aldehyde production during e-cigarette vaping. Environ Sci Technol. 2016;50(23):13080–5.
121. Lerner CA, Sundar IK, Yao H, Gerloff J, Ossip DJ, McIntosh S et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. PLoS One. 2015;10(2):e0116732.
122. Pankow JF, Kim K, McWhirter KJ, Luo W, Escobedo JO, Strongin RM et al. Benzene formation in electronic cigarettes. PLoS One. 2017;12(3):e0173055.
123. Pankow JF, Kim K, Luo W, McWhirter KJ. Gas/particle partitioning constants of nicotine, selected toxicants, and flavor chemicals in solutions of 50/50 propylene glycol/glycerol as used in electronic cigarettes. Chem Res Toxicol. 2018;31(9):985–90.
124. Kubica P, Wasik A, Kot-Wasik A, Namieśnik J. An evaluation of sucrose as a possible contaminant in e-liquids for electronic cigarettes by hydrophilic interaction liquid chromatography–tandem mass spectrometry. Anal Bioanal Chem. 2014;406(13):3013–8.
125. Miao S, Beach ES, Sommer TJ, Zimmerman JB, Jordt SE. High-intensity sweeteners in alterna-

tive tobacco products. Nicotine Tob Res. 2016;18(11):2169–73.
126. Erythropel HC, Kong G, deWinter TM, O'Malley SS, Jordt SE, Anastas PE et al. Presence of high-intensity sweeteners in popular cigarillos of varying flavor profiles. JAMA. 2018;320(13):1380–3.
127. DeVito EE, Jensen KP, O'Malley SS, Gueorguieva R, Krishnan-Sarin S, Valentine G et al. Modulation of "protective" nicotine perception and use profile by flavorants: Preliminary findings in e-cigarettes. Nicotine Tob Res. 2020;22(5):771–81.
128. Lisko JG, Stanfill SB, Watson CH. Quantitation of ten flavor compounds in unburned tobacco products. Anal Meth. 2014;6(13):4698–704.
129. Chen C, Isabelle LM, Pickworth WB, Pankow JF. Levels of mint and wintergreen flavorants: Smokeless tobacco products vs. confectionery products. Food Chem Toxicol. 2010;48(2):755–63.
130. Stanfill SB, Brown CR, Yan X, Watson CH, Ashley DL. Quantification of flavor-related compounds in the unburned contents of bidi and clove cigarettes. J Agric Food Chem. 2006;54(22):8580–8.
131. Polzin GM, Stanfill SB, Brown CR, Ashley DL, Watson CH. Determination of eugenol, anethole, and coumarin in the mainstream cigarette smoke of Indonesian clove cigarettes. Food Chem Toxicol. 2007;45(10):1948–53.
132. Schubert J, Luch A, Schulz TG. Waterpipe smoking: Analysis of the aroma profile of flavored waterpipe tobaccos. Talanta. 2013;115:665–74.
133. Behar RZ, Luo W, McWhirter KJ, Pankow JF, Talbot P. Analytical and toxicological evaluation of flavor chemicals in electronic cigarette refill fluids. Sci Rep. 2018;8(1):8288.
134. Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P, Stewart JH et al. Flavoring chemicals in e-cigarettes: Diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. Environ Health Perspect. 2016;124(6):733–9.
135. Kreiss K, Gomaa A, Kullman G, Fedan K, Simoes EJ, Enright PL. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. NEJM. 2002;347(5):330–8.
136. Kosmider L, Sobczak A, Prokopowicz A, Kurek J, Zaciera M, Knysak J et al. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. Thorax. 2016;71(4):376–7.
137. El-Hage R, El-Hellani A, Haddad C, Salman R, Talih S, Shihadeh A et al. Toxic emissions resulting from sucralose added to electronic cigarette liquids. Aerosol Sci Technol. 2019;53(10):1197–203.
138. Muthumalage T, Prinz M, Ansah KO, Gerloff J, Sundar IK, Rahman I. Inflammatory and oxidative responses induced by exposure to commonly used e-cigarette flavoring chemicals and flavored e-liquids without nicotine. Front Physiol. 2018;8:1130.
139. Sleiman M, Logue JM, Montesinos VN, Russell ML, Litter MI, Gundel LA et al. Emissions from electronic cigarettes: Key parameters affecting the release of harmful chemicals. Environ Sci Technol. 2016;50(17):9644–51.
140. Wagener TL, Meier E, Tackett AP, Matheny JD, Pechacek TF. A proposed collaboration against Big Tobacco: Common ground between the vaping and public health community in the United States. Nicotine Tob Res. 2015;18(5):730–6.
141. Gartner C. How can we protect youth from putative vaping gateway effects without denying smokers a less harmful option? Addiction. 2018;113(10):1784–5.
142. Kennedy RD, Awopegba A, De León E, Cohen JE. Global approaches to regulating electronic cigarettes. Tob Control. 2017;26(4):440–5.
143. Doan TTT, Tan KW, Dickens BSL, Lean YA, Yang Q, Cook AR. Evaluating smoking control policies in the e-cigarette era: a modelling study. Tob Control. 2019:054951.
144. Country laws regulation e-cigarettes: A policy scan. Baltimore (MD): Johns Hopkins Bloomberg School of Public Health, Institute for Global Control; 2020 (https://www.globaltobaccocontrol.org/e-cigarette/country-laws/view?field_policy_domains_tid%5B%5D=119, accessed 17 February 2020).

145. Villanti AC, Byron MJ, Mercincavage M, Pacek LR. Misperceptions of nicotine and nicotine reduction: The importance of public education to maximize the benefits of a nicotine reduction standard. Nicotine Tob Res. 2019;21(Suppl 1):S88–90.
146. Country laws regulation e-cigarettes: Policy domains: Sale. Baltimore (MD): Johns Hopkins Bloomberg School of Public Health, Institute for Global Tobacco Control; 2020 (https://www.globaltobaccocontrol.org/e-cigarette/sale, accessed 15 June 2020).
147. Ingredients/flavors. Baltimore (MD): Johns Hopkins Bloomberg School of Public Health, Institute for Global Tobacco Control; 2020 (https://www.globaltobaccocontrol.org/category/policy-domains/ingredientsflavors, accessed 15 June 2020).
148. Ollila E. See you in court: Obstacles to enforcing the ban on electronic cigarette flavours and marketing in Finland. Tob Control. 2019:055260.
149. Country laws regulating e-cigarettes: Saudi Arabia. Baltimore (MD): Johns Hopkins Bloomberg School of Public Health, Institute for Global Tobacco Control; 2020 (https://www.globaltobaccocontrol.org/e-cigarette/saudi-arabia, accessed 15 June 2020).
150. Enforcement priorities for electronic nicotine delivery systems (ENDS) and other deemed products on the market without premarket authorization. Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/media/133880/download, accessed 17 February 2020).
151. Tanne JH. FDA bans most flavoured e-cigarettes as lung injury epidemic slows. BMJ. 2020;368:m12.
152. Doucette K. Nova Scotia first province to ban flavoured e-cigarettes and juices. CTV News Atlantic, 5 December 2019 (https://atlantic.ctvnews.ca/nova-scotia-first-province-to-ban-flavoured-e-cigarettes-and-juices-1.4716489, accessed 17 February 2020).
153. Ontario considering ban on flavoured vape products: health minister. The Canadian Press, 5 December 2019 (https://www.cbc.ca/news/canada/toronto/ontario-considering-ban-on-flavoured-vape-products-health-minister-1.5386305, accessed 17 February 2020).
154. Tobacco control laws. Legislation. Washington (DC): Campaign for Tobacco-Free Kids; 2020 (https://www.tobaccocontrollaws.org/legislation, accessed 17 June 2020).
155. Vardavas CI, Bécuwe N, Demjén T, Fernández E, McNeill A, Mons U et al. Study protocol of European Regulatory Science on Tobacco (EUREST-PLUS): Policy implementation to reduce lung disease. Tob Induced Dis. 2018;16(2):2.
156. Zatoński M, Herbeć A, Zatoński W, Przewozniak K, Janik-Koncewicz K, Mons U et al. Characterising smokers of menthol and flavoured cigarettes, their attitudes towards tobacco regulation, and the anticipated impact of the Tobacco Products Directive on their smoking and quitting behaviours: The EUREST-PLUS ITC Europe Surveys. Tob Induced Dis. 2018;16:A4.
157. Sussman S, Garcia R, Cruz TB, Baezconde-Garbanati L, Pentz MA, Unger JB. Consumers' perceptions of vape shops in Southern California: an analysis of online Yelp reviews. Tob Induced Dis. 2014;12(1):22.
158. Erinoso O, Clegg Smith K, Iacobelli M, Saraf S, Welding K, Cohen JE. Global review of tobacco product flavour policies. Tob Control. 2020:055404.
159. Oliveira Da Silva AL, Bialous SA, Albertassi PGD, Arquete DADR, Fernandes AMMS, Moreira JC. The taste of smoke: tobacco industry strategies to prevent the prohibition of additives in tobacco products in Brazil. Tob Control. 2019;28(e2):e92–101.
160. Agaku IT, Odani S, Armour BS, King BA. Adults' favorability toward prohibiting flavors in all tobacco products in the United States. Prev Med. 2019;129:105862.
161. Soule EK, Lopez AA, Guy MC, Cobb CO. Reasons for using flavored liquids among electronic cigarette users: A concept mapping study. Drug Alcohol Depend. 2016;166:168–76.
162. Chaiton MO, Nicolau I, Schwartz R, Cohen JE, Soule E, Zhang B et al. Ban on menthol-flavoured tobacco products predicts cigarette cessation at 1 year: a population cohort study. Tob Con-

trol. 2020;29(3):341–7.
163. Tobacco Control Directive. Addis Ababa: Ethiopian Food, Medicine and Healthcare Administration and Control Authority. 2015 (https://www.tobaccocontrollaws.org/files/live/Ethiopia/Ethiopia%20-%20Tobacco%20Ctrl.%20Dir.%20No.%2028_2015%20-%20national.pdf, accessed 18 February 2020).
164. Palandri F, Breccia M, Bonifacio M, Polverelli N, Elli EM, Benevolo G et al. Life after ruxolitinib: Reasons for discontinuation, impact of disease phase, and outcomes in 218 patients with myelofibrosis. Cancer. 2020;126(6):1243–52.
165. Gorukanti A, Delucchi K, Ling P, Fisher-Travis R, Halpern-Felsher B. Adolescents' attitudes towards e-cigarette ingredients, safety, addictive properties, social norms, and regulation. Prev Med. 2017;94:65–71.
166. Huang LL, Baker HM, Meernik C, Ranney LM, Richardson A, Goldstein AO. Impact of non-menthol flavours in tobacco products on perceptions and use among youth, young adults and adults: a systematic review. Tob Control. 2017;26:709–19.
167. Eissenberg T, Soule E, Shihadeh A. "Open-system" electronic cigarettes cannot be regulated effectively. Tob Control. 2020:055499.
168. Drazen JM, Morrissey S, Campion EW. The dangerous flavors of e-cigarettes. N Engl J Med. 2019;380:679–80.
169. Buckell J, Marti J, Sindelar JL. Should flavours be banned in cigarettes and e-cigarettes? Evidence on adult smokers and recent quitters from a discrete choice experiment. Tob Control. 2018:054165.
170. Keklik S, Gultekin-Karakas D. Anti-tobacco control industry strategies in Turkey. BMC Public Health. 2018;18(1):282.
171. McKee M. Evidence, policy, and e-cigarettes. NEJM. 2016;375(5):e6.
172. Jongenelis MI, Kameron C, Rudaizky D, Pettigrew S. Support for e-cigarette regulations among Australian young adults. BMC Public Health. 2019;19(1):67.
173. Courtemanche CJ, Palmer MK, Pesko MF. Influence of the flavored cigarette ban on adolescent tobacco use. Am J Prev Med. 2017;52(5):e139–46.
174. Yang Y, Lindblom EN, Salloum RG, Ward KD. The impact of a comprehensive tobacco product flavor ban in San Francisco among young adults. Addict Behav Rep. 2020;11:100273.
175. Chaiton M, Schwartz R, Cohen JE, Soule E, Eissenberg T. Association of Ontario's ban on menthol cigarettes with smoking behavior 1 month after implementation. JAMA Intern Med. 2018;178(5):710–1.
176. Lidón-Moyano C, Martín-Sánchez JC, Saliba P, Graffelman J, Martínez-Sánchez JM. Correlation between tobacco control policies, consumption of rolled tobacco and e-cigarettes, and intention to quit conventional tobacco, in Europe. Tob Control. 2017;26(2):149–52.
177. Harrell MB, Loukas A, Jackson CD, Marti CN, Perry CL. Flavored tobacco product use among youth and young adults: What if flavors didn't exist? Tob Regul Sci. 2017;3(2):168–73.
178. Chaiton MO, Nicolau I, Schwartz R, Cohen JE, Soule E, Zhang B et al. Ban on menthol-flavoured tobacco products predicts cigarette cessation at 1 year: a population cohort study. Tob Control. 2019:054841.
179. Chaiton MO, Schwartz R, Tremblay G, Nugent R. Association of flavoured cigar regulations with wholesale tobacco volumes in Canada: an interrupted time series analysis. Tob Control. 2019;28(4):457–61.
180. Farley SM, Johns M. New York City flavoured tobacco product sales ban evaluation. Tob Control. 2017;26(1):78–84.
181. Agaku IT, Odani S, Armour B, Mahoney M, Garrett BE, Loomis BR et al. Differences in price of flavoured and non-flavoured tobacco products sold in the USA, 2011–2016. Tob Control. 2019;29:537–47.

182. Glantz SA, Bareham DW. e-Cigarettes: Use, effects on smoking, risks, and policy implications. Annu Rev Public Health. 2018;39:215–35.
183. Pacek LR, Rass O, Sweitzer MM, Oliver JA, McClernon FJ. Young adult dual combusted cigarette and e-cigarette users' anticipated responses to hypothetical e-cigarette market restrictions. Substance Use Misuse. 2019;54(12):2033–42.
184. Brock B, Carlson SC, Leizinger A, D'Silva J, Matter CM, Schillo BA. A tale of two cities: exploring the retail impact of flavoured tobacco restrictions in the twin cities of Minneapolis and Saint Paul, Minnesota. Tob Control. 2019;28(2):176–80.
185. Glantz SA. Net effect of young adult dual combusted cigarette and e-cigarette users' anticipated responses to hypothetical e-cigarette marketing restrictions. Substance Use Misuse. 2020:55(6):1028–30.
186. Krishnan-Sarin S, Jackson A, Morean M, Kong G, Bold KW, Camenga DR et al. e-Cigarette devices used by high-school youth. Drug Alcohol Depend. 2019;194:395–400.
187. Jankowski M, Krzystanek M, Zejda JE, Majek P, Lubanski J, Lawson JA et al. e-Cigarettes are more addictive than traditional cigarettes – A study in highly educated young people. Int J Environ Res Public Health. 2019;16(13):2279.
188. Pacek LR, Villanti AC, McClernon FJ. Not quite the rule, but no longer the exception: Multiple tobacco product use and implications for treatment, research, and regulation. Nicotine Tob Res. 2020;22(11):2114–7.
189. Harrell PT, Naqvi SMH, Plunk AD, Ji M, Martins SS. Patterns of youth tobacco and polytobacco usage: The shift to alternative tobacco products. Am J Drug Alcohol Abuse. 2017;43(6):694–702.
190. Horn K, Pearson JL, Villanti AC. Polytobacco use and the "customization generation"– New perspectives for tobacco control. J Drug Educ. 2016;46(3-4):51–63.
191. Shiffman S, Sembower MA, Pillitteri JL, Gerlach KK, Gitchell JG. The impact of flavor descriptors on nonsmoking teens' and adult smokers' interest in electronic cigarettes. Nicotine Tob Res. 2015;17(10):1255–62.
192. Tackett AP, Lechner WV, Meier E, Grant DM, Driskill LM, Tahirkheli NN et al. Biochemically verified smoking cessation and vaping beliefs among vape store customers. Addiction. 2015;110(5):868–74.
193. Soule EK, Sakuma K-LK, Palafox S, Pokhrel P, Herzog TA, Thompson N et al. Content analysis of internet marketing strategies used to promote flavored electronic cigarettes. Addict Behav. 2019;91:128–35.
194. Cox E, Barry RA, Glantz S. e-Cigarette policymaking by local and state governments: 2009–2014. Milbank Q. 2016;94(3):520–96.
195. Printz C. US Food and Drug Administration considers comments on proposed nicotine product regulations. Cancer. 2018;124(20):3959–60.
196. Printz C. FDA launches public education effort to prevent youth e-cigarette use. Cancer. 2018;124(7):1313–4.
197. Jenssen BP, Walley SC. e-Cigarettes and similar devices. Pediatrics. 2019;143(2):e20183652.
198. Jaffe S. Will Trump snuff out e-cigarettes? Lancet. 2019;394(10213):1977–8.
199. Carpenter CM, Wayne GF, Pauly JL, Koh HK, Connolly GN. New cigarette brands with flavors that appeal to youth: Tobacco marketing strategies. Health Affairs. 2005;24(6):1601–10.
200. Green SH, Bayer R, Fairchild AL. Evidence, policy, and e-cigarettes – Will England reframe the debate? NEJM. 2016;374(14):1301–3.
201. McDaniel PA, Smith EA, Malone RE. The tobacco endgame: a qualitative review and synthesis. Tob Control. 2016;25(5):594–604.
202. Malone RE. Tobacco endgames: what they are and are not, issues for tobacco control strategic planning and a possible US scenario. Tob Control. 2013;22(Suppl 1):i42–4.
203. Balaji S. Electronic cigarettes and its ban in India. Indian J Dental Res. 2019;30:651.

204. Guliani H, Gamtessa S, Çule M. Factors affecting tobacco smoking in Ethiopia: evidence from the demographic and health surveys. BMC Public Health. 2019;19(1):938.
205. Hall W, Gartner C, Forlini C. Nuances in the ethical regulation of electronic nicotine delivery systems. Addiction. 2015;110(7):1074–5.
206. Beaglehole R, Bonita R, Yach D, Mackay J, Reddy KS. A tobacco-free world: a call to action to phase out the sale of tobacco products by 2040. Lancet. 2015;385(9972):1011–8.

10. Global marketing and promotion of novel and emerging nicotine and tobacco products and their impacts

Meagan Robichaud, Caleb Clawson and Ryan David Kennedy, Institute for Global Tobacco Control, Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore (MD), USA

Contents

Abstract

Global tobacco use has decreased in the past few decades due, in large part, to successful work by the public health community to discourage use through evidence-based tobacco control strategies. Recently, nicotine and tobacco manufacturers have developed novel products, including electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENNDS) and heated tobacco products (HTPs). The introduction of these products is complicating global progress in tobacco control. In many markets, these devices are particularly popular among adolescents and young adults. Many users and non-users perceive these devices to be harmless, despite evidence of the potential harm of tobacco and nicotine use. The marketing of these products

leads to experimentation, including by adolescents and young adults who have never used tobacco; robust, worldwide surveillance of product advertising, marketing, promotion and use is therefore essential. Continuous surveillance of ENDS, ENNDS and HTP marketing, including advertising in traditional media, direct-to-consumer marketing, point-of-sale marketing, online marketing (including social media), cross-border marketing and sponsorship, may prove to be a valuable comprehensive strategy to prevent the use of novel and emerging nicotine and tobacco products from undermining work to reduce the global public health burden of tobacco.

10.1 Background

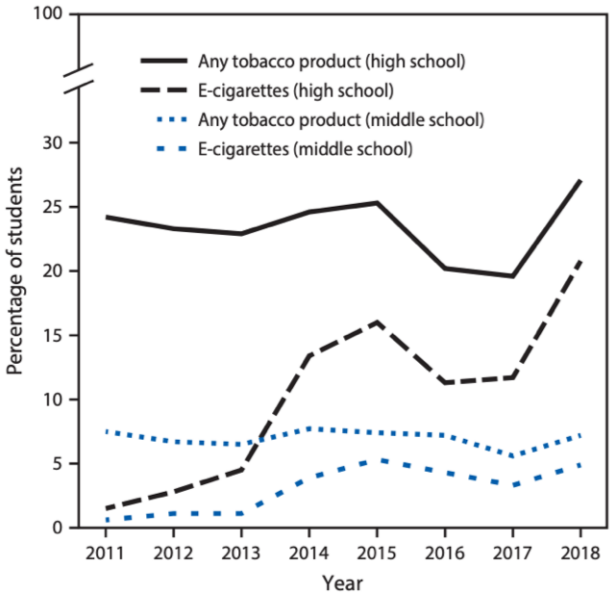
Progress has been made in reducing the public health burden of tobacco use in many countries, due in large part to decreasing use. The global prevalence of tobacco use among people aged ≥ 15 years fell from 33.3% in 2000 to 24.9% in 2015 and is projected to fall to 20.9% by 2025 *(1)*. Surveillance of tobacco use indicates a significant turning-point in 2018, the first year in which a decrease in tobacco use was observed among males, who accounted for approximately 81% of global tobacco users in 2015 *(1)*. An estimated 1.05 billion men used tobacco products in 2000, and this number increased by 22 million between 2000 and 2005, 13 million between 2005 and 2010 and 7 million between 2010 and 2015. The number of male tobacco users in 2018 was 1.093 billion, and this number is expected to drop by 2 million by 2020 and by another 4 million by 2025 *(1)*.

In 2018, 23.6% of the global population aged ≥ 15 years used tobacco, 18.9% used combusted tobacco, and 16.1% used cigarettes *(1)*. Thus, approximately 80% of global tobacco users in 2018 used combusted products. Globally, more than 5.3 trillion cigarettes were sold in 2018 *(2)*. While global cigarette sales are expected to fall by approximately 7% by 2023 *(2)*, the emergence of novel nicotine and tobacco products, such as ENDS, ENNDS and HTPs, has raised concern. It is estimated that 1.2% of adults globally were current ENDS users in 2018, with significant variation in ENDS use by country, WHO region and demographic group *(3)*. The use of these products by children and young adults, including some who had never used tobacco previously, is a particular concern. There is evidence that ENDS use is associated with later use of combusted tobacco, raising concern that both ENDS and HTPs may contribute to re-"normalizing" smoking after decades of work to discourage tobacco use *(4,5)*.

In the USA, increasing use of ENDS by children and young adults contributed to the first increase in overall tobacco use measured in recent decades *(6)* (Fig. 10.1). Results from the 2019 National Youth Tobacco Survey show that the rate of ENDS use among young people has continued to increase dramatically *(7)*. The percentage of high-school students in the USA who currently use e-cigarettes increased from 20.8% in 2018 to 27.5% in 2019, and

the rate among middle-school students increased from 4.9% in 2018 to 10.5% in 2019 *(6,7)*. These increases in ENDS use among the young have motivated federal and state policy-makers to look more closely at strategies to reduce the appeal of these products *(8)*. The results of the 2020 survey had not been published at the time of writing.

Fig. 10.1. Proportions of middle- and high-school students in the USA who currently use e-cigarettes and any tobacco product, 2011–2018



Source: reference *6*.

Policy-makers around the world are considering and implementing various policies to include ENDS and HTPs in existing tobacco prevention frameworks or to regulate or ban these products specifically. The evolving market for such products and the popularity of ENDS among children and young adults lends urgency to sharing information and evidence on the effects of such policies. A substantial body of evidence links marketing of tobacco and nicotine products to greater susceptibility to use of these products and increased rates of product use among both young people and adults. An increased focus on the role of marketing in promoting nicotine and tobacco use is therefore vital for ensuring effective public health measures to reduce tobacco use.

This report extends a background paper prepared for the third meeting of the Global Tobacco Regulators Forum,[1] at which ENDS use and marketing

1 Kennedy RD, Clawson C. Global landscape of electronic nicotine delivery system (ENDS) marketing and promotion. Paper prepared for the Third Meeting of the Global Tobacco Regulators Forum, Geneva, 11–12 September 2019 (unpublished).

was discussed, to include marketing and promotion of ENNDS and HTPs. This report also makes a distinction between ENDS/ENNDS and HTPs with regard to marketing strategies. We address the decisions of the seventh and eighth sessions of the Conference of the Parties to the WHO Framework Convention on Tobacco Control (FCTC/COP7 and FCTC/COP8) to continue monitoring and reporting on market developments, including advertising and promotion, for ENDS and ENNDS as well as HTPs *(9,10)*.

10.2 Electronic nicotine delivery systems and electronic non-nicotine delivery systems

10.2.1 Introduction

ENDS and ENNDS heat a solution (e-liquid) to create an aerosol that frequently contains flavour additives. e-Liquid usually consists of propylene glycol and/or glycerine. ENDS products contain nicotine, whereas ENNDS products do not. While electronic cigarettes are the most common types of these products, ENDS and ENNDS also include electronic hookahs and electronic shishas *(11,12)*. The WHO FCTC defines tobacco products as "products entirely or partly made of leaf tobacco as raw material, which are manufactured to be used for smoking, sucking, chewing or snuffing" *(13)*; therefore, according to the WHO FCTC, ENDS and ENNDS are not tobacco products because they do not contain tobacco. They do not involve combustion or pyrolysis and therefore do not produce "smoke". The concentrations of most toxicants present in ENDS and ENNDS aerosols are much lower than in tobacco smoke; however, ENDS and ENNDS solutions and aerosols contain potentially harmful toxic substances *(14)*.

In order to understand the patterns of use, the diverse array of products on the market and the nonstandard nomenclature of ENDS and ENNDS devices must be identified *(4)*. Many devices resemble traditional tobacco products, such as cigarettes, pipes, hookahs and cigars, while others resemble non-tobacco products, including pens and USB flash drives. Many terms are used to refer to ENDS and ENNDS, including "e-cigarettes", "e-cigs", "cigalikes", "e-hookahs", "mods", "vape pens", "vapes", "shisha pens" and "tank systems". In this report, the terms "ENDS" and "ENNDS" are used to refer to a heterogeneous class of products in a rapidly evolving market.

ENDS and ENNDS have been widely marketed and sold in recent years by the major transnational tobacco companies, with soaring uptake by adolescents in Europe and North America, to levels high enough to alarm public health experts, parents and elected officials *(15)*. According to Euromonitor market research published in 2017, the consumption of "e-vapour" products grew by 818% between 2011 and 2016 *(16)*. Between 2011 and 2014, expenditure for marketing ENDS products increased by nearly 10 times in some markets (e.g.

from US$12 million to > US$ 125 million in the USA for e-cigarettes), stimulating a sharp rise in ENDS use in many countries *(17,18)*. In this section, we focus on major ENDS markets, products and strategies, the prevalence of ENDS use globally, regulation of marketing, monitoring and surveillance of marketing and measures to control advertising, promotion and sponsorship of ENDS.

10.2.2 Markets, products and strategies used in marketing ENDS and ENNDS

During the past two decades, the global market for combusted cigarettes has seen consolidation of manufacturers into powerful transnational tobacco companies. In 2001, the market share of combusted cigarette sales of the five largest transnational tobacco companies, Philip Morris, British American Tobacco (BAT), Japan Tobacco International (JTI), Reemsta and Altadis, was 43% *(19)*. By 2017, the market share of the five largest companies, China National Tobacco Corporation, Philip Morris International (PMI), BAT, Japan Tobacco, Inc. (parent company of JTI) and Imperial Tobacco Group had grown to 81% *(2)*. PMI, BAT, Japan Tobacco and Imperial Tobacco held four of the top six market positions for combusted cigarette retail volume in 2019 *(2)*, in addition to offering a variety of ENDS products. New entrants to the ENDS market, such as JUUL Labs, have received significant investment from the transnational tobacco companies in order to maintain their influence and reach into the global market *(20)*. Significant investment in ENDS innovation by these companies may further complicate efforts to discourage tobacco and nicotine use and to achieve public health goals.

Market players, products and market share

JUUL Labs Inc. (35% owned by Altria). JUUL currently occupies the largest (26.2%) share of the world market for ENDS with its popular nicotine salt variant and the small, ergonomic design of their devices *(16)*. In 2019, JUUL announced plans to launch its product line in India and the Philippines *(21)*; however, the Indian Government banned the production, manufacture, import, export, sale and distribution of ENDS because of concerns about trends in use among young people *(22)*. JUUL is currently testing an app that would allow users to track their nicotine consumption and allow the company to track second-hand sales of newly manufactured products *(23)*. In October 2018, JUUL Labs bought V2 and the parent company VMR Products LLC for US$ 75 million *(24)*, and V2 Cigs closed permanently on 1 November 2018. JUUL Labs currently markets its products in 20 countries *(25)*.

Altria. In December 2018, Altria, the parent company of Philip Morris USA, announced its decision to refocus its work on innovative products, including discontinuation of the production and distribution of all Nu Mark ENDS products, such as MarkTen and Green Smoke products, which had a significant

market share in Canadian and US markets in recent years *(26)*. Additionally, on 20 December 2018, Altria purchased shares of non-voting convertible common stock of JUUL Labs for US$ 12.8 billion through a wholly owned subsidiary, representing a 35% economic interest in JUUL. Altria has since generally agreed not to compete with JUUL in ENDS marketing for at least 6 years *(20)*.

PMI. The PMI website for its "smoke-free" product line notes that the company is "exploring new e-vapour products" and states that

> We are also developing products inspired by technology that we acquired in 2011…. Our scientists continue to develop this technology to replicate the feel and ritual of smoking without tobacco and without burning. One of these products under development is called STEEM…[which] unlike an e-cigarette... generates a nicotine-containing vapor in the form of a nicotine salt *(27)*.

Euromonitor reports sales of other PMI ENDS brands, including Solaris in Spain and Nicocig, Vivid Vapour and MESH in the United Kingdom *(28)*.

JTI. JTI's annual report for 2018 states that "RRP [Reduced Risk Products] is one of the key pillars of our growth strategy in the tobacco business, and we will prioritize allocation of resources into the category" *(29)*. Logic is the company's flagship e-cigarette brand, with products available in 26 countries, including the United Kingdom and the USA *(30)*. On 17 September 2018, JTI launched Logic Compact, a pocket-sized device, in the United Kingdom. Its design bears a striking resemblance to that of JUUL, an ENDS device that has taken a dramatic share of the ENDS market in recent years. Logic Compact has since become available in 25 countries *(29)*. JTI also produces "E-lites", another ENDS product, which is available in Bulgaria and Germany.

BAT. BAT claims that it "is at the forefront of the development and sale of a whole range of potentially reduced-risk products that provide much of the enjoyment of smoking without burning tobacco" *(32)*. Its growing portfolio of what they claim as "potentially reduced-risk products" includes a range of ENDS products. BAT launched their flagship brand Vype in 2013 *(33)*. In 2017, BAT acquired Reynolds Vapor Co., which had launched Vuse in 2013. While BAT has since acquired a number of ENDS brands, including Ten Motives (United Kingdom), Chic (Poland) and VIP (United Kingdom), the company announced on 28 November 2019 that it was migrating its ENDS brands, when possible, to Vuse during 2020 in order to simplify its "new category product portfolio", the other new category products being Velo for "modern oral products" and glo for HTPs *(34)*. By the end of December 2019, BAT's ENDS products were available in 27 markets *(33)*.

Reynolds American Inc. (now owned by BAT). Vuse was the number one e-cigarette product sold in convenience shops in the USA in 2016 *(35)*. The company noted that "The future success of Vuse and other RJR Vapor e-cigarette

offerings, including Vuse Vibe, will depend on the ability to innovate in an evolving category of alternative tobacco products". Vuse products are sold in the USA.

Imperial Brands. The company stated in its annual report in 2018 that, "Through our growing portfolio of Next Generation Products we are providing adult smokers with a range of less harmful alternatives to cigarettes, with a particular focus on the vapour category". The company has prioritized "building a presence in the specialist vape channel and online" *(36)*. Its flagship e-cigarette brand is blu, and it launched myblu and myblu Intense in 2018 *(36)* as the brand's closed-system e-cigarettes, with prefilled pods. myblu Intense is a nicotine salt variant, which the company claims "more closely replicates the experience and satisfaction of smoking a cigarette" *(37)*. Both myblu and myblu Intense have nicotine-free variants *(36,38)*. The blu brand also includes an open-system product, blu pro, and Imperial Brands launched another open-system product, blu ACE, in 2018, which has since been discontinued *(36,39,40)*. At the end of 2019, blu products were available in 16 markets *(38)*.

Marketing strategies to promote sales of ENDS and ENNDS

Nicotine and tobacco companies use a wide range of strategies to market ENDS and ENNDS. These marketing strategies have demonstrated a trend in aggressive marketing to youth, with teenagers increasingly exposed to ENDS advertising from a variety of sources *(41–43)*. Additionally, e-liquids containing nicotine are marketed in thousands of flavours, including confectionery and fruit flavours that appeal to young people. Unless marketing of ENDS and ENNDS is regulated, their use could re-normalize nicotine and tobacco use *(44)*. The following general marketing strategies are used for ENDS and ENNDS.

- Advertisement *(45)*
  - online, including social media (e.g. Facebook, Instagram, Twitter) *(46)* and use of social media influencers
  - television, cinemas *(42)*
  - radio *(42)*
  - print media (e.g. newspapers, magazines) *(47)*
  - billboards and posters *(47)*
  - displays and advertisements at points of sale *(48)*
- Sponsorship
  - sports, cultural and artistic events *(49,50)*
  - events, including school programmes *(51)*
- Youth-oriented marketing tactics

    - use of cartoon characters *(52)*
    - flavours, especially confectionery, fruit and other sweet flavours *(53)*
    - marketing near schools *(54)*
    - targeting schools and youth camps *(55)*
    - marketing with popular online or mobile games (e.g. Pokémon Go) *(56)*
- Glamourizing product use
    - endorsement by celebrities *(45)*
    - promotion at "glamorous" events, e.g. free handouts at New York Fashion Week *(57)*
- Pricing strategies
    - coupons, discounts, discount codes, rebates *(58)*
    - "multi-buy", e.g. buy one, get one free *(59)*
    - free samples *(60)*
- Product innovation *(61)*
- Product design
    - ease of concealment (especially for young people) *(62)*
    - customization with colours and patterns *(63)*
    - sleek, modern design *(64)*
- Sexualization of product use *(49,65)*
- Claims of health or harm reduction *(66–68)*
- ENDS-branded merchandise *(69)*
- Funding of front groups, including *(70)*:
    - think tanks (e.g. European Policy Information Center)
    - public relations firms (e.g. Blue Star Strategies)
- Lobbying and hiring others to lobby on behalf of the industry *(71)*
- Corporate social responsibility and philanthropy to boost the image of the industry *(72)*

Common strategies

Of the six major market players that do not produce only ENDS and ENNDS products, five intend to extend innovation and/or production of their product ventures. The abrupt, substantial surge in ENDS use in some jurisdictions has newly motivated development of novel nicotine and tobacco products, and many recently introduced products that offer higher nicotine concentrations than previous generations of ENDS. For example, JUUL and NJOY offer

products containing 5% and 6% nicotine, respectively*(73)*; and, in 2018, JUUL's manufacturer claimed that one 5% nicotine JUUL pod contained approximately the same amount of nicotine as 20 cigarettes *(74)*. In ENDS products available in 2013–2015, the highest concentration of nicotine was 4.9% *(73)*. Furthermore, as the market moves towards nicotine salt variants, popularized by JUUL, many can deliver high concentrations of nicotine more effectively than previous generations of these products *(75)*. These include PMI's STEEM, JTI's Logic Compact, Imperial Brand's Myblu and less influential brands such as Shenzhen IVPS Technology's Smok Nord *(64)*. The products being developed by the major market players are exclusively closed systems, meaning that users are not intended to refill their devices with e-liquid but must instead purchase refills in the form of pods or capsules. Former smokers and those attempting to quit smoking combusted cigarettes have shown a preference for open systems *(76)*, although this may change with the rising popularity of closed systems with nicotine salts *(77)*. The tobacco industry is purchasing stock and/or majority shares in competitive companies, as seen in the cases of Altria, JUUL Labs and VMR. Expansion into new markets has been a priority, and Imperial Brands, JTI and JUUL have explicitly announced geographical development.

e-Cigarette companies also use indirect marketing tactics to reach consumers, including the young. This is often achieved through front groups, which are defined as organizations that claim to be independent but in reality "serve [an]other party or interest whose sponsorship is hidden or rarely mentioned" *(70)*. Notable front groups include the Foundation for a Smoke-Free World, which has been funded solely by PMI since 2019, and the Freedom Organisation for the Right to Enjoy Smoking Tobacco (Forest), which has fought against revision of the European Union Tobacco Products Directive that would require licensing of e-cigarettes containing nicotine above a certain level *(78,79)*. Front groups also include think tanks, public relations firms and lobbying groups *(70)*.

e-Cigarette manufacturers also use corporate social responsibility strategies to boost their public image and to promote their brands. Corporate social responsibility "refers to voluntary corporate action that claims to act in the public interest by prioritising social goals" *(72)*. The companies frequently use philanthropy as a partial demonstration of their corporate social responsibility, including charitable donations to youth-oriented organizations and to causes relevant to other groups that are disproportionately impacted by tobacco use, including LGBTQ+ communities and racial and ethnic minorities *(72,80)*. For example, in 2018, Altria made charitable contributions to the National Museum of African American History and Culture and to the Boys and Girls Clubs of America *(80)*.

10.2.3 Global use of ENDS and prevalence of use

Sales of ENDS worldwide are increasing rapidly. The global market reached US$ 2.76 billion in sales in 2014 *(81)*, US$ 9.39 billion in 2017 and is expected to reach up to US$ 58.32 billion by 2026 *(82)*.

In 2018, approximately one third of the world's men (32.4%) and 5.5% of women were smokers *(1)*. It is estimated that, in 2018, 1.2% of adults worldwide used ENDS, comprising 1.7% of men and 0.7% of women *(3)*. Use of combusted tobacco and ENDS varies by WHO region. The prevalence of smoking is highest in the European Region (26.2%), and ENDS use is highest in the Western Pacific Region (2.4%) (Table 10.1).

Table 10.1. Prevalence of smoking of combusted tobacco and of ENDS use by WHO region, 2018

Region and country	Smoking (%)			ENDS use (%)		
	All	Males	Females	All	Males	Females
African Region (3 of 46 countries represented)						
Algeria	18.4	33.5	3.2	3.8	7.0	0.6
Nigeria	10.8	16.1	5.4	0.0	0.0	0.0
South Africa	18.9	31.1	7.3	0.4	0.6	0.2
Americas Region (9 of 35 countries represented)						
Canada	14.8	17.1	12.6	3.5	3.7	3.3
Chile	31.8	36.7	27.2	0.5	0.5	0.5
Colombia	11.6	17.0	6.6	0.1	0.1	0.0
Costa Rica	12.5	17.0	8.0	0.2	0.3	0.2
Dominican Republic	9.3	10.4	8.3	0.1	0.1	0.1
Ecuador	15.2	21.8	8.7	0.1	0.1	0.1
Guatemala	6.8	11.4	2.5	0.2	0.3	0.2
Peru	11.4	19.3	3.8	0.4	0.4	0.3
USA	13.7	15.5	11.9	3.8	4.1	3.5
Eastern Mediterranean Region (5 of 22 countries represented)						
Egypt	30.6	54.9	5.3	0.7	1.3	0.1
Morocco	20.3	37.6	3.7	0.7	1.4	0.0
Pakistan	21.0	34.6	6.9	0.0	0.0	0.0
Saudi Arabia	29.8	39.2	15.5	0.3	0.4	0.3
Tunisia	32.1	54.4	11.0	0.6	1.1	0.1
European Region (38 of 53 countries represented)						
Austria	26.2	28.1	24.4	1.2	1.3	1.1
Azerbaijan	26.0	33.1	19.3	0.3	0.5	0.1
Belarus	24.8	46.2	7.0	2.1	3.3	1.1
Belgium	22.0	23.0	21.0	4.4	4.8	4.0

Region and country	Smoking (%)			ENDS use (%)		
	All	Males	Females	All	Males	Females
Bosnia and Herzegovina	38.2	44.5	32.3	1.3	1.3	1.3
Bulgaria	32.2	36.6	28.1	1.1	1.9	0.4
Croatia	27.5	35.5	20.3	1.2	1.6	0.8
Czechia	33.4	37.0	30.0	5.7	6.9	4.5
Denmark	21.1	21.0	21.1	4.8	4.8	4.8
Estonia	23.4	31.0	17.0	1.6	2.2	1.1
Finland	12.2	12.8	11.6	2.0	2.8	1.3
France	26.2	30.5	22.3	4.3	5.0	3.6
Georgia	28.5	54.1	6.2	1.4	2.9	0.1
Germany	21.4	24.0	19.0	5.3	6.6	4.1
Greece	42.1	52.5	32.6	2.4	3.2	1.7
Hungary	28.6	34.5	23.4	2.1	2.9	1.3
Ireland	19.5	19.8	19.3	5.4	5.4	5.3
Israel	23.5	31.3	16.0	0.4	0.5	0.3
Italy	21.1	25.5	17.0	1.5	1.8	1.3
Kazakhstan	30.3	42.0	20.0	4.0	8.2	0.3
Latvia	27.0	42.5	14.4	1.1	2.0	0.4
Lithuania	26.3	37.4	17.1	1.6	1.9	1.3
Netherlands	22.5	25.7	19.3	3.6	4.0	3.3
North Macedonia	31.0	33.0	29.0	1.0	1.1	0.9
Norway	11.0	11.5	10.5	1.5	1.5	1.5
Poland	33.1	34.1	32.2	5.4	7.7	3.3
Portugal	19.1	26.4	12.8	2.2	3.2	1.3
Romania	30.2	39.8	21.2	3.3	5.0	1.8
Russian Federation	33.3	44.4	24.2	1.5	2.2	1.0
Serbia	32.3	35.3	29.5	0.5	0.6	0.5
Slovakia	31.4	45.5	18.3	1.9	2.2	1.6
Slovenia	23.4	26.1	20.9	0.9	1.5	0.2
Spain	25.5	28.7	22.4	1.7	1.8	1.7
Sweden	10.1	11.0	9.2	1.1	1.2	1.0
Switzerland	25.0	28.5	21.6	1.8	2.5	1.2
Ukraine	28.8	36.3	22.7	2.0	2.5	1.6
United Kingdom	14.7	16.5	13.0	6.1	7.7	4.6
Uzbekistan	11.3	19.9	3.1	0.5	0.2	0.7
South-East Asia Region (2 of 11 countries represented)						
India	3.8	6.9	0.6	0.1	0.1	0.0
Indonesia	36.4	67.9	5.0	0.5	1.1	0.0

Region and country	Smoking (%)			ENDS use (%)		
	All	Males	Females	All	Males	Females
Western Pacific Region (7 of 27 countries represented)						
Australia	13.7	15.5	11.9	0.8	1.0	0.6
China	27.8	51.9	2.8	0.2	0.5	0.0
Japan	18.2	29.0	8.1	0.2	0.3	0.1
Malaysia	21.5	40.1	1.5	2.7	4.3	1.0
New Zealand	14.9	16.2	13.6	4.1	2.0	6.1
Philippines	23.3	42.0	4.8	0.3	0.6	0.1
Republic of Korea	22.0	36.7	7.5	4.1	7.1	1.1

Source: reference *3*.

The total prevalence of ENDS use ranged from 0.0% to 6.1% for both sexes, 0.0% to 8.2% for men and 0.0% to 6.1% for women. National data available for 2018 showed that ENDS use tended to be higher in countries in the European Region, in Canada and the USA in the Americas, in New Zealand and the Republic of Korea in the Western Pacific and in Algeria in the African Region. These numbers are consistent with earlier published data *(83–85)*. Nigeria and Pakistan reported no use of ENDS. Consistent with trends in combusted tobacco use, ENDS use rates were typically higher among men than women. ENDS use by WHO region is listed below.

- *African Region*. Information on the prevalence of ENDS use was available for only three of the 46 countries in the Region: Algeria, Nigeria and South Africa. ENDS use among males in Algeria was notably high, at 7.0%.
- *Region of the Americas*. ENDS data were available for nine countries. The highest reported prevalence of ENDS use was in the USA (3.8%), followed by Canada (3.5%). The rates in the other countries in the Region were < 1.0%. The rates were similar by gender, except in Canada and the USA.
- *Eastern Mediterranean Region*. The prevalence of ENDS use was available for Egypt, Morocco, Pakistan, Saudi Arabia and Tunisia. Although smoking rates remain high in several countries in the Region, ENDS have yet to penetrate the market in any significant way, remaining at < 1% in all countries for which data were available.
- *European Region*. The prevalence of ENDS use was available for 38 countries. The highest total prevalence was in the United Kingdom, at 6.1%. The rates were ≥ 5.0% in Czechia, Ireland and Poland and relatively high among males in Kazakhstan (8.2%), France (5.0%), Germany (6.6%) and Romania (5.0%). Consistent with the demographics of smoking, the prevalence of ENDS use in the Nordic states

was similar for men and women. Interestingly, the prevalence in Uzbekistan was higher among women (0.7%) than among men (0.2%)

- *South-East Asia Region*. Data on ENDS use were available only for India and Indonesia. While both countries report high smoking rates, particularly among males, ENDS use is almost non-existent.
- *Western Pacific Region*. ENDS data were available for seven countries. Use is particularly high among men in the Republic of Korea (7.1%). In New Zealand, men are more likely to smoke than women, but women are more likely to use ENDS (6.1%) than men (2.0%).

While these data show the prevalence of ENDS use among adults, in several countries, more young adults aged 18–24 years than adults aged ≥ 25 years have ever or currently use ENDS, and the rate has been increasing steadily in recent years *(84–86)*. The prevalence of ever use of ENDS was 23.5% among adults aged 18–24 years in the USA in 2016 *(875)*, 28% among adults in this age group in the European Union and 29% among adults aged 20–24 years in Canada in 2017 *(84–86)*. Data for 2017–2018 suggest that the introduction into the Canadian and US markets of new-generation products with refillable or disposable pods (pod mods) containing nicotine salt has contributed to recent, more dramatic increases in use of ENDS in the previous 30 days among high-school students (28% in 2019) *(8,88)*. Canada and the USA also reported greater increases in the prevalence of ENDS use by young people between 2017 and 2019 than in the United Kingdom (England), where more comprehensive policies regulate access to and distribution of ENDS *(75)*.

10.2.4 Trends in advertising, promotion and sponsorship of ENDS products

How ENDS manufacturers advertise in markets through social media

Social media platforms represent an important channel for advertising ENDS, with sites that can promote these products worldwide. A scan of ENDS advertisements and promotions was conducted on Instagram and Twitter, the search terms consisting of hashtags with either the brand names of specific ENDS (e.g. #JUUL) or generic terms associated with ENDS use (e.g. #vape), accompanied by the name of a WHO Member State (e.g. #Belarus). As Instagram's search function allows only one search term, the ENDS brand name or search term was combined with the name of a WHO Member State (e.g. #VapeCanada), whereas Twitter's search function accommodated multiple search terms and Boolean operators (e.g. #JUUL AND #Canada).

The survey showed that ENDS are marketed on the social media platforms Twitter and Instagram in at least 149 (77%) WHO Member States. A content analysis of up to six advertisements (three Twitter, three Instagram) per country revealed several common advertising strategies used in the six WHO regions (Table 10.2).

Table 10.2. Common ENDS advertising strategies by WHO region, 2019

WHO region	No. of countries	Data available No. (%)	No. of advertisements	Health warning No. (%)	Nicotine lexical No. (%)	Flavour lexical No. (%)	Design feature lexical No. (%)	Image device No. (%)	Image of e-liquid No. (%)
Africa	46	26 (57)	84	1 (1)	24 (29)	63 (75)	15 (18)	22 (26)	61 (73)
Americas	35	26 (74)	135	3 (2)	14 (10)	55 (41)	72 (53)	86 (64)	59 (44)
South-East Asia	11	9 (82)	42	0	3 (7)	19 (45)	21 (50)	25 (60)	19 (45)
European	53	53 (100)	267	5 (2)	44 (16)	141 (53)	117 (44)	142 (53)	148 (55)
Eastern Mediterranean	22	21 (95)	102	1 (1)	17 (16)	50 (49)	47 (46)	51 (50)	50 (49)
Western Pacific	27	14 (52)	70	3 (4)	11 (16)	34 (49)	36 (51)	42 (60)	35 (50)
All	194	149 (77)	700	13 (2)	113 (16)	362 (52)	308 (44)	368 (53)	372 (53)

Very few of the advertisements identified in this search included a health warning. The advertisements commonly had images of devices or e-liquids and lexical content describing flavours or other design features.

Impact of COVID-19 on ENDS marketing strategies

During the COVID-19 pandemic, several ENDS product manufacturers, retailers and users have aligned their marketing and promotion strategies on social media with messages relevant to the pandemic and containment strategies. Several themes are found in ENDS marketing on Instagram and Twitter.

Coping with boredom and isolation. For example, one Twitter ad by an e-liquid manufacturer stated "Covid lockdowns got you feeling blue? We've got the Antidote. Blue Raspberry and Mango ice in perfect sync – for your dipper, tank or favorite pod system."

Online shopping. For example, one Instagram post from Vuse Middle East states, "Order online with Instashop! We're all hangin' around these days, so while you're staying in, your Vuse order will come right to you."

Working from home. Retailers and manufacturers have used this theme to encourage users to purchase their products online when they are busy "working from home". ENDS users have posted photos of their ENDS products in their home offices.

Obtaining protective equipment and supplies. Some manufacturers have posted advertisements offering protective equipment and supplies, such as masks and hand sanitizer. For example, one Instagram advertisement for the e-cigarette brand MOTI America states, "Compared with cigarettes, #vapes are 95% less harmful to the #lungs. During #Covid_19 pandemic, we recommend using

MOTI to alternate cigarettes for your #health. [What can you get?] 2 pieces of Disposable #SurgicalMasks" *(66)*.

Staying healthy (especially promoting lung health). The above example from MOTI America also shows that brands have also capitalized on a harm reduction theme during the COVID-19 pandemic *(66)*.

Supporting businesses affected by the pandemic. Manufacturers and retailers have posted messages of support for businesses affected by the pandemic in their advertisements. For example, INNOPHASE, a manufacturer and exporter of ENDS products, stated, "Currently, we have a great promotion on the VPOD, to help our partners in these difficult COVID-19 times" in an advertisement on Twitter.

10.2.5 Measures to control advertising, promotion and sponsorship of ENDS products

Many countries currently restrict advertising, promotion or sponsorship of ENDS and ENNDS; however, the regulatory strategies vary significantly. For example, eight countries (Costa Rica, Ecuador, Georgia, Japan, Mexico, New Zealand, Palau and Republic of Moldova) regulate marketing of ENDS products but not ENNDS products, in that the advertising restrictions apply only to "e-cigarettes that contain nicotine or that are regulated as medicines" *(89)*. In European Union Member States, bans on distinctive branding elements are intended to reduce advertising potential, and some have further reduced that potential by requiring out-of-sight retail sales and reduced branding opportunities on packaging. In the USA, the Food and Drug Administration passed several regulations in 2016 on the marketing and promotion of e-cigarettes, including prohibiting free sampling of e-liquid solutions inside shops *(90)*. The Food and Drug Administration also passed measures to prohibit false or misleading advertising (e.g. use of descriptors such as "light", "mild" or "low") and require manufacturers to submit applications for authorization as "modified risk tobacco products", with a full scientific review of the impact of marketing of the product on population health before it can be marketed as modified risk *(90,91)*.

Several countries have focused specifically on marketing to young people. As increasing rates of use among the young are of particular concern, the United States Food and Drug Administration issued a policy in January 2020 that prioritizes enforcement of regulations on flavoured "cartridge-based e-cigarettes" (excluding menthol and tobacco flavours) in an attempt to limit the access of young people to certain flavoured ENDS products *(92)*. Canada has banned all marketing, packaging elements that indicate flavour and design attributes that would appeal to young people *(93,94)*.

Regulation of marketing towards the young, and indeed marketing of any kind, is important in light of evidence linking exposure to tobacco and nicotine

product marketing, advertising and promotion with susceptibility to use of ENDS and ENNDS. It has been noted that social media influencers have been used to promote ENDS. A minimum age is required to open an account on most social media platforms, and several platforms do not accept or run advertisements for tobacco products; however, it is unclear if these policies limit social media influencers from promoting ENDS products. Discussions in the United Kingdom have identified possible solutions for regulating social media influencers, including a minimum number of followers in order to be defined as an "influencer" and requiring online influencers to disclose payment for endorsing any product.

Increased exposure to tobacco advertising and access to price promotions has been associated with increased susceptibility to use of both ENDS and combusted products among adults *(95)*, and increased exposure to ENDS advertisements specifically is associated with greater susceptibility to use and an increased likelihood of current use of ENDS among both adults and young people *(96,97)*. Receptivity to ENDS advertising has also been shown to increase with exposure *(96)*.

Certain aspects of ENDS advertising appear to be associated with an increased likelihood of reporting interest in using ENDS and later ENDS use by young people. ENDS advertising with a social rather than a health message and advertising seen on social media platforms were associated with increased interest in using ENDS and increased ENDS use, respectively *(98,99)*. Endorsements by inspirational figures or celebrities in advertisements are also associated with an increased likelihood of use *(100)*. The newer generation of high-tech ENDS devices associated with some of these advertising strategies and marketing of confectionery- and fruit-flavoured products have quickly become popular among adolescents and young adults *(43,52,101)*.

10.2.6 Recommendations

Recommendations for monitoring trends in marketing, advertising, promotion and sponsorship of ENDS and ENNDS

- **Better surveillance of ENDS and ENNDS marketing, with attention to social media, marketing at points of sale and sponsorship**

  Social media. In order that policy-makers fully understand the marketing tactics of the industry, it is important to monitor traditional and social media advertising channels, paying attention to how the practices are changing over time. Monitoring can be performed independently within government ministries or by using media and Internet monitoring services, industry reports and population-level surveys. Reports should emphasize the extent to which young people are exposed to marketing.

Point-of-sale marketing. The tobacco industry has long used marketing at points of sale as an opportunity for promotion campaigns. This strategy can be monitored through surveillance on the ground.

Sponsorship. Sponsorship continues to be integral to the marketing campaigns of nicotine and tobacco industries. All events should be monitored for sponsorship and the use of testimonials in advertising to understand how the industry uses sponsorship as a promotional tactic and the populations who are exposed to this type of marketing.

- **Collaboration in monitoring marketing trends among governments**

  Cross-border advertising, including through media into bordering jurisdictions, will require collaboration among governments.

- **Monitoring of the access of young people to direct marketing**

  Direct-to-consumer marketing (through the post and e-mail) is a key strategy of the tobacco industry. Policies could be implemented to ensure that material from marketing campaigns is received only by adults and only those who consent to receive such material. Population-level surveys could aid regulators in monitoring this type of advertising.

- **Monitoring of policies for regulating ENDS and ENNDS globally**

  Evidence is lacking on how differences in policies and in the marketing of different products and product characteristics affect perceptions of risk or harm associated with use of ENDS and ENNDS and differences in use of tobacco and nicotine products. Some countries regulate ENNDS differently from ENDS, adding complexity and ambiguity to the regulation of new and emerging products *(89)*. More robust reporting of policy developments will result in more timely, more effective strategies for all Parties to the WHO FCTC.

- **Monitoring of disparities in ENDS and ENNDS marketing**

  Given the tobacco industry's history of targeted advertising to specific demographic groups, such as low-income communities, racial and ethnic minorities and sexual and gender minorities *(102,103)*, differences in both the volume and content of ENDS and ENNDS advertisements in communities and in print and digital media should be monitored.

Recommendations for regulators

- **Consider supporting state, provincial and local regulation of ENDS and ENNDS products.**

  State, provincial and local health departments and local coalitions play important roles in advancing tobacco control and decreasing the burden of tobacco use *(104–106)*.key informants (e.g. local public health center directors Local coalitions have shifted social norms on tobacco use, built support for tobacco control policies and enforced tobacco control measures *(105)*, and such local actors can be used to regulate marketing of ENDS and ENNDS.

- **Consider strategies and policies to protect tobacco control from industry interference.**

  e-Cigarette companies have used various strategies to undermine the regulation of ENDS and ENNDS and efforts to prevent young people from using these products, including sponsoring prevention programmes in schools *(51)*, lobbying against policies to regulate ENDS and ENNDS and corporate social responsibility and philanthropic activities *(107,108)*. Regulators can take measures to implement Article 5.3 of the WHO FCTC, which requires that

  > in setting and implementing their public health policies with respect to tobacco control, Parties shall act to protect these policies from commercial and other vested interests of the tobacco industry in accordance with national law *(109)*.

  These steps include avoiding entering into partnerships with companies that produce ENDS and ENNDS and initiatives funded by those companies (e.g. Foundation for a Smoke-Free World, which received initial funding from PMI) *(110)*, refusing industry contributions (financial or otherwise) and prohibiting industry sponsorship of events, particularly for youth-oriented events *(107,108)*.

- **Remain focused on evidence-based smoking prevention strategies.**

  Governments and health organizations should maintain use of evidence-based measures to reduce smoking (as outlined in the WHO FCTC) and should not be distracted from action in these areas by the promotion and marketing of novel products such as ENDS and ENNDS.

- **Consider cost-effective counter-marketing strategies.**

  Given the global reach of promotion of ENDS and ENNDS on social media, both governments and social media platforms have difficulty in effectively regulating such content, particularly when generated by users. Therefore, counter-marketing may be the most feasible option. Counter-marketing strategies can take various forms, including social media campaigns, which may be more cost-effective than traditional media campaigns. Counter-marketing may also include educating the public about industry activities, in addition to discouraging nicotine and tobacco use.

- **Consider banning all tobacco advertising, promotion and sponsorship, where possible.**

  Throughout its history, the tobacco industry has circumvented nearly all restrictions on advertising, promotion and sponsorship to reach consumers, including young people. Therefore, a complete ban on tobacco marketing might be necessary to minimize exposure of young people to marketing for nicotine and tobacco products. Such a ban would ensure that most information about these products came from national and local governments and public health agencies.

- **Foster collaboration among governments and government sectors in considering, implementing and enforcing marketing regulations for ENDS and ENNDS.**

  Cross-border advertising, including through the media, will require collaboration among governments.

- **Maintain awareness of industry strategies to market ENDS and ENNDS, particularly to young people.**

  In order that policies on ENDS and ENNDS marketing are effective, regulators must learn to recognize the strategies used by the industry to market these products, including targeted advertising, sponsorship and price promotions.

10.2.7 Research gaps for ENDS and ENNDS

- **Additional research on ENDS and ENNDS marketing, especially on social media, is necessary to inform regulators about the marketing and promotion strategies used by companies and retailers.**

As advertising on social media platforms has been associated with increased interest in using ENDS, researchers should continue to build evidence on the marketing tactics used by ENDS and ENNDS manufacturers and retailers on social media *(98,99)*.

- **Additional research should be conducted specifically on ENNDS marketing and its impact on perceptions of risk.**

  As ENNDS are regulated differently from ENDS in some jurisdictions, they may be marketed differently. Many people incorrectly believe that nicotine is the main carcinogen in cigarettes, and, in one study, many participants believed that a cigarette with very low nicotine content was less carcinogenic than currently available cigarettes *(111)*. Studies should therefore be conducted on consumers' perceptions of risk associated with ENNDS and with ENDS and how the marketing and promotion of ENNDS shapes those perceptions.

- **Additional research should be conducted on social media content on ENDS and ENNDS generated by users and its potential effects on risk perceptions, product use and the effectiveness of regulations on marketing.**

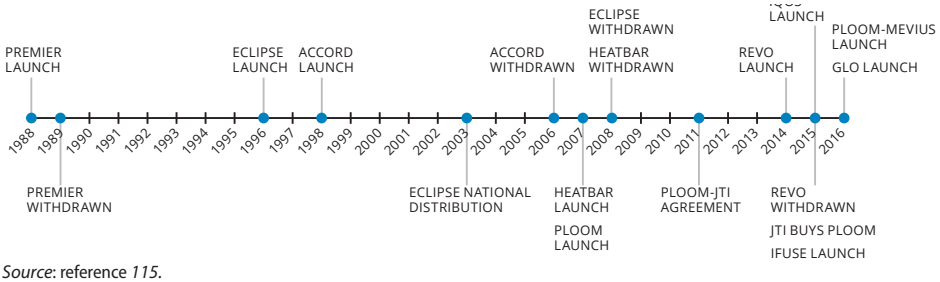
  Social media user content has increased the presence of these products. For example, content related to JUUL continued to be posted widely on social media among peers, even after JUUL stopped posting its own content *(112)*. Given that user-generated content has been used as an important marketing tactic for ENDS and ENNDS companies, it should be monitored in order to understand its impact on risk perception, product use and the effectiveness of marketing regulations.

10.3 Heated tobacco products

10.3.1 Introduction

HTPs "produce aerosols containing nicotine and toxic chemicals when tobacco is heated or when a device containing tobacco is activated" *(113)*. The distinction between HTPs and ENDS is that ENDS deliver nicotine derived from tobacco, whereas HTPs heat tobacco to deliver nicotine to the user *(5,114)*. They also contain non-tobacco additives and are often flavoured. HTPs mimic conventional cigarette smoking behaviour, and some are specially designed as cigarettes that contain tobacco for heating. Although HTP technology has existed since the 1980s, the early products were unsuccessful (Fig. 10.2) *(115)*.

Fig. 10.2. Timeline of heated tobacco products



Source: reference *115*.

10.3.2 Market players, products and strategies

On the basis of data and trends in tobacco sales in 2016, Euromonitor International predicted that the proportion of total tobacco sales represented by combusted cigarettes will continue to decrease but will be offset by market gains from novel and emerging nicotine and tobacco products, such as HTPs *(116)*. Sales of HTPs are expected to grow rapidly, to a market value of US$ 22 billion globally by 2024, from US$ 6.3 billion in 2018 *(117)*. The global market for ENDS was valued at US$ 9.39 billion in 2017 and is expected to reach US$ 58.32 billion by 2026 *(82)*. While continued rapid growth is projected for both ENDS and HTPs, the global market for combusted cigarettes still dwarfs both, as it was valued at US$ 888 billion in 2018 and is expected to reach US$ 1124 billion by 2024 *(118)*.

Market players, products and market share

The HTP market is currently dominated by three leading manufacturers: PMI, JTI and BAT *(115)*. As mentioned above, these three transnational tobacco companies also ranked among the top six manufacturers in terms of combusted cigarette retail sales volume in 2019 *(119)* and have invested significantly in ENDS production globally to augment their product portfolios. Diversification of their production to include ENDS and HTP allows significant consolidation of market power and complicates efforts to combat tobacco use.

PMI. PMI launched IQOS in Japan at the end of 2014. As of 30 June 2020, IQOS was available in 57 markets *(120)*. PMI's report for the second quarter of 2020 and its website note that it is investing in not only the next generation of IQOS products but also new HTPs such as TEEPS, which has a carbon source to heat tobacco *(120,121)*. The total estimated number of IQOS users reached 15.4 million in the second quarter of 2020 *(120)*. Profit margins for PMI's IQOS are 30–50% higher than those for conventional cigarettes *(115)*, and IQOS now makes up more than 10% of PMI's sales volume *(120)*.

JTI. JTI presented the first new-generation HTP in 2013, with the launch of Ploom, which was developed in a joint venture with a company of that name in

the USA, which is now called Pax Labs. After dissolution of the partnership, JTI acquired the Ploom technology and launched a new HTP called Ploom TECH in several Japanese cities in March 2016, in Switzerland in July 2017 *(122)* and in the Republic of Korea in July 2019 *(123)*. JTI has since added three more products to the Ploom brand: Ploom TECH+ (June 2019), Ploom S (August 2019) *(124)* and Ploom S 2.0 (July 2020) *(125)*. Ploom TECH and Ploom TECH+ are the brand's "low-temperature" HTPs, offering "less smell and increased usability", while Ploom S and Ploom S 2.0 are the brand's "high-temperature" tobacco HTPs, which allow consumers "to enjoy an authentic and familiar tobacco taste" and "delivers a superior taste of tobacco leaves" *(126,127)*. Ploom S 2.0 is specifically designed for use with menthol, with "a new heating mode, 'TASTE ACCEL', which lengthens the duration of the peak heating temperature, compared to that of the current Ploom S" *(127)*.

BAT. BAT was the third entrant into the new-generation HTP market, with the introduction of iFuse in Romania in 2015 *(115)*. In 2016, BAT developed and launched glo in Japan and has since launched additional products under the glo brand *(128)*. In 2019, the company launched glo pro which has induction heating instead of the "two-zone heating chamber" of previous glo products in order to improve "consumer satisfaction and their sensorial experience" *(129,130)*. BAT also launched glo nano, a slimmer device, and glo sens, a hybrid product which "combines vaping technology with real tobacco" *(131)*. In 2020, the company launched glo Hyper in Germany, Italy, Japan, Romania and the Russian Federation. glo Hyper is designed to work with the company's "Neo demi-slim range" products, which "contain 30% more tobacco than the existing Neo sticks" *(132,133)*. BAT's tobacco heating products were available in 17 markets at the end of 2019 *(130)*. Its growing portfolio of what it claims to be "potentially reduced-risk products" includes a range of HTPs under the names of five subsidiaries *(32)*.

Korea Tobacco and Ginseng Corporation (KT&G). KT&G entered the HTP market with the launch of lil in the fourth quarter of 2017 in the Republic of Korea. KT&G is the country's leading cigarette producer, in a market that has witnessed the rapid conversion of cigarette users to HTPs; lil was intended to create a domestic presence *(115)*. In 2018, the company launched three products with HTP technology under the lil brand: lil plus, lil mini and lil hybrid *(134)*. Lil plus and lil mini are exclusively HTPs, while lil hybrid has both HTP and ENDS technology *(135)*. In January 2020, KT&G and PMI reached an agreement that will allow PMI to distribute KT&G's smoke-free products, including the HTPs under the lil brand and lil's ENDS product, lil Vapour *(135)*.

Marketing strategies to promote sales of HTPs

Tobacco companies have used a wide range of marketing strategies to promote HTPs, often targeting adolescents and young adults *(136,137)*. The strategies for HTPs include those listed below.

- Advertisements
  - Online, including social media (e.g. Facebook, Instagram, Twitter) *(138)*
  - Television *(138)*
  - Radio *(138)*
  - Newspapers and magazines *(138)*
  - Billboards and posters *(138)*
  - Displays and advertisements at points of sale *(139)*
  - Dedicated retail stores for HTPs *(115)*
  - Bars and pubs *(138)*
- Emphasis on similarities to cigarettes *(115)*
- Acknowledgement of the harms of cigarettes, while presenting HTPs as "cleaner alternatives" *(140)*
  - In the USA, capitalizing on this potential has led manufacturers to try to circumvent stringent regulations on advertising language by applying for designation of HTPs as "modified risk tobacco products" *(92)* For example, in July 2020, PMI successfully obtained an "exposure modification" order from the US Food and Drug Administration for the IQOS system and three of its Marlboro Heatsticks, which "permits the marketing of the products with certain claims".
- Use of brand "ambassadors" (in person and on social media) and demonstrations *(115,141)*
- Product design
  - Sleek, high-tech appearance *(138,142)*
  - Rapid charging *(115)*
  - Less odour *(142)*
  - Less emission of second-hand smoke *(141)*
  - Customization with colours and limited-edition designs *(115)*
- Sponsorship *(141)*
  - Sporting events
  - Art shows
  - Concerts
  - Food and wine festivals
- Pricing strategies
  - "Bait and hook" pricing: discounted prices for devices and recurrent cost for specially designed refills or inserts *(115)*

    - Free samples *(141)*
- Customer service
    - Call centre support *(115)*
    - Dedicated brand retail stores and websites *(115)*
    - Apps to help customers locate nearby stores and to troubleshoot their device *(141,143)*
- Marketing to young people
    - Placement of HTPs near youth-oriented merchandize at points of sale *(139)*
    - Sponsorship of youth-oriented events (e.g. Tel Aviv's TLV Student Day) *(141)*
- Funding front groups (e.g. Foundation for a Smoke-Free World) *(70)*
- Lobbying *(144)*
- Corporate social responsibility to boost industry image *(72)*

Common strategies

The latest generation of HTPs are not only targeted at a specific sub-segment of tobacco users but are marketed and distributed non-traditionally. In expectation of increased sales, tobacco firms are investing heavily in increasing their HTP portfolios. For example, BAT is creating additional features for its glo HTPs, which includes the next generation of devices, additional flavours and blending technologies. PMI's website notes that it is following a similar strategy, with investments in not only the next generation of IQOS products but also new HTPs like TEEPS, which has an alternative source to heat tobacco *(121)*.

HTP manufacturers also use indirect marketing tactics to reach consumers, including young people. This often involves the use of front groups, including the Foundation for a Smoke-Free World, and lobbying *(70)*. HTP companies also use corporate social responsibility strategies to boost their public image and to promote their brands *(72)*, citing philanthropy as evidence of their corporate social responsibility, often making charitable donations to environmental causes, child labour prevention organizations and organizations that extend access to education *(145)*.

10.3.3 Global use and prevalence of use of HTPs

While there are currently no robust, publicly available data from global surveillance of trends in the prevalence of HTP use, national and regional trends have been reported. The Asia–Pacific region currently reports the largest share of revenue from HTP sales and use concentrated in the age group 18–39 years.

Japan accounted for the largest share of revenue at 85% of the global HTP market in 2018 *(146)*, and the fastest rate of growth in HTP revenue was in the Republic of Korea *(147)*. In Japan in 2018, 2.7% of adults had used in HTPs in the previous 30 days and 1.7% had used them daily; nearly all the HTP users surveyed were also current or former smokers of combusted cigarettes *(148)*.

In the Republic of Korea, ever and current use of HTPs among young adults aged 19–24 years grew rapidly after IQOS was introduced in 2017; 5.7% of those surveyed reported ever use after it had been on the market for only 3 months, and 3.5% reported current use *(149)*. HTP inserts accounted for 2.2% of cigarette sales in 2017 and for 9.6% by 2018. One year after HTPs were introduced onto market, 2.8% of Korean adolescents aged 12–18 years reported ever use of HTPs *(150)*.

Market projections for 2019–2025 show significant investment by manufacturers and expectations of robust sales in Europe due to growth in Croatia, Germany, Italy, Poland and the Russian Federation *(151)*. In 2019, Euromonitor reported that Italy represented the largest HTP market outside the Asia–Pacific region; other countries with rapid growth in the market between 2018 and 2019 were Czechia, Germany, Romania, Russian Federation and Ukraine *(152)*. In 2017, only 0.7% of adults in the USA reported ever use of HTPs (2.7% of current smokers of combusted cigarettes); however, that rate increased significantly in only 1 year to 2.4% of adults in 2018 (6.7% of current cigarette smokers) *(124)*. Euromonitor data have also been used to predict the market value of HTPs by 2021; Germany, Japan, the Republic of Korea, Turkey and the USA were those predicted to be highest *(153)*.

While many countries are beginning to survey and report on trends in use of HTPs in adults, evidence is lacking on use of these products by young people and on the preferences and use patterns of adult users. Both are critical areas for future research.

10.3.4 Trends in advertising, promotion and sponsorship of HTPs

How HTPs are advertised in markets through social media

Social media platforms are an emerging channel for advertising HTPs, as sites such as Twitter and Instagram are used by both adult and young populations worldwide. A scan of HTP advertisements and promotions was conducted on Instagram and Twitter with search terms consisting of hashtags with HTP brand names (e.g. #IQOS) and the name of a WHO Member State (e.g. #Belarus). As Instagram's search function allows only one search term, the HTP brand name or search term was combined with the WHO Member State name (e.g. #IQOSCanada), whereas Twitter's search function accommodates several search terms and Boolean operators (e.g. #IQOS AND #Canada). The search showed that HTPs are marketed on Twitter and Instagram in at least 95 WHO Member

States (Table 10.3). Analysis of the content of up to six advertisements (three Twitter, three Instagram) per country indicated use of similar advertisement strategies in the six WHO regions.

Table 10.3. Common HTP advertising strategies on social media, by WHO region, 2020

WHO region	No. of countries	Data available No. (%)	No. of advertisements	Health warning No. (%)	Nicotine lexical No. (%)	Flavour lexical No. (%)	Design feature lexical No. (%)	Image device No. (%)	Image of e-liquid No. (%)
African	46	3 (7)	9	1 (11)	3 (33)	0	0	7 (78)	4 (44)
Americas	35	12 (34)	42	17 (40)	3 (7)	12 (29)	9 (21)	38 (90)	12 (29)
South-East Asia	11	6 (56)	16	11 (69)	3 (19)	3 (19)	4 (25)	14 (89)	4 (25)
European	53	48 (91)	186	86 (46)	21 (11)	41 (22)	22 (12)	146 (78)	30 (16)
Eastern Mediterranean	22	15 (68)	62	12 (19)	17 (27)	17 (27)	4 (6)	55 (89)	18 (29)
Western Pacific	27	11 (41)	39	13 (33)	2 (5)	8 (21)	13 (33)	38 (97)	8 (21)
All	194	95 (49)	354	140 (40)	49 (14)	81 (23)	52 (15)	298 (84)	76 (21)

HTP advertisements were present in approximately half of WHO Member States, and most included an image of the device. Less than half of the social media advertisements for HTPs included a health warning, and almost one quarter mentioned a flavour.

Impact of COVID-19 on marketing strategies for HTPs

During the COVID-19 pandemic, several HTP manufacturers, retailers and users have posted messages relevant to COVID-19 and related containment strategies in marketing and promotion strategies on social media. Themes related to the pandemic and containment that emerged in HTP marketing on Instagram and Twitter included the following.

Coping with boredom and isolation: Manufacturers have marketed their products as a means for users to enjoy themselves safely at home during lockdown measures. For example, an Instagram post from glo's worldwide account stated "Left brain says stay in. Right brain wants to go out. We're loving these new tools that let you party from home with no compromise. #BreakBinary #NetflixParty #Discoverglo #Myglo" *(66)*.

Stocking up on essential supplies: Users have implied that people should "stock up" on their favourite HTPs in preparation for lockdown or quarantine, equating these products to "essential" supplies for the duration of the lockdown. For example, one user posted a photo of several HTP devices (primarily IQOS)

and several packages of HEETS (heated tobacco units inserted into IQOS devices), with the statement "I'm ready for quarantine!" Another user posted a photo on both Instagram and Twitter of an IQOS device and three packages of HEETS, with the caption "#lockdown #essentials and/or #quarantine #addictions. Thanks for the gift @iqos_it".

Stay at home campaigns. Some HTP brands are using "stay at home" campaigns and messages on social media to promote their products. For example, glo Greece held a "stay home challenge", in which participants could win prizes *(66)*. This post capitalized on the #menoumespiti message on Instagram, a popular hashtag meaning "we stay home" in Greek.

Obtaining protective equipment and supplies. Some manufacturers are offering branded face masks and hand sanitizer with the purchase of their products. For example, one Instagram advertisement by glo Kazakhstan shows a woman wearing a glo-branded face mask, with the caption "...Can't find a mask anywhere? We'll give it to you [winking face emoji]. Until Thursday 26 March, you can get a mask for free in the glo space on Nazarbayev 100G. Well, after that you can get the same mask by placing a purchase of the device on the website or in our outlet…" *(66)*.

10.3.5 Measures to control advertising, promotion and sponsorship of HTPs

In the countries that regulate advertising, promotion or sponsorship of HTPs, many have done so by including HTPs in existing regulations, some as novel tobacco products and some in other categories, whereas others have specific regulations for these products. Furthermore, some countries consider HTPs to be tobacco products rather than giving them a separate designation, so that they are subjected to all current national tobacco product regulations *(113,154)*. Continued monitoring of such trends and their effects on use will provide valuable insight for policy-makers across the world who are observing trends in HTP use and for the design of a comprehensive regulatory framework or for updating existing regulations to reduce the harm associated with tobacco use.

While no peer-reviewed evidence is yet available on an association between HTP advertising and promotion and use, researchers have pointed to youth-friendly HTP advertising that has also been used to market ENDS, such as high-tech, novel design features, claims that HTPs are less harmful than combusted products and messages that HTPs may be more socially acceptable than combusted products *(136,150)*. Given the evidence of successful use of these strategies to advertise ENDS products, HTP advertising, promotional messaging and media should be closely monitored, with trends in the susceptibility of children and adolescents to using HTPs.

10.3.6 Recommendations for monitoring trends in marketing, advertising, promoting and sponsorship of HTPs

- **Better surveillance of trends in HTP use and sales**

  To increase the impact of the recommendations below, more robust data should be collected in various countries on trends in HTP use, including demographic data and product preferences. While the new generation of HTPs are relatively new on the tobacco product market, the rapid rise in the popularity of ENDS indicates that more rapid surveillance of HTP use and sales and reporting on national policies will be critical to including HTPs in existing control frameworks.

- **Better surveillance of HTP marketing, with particular attention to social media**

  The robust presence of marketing for alternative tobacco products on youth-friendly social media platforms suggests that increased surveillance of marketing trends is necessary to better understand whether exposure to such marketing is associated with attitudes about and use of HTPs. This should include surveillance of content generated by HTP companies, retailers and users.

- **Scanning of how governments globally are regulating HTPs, including their advertisement, promotion and sponsorship**

  Additional information should be collected on the regulation, marketing and promotion of HTPs in order to understand the global picture. Better reporting of key policy developments across the world will assist in the development of timely, effective strategies for all Parties to the WHO FCTC.

10.3.7 Recommendations for regulators

- **Remain focused on evidence-based smoking prevention strategies.**

  Governments and health organizations should maintain a focus on evidence-based measures to reduce smoking (as outlined in the WHO FCTC) and should not be distracted from action by the promotion and marketing of novel products such as HTPs.

- **Consider cost-effective counter-marketing strategies.**

  Given the global reach of HTP advertising on social media, neither

governments nor social media platforms can effectively regulate the content, particularly when generated by users. Counter-marketing may be the most feasible option. Various forms could be used, including social media campaigns, which may be more cost-effective than traditional media campaigns. Counter-marketing can include education about industry activity, in addition to discouraging nicotine and tobacco use.

- **Apply relevant lessons learnt from regulation of ENDS and ENNDS**

  As HTP companies have adopted many of the same marketing strategies that they used to promote ENDS and ENNDS, regulators can apply lessons learnt from ENDS and ENNDS marketing to regulating HTP marketing and promotion.

- **Foster collaboration among governments and government sectors for implementing and enforcing marketing regulations for HTPs.**

  Cross-border advertising, including transmission of media into neighbouring countries, should be addressed collaboratively at government level.

- **Consider banning all tobacco advertising, promotion and sponsorship, where possible.**

  The tobacco industry has circumvented nearly all restrictions on advertising, promotion and sponsorship to reach consumers, including young people. Therefore, a complete ban on tobacco marketing may be necessary to minimize exposure to marketing for nicotine and tobacco products. Such a ban would ensure that most communication about these products came from national and local governments and public health agencies.

- **Keep informed of industry strategies to market HTPs, particularly to young people.**

  In order for policies to control HTP marketing to be effective, regulators must learn to recognize the strategies used by the industry, including use of health-related claims, sponsorship and price promotions.

10.3.7 Gaps in research on HTPs

- **Additional evidence is required to understand the relations among HTP regulation, perception of the risk of these products and product use.**

  Much of the evidence on novel and emerging nicotine and tobacco products addresses the association between policies and trends in use; however, evidence specific to HTPs is insufficient. Further evaluation is necessary of how different policies and product characteristics change perceptions of risk and/or product use (particularly among young people).

- **Additional research is necessary on HTP marketing, with particular attention to social media, to inform regulators of the marketing and promotion strategies used by HTP companies and retailers.**

  Social media platforms are an important channel for advertising and promoting HTPs worldwide. As advertising seen on social media platforms has been associated with increased interest in using tobacco and nicotine products and also their actual use, research should be conducted on the impact of HTP marketing and promotion on these platforms *(98,99)*.

- **Additional research should be conducted on user-generated HTP content on social media and its effect on risk perception, product use and the effectiveness of marketing regulations.**

  User-generated content has been used as an important marketing tactic for ENDS and ENNDS companies. Therefore, trends in user-generated content related to HTPs should be monitored, with studies of its impact on risk perceptions and product use and on the effectiveness of marketing regulations.

10.4 Summary

Globally, ENDS, ENNDS and HTPs are marketed through both traditional and emerging channels, such as social media. The evidence gathered for this report indicates that ENDS and HTPs are heavily marketed on Twitter and Instagram. The strategies used to regulate the marketing and promotion of these products differ widely among countries, some banning certain products, some regulating only products containing nicotine and others imposing restrictions on flavours, packaging and advertisements. Global systems are necessary to monitor

marketing of ENDS, ENNDS and HTP to understand how these products are advertised; additional evidence is necessary to understand how marketing of these products influences product perception and product use, particularly among adolescents and young adults. All levels of government should regulate the advertising, promotion and sponsorship of ENDS, ENNDS and HTPs when such regulations do not exist.

10.5 References

1. WHO global report on trends in prevalence of tobacco use 2000–2025. Third edition. Geneva: World Health Organization; 2019.
2. The global cigarette industry. Washington (DC): Campaign for Tobacco-Free Kids; 2019.
3. Smoking population – number of adult smokers. London: Euromonitor International Ltd; 2019 (http://www.portal.euromonitor.com.proxy1.library.jhu.edu/portal/statisticsevolution/index).
4. e-Cigarette use among youth and young adults: A report of the Surgeon General. Washington (DC): Department of Health and Human Services; 2016.
5. 6 important things to know about IQOS, the new heated cigarette product. Washington (DC): Truth Initiative; 2019 (https://truthinitiative.org/research-resources/emerging-tobacco-products/6-important-things-know-about-iqos-new-heated, accessed 18 December 2020).
6. Cullen KA, Ambrose BK, Gentzke A, Apelberg BJ, Jamal A, King BA. Notes from the field: Use of electronic cigarettes and any tobacco product among middle and high school students – United States, 2011–2018. Morb Mortal Wkly Rep. 2018;67:629–33.
7. Youth tobacco use: Results from the National Youth Tobacco Survey. Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/tobacco-products/youth-and-tobacco/youth-tobacco-use-results-national-youth-tobacco-survey#1, accessed 18 August 2020).
8. Trump administration combating epidemic of youth e-cigarette use with plan to clear market of unauthorized, non-tobacco-flavored e-cigarette products. Silver Spring (MD): Food and Drug Administration; 2019 (https://www.fda.gov/news-events/press-announcements/trump-administration-combating-epidemic-youth-e-cigarette-use-plan-clear-market-unauthorized-non#:~:text=%E2%80%9CThe%20Trump%20Administration%20is%20making,Human%20Services%20Secretary%20Alex%20Azar, accessed 10 January 2021).
9. Conference of the Parties to the WHO Framework Convention on Tobacco Control. Decision FCTC/COP7(9) Electronic nicotine delivery systems and electronic non-nicotine delivery systems. Geneva: World Health Organization; 2016 (https://www.who.int/fctc/cop/cop7/FCTC_COP7_9_EN.pdf?ua=1, accessed 10 January 2021).
10. Conference of the Parties to the WHO Framework Convention on Tobacco Control. Decision FCTC/COP8(22) Novel and emerging tobacco products. Geneva: World Health Organization; 2018 (https://www.who.int/fctc/cop/sessions/cop8/FCTC_COP8(22).pdf?ua=1, accessed 13 August 2020).
11. Public health consequences of e-cigarettes. Washington (DC): National Academies of Sciences Engineering and Medicine; 2018. doi:10.17226/24952.
12. Williams M, Bozhilov K, Ghai S, Talbot P. Elements including metals in the atomizer and aerosol of disposable electronic cigarettes and electronic hookahs. PLoS One. 2017;12(4):e0175430.
13. World Health Assembly resolution 56.1. Geneva: World Health Organization; 2003 (https://www.who.int/tobacco/framework/final_text/en/). https://www.who.int/tobacco/framework/final_text/en/index3.html, accessed August 16, 2020.
14. Conference of the Parties to the WHO Framework Convention on Tobacco Control. Electronic

nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS): Report by WHO. Geneva: World Health Organization; 2016 (https://www.who.int/fctc/cop/cop7/FCTC_COP_7_11_EN.pdf, accessed 13 August 2020).

15. Stone E, Marshall H. Tobacco and electronic nicotine delivery systems regulation. Transl Lung Cancer Res. 2019;8(S1):S67–76.
16. MacGuill S. Growth in vapour products. London: Euromonitor International; 2017 (https://blog.euromonitor.com/growth-vapour-products/, accessed 13 December 2020).
17. Kim AE, Arnold KY, Makarenko O. e-Cigarette advertising expenditures in the US, 2011–2012. Am J Prev Med. 2014;46(4):409–12.
18. Electronic cigarettes: An overview of key issues. Washington (DC): Campaign for Tobacco-Free Kids; 2020 (https://www.tobaccofreekids.org/assets/factsheets/0379.pdf).
19. Tobacco companies. In: Mackay J, Eriksen M, editors. The tobacco atlas. Geneva: World Health Organization; 2002:51 (https://www.who.int/tobacco/en/atlas18.pdf?ua=1, accessed 13 August 2020).
20. Exhibit 99.1. Altria makes $12.8 billion minority investment in Juul to accelerate harm reduction and drive growth. Washington (DC): United States Securities Exchange Commission; 2019 (https://www.sec.gov/Archives/edgar/data/764180/000119312518353970/d660871dex991.htm, accessed 13 August 2020).
21. Kalra A, Kirkham C. Exclusive: Juul plans India e-cigarette entry with new hires, subsidiary. Reuters, 30 January 2019 (https://www.reuters.com/article/us-juul-india-exclusive-idUSKCN1PO0VV, accessed 11 November 2020).).
22. Gupta S. India is banning all e-cigarettes over fears about youth vaping. CNN, 18 September 2019 (https://edition.cnn.com/2019/09/18/health/india-e-cigarette-ban-intl/index.html#:~:text=India%20is%20banning%20all%20e%2Dcigarettes%20over%20fears%20about%20youth%20vaping&text=Electronic%20cigarette%20devices%20on%20display,risk%2C%20especially%20to%20young%20people).
23. Kastrenakes J, Garun N. Juul launches a Bluetooth e-cigarette that tracks how much you vape. The Verge, 6 August 2019 (https://www.theverge.com/2019/8/6/20754655/juul-c1-bluetooth-e-cigarette-vape-monitor-consumption-age-restriction, accessed 13 August 2020).
24. Turning Point Brands, Inc. announces third quarter 2018 results. Business Wire, 7 November 2018 (https://www.businesswire.com/news/home/20181107005281/en/Turning-Point-Brands-Announces-Quarter-2018-Results, accessed 13 August 2020).
25. Find your country's online store. San Francisco (CA): JUUL Labs (https://www.juul.com/global, accessed 16 August 2020).
26. 2018. Altria Group, Inc. Annual Report. Richmond (VA): Altria Group, Inc.; 2018 (https://www.annualreports.com/HostedData/AnnualReportArchive/a/NYSE_MO_2018.pdf, accessed 10 January 2021).
27. STEEM: Exploring new e-vapor products. Lausanne: Philip Morris International (https://www.pmi.com/smoke-free-products/steem-creating-a-vapor-with-nicotine-salt, accessed 13 August 2020).
28. Brand shares: E-Vapour products. London: Euromonitor International Inc.; 2018 (https://www-portal-euromonitor-com.proxy1.library.jhu.edu/portal/statisticsevolution/index, accessed 13 August 2020).
29. Japan Tobacco Inc. Annual Report 2018. Tokyo: Japan Tobacco Inc.; 2019 (https://www.jt.com/investors/results/annual_report/pdf/2018/annual.fy2018_E2.pdf, accessed 13 August 2020).
30. 2019 earnings report. Geneva: Japan Tobacco International; 2020 (https://www.jti.com/sites/default/files/press-releases/documents/2020/jt-group-2019-financial-results-and-2020-forecast.pdf, accessed 13 August 2020).
31. JTI launches Logic Compact in the UK – the first market to launch this new premium e-ciga-

rette: The moment vaping "just clicks" has arrived. Geneva: Japan Tobacco International; 2018 (https://www.jti.com/jti-launches-logic-compact-uk-first-market-launch-new-premium-e-cigarette, accessed 13 August 2020).

32. British American Tobacco plc. Transforming tobacco: Annual report and Form 20-F 2018. London; 2018 (https://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOAWWGJT/$file/Annual_Report_and_Form_20-F_2018.pdf, accessed 16 December 2020).
33. Vapour products. London: British American Tobacco plc; 2020 (https://www.bat.com/ecigarettes, accessed 13 August 2020).
34. British American Tobacco to focus on three global new category brands to further accelerate their growth. London: British American Tobacco plc; 2019 (https://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOBJBMSE, accessed 16 August 2020).
35. Form 10-K. Reynolds American Inc. Securities registered pursuant to Section 12(b) of the Securities Exchange Act of 1934; Washington (DC): United States Securities Exchange Commission; 2017 (https://www.sec.gov/Archives/edgar/data/1275283/000156459017001245/rai-10k_20161231.htm, accessed 13 August 2020).
36. Something better: Annual report and accounts 2018. London; Imperial Brands plc; 2018 (https://www.imperialbrandsplc.com/content/dam/imperial-brands/corporate/investors/annual-report-and-accounts/2018/annual-report-and-accounts-2018.pdf, accessed 13 August 2020).
37. Imperial Brands CAGNY presentation 21 02 2019. London: Imperial Brands plc; 2019 (https://www.imperialbrandsplc.com/content/dam/imperial-brands/corporate/investors/presentations/conferences/2019/CAGNY Script.pdf.downloadasset.pdf, accessed 13 August 2020).
38. Imperial Brands plc. Annual report and accounts 2019. London: Imperial Brands plc; 2019 (https://www.imperialbrandsplc.com/content/dam/imperial-brands/corporate/investors/annual-report-and-accounts/2019/Annual Report 2019.pdf, accessed 13 August 2020).
39. What happened to the blu ACE device? Amsterdam: Fontem Ventures BV; 2020 (https://support-uk.blu.com/hc/en-gb/articles/360015460600-What-happened-to-the-blu-ACE-device-, accessed 13 August 2020).
40. Imperial Brands plc interim results for the six months ended 31 March 2018. London: Imperial Brands plc; 2018 (https://www.imperialbrandsplc.com/content/dam/imperial-brands/corporate/investors/results-centre/2018/2018-05-09 Interims 18 script.pdf, accessed 13 August 2020).
41. Padon AA, Lochbuehler K, Maloney EK, Cappella JN. A randomized trial of the effect of youth appealing e-cigarette advertising on susceptibility to use e-cigarettes among youth. Nicotine Tob Res. 2018;20(8):954–61.
42. Mantey DS, Cooper MR, Clendennen SL, Pasch KE, Perry CL. e-Cigarette marketing exposure is associated with e-cigarette use among US youth. J Adolesc Health. 2016;58(6):686–90.
43. Jackler RK, Chau C, Getachew BD, Whitcomb MM, Lee-Heidenreich J, Bhatt AM et al. JUUL advertising over its first three years on the market. Berkeley (CA): Stanford Research into the Impact of Tobacco Advertising; 2019 (http://tobacco.stanford.edu/tobacco_main/publications/JUUL_Marketing_Stanford.pdf).
44. Sebastian M. e-Cig marketing budgets growing by more than 100% year over year. AdAge, 14 April 2014 (https://adage.com/article/media/e-cig-companies-spent-60-million-ads-year/292641).
45. Duke JC, Lee YO, Kim AE, Watson KA, Arnold KY, Nonnemaker JM et al. Exposure to electronic cigarette television advertisements among youth and young adults. Pediatrics. 2014;134(1):e29–36.
46. Gregory A. Tobacco companies "pushing e-cigs on youngsters via Facebook and Twitter". The Mirror, 27 November 2013 (https://www.mirror.co.uk/lifestyle/health/tobacco-compani-

es-pushing-e-cigs-youngsters-2854699, accessed 13 August 2020).
47. Chen-Sankey JC, Unger JB, Bansal-Travers M, Niederdeppe J, Bernat E, Choi K. e-Cigarette marketing exposure and subsequent experimentation among youth and young adults. Pediatrics. 2019;144(5):e20191119.
48. Carpenter CM, Wayne GF, Pauly JL, Koh HK, Connolly GN. New cigarette brands with flavors that appeal to youth: Tobacco marketing strategies. Health Aff. 2005;24(6):1601–10.
49. 7 ways e-cigarette companies are copying big tobacco's playbook. Washington (DC): Campaign for Tobacco-Free Kids; 2013 (https://www.tobaccofreekids.org/blog/2013_10_02_ecigarettes, accessed August 16, 2020).
50. 4 marketing tactics e-cigarette companies use to target youth. Washington (DC): Truth Initiative; 2018 (https://truthinitiative.org/research-resources/tobacco-industry-marketing/4-marketing-tactics-e-cigarette-companies-use-target, accessed 16 August 2020).
51. Evidence brief: Tobacco industry sponsored youth prevention programs in schools. Atlanta (GA): Centers for Disease Control and Prevention; 2019 (https://www.cdc.gov/tobacco/basic_information/youth/evidence-brief/index.htm, accessed 16 August 2020).
52. Jackler RK, Ramamurthi D. Unicorns cartoons: marketing sweet and creamy e-juice to youth. Tob Control. 2017;26(4):471–5.
53. Ashley DL, Spears CA, Weaver SR, Huang J, Eriksen MP. e-Cigarettes: How can they help smokers quit without addicting a new generation? Prev Med. 2020:106145.
54. Giovenco DP, Casseus M, Duncan DT, Coups EJ, Lewis MJ, Delnevo CD. Association between electronic cigarette marketing near schools and e-cigarette use among youth. J Adolesc Health. 2016;59(6):627–34.
55. Kaplan S. Juul targeted schools and youth camps, House Panel on Vaping Claims. The New York Times, 25 July 2019 (https://www.nytimes.com/2019/07/25/health/juul-teens-vaping.html, accessed 13 August 2020).
56. Kirkpatrick MG, Cruz TB, Goldenson NI, Allem JP, Chu KH, Pentz MA et al. Electronic cigarette retailers use Pokémon Go to market products. Tob Control. 2017;26(E2):e147.
57. Cardellino C. Electronic cigarettes available for free at Fashion Week. Cosmopolitan. 5 September 2013 (https://www.cosmopolitan.com/style-beauty/fashion/advice/a4736/nyfw-2013-cigarettes/, accessed 13 August 2020).
58. Ali FRM, Xu X, Tynan MA, King BA. Use of price promotions among US adults who use electronic vapor products. Am J Prev Med. 2018;55(2):240–3. 0
59. D'Angelo H, Rose SW, Golden SD, Queen T, Ribisl KM. e-Cigarette availability, price promotions and marketing at the point-of sale in the contiguous United States (2014–2015): National estimates and multilevel correlates. Prev Med Rep. 2020;19:101152.
60. Wadsworth E, McNeill A, Li L, Hammond D, Thrasher JF, Yong HH et al. Reported exposure to e-cigarette advertising and promotion in different regulatory environments: Findings from the International Tobacco Control Four Country (ITC-4C) survey. Prev Med. 2018;112:130–7.
61. De Andrade M, Hastings G, Angus K. Promotion of electronic cigarettes: tobacco marketing reinvented? BMJ. 2013;347:f7473.
62. Lee SJ, Rees VW, Yossefy N, Emmons KM, Tan ASL. Youth and young adult use of pod-based electronic cigarettes from 2015 to 2019: A systematic review. JAMA Pediatr. 2020;174(7):714–20.
63. Bach L. JUUL and youth: Rising e-cigarette popularity. Washongton DC: TobaccoFree Kids; 2019 (https://www.tobaccofreekids.org/assets/factsheets/0394.pdf, accessed 16 August 2020).
64. Hammond D, Wackowski OA, Reid JL, O'Connor RJ. Use of JUUL e-cigarettes among youth in the United States. Nicotine Tob Res. 2018;22(5):827–32.
65. Jivanda T. "Put it in my mouth": Viewers outraged by apparent reference to oral sex in VIP e-cig advert. Independent, 4 December 2013 (https://www.independent.co.uk/news/media/advertising/put-it-my-mouth-viewers-outraged-apparent-reference-oral-sex-vip-e-cig-ad-

vert-8982918.html, accessed 10 January 2021).
66. Hickman A. "Big tobacco" using COVID-19 messaging and influencers to market products. PR Week, 15 May 2020 (https://www.prweek.com/article/1683314/big-tobacco-using-covid-19-messaging-influencers-market-products, accessed 13 August 2020).
67. Yao T, Jiang N, Grana R, Ling PM, Glantz SA. A content analysis of electronic cigarette manufacturer websites in China. Tob Control. 2016;25(2):188–94.
68. Klein EG, Berman M, Hemmerich N, Carlson C, Htut S, Slater M. Online e-cigarette marketing claims: A systematic content and legal analysis. Tob Regul Sci. 2016;2(3):252–62.
69. Hrywna M, Bover Manderski MT, Delnevo CD. Prevalence of electronic cigarette use among adolescents in New Jersey and association with social factors. JAMA Netw Open. 2020;3(2):e1920961.
70. Tobacco tactics. Front groups. Bath: University of Bath; 2019 (https://tobaccotactics.org/wiki/front-groups, accessed 14 October 2020).
71. Tobacco tactics. Lobby groups. Bath: University of Bath; 2019 (https://tobaccotactics.org/topics/lobby-groups/, accessed 14 October 2020).
72. Tobacco tactics. CSR strategy. Bath: University of Bath; 2020 (https://tobaccotactics.org/wiki/csr-strategy/, accessed 15 October 2020).
73. Romberg AR, Miller Lo EJ, Cuccia AF, Willett GJ, Xiao H, Hair EC et al. Patterns of nicotine concentrations in electronic cigarettes sold in the United States, 2013–2018. Drug Alcohol Depend. 2019;203:1–7.
74. How much nicotine is in JUUL? Washington (DC): Truth Initiative; 2019 (https://truthinitiative.org/research-resources/emerging-tobacco-products/how-much-nicotine-juul, accessed December 2020).
75. Hammond D, Rynard VL, Reid JL. Changes in prevalence of vaping among youths in the United States, Canada, and England from 2017 to 2019. JAMA Pediatr. 2020;174(8):797–800.
76. Chen C, Zhuang YL, Zhu SH. e-Cigarette design preference and smoking cessation. Am J Prev Med. 2016;51(3):356–63.
77. e-Cigarettes: Facts, stats and regulations. Washington (DC): Truth Initiative; 2019 (https://truthinitiative.org/research-resources/emerging-tobacco-products/e-cigarettes-facts-stats-and-regulations#:~:text=Between%202012%20and%202013%2C%202.4,among%20adults%20aged%2045%2D64).
78. Tobacco tactics. Forest. Bath: University of Bath; 2020 (https://tobaccotactics.org/wiki/forest/, accessed 15 October 2020).
79. Tobacco tactics. Foundation for a Smoke-Free World. Bath: University of Bath (https://tobaccotactics.org/wiki/foundation-for-a-smoke-free-world/, accessed 10 January 2021).
80. 2018 recipients of charitable contributions from the Altria family of companies. Richmond (VA): Altria; 2018 (https://web.archive.org/web/20200320145936/https:/www.altria.com/-/media/Project/Altria/Altria/responsibility/investing-in-communities/2018Grantees.pdf, accessed 15 October 2020).
81. Statistics and market data on consumer goods & FMCG: Tobacco. New York City (NY): Statista; 2020.
82. Electronic cigarette – global market outlook (2017–2026). Dublin: Research and Markets; 2019 (https://www.researchandmarkets.com/reports/4827644/electronic-cigarette-global-market-outlook, accessed 10 January 2021).
83. Bao W, Xu G, Lu J, Snetselaar LG, Wallace RB. Changes in electronic cigarette use among adults in the United States, 2014–2016. JAMA. 2018;319(19):2039.
84. Wang T, Asman K, Gentzke A, Cullen KA, Holder-Hayes E, Reyes-Guzman C et al. Tobacco product use among adults — United States, 2017. Morb Mortal Wkly Rep. 2017;67(44):1225–32.
85. Canadian Tobacco, Alcohols and Drugs Survey (CTADS): summary of results for 2017. Ottawa:

Health Canada, Statistics Canada; 2019 (https://www.canada.ca/en/health-canada/services/canadian-tobacco-alcohol-drugs-survey/2017-summary.html, accessed 6 December 2020).
86. Special Eurobarometer 458: Attitudes of Europeans toward tobacco and electronic cigarettes. Brussels: European Commission; 2017.
87. Schoenborn CA, Clarke TC. QuickStats: Percentage of adults who ever used an e-cigarette and percentage who currently use e-cigarettes, by age group – National Health Interview Survey, United States, 2016. Morb Mortal Wkly Rep. 2017;66(33):892.
88. Hammond D, Reid JL, Rynard VL, Fong GT, Cummings KM, McNeill A et al. Prevalence of vaping and smoking among adolescents in Canada, England, and the United States: repeat national cross sectional surveys. BMJ. 2019;365:l2219.
89. Country laws regulating e-cigarettes. Advertising, promotion and sponsorship. Baltimore (MD): Institute for Global Tobacco Control; 2020 (https://www.globaltobaccocontrol.org/e-cigarette/advertising-promotion-and-sponsorship, accessed 16 August 2020).
90. e-Cigarettes at the point of sale. CounterTobacco.Org; 2020 (https://countertobacco.org/resources-tools/evidence-summaries/e-cigarettes-at-the-point-of-sale/, accessed 16 August 2020).
91. Modified risk tobacco product applications. Silver Spring (MD): Food and Drug Administration, Center for Tobacco Products; 2020.
92. FDA finalizes enforcement policy on unauthorized flavored cartridge-based e-cigarettes that appeal to children, including fruit and mint. Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/news-events/press-announcements/fda-finalizes-enforcement-policy-unauthorized-flavored-cartridge-based-e-cigarettes-appeal-children, accessed 17 August 2020).
93. Notice of intent – Potential measures to reduce the impact of vaping product advertising on youth and non-users of tobacco products. Ottawa: Health Canada; 2019 (https://www.canada.ca/en/health-canada/programs/consultation-measures-reduce-impact-vaping-products-advertising-youth-non-users-tobacco-products/notice-document.html).
94. Canada Gazette, Part I, Volume 153, Number 25: Vaping Products Labelling and Packaging Regulations. Ottawa: Health Canada; 2019 (http://gazette.gc.ca/rp-pr/p1/2019/2019-06-22/html/reg4-eng.html).
95. Nicksic NE, Snell LM, Rudy AK, Cobb CO, Barnes AJ. Tobacco marketing, e-cigarette susceptibility, and perceptions among adults. Am J Health Behav. 2017;41(5):579–90.
96. Nicksic NE, Snell LM, Barnes AJ. Does exposure and receptivity to e-cigarette advertisements relate to e-cigarette and conventional cigarette use behaviors among youth ? Results from wave 1 of the Population Assessment of Tobacco and Health Study. J Appl Res Child. 2017;8(2):3.
97. Cho YJ, Thrasher JF, Reid JL, Hitchman S, Hammond D. Youth self-reported exposure to and perceptions of vaping advertisements: Findings from the 2017 International Tobacco Control Youth Tobacco and Vaping Survey. Prev Med. 2019;126:105775.
98. Pokhrel P, Fagan P, Herzog TA, Chen Q, Muranaka N, Kehl L et al. e-Cigarette advertising exposure and implicit attitudes among young adult non-smokers. Drug Alcohol Depend. 2016;163:134–40.
99. Camenga D, Gutierrez KM, Kong G, Cavallo D, Simon P, Krishnan-Sarin S. e-Cigarette advertising exposure in e-cigarette naïve adolescents and subsequent e-cigarette use: A longitudinal cohort study. Addict Behav. 2018;81:78–83.
100. Phua J, Jin SV, Hahm JM. Celebrity-endorsed e-cigarette brand Instagram advertisements: Effects on young adults' attitudes towards e-cigarettes and smoking intentions. J Health Psychol. 2018;23(4):550–60.
101. Behind the explosive growth of JUUL. Washington (DC): Truth Initiative; 2019.
102. Marketing tobacco to LGBT communities. Washington (DC): National Institutes of Health; 2020

(https://smokefree.gov/marketing-tobacco-lgbt-communities, accessed 17 August 2020).
103. Tobacco industry marketing. Atlanta (GA): Centers for Disease Control and Prevention; 2020 (https://www.cdc.gov/tobacco/data_statistics/fact_sheets/tobacco_industry/marketing/index.htm, accessed 17 August 2020).
104. Berg CJ, Dekanosidze A, Torosyan A, Grigoryan L, Sargsyan Z, Hayrumyan V et al. Examining smoke-free coalitions in Armenia and Georgia: Baseline community capacity. Health Educ Res. 2019;34(5):495–504.
105. Berg CJ. Local coalitions as an underutilized and understudied approach for promoting tobacco control in low- and middle-income countries. J Glob Health. 2019;9(1):10301.
106. Restricting tobacco advertising. Counter Tobacco; 2020 (https://countertobacco.org/policy/restricting-tobacco-advertising-and-promotions/, accessed 17 August 2020).
107. Public health groups and leaders worldwide urge rejection of Philip Morris International's new foundation. Washington (DC): Campaign for Tobacco-Free Kids; 2020 (https://www.tobaccofreekids.org/what-we-do/industry-watch/pmi-foundation/compilation, accessed 17 August 2020).
108. Spinning a new tobacco industry: How Big Tobacco is trying to sell a do-gooder image and what Americans think about it. Washington (DC): Truth Initiative; 2019 (https://truthinitiative.org/research-resources/tobacco-industry-marketing/spinning-new-tobacco-industry-how-big-tobacco-trying, accessed 17 August 2020).
109. Guidelines for implementation of Article 5.3 of the WHO Framework Convention on Tobacco Control. Geneva: World Health Organization; 2011 (https://www.who.int/fctc/guidelines/article_5_3.pdf?ua=1, accessed 17 August 2020).
110. Van der Eijk Y, Bero LA, Malone RE. Philip Morris International-funded "Foundation for a Smoke-Free World": analysing its claims of independence. Tob Control. 2019;28:712–8.
111. Byron MJ, Jeong M, Abrams DB, Brewer NT. Public misperception that very low nicotine cigarettes are less carcinogenic. Tob Control. 2018;27(6):712–4.
112. Most JUUL-related Instagram posts appeal to youth culture and lifestyles, study finds. Washington (DC): Truth Initiative; 2019 (https://truthinitiative.org/research-resources/emerging-tobacco-products/most-juul-related-instagram-posts-appeal-youth-culture, accessed 15 October 2020).
113. Heated tobacco products. Information sheet. 2nd edition. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/WHO-HEP-HPR-2020.2).
114. Heated tobacco products. Atlanta (GA): Centers for Disease Control and Prevention; 2020 (https://www.cdc.gov/tobacco/basic_information/heated-tobacco-products/index.html, accessed 10 January 2021).
115. Heated tobacco products (HTPs) market monitoring information sheet. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/bitstream/handle/10665/273459/WHO-NMH-PND-18.7-eng.pdf?ua=1).
116. Cigarettes to record US$7.7 billion loss by 2021 as heated tobacco grows 691 percent. Euromonitor International, 24 June 2017 (https://blog.euromonitor.com/cigarettes-record-loss-heated-tobacco-grows-691-percent/).
117. Heat not burn tobacco products market – forecasts from 2019 to 2024. Dublin: Research and Markets; 2019 (https://www.researchandmarkets.com/reports/4849645/heat-not-burn-tobacco-products-market-forecasts).
118. Cigarette market: Global industry trends, share, size, growth, opportunity and forecast 2019–2024. Dublin: Research and Markets; 2019 (https://www.researchandmarkets.com/reports/4752264/cigarette-market-global-industry-trends-share#:~:text=The%20global%20cigarette%20market%20was,4%25%20during%202019%2D2024).
119. The global cigarette industry. Washington (DC): Campaign for Tobacco-Free Kids; 2019 (htt-

ps://www.tobaccofreekids.org/assets/global/pdfs/en/Global_Cigarette_Industry_pdf.pdf, accessed 13 August 2020).
120. 2020 second-quarter & year-to-date highlights. Lausanne: Philip Morris International; 2020 (https://philipmorrisinternational.gcs-web.com/static-files/b88146c3-a4e9-421e-b2aa-b470e74fcdf2, accessed 13 August 2020).
121. Carbon heated tobacco product: TEEPS. Lausanne: Philip Morris International; 2020.
122. Cigarettes in Japan: Country report. London: Euromonitor International; 2020 (https://www.euromonitor.com/cigarettes-in-japan/report, accessed 13 December 2020).
123. Korea – Ploom Tech. Geneva: Japan Tobacco International; 2020 (https://www.jti.com/node/5242, accessed 13 August 2020).
124. Japan Tobacco Inc. Integrated report 2019. Tokyo: Japan Tobacco Inc.; 2020 (https://www.jti.com/sites/default/files/global-files/documents/jti-annual-reports/integrated-report-2019v.pdf, accessed 13 August 2020).
125. Japan Tobacco International. 2020 second quarter results. Lausanne; 2020 (https://www.jt.com/investors/results/forecast/pdf/2020/Second_Quarter/20200731_07.pdf, accessed 13 August 2020).
126. JT launches two new tobacco vapor products under its Ploom brand. Tokyo: Japan Tobacco Inc.; 2019 (https://www.jti.com/sites/default/files/press-releases/documents/2019/JT-launches-two-new-tobacco-vapor-products-under-its-ploom-brand_0.pdf, accessed 13 August 2020).
127. JT launches Ploom S 2.0, an evolved heated tobacco device, in Japan on July 2nd and introduces two new Camel menthol tobacco stick products. Tokyo: Japan Tobacco Inc., 2020 (https://www.jt.com/media/news/2020/0601_01.html, accessed 13 August 2020.
128. Tobacco heating products: Innovating to lead the transformation of tobacco. London: British American Tobacco plc; 2020 (https://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOAWUGNJ, accessed 17 August 2020).
129. BAT Science: Introduction to tobacco heating products. London: British American Tobacco plc; 2020 (https://www.bat-science.com/groupms/sites/BAT_B9JBW3.nsf/vwPagesWebLive/DOBB3CEX, accessed 17 August 2020).
130. Delivering for today & investing in the future: Annual report and form 20-F 2019. London: British American Tobacco plc; 2020 (https://www.bat.com/ar/2019/pdf/BAT_Annual_Report_and_Form_20-F_2019.pdf, accessed 14 August 2020).
131. News release: British American Tobacco expands its new category portfolio with the launch of three innovative new tobacco heating products. London: British American Tobacco plc; 2019 (https://www.bat.com/group/sites/UK__9D9KCY.nsf/vwPagesWebLive/DOBFPCWP, accessed 14 August 2020.
132. British American Tobacco plc half-year report to 30 June 2020. London: British American Tobacco plc; 2020 (https://www.bat.com/group/sites/uk__9d9kcy.nsf/vwPagesWebLive/DO72TJQU/$FILE/medMDBRZQL4.pdf?openelement, accessed 17 August 2020).
133. Introduction to tobacco heating products. London: British American Tobacco plc; 2020 (https://www.bat-science.com/groupms/sites/BAT_B9JBW3.nsf/vwPagesWebLive/DOBB3CEX, accessed 14 August 2020).
134. lil: a little is a lot. Seoul: Korea Tobacco & Ginseng Corp., 2019 (http://en.its-lil.com/brand/main_brand. Published 2019, accessed 14 August 2020).
135. Philip Morris International Inc. announces agreement with KT&G to accelerate the achievement of a smoke-free future. Lausanne: Philip Morris International; 2020 (https://www.pmi.com/media-center/press-releases/press-release-details/?newsId=21786, accessed 14 August 2020).
136. McKelvey K, Popova L, Kim M, Chaffee BW, Vijayaraghavan M, Ling P et al. Heated tobacco products likely appeal to adolescents and young adults. Tob Control. 2018;27(Suppl 1):s41–7.

137. Heated tobacco products. Washington (DC): Campaign for Tobacco-Free Kids; 2020 (https://www.tobaccofreekids.org/what-we-do/global/heated-tobacco-products, accessed 13 August 2020).
138. Gravely S, Fong GT, Sutanto E, Loewen R, Ouimet J, Xu SS et al. Perceptions of harmfulness of heated tobacco products compared to combustible cigarettes among adult smokers in Japan: Findings from the 2018 ITC Japan survey. Int J Environ Res Public Health. 2020;17(7):2394.
139. Bar-Zeev Y, Levine H, Rubinstein G, Khateb I, Berg CJ. IQOS point-of-sale marketing strategies in Israel: A pilot study. Isr J Health Policy Res. 2019;8(1):11.
140. Bialous SA, Glantz SA. Heated tobacco products: Another tobacco industry global strategy to slow progress in tobacco control. Tob Control. 2018;27(Suppl 1):s111–7.
141. Jackler RK, Ramamurthi D, Axelrod AK, Jung JK, Louis-Ferdinand NG, Reidel JE et al. Global marketing of IQOS: The Philip Morris campaign to popularize "heat not burn". Berkeley (CA): Stanford Research into the Impact of Tobacco Advertising; 2020 (http://tobacco.stanford.edu/tobacco_main/publications/IQOS_Paper_2-21-2020F.pdf, accessed 17 August 2020).
142. Hair EC, Bennett M, Sheen E, Cantrell J, Briggs J, Fenn Z et al. Examining perceptions about IQOS heated tobacco product: Consumer studies in Japan and Switzerland. Tob Control. 2018;27(Suppl 1):s70–3.
143. IQOS App. Lausanne: Philip Morris International Management SA; 2020 (https://play.google.com/store/apps/details?id=com.pmi.store.PMIAPPM06278, accessed 14 August 2020).
144. IQOS in the US. Washington (DC): Truth Initiative; 2020 (https://truthinitiative.org/research-resources/emerging-tobacco-products/iqos-us, accessed 15 October 2020).
145. 2018 charitable contributions at a glance. Lausanne: Philip Morris International; 2018 (https://www.pmi.com/resources/docs/default-source/our_company/transparency/charitable-2018.pdf?sfvrsn=d97d91b5_2, accessed 15 October 2020).
146. Uranaka T, Ando R. Philip Morris aims to revive Japan sales with cheaper heat-not-burn tobacco. Reuters, 23 October 2018.
147. Asia Pacific heat-not-burn tobacco product market (2019–2025): Market forecast by product type, by demography, by sales channels, by countries, and competitive landscape. Dublin: Research and Markets; 2019 (https://www.researchandmarkets.com/reports/4911922/asia-pacific-heat-not-burn-tobacco-product-market).
148. Sutanto E, Miller C, Smith DM, O'Connor RJ, Quah ACK, Cummings KM et al. Prevalence, use behaviors, and preferences among users of heated tobacco products: Findings from the 2018 ITC Japan survey. Int J Environ Res Public Health. 2019;16(23):4630.
149. Kim J, Yu H, Lee S, Paek YJ. Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults. Tob Control. 2018;27(Suppl 1):s74–7.
150. Kang H, Cho S. Heated tobacco product use among Korean adolescents. Tob Control. 2020;29:466–8.
151. Heated tobacco products market size, share & trends analysis report by product (stick, leaf), by distribution channel (online, offline), by region, and segment forecasts, 2019–2025. San Francisco (CA): Grand View Research; 2019 (https://www.grandviewresearch.com/industry-analysis/heated-tobacco-products-htps-market).
152. Tobacco tactics. Heated tobacco products. Bath: University of Bath; 2020 (https://tobaccotactics.org/topics/heated-tobacco-products/, accessed 10 January 2021).
153. MacGuill S, Genov I. Emerging and next generation nicotine products (webinar). London: Euromonitor International; 2017 (http://go.euromonitor.com/rs/805-KOK-719/images/Emerging-and-Next-Generation-Nicotine-Products-Euromonitor.pdf, accessed 6 December 2020).
154. Countries that regulate heated tobacco. Baltimore (MD): Institute for Global Tobacco Control; 2020.

Supplementary sections

11. Forms of nicotine in tobacco plants, chemical modifications and implications for electronic nicotine delivery systems products

Nuan Ping Cheah, Pharmaceutical, Cosmetics and Cigarette Testing Laboratory, Health Sciences Authority, Singapore

Najat Saliba, Department of Chemistry, Faculty of Arts and Sciences, American University of Beirut, Beirut, Lebanon; Center for the Study of Tobacco Products, Virginia Commonwealth University, Richmond (VA), USA

Ahmad El-Hellani, Department of Chemistry, Faculty of Arts and Sciences, American University of Beirut, Beirut, Lebanon; Center for the Study of Tobacco Products, Virginia Commonwealth University, Richmond (VA), USA

Contents

Abstract

The impact of the form of nicotine, i.e. free base or salt, on its delivery from tobacco products and electronic nicotine delivery systems (ENDS) has been debated by scientists and regulators. In this paper, we briefly discussed the various ways of modifying the ratio of nicotine forms in tobacco products and ENDS. We focus on partitioning of nicotine forms in ENDS liquids, especially in the recently introduced pod-based ENDS. We discuss the influence of various parameters on nicotine delivery from ENDS, such as the form of nicotine,

counter-anions in nicotine salts, the power output of devices and user puffing topography. Recommendations are made on means to avoid capping nicotine concentrations in ENDS liquids as the sole measure for regulating nicotine delivery from ENDS and on adoption of "nicotine flux" as a regulatory tool that accounts for all the parameters that affect nicotine delivery from ENDS. We highlight the importance of including the form of nicotine in constructing a nicotine flux model and of minimizing possible customization of ENDS by users. While research is still necessary on methods for testing nicotine forms in ENDS liquids and aerosols and on absorption of the different forms by the body in the presence or absence of flavours, it is recommended that WHO urge countries to include nicotine flux and form in ENDS regulation to better inform users about nicotine delivery from their devices.

11.1 Background

This paper served as a "horizon" paper for the 10th meeting of the WHO Study Group on Tobacco Product Regulation and a platform for discussion and consideration of nicotine in ENDS products.

Nicotine can exist either as a free base or in combination with organic acids as various salts. This report provides a brief review of relevant published scientific information on nicotine, its presence in tobacco products, its modifications before manufacture and its forms in finished tobacco products. We also discuss the implications of the form of nicotine in ENDS for their appeal, addictive potential and health impact. The effect of the form of nicotine on tobacco control, regulation and research is also presented. In addition, we briefly discuss the relevance of nicotine flux for regulation of nicotine delivery from ENDS, arguing that the form of nicotine could be incorporated into the flux model.

Nicotine is the primary alkaloid in tobacco *(1)* and is the most abundant pyridine alkaloid in the leaves of 33 species; nornicotine is the most abundant in 24 species, anabasine in two species (*N. glauca* and *N. debneyi*) and anatabine in one species (*N. otophora*). In the roots, nicotine predominates in 51 species, nornicotine in two species (*N. alata* and *N. africana*) and anabasine in seven species (*N. glauca*, *N. solanifolia*, *N. benavidesii*, *N. cordifolia*, *N. debneyi*, *N. maritima* and *N. hesperis*) *(2)*. Nicotine is synthesized in the roots of tobacco *(3)* by an enzymatic pathway, with condensation of nicotinic acid (pyridine ring) and *N*-methyl-Δ^1-pyrrolinium cation (pyrrolidine ring) *(4)*. The amounts of nicotine and three other major pyridine alkaloids in selected *Nicotiana* species are shown in Table 11.1.

Table 11.1. Nicotine and major alkaloids contents in selected Nicotiana species

Subgenus, section	Species	Content (mg/g dry weight)		Percentage of total							
				Nicotine		Nornicotine		Anabasine		Anatabine	
		Leaves	Root	Leaves	Root	Leaves	Root	Leaves	Root	Leaves	Root
Rustica, Paniculatae	*N. glauca*	8 872	5 246	12.5	35.5	1.5	2.8	85.1	51.3	0.9	10.4
	N. solanifolia Walpers	848	9 326	3.2	27.7	81.4	10.0	15.4	60.3	Trace	2.0
	N. benavidesii Goodspeed*	2 166	14 666	82.7	44.9	1.3	0.8	14.8	48.1	1.2	6.2
	N. cordifolia Philippi	789	13 435	58.4	26.4	6.1	2.5	29.0	64.4	6.5	6.7
Rustica, Rusticae	*N. rustica* L.	7 752	8 439	96.4	81.6	0.9	1.7	1.1	6.6	1.6	10.1
Tabacum, Tomentosae	*N. otophora* Grisebach*	377	7 924	6.9	61.3	32.9	27.0	Trace	0.6	60.2	11.1
Tabacum, Genuinae	*N. tabacum* L.	11 462	2 176	94.8	81.3	3.0	6.0	0.3	1.7	1.9	11.0
Petunioides, Alatae	*N. alata* Link & Otto	26	1 998	100	37.7	Trace	46.4	–	Trace	–	15.8
Petunioides, Suaveolentes	*N. debneyi* Domin	2 457	3 038	31.1	34.7	15.8	1.4	46.0	53.2	7.1	10.7
	N. maritima Wheeler	608	14 030	7.2	20.8	70.4	30.0	15.8	44.5	6.6	4.6
	N. hesperis Burbridge	4 108	1 930	52.1	22.1	0.4	1.2	44.3	74.9	3.2	1.8
	N. africana Merxmuller & Buttler*	6 776	7 698	4.7	45.0	92.4	45.1	0.3	1.0	2.6	8.9

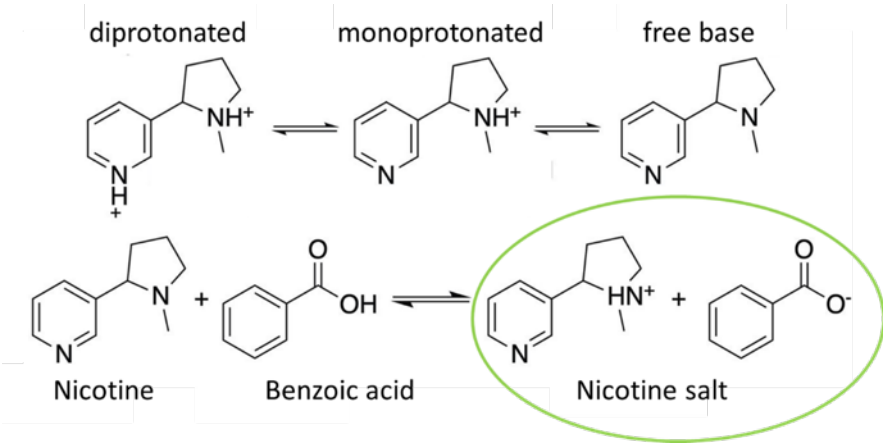
Source: reproduced from reference *2*.
* Species did not bloom.

The amount of biosynthesized nicotine in cultivated tobacco (*N. tabacum* L. and *N. rustica* L.) has been through gene modifications *(5)* and targeted gene manipulation for industrial applications *(6–8)*. *N. tabacum L.* and *N. rustica L.* are the major species used in the manufacturing of tobacco products due to the abundant level of nicotine present in these species *(9,10)*. Typical nicotine concentrations range from 15 to 35 mg per g tobacco *(3)*, with total alkaloid concentrations reaching up to 79 mg per g tobacco *(11)*.

The structure of nicotine comprises a pyrrolidine ring connected to a pyridine ring. The form of nicotine, free base, monoprotonated or diprotonated nicotine, depends on protonation of two nitrogen centres by naturally occurring acids in the leaves (Fig. 11.1). Protonated forms, also known as nicotine salts, predominate in unprocessed tobacco leaves; however, tobacco products have

different ratios of free base to salts. At pH 7, 8 and 9, free base is present in the solution at 9%, 49% and 90.5%, respectively; correspondingly, the nicotine salt is available at 91%, 51% and 9.5%.

Fig. 11.1. Free-base nicotine and monoprotonated and diprotonated nicotine salts



Source: references *12* and *13*.
The lower part of the figure shows protonation of nicotine with benzoic acid, which may occur naturally in tobacco leaves or during manufacture of tobacco products.

The stimulatory and addictive effects of nicotine are attributed to the action of the pyridine alkaloid on neuronal nicotinic acetylcholine receptors in the brain. Currently, cigarette smoking is the most effective form of nicotine delivery. Nicotine in mainstream smoke from combusted tobacco is rapidly absorbed into the lungs and can reach the brain in as little as 7 s *(14)*. Although tobacco smoking has been the most prevalent form of nicotine intake for decades, alternative tobacco products recently introduced onto the market (e.g. ENDS, heated tobacco products) are becoming popular around the globe, leading to an overall increase in total use of nicotine and tobacco products, especially among vulnerable populations such as young people. Thus, despite significant progress in tobacco control and prevention, nicotine and tobacco product use continues to grow. This report addresses nicotine abuse liability with one of the most widely marketed and most popular nicotine delivery products: ENDS. ENDS products, which are marketed in myriad combinations, allow users more customization than other nicotine and tobacco products *(14)*, hence the challenge of implementing one standard set of regulations. The impact of the form of nicotine (free base vs salt) on delivery from these devices is therefore being investigated *(15)*.

11.2 Chemical modification of nicotine and influence on nicotine delivery

11.2.1 Brief summary of the effect of curing on nicotine

The main determinant of the dependence potential of a nicotine and tobacco product is its ability to deliver pharmacologically active levels of nicotine rapidly *(16,17)*. Nicotine dosage is carefully controlled by manufacturers to ensure that it is sufficient to produce the desired effects, such as relaxation and mental acuity, while minimizing the risk of undesirable effects, such as nausea and intoxication *(18)*. Nicotine constitutes 2–8% of the dry weight of cured tobacco leaf, with wider ranges for some *Nicotiana* species *(19)*. The three main types of tobacco leaf used in commercial cigarettes are flue-cured, Burley and oriental (*20*, Table 11.2). Conventional cigarettes are made up of blends of these tobaccos. The primary blend differs among countries, but flue-cured and Burley tobaccos are used in the highest volume in commercial cigarettes. Most cigarettes contain primarily either flue-cured tobacco (e.g. in Canada) or a mixture of mainly flue-cured and Burley, with a minor amount of oriental tobacco (American blend) added.

Table 11.2. Types of tobacco, curing processes and nicotine content in tobacco leaf from the upper stalk position reported in literature

Tobacco type	Curing process	Tobacco products	Nicotine content (mg/g)
Virginia (or Bright)	Flue-cured by hanging the tobacco leaves in an enclosed area with heated air for 1 week	Blended cigarettes Virginia cigarettes	6.52–60.4
Burley	Air-cured in an air-ventilated area for 4–8 weeks	Blended cigarettes Kretek cigarettes (clove-flavoured)	35.6–47.73
Oriental	Cured by hanging tobacco leaves in the sun for 2 weeks	Blended cigarettes	1.80–12.6

Source: reference *21*.

Air-curing may decrease the final level of nicotine in tobacco leaves *(22–24)* due to oxidation of nicotine to cotinine or other oxidation products and conversion of nicotine to nornicotine by demethylation *(23,25,26)*. Flue-curing retains higher levels of sugars in the leaves; as these are precursors of organic acids in tobacco smoke, there is a smaller fraction of free-base nicotine in the smoke *(27)*.

11.2.2 Modification with alkali

Tobacco and "smoke pH" can be raised by using ammonia compounds (e.g. diammonium phosphate) and other substances (e.g. calcium carbonate) in tobacco processing. Calcium and sodium carbonates are added to cigarette filters to increase "smoke pH", possibly eliminating the addition of bases to tobacco

filler *(28,29)*. Ammonia has been used in the manufacture of tobacco since the accidental finding in the 1960s that elevated pH facilitates nicotine absorption, increasing free-base nicotine in cigarette smoke and tobacco products *(30–32)*, despite industry denial *(33,34)*. Ammonia also reacts with natural organic hydroxy compounds from tobacco and improves the quality of smoke, giving a smoother, "chocolate-like", less acidic taste *(35,36)*.

Other commonly used alkaline substances that increase smoke pH and improve smoke flavour include urea, diammonium phosphate, ethanolamines and carbonates *(37,38)*. In an alkaline or high-pH environment, nicotine in its un-ionized (free base) form is rapidly absorbed across mucous membranes; however, this rapid flux is irritating to the user.

11.2.3 Modification with acid

When cigarette smoke is perceived as too harsh, smokers inhale less deeply *(39)*. Additives such as levulinic acid make smoke appear smoother to the upper respiratory tract by lowering the fraction of free-base nicotine. As a result, the smoke is easier to inhale into the lungs *(40)*. Levulinic acid has also been reported to increase nicotine yield *(41)*. Addition of inorganic salts such as magnesium nitrate was found to lower the transfer of nicotine to tobacco smoke *(42)*. In acidic conditions, nicotine is ionized (protonated) and therefore crosses biological membranes much more slowly and is less irritating *(43)*. Table 11.3 summarizes the results of studies of the addition of acids to tobacco products.

Table 11.3. Results of adding acids to tobacco products

Type of acid	Purpose of addition
Lactic acid	Decreased harshness and bitterness, resulting in a sweeter flavour and smoothness *(44)*
Citric acid	Reduced harshness, modified flavour, lowered smoke pH, "neutralized" the impact of nicotine, enhanced sheet formation in reconstituted tobacco *(45,46)*
Tartaric acid	Similar to lactic acid, reduced the pH of smoke *(46,47)*
Malic acid	Did not promote migration in typical construction and storage procedures *(48,49)*
Formic acid	Increased nicotine delivery, but had a distinct sour taste and failed to improve subjective performance *(50,51)*
Levulinic acid	Reduced harshness without decreasing nicotine delivery in smoke and with no unpleasant taste. Nicotine salt of levulinic acid also increased smoke nicotine delivery *(41,52)*.
Benzoic and sorbic acid	Reduced harshness, increased nicotine delivery. Form salts with nicotine.
Pyruvic and lauric acid	Typically added to form nicotine salt *(53,54)*

11.3 Implications for ENDS products and diversity

11.3.1 Free-base nicotine vs nicotine salt in ENDS

The previous section showed that the form and dosage of nicotine in combustible cigarettes can be controlled by the manufacturer during tobacco curing or

processing. We reported above that the distribution of different forms of nicotine in tobacco smoke affects the inhalability of nicotine. Free-base nicotine is readily absorbed in the upper respiratory tract, while nicotine salts are delivered to the bronchioalveolar region *(55)*. Although the sites of absorption of the different nicotine forms are known, there is still controversy about how the site affects the rate of nicotine delivery to the brain *(56)*.

ENDS allow users greater customization of their experience with nicotine in terms of dose and form. The ratios of nicotine forms in ENDS liquids results in pH in the entire range (5.3–9.3) *(57)*, although the aerosol of the most popular ENDS (e.g. pod-based ENDS) has a low pH and high levels of nicotine salts. Added acids, such as levulinic acid, form monoprotonated and diprotonated nicotine forms, making inhalation of aerosols from ENDS smoother on the throat and upper airways. Other common acids used to form nicotine salts are lactic, benzoic, sorbic, pyruvic, salicylic, malic, lauric and tartaric acids *(54)*. One report stated that flavour additives such as phenols, vanillin and ethyl vanillin can act as protonating agents in e-liquids *(58)*. A study based on a randomized controlled trial *(59)* indicated that the presence of nicotine salts in ENDS reduces craving to the same extent as conventional cigarettes. Pharmacokinetics and subjective data demonstrate that nicotine lactate delivers nicotine via the pulmonary route for rapid absorption, albeit with a maximum nicotine level that does not exceed that in conventional cigarettes, and also showed acceptable subjective satisfaction and relief of a desire to smoke *(59)*.

Nicotine in its three forms is considered the main addictive chemical in tobacco products. By the 1990s, it was increasingly accepted that tobacco products without nicotine would not sustain addiction *(16,60)*. It is therefore important to focus on the interaction between flavours and nicotine in user perceptions of ENDS aerosols. Flavours could reduce the upper respiratory tract irritation of high nicotine levels in ENDS aerosols or contribute to the sensory impact of aerosols with low nicotine levels, as was shown with menthol *(61)*. Moreover, published data show that some flavours, like apple, may increase the reinforcing effects of nicotine in ENDS aerosols *(62)*, as was shown to be the case with menthol in cigarette smoke *(63)*.

Nicotine salts such as nicotine benzoate are monoprotonated salts. These are reported to produce a high degree of satisfaction in users, as evidenced by the popular JUUL product *(64)*, a patented formulation with benzoate salts *(54)* and similar ENDS *(65)*. During aerosolization, nicotine salt dissociates during evaporation to give free-base nicotine and acid molecules that recombine upon contact with ambient air to condense into inhalable aerosols *(54)*. Chromatography identifies the counter-anions derived from added acids, such as salicylate, tartrate, levulinate and malate in e-liquid or aerosols *(66,67)*.

11.3.2 Feasible concentrations and abuse liability

Several investigators have adapted or developed analytical methods for determining the nicotine content of ENDS liquids and aerosols *(68–70)*. The concentrations in ENDS liquids and prefilled cartridges range widely, from 0 in nicotine-free cartridges and liquids to about 130 mg/mL in some "do-it-yourself" liquids *(71–73)*. In the early years of the ENDS epidemic, cartridge-based ENDS (closed systems) had lower nicotine concentrations than open systems *(71)*; however, the recently introduced pod-based ENDS contain very high levels of nicotine of > 60 mg/mL *(69,74)*. The appeal of ENDS is related not only to the nicotine concentration but also to the form of nicotine, free base or salt *(75–77)*. The few reports to date of analyses of the form of nicotine in ENDS liquids showed a wide range of pH values and ratios of nicotine forms *(68,78,79)*. A variety of approaches was used in these studies, including pH measurement and then estimation of the ratio of nicotine forms with the Henderson–Hasselbalch equation or an organic solvent extraction of nicotine from ENDS liquid dissolved in water to measure the different forms of nicotine by gas chromatography *(68)* or determining the ratios of different forms of nicotine by proton nuclear magnetic resonance spectroscopy *(80)*. Moreover, nicotine present in the liquid is transferred efficiently to the aerosol and subsequently influences the resulting subjective effects *(67)*. Recent work by the authors of this report showed that the form of nicotine does not affect the total yield of nicotine delivered in aerosols *(81)*.

Several factors contribute to the appeal and continued use of ENDS, including flavours, high "customizability" and nicotine delivery *(82,83)*. In the USA, use of ENDS, unlike any other non-cigarette tobacco product in the past decade, has surpassed cigarette smoking among children and young adults *(84)*. The possibility of unlimited combinations of operating parameters (i.e. power, liquid composition, puff topography) in some ENDS allows delivery of nicotine at doses ranging from trace amounts to orders of magnitude higher than those delivered by a combustible cigarette *(71,85,86)*. This wide range of nicotine delivery may increase the risk of abuse liability and nicotine dependence for users *(87)*. Addiction to nicotine, like other drugs, is a function of the dose delivered and the speed of delivery *(88)*. Smoking a combustible tobacco cigarette is an efficient, rapid means of nicotine delivery, hence its addictive character *(89)*. The same applies to ENDS: recent brain imaging studies showed that ENDS can deliver nicotine to the brain at a rate similar to that of a combustible cigarette *(90,91)*.

It is important to note that ENDS (and heated tobacco products) are often used as complements to cigarette smoking and not as substitutes, especially in smoke-free environments *(92)*. Thus, dual use of ENDS and cigarettes is a common practice that sustains nicotine dependence *(93)*. Longitudinal studies have also shown that ENDS users concurrently smoke combustible cigarettes, perhaps due to greater nicotine dependence *(94,95)*. There is thus a growing trend of dual use of ENDS with combustible cigarettes *(96,97)*.

11.3.3 Potential masking of the harshness of products

Nicotine delivery is one of the main reasons for using ENDS *(98)*. Another factor that contributes to the popularity of ENDS is the wide availability of unique flavours *(99,100)*, the number of which has grown dramatically in recent years *(101)*. The most common flavours are tobacco, menthol or mint, fruit, candy or dessert and beverages *(102–104)*. Flavours can mask the harshness associated with inhaled free-base nicotine, especially if they induce a cool sensation, such as mint and menthol *(105)*. An interesting area of research would therefore be the correlation between flavour choice and nicotine form used by novice and by experienced users.

11.3.4 Health implications and potential regulations

ENDS are commonly perceived as safer and less addictive than cigarette smoking, which may contribute to their rising popularity *(106,107)*. Global use of ENDS has increased rapidly in the past decade, especially among young people, and there is evidence of nicotine dependence in this population *(81,108–113)*. Early ENDS devices were deemed inefficient in delivering nicotine to the user *(114)*; however, as the devices evolved and users became more experienced in their use, the efficiency of nicotine delivery greatly increased *(115–117)*.

ENDS products are notably heterogeneous, with differences in materials, configurations, electrical power output, solvents and composition *(118)*. Nicotine yield therefore depends on a combination of variables, such as device power, liquid composition and user puffing behaviour *(84,119)*. As noted above, ENDS provide users unprecedented opportunities for customizing the nicotine concentration and sometimes form, and thus their nicotine dose, by preparing their own liquids and modifying operating parameters.

Nicotine delivery from ENDS is a subject of much debate among scientists and policy-makers. Some argue that, if ENDS products deliver nicotine at a dose and rate comparable to those of a combustible cigarette, ENDS may help smokers to reduce or quit smoking and subsequently reduce their exposure to the associated harm *(120)*. Comparably efficient nicotine delivery may, however, make ENDS users, including previously nicotine-naïve individuals, more addicted to nicotine *(110,121,122)*. A recent study showed that imposing a limit on the nicotine concentration of ENDS liquid is not sufficient to ensure nicotine yields lower than those of a combustible cigarette *(123)*, as users can increase the power of the device to obtain the levels of nicotine in combustible cigarettes. Moreover, users who switch to higher-power devices inhale more aerosol and thus more toxicants, with unintended health consequences *(86)*.

Most countries have not revised their legislation to include regulations on ENDS. Researchers and regulators, mainly in Europe, have considered that a first regulatory measure to mitigate risk could be to cap the nicotine content

of ENDS liquids to control nicotine delivery. Such a policy has been effective in the European Union since 2014, with a limit of 20 mg/mL on the nicotine concentration in ENDS liquids. Similar approaches could be considered in other jurisdictions. This policy does not, however, account for variations in ENDS product characteristics, such as power and puff topography. For example, users in a jurisdiction in which the nicotine concentration is limited may circumvent the aim of the regulation by choosing devices with higher power to obtain a nicotine yield that exceeds that of a combustible cigarette. Shihadeh and Eissenberg *(124)* proposed measurement of "nicotine flux", which is the amount of nicotine delivered from a mouthpiece in a unit time (mg/s), as a suitable regulatory tool that encapsulates all the relevant operating parameters of ENDS that affect the rate and dose of nicotine delivered to the user. Current work from this group focuses on incorporating the form of nicotine into the nicotine flux construct. Clinical studies of the addictiveness and abuse liability of ENDS will determine the impact of the form of nicotine on the speed of delivery. The form of nicotine may also affect toxicity, as demonstrated by Pankow et al. *(125)*, who showed that use of benzoic acid in the preparation of nicotine salt may lead to formation of benzene in ENDS emissions.

11.4 Discussion

Industry has used many approaches to enhance the efficiency of nicotine delivery from cigarettes, including manipulating the ratio of nicotine forms in cigarette filler. Nonetheless, a balance between nicotine delivery and harshness in the generated smoke dictated the manufacture of conventional cigarettes. A similar approach has recently been taken in the design of ENDS *(126)*. The liquids used in ENDS that have the largest market share have a lower pH, due to the addition of organic acids, which masks the harshness of the large quantity of nicotine delivered during aerosolization. Nicotine salts, however, may contribute to the toxicity of electronic cigarette aerosols due to the degradation of counter-anions *(125)*.

11.5 Research gaps, priorities and questions to members regarding further work or a full paper

The evidence indicates that various forms of nicotine, i.e. free-base nicotine and monoprotonated and diprotonated nicotine salts, are already available on the market of nicotine and tobacco products and are spreading quickly to other products. Recently, the industry has begun to manufacture synthetic nicotine, which is becoming cheaper to produce than previous technologies. It has already been used in e-liquids *(127)*. This may be a challenge for regulation in certain jurisdictions, as the nicotine is not of tobacco origin.

Research and development are required to:

- develop and/or validate standard methods for measuring free-base nicotine and determining the ratio of free base to protonated and diprotonated nicotine in e-liquids and aerosols of ENDS;
- quantify total and different forms of nicotine and organic acids in ENDS liquids and aerosols *(68,81)*;
- determine the impact of the form of nicotine on nicotine delivery to ENDS users and the dependence potential, including maintenance of addiction in a study conducted in the presence and absence of confounders;
- investigate the health implications of the use of organic acids to change nicotine pharmacokinetics *(128)* and the impact on toxicity; and
- validate nicotine flux, with nicotine form, as a tool for regulating nicotine delivery from ENDS.
- If these gaps are addressed, the global priorities could be to:
- ensure that the ratio of nicotine forms in ENDS helps smokers of combustible cigarettes to quit and does not lead novice users to become nicotine addicts; and
- on the basis of rigorous evidence, restrict manipulation of nicotine concentration and form by manufacturers.

In view of the importance of nicotine delivery from ENDS and the possible combined effect of nicotine form and concentration in ENDS liquids on its appeal, attractiveness and addictiveness, consideration should be given to requesting a full paper in the future.

11.6 Recommendation

Consideration should be given to preparation of a full paper on nicotine forms for a future meeting, if the topic is considered a priority and sufficient information is available.

11.7 Considerations

When countries strengthen their tobacco regulatory framework, a primary goal should be to reduce exposure to nicotine, the most important addictive substance in tobacco. Many countries have the authority to regulate products made of or derived from tobacco, as covered in Article 1 of the WHO Framework Convention on Tobacco Control. So far, the only regulation on nicotine delivery from ENDS is that of the European Union, which limits the nicotine content of

ENDS liquids. We argue above that this may be ineffective in addressing all the capabilities of this new category of nicotine delivery product, as it does not reflect the fact that the nicotine yield from ENDS is a result of many factors, such as nicotine concentration, power output and user puffing regime. Nicotine flux may be an option for regulatory consideration.

Moreover, the impact of the form of nicotine on its delivery, pharmacokinetics and pharmacodynamics is not well studied, and more research is necessary. Regulators should also consider minimizing the extent of possible customization of ENDS by users in terms of nicotine load and form and other features such as flavours.

Countries might have to review their legislation to regulate nicotine-containing products comprehensively, regardless of the origin of the nicotine, in the interests of public health. If nicotine delivery products are not regulated, the work of countries and WHO in reducing tobacco use and nicotine abuse liability may be compromised. Finally, WHO should consider discussion of the inclusion of ENDS in the WHO Framework Convention on Tobacco Control or a provision within the Convention to address regulatory issues specific to these products.

11.8 References

1. Wernsman E. Time and site of nicotine conversion in tobacco. Tob Sci. 1968;12:226–8.
2. Saitoh F, Noma M, Kawashima N. The alkaloid contents of sixty Nicotiana species. Phytochemistry. 1985;24(3):477–80.
3. Collins W, Hawks S. Principles of flue-cured tobacco production. Raleigh (NC): HarperCollins Publishers; 1993.
4. Sun B, Tian YX, Zhang F, Chen Q, Zhang Y, Luo Y et al. Variations of alkaloid accumulation and gene transcription in Nicotiana tabacum. Biomolecules. 2018;8(4):114.
5. Liu H, Kotova TI, Timko MP. Increased leaf nicotine content by targeting transcription factor gene expression in commercial flue-cured tobacco (Nicotiana tabacum L.). Genes. 2019;10(11):10.3390/genes10110930.
6. Saunders JW, Bush LP. Nicotine biosynthetic enzyme activities in Nicotiana tabacum L. genotypes with different alkaloid levels. Plant Physiol. 1979;64(2):236–40.
7. Moghbel N, Ryu B, Ratsch A, Steadman KJ. Nicotine alkaloid levels, and nicotine to nornicotine conversion, in Australian Nicotiana species used as chewing tobacco. Heliyon. 2017;3(11):e00469.
8. Griffith R, Valleau W, Stokes G. Determination and inheritance of nicotine to nornicotine conversion in tobacco. Science. 1955;121(3140):343–4.
9. Chaplin JF, Burk L. Agronomic, chemical, and smoke characteristics of flue-cured tobacco lines with different levels of total alkaloids 1. Agron J. 1984;76(1):133–6.
10. Chaplin JF, Burk L. Genetic approaches to varying chemical constituents in tobacco and smoke. Beitr Tabakforsch. 1977;9(2):102–6.
11. Tso TC. Production, physiology, and biochemistry of tobacco plant. Beltsville (MD): Ideals; 1990.
12. Baxendale IR, Brusotti G, Matsuoka M, Ley SV. Synthesis of nornicotine, nicotine and other functionalised derivatives using solid-supported reagents and scavengers. J Chem Soc Perkin Trans. 2002;2002(2):143–54.
13. Domino EF, Hornbach E, Demana T. The nicotine content of common vegetables. N Engl J

Med. 1993;329(6):437.
14. Maisto SA, Galizio M, Connors GJ, editors. Drug use and abuse. Seventh edition. Belmont (CA): Cengage Learning; 2014.
15. Gholap VV, Kosmider L, Golshahi L, Halquist MS. Nicotine forms: Why and how do they matter in nicotine delivery from electronic cigarettes? Expert Opin Drug Delivery. 2020;1–10.
16. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction – the implications for tobacco regulation. New Engl J Med. 1994;331(2):123–5.
17. Henningfield J, Benowitz N, Slade J, Houston T, Davis R, Deitchman S. Reducing the addictiveness of cigarettes. Tob Control. 1998;7(3):281.
18. Carpenter CM, Wayne GF, Connolly GN. Designing cigarettes for women: new findings from the tobacco industry documents. Addiction. 2005;100(6):837–51.
19. Gorrod JW, Jacob P III, editors. Analytical determination of nicotine and related compounds and their metabolites. Amsterdam: Elsevier Science; 1999.
20. Paschke T, Scherer G, Heller WD. Effects of ingredients on cigarette smoke composition and biological activity: a literature overview. Beitr Tabakforsg. 2002;20(3):107–244.
21. Djordjevic MV, Gay SL, Bush LP, Chaplin JF. Tobacco-specific nitrosamine accumulation and distribution in flue-cured tobacco alkaloid isolines. J Agric Food Chem. 1989;37(3):752–6.
22. Burton H, Bush L, Hamilton J. Effect of curing on the chemical composition of burley tobacco. Rec Adv Tob Sci. 1983;9:91–153.
23. Wahlberg I, Karlsson K, Austin DJ, Junker N, Roeraade J, Enzell C et al. Effects of flue-curing and ageing on the volatile, neutral and acidic constituents of Virginia tobacco. Phytochemistry. 1977;16(8):1217–31.
24. Burton HR, Kasperbauer M. Changes in chemical composition of tobacco lamina during senescence and curing. 1. Plastid pigments. J Agric Food Chem. 1985;33(5):879–83.
25. Bush L. Physiology and biochemistry of tobacco alkaloids. Recent Adv Tob Sci. 1981;7:75–106.
26. Frankenburg WG, Gottscho AM, Mayaud EW, Tso TC. The chemistry of tobacco fermentation. I. Conversion of the alkaloids. A. The formation of 3-pyridyl methyl ketone and of 2,3´-dipyridyl. J Am Chem Soc. 1952;74(17):4309–14.
27. Elson L, Betts T, Passey R. The sugar content and the pH of the smoke of cigarette, cigar and pipe tobaccos in relation to lung cancer. Int J Cancer. 1972;9(3):666–75.
28. Leffingwell JC. Tobacco, production, chemistry and technology. Oxford: Blackwell;. 1999.
29. Douglas C. Tobacco manufacturers manipulate nicotine content of cigarettes to cause and sustain addiction. Tobacco: the growing epidemic. Berlin: Springer; 2000:209–11.
30. Brambles Australia Ltd (Brambles) v British American Tobacco Australia Services Ltd (BATAS). 2007. Bates No.: proctorr20071203b (https://www.industrydocuments.ucsf.edu/docs/tmyg0225, accessed 18 March 2020).
31. Fant RV, Henningfield JE, Nelson RA, Pickworth WB. Pharmacokinetics and pharmacodynamics of moist snuff in humans. Tob Control. 1999;8(4):387–92.
32. Henningfield JE, Radzius A, Cone EJ. Estimation of available nicotine content of six smokeless tobacco products. Tob Control. 1995;4(1):57.
33. Stevenson T, Proctor RN. The secret and soul of Marlboro. Am J Public Health. 2008;98(7):1184–94.
34. Hind JD, Seligman RB. Tobacco sheet material. US Patent. 3,353,541. 1967. Filed 16 June 1966 and issued 21 November 1967.
35. Teague CE Jr. Modification of tobacco stem materials by treatment with ammonia and other substances. Winston-Salem (NC): RJ Reynolds; 1954. Bates no. 504175083-5084 (http://legacy.library.ucsf.edu/tid/gpt58d00, accessed 9 November 2020).
36. Pankow JF, Mader BT, Isabelle LM, Luo W, Pavlick A, Liang C. Conversion of nicotine in tobacco smoke to its volatile and available free-base form through the action of gaseous ammonia. Environ Sci Technol. 1997;31(8):2428–33.

37. Seligman R. The use of alkalis to improve smoke flavor. Philip Morris. 1965. Bates no. 2026351158-2026351163 (https://www.industrydocuments.ucsf.edu/docs/tfpv0109, accessed 4 December 2020).
38. Armitage AK, Dixon M, Frost BE, Mariner DC, Sinclair NM. The effect of tobacco blend additives on the retention of nicotine and solanesol in the human respiratory tract and on subsequent plasma nicotine concentrations during cigarette smoking. Chem Res Toxicol. 2004;17(4):537–44.
39. Henningfield JE, Fant RV, Radzius A, Frost S. Nicotine concentration, smoke pH and whole tobacco aqueous pH of some cigar brands and types popular in the United States. Nicotine Tob Res. 1999;1(2):163–8.
40. Scientific Committee on Emerging and Newly Identified Health Risks. Addictiveness and attractiveness of tobacco additives. Brussels: European Commission, Directorate-General for Health and Consumers; 2010 (https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf, accessed 9 November 2020).
41. Keithly L, Ferris Wayne G, Cullen DM, Connolly GN. Industry research on the use and effects of levulinic acid: a case study in cigarette additives. Nicotine Tob Res. 2005;7(5):761–71.
42. Kobashi Y, Sakaguchi S. The influence of inorganic salts on the combustion of cigarette and on the transfer of nicotine on to smoke. Agric Biol Chem. 1961;25(3):200–5.
43. van Amsterdam J, Sleijffers A, van Spiegel P, Blom R, Witte M, van de Kassteele J et al. Effect of ammonia in cigarette tobacco on nicotine absorption in human smokers. Food Chem Toxicol. 2011;49(12):3025–30.
44. Meyer L. Lactic acid sprayed cellulose acetate filters. 1963, Bates No.: 1003105149-1003105150 (https://www.industrydocuments.ucsf.edu/docs/qjwd0107, accessed 5 April 2020).
45. Morris P. Citric acid. 1989. Bates No.: 2028670128-2028670129 (https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=nzfm0111, accessed 5 April 2020).
46. Winterson WD, Cochran TD, Holland TC, Torrence KM, Rinehart S, Scott GR. Method of making pouched tobacco product. US Patent no. US 7,980,251 B2; 2011.
47. JD Backhurst. The effects of ameliorants on the smoke from Burley tobacco. 1968. Bates No.: 302075334-302075350 (https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=jnvj0189, accessed 5 April 2020).
48. Sudholt MA. Increased impact of cellulose–malic acid filter containing migrated nicotine. 1985. Bates No.: 81122186-81122188 (https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=jnfk0037, accessed 5 April 2020).
49. Sudholt MA. Continuation of study of malic acid treated cellulose filters. 1985. Bates No.: 80551009-80551010 (https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=kmfk0037, accessed 5 April 2020).
50. Cipriano JJ, Kounnas CN, Spielberg HL. Manipulation of nicotine delivery by addition of acids to filler. 1979. Bates No.: 3990037328-3990037339 https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=kpxp0180, accessed 5 April 2020).
51. Cipriano JJ, Kounnas CN, Spielberg HL. Manipulation of nicotine delivery by addition of acids to filter. 1975. Bates No.: 3990093180-3990093188 (https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=zpgp0180, accessed 5 April 2020).
52. Levulinic acid. RJ Reynolds Collection. 1991. Bates No.: 512203269-512203295 (https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=rymk0089, accessed 5 April 2020).
53. Bowen A, Xing C. Nicotine salt formulations for aerosol devices and methods thereof. US Patent no. USS 9,215,895 B2; 2015.
54. Bowen A, Xing C. Inventors; JUUL Labs, Inc., assignee (2016). Nicotine salt formulations for aerosol devices and methods thereof. US patent 20,160,044,967. 28 October 2015.
55. Armitage A, Dollery C, Houseman T, Kohner E, Lewis P, Turner D. Absorption of nicotine by

man during cigar smoking. Br J Pharmacol. 1977;59(3):493P.
56. Pankow JF. A consideration of the role of gas/particle partitioning in the deposition of nicotine and other tobacco smoke compounds in the respiratory tract. Chem Res Toxicol. 2001;14(11):1465–81.
57. El-Hellani A, Salman R, El-Hage R, Talih S, Malek N, Baalbaki R et al. Nicotine and carbonyl emissions from popular electronic cigarette products: correlation to liquid composition and design characteristics. Nicotine Tob Res. 2018;20(2):215–23.
58. Pankow JF, Duell AK, Peyton DH. Free-base nicotine fraction αfb in non-aqueous versus aqueous solutions: electronic cigarette fluids without versus with dilution with water. Chem Res Toxicol. 2020;33(7):1729–35.
59. O'Connell G, Pritchard JD, Prue C, Thompson J, Verron T, Graff D et al. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. Intern Emerg Med. 2019;14(6):853–61.
60. Henningfield J, Pankow J, Garrett B. Ammonia and other chemical base tobacco additives and cigarette nicotine delivery: issues and research needs. Nicotine Tob Res. 2004;6(2):199–205.
61. Rosbrook K, Green BG. Sensory effects of menthol and nicotine in an e-cigarette. Nicotine Tob Res. 2016;18(7):1588–95.
62. Avelar AJ, Akers AT, Baumgard ZJ, Cooper SY, Casinelli GP, Henderson BJ. Why flavored vape products may be attractive: Green apple tobacco flavor elicits reward-related behavior, upregulates nAChRs on VTA dopamine neurons, and alters midbrain dopamine and GABA neuron function. Neuropharmacology. 2019;158:107729.
63. Ahijevych K, Garrett BE. The role of menthol in cigarettes as a reinforcer of smoking behavior. Nicotine Tob Res. 2010;12(Suppl 2):S110–6.
64. Fadus MC, Smith TT, Squeglia LM. The rise of e-cigarettes, pod mod devices, and Juul among youth: Factors influencing use, health implications, and downstream effects. Drug Alcohol Depend. 2019;201:85–93.
65. Barrington-Trimis JL, Leventhal AM. Adolescents' use of "pod mod" e-cigarettes – urgent concerns. New Engl J Med. 2018;379(12):1099–102.
66. Tracy M, Liu X. Analysis of nicotine salts by HPLC on an anion-exchange/cation-exchange/reversed-phase tri-mode column. Sunnyvale (CA): Dionex Corp.; 2011 (https://www.chromatographyonline.com/view/analysis-nicotine-salts-hplc-anion-exchangecation-exchangereversed-phase-tri-mode-column, accessed 7 March 2020).
67. Sádecká J, Polonský J. Determination of organic acids in tobacco by capillary isotachophoresis. J Chromatogr A. 2003;988(1):161–5.
68. El-Hellani A, El-Hage R, Baalbaki R, Salman R, Talih S, Shihadeh A et al. Free-base and protonated nicotine in electronic cigarette liquids and aerosols. Chem Res Toxicol. 2015;28(8):1532–7.
69. Omaiye EE, McWhirter KJ, Luo W, Pankow JF, Talbot P. High-nicotine electronic cigarette products: toxicity of JUUL fluids and aerosols correlates strongly with nicotine and some flavor chemical concentrations. Chem Res Toxicol. 2019;32(6):1058–69.
70. Duell AK, Pankow JF, Peyton DH. Free-base nicotine determination in electronic cigarette liquids by 1H NMR spectroscopy. Chem Res Toxicol. 2018;31(6):431–4.
71. El-Hellani A, Salman R, El-Hage R, Talih S, Malek N, Baalbaki R et al. Nicotine and carbonyl emissions from popular electronic cigarette products: correlation to liquid composition and design characteristics. Nicotine Tob Res. 2018;20(2):215–23.
72. Grana RA, Ling PM. "Smoking revolution": a content analysis of electronic cigarette retail websites. Am J Prev Med. 2014;46(4):395–403.
73. Davis B, Dang M, Kim J, Talbot P. Nicotine concentrations in electronic cigarette refill and do-it-yourself fluids. Nicotine Tob Res. 2015;17(2):134–41.
74. Talih S, Salman R, El-Hage R, Karam E, Karaoghlanian N, El-Hellani E et al. Characteristics and

toxicant emissions of JUUL electronic cigarettes. Tob Control. 2019;28(6):678–80.
75. St Helen G, Ross KC, Dempsey DA, Havel CM, Jacob P, Benowitz NL. Nicotine delivery and vaping behavior during ad libitum e-cigarette access. Tob Regul Sci. 2016;2(4):363–76.
76. Kong G, Bold KW, Morean ME, Bhatti H, Camenga DR, Jackson A et al. Appeal of JUUL among adolescents. Drug Alcohol Depend. 2019;205:107691.
77. Seeman JI, Fournier JA, Paine JB, Waymack BE. The form of nicotine in tobacco. Thermal transfer of nicotine and nicotine acid salts to nicotine in the gas phase. J Agric Food Chem. 1999;47(12):5133–45.
78. Stepanov I, Fujioka N. Bringing attention to e-cigarette pH as an important element for research and regulation. Tob Control. 2015;24(4):413–4.
79. Lisko JG, Tran H, Stanfill SB, Blount BC, Watson CH. Chemical composition and evaluation of nicotine, tobacco alkaloids, pH, and selected flavors in e-cigarette cartridges and refill solutions. Nicotine Tob Res. 2015;17(10):1270–8.
80. Gholap VV, Heyder RS, Kosmider L, Halquist MS. An analytical perspective on determination of free base nicotine in e-liquids. J Anal Meth Chem. 2020;2020:6178570.
81. Talih S, Salman R, El-Hage R, Karaoghlanian N, El-Hellani A, Saliba N et al. Effect of free-base and protonated nicotine on nicotine yield from electronic cigarettes with varying power and liquid vehicle. Sci Rep.2020;10:16263.
82. Cobb CO, Lopez AA, Soule EK, Yen MS, Rumsey H, Lester Scholtes R et al. Influence of electronic cigarette liquid flavors and nicotine concentration on subjective measures of abuse liability in young adult cigarette smokers. Drug Alcohol Depend. 2019;203:27–34.
83. Camenga DR, Morean M, Kong G, Krishnan-Sarin S, Simon P, Bold K. Appeal and use of customizable e-cigarette product features in adolescents. Tob Regul Sci. 2018;4(2):51–60.
84. Youth and tobacco use. Atlanta (GA): Centers for Disease Control and Prevention; 2019 (https://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/tobacco_use/index.htm, accessed 21 January 2020).
85. Talih S, Balhas Z, Salman R, El-Hage R, Karaoghlanian N, El-Hellani A et al. Transport phenomena governing nicotine emissions from electronic cigarettes: Model formulation and experimental investigation. Aerosol Sci Technol. 2017;51(1):1–11.
86. Voos N, Goniewicz ML, Eissenberg T. What is the nicotine delivery profile of electronic cigarettes? Expert Opin Drug Delivery. 2019;16(11):1193–203.
87. Dawkins L, Cox S, Goniewicz M, McRobbie H, Kimber C, Doig M et al. "Real-world" compensatory behaviour with low nicotine concentration e-liquid: subjective effects and nicotine, acrolein and formaldehyde exposure. Addiction. 2018;113(10):1874–82.
88. Allain F, Minogianis EA, Roberts DCS, Samaha AN. How fast and how often: The pharmacokinetics of drug use are decisive in addiction. Neurosci Biobehav Rev. 2015;56:166–79.
89. Berridge MS, Apana SM, Nagano KK, Berridge CE, Leisure GP, Boswell MV. Smoking produces rapid rise of [11C]nicotine in human brain. Psychopharmacology. 2010;209(4):383–94.
90. Baldassarri SR, Hillmer AT, Anderson JM, Jatlow P, Nabulsi N, Labaree D et al. Use of electronic cigarettes leads to significant beta2-nicotinic acetylcholine receptor occupancy: Evidence from a PET imaging study. Nicotine Tob Res. 2017;20(4):425–33.
91. Solingapuram Sai KK, Zuo Y, Rose JE, Garg PK, Garg S, Nazih R et al. Rapid brain nicotine uptake from electronic cigarettes. J Nuclear Med. 2019;10.2967.
92. Shi Y, Cummins SE, Zhu SH. Use of electronic cigarettes in smoke-free environments. Tob Control. 2017;26(e1):e19–22.
93. Owusu D, Huang J, Weaver SR, Pechacek TF, Ashley DL, Nayak P et al. Patterns and trends of dual use of e-cigarettes and cigarettes among US adults, 2015–2018. Prev Med Rep. 2019;16:101009.
94. Stanton CA, Sharma E, Edwards KC, Halenar MJ, Taylor KA, Kasza KA et al. Longitudinal trans-

itions of exclusive and polytobacco electronic nicotine delivery systems (ENDS) use among youth, young adults and adults in the USA: findings from the PATH Study waves 1–3 (2013–2016). Tob Control. 2020;29(Suppl 3):s147–54.
95. Aleyan S, Hitchman SC, Ferro MA, Leatherdale ST. Trends and predictors of exclusive e-cigarette use, exclusive smoking and dual use among youth in Canada. Addict Behav. 2020:106481.
96. Piper ME, Baker TB, Benowitz NL, Jorenby DE. Changes in use patterns over 1 year among smokers and dual users of combustible and electronic cigarettes. Nicotine Tob Res. 2020;22(5):672–80.
97. Roh EJ, Chen-Sankey JC, Wang MQ. Electronic nicotine delivery system (ENDS) use patterns and its associations with cigarette smoking and nicotine addiction among Asian Americans: Findings from the national adult tobacco survey (NATS) 2013–2014. J Ethnicity Subst Abuse. 2020:1–19.
98. Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. Nicotine Tob Res. 2014;17(7):847–54.
99. Soule EK, Lopez AA, Guy MC, Cobb CO. Reasons for using flavored liquids among electronic cigarette users: A concept mapping study. Drug Alcohol Depend. 2016;166:168–76.
100. Romijnders KAGJ, van Osch L, de Vries H, Talhout R. Perceptions and reasons regarding e-cigarette use among users and non-users: a narrative literature review. Int J Environ Res Public Health. 2018;15(6):1190.
101. Soule EK, Sakuma KLK, Palafox S, Pokhrel P, Herzog TA, Thompson N et al. Content analysis of internet marketing strategies used to promote flavored electronic cigarettes. Addict Behav. 2019;91:128–35.
102. Krüsemann EJZ, Boesveldt S, de Graaf K, Talhout R. An e-liquid flavor wheel: a shared vocabulary based on systematically reviewing e-liquid flavor classifications in literature. Nicotine Tob Res. 2019;21(10):1310–9.
103. Krüsemann EJZ, Havermans A, Pennings JLA, de Graaf K, Boesveldt S, Talhout R. Comprehensive overview of common e-liquid ingredients and how they can be used to predict an e-liquid's flavour category. Tob Control. 2020: 055447.
104. E-Cigarette market – growth, trends and forecast (2019–2024). Hyderabad: MordorIntelligence; 2018.
105. Wickham RJ. How menthol alters tobacco-smoking behavior: a biological perspective. Yale J Biol Med. 2015;88(3):279–87.
106. Huang J, Feng B, Weaver SR, Pechacek TF, Slovic P, Eriksen MP. Changing perceptions of harm of e-cigarette vs cigarette use among adults in 2 US national surveys from 2012 to 2017. JAMA Network Open. 2019;2(3):e191047.
107. Amrock SM, Lee L, Weitzman M. Perceptions of e-cigarettes and noncigarette tobacco products among US youth. Pediatrics. 2016;138(5):e20154306.
108. Cullen KA, Gentzke AS, Sawdey MD, Chang JT, Anic GM, Wang TW et al. e-Cigarette use among youth in the United States, 2019. JAMA. 2019;322(21):2095–103.
109. Cullen KA, Ambrose BK, Gentzke AS, Apelberg BJ, Jamal A, King BA. Notes from the field: use of electronic cigarettes and any tobacco product among middle and high school students – United States, 2011–2018. Morb Mortal Wkly Rep. 2018;67:1276–7.
110. Soule EK, Lee JGL, Egan KL, Bode KM, Desrosiers AC, Guy MC et al. "I cannot live without my vape": Electronic cigarette user-identified indicators of vaping dependence. Drug Alcohol Depend. 2020:107886.
111. Gentzke AS, Creamer M, Cullen KA, Ambrose BK, Willis G, Jamal A et al. Vital signs: tobacco product use among middle and high school students – United States, 2011–2018. Morbid Mortal Wkly Rep. 2019;68(6):157–64.

112. Dai H, Leventhal AM. Prevalence of e-cigarette use among adults in the United States, 2014–2018. JAMA. 2019;322(18):1824–7.
113. WHO global report on trends in prevalence of tobacco smoking. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/bitstream/handle/10665/156262/9789241564922_eng.pdf?sequence=1&isAllowed=y, accessed 9 November 2020)..
114. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. Tob Control. 2010;19(1):87–8.
115. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. Nicotine Tob Res. 2013;15(1):267–70.
116. Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. Psychopharmacology. 2014;231(2):401–7.
117. Dawkins L, Kimber C, Puwanesarasa Y, Soar K. First- versus second-generation electronic cigarettes: predictors of choice and effects on urge to smoke and withdrawal symptoms. Addiction. 2015;110(4):669–77.
118. Breland A, Soule E, Lopez A, Ramôa C, El-Hellani A, Eissenberg T. Electronic cigarettes: what are they and what do they do? Ann NY Acad Sci. 2017;1394(1):5–30.
119. Talih S, Balhas Z, Eissenberg T, Salman R, Karaoghlanian N, El-Hellani A et al. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. Nicotine Tob Res. 2015;17(2):150–7.
120. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. New Engl J Med. 2019;380(7):629–37.
121. Jankowski M, Krzystanek M, Zejda JE, Majek P, Lubanski J, Lawson JA et al. E-cigarettes are more addictive than traditional cigarettes – A study in highly educated young people. Int J Environ Res Public Health. 2019;16(13):2279.
122. Vogel EA, Prochaska JJ, Ramo DE, Andres J, Rubinstein ML. Adolescents' e-cigarette use: increases in frequency, dependence, and nicotine exposure over 12 months. J Adolesc Health. 2019;64(6):770–5.
123. Talih S, El-Hage R, Karaoghlanian A, Saliba NA, Salman R, Karam EE et al. Might limiting liquid nicotine concentration result in more toxic electronic cigarette aerosols? Tob Control. 2020: 10.1136/tobaccocontrol-2019-055523.
124. Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. Nicotine Tob Res. 2015;17(2):158–62.
125. Pankow JF, Kim K, McWhirter KJ, Luo W, Escobedo JO, Strongin RM et al. Benzene formation in electronic cigarettes. PLoS One. 2017;12(3):e0173055.
126. Duell AK, Pankow JF, Peyton DH. Nicotine in tobacco product aerosols: "It's déjà vu all over again". Tobacco Control. 2019;29(6):656–62.
127. Process for preparing racemic nicotine. United States Patent US 8,884,021 B2; 2014 (https://patentimages.storage.googleapis.com/d1/cd/24/4141350fb210fc/US8884021.pdf).
128. El-Hellani A, El-Hage R, Salman R, Talih S, Shihadeh A, Saliba NA. Carboxylate counteranions in electronic cigarette liquids: Influence on nicotine emissions. Chem Res Toxicol. 2017;30(8):1577–81.

12. EVALI: e-cigarette or vaping product use-associated lung injury

Farrah Kheradmand, Professor of Medicine, Immunology and Pathology at Baylor College of Medicine and Staff Physician at Michael E DeBakey VA, Houston (TX), USA

Laura E. Crotty Alexander, Associate Professor of Medicine, University of California at San Diego and Section Chief of Pulmonary and Critical Care at Veterans Administration San Diego Healthcare System, San Diego (CA), USA

Contents

Abstract

The beneficial or detrimental effects of electronic nicotine delivery systems (ENDS, e-cigarettes) on lung health have been heavily debated over the past decade, both in academic circles and by the press. In the summer of 2019, the debates took a new direction after reports of several clusters of e-cigarette users who presented with acute respiratory failure, resulting in hospitalization and, in some cases, death. We describe the outbreak of e-cigarette or vaping product use-associated lung injury (EVALI), the latest information on its clinical features and lung pathology and investigations of the causal chemicals identified in

many commercial and/or illicit products used by affected individuals. Although news reports highlighted several clusters of EVALI in the USA, isolated case reports of vaping-associated respiratory failure have also been reported in other jurisdictions, including European countries. Many unanswered questions remain about the acute and long-term effects of exposure to the chemicals in the aerosols of e-cigarettes and other vaping products. A comprehensive approach, guided by epidemiological, translational and basic research, is necessary to assess the risks associated with inhalation of the emissions of these products, which are used in many countries around the world.

12.1 Background

12.1.1 Respiratory effects associated with e-cigarettes and vaping

Use of electronic nicotine delivery system (ENDS), commonly known as e-cigarettes or vape devices, is relatively new but is rapidly evolving among people of all ages in many countries and especially among young people in some countries, such as Canada and the USA. Vaping devices deliver nicotine to the lungs by aerosolizing liquid carriers that contain hydrophilic solvents, propylene glycol and vegetable glycerine. As the taste of the combinations of these heated chemicals is not appealing, > 99% of e-liquids contain chemical flavourings. While the long-term respiratory and/or systemic effects of these devices remain unknown, their use has been associated with acute and subacute effects on the lungs, including eosinophilic pneumonia, hypersensitivity pneumonitis, lipoid pneumonia, acute respiratory distress syndrome and diffuse alveolar haemorrhage *(1,2)*. "Vaping", an informal term used to refer to the use of these products, has also been reported to exacerbate pre-existing lung disease, particularly airway hyperreactivity and cough in asthma *(3)*. This report provides information on the outbreak of lung injury associated with vaping products in 2019.

N.B. The term "vaping" may have positive connotations because of the association with "water vapour", which may imply that the products are risk-free; however, e-cigarettes are not harmless.

12.1.2 E-cigarette or vaping product use-associated lung injury (EVALI)

In the summer of 2019, several clusters of lung injuries caused by vaping or e-cigarette use were recognized in the USA. The term EVALI was coined by the US Centers for Disease Control and Prevention (US CDC) on 11 October 2019. Epidemiological analyses in the USA have confirmed that the specific disease entity EVALI did not exist before 2019. Although lung diseases induced by e-cigarette or vaping were reported before 2019, EVALI is believed to have been caused by different chemical exposures, via disparate pathological mechanisms *(4)*. EVALI reached epidemic levels in September 2019; however, although the

number of emergency department visits associated with EVALI has decreased, cases are still occurring across the country. As of February 2020, more than 2800 cases requiring hospitalization had been confirmed, with 68 deaths. Various types of lung pathology have been identified, including diffuse alveolar damage *(5)*.

12.1.3 Products and chemicals implicated in EVALI

Survivors of EVALI reported using various e-cigarettes, vaping devices, e-liquids and flavours, and no specific brand or device was common to all cases. Over 80% of affected individuals reported that marijuana and other cannabinoids (Δ^9-tetrahydrocannabinol; THC) were present in their e-liquids, and half vaped both THC and nicotine. All THC-containing e-liquids have been identified as potentially dangerous. e-Liquids containing vitamin E acetate have also been incriminated in this illness, as this substance was detected in the majority of e-liquids used by the affected patients as well as in their bronchoalveolar lavage fluid *(6)*. Although many brands of e-liquid have been associated with this disease, dealers often fill empty cartridges with "in-house blends" of e-liquids. Therefore, no e-devices or e-liquids can be considered safe.

As over 80% of patients with EVALI reported using THC, and most of the e-liquids they used tested positive for THC, THC-containing e-cigarette or vaping products are believed to have played a major role in the outbreak. Although 14% of the people with EVALI vaped only nicotine, experts believe that they had other forms of vaping-induced lung injury and not EVALI. This conclusion is supported by the broad, nonspecific definition of EVALI and the fact that most of the patients in this nicotine-only cohort were older women. The carriers used for these products, particularly those from in-person or online dealers, have been strongly implicated. Of the 152 different THC-containing product brands identified, Dank Vapes (cartridges containing THC liquids of unknown source sold at many sites) are the most common in north-east and southern USA; TKO and Smart Cart brands have been reported in the west, and Rove has been found in mid-west states. These findings suggest that EVALI is associated with THC-containing products and is probably not due to a single brand. Both public health agencies and the US Food and Drug Administration have identified vitamin E acetate as the chemical most strongly associated with EVALI, as vitamin E acetate was detected in 48 of 51 bronchoalveolar lavage fluid samples obtained from EVALI patients *(6)*.

12.2 EVALI

12.2.1 Detailed description and history

The first outbreaks of EVALI in the United States were identified in Illinois and Wisconsin in July 2019 *(7,8)*. The features of EVALI cases were identified as:

vaping within 90 days of symptom onset, bilateral lung infiltrates on either chest X-ray or chest computed topography and the absence or unlikely evidence of an infectious cause. The US CDC then categorized EVALI cases as either probable, when microbial studies were positive but were unlikely to have caused the clinical presentation, or confirmed, if clinicians could rule out a respiratory infection *(9)*. For example, if *Staphylococcus aureus* grew from a sputum culture, the case could be considered probably EVALI, with *S. aureus* as merely a colonizer and not the cause of the symptoms. If the most common tests for respiratory microbes were negative (e.g. for influenza, other respiratory viruses, including SARS-CoV2, sputum Gram stain and culture, *Streptococcus pneumonia* urine antigen, and *Legionella pneumonia* urine antigen), the case would meet the criteria for confirmed EVALI.

After categorization by the US CDC, several hundred additional cases were confirmed across the USA *(10,11)*. The peak of the epidemic occurred in September 2019, since when the numbers of reported and confirmed cases has dropped. Possible explanations for the subsequent decrease include the following.

- The intense media interest in EVALI may have led vapers to quit e-cigarettes, buy them from reliable sources or quit vaping THC-containing products in particular.
- Fewer health care professionals were reporting cases, as the diagnosis is not unique or novel.
- Makers of e-cigarette or vaping liquid may have stopped adding chemicals associated with EVALI to e-liquids.

12.2.2 Symptoms

The concurrent presence of gastrointestinal and respiratory symptoms is the most specific sign of EVALI. The most frequent findings in EVALI cases include abdominal pain, nausea, vomiting or diarrhoea with shortness of breath, cough, dyspnoea on exertion or chest pain. Less specific symptoms include fever, malaise, fatigue and weight loss *(12,13)*.

12.2.3 Clinical presentation

Some patients sought clinical care within hours of the appearance of their first symptoms, but others had symptoms for weeks to months before their initial presentation, complicating understanding of variations in disease onset. Half of hospitalized EVALI patients have hypoxia that requires admission to an intensive care unit, and approximately half require mechanical ventilation and or extracorporeal membrane oxygenation. Moderate cases in which patients require 2–6 L of oxygen are quite common. Mild cases are increasingly recognized

in which patients do not require supplemental oxygen to maintain oxygen saturation > 94% but have symptoms and findings similar to those in moderate and severe cases. Pneumothorax and pneumomediastinum have been reported commonly, raising the spectre of damage to the lung parenchyma leading to bronchopulmonary fistulas *(12,13)*. Recently, several EVALI patients have been reported to have died 2–3 days after discharge from hospital, perhaps due to sudden pneumothorax.

12.2.4 Reported cases

The US CDC reported only the number of hospitalized patients from January 2020, reflecting a bias to reporting moderate-to-severe cases, and stopped reporting the numbers of EVALI cases completely on 25 February 2020. Canada, Japan, Mexico and the United Kingdom are among other countries that have reported cases of vaping-associated lung injury. Some of these reports predate the description of EVALI. Most patients required hospitalization, and the radiographic and clinical descriptions of their illness mirrored those of EVALI. As vaping was known to cause a wide variety of lung diseases before the emergence of EVALI and inhalation-induced lung diseases have similar presentations, it is likely that the cases were not related to THC or vitamin E acetate and were not EVALI. No systematic review of cases of vaping-induced lung disease, trends, prevalence or clusters of case reports has been reported from other countries.

12.3 Identification of EVALI

A universal definition of EVALI could be established if it has one causal agent, as for the global consensus among international pulmonary experts on the definition of acute respiratory distress syndrome. Any definition will have to be more specific and detailed than the current one *(9)*, which includes everyone who has vaped within 90 days, has bilateral lung infiltration and no clear infectious cause. Ideally, the definition of EVALI will exclude other vaping-related lung diseases as well as non-vaping-related diseases. The addition of specific testing to exclude lung diseases that are idiopathic or vaping-related but not EVALI would be helpful. The pathological picture of EVALI is broad and overlaps with those of acute interstitial pneumonia, hypersensitivity pneumonitis, diffuse alveolar haemorrhage, lipoid pneumonia and adult respiratory disease syndrome.

12.4 Surveillance for EVALI

12.4.1 National surveillance mechanisms

It has been difficult to collect all the cases in the USA, as the US CDC and the Food and Drug Administration rely on local and regional public health departments, which are robust and reliable but decide to share their data

according to local priorities and state health privacy laws. Another difficulty has been in educating health care providers, as most have not asked specifically about the use of e-cigarettes, vaping devices or THC-specific devices. It has been proposed that an open portal for reporting be established for both patients and health care providers in order to identify more cases *(14)*. Privacy issues are the main deterrent; however, a similar method has been used for other diseases, such as lead poisoning and infectious diseases.

12.4.2 Regional surveillance mechanisms

A regional surveillance mechanism was described recently *(11)*. Regional surveillance could help each health care system to accurately detect and track all EVALI cases, and the data could then be shared with regional public health departments and with the US CDC and the Food and Drug Administration in the USA. The United Kingdom has a system known as the "yellow card scheme", which is available on the website of the Medicines and Healthcare Products Regulatory Agency *(15)*. The scheme allows reporting of information on adverse or suspected adverse events related to medicines and makes provision for reporting of any side-effects of the use of e-cigarettes or safety concerns related to these products or their e-liquids. Members of the public and health care personnel in each country of the United Kingdom can file reports through the system.

12.4.3 International surveillance mechanisms and validation

One challenge in surveillance is identifying cases in both medical centres and rural areas in similar investigations and with similar confirmation methods to control and respond in each case. WHO sponsors a global network of over 250 institutions dedicated to responding and raising awareness about acute public health events, the Global Outbreak Alert and Response Network *(16)*.

Another difficulty is in defining EVALI, as the current definition is broad, making identification difficult. To improve surveillance, standards (e.g. case definitions) and training in recognition of EVALI are required at national and international levels. The US CDC has reported that nearly 3% of EVALI patients have required rehospitalization, and nearly one in seven deaths from EVALI has occurred after hospital discharge, particularly among people with one or more chronic diseases *(17)*.

12.5 Discussion

It is estimated that 35–40 million adults and children globally vape, indicating a large number of people who are vulnerable to EVALI and other vaping-associated health outcomes. e-Cigarette use or vaping itself carries health risks and may harm health beyond the lungs. Further, the risks are increased by lacing of products with drugs and other substances, and the products should be properly regulated.

The outbreak of EVALI in the USA highlights the importance of broadening the definition of e-cigarette toxicity beyond that of smoking, as vaping results in disease risks that are different from those associated with smoking *(18)*. A major concern during the coronavirus disease 2019 (COVID-19) pandemic is the delay in recognizing and reporting EVALI in patients admitted with respiratory failure. For example, in April 2020, eight patients admitted to hospital for respiratory failure met the US CDC case definition of EVALI, but physicians first considered EVALI in differential diagnoses only 1–8 days (median day 3) after hospitalization *(19)*. This report highlights some of the difficulties in recognizing respiratory failure due to EVALI, which may therefore be underdiagnosed during COVID-19 pandemic.

A priority at national and international level is to establish registries of EVALI patients that can be accessed by researchers and clinicians in order to assess the long-term effects and clinical outcomes. Further, acquisition and analysis of specimens from humans (e.g. whole blood, tracheal aspirates, bronchoalveolar lavage fluid, lung biopsy specimens, urine and autopsy specimens) could provide insight into the pathophysiology of EVALI. More mechanistic studies should be conducted to understand the toxic effect of vaping products in the lungs. Specifically, it is unclear whether and how vaping of propylene glycol or vegetable glycerine before exposure to vitamin E acetate causes lung injury. Further, vaping temperature, especially in high-powered devices, plays a role in lung injury *(20)*. Animal models of EVALI would be useful for studying the potential causes of toxicity to the lungs related to vaping and use of THC products *(14)*.

12.6 Considerations

A full report on the many aspects of the EVALI disease spectrum and its potential contribution to lung injury in other countries is recommended. Several key questions should be addressed to improve current understanding of care for patients who develop EVALI and respiratory failure.

- A significant challenge is ensuring that physicians recognize an EVALI case, particularly during the COVID-19 pandemic. Physicians should be made aware of the risk of EVALI and ask about nicotine or THC use in electronic products as part of a routine history for patients who present with respiratory failure.
- EVALI must be better defined to guide primary care and paediatric physicians in the correct diagnosis.
- Studies should address whether e-cigarette use also increases vulnerability to SARS-CoV-2 infection in adults and children. Preclinical models of e-cigarette product use have provided strong evidence that chronic use alters lung defence immunity against influenza, a common viral pathogen *(18)*.

12.7 Recommendations

12.7.1 Key recommendations

- National and international registries of EVALI patients and people with other vaping-associated lung diseases should be established to improve monitoring of long-term clinical outcome in survivors.
- A strong international campaign should be organized to alert parents, children and young adults to the hazards of inhaling the chemicals contained in the aerosols of electronic vaping products.
- Consideration should be given to writing a full paper on EVALI when more information becomes available.

12.7.2 Other recommendations

- Specimens such as blood, tracheal aspirates, bronchoalveolar lavage fluid, lung tissue and urine should be obtained and analysed in order to better understand the pathophysiology of EVALI.
- Animal models of EVALI should be developed to gain insight into the cellular and molecular mechanisms underlying the toxicity caused in the lungs and systemically by vaping both nicotine and THC and also the health effects of the vehicle and flavour chemicals contained in these products.
- Research should be pursued to define the mechanisms by which vaping products harm the lungs.

12.8 References

1. Arter ZL, Wiggins A, Hudspath C, Kisling A, Hostler DC, Hostler JM. Acute eosinophilic pneumonia following electronic cigarette use. Respir Med Case Rep. 2019;27:100825.
2. Sommerfeld CG, Weiner DJ, Nowalk A, Larkin A. Hypersensitivity pneumonitis and acute respiratory distress syndrome from e-cigarette use. Pediatrics. 2018;141(6):20163927.
3. Lappas AS, Tzortzi AS, Konstantinidi EM, Teloniatis SI, Tzavara CK, Gennimata SA et al. Short-term respiratory effects of e-cigarettes in healthy individuals and smokers with asthma. Respirology. 2018;23:291–7.
4. McCauley L, Markin C, Hosmer D. An unexpected consequence of electronic cigarette use. Chest. 2012;141:1110–3.
5. Butt YM, Smith ML, Tazelaar HD, Vaszar LT, Swanson KL, Cecchini MJ et al. Pathology of vaping-associated lung injury. N Engl J Med. 2019;381(18):1780–1.
6. Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M et al. Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. N Engl J Med. 2020;382:697–705.
7. Layden JE, Ghinai I, Pray I, Kimball A, Layer M, Tenforde M et al. Pulmonary illness related to

e-cigarette use in Illinois and Wisconsin – preliminary report. N Engl J Med. 2020;382:903–16.
8. Ghinai I, Pray IW, Navon L, O'Laughlin K, Saathoff-Huber L, Hoots B et al. e-Cigarette product use, or vaping, among persons with associated lung injury – Illinois and Wisconsin, April–September 2019. Morb Mortal Wkly Rep. 2019;68:865–9.
9. 2019 lung injury surveillance. Primary case definitions. September 18, 2019. Atlanta (GA): Centers for Disease Control and prevention; 2019 (https://www.cdc.gov/tobacco/basic_information/e-cigarettes/assets/2019-Lung-Injury-Surveillance-Case-Definition-508.pdf, accessed 10 January 2021).
10. Blagev DP, Harris D, Dunn AC, Guidry DW, Grissom CK, Lanspa MJ. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study. Lancet. 2019;394(10214):2073–83.
11. Alexander LEC, Perez MF. Identifying, tracking, and treating lung injury associated with e-cigarettes or vaping. Lancet. 2019;394(10214):2041–3.
12. Zou RH, Tiberio PJ, Triantafyllou GA, Lamberty PE, Lynch MJ, Kreit JW et al. Clinical characterization of e-cigarette, or vaping, product use associated lung injury in 36 patients in Pittsburgh, PA. Am J Respir Crit Care Med. 2020;201(10):1303–6.
13. Chatham-Stephens K, Roguski K, Jang Y, Cho P, Jatlaoui TC, Kabbani S et al. Characteristics of hospitalized and nonhospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury – United States, November 2019. Morb Mortal Wkly Rep. 2019;68:1076–80.
14. Crotty Alexander LE, Ware LB, Calfee CS, Callahan SJ, Eissenberg T, Farver C et al. NIH workshop report: E-cigarette or vaping product use associated lung injury: Developing a research agenda. Am J Respir Crit Care Med. 2020;202(6):795–802.
15. Yellow card. London: Medicines and Healthcare Products Regulatory Agency; 2020 (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/#:~:text=The%20Yellow%20Card%20scheme%20is,by%20health%20professionals%20and%20patients, accessed 10 January 2021).
16. Global Outbreak Alert and Response Network. Geneva: World Health Organization; 2020 (https://extranet.who.int/goarn/, accessed 10 January 2021).
17. Evans ME, Twentyman E, Click ES, Goodman AB, Weissman DN, Kiernan E et al. Update: Interim guidance for health care professionals evaluating and caring for patients with suspected E-cigarette, or vaping, product use-associated lung injury and for reducing the risk for rehospitalization and death following hospital discharge – United States, December 2019. Morb Mortal Wkly Rep.2020;68(5152):1189–94.
18. Madison MC, Landers CT, Gu BH, Chang CY, Tung HY, You R et al. Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine. J Clin Invest. 2019;129:4290–304.
19. Armatas C, Heinzerling A, Wilken JA. Notes from the field: e-cigarette, or vaping, product use-associated lung injury cases during the COVID-19 response – California, 2020. Morb Mortal Wkly Rep. 2020;69:801–2.
20. Chaumont M, Bernard A, Pochet S, Mélot C, El Khattabi C, Reye F et al. High-wattage e-cigarettes induce tissue hypoxia and lower airway injury: A randomized clinical trial. Am J Crit Care Med. 2018;198(1):123–6.

13. Overall recommendations

The WHO Study Group on Tobacco Product Regulation publishes reports to provide a scientific basis for tobacco product regulation. In line with Articles 9 and 10 of the WHO Framework Convention on Tobacco Control (FCTC), the reports identify evidence-based approaches to the regulation of the contents, emissions and design features of tobacco products.

The 10th meeting of the Study Group, the deliberations, outcomes and recommendations of which are included in this report, specifically addressed novel and emerging nicotine and tobacco products, including electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) and heated tobacco products (HTPs). Despite this focus, which is partly informed by the decision of the Eighth Conference of the Parties (COP8) to the WHO FCTC on novel and emerging tobacco products (decision FCTC/COP8(22) *(1)*, all tobacco products fall under the remit of the Study Group. This allows a comprehensive approach to synthesizing and making available evidence to countries on both conventional and newer products to address challenges in tobacco control, which remains a global priority.

Regulators are reminded that tobacco kills more than 8 million people a year *(2,3)*, with more than 7 million of those deaths attributed to direct tobacco use and about 1.3 million to exposure of non-smokers to second-hand smoke *(4,5)*. Tobacco also eventually kills up to half of its users and therefore remains a global health emergency *(2)*. The introduction of novel and emerging nicotine and tobacco products, which are aggressively marketed and promoted by manufacturers, including to children and adolescents, in some jurisdictions further complicates tobacco control and has been a distraction for regulators. Thus, the recommendations of this report are intended to be taken in the context of wider tobacco control and to complement the recommendations of the Study Group in other reports on tobacco product regulation *(6–12)*, which addressed cigarettes, smokeless tobacco and waterpipe tobacco.

The aggressive marketing and promotion of novel and emerging nicotine and tobacco products poses a serious threat to tobacco control. The Study Group, having considered the requests by countries for technical support on regulating these products, concluded that a focus must be maintained on wider tobacco control and that regulators should not allow themselves to be distracted by tobacco and related industry tactics and aggressive promotion of these products. The report highlights the importance of the following:

- good science and verification of industry research;
- full disclosure of product information to regulators;
- clarification of the source of research funding to identify undue influence;

- independent research;
- application of tobacco control laws to all tobacco products, without exception;
- monitoring the activities of tobacco and related industries; and
- protecting policies from the influence of nicotine and tobacco industries, especially in the context of Article 5.3 of the WHO FCTC and its guidelines *(13,14)*.

Sections 2–12 of the report provide scientific information, policy recommendations and guidance to bridge regulatory gaps in tobacco control. The report also identifies areas for further work and research, with a focus on the regulatory needs of countries while accounting for regional differences, thus providing a strategy for continued, targeted technical support to all countries, especially WHO Member States. The main recommendations of the Study Group are outlined below.

13.1 Main recommendations

The main recommendations to policy-makers and all other interested parties are the following:

- to ensure continued focus on evidence-based measures to reduce tobacco use as outlined in the WHO FCTC and seek to avoid being distracted from tobacco industry actions to promote novel and emerging tobacco products, such as heated tobacco products;
- to use existing regulations for tobacco products to regulate heated tobacco products (including the device) and consider broadening the scope of existing regulations in which regulatory loopholes may be exploited by the tobacco industry, including in countries in which heated tobacco products are currently not legally available;
- to apply the most restrictive tobacco control regulations to heated tobacco products (including the device), as appropriate within national laws, taking into account a high level of protection for human health;
- to prohibit all manufacturers and associated groups from making claims about reduced harm of heated tobacco products, as compared with other products, or portraying heated tobacco products as an appropriate approach for cessation of use of any tobacco product and to ban their use in public spaces unless robust independent evidence emerges to support a change in policy;
- to ensure that the public is well informed about the risks associated with use of heated tobacco products, including the risks of dual use

with conventional cigarettes and other smoked tobacco products, and also their use during pregnancy; to correct false perceptions, counter misinformation and stress that reduced exposure does not necessarily mean reduced harm;

- to rely on independent data and to support continuing independent research on the public health impact of use of heated tobacco products, with critical analysis and interpretation of tobacco industry-funded data, including data on the emissions and toxicity of heated tobacco products and associated exposures and effects in users and non-users;
- to require tobacco manufacturers to disclose all product information – including product design, chemical profile, total nicotine content, nicotine forms, toxicity, other findings of product testing and testing methods – to appropriate regulatory agencies at least once a year; any modifications to products should require updating of the report;
- to ban all commercial marketing of electronic nicotine delivery systems, electronic non-nicotine delivery systems and heated tobacco products, including in social media and through organizations funded by and associated with the tobacco industry;
- to prohibit the sale of electronic nicotine delivery systems and electronic non-nicotine delivery systems in which the user can control device features and liquid ingredients (that is, open systems);
- to prohibit the sale of electronic nicotine delivery systems with a higher abuse liability than conventional cigarettes, for example by restricting the emission rate or flux of nicotine; and
- to prohibit the addition of pharmacologically active substances such as cannabis and tetrahydrocannabinol (in jurisdictions where they are legal), other than nicotine in electronic nicotine delivery systems, to electronic nicotine delivery systems and electronic non-nicotine delivery systems.

Countries are urged to implement the above recommendations, as there is enough information about nicotine and tobacco products for countries to act to protect the health of their populations, especially the younger generation. While the report acknowledges that still more is to be learnt about these products and emphasizes that continued independent research is necessary to build further intelligence on the products, including their marketing, features, prevalence of use and availability, and on the promotional strategies of tobacco and related industries, there are more than a billion tobacco users, and millions of people use the newer products. Therefore, the public health community should answer the

call for continued acceleration of evidence-based policies and recommendations, such as those in the WHO FCTC, WHO MPOWER measures and the relevant COP reports. Countries should thus implement proven policy measures and, in addition, consider implementing the recommendations in this report. Specific recommendations on each of the topics considered can be found in sections 2.8, 3.5.4, 4.9, 5.11, 6.7, 7.11, 8.5, 8.7, 9.8, 10.2.6, 10.3,7, 11.6 and 12.7.

13.2 Significance for public health policies

The Study Group's report provides helpful guidance to the science, research and evidence on all tobacco products, including cigarettes, smokeless tobacco and waterpipe tobacco. Recently, the Study Group has extended its work by providing much needed information to regulators on the contents, emissions, variation in and features of novel and emerging nicotine and tobacco products, in particular, ENDS, ENNDS and HTPs. The report highlights the public health impact of these products and their features on users and non-users, including: their addictive potential; perception and use of the products; their attractiveness; their potential role in initiating and stopping tobacco use; marketing, including promotional strategies and impacts; claims of reduced harm; variation in products; quantification of risk to the health of individuals and populations; regulatory mapping and the experience of selected countries; impact on tobacco control; and research gaps. The Study Group's recommendations, outlined above, directly address some of the unique regulatory challenges faced by certain Member States because of the penetration of these products into their markets. Further, the report will help Member States to update their knowledge on novel and emerging nicotine and tobacco products and aid in the formulation of effective regulatory strategies for nicotine and tobacco products.

The Study Group, because of its unique composition of regulatory, technical and scientific experts, navigates and distils complex data and research and synthesizes them into policy recommendations, which inform policy development at national, regional and global levels. This authoritative report by a multidisciplinary team of experts goes to the heart of the challenges faced by governments on novel and emerging products. The nature of the report means that regulators, governments and interested parties can rely on the science and evidence presented to counter the arguments of tobacco and related industries, as appropriate. The identification of gaps in policy and research on nicotine and tobacco products indicates areas in which there is insufficient information. Countries, in formulating their research agendas, could focus on areas pertinent to their policy goals, objectives and national context. This is a critical role of the Study Group, especially for governments with inadequate resources or capacity to navigate technical information on tobacco product regulation.

The recommendations made in the report promote international coordination of regulatory efforts and the adoption of best practices in product regulation, strengthen capacity in product regulation in all WHO regions, provide a ready resource for Member States that is based on sound science and support implementation of the WHO FCTC by its States Parties. Tobacco product regulation complements other provisions of the WHO FCTC on demand reduction. The recommendations of the Study Group, if effectively implemented, would contribute to reducing tobacco use, thus reducing tobacco use prevalence and promoting good health.

13.3 Implications for the Organization's programmes

The report fulfils the mandate of the WHO Study Group on Tobacco Product Regulation to provide the Director-General with scientifically sound, evidence-based recommendations for Member States about tobacco product regulation,[1] which is a highly technical area of tobacco control in which Member States face complex regulatory challenges. The outcomes of the Study Group's deliberations and main recommendations will improve Member States' understanding of ENDS, ENNDS and HTPs and the implications of the proliferation of these products on markets in many countries in the broader context of tobacco control.

The contribution of the report to the body of knowledge on product regulation will inform the work of the tobacco programme in WHO's Department of Health Promotion, especially in providing technical support to Member States. It will also contribute to updating Member States and regulators through meetings of the WHO Global Tobacco Regulators' Forum and information-sharing via the Forum's EZCollab network. States Parties to the WHO FCTC will be updated through a comprehensive report on research and evidence on novel and emerging tobacco products, which was requested by the Conference of the Parties at its eighth session.[2] The comprehensive report will include the key messages and recommendations of the eighth report of the Study Group. All of these will contribute to meeting target 3.a of the Sustainable Development Goals (that is, strengthening implementation of the WHO Framework Convention on Tobacco Control) and the triple billion targets of WHO's Thirteenth Global Programme of Work.

The report, which is a WHO global public health good (i.e. an initiative developed or undertaken by WHO that is of benefit either globally or to many countries in many regions *(15)*), is available to all countries to help drive impact at country level and globally, towards reducing tobacco use and improving overall public health.

1 In November 2003, the Director-General formalized the status of the former Scientific Advisory Committee on Tobacco Product Regulation from a scientific advisory committee to a study group.

2 See decision FCTC/COP8(22), paragraph 2(a).

13.4 References

1. Novel and emerging tobacco products. Decision FCTC/COP8(22) of the Conference of the Parties to the WHO Framework Convention on Tobacco Control at its Eighth session. Geneva: World Health Organization; 2018 (https://www.who.int/fctc/cop/sessions/cop8/FCTC__COP8(22).pdf?ua=1, accessed 19 December 2020).
2. WHO report on the global tobacco epidemic, 2019. Geneva: World Health Organization; 2019 (http://www.who.int/tobacco/global_report/en, accessed 19 December 2020).
3. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1223–49.
4. Tobacco. Fact sheet. Geneva: World Health Organization; 2020 (https://www.who.int/news-room/fact-sheets/detail/tobacco, accessed 23 December 2020).
5. Findings from the Global Burden of Disease Study 2017: GBD Compare. Seattle (WA): Institute for Health Metrics and Evaluation; 2018 (http://vizhub.healthdata.org/gbd-compare, accessed 19 December 2020).
6. The scientific basis of tobacco product regulation. Report of a WHO study group (WHO Technical Report Series, No. 945). Geneva: World Health Organization; 2007 (https://www.who.int/tobacco/global_interaction/tobreg/who_tsr.pdf, accessed 10 January 2021).
7. The scientific basis of tobacco product regulation. Second report of a WHO study group (WHO Technical Report Series, No. 951). Geneva: World Health Organization; 2008 (https://apps.who.int/iris/bitstream/handle/10665/43997/TRS951_eng.pdf?sequence=1, accessed 10 January 2021).
8. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: Third report of a WHO study group (WHO Technical Report Series, No. 955). Geneva: World Health Organization; 2009 (https://apps.who.int/iris/bitstream/handle/10665/44213/9789241209557_eng.pdf?sequence=1, accessed 10 January 2021).
9. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: Fourth report of a WHO study group (WHO Technical Report Series, No. 967). Geneva: World Health Organization; 2012 (https://apps.who.int/iris/bitstream/handle/10665/44800/9789241209670_eng.pdf?sequence=1, accessed 10 January 2021).
10. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: Fifth report of a WHO study group (WHO Technical Report Series, No. 989). Geneva: World Health Organization; 2015 (https://apps.who.int/iris/bitstream/handle/10665/161512/9789241209892.pdf?sequence=1, accessed 10 January 2021).
11. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: Sixth report of a WHO study group (WHO Technical Report Series, No. 1001). Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/handle/10665/260245/9789241210010-eng.pdf?sequence=1, accessed 10 January 2021).
12. WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: Seventh report of a WHO study group (WHO Technical Report Series, No. 1015). Geneva: World Health Organization; 2019 (https://apps.who.int/iris/bitstream/handle/10665/329445/9789241210249-eng.pdf, accessed 10 January 2021).
13. Article 5.3. WHO Framework Convention on Tobacco Control. Geneva: World Health Organization; 2005 (https://apps.who.int/iris/bitstream/handle/10665/42811/9241591013.pdf;jsessionid=1DE94B49AE5482D746B237CAC38D5658?sequence=1, accessed 19 December 2020).
14. Guidelines for implementation of Article 5.3 of the WHO Framework Convention on Tobacco Control on the protection of public health policies with respect to tobacco control from commercial and other vested interests of the tobacco industry. Geneva: World Health Organization;

2008 (https://www.who.int/fctc/guidelines/article_5_3.pdf, accessed 19 December 2020).
15. Thirteenth General Programme of Work 2019–2023. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/bitstream/handle/10665/324775/WHO-PRP-18.1-eng.pdf, accessed 29 December 2020).

WHO study group on tobacco product regulation

This report fulfils the mandate of the WHO Study Group on Tobacco Product Regulation to provide the Director-General with scientifically sound, evidence-based recommendations for Member States about tobacco product regulation. This report presents the outcomes and recommendations made by the members of the Study Group at its tenth meeting, which addressed novel and emerging nicotine and tobacco products, such as electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENNDS) and heated tobacco products (HTPs). The group reviewed nine background papers and two horizon scanning papers, specially commissioned for the meeting, which addressed the following topics:

1. Toxicants in HTPs, exposure, health effects and claims of reduced risk (section 2);
2. The attractiveness and addictive potential of HTPs: effects on perception and use and associated effects (section 3);
3. Variations among HTPs, considerations and implications (section 4);
4. Use of HTPs: product switching and dual or poly product use (section 5);
5. Regulations on HTPs, ENDS and ENNDS, with country approaches, barriers to regulation and regulatory considerations (section 6);
6. Estimation of exposure to nicotine from use of ENDS and from conventional cigarettes (section 7);
7. Exploration of methods for quantifying individual risks associated with ENDS, ENNDS and HTPs: impact on population health and implications for regulation (section 8).
8. Flavours in novel and emerging nicotine and tobacco products (section 9);
9. Global marketing and promotion of novel and emerging nicotine and tobacco products and their impacts (section 10);
10. Forms of nicotine in tobacco plants, chemical modifications and implications for ENDS products (section 11); and
11. EVALI: "e-cigarette or vaping product use-associated lung injury" (section 12).

The Study Group's recommendations on each of these topics are set out at the end of the relevant section, and overall recommendations are summarized in the final section of the report. These, as well as the deliberations of the Study Group, will improve Member States' understanding of ENDS, ENNDS and HTPs. The report, which is a WHO global public health good (i.e. an initiative developed or undertaken by WHO that is of benefit either globally or to many countries in many regions), is available to all countries to help in reducing tobacco use and improving overall public health at country level and globally.

9789240022720