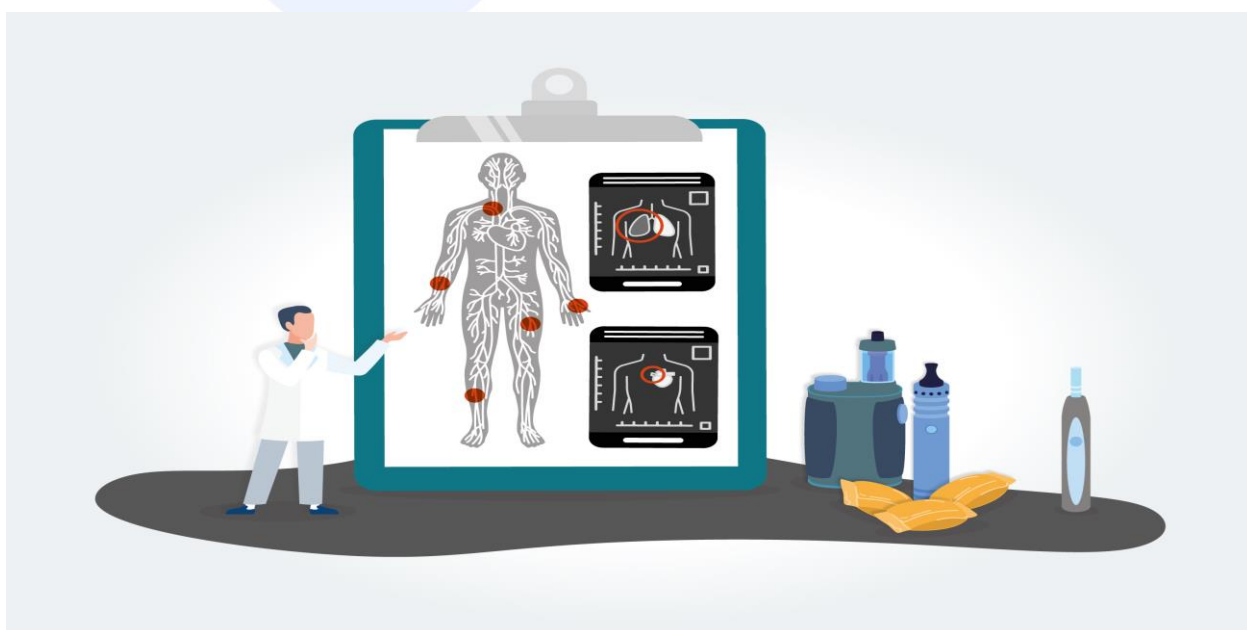


Health outcomes associated with the use of e-cigarettes, heated tobacco products, and nicotine pouches

Perez-Cornago, A., Sarasa-Renedo, A., Jarach, C., Wollgast, J., Maragkoudakis, P.

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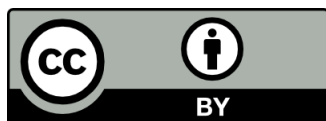
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Abstract

Tobacco consumption is the single most preventable cause of illness and death in the European Union, accounting for almost 520 000 deaths in 2021. The emergence of new tobacco and nicotine-related products, including electronic cigarettes (e-cigarettes), heated tobacco products, and nicotine pouches, has raised concerns about their potential health effects and role in smoking initiation and cessation. This report synthesises the evidence and interpretations from authoritative public health organisations, national health authorities, and official risk assessment bodies, on the associations between these emerging products and health outcomes, smoking initiation, and smoking cessation.

Given the limited time these products have been on the market, the current evidence is largely restricted to short- and medium- term health outcomes, while there is lack of long-term evidence, for which the assessed reports highlight the need for further research to enable accurate risk estimation. E-cigarettes are not harmless and are associated with adverse short- and medium-term health outcomes, including cardiovascular and respiratory outcomes. There are also concerns surrounding the inhalation of nicotine, together with metals and other substances with unclear toxicity. Heated tobacco products, though there is less evidence available, have been associated with similar health risks as e-cigarettes. In turn, nicotine pouches lack sufficient evidence regarding their health effects due to limited time on the market. Finally, the role of these products in smoking initiation and cessation is still unclear, with some studies suggesting that e-cigarettes may act as a “gateway” to smoking, particularly among youth. Our analysis also suggests that e-cigarettes may be linked to smoking initiation. Evidence on this potential “gateway” effect is currently lacking for heated tobacco products and nicotine pouches, and the role of these products in smoking cessation remains unclear.

This report concludes that several of the examined sources recommend a precautionary approach towards these emerging products due to the concerning associations with short- and medium- health outcomes and the lack of long-term evidence. Furthermore, long-term follow-up is necessary to accurately estimate their health risks. Effective tobacco control policies and public health strategies are crucial for reducing the burden of tobacco-related diseases in the European Union, and the insights from this report can inform and support such efforts.

Acknowledgements

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Executive summary

Tobacco consumption remains a significant public health challenge in the European Union (EU), accounting for almost 520 000 deaths in 2021. The prevalence of smoking among young Europeans aged 15–24 is particularly concerning, with 22.9% currently smoking daily or occasionally, and 14.8% smoking daily. Tobacco consumption is linked to a higher risk of multiple diseases, including cancer, respiratory and cardiovascular diseases.

The emergence of new tobacco and nicotine-related products in the European market, such as e-cigarettes, heated tobacco products (HTPs), and nicotine pouches, is likely to pose additional risks that are not yet fully understood.

This report provides an overview of the current evidence on the association of emerging tobacco and nicotine products, including e-cigarettes, HTPs, and nicotine pouches with health outcomes. This report synthesises findings from authoritative public health organisations, national health authorities, and official risk assessment bodies.

Policy context

Tobacco control measures aim to protect citizens from the harmful effects of tobacco, help smokers to quit, or prevent people from starting in the first place. The rapidly changing market and the rise in novel and emerging tobacco and nicotine products make it necessary to keep up with these changes and assess the current legislation in relation to the potential negative health effects of those products, including their toxicity and addictive potential, as well as the way they are marketed to the public.

The report supports the EU's ongoing efforts to reduce tobacco consumption and promote public health, and the Europe's Beating Cancer Plan goal to achieve a 'tobacco-free generation' by 2040. Specifically, the report provides a summary of the evidence on novel and emerging tobacco and nicotine products, supporting the Commission's Evaluation of the legislative framework for tobacco control and contributing to evidence-based policy making.

Key conclusions

The findings of this report have important implications for tobacco control policies and public health strategies aimed at reducing the burden of tobacco-related diseases in the EU.

Due to the associations of some of these emerging products with certain short- and medium-term health outcomes, and the lack of evidence for long-term health impacts (since they have not been marketed for long enough), several reports recommend adopting a precautionary approach towards e-cigarettes, HTPs, and nicotine pouches. Moreover, long-term follow-up is necessary to accurately estimate their health risks.

Therefore, the current report supports a precautionary approach to tobacco control and recognises the need for further research to address the evolving landscape of tobacco and nicotine use.

Main findings

— The majority of sources analysed for this JRC report focused on e-cigarettes, with fewer studies available on HTPs and nicotine pouches.

- E-cigarettes: E-cigarettes are related to adverse short- and medium-term outcomes, mainly in the cardiovascular and respiratory systems, and may have some tumorigenic effects and detrimental pregnancy impacts. They can cause addiction and dependence, and pose health risks, despite potentially being less harmful than conventional tobacco. Moreover, there are concerns surrounding the inhalation of nicotine, together with metals and other substances with unclear toxicity. Variation in substance content among different products further complicates assessing their effects. Additionally, e-cigarettes may serve as a “gateway” to conventional tobacco products for non-smokers, particularly in young people, while their role in smoking cessation is unclear.
- Heated tobacco products: Heated tobacco products have been associated with cardiovascular and respiratory diseases and may also be associated with negative developmental and pregnancy outcomes. Moreover, there are concerns regarding exposure to substances with unclear toxicity and their addiction potential. None of the examined reports evaluated HTPs' role in conventional smoking initiation, and there is no evidence that HTPs are useful for smoking cessation.
- Nicotine pouches: Nicotine pouches lack sufficient evidence on their health effects, primarily due to insufficient time on the market. Most evidence comes from nicotine content and its effects. Compared to tobacco products, they seem to deliver less toxicants and pollutants.
- Lack of long-term evidence: Significant knowledge gaps remain regarding the long-term health effects of these products, since they have not been on the market long enough.

Related and future Joint Research Centre work

In addition to this report, the JRC has published other Science for Policy reports that provide evidence-based insights to support the evaluation of the legislative framework for tobacco control and the development of effective tobacco control policies. These reports complement the current report, covering [trends and patterns of use of tobacco and nicotine products in the EU](#), and the [health-related costs attributable to tobacco in the EU](#). These Science for Policy reports contribute to understand the complex issues surrounding the use of tobacco and nicotine-related products and inform evidence-based policy making at the EU level.

Quick guide

This report examines the associations of emerging tobacco and nicotine products, such as e-cigarettes, HTPs, and nicotine pouches, with health outcomes, by assessing reports from public health organisations and authorities. Other key terms include Electronic Nicotine Delivery Systems, Tobacco Products Directive and Tobacco Advertising Directive.

1 Introduction

In the EU, tobacco consumption is the single most preventable cause of illness and death, accounting for almost 520 000 deaths in 2021 (Global Burden of Disease estimate for 2021). (1) Approximately 50% of smokers experience premature death, with an average loss of 14 years compared to non-smokers. Although progress has been made, the prevalence of smoking in the European Union remains significant. In 2019, the European Health Interview Survey found that 24.2% of the overall population were smokers (19.3% daily smokers), while 22.9% of Europeans aged 15–24 smoked, with 14.8% smoking daily. (2) In 2023, Eurobarometer recorded similar prevalence estimates. (3)

Tobacco consumption is linked to a higher risk of multiple diseases. In Europe, smoking accounts for approximately 20% of cancer cases, causing at least 16 different types of cancer and contributing to over 80% of all lung cancer deaths, accounting for over 250 000 deaths from trachea, bronchus and lung cancer in 2022. (4–7) Tobacco is also a primary cause of chronic obstructive pulmonary disease (COPD) and cardiovascular diseases, accounting for 16% of deaths caused by ischaemic heart disease. (8) It is essential to note that tobacco's harm, both from tobacco use and exposure to tobacco smoke, extends throughout the lifespan. During foetal development, maternal smoking contributes to increased rates of stillbirth and certain congenital abnormalities. In infancy, it can result in sudden infant death syndrome, while in childhood and adolescence, tobacco leads to disability from respiratory conditions. (8) Moreover, tobacco contributes significantly to the burden of communicable diseases. For instance, in relation to COVID-19, smokers have a higher risk of both contracting the virus and experiencing severe infections because their lung health is already compromised. (9)

In recent years, a diverse range of new tobacco and nicotine-related products, with and without tobacco, have emerged on the European market. (10) In particular, there has been an increase in the consumption of electronic-cigarettes (e-cigarettes), heated tobacco products (HTPs), and nicotine pouches, probably posing risks to health that are not yet fully understood. (11) The European Commission is currently evaluating the legal framework for tobacco control, (12) assessing whether this framework fulfilled its goals and is able to support a 'tobacco-free generation' by 2040, as announced in Europe's Beating Cancer Plan. (13) Tobacco control measures aim to protect citizens from the harmful effects of tobacco, help smokers to quit or prevent people from starting in the first place. In that context, with a rapidly changing market and a rise in novel and emerging tobacco and nicotine products (hereinafter 'emerging products'), there is a need to keep up with these changes and assess the functioning of the legislation in relation to the potential negative health effects of those products, including their toxicity and addictive potential.

Moreover, some reports have claimed that e-cigarettes and other emerging products (heated tobacco products, nicotine pouches) may be a cessation tool in relation to combustible cigarette smoking ("smoking cessation"). However, these emerging products could also play a role in non-smokers initiating nicotine use and transitioning to conventional tobacco use including conventional cigarette smoking, here expressed as "gateway effect". (10)

The objective of this overview is to synthesise the evidence and interpretations on the associations between e-cigarettes and other emerging products (heated tobacco products, nicotine pouches) with health outcomes, gateway to smoking, and smoking cessation, as reported by authoritative public health organisations, national health authorities, and official risk assessment bodies.

2 Methodology

This section outlines the methodology employed to gather, analyse, and synthesise statements made by health-related organisations on e-cigarettes and other emerging products, namely heated tobacco products and nicotine pouches, which were included in this overview.

2.1 Sources of information and reporting

This overview is based on the findings of international organisations, governmental bodies, competent authorities/institutions, scientific and academic associations, and public health professional associations both from within and outside the EU. Reports were identified through digital search engines Google and Web of Science, as well as through direct correspondence with the World Health Organization (WHO). Reports published in languages other than English were also included, and the reports were translated using the European Commission's 'Digital Europe Programme Language Technologies'. There was no restriction based on the year of publication, while the end of report extraction was November 2024.

Table 1 provides the list and details of the reports included in this overview, including the body, publication year, title, methodology, and which exposure (product) was included, and whether it was a commissioned report not authored by the body itself. Within the 'methodology' column of this table, the underlying methodology used in that specific report to gather the scientific evidence is included. Additionally, in the same column, it is reported if an expert panel was involved to interpret the findings or if no details about the methodology at all were given in the report.

Table 1. List and details of the reports included in this overview.

Body, year	Title	Commissioned report ¹	Methodology	Exposure (product) ²
NZ - MoH, 2024 (14)	Briefings and aides mémoire heated tobacco products	No	Risk assessment based on rapid literature review	E-cigarettes HTPs Nicotine pouches
Cochrane living SR, 2024 (15)	Electronic cigarettes for smoking cessation	No	(Living) Systematic review and meta-analyses	E-cigarettes (ENDS)
IARC, 2024 (16)	IARC Monographs on the Identification of Carcinogenic Hazards to Humans Report of the Advisory	No	Systematic reviews Expert panel	E-cigarettes (ENDS)

¹ Reports not authored by the institution/body, but prepared at their request, commissioned to contractors/experts.

² As stated in the scope of each individual original report.

	Group to Recommend Priorities for the IARC Monographs during 2025–2029			
DE - DKFZ, 2023 (17)	Risiken von E-Zigaretten und Tabakerhitzern	No	Risk assessment based on literature Methodology not described	E-cigarettes HTPs
WHO, 2023a (18)	Technical note on the call to action on electronic cigarettes	No	Technical note Methodology not described	E-cigarettes
UK - NICE, 2023 (19)	Tobacco: preventing uptake, promoting quitting and treating dependence	No	Systematic reviews Expert panel	E-cigarettes (ENDS)
WHO, 2023b (20)	Heated tobacco products. Summary of research and evidence of health impacts	No	Narrative literature review; summary of the 8th report from WHO TobReg Methodology not described	HTPs
WHO TobReg, 2023 (21)	Report on the scientific basis of tobacco product regulation: ninth report of a WHO study group	No	Narrative literature review of peer-reviewed publications; web search, market data analysis, questionnaire to WHO regional advisors (2020), questionnaires to WHO Global Tobacco Regulators Forum (2021 and 2022); review of legislation in EU MS.	Nicotine pouches
BE - SHC, 2022 (22)	Elektronische Sigaret: Evolutie	No	Review of scientific journals and from reports from national and international organisations Expert panel	E-cigarettes
UK - OHID, 2022 (23)	Nicotine vaping in England: an evidence update including health risks and perceptions, 2022	Yes	Systematic reviews Expert panel	E-cigarettes
DE - BfR, 2022 (24)	Health risk assessment of nicotine pouches	No	Health risk assessment based on experimental studies and published scientific literature. There is no methodology section, though	Nicotine pouches

				the experiments are described	
US - AACR/ASCO, 2022 (25)	Electronic Nicotine Delivery Systems: An Updated Policy Statement From the American Association for Cancer Research and the American Society of Clinical Oncology	No	Narrative review by a joint Writing Group with members of different scientific societies Methodology not described	E-cigarettes (ENDS)	
AU - NHMRC, 2022 (26)	Inhalation toxicity of non-nicotine e-cigarette constituents: risk assessments, scoping review and evidence map	Yes	Toxicology assessment and scoping literature review	e-liquids constituents/ingredients	
Cochrane living SR, 2022 (27)	Electronic cigarettes for smoking cessation	No	Systematic review	E-cigarettes	
SCHEER, 2021 (10)	SCHEER Opinion on electronic cigarettes	No	Risk assessment based on literature Expert panel	E-cigarettes (ENDS)	
WHO, 2021a (28)	WHO report on the global tobacco epidemic 2021: addressing new and emerging products	No	Narrative review Methodology not described	E-cigarettes	
NZ - ESR, 2021 (29)	Health risk assessment: E-cigarette liquids, acute toxicity hazards and health risks	Yes	Narrative review Methodology not described	E-cigarettes	
WHO, 2021b (30)	Report on the scientific basis of tobacco product regulation: eighth report of a WHO study group	No	Narrative literature review Methodology not described	E-cigarettes HTPs	
UK - PHE, 2021 (31)	Vaping in England: an evidence update including vaping for smoking cessation, February 2021	Yes	Analysis of several surveys; systematic literature review, analysis of NHS digital stop smoking services, analysis of adverse reactions recorded in the MHRA Yellow Card system	E-cigarettes (ENDS)	
WHO, 2020 (32)	Electronic nicotine and non-nicotine delivery systems: a brief	No	Policy brief Methodology not described	E-cigarettes	

UK - COT, 2020 (33)	Statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)	No	Narrative review by COT, based on systematic reviews, summary overviews of published literature reviews, short data summaries, and follow-on papers focussing in more depth on specific aspects raised during discussions	E-cigarettes
BE - SHC, 2020 (34)	New Tobacco Products: Heated Tobacco Products	No	Review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), Expert panel	HTPs
WHO, 2019 (35)	WHO report on the global tobacco epidemic 2019: offer help to quit tobacco use	No	Narrative review Methodology not described	HTPs
US - NASEM, 2018 (36)	Public health consequences of e-cigarettes	No	Systematic review, included human, <i>in vivo</i> animal and <i>in vitro</i> evidence Modeling study of smoking transitions is also presented Expert panel	E-cigarettes
US - HHS, 2016 (37)	E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General	No	Report drafted by selected experts based on scientific literature (narrative review) Several rounds of peer review	E-cigarettes
UK - RCP, 2016 (38)	Nicotine without smoke Tobacco harm reduction	No	Narrative review Methodology not described	E-cigarettes (ENDS)
NL - RIVM, 2015 (39)	The health risks of using e-cigarettes	No	Risk assessment based on literature, a survey and measurements	E-cigarettes
ECHA, 2015 (40)	Committee for Risk Assessment (RAC) Opinion proposing harmonised	No	Opinion adopted by RAC by consensus	Nicotine (pure)

	classification and labelling at EU level of Nicotine (ISO); 3-[(2S)-1-methylpyrrolidin-2-yl]pyridine		based on the dossier submitted by the NL. After public consultation, the RAC adopted its opinion	
NO - NIPH, 2015 (41)	Health risks associated with the use of electronic cigarettes - Summary in English	No	Health risk assessments Methodology only described in the full report (Norwegian) report Expert panel	E-cigarettes (ENDS)
WHO, 2015 (42)	A systematic review of health effects of electronic cigarettes	Yes	Systematic review	E-cigarettes
BE - SHC, 2015 (43)	Recommendations of the Superior Health Council no. 9265 State of affairs: the electronic cigarette	No	Risk assessment for e-cigarettes (ENDS and ENNDS) for smokers, non-smokers and users of e-cigarettes. Expert study group, based on expertise, declarations of conflict of interests. Recommendations based on overview of peer-reviewed literature (journals and reports), and opinions of the experts.	E-cigarettes
WHO, 2014 (44)	Electronic nicotine delivery systems: Report by WHO	No	Methodology not described	E-cigarettes (ENDS)

Source: JRC own production

2.2 Exposures (products) of interest

This overview focuses on three exposures (products) of interest: e-cigarettes, heated tobacco products and nicotine pouches. The definitions may vary depending on the report consulted. Nonetheless, where available, the legal definition is provided below. For nicotine pouches, the definition is sourced from WHO.

- **E-cigarettes:** as described in the Directive 2014/40/EU, an e-cigarette is a “product that can be used for consumption of nicotine-containing vapour via a mouthpiece, or any component of that product, including a cartridge, a tank and the device without cartridge or tank. Electronic cigarettes can be disposable or refillable by means of a refill container and a tank, or rechargeable with single use cartridges”. (45) Commercially available devices can be electronic nicotine (ENDS) and non-nicotine delivery systems (ENNDS). Only ENDS are

regulated by the Tobacco Products Directive. In this report, 'e-cigarettes' refer to both ENDS and ENNDS.

- Heated tobacco products: as stated in the Commission Delegated Directive 2022/2100 amending Directive 2014/40/EU, a heated tobacco product is a “novel tobacco product that is heated to produce an emission containing nicotine and other chemicals, which is then inhaled by user(s), and that, depending on its characteristics, is a smokeless tobacco product or a tobacco product for smoking”. (46)
- Nicotine pouches: Following the WHO definition, nicotine pouches “are pre-portioned pouches that contain nicotine and are similar to traditional smokeless tobacco products such as snus in some respects including appearance, inclusion of nicotine and manner of use (placing them between the gum and lip)”. (47)

2.3 Outcomes of interest

The outcomes of interest considered in this overview were the following:

- Potential health outcomes, including short-, medium-, and long-term outcomes: cardiovascular-related diseases, cancer, respiratory diseases, toxicity, uptake of toxic substances and of other potentially harmful compounds, as well as reproductive, developmental, and pregnancy outcomes, addiction, dependence and nicotine uptake, and other outcomes (e.g., overall health, accidental outcomes and other health outcomes). Some of these health outcomes might be intermediate outcomes (e.g., biomarkers).
- Use of e-cigarettes, heated tobacco products and nicotine pouches as risk factors for transitioning to traditional tobacco products (i.e., transition to smoking regular combustible cigarettes, expressed as gateway effect in this report).
- E-cigarettes, heated tobacco products and nicotine pouches as potential tools for smoking cessation and overcoming nicotine addiction.

3 Results

In total, 32 reports from international organisations or national governmental institutions and public authorities were examined, and statements on the associations of health outcomes with e-cigarettes, heated tobacco products and nicotine pouches were extracted. The majority of these reports were based on systematic reviews and meta-analyses, some included risk assessments, while others also included an expert panel (**Table 1**).

Most of these reports primarily evaluated the health risks associated with the use of e-cigarettes, with less information available on heated tobacco products and nicotine pouches. A significant number of these reports also aimed to investigate if these products may promote initiation to smoking (gateway effect) and their potential role as a tool for smoking cessation.

The health-related assessment of these products can have a focus on the harm intrinsically associated to their use, or on the harm as compared to the use of other products (usually conventional combustible cigarette smoking). This has been reflected in the tables below as far as possible by including the comparison groups, as presented in the original source.

To simplify the presentation, the health outcomes mentioned in these reports were categorised into broader groups, with the most frequently mentioned being diseases of the cardiovascular and respiratory systems and cancer. Moreover, most of these reports were published in 2021 or later.

Importantly, e-cigarettes, heated tobacco products and nicotine pouches have not been on the market long enough to show associations with long-term health outcomes (e.g. on diseases such as cancer or cardiovascular diseases). This explains the absence of, or very limited evidence on, long-term outcomes. Several more years of observation are required to assess the long-term risks associated with their use. There are, however, immediate or short-term effects that may be precursors/early markers of longer-term conditions, all of which are considered in this overview.

3.1 Electronic cigarettes: electronic nicotine and non-nicotine delivery systems (ENDS and ENNDS)

A total of 25 reports addressing e-cigarettes from health-related organisations were identified. Most of these reports focus on the impact of e-cigarettes on health, although some reports also explore their role in smoking initiation and cessation.

3.1.1 Health outcomes

Most of these reports do not distinguish the health outcomes between e-cigarettes containing nicotine and those without it; therefore, unless otherwise specified, the overall summary tables below refer to both ENDS and ENNDS. Moreover, it should be noted that in some instances they address the impact of nicotine on health without necessarily being specific to nicotine in e-cigarettes.

3.1.1.1 Cardiovascular-related diseases

Ten of the examined reports evaluated the association of e-cigarettes with cardiovascular outcomes.

Immediate, short-term, and medium-term health outcomes:

The immediate, short-term, and medium-term cardiovascular outcomes related to the use and/or exposure to e-cigarettes from the examined reports can be summarised as follows (**Table 2**):

- Cardiovascular effects, nicotine: There is sufficient evidence that nicotine narrows blood vessels and increases blood pressure.
- Blood pressure (short-term): There is moderate evidence that diastolic blood pressure increases shortly after nicotine intake from e-cigarettes, while there is limited evidence that e-cigarette use is associated with a short-term increase in systolic blood pressure.
- Heart rate: While some reports mention that there is sufficient evidence that nicotine from e-cigarettes increases heart rate, others state that there is limited evidence to support this statement. Nicotine as a substance increases heart rate.
- Biomarkers, endothelial dysfunction and arterial stiffness: There is limited evidence of altered acute biomarkers of cardiovascular stress upon e-cigarette use. There is limited evidence that e-cigarette use is associated with changes in biomarkers of oxidative stress, increased endothelial dysfunction and arterial stiffness, and autonomic control.
- People with cardiovascular disease may be more vulnerable to adverse effects from e-cigarettes on the cardiovascular system than those without cardiovascular disease.
- Metals in aerosols: The number of metals in vaping aerosols could be greater than in combustible tobacco cigarettes, and in some cases, they are found at higher concentrations than in cigarette smoke. Exposure to certain levels of metals in vaping aerosols may cause diseases of the cardiovascular system.
- Switch to e-cigarettes: The effect on the cardiovascular system from switching from conventional cigarette smoking to e-cigarettes does not seem to be significant.

Long-term health outcomes:

From the statements of health-related organisations in **Table 2**, it can be summarised that there is insufficient research on the long-term cardiovascular effects (e.g. coronary heart disease, stroke) of the use of e-cigarettes.

- Biomarkers: There is evidence of the presence of certain substances in e-cigarette aerosols that can promote oxidative stress or pro-inflammatory responses related to cardiovascular disease. This supports the biological plausibility³ of tissue injury and disease from long-term exposure to e-cigarette aerosols.
- There is insufficient evidence on cardiovascular medium- and long-term outcomes linked to EN(N)DS use, such as subclinical atherosclerosis or long-term increased systolic/diastolic blood pressure.

³ In epidemiology, 'biological plausibility' is the consistency of a proposed exposure-outcome relationship with the current body of knowledge

Table 2. Associations of e-cigarettes with the cardiovascular-related diseases as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
DE - DKFZ, 2023 (17)	<p>Nicotine, ENDS: Nicotine has high addiction potential, <u>increases heart rate, narrows blood vessels, increases blood pressure</u> and is toxic in larger amounts.</p> <p><i>Comparison group: not mentioned</i></p> <p>Cardiovascular system: E-cigarette use can lead to <u>endothelial dysfunction</u> and causes short-term <u>cardiovascular activation</u> and <u>oxidative stress</u>, even independently of nicotine. This poses a certain risk for <u>cardiovascular diseases</u>, especially for people with existing cardiovascular diseases.</p> <p><i>Comparison group: not mentioned</i></p> <p>Cardiovascular system: The complete switch from tobacco cigarettes to e-cigarettes reduces exposure to pollutants. Many biomarkers for harmful substances and harmful effects are lower for e-cigarette consumers than for smokers. On the cardiovascular system, <u>the switch does not seem to have a significant effect</u>.</p> <p><i>Comparison group: conventional cigarette smokers</i></p>
UK - OHID, 2022 (23)	<p>Cardiovascular system: Overall, the extent to which vaping presents a risk for cardiovascular health remains uncertain. But based on the <u>toxicant profile</u> in vaping products and <u>aerosols</u>, the risk is expected to be <u>much less</u> than that of cigarette smoking.</p> <p><i>Comparison group: conventional cigarette smokers</i></p> <p>Cholesterol circulating concentrations: Looking at biomarkers of potential harm relevant to multiple diseases, studies of low-density lipoprotein (<u>LDL</u>) cholesterol showed no differences after acute and short-to medium use of vaping products, smoking or non-use. Similar findings were seen for high-density lipoprotein (<u>HDL</u>) cholesterol (or ‘good cholesterol’), except among large-scale samples of non-users where HDL levels were significantly higher than among vapers and smokers.</p> <p><i>Comparison group: conventional cigarette smokers and non-smokers</i></p> <p>Oxidative stress within the cardiovascular disease section of the original report: The findings were more mixed for markers of oxidative stress 8-isoprostane and sNOX2-dp. However, as these oxidative stress biomarkers are influenced by other factors, we could not make strong conclusions on their associations with vaping product use.</p> <p><i>Comparison group: not mentioned</i></p> <p>Inflammation within the cardiovascular disease section of the original report: For inflammation markers, differing study designs prevented us from making strong conclusions.</p> <p><i>Comparison group: not mentioned</i></p> <p>Heart rate, short-term effects: <u>Acutely</u>, immediately after use, vaping increased heart rate <u>less than smoking</u>. Heart rate after short exposure to vaping was similar to heart rate after not using tobacco or nicotine products.</p> <p><i>Comparison group: conventional cigarette smokers and non-smokers</i></p> <p>Heart rate, ENDS: There was no difference in heart rate after nicotine and non-nicotine vaping. Meta-analyses of cross-over studies from vaping nicotine and non-nicotine products for heart rate and blood pressure found no differences. Studies that we could not meta-analyse did not consistently find this.</p>

Comparison group: ENNDS

Heart rate, long-term effects: Comparing longer-term changes in heart rate, people who vaped had lower heart rate than people who smoked when the groups were mutually exclusive (people who vaped did not also smoke).

Comparison group: conventional cigarette smokers

Arterial stiffness: peripheral resistance or arterial stiffness (PWV) generally increased after acute exposure to vaping nicotine, but not after non-nicotine vaping, suggesting that any acute effects of vaping on PWV are due to nicotine.

Comparison group: nicotine vaping vs non-nicotine vaping

Arterial stiffness & left ventricular mass and function, ENDS: Animal studies also show an increase in biomarkers of arterial stiffness linked to exposure to vaping products. This may be similar to or smaller than increases caused by smoking. Left ventricular mass and vessel wall thickness (in the heart) were increased and left ventricular function reduced after vaping product aerosol exposure. These effects were potentially less than for exposure to cigarette smoke, and there were inconsistencies in findings across studies. These vaping product-induced effects appeared largely to be nicotine-dependent.

Comparison group: conventional cigarette smokers

Biomarkers: Exposure to vaping product aerosol was associated with decreases in animals' blood vessel health, as well as increases in markers of thrombosis risk, inflammation, oxidative stress, scarring, and cell health. Although, it is inconclusive as to which constituents of the aerosol play important roles in the observed effects.

Comparison group: not mentioned

Cardiovascular system, ENDS: The evidence does not allow us to distinguish pathways to cardiovascular disease. One potential pathway is through nicotine, and the biomarkers of exposure and pharmacokinetic studies show that people who vape can achieve nicotine levels similar to people who smoke. The animal studies suggested that nicotine did play a role in some of the changes seen in cardiovascular biomarkers, specifically: blood pressure, arterial stiffness, and left ventricular mass and function.

Comparison group: conventional cigarette smokers

SCHEER, 2021 (10)

Cardiovascular system: The overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is moderate.

Comparison group: non-smokers

Second-hand exposure: The overall weight of evidence for risks of systemic cardiovascular effects in second-hand exposed persons due to exposure to nicotine is weak to moderate.

Comparison group: non-smokers

WHO, 2020 (32)

Metals: The main substances in the aerosol that raise health concern are metals, such as chromium, nickel, and lead, [and carbonyls, such as formaldehyde, acetaldehyde, acrolein and glyoxal].

Exposure to certain levels of some metals may cause serious health effects, such as diseases of the nervous, cardiovascular and respiratory systems. The number of metals in the aerosol could be greater than in combustible tobacco cigarettes, and in some cases is found at higher concentrations than in cigarette smoke.

Comparison group: not mentioned

Long-term effects: Scientists are still learning about the long-term health effects of EN&NNDS. Currently, there is insufficient research to determine with certainty whether unadulterated and appropriately regulated EN&NNDS use is associated with cardiovascular, lung or cancer diseases.

	<i>Comparison group: not mentioned</i>
UK - COT, 2020 (33)	<p>Cardiovascular system: In the evaluation of absolute risk from exposure to E(N)NDS emissions, the Committee considered adverse health effects that could be of concern include the potential for sensory irritation, the promotion or augmentation of respiratory symptoms in people with respiratory disease or conditions, and the potential to enhance adverse cardiovascular symptoms in <u>people with cardiovascular disease</u>.</p> <p><i>Comparison group: not mentioned</i></p>
US - NASEM, 2018 (36)	<p>Cardiovascular system: There is no available evidence whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima-media thickness and coronary artery calcification).</p> <p><i>Comparison group: not mentioned</i></p> <p>Heart rate, ENDS: There is substantial evidence that heart rate increases shortly after nicotine intake from e-cigarettes.</p> <p><i>Comparison group: not mentioned</i></p> <p>Diastolic blood pressure, ENDS: There is moderate evidence that diastolic blood pressure increases shortly after nicotine intake from e-cigarettes.</p> <p><i>Comparison group: not mentioned</i></p> <p>Cardiovascular system: There is limited evidence that e-cigarette use is associated with a short-term increase in systolic blood pressure, changes in biomarkers of oxidative stress, increased endothelial dysfunction and arterial stiffness, and autonomic control. There is substantial evidence that e-cigarette aerosols can induce acute endothelial cell dysfunction, although the long-term consequences and outcomes on these parameters with long-term exposure to e-cigarette aerosol are uncertain.</p> <p><i>Comparison group: not mentioned</i></p> <p>Cardiovascular system: There is insufficient evidence that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function.</p> <p><i>Comparison group: not mentioned</i></p>
UK - RCP, 2016 (38)	<p>Oxidants and other toxins: Some of the carcinogens, oxidants and other toxins present in tobacco smoke have also been detected in e-cigarette vapour, raising the possibility that long-term use of e-cigarettes may increase the risks of lung cancer, COPD, cardiovascular and other smoking-related diseases. However, the magnitude of such risks is likely to be substantially lower than those of smoking, and extremely low in absolute terms.</p> <p><i>Comparison group: conventional cigarette smokers</i></p>
NO - NIPH, 2015 (41)	<p>Cardiovascular system, ENDS: The intake of nicotine from e-cigarettes seems to be similar to that found with tobacco smoking and snus consumption, indicating that similar nicotine-related effects are expected on the <u>cardiovascular system</u>, lung development in unborn children and in later life, reproductive health (premature birth, stillbirth and preeclampsia) and cognitive effects.</p> <p><i>Comparison group: conventional cigarette smokers & snus users</i></p> <p>Cardiovascular system, ENDS: It is reasonable to assume that people with existing cardiovascular disease will be more vulnerable to adverse effects on the cardiovascular system (both acute and chronic) than people without heart disease. Furthermore, unborn babies, children and adolescents are considered to be particularly sensitive to <u>nicotine exposure</u>.</p> <p><i>Comparison group: people without heart disease</i></p>

Cardiovascular system, ENDS: Nicotine levels in the environment from passive exposure to aerosols from e-cigarettes can result in similar high nicotine levels in the blood of a passive smoker of regular cigarettes. This means that similar harmful nicotine-related effects can be expected for passive exposure to e-cigarettes as for regular cigarettes. This means that passive exposure to aerosol from e-cigarettes may act on the cardiovascular system, have stimulatory effects and contribute to addiction.

Comparison group: people without heart disease

WHO, 2015 (42) **Negative health effects:** Negative health effects should be expected from the pulmonary system but adverse effects from (for example) the cardiovascular system and a carcinogenic effect cannot be ruled out either.

Comparison group: not mentioned

BE - SHC, 2015 (43) **Stop smoking altogether:** E-cigarette as quitting aid makes little sense if the smoker continues to smoke tobacco while using the e-cigarette. He must cut down his tobacco smoking by 85% to have a positive effect on chronic bronchitis (COPD) and stop smoking altogether to have a positive effect on cardiovascular disease.

Comparison group: not mentioned

Source: JRC own production

3.1.1.2 Cancer

A total of 13 reports assessed the association of e-cigarettes with cancer (**Table 3**).

Immediate, short-term, and medium-term health outcomes:

To date, statements from these reports show that e-cigarette use exposes users to carcinogens and might be associated with an increased cancer risk, though to a much lower extent than conventional combustible cigarette smoking (**Table 3**):

- Carcinogenicity (potential/risk to cause cancer): Some evidence for carcinogenicity (potential/risk to cause cancer) has been found in animals experimentally exposed to e-cigarettes, although the risk appears to be lower than that associated with conventional cigarettes.
- Mutagenic and DNA damage: There is some evidence that e-cigarette aerosol can be mutagenic or cause DNA damage in humans, based on findings from animal models and studies on human cells in culture. There is evidence that some chemicals present in e-cigarette aerosols (e.g., formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis.
- Gene expression, comparison to conventional cigarettes: E-cigarette use may trigger alterations in gene expression, but at a lower extent than exposure to tobacco smoke.
- Carcinogenic substances, comparison to conventional cigarettes: E-cigarette use generally leads to lower exposure to many of the carcinogens responsible for the considerable health risks of conventional cigarette smoking. Biomarkers of exposure to several human carcinogens in tobacco smoke show lower measured levels in people who vape compared with those who smoke.

Long-term health outcomes:

To date, these reports highlight that there is no conclusive evidence that e-cigarettes cause cancer in humans, stating that it may take several decades of exposure and extensive follow-up studies to fully understand the association between e-cigarettes and the risk of developing cancer (**Table 3**). In summary, these reports state the following:

- Biomarkers: To date, there are insufficient data about the long-term implications for health of certain intermediate outcomes (intermediate biomarkers of cancer, presence of relevant urinary metabolites, DNA damage, mutagenesis) observed after exposure to e-cigarettes. There is evidence of the presence of certain substances in e-cigarette aerosols that can promote oxidative stress, DNA damage, mutations, or pro-inflammatory responses. This supports the biological plausibility of tissue injury and disease from long-term exposure to e-cigarette aerosols.
- Cancer risk compared to conventional cigarettes: Although the risk of cancer associated with e-cigarettes appears to be lower than that of conventional cigarettes, it is not zero, and further research is required to better understand the potential risks.
- Switching from conventional cigarettes to e-cigarettes may result in a considerable reduction in lung cancer risk due to lower exposure to tobacco-related carcinogens.

Table 3. Association of e-cigarettes with cancer as described by health-related organisations. Most reports do not differentiate between ENDS (or nicotine) and ENNDS. If the statement explicitly refers to ENDS or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
IARC, 2024 (16)	<p>Evidence in humans: There is no evidence regarding cancer in humans. <i>Comparison group: not mentioned</i></p> <p>Evidence in animals: Overall, there is some evidence for cancer in experimental animals. <i>Comparison group: not mentioned</i></p> <p>Mechanisms, ENDS: Ample mechanistic evidence is available, suggesting that ENDS exhibit multiple key characteristics across the full range of systems, including exposed humans. The Advisory Group therefore considered an IARC Monographs evaluation of ENDS to be warranted. <i>Comparison group: not mentioned</i></p>
DE - DKFZ, 2023 (17)	<p>Carcinogenic effect (if e-cigarettes cause cancer): The studies available so far do not provide any reliable evidence of the possible carcinogenic effect of e-cigarette use. <i>Comparison group: not mentioned</i></p>
UK - OHID, 2022 (23)	<p>Biomarkers: In our review of human studies, biomarkers of exposure to several human carcinogens in tobacco smoke show lower measured levels in people who vape compared with those who smoke. So, the <u>biomarker of exposure</u> studies compiled in this review (see chapter 7 on biomarkers of exposure) provide conclusive evidence that vaping generally leads to lower exposure to many of the carcinogens responsible for the health risks of smoking. <i>Comparison group: conventional cigarette smokers</i></p> <p>Risk in cancer patients and cancer survivors: There were no studies that assessed how vaping affects people with an existing or previous cancer condition.</p>

Comparison group: not mentioned

Vaping aerosols, gene expression: there are suggestions from this literature that vaping aerosols are not benign to people who have never smoked. And that exposure to these aerosols may be implicated in negative outcomes that could affect the viability of cancer treatment for people with pre-existing disease. However, cell and animal studies appear to support the human studies and suggest vaping may trigger alterations in gene expression, but at a lower extent than we see from exposure to tobacco smoke.

Comparison group: never smokers, people with pre-existing disease, conventional cigarette smokers

Carcinogens exposure: Vaping generally leads to lower exposure to many of the carcinogens responsible for the considerable health risks of smoking. However, studies of biomarkers of exposure that are associated with cancer risk in humans need to have longer follow up periods than has been the case to date, as this will give us better information if vaping reduces cancer risk compared with smoking. More research is needed on biomarkers of potential harm in humans.

Comparison group: not mentioned

Inflammation and oxidative stress: Findings from studies of inflammation and oxidative stress do not show any systematic relationship with mixed evidence of differences (or no difference) in levels between vapers and smokers and non-users. So, this evidence is currently insufficient to draw conclusions.

Comparison group: conventional cigarette smokers and non-smokers

**US -
AACR/ASCO
, 2022 (25)**

Carcinogens exposure, ENDS: The results of ENDS use investigated to date clearly indicate that vaping exposes the user to carcinogens and therefore likely increases long-term cancer risk, but for most carcinogens at levels far lower than from smoking combustible tobacco cigarettes.

Comparison group: conventional cigarette smokers

Carcinogenesis (biological process of cancer development), ENDS: These findings suggest that ENDS vapor can promote replication of precancerous cells and therefore promote cancer-predisposing DNA mutations. A growing body of evidence points toward a biologically plausible role for ENDS use in contributing to human carcinogenesis, based on the presence of carcinogens in ENDS aerosols, metabolites of carcinogens in human urine samples, inflammation markers in human lung swabs and blood samples, and cell culture and mouse experiments exhibiting DNA damage and inflammation.

Comparison group: not mentioned

Long-term effect, ENDS: The lack of well-designed epidemiologic studies is a critical hurdle to definitively characterizing cancer risk. ENDS remain relatively new products, so it may take decades for enough exposure to occur that would enable studies with sufficient follow-up to fully characterize the associations between ENDS use and cancer.

Comparison group: not mentioned

Biomarkers, ENDS: The evidence from biomarker studies tends to show lower carcinogen exposures in ENDS users compared with dual users and exclusive smokers of combustible tobacco, likely due to the absence of combustion-related carcinogens.

Comparison group: conventional cigarette smokers

Carcinogens, ENDS: ENDS emit fewer carcinogens than combustible tobacco primarily due to the absence of combustion products, and for some ENDS the absence of some tobacco-specific nitrosamines, but it is clear that they still pose health risks.

Comparison group: conventional cigarette smokers

SCHEER, 2021 (10)	<p>Carcinogenicity (potential/risk to cause cancer): The overall weight of evidence for risks of carcinogenicity of the respiratory tract due to long-term, cumulative exposure to <u>nitrosamines</u> and due to exposure to <u>acetaldehyde</u> and <u>formaldehyde</u> is weak to moderate. The weight of evidence for risks of adverse effects, specifically carcinogenicity, due to <u>metals in aerosols</u> is weak.</p> <p><i>Comparison group: not mentioned</i></p> <p>Exposure to nitrosamines: The overall weight of evidence for carcinogenic risk due to cumulative exposure to <u>nitrosamines</u> is weak to moderate.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2021b (30)	<p>Long-term effect: 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 <u>e-cigarettes have not been available for the time necessary</u> to develop chronic health effects such as <u>cancer</u>.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2020 (32)	<p>Substances in the aerosol: The main substances in the aerosol that raise health concern are <u>metals</u>, such as chromium, nickel, and lead, and carbonyls, such as formaldehyde, acetaldehyde, acrolein and glyoxal. Carbonyl compounds are potentially hazardous to users. Formaldehyde is a human carcinogen, acetaldehyde is possibly <u>carcinogenic</u> to humans, acrolein is a strong irritant of the respiratory system and glyoxal shows mutagenicity. The number and levels of carbonyls detected in the aerosol are lower than in smoke from combustible tobacco, but even these levels raise health concerns.</p> <p><i>Comparison group: conventional cigarette smokers</i></p> <p>Long-term effect: Scientists are still learning about the long-term health effects of EN&NNDS. Currently, there is insufficient research to determine with certainty whether unadulterated and appropriately regulated EN&NNDS use is associated with cardiovascular, lung or cancer diseases.</p> <p><i>Comparison group: not mentioned</i></p>
UK - COT, 2020 (33)	<p>Lung cancer: A considerable reduction in risk of lung cancer would be anticipated due to lower exposure to tobacco-related carcinogens, but this would not necessarily be the case for all endpoints. The expectation of lower risk associated with E(N)NDS use compared with conventional cigarettes smoking relates to individuals making a complete switch from conventional cigarettes smoking to E(N)NDS.</p> <p><i>Comparison group: conventional cigarette use</i></p>
US - NASEM, 2018 (36)	<p>Intermediate cancer endpoints: There is no available evidence whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for e-cigarette use compared with use of combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products.</p> <p><i>Comparison group: conventional cigarette use and non-smokers</i></p> <p>DNA damage: There is limited evidence that e-cigarette aerosol can be <u>mutagenic</u> or cause <u>DNA damage in humans, animal models, and human cells in culture</u>. There is substantial evidence that some chemicals present in e-cigarette aerosols (e.g., formaldehyde, acrolein) are capable of causing <u>DNA damage and mutagenesis</u>. This supports the <u>biological plausibility</u> that long-term exposure to e-cigarette aerosols could increase <u>risk of cancer</u> and adverse reproductive outcomes. Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined.</p> <p><i>Comparison group: not mentioned</i></p>

	<p>Long-term effect: There is limited evidence from <i>in vivo</i> <u>animal studies</u> using <u>intermediate biomarkers of cancer</u> to support the hypothesis that long-term e-cigarette use could increase the risk of cancer; there is no available evidence from adequate long-term animal bioassays of e-cigarette aerosol exposures to inform cancer risk.</p> <p><i>Comparison group: not mentioned</i></p>
UK - RCP, 2016 (38)	<p>Carcinogens: Some of the carcinogens, oxidants and other toxins present in tobacco smoke have also been detected in e-cigarette vapour, raising the possibility that long-term use of e-cigarettes may increase the risks of <u>lung cancer</u>, COPD, cardiovascular and other smoking-related diseases. However, the magnitude of such risks is likely to be substantially lower than those of smoking, and extremely low in absolute terms.</p> <p><i>Comparison group: conventional cigarette use</i></p>
NL - RIVM, 2015 (39)	<p>Nitrosamines: While the vapour concentrations of tobacco-specific nitrosamines are many times lower than in tobacco smoke, they are sufficiently high in some cases to give an elevated risk of tumour development.</p> <p><i>Comparison group: conventional cigarette use</i></p>
NO - NIPH, 2015 (41)	<p>Aerosol substances: TSNA, formaldehyde, acetaldehyde, PAH compounds and various metals (nickel, cadmium) are known to contribute to the carcinogenic effect of tobacco smoking. Exposure concentrations to these substances with e-cigarette use are very low and we consider the cancer risk to be negligible. However, this conclusion is based on the separate assessment of the individual substances in aerosols. Further research based on inhalation of aerosols from e-cigarettes is required to verify these conclusions.</p> <p><i>Comparison group: conventional cigarette use</i></p> <p>Cancer risk reduction: For smokers who are unable to quit smoking, it must be assumed that a full transition to e-cigarettes will incur a risk reduction, particularly with regards to cancer development.</p> <p><i>Comparison group: conventional cigarette use</i></p>
WHO, 2015 (42)	<p>Negative health effects: Negative health effects should be expected from the pulmonary system but adverse effects from (for example) the cardiovascular system and a carcinogenic effect cannot be ruled out either.</p> <p><i>Comparison group: not mentioned</i></p>

Source: JRC own production

3.1.1.3 Respiratory diseases

A total of ten reports assessed the association of e-cigarettes with the respiratory diseases (**Table 4**).

Immediate, short-term, and medium-term health outcomes:

The key statements from the examined reports are summarised below (**Table 4**).

- Respiratory tract damage: There is some evidence of negative effects on the respiratory tract arising from *in vivo* and *in vitro* studies.
- Aerosols: Some evidence points at local irritative damage and damage to the respiratory epithelium from certain substances present in e-cigarette aerosols (e.g. acrolein, polyols).

- Substances, comparison to conventional cigarettes: Most of the potentially hazardous substances to the respiratory tract are found in lower concentrations in e-cigarette aerosols than in conventional combustible cigarettes, with the exception of certain metals and carrier substances glycerol and propylene glycol (polyols). There is moderate evidence that the levels of biomarkers of exposure to and harm from respiratory toxicants are lower in e-cigarette users than in conventional cigarette users.
- Switch to e-cigarettes in adult smokers with asthma: There is limited evidence for improvement in lung function, and less respiratory and chronic obstructive pulmonary disease (COPD) symptoms among adult smokers with asthma who switch to e-cigarettes completely or in part (dual use).

Long-term health outcomes:

These reports state that, to date, there are not enough reliable studies on the long-term association of e-cigarette use, either ENDS or ENNDS, with the human respiratory tract. However, they state that long-term use of e-cigarettes may increase the risk of certain respiratory diseases, even if the risks are likely lower than those linked to cigarette smoking (**Table 4**).

Table 4. Associations of e-cigarettes with respiratory diseases as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
DE - DKFZ, 2023 (17)	<p>Respiratory tract damage: <u>Animal</u> and <u>cell</u> tests suggest that e-cigarette use has negative effects on the respiratory tract; there is a lack of reliable studies on the long-term effects of e-cigarette consumption on the respiratory tract in <u>humans</u>.</p> <p><i>Comparison group: not mentioned</i></p> <p>Lung damage: E-cigarette use can cause <u>e-cigarette or vaping-associated lung injury (EVALI)</u>. In many of the cases observed, liquids containing <u>THC</u> containing <u>vitamin-E acetate</u> were used; however, there are also some cases without the involvement of THC and vitamin E acetate.</p> <p><i>Comparison group: not mentioned</i></p> <p>Lung function: Several studies suggest that a short-term switch to e-cigarettes improves the <u>lung function</u>.</p> <p><i>Comparison group: conventional cigarette use</i></p>
UK - OHID, 2022 (23)	<p>Respiratory toxicants: We identified conclusive evidence that under typical use conditions, acute (from single use to 7 days) and short to medium (from 8 days to 12 months) exposure to most <u>potential respiratory toxicants</u> from vaping is significantly lower compared with smoking tobacco cigarettes. And there are substantial reductions in some <u>biomarkers</u>. For the respiratory toxicants that were assessed at long-term exposure (more than 12 months), evidence was moderate that biomarkers of exposure are lower for vaping than smoking.</p> <p><i>Comparison group: conventional cigarette use</i></p> <p>Asthma: Sample sizes were generally very small, and the findings were inconclusive as to whether there are improvements in <u>lung function</u> and <u>respiratory symptoms</u> among adult smokers with asthma who switch to vaping completely. There was limited evidence that vaping negatively affects lung function among adults with asthma.</p> <p><i>Comparison group: conventional cigarette use & adults with asthma</i></p>

Chronic Obstructive Pulmonary Disease (COPD): There is limited evidence for reduction of COPD exacerbations among adult smokers with COPD who switch to vaping completely and continue vaping for up to 5 years.

Comparison group: conventional cigarette use

The lack of consistency across the studies meant we could not perform meta-analyses of respiratory measures, which limits the conclusions that we can draw.

People with asthma: More studies have been carried out with people suffering from asthma, but the different designs, diagnoses, and measurements taken prevent us from making any conclusions.

Comparison group: not mentioned

**SCHEER,
2021** (10)

Local irritative damage to the respiratory tract: The overall weight of evidence is moderate for risks of local irritative damage to the respiratory tract mainly due to exposure to glycols.

Comparison group: not mentioned

Pulmonary disease: The overall weight of evidence for risks of other long-term adverse health effects, such as pulmonary disease, CNS and reprotoxic effects based on the hazard identification and human evidence, is weak, and further consistent data are needed.

Comparison group: not mentioned

WHO, 2020
(32)

Respiratory system: The main substances in the aerosol that raise health concern are metals, such as chromium, nickel, and lead, and carbonyls, such as formaldehyde, acetaldehyde, acrolein and glyoxal. Carbonyl compounds are potentially hazardous to users. Formaldehyde is a human carcinogen, acetaldehyde is possibly carcinogenic to humans, acrolein is a strong irritant of the respiratory system and glyoxal shows mutagenicity. The number and levels of carbonyls detected in the aerosol are lower than in smoke from combustible tobacco, but even these levels raise health concerns. Exposure to certain levels of some metals may cause serious health effects, such as diseases of the nervous, cardiovascular and respiratory systems. The number of metals in the aerosol could be greater than in combustible tobacco cigarettes, and in some cases is found at higher concentrations than in cigarette smoke.

Comparison group: not mentioned/ conventional cigarette use

Lung disease: Currently, there is insufficient research to determine with certainty whether unadulterated and appropriately regulated EN&NNDS use is associated with cardiovascular, lung or cancer diseases.

Comparison group: not mentioned

**UK - COT,
2020** (33)

Respiratory disease: In the evaluation of absolute risk from exposure to E(N)NDS emissions, the Committee considered adverse health effects that could be of concern include the potential for sensory irritation, the promotion or augmentation of respiratory symptoms in people with respiratory disease or conditions, and the potential to enhance adverse cardiovascular symptoms in people with cardiovascular disease.

Comparison group: not mentioned

**US -
NASEM,
2018** (36)

Animal and *in vitro* studies: There is limited evidence of adverse effects of e-cigarette exposure on the respiratory system from animal and *in vitro* studies.

Comparison group: not mentioned

Respiratory disease: There is no available evidence whether or not e-cigarettes cause respiratory diseases in humans.

Comparison group: not mentioned

Asthma: There is limited evidence for improvement in lung function and respiratory symptoms among adult smokers with asthma who switch to e-cigarettes completely or in part (dual use).

Comparison group: conventional cigarette user with asthma.

Asthma (adolescents): There is moderate evidence for increased cough and wheeze in adolescents who use e-cigarettes and an association with e-cigarette use and an increase in asthma exacerbations.

Comparison group: Adolescents with asthma

Chronic Obstructive Pulmonary Disease (COPD): There is limited evidence for reduction of chronic obstructive pulmonary disease (COPD) exacerbations among adult smokers with COPD who switch to e-cigarettes completely or in part (dual use).

Comparison group: conventional cigarette user with COPD

**UK - RCP,
2016 (38)**

Toxins and risk of COPD: Some of the carcinogens, oxidants and other toxins present in tobacco smoke have also been detected in e-cigarette vapour, raising the possibility that long-term use of e-cigarettes may increase the risks of lung cancer, COPD, cardiovascular and other smoking-related diseases. However, the magnitude of such risks is likely to be substantially lower than those of smoking, and extremely low in absolute terms".

Comparison group: conventional cigarette use

**NL - RIVM,
2015 (39)**

Damage to respiratory epithelium: Exposure to the polyols can damage the respiratory epithelium and reduce the lymphocyte count.

Comparison group: not mentioned

Toxic substances and metals: The concentrations of a number of substances detected in e-liquid vapour are lower or much lower than the concentrations in tobacco smoke. By contrast, the concentrations of the carrier substances glycerol and propylene glycol are higher in e-cigarette vapour than in tobacco smoke. The main effects of the latter two substance[s] are damage to the respiratory epithelium and (where propylene glycol is concerned) a reduced lymphocyte count. The vapour concentrations of aldehydes can also be sufficient to induce effects on the respiratory tract, although the concentrations in question are probably attributable to the heating process rather than the properties of particular e-liquids. Conventional tobacco smoking was associated with higher or much higher concentrations of cadmium, lead, nickel and arsenic than vaping; the chromium concentrations were comparable. While the possibility of health effects at the measured metal concentrations cannot be excluded, it is safe to say that the risks are lower with vaping than with smoking. A more precise assessment of the possible risks posed by metals in e-cigarette vapour will require further research.

Comparison group: conventional cigarette use

**WHO, 2015
(42)**

Respiratory system: Negative health effects should be expected from the pulmonary system but adverse effects from (for example) the cardiovascular system and a carcinogenic effect cannot be ruled out either.

Comparison group: not mentioned

Findings causing concern include the following: [among a long list, here only those linked to the respiratory system]

- airway obstruction in human experimental studies
- airway inflammation, asthma and chronic obstructive pulmonary disease development in animal studies

Comparison group: not mentioned

BE - SHC, 2015 (43)	<p>Respiratory disease: This [e-cigarette as quitting aid] makes little sense if the smoker continues to smoke tobacco while using the e-cigarette. He must cut down his tobacco smoking by 85% to have a positive effect on <u>chronic bronchitis (COPD)</u> and stop smoking altogether to have a positive effect on cardiovascular disease. The e-cigarette, therefore, along with the many other available treatments, must be seen as a potential aid to stop smoking altogether, after which the e-cigarette should in time be given up.</p> <p><i>Comparison group: conventional cigarette use (Substitution of combustible cigarette with e-cigarette)</i></p>
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Source: JRC own production

3.1.1.4 Toxicity, uptake of toxic substances and of other potentially harmful compounds

A total of 15 reports assessed the toxicity, uptake of toxic substances and of other potentially harmful compounds in e-cigarette aerosols (**Table 5**). Because of the nature of these health outcomes, no differentiation between long-term and short-term outcomes was made.

- Presence of toxic substances: e-cigarette aerosols contain various toxic substances, including metals, carbonyl compounds (formaldehyde, acetaldehyde), and volatile organic compounds.
- Metals: Product characteristics and use patterns may affect the actual metals present and their concentrations in e-cigarette aerosols. Some of these metals may lead to serious health effects.
- Nicotine's harmful effects, ENDS: Nicotine in e-cigarettes poses acute toxicity risks, especially in children.
- Uncertainty around flavouring chemicals: Their inhalation raises concerns about cytotoxicity, inflammation, and unknown long-term effects. Moreover, there is a large number of possible flavouring compounds used and insufficient toxicological data relating to inhaled exposure.
- Products heterogeneity: User exposure to nicotine and toxic substances is highly variable and depends on the e-cigarette product and usage patterns.
- Chemical: A large proportion of chemicals examined in these reports did not have toxicological assessment data available on inhalation toxicity and it cannot be concluded that absence of toxicological assessment data equates to absence of harm. Where toxicological assessment data was available, the majority of chemicals currently known to be used in e-cigarettes were associated with risks to health.
- Comparison with conventional cigarettes: Some reports mention that e-cigarettes release fewer toxic substances than combustible tobacco products. Moreover, simultaneous use of e-cigarettes and tobacco cigarettes (dual use) does not necessarily reduce exposure to pollutants and does not seem to bring health benefits to smokers. E-cigarette aerosols may have a higher number of metals than combustible tobacco cigarettes, and in some cases, these metals are present in higher concentrations than in cigarette smoke.
- Nicotine's harmful effects, ENDS versus conventional combustible cigarette smoking: Any toxicological risks related to nicotine exposure are not expected to be increased when switching from conventional cigarettes smoking to ENDS use. Nicotine intake from e-

cigarettes among experienced adult users can be comparable to that from combustible tobacco cigarettes.

- E-cigarettes emit several potentially harmful substances with normal use. There is limited evidence for e-cigarette aerosol causing short term health problems from second-hand exposure.
- Long-term toxicity: Significant gaps exist in understanding the long-term toxicity and risks of inhaled flavouring chemicals and nicotine.

Table 5. Toxicity, uptake of toxic substances and of other potentially harmful compounds in e-cigarettes as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
Cochrane living SR, 2024 (15)	<p>Toxin concentrations and biomarkers: In some studies, reduced toxin concentrations and biomarkers of harm were observed in people who smoked and switched to vaping, consistent with reductions seen in people who stopped smoking without electronic cigarettes.</p> <p><i>Comparison group: conventional cigarette use</i></p>
DE - DKFZ, 2023 (17)	<p>Toxicity: E-cigarette-aerosol is cytotoxic, causes oxidative stress, affects cell division, damages DNA and alters the reading and transfer of genetic information.</p> <p><i>Comparison group: not mentioned</i></p> <p>Toxicity, ENDS: Nicotine has high addiction potential, increases heart rate, narrows blood vessels, increases blood pressure and is toxic in larger amounts.</p> <p><i>Comparison group: not mentioned</i></p> <p>Exposure to pollutants, complete switch: The complete switch from tobacco cigarettes to e-cigarettes reduces exposure to pollutants.</p> <p><i>Comparison group: conventional cigarette use, dual use</i></p> <p>Exposure to pollutants: E-cigarette aerosol can cause short term health problems for exposed persons present in the room. E-cigarette-aerosol exposure to pollutants is lower than exposure to passive smoking.</p> <p><i>Comparison group: not mentioned/ second-hand exposure to conventional combustible cigarette smoke</i></p> <p>Exposure to pollutants, dual use: The simultaneous use of e-cigarettes and tobacco cigarettes (dual consumption) does not necessarily reduce exposure to pollutants and does not seem to bring health benefits to smokers.</p> <p><i>Comparison group: conventional combustible cigarette smoking</i></p>
BE - SHC, 2022 (22)	<p>Toxicity information: E-liquids contain many substances for which there is insufficient information about their <u>toxicity</u> when inhaled.</p> <p><i>Comparison group: not mentioned</i></p>
AU - NHMRC, 2022 (26)	<p>Toxicological assessments: In line with other published literature, this report found that where data was available, the majority of <u>chemicals</u> currently known to be used in e-cigarettes are <u>associated with health risks</u>, based on toxicological assessments. A large proportion of chemicals examined did not have toxicological assessment data available on <u>inhalation toxicity</u> and it <u>cannot be concluded that absence of toxicological assessment data equates to absence of harm</u>. Although some of the chemicals were identified to be permit-</p>

ted for use in food and medicine in Australia, a number were found to be harmful when inhaled. This is important to consider given the current use of these chemicals in e-liquids and that these chemicals are inhaled via e-cigarettes.

Comparison group: not mentioned

NZ - ESR, 2021 (29)

Toxicity, ENDS: Electronic cigarette liquids containing nicotine are highly toxic by all routes of exposure, and there is clear evidence of acute intoxications, including deaths, overseas.

Comparison group: not mentioned

Neurotoxicant, ENDS: Nicotine is a potent acute neurotoxicant and drives the acute toxicity consideration for e-liquids.

Comparison group: not mentioned

Flavouring chemicals: Flavouring chemicals are regulated under SERPR, and although many are “Generally Recognised As Safe” by the U.S. Food and Drug Administration, some flavouring chemicals have been found to be cytotoxic to pulmonary and immune cells *in vitro*, and to induce pro-inflammatory responses.

Comparison group: not mentioned

WHO, 2021b (30)

Toxicants, ENDS: 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.

Comparison group: not mentioned

Flavours, ENDS: 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.

Comparison group: not mentioned

WHO, 2020 (32)

Metals in the aerosol: The main substances in the aerosol that raise health concern are metals, such as chromium, nickel, and lead, and carbonyls, such as formaldehyde, acetaldehyde, acrolein and glyoxal. Exposure to certain levels of some metals may cause serious health effects, such as diseases of the nervous, cardiovascular and respiratory systems. The number of metals in the aerosol could be greater than in combustible tobacco cigarettes, and in some cases is found at higher concentrations than in cigarette smoke.

Comparison group: conventional cigarette use

Carbonyl compounds are potentially hazardous to users.

Comparison group: not mentioned

The number and levels of carbonyls detected in the aerosol are lower than in smoke from combustible tobacco, but even these levels raise health concerns.

Comparison group: conventional cigarette use

Toxicants in aerosols, EN(N)DS: The aerosol users breathe from EN&NNDS contains numerous potentially toxic substances, in addition to nicotine when included in the e-liquid. The number, quantity and characteristics of potentially toxic substances in the aerosol emitted by EN&NNDS are highly variable and depend on product characteristics (including device and e-liquid features) and how the device is operated by the user. Under typical conditions of use, however, the number and concentrations of potentially toxic substances emitted from unadulterated EN&NNDS are lower than in tobacco smoke, except for some metals. Certain flavourings, such as diacetyl, cinnamaldehyde and benzaldehyde, have been cited as a source of health concerns when heated and inhaled.

Comparison group: not mentioned/conventional combustible cigarette smoke

Other potentially harmful compounds in the aerosol: Other substances in the aerosol of possible health concern are particulate matter and some flavourings. The particle count and size in EN&NDS aerosols do not differ greatly from those found in mainstream combustible tobacco smoke. The composition of the particles nevertheless is dissimilar and likely to have a different health impact. Aerosol particulates from EN&NDS consist mostly of a mix of aqueous and humectant droplets, whereas particles in combustible tobacco smoke are mostly complex organic constituents that contain known or suspected carcinogens. Although of health concern, particles from EN&NDS are therefore expected to have smaller health risks than particles in tobacco smoke.

Comparison group: conventional cigarette use

**UK - COT,
2020 (33)**

Flavouring chemicals: Inhalation of flavouring ingredients is an area of particular uncertainty. This is a difficult aspect to address due to the large number of possible flavouring compounds used and the lack of toxicological data relating to inhalation exposure.

Comparison group: not mentioned

The use of a wide range of flavouring products in e-liquids, for which data on toxicity by inhalation, particularly of any thermally-derived products, are generally not available, is an area of uncertainty. While there is currently no information that this is leading to adverse effects on human health, this is an important data gap.

Comparison group: not mentioned

Potential contaminants and impurities: Potential contaminants and impurities of concern include metal particles, which may leach into e-liquids from E(N)NDS devices, and silicates. Breakdown of e-liquid contents during aerosolization can result in the formation of degradation products such as formaldehyde or other carbonyl compounds, although the extent to which this would occur during normal use of E(N)NDS by users has not been established. Breakdown products of e-liquid solvents and flavouring compounds could combine to produce species of toxicological concern. Data on this latter aspect are also lacking.

Comparison group: not mentioned

Potentially harmful exposures: Particulate matter and nicotine were identified as two principal exposures deriving from normal use of E(N)NDS that may potentially be associated with adverse health effects.

Comparison group: not mentioned

Systemic nicotine exposure, ENDS: Pharmacokinetic studies have indicated that systemic exposure to nicotine from the types of ENDS products that have been studied to date is lower than or equivalent to that from conventional cigarettes smoking, but generally not higher. Therefore, any toxicological risks related to nicotine exposure would not be expected to be increased on switching from conventional cigarettes smoking to ENDS use.

Comparison group: conventional combustible cigarettes

Second-hand exposure to nicotine, ENDS: There is also the risk that nicotine addiction may develop in nicotine-naïve users. There is good evidence from animal studies for an increased risk of adverse effects on development associated with nicotine exposure, but the data set on this aspect was not adequate for the level of such risk in humans from exposure to ENDS emissions to be assessed. The possibility of adverse effects of nicotine in bystanders cannot be excluded, although in most exposure scenarios the level of exposure to nicotine from ambient air would be low. E(N)NDS use is associated with some emissions into ambient air, including nicotine. For most health effects, the risks to bystanders will probably be low in conventional exposure scenarios, although pharmacological effects from exposure to nicotine in ambient air may occur in some individuals.

Comparison group: not mentioned

Knowledge gaps: The COT review identified several important gaps in knowledge on potential toxicological effects of E(N)NDS. There is a large data gap regarding long-term toxicity from E(N)NDS use. It is not known what the nature of the effects would be as they may not be the same as the known effects of CC [conventional cigarettes] smoking, and long-term effects of E(N)NDS would become apparent only after many years. Prospective epidemiological studies would help to address this data gap. Other data gaps include the lack of knowledge regarding inhalation exposure to flavouring chemicals, including potential breakdown products, and long-term toxicological effects of inhaled nicotine itself in humans.

Comparison group: conventional combustible cigarettes There are large evidence gaps within the literature and available information. It is not possible to fully assess the risks related to all possible constituents in E(N)NDS products. There are very little data available for products that do not contain nicotine (ENNDS). It is not currently possible to predict the adverse health effects that could be associated with use of E(N)NDS products in the long term.

Comparison group: not mentioned

**US -
NASEM,
2018 (36)**

Airborne concentrations: There is conclusive evidence that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with background levels.

Comparison group: background levels

There is limited evidence that e-cigarette use increases levels of nicotine and other e-cigarette constituents on a variety of indoor surfaces compared with background levels.

Comparison group: background levels

Emission of potentially toxic substances: There is conclusive evidence that in addition to nicotine, most e-cigarette products contain and emit numerous potentially toxic substances.

Comparison group: not mentioned

There is conclusive evidence that, other than nicotine, the number, quantity, and characteristics of potentially toxic substances emitted from e-cigarettes are highly variable and depend on product characteristics (including device and e-liquid characteristics) and how the device is operated.

Comparison group: not mentioned

There is substantial evidence that except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes.

Comparison group: conventional cigarette use

Metals: There is substantial evidence that e-cigarette aerosol contains metals. The origin of the metals could be the metallic coil used to heat the e-liquid, other parts of the e-cigarette device, or e-liquids. Product characteristics and use patterns may contribute to differences in the actual metals and metal concentrations measured in e-cigarette aerosol. There is limited evidence that the number of metals in e-cigarette aerosol could be greater than the number of metals in combustible tobacco cigarettes, except for cadmium, which is markedly lower in e-cigarettes compared with combustible tobacco cigarettes.

Comparison group: conventional cigarette use

Toxicity: There is conclusive evidence that intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects including but not limited to seizures, anoxic brain injury, vomiting, and lactic acidosis.

Comparison group: not mentioned

There is conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes.

Comparison group: conventional cigarette use

**US - HHS,
2016** (37)

Nicotine harm, ENDS: The use of products containing nicotine poses dangers to youth, pregnant women, and fetuses. The use of products containing nicotine in any form among youth, including in e-cigarettes, is unsafe.

Comparison group: not mentioned

Aerosol components: E-cigarettes can expose users to several chemicals, including nicotine, carbonyl compounds, and volatile organic compounds, known to have adverse health effects. The health effects and potentially harmful doses of heated and aerosolized constituents of e-cigarette liquids, including solvents, flavorants, and toxicants, are not completely understood.

Comparison group: not mentioned

E-cigarette aerosol is not harmless "water vapor," although it generally contains fewer toxicants than combustible tobacco products.

Comparison group: not mentioned

**NL - RIVM,
2015** (39)

Formaldehyde concentration (toxic at high amounts): Formaldehyde concentrations in e-cigarette vapour can be up to three times higher than that in conventional cigarette smoke.

Comparison group: conventional cigarette use

WHO, 2015
(42)

Findings causing concern include the following [among a long list, here only those linked to the toxicity, toxins, and other potentially harmful compounds]:

- Substantial levels of nanoscale particles
- Detectable levels of many different toxic materials
- Recent large sample toxicity assessment
- Presence of diacetyl ("popcorn lung") in flavored samples
- Cytotoxicity, oxidative stress, and inflammation in *in vitro* studies
- Dysregulation of gene expression
- DNA strand breakage
- Urinary toxicant and carcinogen metabolites found in vapors
- Toxicants found in exhaled vapour

Comparison group: not mentioned

**BE - SHC,
2015** (43)

Toxic substances: Nicotine aside, e-cigarettes are significantly less toxic than tobacco. Vaping releases none of the products of tobacco combustion, just a relatively low quantity of a small number of toxins. This conclusion assumes that all e-cigarettes meet the strict set of conditions set out in the European Commission Directive.

Comparison group: conventional cigarette use

Inhalation of compounds: The toxicity of the scents, colourings and flavourings currently used and permitted in e-cigarettes has not been adequately tested in the context of e-cigarette use. The substances can be safely used in foods, but in the case of the e-cigarette they are heated and inhaled, which is very different to ingestion by eating.

Comparison group: not mentioned

NO - NIPH, 2015 (41) **Nicotine intake, ENDS:** It should be emphasized that the use of e-cigarettes alone will still involve a risk of adverse health outcomes among users, particularly associated with the intake of nicotine.

Comparison group: not mentioned

WHO, 2014 (44) **Exposure to toxicants, ENDS:** ENDS use poses serious threats to adolescents and fetuses. In addition, it increases exposure of non-smokers and bystanders to nicotine and a number of toxicants.

Comparison group: not mentioned

Nevertheless, the reduced exposure to toxicants of well-regulated ENDS used by established adult smokers as a complete substitution for cigarettes is likely to be less toxic for the smoker than conventional cigarettes or other combusted tobacco products. The amount of risk reduction, however, is presently unknown.

Comparison group: conventional cigarette use

Source: JRC own production

3.1.1.5 Reproductive, developmental, and pregnancy outcomes

A total of nine reports assessed the association of e-cigarettes with reproductive, developmental, and pregnancy outcomes (**Table 6**).

Immediate, short-term, and medium-term health outcomes:

In summary, these reports state the following (**Table 6**):

- Nicotine exposure and pregnancy outcomes: There is evidence of negative health effects derived from exposure to nicotine during pregnancy, including preeclampsia, premature birth, stillbirth, sudden infant death syndrome, lung development in unborn children and in later life, and possibly deficits in auditory processing and altered corpus callosum.
- Nicotine exposure and adolescent development: Nicotine exposure during adolescence can cause addiction and can harm the developing adolescent brain.

Long-term health outcomes:

- Long-term, reproductive outcomes: There is insufficient data available to date about the long-term association of e-cigarettes with reproductive outcomes (**Table 6**).
- DNA damage and mutagenesis: There is substantial evidence that some chemicals present in e-cigarette aerosols (e.g., formaldehyde, acrolein) can cause DNA damage and mutagenesis, which supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of adverse reproductive outcomes.

Table 6. Association of e-cigarettes with reproductive, developmental, and pregnancy outcomes diseases as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
DE - DKFZ, 2023 (17)	<p>Developmental effects: <u>Animal and cell</u> trials suggest that e-cigarette consumption during pregnancy could harm the development of the foetus. Three studies on the <u>birth weight and size of children</u> of women using e-cigarettes during pregnancy provide contradictory results.</p> <p><i>Comparison group: not mentioned</i></p>
UK - OHID, 2022 (23)	<p>Reproduction and pregnancy: The evidence base on <u>reproductive health</u> or <u>pregnancy outcomes</u> remains insufficient.</p> <p><i>Comparison group: conventional cigarette use</i></p> <p>In vitro and in vivo studies: The one cell and 31 animal studies provided insights into <u>molecular mechanisms</u> by which vaping products may affect the central nervous, digestive and <u>reproductive systems</u> as well as other target sites relative to exposure to tobacco or no exposure. However, the data are still limited and too inconsistent to evaluate the compounds of vaping product aerosol causing any alterations; variability of animal models, exposure methods and comparators added to the uncertainty.</p> <p><i>Comparison group: conventional cigarette smoke</i></p>
WHO, 2021a (28)	<p>Developmental effects and pregnancy: <u>Nicotine</u> is deleterious to <u>adolescent brain development</u> and poses risks during <u>pregnancy</u>. Nicotine also poses health risks to children, adolescents and pregnant women.</p> <p><i>Comparison group: not mentioned</i></p>
SCHEER, 2021 (10)	<p>The overall weight of evidence for risks of other long-term adverse health effects, such as pulmonary disease, CNS and <u>reprotoxic effects</u> based on the hazard identification and human evidence, is weak, and further consistent data are needed.</p> <p><i>Comparison group: not mentioned</i></p>
UK - COT, 2020 (33)	<p>Second-hand exposure to nicotine, ENDS: There is also the risk that nicotine addiction may develop in nicotine-naïve users. There is good evidence from animal studies for an increased risk of <u>adverse effects on development</u> associated with nicotine exposure, but the data set on this aspect was not adequate for the level of such risk in humans from exposure to ENDS emissions to be assessed. The possibility of adverse effects of nicotine in bystanders cannot be excluded, although in most exposure scenarios the level of exposure to nicotine from ambient air would be low.</p> <p><i>Comparison group: not mentioned</i></p>
US - NASEM, 2018 (36)	<p>DNA damage: There is limited evidence that e-cigarette aerosol can be <u>mutagenic</u> or cause <u>DNA damage in humans, animal models, and human cells in culture</u>. There is substantial evidence that some chemicals present in e-cigarette aerosols (e.g., formaldehyde, acrolein) are capable of causing <u>DNA damage and mutagenesis</u>. This supports the <u>biological plausibility</u> that long-term exposure to e-cigarette aerosols could increase risk of cancer and <u>adverse reproductive outcomes</u>. Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined.</p> <p><i>Comparison group: not mentioned</i></p> <p>Pregnancy outcomes: There is no available evidence whether or not e-cigarettes affect pregnancy outcomes.</p>

Comparison group: not mentioned

Developmental effects: There is insufficient evidence whether or not maternal e-cigarette use affects fetal development.

Comparison group: not mentioned

US - HHS, 2016 (37) **Developmental effects and pregnancy outcomes:** E-cigarette aerosol is not harmless. It can contain harmful and potentially harmful constituents, including nicotine. Nicotine exposure during adolescence can cause addiction and can harm the developing adolescent brain. Nicotine can cross the placenta and has known effects on fetal and postnatal development. Therefore, nicotine delivered by e-cigarettes during pregnancy can result in multiple adverse consequences, including sudden infant death syndrome, and could result in altered corpus callosum, deficits in auditory processing, and obesity.

Comparison group: not mentioned

NO - NIPH, 2015 (41) **Pre-natal, post-natal development; pregnancy outcomes:** The intake of nicotine from e-cigarettes seems to be similar to that found with tobacco smoking and snus consumption, indicating that similar nicotine-related effects are expected on the cardiovascular system, lung development in unborn children and in later life, reproductive health (premature birth, stillbirth and preeclampsia) and cognitive effects.

Comparison group: conventional cigarette use

WHO, 2014 (44) **Developmental effects:** ENDS use poses serious threats to adolescents and fetuses. In addition, it increases exposure of non-smokers and bystanders to nicotine and a number of toxicants.

Comparison group: not mentioned

Source: JRC own production

3.1.1.6 Addiction, dependence and nicotine uptake

A total of ten reports assessed the role of e-cigarettes on addiction, dependence, and nicotine uptake (**Table 7**). In summary, these reports state the following:

- Nicotine is absorbed from ENDS in a similar way as from regular tobacco smoking, and the amount of nicotine intake can be comparable to that from conventional combustible cigarettes. However, the amount of nicotine inhaled is highly variable and depends on product characteristics and operation by the user.
- Flavours are a key driver of youth initiation of ENDS.
- Nicotine pharmacology, the way nicotine affects the body and brain, leads to addiction and continued, repetitive use.
- Second-hand exposure: While one report states that second-hand exposure to ENDS aerosols can result in similar nicotine blood levels as second-hand exposure to cigarette smoke and can contribute to addiction, another report states that there is moderate evidence that the second-hand exposure to nicotine and particulates is lower from e-cigarettes compared with combustible tobacco cigarettes.
- Dependence: There is substantial evidence that e-cigarette use results in symptoms of dependence, which probably depends on the amount of nicotine.

- **Addiction:** Use of ENDS in never smokers is associated with nicotine dependence, which increases risk of long-term use, and is therefore not recommended. Nicotine from ENDS has the potential to cause addiction. Flavours are a key driver of youth initiation of ENDS, with the pharmacology of nicotine leading to addiction and continued, repetitive use.

Table 7. Association of e-cigarettes with addiction, dependence and nicotine uptake as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
NZ - MoH, 2024 (14)	<p>Never smokers: Use of vaping products among never smokers is associated with a range of harms, including nicotine <u>addiction</u>, which increases the <u>risk of long-term use</u>.</p> <p><i>Comparison group: never smokers</i></p>
DE - DKFZ, 2023 (17)	<p>Addictive potential of e-cigarettes: Nicotine has high <u>addiction potential</u>, increases heart rate, narrows blood vessels, increases blood pressure and is toxic in larger amounts. E-cigarette consumption can cause symptoms of <u>dependence</u>. E-cigarettes may have a <u>lower potential for addiction than tobacco cigarettes</u> and a <u>higher one than medical nicotine replacement products</u>. Probably, the <u>amount of nicotine and aromas</u> may influence the potential for dependence. The nicotine is absorbed from the aerosol in a similarly <u>effective way</u> as from cigarettes, so it can be assumed that the potential for addiction is <u>comparable to smoking</u>.</p> <p><i>Comparison group: not mentioned</i></p>
BE - SHC, 2022 (22)	<p>Never smokers: For non-smokers (adults and especially minors), it is still recommended not to use any nicotine-containing product. This can help non-smokers avoid nicotine <u>addiction</u> and the clearly harmful effects of tobacco cigarettes, as well as the potentially harmful effects of e-cigarettes and e-liquids to a lesser extent.</p> <p><i>Comparison group: not mentioned</i></p> <p>Never smokers: The relative risk of e-cigarettes (with or without nicotine) compared to not smoking is clear: e-cigarettes are not without risk, they are potentially harmful. E-liquids contain many substances for which there is insufficient information about their toxicity when inhaled. In addition, there is still insufficient long-term data on the use of e cigarettes. The consumption of <u>nicotine-containing products</u> is also not recommended for non-smokers because of the <u>addictive effect</u>. It is therefore not recommended for non-smokers, including young people.</p> <p><i>Comparison group: not mentioned</i></p>
US - AACR/ASCO, 2022 (25)	<p>Youth: <u>Flavors</u> are a key driver of youth initiation of ENDS, with the pharmacology of <u>nicotine</u> leading to <u>addiction and continued, repetitive use</u>.</p> <p><i>Comparison group: not mentioned</i></p> <p>Youth: ENDS emit fewer carcinogens than combustible tobacco primarily due to the absence of combustion products, and for some ENDS the absence of some tobacco-specific nitrosamines, but it is clear that they still pose health risks. Additionally, e-cigarettes have <u>addicted a new generation of youth and young adults to nicotine</u> and threaten to hinder progress against tobacco-related illnesses.</p> <p><i>Comparison group: combustible cigarette use</i></p>
WHO, 2020 (32)	<p>Nicotine intake: When the e-liquid contains nicotine, the aerosol contains nicotine. The <u>amount of nicotine inhaled</u> by ENDS users is <u>highly variable</u> and depends on product characteristics (including device and e-liquid characteristics) and how the device is</p>

operated. There is substantial evidence that nicotine intake from ENDS among experienced adult ENDS users can be comparable to that from combustible tobacco cigarettes.

Comparison group: combustible cigarette use

US - NASEM, 2018 (36)

E-cigarette dependence: There is substantial evidence that e-cigarette use results in symptoms of dependence on e-cigarettes. There is moderate evidence that variability in e-cigarette product characteristics (nicotine concentration, flavoring, device type, and brand) is an important determinant of risk and severity of e-cigarette dependence.

Comparison group: not mentioned

E-cigarette dependence: There is moderate evidence that risk and severity of dependence are lower for e-cigarettes than combustible tobacco cigarettes.

Comparison group: combustible cigarette use

Nicotine levels, ENDS: There is conclusive evidence that exposure to nicotine from e-cigarettes is highly variable and depends on product characteristics (including device and e-liquid characteristics) and how the device is operated.

Comparison group: not mentioned

Nicotine levels, ENDS: There is substantial evidence that nicotine intake from e-cigarette devices among experienced adult e-cigarette users can be comparable to that from combustible tobacco cigarettes.

Comparison group: conventional combustible cigarettes

Nicotine levels, ENDS: There is moderate evidence that second-hand exposure to nicotine and particulates is lower from e-cigarettes compared with combustible tobacco cigarettes.

Comparison group: exposure to conventional combustible cigarette second second-hand smoke

US - HHS, 2016 (37)

Addictive potential of e-cigarettes: E-cigarette aerosol is not harmless. It can contain harmful and potentially harmful constituents, including nicotine. Nicotine exposure during adolescence can cause addiction and can harm the developing adolescent brain.

Comparison group: not mentioned

NO - NIPH, 2015 (41)

Addictive potential of e-cigarettes: From a public health perspective, it is important to prevent new generations from becoming addicted to nicotine, and using e-cigarettes as a gateway to other forms of nicotine such as regular smoking and snus consumption.

Comparison group: not mentioned

Nicotine levels, ENDS: Nicotine levels in the environment from passive exposure to aerosols from e-cigarettes can result in similar high nicotine levels in the blood of a passive smoker of regular cigarettes. This means that similar harmful nicotine-related effects can be expected for passive exposure to e-cigarettes as for regular cigarettes. This means that passive exposure to aerosol from e-cigarettes may act on the cardiovascular system, have stimulatory effects and contribute to addiction.

Comparison group: exposure to conventional combustible cigarette second-hand smoke

WHO, 2015 (42)

Addictive potential of e-cigarettes: E-cigarettes are highly addictive and there is insufficient evidence on the safety of long-term use of nicotine.

Comparison group: not mentioned

BE - SHC, 2015 (43) **Patterns of use:** Initial studies show that more and more people [non-smokers] are trying the e-cigarette, but do not become regular users in the long term.
Comparison group: not mentioned

Source: JRC own production

3.1.1.7 Other outcomes

3.1.1.7.1 Overall health

A total of 16 reports assessed the role of ENDS or ENNDS on overall health (**Table 8**). These statements refer to general health, and therefore, they could not be assigned to any of the diseases mentioned above.

Immediate, short-term, and medium-term health outcomes:

In summary, these reports state the following (**Table 8**):

- Never smokers: *De novo* uptake of E(N)NDS use by non-users of tobacco products is likely to be associated with some adverse health effects to which the user would not otherwise have been subject. E-cigarettes are not harmless and are therefore not recommended for non-smokers, especially young people.
- EN(N)DS aerosols: The risks to health of exposure to exhaled EN(N)DS aerosols remain unknown. It is expected, however, to present some health risks for bystanders, although at lower levels than from exposure to second-hand combustible tobacco smoke.
- Dual use: The association of dual use (e-cigarettes and conventional cigarettes) with health outcomes remains unclear due to insufficient long-term evidence. While some studies suggest it may pose greater risks than smoking alone, depending on use patterns, others state that there is not enough evidence to confirm this.
- Health risk compared to combustible cigarette use: The use of E(N)NDS as a replacement for conventional cigarettes smoking, produced according to appropriate manufacturing standards and used as recommended, is likely to be associated with a reduction in overall risk of adverse health effects. The magnitude of the decrease will depend on the effect in question, and the use of E(N)NDS is still harmful to health.

Long-term health outcomes:

There is no available evidence to know whether there are long-term harms from e-cigarette use. (**Table 8**).

Table 8. Association of e-cigarettes with overall health as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
NZ - MoH, 2024 (14)	Overall, evidence shows vaping is less harmful than smoking tobacco, but not harmless. For people who smoke, switching to vaping products is highly likely to reduce the risks to their health and the health of those around them. <i>Comparison group: not mentioned</i>

Cochrane living SR, 2024 (15)	<p>None of the included studies (short to midterm, up to two years) detected serious adverse events considered possibly related to EC [electronic cigarettes] use. However, more long-term data are needed, and this conclusion relates specifically to people using EC to quit smoking and not to people who have never smoked.</p> <p><i>Comparison group: combustible cigarette use</i></p>
DE - DKFZ, 2023 (17)	<p>So far, there is limited scientific evidence on the health risks of e-cigarette use (research on animals and cells, and few short-term clinical trials); the studies are difficult to compare between them because of the use of different methods, and the results of animal and cell experiments are only transposable to humans to a limited extent.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2023a (18)	<p>Electronic cigarettes are harmful.</p> <p><i>Comparison group: not mentioned</i></p>
UK - NICE, 2023 (19)	<p>The extensive harms of smoking are well known, and the committee agreed it is unlikely that e-cigarettes could cause similar levels of harm. But they also agreed that for people who do not smoke, it is unlikely that inhaling vapour from an e-cigarette is as low risk as not doing so, although the extent of that risk is not yet known.</p> <p><i>Comparison group: combustible cigarette use and non-users</i></p> <p>There is not enough evidence to know whether there are long-term harms from e-cigarette use.</p> <p><i>Comparison group: not mentioned</i></p> <p>Use of e-cigarettes is likely to be substantially less harmful than smoking.</p> <p><i>Comparison group: combustible cigarette</i></p> <p>Any smoking is harmful, so people using e-cigarettes should stop smoking tobacco completely.</p> <p><i>Comparison group: not mentioned</i></p> <p>There were only 2 studies about the long-term harms of using nicotine-containing e-cigarettes, and the committee discussed the uncertainty of the evidence and their concerns with these studies. A call for evidence did not produce any additional evidence in this area. The committee agreed that there is insufficient evidence to tell whether e-cigarettes cause long-term effects. E-cigarettes are relatively new devices, and it is important to understand whether they cause any health harms or benefits aside from their potential to reduce smoking-related harm.</p> <p><i>Comparison group: not mentioned</i></p> <p>The committee used their knowledge and experience to supplement the insufficient evidence to tell whether e-cigarettes cause long-term effects and agreed that because many of the harmful components of cigarettes are not present in e-cigarettes, switching to nicotine-containing e-cigarettes was likely to be significantly less harmful than continuing smoking.</p> <p><i>Comparison group: combustible cigarette</i></p>
BE - SHC, 2022 (22)	<p>It should be noted that e-cigarettes are not harmless and are therefore not recommended for non-smokers, especially young people.</p> <p><i>Comparison group: not mentioned</i></p>
Cochrane living SR, 2022 (27)	<p>Overall incidence of SAEs was low across all study arms. We did not detect evidence of serious harm from nicotine EC, but longest follow-up was two years and the number of studies was small.</p>

	<i>Comparison group: not mentioned</i>
WHO, 2021a (28)	<p>There is growing evidence of harmful effects of ENDS.</p> <p>Other e-liquid components can also be harmful to health.</p> <p>Second-hand emissions have the potential to harm bystanders.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2021b (30)	<p>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.</p> <p><i>Comparison group: combustible cigarette use and never smokers</i></p>
WHO, 2020 (32)	<p>No available studies have evaluated the health effects of second-hand EN&NNDS exposure, so the risks to health of exposure to exhaled aerosol remain unknown. It is expected, however, to present some health risks for bystanders, although at lower levels than from exposure to second-hand tobacco smoke.</p> <p><i>Comparison group: combustible cigarette use</i></p>
UK - COT, 2020 (33)	<p>In considering the comparison of E(N)NDS use with conventional cigarettes smoking, the Committee concluded that the relative risk of adverse health effects would be expected to be substantially lower from E(N)NDS. This risk reduction would occur if people who are already smoking conventional cigarettes switch to E(N)NDS, or if E(N)NDS are taken up instead of conventional cigarettes. This is supported by biomonitoring studies which show lower levels of tobacco-related toxicants in E(N)NDS users compared with conventional cigarettes smokers. However, the reduction in risk would depend on the endpoint considered. The expectation of lower risk associated with E(N)NDS use compared with conventional cigarettes smoking relates to individuals making a complete switch from conventional cigarettes smoking to E(N)NDS. Although the Committee did not consider in detail the potential risks relating to dual use of E(N)NDS and conventional cigarettes, there is some evidence that dual use could lead to increased risk compared with conventional cigarettes smoking only, depending on use patterns.</p> <p><i>Comparison group: combustible cigarette use</i></p> <p>The use of E(N)NDS products, produced according to appropriate manufacturing standards and used as recommended, as a replacement for conventional cigarettes smoking, is likely to be associated with a reduction in overall risk of adverse health effects, although the magnitude of the decrease will depend on the effect in question.</p> <p>Uptake of E(N)NDS product use <i>de novo</i> by non-users of tobacco products is likely to be associated with some adverse health effects to which the user would not otherwise have been subject.</p> <p><i>Comparison group: never smokers</i></p>
US - NASEM, 2018 (36)	<p>There is no available evidence whether or not long-term e-cigarette use among smokers (dual use) changes morbidity or mortality compared with those who only smoke combustible tobacco cigarettes.</p> <p><i>Comparison group: combustible cigarette use</i></p> <p>There is insufficient evidence that e-cigarette use changes short-term adverse health outcomes in several organ systems in smokers who continue to smoke combustible tobacco cigarettes (dual users).</p> <p><i>Comparison group: dual users</i></p>

The evidence about harm reduction suggests that across a range of studies and outcomes, e-cigarettes pose less risk to an individual than combustible tobacco cigarettes.

Comparison group: combustible cigarette use

**UK - RCP,
2016** (38)

Some of the carcinogens, oxidants and other toxins present in tobacco smoke have also been detected in e-cigarette vapour, raising the possibility that long-term use of e-cigarettes may increase the risks of lung cancer, COPD, cardiovascular and other smoking-related diseases. However, the magnitude of such risks is likely to be substantially lower than those of smoking, and extremely low in absolute terms". These potential health risks arise primarily from contaminants and components generated by the vaporisation process, which should be amenable to reduction through technological and purity improvements.

Comparison group: combustible cigarette use

Although the long-term hazards of e-cigarette use are not yet clearly defined, e-cigarettes are probably close to NRT in the harm that their use confers on the user and others.

E-cigarettes are not currently made to medicines standards and are probably more hazardous than NRT. However, the hazard to health arising from long-term vapour inhalation from the e-cigarettes available today is unlikely to exceed 5% of the harm from smoking tobacco.

Comparison group: combustible cigarette use

**NL - RIVM,
2015** (39)

Nicotine-containing e-liquids can also affect health in various ways.

The level of risk and the seriousness of the potential effects depend considerably on the e-cigarette usage pattern. Health risks are liable to increase sharply at higher intensities of use. However, insufficient dose-response relationship data are available to support evaluation of the complex and fluctuating exposure patterns associated with e-cigarette use.

Comparison group: not mentioned

It may be concluded that the health risks associated with smoking conventional cigarettes are considerably higher than those associated with using e-cigarettes, based on the findings described in RIVM report 2014-143 (Visser W 2015) (subsections 10.3.2.1 and 10.3.2.2). That conclusion assumes comparable usage patterns (a similar number of inhalations over a comparable period). The health risks are strongly dependent on individual vaping and smoking habits.

Comparison group: combustible cigarette use

**NO - NIPH,
2015** (41)

Until now there have been no independent data that documents how smokers as a group switch to e-cigarettes. It is therefore very uncertain to what extent the use of e-cigarettes, combined with regular smoking, will lead to reduced health risks.

Comparison group: combustible cigarette use

The health risks from long-term e-cigarette use in the population is unknown.

Comparison group: not mentioned

WHO, 2015 (42) Even though no firm conclusions can be drawn on the safety of e-cigarettes there is an increasing body of evidence indicating harm.

Comparison group: not mentioned

Due to the many methodological problems, the many studies with severe conflicts of interest, the inconsistencies and contradictions in results, the relatively few high-quality studies, the rapidly changing designs of the product and the lack of long-term follow-up, it seems very premature to perform calculations for how harmful vaping is compared with smoking, and much is still left to subjective interpretation.

Comparison group: combustible cigarette use

In a simple product-to-product comparison most e-cigarettes are probably less, and some products may even be much less, harmful than conventional cigarettes, but as the large majority of e-cigarette users continue to smoke, the health risks of dual use must be taken into account in assessment of the harm of vaping.

Comparison group: combustible cigarette use

We have almost no evidence on the health effects of dual use of e-cigarettes and conventional cigarettes.

Comparison group: dual users

For ex-smokers and never smokers, use of e-cigarettes will increase the risk of harm on health.

Comparison group: ex-smokers and never smokers

Systematic high-quality research is urgently needed, especially on health effects of dual use.

Comparison group: dual users

Source: JRC own production

3.1.1.7.2 Accidental outcomes

A total of seven reports assessed the role of ENDS or ENNDS on accidental outcomes such as poisonings and injuries from explosions and burns. In summary, these reports state the following (**Table 9**):

- Neurotoxicity: Nicotine is a potent acute neurotoxicant. E-liquids contain high concentrations of nicotine, and their ingestion can cause acute toxicity and death.
- Child poisoning risks, ingestion: Nicotine-containing e-liquids present a new risk of acute poisoning, especially via accidental ingestion. The presence of flavourings can make these liquids more attractive to children and may increase the likelihood of acute poisoning.
- Child poisoning risks, dermal exposure: Exposure of skin to nicotine-containing e-liquids can also produce acute toxicity.
- Burns and injuries: Explosion events leading to injuries are not frequent and seem to be linked to the quality of the device/battery and to the user mishandling or tampering the device. However, if they occur, they can lead to serious injuries, burns and death.

Table 9. Association of e-cigarettes with accidental outcomes as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
DE - DKFZ, 2023 (17)	<p>Burns and injuries: While e-cigarette <u>explosions</u> are rare and mostly due to <u>mishandling</u> and <u>malfunctioning</u>, they can lead to <u>serious injuries, burns and death</u>.</p> <p><i>Comparison group: not mentioned</i></p> <p>Poisoning, ENDS: <u>Intentional or unintentional ingestion</u> of <u>nicotine-containing liquids</u> may lead to poisoning. These tend to be mild but can lead to <u>death</u> in rare cases. <u>Accidental poisoning</u> occurs mainly in <u>children</u> under the age of six.</p> <p><i>Comparison group: not mentioned</i></p>
SCHEER, 2021 (10)	<p>Burns and injuries: The overall weight of evidence for risks of poisoning and <u>injuries due to burns and explosion</u>, is strong. However, the incidence is <u>low</u>.</p> <p><i>Comparison group: not mentioned</i></p> <p>Poisoning: The overall weight of evidence for risks of poisoning and injuries due to burns and explosion, is <u>strong</u>. However, the <u>incidence is low</u>.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2021a (28)	<p>Burns and injuries: Electronic delivery systems have also been linked to a number of <u>physical injuries</u>, including <u>burns</u> from <u>explosions or malfunctions</u>, when the products are not of the expected <u>standard</u> or are <u>tampered</u> with by users.</p> <p><i>Comparison group: not mentioned</i></p> <p>Poisoning, ENDS: <u>Accidental exposure</u> to the <u>high nicotine concentrations</u> in e-liquid can also be very dangerous and even cause <u>death</u>. Cases of accidental ingestion of the poisonous e-liquid by <u>children</u> are particularly concerning.</p> <p><i>Comparison group: not mentioned</i></p>
NZ - ESR, 2021 (29)	<p>Burns and injuries: <u>Explosion and burn injuries</u> have been reported internationally, and may be on the rise, but although at least one case of an exploding device was noted, no injuries from e-cigarette explosions in New Zealand have been reported. <u>Product safety QA/QC [quality assurance and quality control] measures for batteries and device design</u> may help prevent such events, although exploring precise elements of such measures would require a separate review.</p> <p><i>Comparison group: not mentioned</i></p> <p>Acute toxicity, ENDS: Electronic cigarette liquids containing nicotine are highly toxic by all routes of exposure, and there is clear evidence of <u>acute intoxications</u>, including <u>deaths</u>, overseas.</p> <p><i>Comparison group: not mentioned</i></p> <p>Acute neurotoxicant, ENDS: Nicotine is a potent <u>acute neurotoxicant</u> and drives the <u>acute toxicity</u> consideration for e-liquids.</p> <p><i>Comparison group: not mentioned</i> Child exploration: Child exploration is clearly a major concern for e-liquid exposures and represents the majority of calls (62%) to the New Zealand NPC. An acute oral dose as small as 0.5 mL of a 1.8 mg/mL nicotine e-liquid solution could pose a risk of <u>acute intoxication</u> and possibly <u>death</u> in a <u>toddler</u>, according to historical assumptions about nicotine toxicity. The maximally allowed nicotine content in e-liquids (20 mg/mL as free base under SERPR) poses an even greater serious acute toxicity risk for small children. Child exploration accounts for over half of the NPC calls,</p>

and the potential for child exposures resulting in nicotine poisoning is widely recognised internationally as a main concern over the health risks of e-liquid exposures outside their intended use. Child exploration oral or dermal exposure to glycols and flavouring chemicals in e-liquids is unlikely to present an acute life-threatening situation, but acutely toxic doses and non-life threatening illness can still be achieved in the oral ingestion scenarios presented in this report.

Comparison group: not mentioned

Toxicity: The presence of flavourings enhance the attractiveness to these liquids to children and could amplify the likelihood of acute poisoning.

Comparison group: not mentioned

Intoxications: The vast majority of reported intoxications and calls to the New Zealand NPC from e-liquids involve oral ingestion. An acute dermal dose to achieve toxicity is less likely, though still achievable. Spilling a small volume of e-liquids on skin can also produce acute toxicity.

Comparison group: not mentioned

US - NASEM, 2018 (36)

Burns and injuries: There is conclusive evidence that e-cigarette devices can explode and cause burns and projectile injuries. Such risk is significantly increased when batteries are of poor quality, stored improperly, or modified by users.

Comparison group: not mentioned

Death: There is conclusive evidence that intentionally or unintentionally drinking or injecting e-liquids can be fatal.

Comparison group: not mentioned

US - HHS, 2016 (37)

Death, ENDS: Ingestion of e-cigarette liquids containing nicotine can cause acute toxicity and possibly death if the contents of refill cartridges or bottles containing nicotine are consumed.

Comparison group: not mentioned

BE - SHC, 2015 (43)

Intoxication: Liquid refill containers containing nicotine could lead to acute and even fatal poisoning in case of accidental or improper use (if a child drinks the liquid, for example). This is much less common in the case of tobacco products. It is a new risk which manufacturers and users must take into account.

Comparison group: not mentioned

Source: JRC own production

3.1.1.7.3 Other health outcomes

A total of 11 reports assessed the role of ENDS or ENNDS on other health outcomes than those reported in **Tables 2 to 9**. In summary, these reports state the following (**Table 10**):

- Oral or dental health: There is limited evidence suggesting that ENDS and ENNDS aerosols can adversely affect oral or dental health in non-smokers and can produce irritation. There is limited evidence suggesting that switching to e-cigarettes will improve periodontal disease in smokers.
- Central nervous system: The data are still limited and too inconsistent to evaluate the compounds of vaping product aerosol causing any alterations to the central nervous system. There is substantial evidence that components of e-cigarette aerosols can promote

formation of reactive oxygen species/oxidative stress (generally lower from e-cigarettes than from conventional combustible cigarette smoke).

- Lymphocyte count: One report mentions that exposure to propylene glycol (carrier substance) can reduce lymphocyte count.
- DNA repair: ENDS use may inhibit DNA repair, which in turn could exacerbate DNA damage and related DNA mutations caused by smoking in people who dual use.
- Allergic reactions: Allergic reactions to e-liquids have not been tracked, but some components of e-liquids are known skin sensitising agents.

Table 10. Association of e-cigarettes with other diseases such as oral health, wound healing, digestive system and immune response as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
DE - DKFZ, 2023 (17)	<p>Oral health: With regard to the use of e-cigarettes for oral health, the scientific evidence for reliable statements is <u>insufficient</u>.</p> <p><i>Comparison group: not mentioned</i></p> <p>Wound healing: <u>Animal and cell tests</u>, as well as some <u>case reports</u> on skin transplantation, suggest that the use of e-cigarettes could have similar <u>negative effects</u> to wound healing as cigarette smoke. The evidence for this is assessed as low.</p> <p><i>Comparison group: conventional combustible cigarette smokers</i></p>
US - AACR/ASCO, 2022 (25)	<p>DNA damage: It is possible that <u>inhibition of DNA repair</u> from <u>ENDS use</u> could exacerbate <u>DNA damage</u> and related DNA <u>mutations</u> caused by smoking in people who <u>dual use</u>.</p> <p><i>Comparison group: conventional combustible cigarette smokers</i></p>
UK - OHID, 2022 (23)	<p>Central nervous system, <i>in vivo</i> and <i>in vitro</i> studies: The data are still <u>limited</u> and too <u>inconsistent</u> to evaluate the compounds of vaping product aerosol causing any alterations to systems in the body. Also, variability of animal models, exposure methods and comparators added to the uncertainty.</p> <p><i>Comparison group: conventional combustible cigarette smoke</i></p> <p>Oral health: Oral or dental health has been researched more extensively than other health areas. However, the quality of the studies was often low. Recent reviews concluded that vaping would be <u>detrimental to oral or dental health among people who have never vaped or smoked</u> but would <u>likely be beneficial for smokers switching</u>. We found no studies that would change that conclusion.</p> <p><i>Comparison groups: never EN(N)DS users and never smokers; conventional combustible cigarette smokers switching to EN(N)DS</i></p> <p>Digestive system, <i>in vivo</i> and <i>in vitro</i> studies: The data are still <u>limited</u> and too <u>inconsistent</u> to evaluate the compounds of vaping product aerosol causing any alterations to systems in the body. Also, variability of animal models, exposure methods and comparators added to the uncertainty.</p> <p><i>Comparison group: not mentioned</i></p>
NZ - ESR, 2021 (29)	<p>Allergic reactions: Allergic reactions to e-liquids have not been tracked, but some components of e-liquids are known <u>skin sensitising agents</u>. The SERPR provides a</p>

	<p>mechanism to identify and prohibit respiratory allergens in e-liquids, and as <u>flavouring</u> chemicals are becoming better studied, it is recommended that this area be watched for scientific developments.</p> <p><i>Comparison group: not mentioned</i></p> <p>Inflammation: Flavouring chemicals are regulated under SERPR, and although many are “Generally Recognised As Safe” by the U.S. Food and Drug Administration, some <u>flavouring chemicals</u> have been found to be cytotoxic to pulmonary and immune cells <i>in vitro</i>, and to induce <u>pro-inflammatory</u> responses.</p> <p><i>Comparison group: not mentioned</i></p>
SCHEER, 2021 (10)	<p>Central nervous system: The overall weight of evidence for risks of other long-term adverse health effects, such as pulmonary disease, <u>CNS</u> and reprotoxic <u>effects</u> based on the hazard identification and human evidence, is weak, and further consistent data are needed.</p> <p><i>Comparison group: not mentioned</i></p>
UK - COT, 2020 (33)	<p>Irritation, EN(N)DS: In the evaluation of absolute risk from exposure to E(N)NDS <u>emissions</u>, the Committee considered adverse health effects that could be of concern include the <u>potential</u> for <u>sensory irritation</u>, the promotion or augmentation of respiratory symptoms in people with respiratory disease or conditions, and the potential to enhance adverse cardiovascular symptoms in people with cardiovascular disease.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2020 (32)	<p>Central nervous system: The main substances in the aerosol that raise health concern are metals, such as chromium, nickel, and lead, and carbonyls, such as formaldehyde, acetaldehyde, acrolein and glyoxal. Exposure to certain levels of some <u>metals</u> may cause serious health effects, such as diseases of the <u>nervous</u>, cardiovascular and respiratory <u>systems</u>. The number of metals in the aerosol could be greater than in combustible tobacco cigarettes, and in some cases is found at higher concentrations than in cigarette smoke.</p> <p><i>Comparison group: not mentioned</i></p>
US - NASEM, 2018 (36)	<p>Oral health: There is limited evidence suggesting that switching to e-cigarettes will improve periodontal disease in smokers.</p> <p><i>Comparison group: smokers with periodontal disease</i></p> <p>Oral health, EN(N)DS: There is limited evidence suggesting that nicotine- and non-nicotine-containing e-cigarette aerosol can adversely affect <u>cell viability</u> and cause <u>cell damage</u> of <u>oral tissue in non-smokers</u>.</p> <p><i>Comparison group: not mentioned</i></p> <p>Oxidative stress: There is substantial evidence that components of e-cigarette aerosols can promote formation of <u>reactive oxygen species/oxidative stress</u>. Although this supports the <u>biological plausibility</u> of tissue injury and disease from long-term exposure to e-cigarette aerosols, generation of reactive oxygen species and oxidative stress induction is generally <u>lower</u> from <u>e-cigarettes</u> than from <u>combustible tobacco cigarette smoke</u>.</p> <p><i>Comparison group: not mentioned/combustible cigarette smoke</i></p>
NO - NIPH, 2015 (41)	<p>Central nervous system: <u>Nicotine levels</u> in the environment from passive exposure to aerosols from e-cigarettes can result in similar high nicotine levels in the blood of a passive smoker of regular cigarettes. This means that similar harmful nicotine-</p>

related effects can be expected for passive exposure to e-cigarettes as for regular cigarettes. This means that passive exposure to aerosol from e-cigarettes may act on the cardiovascular system, have stimulatory effects and contribute to addiction.

Comparison group: exposure to conventional combustible cigarette second-hand smoke

Irritation: Substances such as propylene glycol and acrolein may cause irritation during e-cigarette use.

Comparison group: not mentioned

WHO, 2015 (42)

Immune response: Findings causing concern include the following [among a long list, here only those linked to the immune response]:

- cytotoxicity, oxidative stress and inflammation found in most *in vitro* studies
- airway inflammation, asthma and chronic obstructive pulmonary disease development in animal studies
- impaired pulmonary antimicrobial defences in animal study
- dysregulation of gene expression
- DNA strand breakage
- urinary toxicant and carcinogen metabolites found in vapers
- interaction with radon

Comparison group: not mentioned

NL - RIVM, 2015
(39)

Immune response: Exposure to polyols can damage the respiratory epithelium and reduce the lymphocyte count.

Comparison group: not mentioned

Immune response: The concentrations of a number of substances detected in e-liquid vapour are lower or much lower than the concentrations in tobacco smoke. By contrast, the concentrations of the carrier substances glycerol and propylene glycol are higher in e-cigarette vapour than in tobacco smoke. The main effects of the latter two substances are damage to the respiratory epithelium and (where propylene glycol is concerned) a reduced lymphocyte count.

Comparison group: conventional combustible tobacco smoke

Source: JRC own production

3.1.2 Gateway to smoking

A total of nine reports assessed the role of ENDS or ENNDS on the transition to smoking regular combustible cigarettes or using other tobacco products. The key statements from the examined reports are summarised below (**Table 11**).

- Use of tobacco products: There is evidence that using e-cigarettes increases the likelihood of young people using other tobacco products, including conventional combustible cigarettes.
- Smoking initiation: Never smokers, including children and young people, might progress to regular smoking after taking up e-cigarettes.
- Smoking intensity, frequency and duration: E-cigarette users who ever try cigarette smoking are more likely to progress to smoke at higher intensity, frequency and duration than non-e-cigarette users.

- Flavours might make e-cigarettes more appealing, and their use may renormalise smoking, making it seem normal and attractive again.

Table 11. Association of e-cigarettes with initiation of conventional combustible cigarette smoking as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
DE - DKFZ, 2023 (17)	<p>Smoking initiation: E-cigarette consumption <u>increases the likelihood of starting smoking</u> by about <u>three times</u>. There is not necessarily a causal link, and other factors may play a role.</p> <p><i>Comparison group: not using e-cigarettes</i></p>
SCHEER, 2021 (10)	<p>Smoking initiation, ENDS: There is moderate evidence that electronic cigarettes are a <u>gateway to smoking</u> for young people. There is strong evidence that nicotine in e-liquids is implicated in the development of addiction.</p> <p><i>Comparison group: not mentioned</i></p> <p>E-cigarette initiation: There is strong evidence that <u>flavours</u> have a relevant contribution for <u>attractiveness of use of electronic cigarette and initiation</u>.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2021a (28)	<p>Smoking initiation, ENDS: ENDS use among children and adolescents <u>increases the chances</u> they will use <u>conventional cigarettes</u> and other tobacco products. ENDS use among children and adolescents may act as a <u>gateway to tobacco use</u>. When children use ENDS, or even try them, they are <u>more than twice as likely to use conventional cigarettes</u>.</p> <p><i>Comparison group: not using e-cigarettes</i></p>
UK - COT, 2020 (33)	<p>E-cigarette and smoking initiation EN(N)DS: Non-users of tobacco products who take up E(N)NDS use <i>de novo</i>. In this case, the absolute risk would be important. However, the Committee noted that people who take up use of E(N)NDS <u>may otherwise have taken up conventional cigarettes smoking</u>. It is also possible that people in this group may <u>progress from E(N)NDS use to conventional cigarettes smoking</u>.</p> <p><i>Comparison group: non-users of tobacco products</i></p>
WHO, 2019 (35)	<p>Smoking initiation, ENDS: ENDS products may serve as a <u>gateway to conventional smoking</u> among young people or the <u>renormalization of smoking</u> in society.</p> <p><i>Comparison group: not using e-cigarettes</i></p>
US - NASEM, 2018 (36)	<p>Smoking initiation: There is substantial evidence that e-cigarette use <u>increases risk of ever using combustible tobacco cigarettes</u> among youth and young adults.</p> <p><i>Comparison group: not using e-cigarettes</i></p> <p>Progression to frequent and intense smoking: Among youth and young adult e-cigarette users who <u>ever use combustible tobacco cigarettes</u>, there is moderate evidence that e-cigarette use <u>increases the frequency and intensity of subsequent combustible tobacco cigarette smoking</u>.</p> <p><i>Comparison group: not using e-cigarettes</i></p> <p>Progression to duration of smoking: Among youth and young adult e-cigarette users who <u>ever use combustible tobacco cigarettes</u>, there is limited evidence that e-cigarette use <u>increases, in the near term, the duration of subsequent combustible tobacco cigarette smoking</u>.</p>

Comparison group: not using e-cigarettes

**UK - RCP,
2016** (38)

Smoking initiation: None of these products has to date attracted significant use among adult never-smokers, or demonstrated evidence of significant gateway progression into smoking among young people.

Comparison groups: adult non-smokers; not using e-cigarettes

Relationship with smoking: There are concerns that e-cigarettes will increase tobacco smoking by renormalising the act of smoking, acting as a gateway to smoking in young people, and being used for temporary, not permanent, abstinence from smoking. To date, there is no evidence that any of these processes is occurring to any significant degree in the UK. Rather, the available evidence to date indicates that e-cigarettes are being used almost exclusively as safer alternatives to smoked tobacco, by confirmed smokers who are trying to reduce harm to themselves or others from smoking, or to quit smoking completely.

Comparison group: conventional smokers not using e-cigarettes

**BE - SHC,
2015** (43)

Smoking initiation: Very few new users of the e-cigarette switch over to the tobacco cigarette.

Comparison group: not mentioned

Relationship with smoking: Young e-cigarette users, like adult users, are often tobacco smokers already.

Comparison group: not mentioned

E-cigarette initiation, EN(N)DS: The control period is too short and vaping is not yet sufficiently established to allow a definitive statement on this subject [ENDS and ENNDS for non-smokers]. The SHC views this uncertainty as a reason for advising caution and vigilance in the introduction of e-cigarettes. Because:

- The hypothesis that e-cigarettes are a gateway to tobacco use is still acceptable and deserving of further attention.

- The tobacco industry has become involved in the manufacture of e-cigarettes and will probably intensify and diversify e-cigarette advertising (young audience, female audience, internet and social networks, etc.), as it did for tobacco cigarettes.

- The e-cigarette must not give smoking the “positive”, “fun” and “healthy” image it once had in the early days of tobacco advertising. Disposable, flavoured and novelty (lights, coloured vapour, etc.) e-cigarettes carry the risk of making smoking appear normal again and attracting non-smokers to the product.

Comparison group: not mentioned

**NO - NIPH,
2015** (41)

Smoking initiation, nicotine use initiation: From a public health perspective, it is important to prevent new generations from becoming addicted to nicotine, and using e-cigarettes as a gateway to other forms of nicotine such as regular smoking and snus consumption.

Comparison group: not mentioned

Source: JRC own production

3.1.3 Smoking cessation

A total of 15 reports assessed the role of ENDS or ENNDS on the cessation or reduction of smoking regular combustible cigarettes or using other tobacco products (**Table 12**). In summary, these reports state the following:

- ENDS: While some reports state that there is some evidence of the potential of ENDS as a smoking cessation tool, other reports argue that e-cigarettes have not been proven to be effective for cessation at the population level and may lead to ongoing nicotine dependence.
- Switch from tobacco cigarettes: E-cigarettes have not undergone any procedures as required for recognised medical products. There is currently no known long-term health change due to the switch from tobacco cigarettes to e-cigarettes.
- Dual use: People should be discouraged from continuing to smoke when using e-cigarettes, even if they are smoking less, because there is no information on whether this will reduce their harm from smoking.
- Use of e-cigarette as a smoking cessation tool: Addiction therapists argue for a pragmatic approach under certain conditions and with certain groups of smokers (harm reduction approach).
- The risk of relapse into cigarette smoking among persistent e-cigarette users and dual users is still under study. Insufficient nicotine intake may increase the risk of returning to smoking, so individuals should be guided on how to use these products effectively.

Table 12. Association of e-cigarettes with cessation or reduction of conventional combustible cigarette smoking as described by health-related organisations. If the statement explicitly refers to ENDS (or nicotine) or ENNDS, this is shown at the beginning of the statement.

Body, year	Statement
NZ - MoH, 2024 (14)	E-cigarettes as a tool for smoking cessation: Vaping products are an effective quitting tool; more effective than nicotine replacement therapy (NRT). <i>Comparison group: Nicotine replacement therapy (NRT)</i>
Cochrane living SR, 2024 (15)	ENDS as a tool for smoking cessation: There is high-certainty evidence that ECs with nicotine increase quit rates compared to NRT and moderate-certainty evidence that they increase quit rates compared to ECs without nicotine. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain due to risk of bias inherent in the study design. <i>Comparison groups: NRT, ENNDS, usual care/no treatment</i>
DE - DKFZ, 2023 (17)	ENDS as a tool for smoking cessation: Nicotine-containing e-cigarettes seem to have the <u>potential</u> to help some smokers <u>stop smoking</u> . It appears that many smokers <u>continue</u> to use e-cigarettes in the <u>longer</u> term after stopping smoking. <i>Comparison group: conventional combustible cigarette smoking</i> ENDS as a tool for smoking cessation E-cigarettes have <u>not undergone any procedures</u> as required for recognised <u>medical products</u> . There is currently no known long-term health change due to the switch from tobacco cigarettes to e-cigarettes. <i>Comparison group: not mentioned</i>

E-cigarettes as a tool for smoking cessation: The effectiveness, and in particular the use of e-cigarettes in tobacco cessation, is judged in different ways by representatives of different disciplines. Specialist medical societies in Germany and several international health organisations oppose a general recommendation of e-cigarettes in tobacco cessation. Addiction therapists argue for a pragmatic use of e-cigarettes for tobacco cessation under certain conditions and for certain groups of smokers.

Comparison group: conventional combustible cigarette smoking

**WHO,
2023a** (18)

E-cigarettes as a tool for smoking cessation: Electronic cigarettes as actually used in the population as consumer products have not been proven to be effective for cessation at the population level and may lead to ongoing nicotine dependence.

Comparison group: not mentioned

**UK - NICE,
2023** (19)

ENDS as a tool for smoking cessation: Evidence showed that nicotine-containing e-cigarettes can help people to stop smoking and are of similar effectiveness to other cessation options such as varenicline or long-acting and short-acting NRT.

Comparison group: varenicline, nicotine replacement therapy (NRT)

ENDS as a tool for smoking cessation: The committee agreed that with the limited data on effects of longer-term use, people should only use e-cigarettes for as long as they help prevent them going back to smoking.

Comparison group: not mentioned

ENDS as a tool for smoking cessation and dual use: They also agreed that people should be discouraged from continuing to smoke when using e-cigarettes, even if they are smoking less, because there is no information on whether this will reduce their harm from smoking.

Comparison group: not mentioned

ENDS as a tool for smoking cessation, nicotine content: The committee discussed that it is more likely that people will not get enough nicotine to help them stop smoking, than get too much. They agreed that not getting enough nicotine is likely to increase the risk that the person will return to smoking, so they recommended that people should be encouraged to use as much as they need and told how to use the products effectively.

Comparison group: not mentioned

**BE - SHC,
2022** (22)

E-cigarettes as a tool for smoking cessation for vulnerable groups: Since smoking is closely associated with a socially vulnerable position (such as psychiatric patients, people in prisons, people with limited education, those with lower incomes, etc.), e-cigarettes can also play a positive role in future smoking cessation policies for these vulnerable groups of persistent heavy smokers. Based on current knowledge, their exclusive use by (ex-)smokers could lead to a significant reduction in health risks, provided they effectively quit smoking. They offer smokers a better alternative to smoking and can be used as a smoking cessation aid.

E-cigarettes should be seen as a temporary tool to quit smoking completely and, ideally, to stop vaping afterward (unless there is a risk that the vaper might start smoking again). The risk of relapse into cigarette smoking among persistent vapers, as well as dual use, is still being studied.

Comparison group: not mentioned

ENDS as a tool for smoking cessation: The relative risk of e-cigarettes compared to smoking is also clear: e-cigarettes are considered to be substantially less harmful than smoking. They offer smokers a better alternative to smoking and can be used as a smoking cessation aid. According to current knowledge, the exclusive use of e-cigarettes by (ex-

)smokers, provided they effectively quit smoking, could lead to a significant reduction in health risks. In the context of public health, current scientific data show that e-cigarettes, when used exclusively, are less harmful than traditional smoking and can offer health benefits as an alternative to smoking. However, there is still insufficient data on the long-term effects of e-cigarette use.

Comparison group: not mentioned

ENDS as a tool for smoking cessation: The SHC believes that the use of e-cigarettes with nicotine, under certain conditions, can have a place in tobacco discouragement policies. The SHC advocates making the reduction of smoking, vaping, and other nicotine use an important part of the policy. However, caution is necessary to ensure that limiting vaping and nicotine use does not undermine the goal of reducing smoking prevalence. Furthermore, from a public health perspective, the SHC considers unlimited (ongoing) use of e-cigarettes less desirable than "time-limited" vaping, particularly in the context of smoking cessation. There is also a need for caution to ensure that the goal of helping smokers quit does not undermine the protection of non-smokers from e-cigarette use. For some smokers, it is preferable to quit with the help of a nicotine replacement product (Nicotine Replacement Therapy or NRT) or by using an e-cigarette with nicotine, even in the long term if necessary, rather than risk relapsing into tobacco smoking.

Comparison group: not mentioned

ENDS as a tool for smoking cessation: There is high-certainty evidence that ECs with nicotine increase quit rates compared to NRT and moderate-certainty evidence that they increase quit rates compared to ECs without nicotine.

Comparison group: Nicotine replacement therapy (NRT), ENNDS

Cochrane living SR, 2022 (27)

ENDS as a tool for smoking cessation: Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain.

Comparison group: usual care/no treatment

E-cigarettes as a tool for smoking cessation and smoking reduction: There is weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit. The evidence on smoking reduction is assessed as weak to moderate.

SCHEER, 2021 (10)

Comparison group: conventional combustible cigarette smokers not using EN(N)DS

WHO, 2021a (28)

ENDS as a tool for smoking cessation: Evidence on the potential role for ENDS in cessation is still inconclusive. [...] Given the diverse nature of ENDS, more evidence is needed to inform a conclusive statement on the potential of any specific ENDS product as a cessation tool. At this time, there are still a number of unknown factors which mean that ENDS cannot be recommended as cessation aids at the population level.

Comparison group: not mentioned

Risks linked to using ENDS as a tool for smoking cessation: ENDS may discourage smokers from fully quitting by prolonging dual use or continuing their use of nicotine products. ENDS may entice former smokers to take up ENDS. 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.

Comparison group: not mentioned

ENDS as a tool for smoking cessation: 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.

Comparison group: not mentioned

ENDS as a tool for smoking cessation, nicotine pharmacology: 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).

Comparison group: not mentioned

ENDS as a tool for smoking cessation and reduction, flavours: 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.

Comparison group: not mentioned

**UK - PHE,
2021 (31)**

ENDS as a tool for smoking cessation and smoking reduction: Compared to the 2018 review, there is stronger evidence in this year's report that nicotine vaping products are effective for smoking cessation and reduction.

Comparison group: not mentioned

**WHO, 2020
(32)**

EN(N)DS as a tool for smoking cessation: EN&NNDS are not harmless. Although the consequences for long-term effects on morbidity and mortality have not yet been studied sufficiently, EN&NNDS are not safe for young people, pregnant women and adults who have never smoked. While it is expected that use of EN&NNDS in these groups might increase their health risks, non-pregnant adult smokers who completely switch from combustible tobacco cigarettes to use of unadulterated and appropriately regulated EN&NNDS alone might reduce their health risks.

Comparison group: not mentioned

E-cigarette as a tool for smoking cessation: Overall, there is limited evidence that e-cigarettes may be effective aids to promote smoking cessation.

Comparison group: not mentioned

ENDS as a tool for smoking cessation: There is moderate evidence from randomized controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation.

Comparison group: ENNDS

E-cigarette as a tool for smoking cessation: There is insufficient evidence from randomized controlled trials about the effectiveness of e-cigarettes as cessation aids compared with no treatment or to Food and Drug Administration–approved smoking cessation treatments.

Comparison group: no treatment, FDA-approved treatments

**US -
NASEM,
2018 (36)**

E-cigarette as a tool for smoking cessation: While the overall evidence from observational trials is mixed, there is moderate evidence from observational studies that more frequent use of e-cigarettes is associated with an increased likelihood of cessation.

Comparison group: less frequent use of e-cigarettes

E-cigarette as a tool for smoking cessation, health effects: There is substantial evidence that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems.

Comparison group: conventional combustible cigarette smoking

E-cigarette as a tool for smoking cessation, dual use: NICE guidance recommends dual use of NRT for harm reduction, largely because dual users are more likely eventually to quit smoking. Evidence on the natural history of smoking among dual users of e-cigarettes is less well established, but a similar effect is likely.

Comparison group: not mentioned

E-cigarette as a tool for smoking cessation: E-cigarettes appear to be effective when used by smokers as an aid to quitting smoking.

Comparison group: not mentioned

ENDS as a tool for smoking cessation: Promotion of the use of non-tobacco nicotine, including e-cigarettes, as widely as possible as a substitute for smoking, in the context of a regulatory framework designed to discourage use among youth and never-smokers, is therefore likely to generate significant health gains in the UK.

**UK - RCP,
2016 (39)**

Comparison group: not mentioned

ENDS as a tool for smoking cessation: The e-cigarette containing nicotine appears to be an effective quitting aid for smokers. Although the control period is still too short, initial results are positive and encouraging; however, confirmation through further study is recommended.

Comparison group: not mentioned

ENNDs as a tool for smoking cessation or e-cigarette use reduction: At the present time we do not know whether an e-cigarette without nicotine can help a smoker to stop, or whether an e-cigarette without nicotine can help reduce e-cigarette use. Further study is needed and caution is advised.

Comparison group: not mentioned

ENDS as a tool for smoking cessation, health risks: Not enough is known about the long-term health effects of chronic e-cigarette use at present. However, if stopping the e-cigarette is not possible, or desirable, it is better to keep using the e-cigarette in the long term than to risk returning to tobacco smoking. In the process, an attempt can be made to gradually reduce the nicotine dose in the e-cigarette.

**BE - SHC,
2015 (43)**

Comparison group: not mentioned

Nevertheless, the reduced exposure to toxicants of well-regulated ENDS used by established adult smokers as a complete substitution for cigarettes is likely to be less toxic for the smoker than conventional cigarettes or other combusted tobacco products. The amount of risk reduction, however, is presently unknown.

**WHO, 2014
(44)**

Comparison group: conventional cigarette use

Source: JRC own production

3.2 Heated tobacco products

A total of seven reports which focused on heated tobacco products were identified. Most of the reports focused on health outcomes, with six reports giving indications on the role in smoking cessation; no report was identified for a potential role in smoking initiation (“gateway” effect).

3.2.1 Health outcomes

3.2.1.1 Cardiovascular-related diseases

A total of three reports evaluated the effects of HTPs in the cardiovascular system (**Table 13**). In summary, they state the following:

- There is evidence of cardiovascular impacts.
- Biomarkers: Specific biomarkers of cardiovascular disease did not decrease and in some cases increased upon switching from conventional cigarettes to HTPs, suggesting that HTPs have similar or greater cardiotoxicity than conventional cigarettes.

Table 13. Association of heated tobacco products (HTPs) with cardiovascular-related diseases as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	<p>Cardiovascular effects: Some evidence of <u>harm from HTPs</u> was identified. This included increased risks of dependency and addiction, exposure to toxicants, <u>cardiovascular impacts</u>, chronic respiratory disease, or developmental impacts. Due to the <u>relative newness</u> of HTPs, it is <u>likely that more health outcomes will emerge over time</u>.</p> <p><i>Comparison group: not mentioned</i></p>
DE - DKFZ, 2023 (17)	<p>Cardiovascular effects: The studies available so far point to <u>negative effects on the cardiovascular system</u>.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2021b (30)	<p>Cardiovascular outcomes in conventional combustible cigarette users switching to HTPs: <u>Industry publications</u> 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. [...] In addition, the levels of <u>biomarkers of many cardiovascular</u> 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 <u>cardiovascular toxicity</u> than conventional cigarettes. [...] As summarized above, the data indicate <u>no improvement in several pulmonary and cardiovascular indicators</u> and a <u>high prevalence of dual use</u> (with smoking) in participants in switching studies.</p> <p><i>Comparison group: conventional combustible cigarette smoking</i></p> <p>Effects on non-smokers taking up HTPs: Uptake of HTPs by non-users of any tobacco product will therefore <u>increase their risk for adverse outcomes</u> such as respiratory, <u>cardiovascular</u> and potentially other diseases.</p> <p><i>Comparison group: non-smokers</i></p>

Source: JRC own production

3.2.1.2 Cancer

A total of four reports evaluated the potential role of HTPs on cancer (**Table 14**). The evidence found can be summarised as follows:

- Comparison with conventional combustible cigarettes: Industry-published studies suggest a reduced mutagenicity and lower carcinogenic biomarkers in cell cultures exposed to HTP aerosols compared to conventional cigarette smoke, as well as fewer histological changes in animals after exposure to HTP aerosols.
- Comparison with air exposure: Both industry and independent publications show that cytotoxicity, mutagenicity and expression of certain ribonucleic acids (RNAs) are higher after exposure to HTP aerosol than after exposure to air and follow a dose-response relationship.
- Dermal tumorigenicity: The examined sources report that 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.
- Switching from conventional cigarettes to HTPs: The examined sources report that industry studies indicate reduced biomarkers of exposure and mutagenicity in smokers who switch to HTPs.
- The risk of cancer is still largely unknown.

Table 14. Association of heated tobacco products (HTPs) with cancer as described by health-related organisations.

Body, year	Statement
DE - DKFZ, 2023 (17)	Effects on HTPs users: The <u>risk of cancer</u> is <u>still largely unknown</u> . Studies show that <u>carcinogenic substances</u> enter the body when using tobacco heaters. <i>Comparison group: not mentioned</i>
WHO, 2023b (20)	Exposure to carcinogens in HTPs users: <u>Exposure to major carcinogens</u> found in CC smoke <u>may be reduced</u> ; however, <u>limited</u> data are available on effects on <u>health risks</u> . <i>Comparison group: conventional combustible cigarette smoke</i>
WHO, 2021b (30)	In vitro studies, aerosols: <u>Industry-published studies</u> generally claim <u>reduced</u> cytotoxicity and <u>mutagenicity</u> and lower levels of a range of toxicological and inflammatory biomarkers after exposure <i>in vitro</i> to <u>HTP aerosols</u> as compared with <u>conventional cigarette smoke</u> . Increasing smoking <u>intensity</u> , however, results in substantial increases in these <u>effects</u> . [...] <u>Both industry and independent publications</u> show that cytotoxicity, <u>mutagenicity</u> and expression of certain RNAs are higher after exposure to HTP aerosol than after exposure to <u>air</u> . <i>Comparison group: conventional combustible cigarette smoke, air exposure</i> Animal studies: <u>Industry studies</u> of dermal tumorigenicity and acute and chronic inhalation toxicity in <u>rodents</u> reported that animals treated with HTP aerosol had <u>lower tumour incidence and multiplicity</u> , fewer inflammatory and cellular stress responses and <u>fewer histological changes</u> than animals treated with <u>conventional cigarette smoke</u> . Analysis of these publications, however, reveals <u>dose-response relations</u> for many of these effects and consistently <u>greater responses in animals treated with HTPs than in air controls</u> .

Comparison group: conventional combustible cigarette smoke, air exposure

Effects on smokers switching to HTPs products: 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.

Comparison group: e-cigarette use, abstinence from tobacco, conventional combustible cigarette smoking

Dermal tumorigenicity: 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.

Comparison group: conventional combustible cigarette smoking

BE - SHC, 2020 (34) **Carcinogenic potential of HTPs:** It is currently not possible to draw conclusions on the long-term and medium-term effects on health (cfr., the carcinogenic potential) of using heated tobacco products compared to smoking conventional cigarettes. The risk associated with the various unique carcinogens in aerosols of heated tobacco products needs to be further examined (effect of inhalation, etc.).

Comparison group: conventional combustible cigarettes

Source: JRC own production

3.2.1.3 Respiratory diseases

A total of three reports evaluated the association of HTPs with respiratory diseases (**Table 15**). In summary, these reports state the following:

- There is evidence of a higher risk of respiratory diseases in non-smokers who use HTPs.
- No improvement seems to exist for several pulmonary indicators for smokers who switched to HTPs.

Table 15. Associations of heated tobacco products (HTPs) with respiratory diseases as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	Respiratory effects: Some evidence of harm from HTPs was identified. This included <u>increased risks</u> of dependency and addiction, exposure to toxicants, cardiovascular impacts, <u>chronic respiratory disease</u> , or developmental impacts. <i>Comparison group: not mentioned</i>
DE - DKFZ, 2023 (17)	Respiratory effects: The use of tobacco heaters has a <u>negative impact</u> on the <u>airways</u> . <i>Comparison group: not mentioned</i>

WHO, 2021b (30) **Effects on conventional combustible cigarette users switching 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.

Comparison group: conventional combustible cigarette smoking

Effects on non-smokers: 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.

Comparison group: non-smokers

Source: JRC own production

3.2.1.4 Toxicity, uptake of toxic substances and of other potentially harmful compounds

A total of six reports reported information on the toxicity, uptake of toxic substances and of other potentially harmful compounds in HTPs (**Table 16**). In summary, these reports state the following:

- Long-term toxicity: As these products have been introduced recently into the tobacco market, scientific evidence on their toxicity and long-term health effects is still accumulating.
- Comparison of toxicants with conventional combustible cigarette smoke: While HTPs may expose users to lower levels of some toxicants present in conventional combustible cigarettes, they might expose them to higher levels of other toxicants. Moreover, a lower level of some toxicants does not necessarily mean a reduction in health risk.
- Comparison of specific toxicants with conventional combustible cigarette smoke: Levels of some harmful constituents that derive from the combustion process, such as tobacco-specific nitrosamines and some carbonyl compounds, can be lower in HTP aerosols than in cigarette smoke. However, some reports indicate a comparable or even higher presence of pyridine, dimethyl trisulfide, acetoin and methylglyoxal than in conventional combustible cigarettes.
- Comparison with specific toxicants in e-cigarettes aerosol: When HTP aerosols are compared to e-cigarettes aerosols, higher presence of TSNA, CO, benzo[a]pyrene and carbonyls are reported.
- Comparison with air exposure: exposure to HTP aerosol leads to higher cytotoxicity, mutagenicity, and expression of certain RNAs compared to exposure to air.
- Dose-response exposure: Toxicant exposure from HTPs varies significantly among users. Increased use leads to higher toxicant levels and stronger cytotoxic and mutagenic effects in a dose-response manner.

Table 16. Toxicity, uptake of toxic substances and of other potentially harmful compounds in HTPs as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	<p>Exposure to toxic compounds: Some evidence of harm from HTPs was identified. This included increased risks of dependency and addiction, <u>exposure to toxicants</u>, cardiovascular impacts, chronic respiratory disease, or developmental impacts. Due to the relative newness of HTPs, it is likely that more health outcomes will emerge over time.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2023b (20)	<p>Potentially harmful constituents: Even if HTPs deliver <u>lower concentrations</u> of HPHCs [harmful and potentially harmful constituents] in emissions <u>than</u> are found in <u>CC</u> smoke, there are still <u>measurable levels</u> of HPHCs <u>and additional constituents</u> that have <u>not usually</u> been <u>assessed</u>. Furthermore, changes to products over time could render previous measurements moot. It is not appropriate to draw general conclusions about the entire class of HTPs or other HTPs on the basis of data for one particular product.</p> <p><i>Comparison group: Conventional combustible cigarettes</i></p> <p>Carcinogens: <u>Exposure to major carcinogens found in CC smoke may be reduced</u>; however, limited data are available on <u>effects on health risks</u>.</p> <p><i>Comparison group: Exclusive HTP use versus dual use or CC</i></p> <p>Exposure to HPHCs: The existing evidence:</p> <ul style="list-style-type: none"> - indicates that HTPs are probably not harmless to <u>users and bystanders</u> and that, while <u>smokers who switch completely from CCs to HTPs may reduce their exposure to some HPHCs, they do not reduce their exposure to all of them</u>; - is inconclusive about whether smokers who switch completely from CCs to HTPs are exposed to less harm from tobacco-related diseases than smokers who continue to use CCs; and - is inconclusive about whether HTPs overall help to transition smokers from CCs either partially or entirely. <p><i>Comparison group: Conventional combustible cigarette smokers</i></p> <p>Exposure to HPHCs: The existing evidence indicates that HTPs are probably <u>not harmless to users and bystanders</u> and that, while smokers who switch completely from CCs to HTPs may <u>reduce their exposure to some HPHCs</u>, they do not reduce their exposure to all of them.</p> <p><i>Comparison group: not mentioned</i></p>
Cochrane living SR, 2022 (27)	<p>Exposure to toxicants: There was <u>moderate-certainty</u> evidence that heated tobacco users have <u>lower exposure to toxicants/carcinogens than cigarette smokers</u> and <u>very low- to moderate-certainty</u> evidence of <u>higher exposure than those attempting abstinence</u> from all tobacco.</p> <p><i>Comparison group: Conventional combustible cigarette smokers, people attempting to abstain from all tobacco use</i></p>
WHO, 2021b (30)	<p>Levels of harmful constituents in HTP aerosols: The levels of many <u>harmful constituents</u> that derive from the combustion process are consistently reported to be <u>significantly lower in HTP aerosol than in conventional cigarette smoke</u>. These include <u>CO, PAH, some carbonyl compounds (formaldehyde, acetaldehyde) and other volatile toxicants</u>, as well as components such as <u>black carbon, nitrogen oxide and ammonia</u>. The levels of <u>tobacco-specific nitrosamines (TSNAs)</u> are also <u>lower in HTP aerosols</u> than in cigarette smoke. Some reports, however, indicate that <u>the levels of other constituents, such as pyridine,</u></p>

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.

Comparison groups: Conventional combustible cigarette smoke, electronic cigarette aerosol

***In vitro* studies:** 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.

Comparison groups: Exposure to conventional combustible cigarette smoke, air controls

***In vivo* studies:** 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.

Comparison groups: Exposure to conventional combustible cigarette smoke, air controls

Exposure to toxicants: 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.

Comparison group: differences in puffing intensity

Unique harmful constituents: 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.

Comparison group: Conventional combustible cigarette smoking

Exposure to toxicants: 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.

While HTPs may expose users to lower levels of some toxicants than cigarettes, they might expose them to higher levels of other toxicants.

Comparison group: Conventional combustible cigarette smoking

Toxicity: As these products have been introduced recently into the tobacco marketplace, scientific evidence on their toxicity and long-term health effects is still accumulating.

Comparison group: not mentioned

Second-hand exposure: Second-hand exposure of non-users. Exposure to particulates, nicotine and other components of HTP aerosols may pose risks to non-users.

Comparison group: not mentioned

BE - SHC, 2020 (34) ***In vitro* studies:** Despite the methodological limitations of the tests, the *in vitro* studies generally show a decrease in the induction potency of cytotoxicity and mutagenicity due to exposure to a heated tobacco product, compared to conventional cigarettes. However, they cannot be considered risk-free. There is not enough scientific research to formulate a clear answer to the question of toxicity according to the category of the heated tobacco product.

Comparison group: Conventional combustible cigarette smoking

Particulate matter: The particulate matter emitted, the conclusions of the various studies diverge as to the relevance of the low levels detected.

Comparison group: Not mentioned

Levels of and exposure to harmful constituents in HTP aerosols: Although heated tobacco products do not burn the tobacco, they do release nicotine and harmful and potentially harmful constituents. The emissions and exposure levels of these products are lower, but not necessarily negligible, compared to conventional cigarettes. Moreover, other compounds – either not present or in small amounts, including possible carcinogens – have been detected in these new heated tobacco products.

Comparison group: conventional combustible cigarette smoke

WHO, 2019 (35) **Toxic emissions for HTP users and second-hand exposure:** HTPs produce toxic emissions, many of which are similar to toxicants found in cigarette smoke.

Comparison group: Conventional combustible cigarette smoke

HTP users are exposed to toxic emissions from the products, and bystanders could also be exposed to these toxic second-hand emissions.

Comparison group: Not mentioned

Levels of toxicants in HTP emissions: Although the levels of several toxicants in HTPs are lower than those found in conventional cigarettes, the levels of others are higher. A lower level of some toxicants does not necessarily mean a reduction in health risk.

Comparison group: Conventional combustible cigarette smoke

Source: JRC own production

3.2.1.5 Reproductive, developmental, and pregnancy outcomes

A total of three reports assessed the association of HTPs with reproductive, developmental, and pregnancy outcomes (**Table 17**), and in summary they state the following:

- Use during pregnancy: The use of tobacco heaters during pregnancy may be associated with an increased risk for mothers and newborns.
- HTP-delivered nicotine: A potential detrimental effect of nicotine from HTPs was hypothesised as harmful for both reproduction and brain development.
- Developmental harm of HTPs: Some evidence suggests potential detrimental developmental impacts.

Table 17. Association of heated tobacco products (HTPs) with reproductive, developmental, and pregnancy outcomes as described by health-related organisations.

Body, year	Statement
DE - DKFZ, 2023 (17)	HTP use during pregnancy: The use of tobacco heaters during pregnancy <u>may be associated with an increased risk for mothers and newborns.</u> <i>Comparison group: not mentioned</i>
WHO, 2023b (20)	Effect of HTP-delivered nicotine: The <u>nicotine</u> delivered by HTPs may have <u>detrimental effects on reproduction</u> and be <u>harmful to the developing brains of youth and young adults.</u> <i>Comparison group: exclusive HTP use versus dual use or conventional combustible cigarette use</i>
NZ - MoH, 2024 (14)	Developmental harm of HTPs: Some evidence of harm from HTPs was identified. This included increased risks of dependency and addiction, exposure to toxicants, cardiovascular impacts, chronic respiratory disease, or <u>developmental impacts.</u> Due to the relative newness of HTPs, it is likely that more health outcomes will emerge over time. <i>Comparison group: not mentioned</i>

Source: JRC own production

3.2.1.6 Addiction, dependence and nicotine uptake

A total of six reports assessed the association of HTPs with addiction, dependence and nicotine uptake (**Table 18**). In summary they state the following:

- Nicotine exposure: HTPs contain and deliver nicotine. Nicotine from HTPs is absorbed from the aerosol in a similarly effective way as from conventional combustible cigarettes, and so the addictive potential of heated tobacco products is probably comparable to that of conventional cigarettes.
- HTP-delivered nicotine compared to conventional combustible cigarettes: more nicotine is delivered into cells exposed to HTPs than into those exposed to smoke from reference cigarettes.
- Addiction: There are differences in the amount of nicotine delivered between different models, and this may affect their addictive potential.

Table 18. Association of heated tobacco products (HTPs) with addiction, dependence and nicotine uptake as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	Risk of dependency and addiction: Some <u>evidence of harm</u> from HTPs was identified. This included <u>increased risks of dependency and addiction,</u> exposure to toxicants, cardiovascular impacts, chronic respiratory disease, or developmental impacts. Due to the relative newness of HTPs, it is likely that more health outcomes will emerge over time. <i>Comparison group: not mentioned</i>
DE - DKFZ, 2023 (17)	Addictive potential: The <u>nicotine</u> is absorbed from the aerosol in a similarly <u>effective way</u> as from cigarettes, so it <u>can be assumed</u> that the <u>potential for addiction</u> is <u>comparable to smoking.</u>

Comparison group: not mentioned

WHO, 2023b (20) **Addictive potential:** Overall, the studies of the addiction potential of HTPs suggest that the most recent version of IQOS delivers a similar amount of nicotine and is as effective in reducing craving as CCs. Other HTPs may be less effective, but the data are limited.

Comparison group: not mentioned

WHO, 2021b (30) **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.

Comparison group: not mentioned

Nicotine content: Most publications, including non-industry studies, show that the levels of nicotine in HTPs and conventional cigarettes (on per-stick basis) are comparable.

Nicotine impact: Furthermore, more nicotine is delivered into cells exposed to HTPs than into those exposed to smoke from reference cigarettes.

BE - SHC, 2020 (34) **Addictive potential:** The addictive potential of heated tobacco products is considered to be comparable to that of conventional cigarettes.

Comparison group: conventional combustible cigarettes

WHO, 2019 (35) **Addictive potential:** HTPs contain nicotine. Nicotine is highly addictive and linked to health harms, particularly in children, pregnant women and adolescents.

Comparison group: not mentioned

Source: JRC own production

3.2.1.7 Other outcomes

3.2.1.7.1 Overall health

A total of seven reports examined the association of HTPs with other outcomes not covered above (**Table 19**), and the key concepts are summarised below.

- Overall health risks: Evidence on long-term health risks and relative harm compared to conventional cigarettes is insufficient and inconclusive.
- There is insufficient evidence to support claims of HTPs being safer or effective for harm reduction or smoking cessation.
- Second-hand exposure: HTP emissions expose bystanders to harmful components, with lower levels than cigarette smoke but higher than clean air or e-cigarettes.
- Switching from conventional cigarettes to HTPs may reduce exposure to some harmful constituents but does not eliminate all risks or guarantee reduced harm.
- Impact on non-smokers: Initiation of HTP use by non-smokers increases their risk for chronic diseases.
- Independent research needed: Most evidence comes from industry studies, and more independent, long-term studies are required to evaluate risks accurately.

Table 19. Association of heated tobacco products (HTPs) with overall health as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	<p>Harm from HTPs: There is <u>no clear independent evidence</u> that HTPs are <u>significantly less harmful</u> than cigarettes. Industry claims that because the tobacco is heated rather than burned, HTPs are less harmful. However, HTPs contain toxicants at lower levels than cigarettes in some cases, but also contain some toxicants that cigarettes do not.</p> <p><i>Comparison group: conventional combustible cigarette</i></p> <p>Relative safety of HTPs: This proposal [of tax reduction for HTPs] <u>could also signal to youth and non-smokers</u> that <u>smokeless tobacco products are safer or less harmful to use</u> compared to cigarettes, when there is <u>insufficient independent evidence</u> to support this currently.</p> <p><i>Comparison group: conventional combustible cigarette</i></p> <p>Harm from HTPs: Some <u>evidence of harm</u> from HTPs was identified. This included increased risks of dependency and addiction, exposure to toxicants, cardiovascular impacts, chronic respiratory disease, or developmental impacts. Due to the <u>relative newness of HTPs</u>, it is <u>likely that more health outcomes will emerge</u> over time.</p> <p><i>Comparison group: not mentioned</i></p> <p>Potential risk from HTPs: The data identified [in this table] are <u>insufficient evidence</u> to provide a <u>fully informed risk assessment</u> for HTPs. As such, given the <u>potential risk to health</u>, it would be advisable to follow a <u>precautionary principal to manage any risks</u> of HTPs against an unknown benefit. This could include establishing <u>strong monitoring pathways</u>, and <u>monitoring international data and evidence as it emerges</u>.</p> <p><i>Comparison group: not mentioned</i></p>
DE - DKFZ, 2023 (17)	<p>Harm from HTPs: The <u>aerosol</u> from heated tobacco products contains <u>harmful and potentially harmful components</u>. The aerosol also <u>contains harmful substances that are not present in tobacco smoke</u>. Compared to cigarette smoke, <u>most pollutant levels are lower</u>.</p> <p><i>Comparison group: conventional combustible cigarette smoke</i></p> <p>Potential risk from HTPs: The body absorbs aerosol pollutants; tobacco-associated <u>biomarkers</u> responsible for causing <u>damage to health</u> have been detected.</p> <p><i>Comparison group: not mentioned</i></p> <p>Potential risk from HTPs: In <u>animal and cell experiments</u> different <u>changes</u> were observed, indicating a <u>potential health risk</u>.</p> <p><i>Comparison group: not mentioned</i></p> <p>Second-hand exposure: When using tobacco heaters, emissions with harmful or potentially harmful components are released into indoor air. Compared to smoking, the use of tobacco heaters causes <u>less intense and shorter air pollution</u>. Pollutants from the aerosol can be absorbed into the body by non-consumers from the indoor air. <u>Health consequences</u> cannot be ruled out.</p> <p><i>Comparison group: conventional combustible cigarette smoke</i></p>
WHO, 2023b (20)	<p>Potential risk from HTPs: Exposure to major carcinogens found in CC smoke may be reduced; however, limited data are available on <u>effects on health risks</u>.</p> <p><i>Comparison group: conventional combustible cigarette</i></p> <p>Potential harm from HTP use and second-hand exposure: The existing evidence:</p>

-
- indicates that HTPs are probably not harmless to users and bystanders and that, while smokers who switch completely from CCs to HTPs may reduce their exposure to some HPHCs, they do not reduce their exposure to all of them;
 - is inconclusive about whether smokers who switch completely from CCs to HTPs are exposed to less harm from tobacco-related diseases than smokers who continue to use CCs; and
 - is inconclusive about whether HTPs overall help to transition smokers from CCs either partially or entirely.

Comparison groups: not mentioned/conventional combustible cigarette smokers switching to HTPs

The existing evidence is inconclusive about whether smokers who switch completely from CCs to HTPs are exposed to less harm from tobacco-related diseases than smokers who continue to use CCs

Comparison groups: conventional combustible cigarette smokers switching to HTPs

Cochrane living SR, 2022 (27)

Potential risk from HTPs: There was insufficient evidence for differences in risk of adverse or serious adverse events between people randomised to switch to heated tobacco, smoke cigarettes, or attempt tobacco abstinence in the short-term.

Comparison groups: conventional combustible cigarette smoking, attempting tobacco abstinence

WHO, 2021b (30)

Effects on non-smokers: 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.

Comparison groups: non-smokers

Second-hand exposure: 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.

Long-term health effects: As these products have been introduced recently into the tobacco marketplace, scientific evidence on their toxicity and long-term health effects is still accumulating.

Comparison groups: not mentioned

BE - SHC, 2020 (34)

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

Comparison group: not mentioned

Reduced harm: At present, it is not possible to comment on the usefulness of the product as a way of limiting harm or as a means of smoking cessation, although users and the tobacco industry make such claims in order to use the product and place it on the market. Independent research must be conducted in the future, in particular human studies, to assess the short- and long-term health effects of using heated tobacco products.

Comparison group: not mentioned

Aerosol exposure and histopathological changes (animal studies): Sub-chronic *in vivo* exposure to IQOS aerosols produces little or less severe histopathological changes than sub-chronic exposure at similar concentrations to conventional cigarettes. However, the correlation between these effects and clinical changes in humans is not known.

Comparison group: exposure to conventional combustible cigarette smoke

Potential reduced harm: Although positive biological changes in a few biomarkers have been observed in clinical studies, suggesting a potential reduction in risk, it is not yet known to what extent

heated tobacco products are less risky than conventional cigarettes or whether they will contribute to a reduction in tobacco-related diseases. Additional short- and long-term health studies, molecular-epidemiological research and, above all, more independent research, are needed.

Comparison group: conventional combustible cigarette smoking

Biomarkers of exposure to HPHCs: In clinical studies, following a switch from conventional cigarettes to heated tobacco products (IQOS or GLO), significant decreases in biomarker levels of exposure to harmful and potentially harmful constituents have been observed, although they cannot be considered to be completely safe. The same deduction can be made in light of the asymptotic relationship between dose and effect of tobacco smoke, which suggests that even if the intensity of exposure to heated tobacco products is no more than 5% of the exposure to tobacco smoke, the risk associated with the use of these products should clearly not be overlooked.

Comparison group: switch from conventional combustible cigarette to HTPs

WHO, 2019 (35)

Potential harm from HTPs: Although the levels of several toxicants in HTPs are lower than those found in conventional cigarettes, the levels of others are higher. A lower level of some toxicants does not necessarily mean a reduction in health risk.

Comparison group: conventional combustible cigarette smoking

Potential harm from HTP use and second-hand exposure: The long-term health impacts of HTP use and exposure to their emissions remain unknown. There is currently insufficient independent evidence on the relative and absolute risk. Independent studies are needed to determine the health risk they pose to users and bystanders.

Comparison group: not mentioned

Source: JRC own production

3.2.2 Gateway to smoking

No reports examining the role of HTPs on initiation of conventional combustible cigarette smoking were identified.

3.2.3 Smoking cessation

Six reports evaluated the role of HTPs as a smoking cessation tool (**Table 20**). In summary, they state the following:

- To date, there is no conclusive evidence on their usefulness to transition away from conventional combustible cigarette smoking or other tobacco use, nor on their effectiveness for such a purpose.
- There is no evidence to support HTPs as effective in complete smoking cessation, with some studies suggesting HTP users are less likely to transition away from conventional cigarettes.
- HTPs are not recommended in smoking cessation guidelines.
- There is some evidence of a negative association between HTPs and smoking cessation/intention to quit, and rates of dual use (HTPs and conventional cigarettes) in cessation studies point in this direction too.

Table 20. Association of heated tobacco products (HTPs) with smoking cessation as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	<p>HTPs as a cessation tool: There is <u>no evidence</u> to support HTPs as being <u>effective in helping people transition to becoming completely smoke free</u>. Some studies suggest that <u>former smokers that use HTPs</u> are more likely to <u>relapse</u>. Other studies suggest HTP users are <u>less likely to transition away</u> from smoking conventional cigarettes than those users exclusively smoking cigarettes.</p> <p>This review identified <u>no compelling evidence</u> of <u>any benefit</u> from the use of HTPs as a <u>smoking cessation tool</u>. Studies lacked population-level data, had limited information on exposure and health effects, and there was an absence of empirical studies on the <u>complete transition from smoking or nicotine use</u>.</p> <p><i>Comparison group: Former smokers</i></p> <p>Comparison with electronic cigarettes as cessation tool: Vaping has been a key factor in recent drops in New Zealand’s smoking rates and there is a stronger evidence base to support the use of vaping products as a quit tool. <u>Incentivising HTPs [via reduced taxation] could divert those switching from cigarettes away from vaping</u>, to a product that has a <u>weaker evidence base</u> for use as a quit tool.</p> <p><i>Comparison group: electronic cigarettes as a cessation tool</i></p>
DE - DKFZ, 2023 (17))	<p>HTPs as a cessation tool: The <u>usefulness</u> of tobacco heaters in cessation of tobacco is <u>unknown</u>. Tobacco heaters have <u>not undergone any test procedures</u> similar to those required for recognised medical products. In the guidelines for tobacco cessation, <u>heaters are not recommended to quit smoking</u>.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2023b (20)	<p>Complete switch to HTPs: The available <u>data do not indicate</u> that smokers who start using HTPs <u>switch successfully to exclusive use</u> of these products. Instead, <u>most become dual users</u> and <u>do not substantially reduce their risk</u> from tobacco products.</p> <p><i>Comparison group: not mentioned</i></p> <p>HTPs as a cessation tool: The existing evidence:</p> <ul style="list-style-type: none"> - indicates that HTPs are probably not harmless to users and bystanders and that, while smokers who switch completely from CCs to HTPs may reduce their exposure to some HPHCs, they do not reduce their exposure to all of them; - is <u>inconclusive</u> about whether smokers who <u>switch completely</u> from CCs to HTPs are <u>exposed to less harm from tobacco-related diseases</u> than smokers who continue to use CCs; and - is <u>inconclusive</u> about whether HTPs overall help to <u>transition smokers from CCs either partially or entirely</u>. <p><i>Comparison group: conventional combustible cigarette smokers who continue smoking</i></p>
Cochrane living SR, 2022 (27)	<p>HTPs as a cessation tool: No studies reported on cigarette smoking cessation, so the <u>effectiveness</u> of heated tobacco for this purpose remains <u>uncertain</u>.</p> <p><i>Comparison group: not mentioned</i></p>
WHO, 2021b (30)	<p>HTPs as a cessation tool: Although <u>industry data</u> suggest that HTPs could be used as a <u>long-term substitute</u> in highly controlled settings, independent population-based studies</p>

have raised concern that “real-world” concurrent use of cigarettes and HTPs might prolong smoking behaviour.

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.

Comparison group: not mentioned

BE - SHC, 2020 (34) **HTPs as a cessation tool:** There is no evidence that heated tobacco products will be used exclusively as substitutes for conventional cigarettes. The high incidence of dual use indicates complementary use of heated tobacco products rather than a substitution of conventional tobacco products. It is suggested here that smokers use heated tobacco products as a supplement to, rather than a substitute for, conventional cigarettes.

Comparison group: not mentioned

HTPs as a cessation tool: At present, it is not possible to comment on the usefulness of the product as a way of limiting harm or as a means of smoking cessation, although users and the tobacco industry make such claims in order to use the product and place it on the market. Rather, several studies indicate a negative association between heated tobacco products and smoking cessation/intention to quit. *Comparison group: not mentioned*

HTPs as a cessation tool: Heated tobacco products do not appear able to play any role in smoking cessation and Public Health England does not attribute any role to these products in this regard. They are actually nicotine replacement products.

Comparison group: not mentioned

Source: JRC own production

3.3 Nicotine pouches

3.3.1 Health outcomes

A total of three reports evaluated the association of health outcomes with nicotine pouches.

It is important to note that none of the examined reports evaluated the long-term health outcomes related to consuming nicotine pouches, likely because these products have not been on the market long enough for such effects to be observed.

3.3.1.1 Cardiovascular-related diseases

Three reports examined the association of nicotine pouches with cardiovascular outcomes (**Table 21**).

- Cardiovascular impacts: There seems to be some evidence of cardiovascular impacts from nicotine pouches consumption.
- Nicotine: Nicotine is harmful to health, including to the cardiovascular system.
- People with cardiovascular disease are considered high-risk if they use nicotine pouches due to nicotine's strong effects on the cardiovascular system.

Table 21. Association of nicotine pouches with the cardiovascular-related diseases as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	<p>Cardiovascular impacts from nicotine pouches: <u>Some evidence of harm</u> from snus or nicotine pouches was identified. This included <u>increased risks</u> of dependency and addiction, exposure to toxicants, <u>cardiovascular impacts</u>, chronic respiratory disease, or developmental impacts.</p> <p><i>Comparison group: not mentioned</i></p>
WHO To- bReg, 2023 (21)	<p>Harm from nicotine: Nicotine is <u>harmful to health</u>, including to the nervous and <u>cardiac systems</u>.</p> <p><i>Comparison group: not mentioned</i></p>
DE - BfR, 2022 (24)	<p>Definition of high-risk groups: In terms of effects on health, the BfR defines the following <u>high-risk groups</u>: <u>People with cardiovascular disease</u>, as nicotine has <u>strong effects on the cardiovascular system</u>.</p> <p><i>Comparison group: not mentioned</i></p>

Source: JRC own production

3.3.1.2 Cancer

The association of nicotine pouches with cancer outcomes was not addressed by any of the identified reports.

3.3.1.3 Respiratory diseases

One report indicated some evidence of harm from nicotine pouches in relation to chronic respiratory disease (**Table 22**).

Table 22. Association of nicotine pouches with respiratory diseases as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	<p>Respiratory impacts from nicotine pouches: <u>Some evidence of harm from</u> snus or nicotine pouches was identified. This included <u>increased risks</u> of dependency and addiction, exposure to toxicants, cardiovascular impacts, <u>chronic respiratory disease</u>, or developmental impacts.</p> <p><i>Comparison group: not mentioned</i></p>

Source: JRC own production

3.3.1.4 Toxicity, uptake of toxic substances and of other potentially harmful compounds

Two reports assessed the toxicity, uptake of toxic substances and of other potentially harmful compounds in nicotine pouches (**Table 23**).

- Toxicants: The potential hazards of nicotine pouches regarding exposure to toxicants and potentially harmful compounds are mentioned in these two reports.
- Comparison with conventional tobacco: Nicotine pouches contain fewer toxicants and expose users to fewer harmful constituents than conventional tobacco products.

Table 23. Toxicity, uptake of toxic substances and of other potentially harmful compounds in nicotine pouches as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	Effects from nicotine pouches: <u>Some evidence of harm</u> from snus or nicotine pouches was identified. This included <u>increased risks</u> of dependency and addiction, <u>exposure to toxicants</u> , cardiovascular impacts, chronic respiratory disease, or developmental impacts. <i>Comparison group: not mentioned</i>
WHO To-bReg, 2023 (21)	HPHCs in nicotine pouches: They contain <u>fewer toxicants</u> and therefore <u>expose users to fewer harmful and potentially harmful constituents</u> than conventional tobacco products; however, no use of non-therapeutic nicotine and of tobacco products is recommended for maximum protection of health, as the benefits of quitting tobacco use are apparent almost immediately. <i>Comparison group: conventional tobacco products</i>

Source: JRC own production

3.3.1.5 Reproductive, developmental, and pregnancy outcomes

Two reports evaluated the association of nicotine pouches with reproductive, developmental and pregnancy outcomes (**Table 24**).

- Developmental impacts: There is some evidence suggesting that nicotine pouches may have developmental impacts.
- Pregnant and breastfeeding women are considered high-risk if they use nicotine pouches due to the effects of nicotine on health during pregnancy and its passage into breast milk.

Table 24. Association of nicotine pouches with reproductive, developmental, and pregnancy outcomes as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	Effects from nicotine pouches: <u>Some evidence of harm</u> from snus or nicotine pouches was identified. This included <u>increased risks</u> of dependency and addiction, exposure to toxicants, cardiovascular impacts, chronic respiratory disease, or <u>developmental impacts</u> . Due to the relative newness of nicotine pouches and the lack of studies on snus, it is likely that more health outcomes will emerge over time. <i>Comparison group: not mentioned</i>
DE - BfR, 2022 (24)	Definition of high-risk groups: In terms of effects on health, the BfR defines the following high-risk groups: <u>Pregnant and breastfeeding women</u> , because of the <u>effects of nicotine</u> during <u>pregnancy and its passage into breast milk</u> . <i>Comparison group: not mentioned</i>

Source: JRC own production

3.3.1.6 Addiction, dependence and nicotine uptake

A total of three reports examined the role of nicotine pouches on addiction, dependence and nicotine uptake (**Table 25**). In summary, they state the following:

- Addiction and dependence: There is a risk associated with nicotine pouches, as they deliver sufficient nicotine to induce and sustain nicotine dependence and addiction.
- Nicotine: Nicotine is harmful to health.

Table 25. Association of nicotine pouches with addiction, dependence and nicotine uptake as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	<p>Addiction: Like all nicotine products there is a <u>risk of addiction</u>.</p> <p><i>Comparison group: not mentioned</i></p> <p>Effects from nicotine pouches: <u>Some evidence of harm</u> from snus or nicotine pouches was identified. This included <u>increased risks</u> of <u>dependency and addiction</u>, exposure to toxicants, cardiovascular impacts, chronic respiratory disease, or developmental impacts.</p> <p><i>Comparison group: not mentioned</i></p>
WHO TobReg, 2023 (21)	<p>Nicotine content and addiction: Nicotine pouches <u>deliver sufficient nicotine to induce and sustain nicotine addiction</u>.</p> <p><i>Comparison group: not mentioned</i></p> <p>Nicotine content and addiction: Uptake of nicotine pouches results in <u>exposure to toxic nicotine</u>, which may cause nicotine <u>addiction</u> and subsequently lead to use of other nicotine and tobacco products.</p> <p><i>Comparison group: not mentioned</i></p> <p>Harm from nicotine: Nicotine is <u>harmful</u> to health, including to the <u>nervous and cardiac systems</u>.</p> <p><i>Comparison group: not mentioned</i></p>
DE - BfR, 2022 (24)	<p>Harm from nicotine: For people who have not previously smoked or otherwise consumed nicotine, any form of nicotine consumption represents an increased risk to their health.</p> <p><i>Comparison group: non-smokers/nicotine consumers</i></p>

Source: JRC own production

3.3.1.7 Other outcomes

3.3.1.7.1 Overall health

Three reports examined the impact on nicotine pouches on overall health (**Table 26**).

- Other health outcomes: Due to limited studies on nicotine pouches, more health outcomes may emerge.
- Precautionary approach: To date, data on nicotine pouches is insufficient for a complete risk assessment, and a precautionary approach due to potential risks is recommended.

- Switching from cigarettes to nicotine pouches may represent a reduction in health risks, but measures should be taken to avoid increased nicotine intake.

Table 26. Association of nicotine pouches with overall health as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	<p>Effects from nicotine pouches: <u>Some evidence of harm</u> from snus or nicotine pouches was identified. This included increased risks of dependency and addiction, exposure to toxicants, cardiovascular impacts, chronic respiratory disease, or developmental impacts. Due to the relative newness of nicotine pouches and the lack of studies on snus, it is <u>likely</u> that <u>more health outcomes</u> will emerge over time.</p> <p><i>Comparison group: not mentioned</i></p> <p>Potential risks from nicotine pouches: The data identified in this table are <u>insufficient evidence</u> to provide a <u>fully informed risk assessment</u> for snus and nicotine pouches. As such, given the <u>potential risk to health</u>, it would be advisable to follow a precautionary principle to manage any risks of these products against an unknown benefit. This could include establishing strong monitoring pathways, and monitoring international data and evidence as it emerges.</p> <p><i>Comparison group: not mentioned</i></p>
WHO TobReg, 2023 (21)	<p>Potential risks from nicotine pouches: There are <u>few data</u> on nicotine pouches because they have been on the market for only a short time. A <u>cautionary approach</u> is warranted, given their similarities to conventional oral tobacco products, in particular snus.</p> <p><i>Comparison group: not mentioned</i></p> <p>Potential risks from nicotine pouches: They contain fewer toxicants and therefore expose users to fewer harmful and potentially harmful constituents than conventional tobacco products; however, no use of non-therapeutic nicotine and of tobacco products is recommended for <u>maximum protection of health</u>, as the benefits of quitting tobacco use are apparent almost immediately.</p> <p><i>Comparison group: conventional tobacco products</i></p>
DE - BfR, 2022 (24)	<p>Potential risk reduction: Keeping this model of <u>risk minimisation</u> in mind, switching from cigarettes to nicotine pouches could represent a <u>reduction in health risks</u> for a <u>person who smokes</u>. However, measures should be taken to avoid that use of nicotine pouches leads to a higher nicotine intake compared with other products on the market.</p> <p><i>Comparison group: conventional tobacco products</i></p>

Source: JRC own production

3.3.1.7.2 Other health outcomes

One report examined the effects of nicotine pouches on health outcomes beyond those previously mentioned, briefly stating that nicotine is harmful to the nervous system (**Table 27**).

Table 27. Association of nicotine pouches with other health outcomes as described by health-related organisations

Body, year	Statement
WHO TobReg, 2023 (21)	Harm from nicotine: Nicotine is <u>harmful</u> to health, including to the <u>nervous and cardiac systems</u> . <i>Comparison group: not mentioned</i>

Source: JRC own production

3.3.2 Gateway to smoking

One report assessed the role of nicotine pouches on initiation of conventional combustible cigarette smoking, stating that their use exposes users to addictive nicotine, which may lead to nicotine addiction and increase the risk of transitioning to other nicotine or tobacco products (**Table 28**).

Table 28. Association of nicotine pouches with initiation of conventional combustible cigarette smoking as described by health-related organisations.

Body, year	Statement
WHO TobReg, 2023 (21)	Potential to initiation of conventional combustible cigarette smoking: Up-take of nicotine pouches results in <u>exposure to toxic nicotine</u> , which may cause nicotine addiction and subsequently <u>lead to use of other nicotine and tobacco products</u> . <i>Comparison group: not mentioned</i>

Source: JRC own production

3.3.3 Smoking cessation

One report evaluated the role of nicotine pouches on cessation or reduction of conventional combustible cigarette smoking. This report highlights that nicotine pouches are a relatively new product with limited evidence supporting their safety or effectiveness as a smoking cessation tool (**Table 29**).

Table 29. Association of nicotine pouches with cessation or reduction of conventional combustible cigarette smoking as described by health-related organisations.

Body, year	Statement
NZ - MoH, 2024 (14)	Nicotine pouches as smoking cessation tool: Nicotine pouches are relatively new to the international market and, as such, <u>evidence</u> of their <u>safety and effectiveness</u> to help people stop smoking is <u>limited</u> . Most published data are from industry and show that nicotine pouches have substantially lower levels of toxicants compared to smoked tobacco. Like all nicotine products there is a risk of addiction. This review identified <u>no compelling evidence of any benefit</u> from the use of snus or nicotine pouches <u>as a smoking cessation tool</u> . Studies lacked population-level data, had limited information on exposure and health effects, and there was an absence of empirical studies on the <u>complete transition from smoking or nicotine use</u> with these products. <i>Comparison group: not mentioned</i>

Source: JRC own production

4 Challenges

The following challenges were identified. Some reports evaluated the association of nicotine as a substance with health outcomes rather than specifically assessing its effects in the context of its presence in e-cigarettes and other emerging products. In addition, on several occasions, it was not possible to differentiate between the association of ENDS and ENNDS with health outcomes, as this distinction was not made in the examined reports.

Moreover, dual use of conventional cigarettes with e-cigarettes or other emerging products was not thoroughly examined in the reviewed reports. We believe this is likely due to the complexity of assessing health outcomes related to dual use, given the uncertainty regarding the intensity and frequency of both conventional cigarette smoking and the use of emerging products. Additionally, it remains unclear whether dual use may lead to an accumulative or synergistic effect.

5 Conclusions

The majority of sources analysed for this JRC report focused on e-cigarettes, with fewer studies available on HTPs and nicotine pouches. This reflects the chronology of the introduction of the different products in the market together with the time lag until potential health outcomes manifest and can be studied. Due to the associations of these emerging products with certain short-term health outcomes and the lack of long-term evidence (since they have not been on the market long enough to reveal their long-term health impacts), some reports recommend adopting a precautionary approach toward e-cigarettes, HTPs, and nicotine pouches.

E-cigarettes

There is enough evidence to show that e-cigarettes are not harmless, and they have shown to be related to some adverse short- and medium-term outcomes, mainly in the cardiovascular and respiratory systems, and may have some tumorigenic and pregnancy impact. For ENDS, the amount of nicotine intake can be comparable to that from conventional combustible cigarettes, and they have potential to cause addiction and dependence.

Moreover, there are concerns surrounding the inhalation of nicotine, together with metals and other substances with unclear toxicity. Variation in substance content among different products further complicates assessing their effects. Although the evaluated reports state that, e-cigarettes may be less harmful than conventional tobacco, they still pose health risks and require long-term follow-up for accurate risk estimation. Moreover, e-cigarettes' long-term health risks remain uncertain due to limited evidence to date, as they have not been on the market long enough.

E-cigarettes may serve as a gateway for non-smokers to transition to conventional tobacco products, while the role of e-cigarettes as a smoking cessation tool remains unclear.

Heated tobacco products.

Heated tobacco products have been associated with cardiovascular and respiratory diseases and may also be associated with developmental and pregnancy outcomes. Moreover, there are concerns regarding exposure to substances with unclear toxicity and their addiction potential. However, more extensive follow-up is needed for accurate risk estimation.

None of the examined reports evaluated HTPs' role in conventional smoking initiation, and there is no evidence that HTPs are useful for smoking cessation.

Nicotine pouches

Nicotine pouches lack sufficient evidence on their health effects, primarily due to insufficient time on the market. Most evidence comes from nicotine content and its effects, and compared to tobacco products, they seem to deliver less toxicants and pollutants.

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List of abbreviations

Abbreviations	Definitions
AACR	American Association for Cancer Research
ASCO	American Society of Clinical Oncology
AU	Australia
BE	Belgium
BfR	Bundesinstitut für Risikobewertung (German Federal Institute for Risk Assessment)
CC	Conventional Cigarettes
CC16	Club cell 16-kDa secretory protein
CNS	Central Nervous System
CO	Carbon monoxide
Col	Conflict of Interests
COPD	Chronic Obstructive Pulmonary Disease
COT	Committee on Toxicity
DE	Deutschland (Germany)
DKFZ	Deutsches Krebsforschungszentrum (German Cancer Research Center)
DNA	Deoxyribonucleic acid
EC	Electronic cigarettes
ECHA	European Chemicals Agency
ECIS	European Cancer Information System
ENDS	Electronic Nicotine Delivery Systems
ENNDS	Electronic non-Nicotine Delivery Systems [other possible abbreviations: EN&NDS E(N)NDS]
ESR	Institute of Environmental Science and Research
EU	European Union
EVALI	E-cigarette or vaping use-associated lung injury
GLO	Commercial name of the HTP system by British American Tobacco
HDL	High-density lipoprotein
HGR	Hoge Gezondheidsraad (Superior Health Council)
HHS	Department of Health and Human Services

Abbreviations	Definitions
HPHC	Harmful and potentially harmful constituents
HTP	Heated tobacco product
IARC	International Agency for Research on Cancer
IQOS	Commercial name of the HTP system by Philip Morris International
JRC	Joint Research Center
LDL	Low-density lipoprotein
MHRA	Medicines and Healthcare products Regulatory Agency
MoH	Ministry of Health
MS	Member State
NASEM	National Academies of Sciences, Engineering, and Medicine
NHMRC	National Health and Medical Research Council
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NIPH	Norwegian Institute of Public Health
NL	Netherlands
NO	Norway
NPC	National Poisons Centre
NRT	Nicotine replacement therapy
NZ	New Zealand
OHID	Office for Health Improvement and Disparities
PAH	Polycyclic aromatic hydrocarbons
PHE	Public Health England
PWV	Pulse Wave Velocity
QA/QC	Quality assurance and quality control
RAC	Committee for Risk Assessment
RCP	Royal College of Physicians
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment)
RNAs	Ribonucleic Acids
SAE	Serious Adverse Events

Abbreviations	Definitions
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SERPR	Smokefree Environments and Regulated Products Regulations
SHC	Superior Health Council
sNOX2-dp	Soluble Nox2-derived peptide
SR	Systematic review
THC	Tetrahydrocannabinol
TSNA	Tobacco-specific nitrosamines
TobReg	WHO Study Group on Tobacco Product Regulation
UK	United Kingdom
US	United States
WHO	World Health Organization

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