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E-cigarettes, synthetic nicotine, heated-tobacco and smokeless nicotine delivery products: the nicotine landscape beyond combustible cigarettes

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Summary

Cigarette smoking remains an enormous public health problem causing millions of preventable deaths annually worldwide. Although safe and efficient smoking cessation pharmacotherapies such as nicotine replacement products and the medications varenicline and bupropion are available, long-term abstinence rates remain low and new approaches to help smokers successfully quit smoking are needed. In recent years, electronic nicotine delivery systems such as e-cigarettes and heated-tobacco products, and novel smokeless nicotine delivery products like nicotine pouches have gained widespread popularity. These products can deliver nicotine without combustion of tobacco and might thus present an alternative to the currently available smoking cessation methods if they prove able to help smokers quit smoking conventional cigarettes while decreasing their exposure to toxicants. In this narrative review, we provide a summary of the characteristics of these novel nicotine delivery products and the available data regarding their efficacy as smoking cessation tools and safety profile with a focus on the current situation in Switzerland.

Introduction

Tobacco smoking remains an enormous public health problem and one of the main preventable causes of mortality and morbidity, causing more than 8 million premature deaths worldwide every year [1]. According to data from Switzerland from the last decade, tobacco smoking causes approximately 9500 deaths annually in the country, while approximately 30% of the population are smokers [2]. According to the Tobacco Control Scale 2021 in Europe, Switzerland was the only participating country that had not ratified the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC), which includes policies such as bans on smoking in public spaces and workplaces and higher taxes on cigarettes and other tobacco products. The country was ranked second to last based on the total Tobacco Control Scale score [3].

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Tobacco smoking causes various health problems including cancer, heart and lung disease therefore persuading smokers to quit is crucial for public health. Although most smokers do want to quit, the strong addiction caused by nicotine can make this process very difficult [4–6]. Currently available pharmacotherapies to support smokers trying to quit include nicotine replacement products (such as long-acting nicotine patches and short-acting products such as nicotine gum, inhaler and spray), the α4β2 nicotinic acetylcholine receptor partial agonist varenicline, and the dopamine and noradrenaline reuptake inhibitor bupropion [5, 6]. The usual therapy duration is three months and combinations can be used in some cases (e.g. a long- and short-acting nicotine replacement product or a nicotine replacement product in combination with bupropion). Extensive research over the past few decades has shown that these pharmacotherapies are efficient and safe, yet smoking abstinence rates after 6–12 months still remain very low (<30%), which highlights the strong physical and psychological addiction caused by smoking, and the need for novel approaches in the context of smoking cessation [5, 6].

Nicotine is the main driver of addiction in tobacco cigarettes. However, numerous deleterious effects of smoking can be mainly attributed to other compounds. The combustion of tobacco has been shown to generate a plethora of carcinogenic and/or otherwise harmful toxicants [4, 6]. Means of delivering nicotine that do not involve combustion could be a useful tool for people trying to abstain from cigarette smoking, by alleviating their withdrawal symptoms and cravings without exposing them to harmful combustion products. Although this is in principle the mechanism of action of nicotine replacement products, they commonly lead to lower nicotine blood concentrations, with peak levels achieved less rapidly compared to smoking [7]. Since smokers have been shown to titrate their cigarette use in order to maintain satisfactory nicotine blood concentrations [8], providing smokers with inadequately low nicotine levels might cause relapse.

In recent years, electronic and non-electronic products designed to provide nicotine without the harmful substances contained in cigarette smoke have become widely popular.

Some of these products are capable of providing larger amounts of nicotine compared to the licensed nicotine replacement products while delivering fewer toxicants than tobacco cigarettes. An overview of various currently available nicotine products is provided in table 1.

However, although the body of evidence regarding the efficacy especially of e-cigarettes as smoking cessation tools is constantly growing, research on aspects such as their long-term safety profile is still sparse [14, 15]. Additionally, this market evolves quickly with newer products appearing constantly, which poses difficulties regarding the investigation of their characteristics, safety and toxicity profiles and the discussions regarding their regulation. Importantly, some of these products are popular among young people and are often marketed as lifestyle products, thus raising important risks from a public health view when previously nicotine-naïve individuals start using them.

Based on the nicotine risk continuum, a concept in harm reduction which places nicotine products in order of risk, with tobacco cigarettes at one end (highest risk) and nicotine replacement products at the other (lowest risk), switching from a high-risk to a lower-risk product should result in less harm to the user [16]. In this narrative review, we provide an overview of the current newer electronic and non-electronic delivery systems, the available data on their efficacy and safety in the context of smoking cessation and some of the implications related to public health and regulatory aspects, with a focus on the current situation in Switzerland.

Electronic nicotine delivery systems (ENDS)

Electronic cigarettes (e-cigarettes)

In Switzerland, in 2022, 1.7% of the overall population used e-cigarettes (also called "vaporisers") daily; the age group of 15–24-year-olds had the highest prevalence of monthly e-cigarette use (5.5%) and 32.3% reported having already tried vaping [17]. E-cigarettes were one of the first approaches for delivering nicotine without the combustion of tobacco; the original idea dates back to the 1960s (Gilbert HA, Smokeless non-tobacco cigarette US Patent [18]) and the first commercially launched e-cigarette was introduced in China in the early 2000s (Hon Lik, Ruyan) [19]. There have been several "generations" of e-cigarettes since: 1st generation devices (also called "cig-a-likes" due to their resemblance to combustible cigarettes) were non-rechargeable and non-reusable; they were followed by rechargeable and refillable 2nd generation e-cigarettes (usually "pen"- or "tank"-shaped) and then 3rd generation devices that commonly allowed the user to modify some of the settings such as power [20]. The newer 4th generation of "pod mod" devices are commonly discreet in design and easy to use, and can deliver nicotine in high concentrations [21]. Regardless of the generation, all e-cigarettes use a liquid ("e-liquid"), commonly containing nicotine, heated by the device to produce an aerosol (which is not smoke) that can then be inhaled by the user. Besides nicotine, e-liquids typically contain propylene glycol (PG) and vegetable glycerin (VG) in various ratios and flavours [22, 23]. First generation e-cigarettes contained nicotine in its free-base form, meaning that the nicotine is mainly non-

Table 1:
Overview of currently available nicotine products.

Product		Contains nicotine	Contains tobacco	Contains flavours	Contains synthetic nicotine	Temperature reached	Nicotine content	Description
Combustible	Tobacco cigarettes	+	+	(+)	–	640–780 °C [9]	~13.5 mg per cigarette (range: 11.9–14.5 mg); nicotine yield to users: 1–1.5 mg/cigarette [6]	Tobacco filled in paper; combustion
Electronic Nicotine Delivery Systems	"Heated tobacco"	+	+	(+)	–	~160–330 °C [9]	Nicotine delivery can be equal to conventional cigarettes	Tobacco sticks; non-complete combustion; pyrolysis occurs
	E-cigarettes	+	–	+	(+)	Typically 100–240 °C [9] (higher temperatures reached under e.g. dry conditions) [10]	E-liquid nicotine content from 0 to 20 mg/ml available in Switzerland. Nicotine delivery can be equal to tobacco cigarettes, depending on device, puffing behaviour and e-liquid constituents	Heats up liquid; propylene glycol and glycerine as main ingredients
Smokeless nicotine products	Snus	+	+	+	–	–	Depending on the strength, 12.8 mg on average per serving [11]	Tobacco-containing pouch placed under the lip
	Nicotine pouches	+	–	+	(+)	–	Depending on the strength, 1.79–47.5 mg/pouch (9.48 mg/pouch in median) [12]	Non-tobacco-containing pouch placed under the lip
Currently approved first-line nicotine replacement therapy	Patches	+	–	–	–	–	7–25 mg/patch, delivery dependent on duration of use [13]	Long-acting; transdermal nicotine delivery
	Gum	+	–	+	–	–	2–4 mg/gum [13]	Short-acting
	Inhaler	+	–	+	–	–	~15 µg per inhalation [13]	Short-acting; non-heated aerosol
	Spray	+	–	+	–	–	~1 mg per application [13]	Short-acting; liquid sprayed into mouth
	Lozenge	+	–	+	–	–	1–2 mg per lozenge [13]	Short-acting; dissolves in mouth
	Sublingual tablet	+	–	(+)	–	–	2 mg per tablet [13]	Short-acting; dissolves under the tongue

–: no or non-applicable; +: present; (+): optionally present.

protonated due to its alkaline environment. However, the newer "pod"-like devices commonly contain acidic additives to produce a protonated nicotine salt. Nicotine salt-containing liquids have been shown to be less irritating when inhaled and can thus deliver nicotine in higher concentrations without users finding it unpleasant [24]. This trend can also be seen in the e-liquid market, where free-base e-liquids typically contain lower concentrations than nicotine salt formulations [25]. Local regulations on maximum allowed nicotine concentrations exist in some countries (e.g. 20 mg/ml in Europe [26]), while in other countries, such as the United States, much higher concentrations are available. However, products on the market have been found to contain different amounts of nicotine than declared on the package and nicotine has also been found in products declared nicotine-free [27].

A more recent development is the use of synthetic nicotine in e-cigarettes, initially used by some companies in an effort to circumvent the U.S. Food and Drug Administration (FDA) regulations on tobacco products that were defined as "tobacco-derived" [28]. Although this loophole was closed in 2022, those products are still available on the market. Some users regard them as more "pure" due to their use of synthetic and not tobacco-derived nicotine, although the source of the nicotine does not correlate with the purity grade (for example, licensed nicotine replacement products also contain tobacco-derived nicotine). Another important aspect related to the use of synthetic nicotine is that tobacco-derived nicotine contains mainly (99%) the *S*-nicotine enantiomer, while synthetic nicotine products can be pure *S*-nicotine or a racemic mixture, containing both enantiomers (*S*- and *R*-) [28–30]. While the effects of tobacco-derived nicotine in humans have been intensively studied in the past decades, the effects and pharmacological characteristics of the *R*-nicotine enantiomer in humans mainly remain unknown. Currently available data shows different disposition kinetics of the enantiomers in some animal species and a lower potency of *R*-nicotine at nicotine receptors [28, 31–33]. Such effects could have relevant health implications for users and need to be considered for further regulation policies.

Other components of e-liquids with potential implications regarding patterns of use and safety are the various flavourants. There are currently thousands of different flavours available, ranging from more "traditional" ones like tobacco and menthol to the more "creative" ones such as candies, fruits and beverages [34]. While offering a variety of flavours might be helpful for smokers seeking to quit by increasing the taste appeal of these alternative products, concerns regarding flavours include advertising targeted at young people, e.g. with candy- and sweet-like flavours, and the toxicological properties of the particular flavours. This has led some countries to restrict all or some flavours (e.g. only tobacco and menthol flavours can be sold without authorisation in cartridge-based e-cigarettes in the United States [35]). Diacetyl, which is associated with pulmonary dysfunction (bronchiolitis obliterans) in occupationally heavily-exposed workers (first discovered in popcorn manufacturing), has been found in some e-liquids as a flavourant compound [36], but at lower levels than in tobacco cigarette smoke [37]. A toxicological assessment concludes that exposure to diacetyl from e-cigarettes is associated with a significantly increased non-carcinogenic pulmonary health risk [38]. Benzaldehyde, a respiratory irritant, has been found in higher concentrations in cherry-flavoured than other e-liquids and often higher than in tobacco cigarette smoke, however at levels >1000 times below occupational exposure [39]. Cinnamon flavour is also of concern, related to cinnamaldehyde levels, as in vitro studies have shown a dose-dependent impairment of mitochondrial function and glycolysis [40]. Flavour aldehydes can also react with other components of the e-liquid, leading to unpredictable toxicological properties [41]. Importantly, even if many of these flavourants are in general considered safe when added in products intended to be ingested, this doesn't necessarily translate to safety when inhaled [21, 36, 38]. Furthermore, metals can transfer from heating coils to e-liquids [42], thereby posing potential health risks. Of special note in this context are also the e-cigarette or vaping-associated lung injury (EVALI) cases reported in the United States during the summer of 2019, which were later associated with the use of tetrahydrocannabinol (THC)-containing e-liquids adulterated with vitamin E acetate [14]. There is little evidence that vitamin E acetate was present in nicotine e-cigarettes, but this does point to the possibility that adulterants can have unexpected serious adverse consequences. In general, although long-term safety data is still missing, e-cigarettes, when used as intended by the manufacturer, appear not to cause significant adverse effects when used as short-term substitutes for tobacco cigarettes. In the context of smoking cessation, safety should also be seen in relation to the alternative, i.e. continuation of combustible cigarette smoking, which is expected to be much more harmful than the use of e-cigarettes. However, at the same time it is important to discourage the use of such products among non-smokers and especially young people. It is noteworthy that data from the United States shows a historical decrease in smoking prevalence among adolescents in recent years while the prevalence of e-cigarette use has increased at the same time, which might indicate that vaping displaces tobacco cigarettes for some who would have otherwise started to smoke [43]. However, other data does not support this hypothesis [44], and it cannot be excluded that vaping acts as a gateway to smoking for some [43].

In addition to toxicity and safety, data on the efficacy of e-cigarettes as smoking cessation aids is needed to inform decisions regarding their regulation and their potential future inclusion as approved alternatives to established evidence-based smoking cessation therapies. However, many vapers currently use e-cigarettes for pleasure and not as an alternative to combustible products, and might choose to continue their use even after successful smoking cessation. Although the nicotine blood concentrations reached can vary widely depending on the device and the e-liquid formulation used, some e-cigarettes have been found to reach similar concentrations as combustible cigarettes [45, 46]. With standardised puffing to resemble cigarette smoking, the pharmacokinetic curve of e-cigarette usage is similarly shaped to smoking a combustible cigarette, which implicates addictive potential [47]. However, most e-cigarette users do not vape in the same pattern as a cigarette is smoked, but rather take smaller clusters of puffs at frequent intervals throughout the day.

Although high-quality smoking cessation studies using e-liquid formulations and e-cigarettes of the latest generations and long-term safety outcomes are still relatively sparse, a recent study from the UK found double the abstinence rates with e-cigarettes compared to nicotine replacement products (18% vs 9.9%) [48]. A large pragmatic study recently conducted in Switzerland found that the addition of e-cigarettes to the smoking cessation toolkit significantly increased continuous tobacco abstinence at 6 months (28.9% vs 16.3%) [49]. The regularly updated Cochrane review concluded that, despite the limitation of only a small number of high-quality randomised clinical trials, there is currently high-certainty evidence that nicotine-containing e-cigarettes can increase abstinence rates compared to nicotine replacement products [14]. Currently, the above-mentioned Swiss trial is still active, with follow-ups of up to 60 months planned, and is expected to provide evidence on the long-term efficacy and safety of these products [49]. The growing evidence of safety and efficacy supports the addition of e-cigarettes to the currently available tools for smoking cessation and current cautious positions on e-cigarettes might need to be reconsidered [50].

As suggested by the high number of participants who continued using e-cigarettes after one year in the Hajek et al. study (80% vs 9% for nicotine replacement therapy) [48], quitting vaping can also prove difficult for the majority of users, even after quitting smoking of combustible cigarettes. Data on how to effectively assist e-cigarette users who would like to quit vaping is sparse and therapies that work for smoking cessation are largely unproven. A recent randomised clinical trial investigated the efficacy of varenicline in e-cigarette users and found higher continuous abstinence rates during active treatment and after 3 months' follow-up of no intervention compared to placebo [51], while there are also first reports of a benefit of cytisine in vaping cessation [52]. Another randomised clinical trial investigated a text message-based vaping cessation programme and found higher 30-day point prevalence abstinence rates compared to controls; however, the primary outcome was self-reported [53]. Vaping cessation guidances exist but are largely based on translatability of results from smoking cessation studies [54].

Treatment options for smoking cessation in pregnant smokers are quite limited, with both varenicline and bupropion having safety concerns regarding use during pregnancy [55], thus nicotine replacement therapy is often used first-line. Even though there are concerns about nicotine use during pregnancy in general, nicotine replacement is routinely used by smoking cessation counselling services, as it is considered safer than continuing smoking [56]. A large clinical trial comparing e-cigarettes and nicotine patches in pregnant smokers found that e-cigarettes were twice as effective as nicotine patches when accounting for cross-overs, had similar safety as nicotine patches and decreased the incidence of low birth weight [57]. In people with preexisting cardiovascular disease, e-cigarettes might contribute to acute cardiovascular events through the sympathomimetic effects of nicotine, but with a risk substantially lower than with tobacco smoking [58]. Exclusive e-cigarette use was not associated with cardiovascular disease in observational studies [59].

Regulation of e-cigarettes varies widely between countries: some countries give more consideration to the potential benefits of smoking cessation, including e-cigarettes in their official stop-smoking intervention guidelines (e.g. UK [60]); others have banned nicotine-containing e-liquids completely (e.g. Japan [61]) or made them available only with a physician's prescription (e.g. Australia [62]). In Switzerland, nicotine-containing e-liquids are currently available in concentrations up to 20 mg/ml nicotine. Until October 2024, e-cigarettes were regulated under the law on alimentary goods; however, under the new law, they are classified as tobacco products, with sales to minors explicitly prohibited [63, 64]. Until this change in legislation, there was no age limit for the purchase of nicotine-containing e-liquids at a national level, but some cantons had banned their sale to minors [65]. In Switzerland, there is currently insufficient surveillance data on the use of e-cigarettes (e.g. prevalence of specific products and devices), especially of newer products such as those containing synthetic nicotine [65].

In general, although more data is needed to adequately evaluate the efficacy of e-cigarettes as smoking cessation aids and their potential long-term health risks, future debates in this area should include a balanced weighing up of the potential benefits and risks of these products. The relative risk might be beneficial for certain populations, as they could represent a safer alternative to combustible cigarettes for smokers trying to quit. At the same time however, the absolute risk is of concern for minors and non-smokers and policies to limit e-cigarette use among young people are needed. It should be noted however that very strict restrictions might lead to people seeking other ways to purchase these products (as evidenced by a growing black market in Australia [66]) or smokers relapsing to combustible cigarettes (as seen after the tax increase for e-cigarettes in Minnesota [67]). Dual use of tobacco cigarettes and e-cigarettes is common when smokers begin experimenting with e-cigarettes as a substitute for smoking and might be needed for some time before they can definitively quit smoking. Sustained dual use should be discouraged as the relationship between number of cigarettes per day and cardiovascular risk is non-linear (relevant risk present also with smoking of a very low number of cigarettes per day) [68] and the toxicant exposure has been shown to be reduced with exclusive e-cigarette use but not necessarily with dual use of e-cigarettes and combustible cigarettes [69]. The ideal end goal for minimising health risks should be tobacco and e-cigarette abstinence in general, but total nicotine abstinence might not be possible for some heavily addicted smokers in whom continued use of e-cigarettes instead of tobacco cigarettes might still represent a useful harm-reduction tool.

"Heated-tobacco" products

"Heated-tobacco" products (also called "heat-not-burn") represent another category of electronic nicotine delivery systems. Instead of heating a liquid, these devices deliver nicotine by heating tobacco to a temperature of approximately 160–330 °C, lower than the temperatures reached by conventional cigarettes (~800 °C) [9]. In Switzerland, the currently available heated-tobacco products have been on the market since 2015, were defined as "other tobacco

products" until October 2024, but are now regulated as "tobacco products" [64, 70]. Although currently available in many countries, their popularity varies depending on the region, with countries such as Japan and South Korea among those with the highest prevalence of use [61, 71, 72]. Since the introduction of heated-tobacco products in Japan in 2016, tobacco cigarette sales have seen an accelerated decline, suggesting that these newer products are used as alternatives to the latter [73, 74]. However, this association is purely observational and other factors could have caused this decline, a decrease in sales does not necessarily translate to increased smoking cessation numbers and the situation in Japan does not necessarily translate to other countries. Longitudinal data suggests that heated-tobacco product use does not contribute to quitting among current smokers nor prevent former smokers from relapsing [75]. In Italy, tobacco cigarette smoking prevalence has increased for the first time in decades since the introduction of electronic nicotine delivery systems (heated-tobacco products and e-cigarettes), highlighting the importance of the environment in which these products exist [76].

Heated-tobacco products are often advertised as less harmful alternatives to conventional cigarettes due to the lack of combustion [9, 61]. In 2020, the FDA authorised advertising of certain heated-tobacco products with "reduced exposure" statements but denied "reduced risk" claims [77]. Toxicants are produced even in the absence of combustion and setting a "safe" temperature limit is difficult [9]. Although a reduced exposure to some toxicants commonly found in tobacco smoke has been reported, some studies have found higher exposures to other toxicants [78]. Based on data from surveys, heated-tobacco products are sometimes perceived as equally or more harmful than e-cigarettes and as less harmful than tobacco cigarettes, albeit not as often as e-cigarettes [79]. However, it is currently still challenging to position such products on the continuum of risk for tobacco products in comparison to other currently available nicotine and tobacco products [80, 81]. A particular challenge is that most current studies with heated-tobacco products are tobacco industry-sponsored and there is generally less data available compared to other electronic nicotine delivery systems such as e-cigarettes [15]. A Cochrane review aiming to investigate the available evidence for heated-tobacco products in the context of smoking cessation stated that cessation was not reported in any of the included studies and that there is currently moderate-certainty evidence that these products lead to lower toxicant exposures compared to conventional cigarettes [15].

Non-electronic smokeless nicotine delivery products

Various smokeless tobacco and nicotine products exist in different regions of the world. For example, in South-East Asia lime-flavoured tobacco leaf flakes called zarda are often chewed in combination with betel quid; in South America, mainly Venezuela, a cooked tobacco paste called chimó is used by placing it under the tongue or between the lip and the gum [82]. In some parts of Europe, snus has traditionally been the predominant form of tobacco consumption. It originated in Sweden and has a long tradition of use in Nordic European countries [83]. Snus is moistened ground tobacco, which is often mixed with flavourants and sold loose or in portioned sachets. Users place snus between the upper lip and the gum, where its constituents, such as nicotine, are absorbed through the oral mucosa. Nicotine pouches are products that look very similar to snus and have entered the market in recent years. They are sachets filled with a cellulose matrix containing nicotine, flavourants and other adjuvants [84]. However, an important difference between snus and nicotine pouches is that the latter do not contain tobacco.

The sale of snus, as with all oral tobacco products, has been banned in the European Union since 1992. However an exemption was granted to Sweden when it joined the European Union in 1995, owing to its long historical use of the product [85]. Switzerland banned snus in 1995, but lifted the ban in 2019 [86]. However, the sale of nicotine pouches was never prohibited by the European Union or Switzerland, as they do not contain tobacco and are therefore not covered by these regulations. Nevertheless, the regulation of nicotine pouches within the European Union varies widely as the Netherlands and Belgium both banned their sale in 2023 [87]. In Switzerland, 2% of the population reported using snus or nicotine pouches in 2022. Users are commonly young (6.5% of the 15–24 vs 0.6% of the 45–64 year age groups) and male (3.5% of men vs 0.6% of women) [17]. In comparison, use of snus in Sweden is much more widespread with 17.1% of the population using snus in 2022. While – similarly to Switzerland – men were more likely to use snus than women (23.7% vs 10.4%), age differences were less pronounced (21.6% of 16–29-year-olds vs 17.5% of 45–64-year-olds) [88]. In the United States, nicotine pouches entered the market in 2016, whereas they were introduced in Europe in 2018 [87]. In a survey conducted in the United States in 2022, 14% of 15–24-year-olds reported past-30-day use of nicotine pouches [89]. According to data from Norway, a decline in smoking prevalence has been seen with a simultaneous increase of snus prevalence, especially among young women [90]. In 2019, the FDA granted for the first time a modified-risk tobacco product status, which was given to specific snus products [91]. This status allows certain manufacturers to actively promote these products with a reduced harm claim. Similarly to e-cigarettes, many countries' regulations fail to cover nicotine pouches containing synthetic nicotine [92].

Snus and nicotine pouches have similar pharmacokinetic properties [93] and can therefore be viewed similarly for many aspects of abuse liability and their potential role in smoking cessation therapy. However, while nicotine content in snus is reported to be relatively uniform without any massive outliers (average of 12.4 mg per pouch) [11, 94], some nicotine pouches have been reported to contain up to 47.5 mg nicotine [12]. Furthermore, manufacturers often describe the strength of nicotine pouches with arbitrary scoring systems or descriptors, such as "easy", "medium" or "extreme", without any clear label such as "mg nicotine per pouch" or "mg per gram". Compared to combustible cigarettes, snus and nicotine pouches can reach similar nicotine peak concentrations (C_{max}) and exposure (estimated by the area under the concentration-time curve [AUC]). However, the time to peak concentration (t_{max}) of 60 min is longer than with combustible cigarettes (approximately 2 min after finishing smoking) [95, 96]. Rapid systemic uptake is a crucial determinant of abuse liability, with faster

uptake leading to stronger reinforcement [97]. Therefore, snus and nicotine pouches can be expected to have less abuse liability than combustible cigarettes. Nevertheless, snus can cause strong addiction, as highlighted by a Swedish survey in which participants reported using snus a median of 70% of their daily waking hours [98]. At the same time, rapid uptake of nicotine is also a determinant of how satisfactory these products are [99], since slow or inadequate delivery of nicotine might not be satisfying enough for users, leading to failure to compete with and replace tobacco cigarettes. There is thus a connection between abuse liability, satisfaction and competitiveness of nicotine products that needs to be considered in the context of regulatory discussions and decisions.

Unlike cigarette smoking, snus does not expose users to toxicants generated by combustion of tobacco. Nevertheless, snus contains various known toxicants and carcinogens, of which tobacco-specific nitrosamines (TSNA) are the most prevalent [100]. Tobacco-specific nitrosamines are generated during curing of tobacco and are present in all tobacco products. However, large regional differences exist. Snus from e.g. the United States commonly contains higher levels of tobacco-specific nitrosamines than snus from northern European countries (Swedish-style snus) [101]. This can be largely attributed to voluntary quality standards introduced by the industry for Swedish-style snus [83], leading to decreases in tobacco-specific nitrosamine levels of 85% between 1983 and 2004 [102]. Use of smokeless tobacco products has been associated with adverse health outcomes in studies from the United States. It has been found to be associated with a higher prevalence of oral cancer [103], stroke and heart disease [104], whereas mixed results exist for overall mortality [105] compared to no use. Studies investigating Swedish-style snus on the other hand found no association with oral cancer [106], whereas there seems to be an increased risk of oesophageal and pancreatic cancer [107]. Pooled analyses of prospective studies conducted in Sweden found no increased risk of myocardial infarction and stroke in snus users [108, 109] whereas other studies found increased risk of stroke in snus users who never smoked [110] and nearly halved mortality risk in snus users who quit after myocardial infarction [111]. There is evidence for higher overall mortality for snus users, even after accounting for smoking [112]. In summary, the evidence indicates that the risk of oral cancer in particular and total cancer in general are much lower with the use of snus compared to cigarette smoking [107, 113]. In general, the consumption of smokeless tobacco seems to be less harmful in Sweden than in other regions such as the United States, which can most likely be explained by reduced toxicant levels [105].

Nicotine pouch manufacturers often advertise their products with direct or indirect health claims, depending on the countries' respective advertising regulations. For example, in Switzerland, some manufacturers advertise their products with statements such as "99% less toxicants" [114], while in the United States manufacturers use indirect health claims by stating that their products are "smoke-free" or "tobacco-free" [115]. Recent studies show that nicotine pouches contain very low levels of tobacco-specific nitrosamines; however traces can still be found in some products [12, 116]. Compared to licensed nicotine replacement products, which are manufactured according to high pharmaceutical standards, tobacco-specific nitrosamine traces seem to be higher in nicotine pouches, reflecting their laxer regulation [12]. Other toxicants known to be present in tobacco smoke or oral tobacco, such as metals or volatile organic compounds, are lower/not detectable in nicotine pouches compared to snus or tobacco cigarettes [116]. Only formaldehyde has been found in comparable levels to snus, however it probably represents no toxicological concerns at such low levels [116]**.** In a study from the same research group, users of nicotine pouches were compared to never smokers and had comparable levels of biomarkers of exposure to known toxicants, such as tobacco-specific nitrosamines, volatile organic compounds or polycyclic aromatic hydrocarbons [117]. Long-term studies of health outcomes in nicotine pouches users are still lacking.

Studies on cessation of smokeless tobacco products have mostly investigated the same evidence-based therapies that are used for smoking cessation. The current knowledge has been summarised in a Cochrane meta-analysis [118]: Most available data is on varenicline, which seems to have a positive effect (relative risk [RR] 1.34, confidence interval [CI] 1.08–1.68), while a possible benefit of bupropion was inconclusive, partly due to a low number of overall participants (RR 0.89, CI 0.54–1.44). Nicotine lozenges seem to increase abstinence rates (RR 1.36, CI 1.17–1.59), however confidence in this effect seems limited due to risk of bias. Other nicotine replacement therapies, such as nicotine patches (RR 1.13, CI 0.93–1.37) or nicotine gums (RR 0.99, CI 0.68–1.43), do not seem to have a positive effect. The efficacy of these pharmacological interventions seems to be lower than in smoking cessation. Similarly to tobacco cigarette smokers, behavioural interventions, such as telephone support (RR 1.77, CI 1.57–2.00), can increase abstinence rates [118].

The smokeless nicotine market is dynamic as novel products continue to appear. New products often follow the trend of pharmaceuticalisation in the tobacco industry [119], so that recreational nicotine products more strongly resemble approved nicotine replacement therapies. More niche products include dissolvable products, such as lozenges or gums for recreational use or nicotine toothpicks [120]. While dependence on licensed nicotine replacement products among never-smokers is relatively uncommon [121], these products are also not targeted at never-smokers. In the United States, recreational nicotine lozenges and gums are sold by major tobacco manufacturers [122]. Although they resemble approved nicotine replacement therapy products, they are sold in various sweet or fruity flavours (e.g. mango or citrus), are not approved for cessation therapy and specifically target recreational users [122]. Furthermore, flavoured nicotine gummies are sold, which clearly resemble candies [122], raising again major concerns about their appeal to children and young adolescents [120].

Conclusion

Potential new approaches to assist smokers willing to quit by providing to them nicotine without the step of tobacco combustion include electronic systems such as e-cigarettes and "heated tobacco" and non-electronic products such as

nicotine pouches that – in contrast to snus – do not contain tobacco. Evidence-based education of the public about the potential risks of the various currently available nicotine products and their place in the nicotine harm continuum [16] is pivotal to promote smoking cessation among adult smokers and to prevent their use by young people [123]. However, in this highly dynamic market with new products constantly appearing within a currently still lax regulatory environment, it is difficult for research to keep pace by conducting in-depth studies on their potential efficacy and toxic effects. Further challenges include the establishment of adequate regulations in order to promote smoking cessation while at the same time protecting vulnerable populations such as young people from nicotine addiction and toxicant exposure. Independent randomised clinical trials as well as policy analyses and social science research investigating the questions mentioned above are urgently needed to provide the necessary basis to address these uncertainties and lead future discussions. Nevertheless, current data has already provided reasonable grounds for adding e-cigarettes to toolkits in smoking cessation therapy and cautious positions might need to be reconsidered. Smokers willing to quit should be encouraged to use approved smoking cessation therapies as first-line and to avoid dual use of tobacco cigarettes if they decide to use an alternative nicotine product; at the same time it is crucial to discourage use by young people and non-smokers [123].

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. *NB* serves as a consultant to Achieve Life Sciences and Qnovia, companies that are developing new smoking cessation medications, and has been an expert witness in litigation against tobacco companies. *EL* reports smoking cessation counselling as part of clinical work at the University Hospital of Bern, Switzerland, and academic institution research support for investigation of the pharmacology and toxicology of e-cigarettes. All authors declare that they have no conflict of interest in relation to the content of this work. No other potential conflict of interest related to the content of this manuscript was disclosed.

References

1. World Health Organization (WHO). Tobacco, Overview. 2024; Available from: https://www.who.int/health-topics/tobacco#tab=tab_1
2. Federal Department of Home Affairs FDHA. Zahlen & Fakten: Tabak. 2023; Available from: www.bag.admin.ch
3. Joossens L, Olefir L, Feliu A, Fernandez E. The Tobacco Control Scale 2021 in Europe, C.I.o.O. Brussels: Smoke Free Partnership, Editor. 2022.
4. Benowitz NL. Nicotine addiction. N Engl J Med. 2010 Jun;362(24):2295–303. http://dx.doi.org/10.1056/NEJMra0809890.
5. Rigotti NA, Kruse GR, Livingstone-Banks J, Hartmann-Boyce J. Treatment of Tobacco Smoking: A Review. JAMA. 2022 Feb;327(6):566–77. http://dx.doi.org/10.1001/jama.2022.0395.
6. Prochaska JJ, Benowitz NL. Current advances in research in treatment and recovery: nicotine addiction. Sci Adv. 2019 Oct;5(10):eaay9763. http://dx.doi.org/10.1126/sciadv.aay9763.
7. Rigotti NA. Strategies to help a smoker who is struggling to quit. JAMA. 2012 Oct;308(15):1573–80. http://dx.doi.org/10.1001/jama.2012.13043.
8. Benowitz NL. Clinical pharmacology of nicotine: implications for understanding, preventing, and treating tobacco addiction. Clin Pharmacol Ther. 2008 Apr;83(4):531–41. http://dx.doi.org/10.1038/clpt.2008.3.
9. Auer R, Diethelm P, Berthet A. Heating Tobacco Sticks Instead of Combusting Conventional Cigarettes and Future Heart Attacks: Still Smoke, and Risk. Circulation. 2021 Nov;144(19):1539–42. http://dx.doi.org/10.1161/CIRCULATIONAHA.121.056959.
10. Chen W, Wang P, Ito K, Fowles J, Shusterman D, Jaques PA, et al. Measurement of heating coil temperature for e-cigarettes with a “top-coil” clearomizer. PLoS One. 2018 Apr;13(4):e0195925. http://dx.doi.org/10.1371/journal.pone.0195925.
11. Vedøy TF, Lund KE. Nicotine Content in Swedish-Type Snus Sold in Norway From 2005 to 2020. Nicotine Tob Res. 2022 Jun;24(7):1130–3. http://dx.doi.org/10.1093/ntr/ntac006.
12. Mallock N, Schulz T, Malke S, Dreiack N, Laux P, Luch A. Levels of nicotine and tobacco-specific nitrosamines in oral nicotine pouches. Tob Control. 2024 Feb;33(2):193–9. http://dx.doi.org/10.1136/tc-2022-057280.
13. Refdata. Swissmedic Arzneimittelinformation-Publikationssystem (AIPS); Available from: http://www.swissmedicinfo.ch/
14. Lindson N, Butler AR, McRobbie H, Bullen C, Hajek P, Begh R, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2024 Jan;1(1):CD010216.
15. Tattan-Birch H, Hartmann-Boyce J, Kock L, Simonavicius E, Brose L, Jackson S, et al. Heated tobacco products for smoking cessation and reducing smoking prevalence. Cochrane Database Syst Rev. 2022 Jan;1(1):CD013790.
16. McNeill A, Munafò MR. Reducing harm from tobacco use. J Psychopharmacol. 2013 Jan;27(1):13–8. http://dx.doi.org/10.1177/0269881112458731.
17. Bundesamt für Gesundheit BAG, Erhebung Gesundheit und Lifestyle 2022. 2023. Available from: https://www.bag.admin.ch/bag/de/home/das-bag/ressortforschung-evaluation/forschung-im-bag/forschung-nichtuebertragbare-krankheiten/monitoring-systemncd/erhebung-gesundheit-lifestyle/erhebung-gesundheit-lifestyle-2022.html
18. Gilbert HA. Smokeless non-tobacco cigarette, U.S.P. Office, Editor. 1963. Available from: https://patents.google.com/patent/US3200819A/en
19. Caponnetto P, Campagna D, Papale G, Russo C, Polosa R. The emerging phenomenon of electronic cigarettes. Expert Rev Respir Med. 2012 Feb;6(1):63–74. http://dx.doi.org/10.1586/ers.11.92.
20. Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, et al.; American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Electronic cigarettes: a policy statement from the American Heart Association. Circulation. 2014 Oct;130(16):1418–36. http://dx.doi.org/10.1161/CIR.0000000000000107.
21. Barrington-Trimis JL, Samet JM, McConnell R. Flavorings in electronic cigarettes: an unrecognized respiratory health hazard? JAMA. 2014 Dec;312(23):2493–4. http://dx.doi.org/10.1001/jama.2014.14830.
22. Orellana-Barrios MA, Payne D, Mulkey Z, Nugent K. Electronic Cigarettes—A Narrative Review for Clinicians. Am J Med. 2015 Jul;128(7):674–81. http://dx.doi.org/10.1016/j.amjmed.2015.01.033.
23. Etter JF, Bullen C, Flouris AD, Laugesen M, Eissenberg T. Electronic nicotine delivery systems: a research agenda. Tob Control. 2011 May;20(3):243–8. http://dx.doi.org/10.1136/tc.2010.042168.
24. Barua RS, Rigotti NA, Benowitz NL, Cummings KM, Jazayeri MA, Morris PB, et al. 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2018 Dec;72(25):3332–65. http://dx.doi.org/10.1016/j.jacc.2018.10.027.
25. Jackler RK, Ramamurthi D. Nicotine arms race: JUUL and the high-nicotine product market. Tob Control. 2019 Nov;28(6):623–8. http://dx.doi.org/10.1136/tobaccocontrol-2018-054796.
26. European Commission. EU Rules on Tobacco Products. 2016; Available from: https://health.ec.europa.eu/document/download/7223d20d-4dad-451e-bcc7-ac134fb6d1d7_en?filename=tobacco_info-graph2_en.pdf
27. Taylor A, Dunn K, Turfus S. A review of nicotine-containing electronic cigarettes-Trends in use, effects, contents, labelling accuracy and detection methods. Drug Test Anal. 2021 Feb;13(2):242–60. http://dx.doi.org/10.1002/dta.2998.
28. Jordt SE. Synthetic nicotine has arrived. Tob Control. 2023 Apr;32 e1:e113–7. http://dx.doi.org/10.1136/tobaccocontrol-2021-056626.
29. Zhang H, Pang Y, Luo Y, Li X, Chen H, Han S, et al. Enantiomeric composition of nicotine in tobacco leaf, cigarette, smokeless tobacco, and e-liquid by normal phase high-performance liquid chromatography. Chirality. 2018 Jul;30(7):923–31. http://dx.doi.org/10.1002/chir.22866.
30. Berman ML, Zettler PJ, Jordt SE. Synthetic Nicotine: Science, Global Legal Landscape, and Regulatory Considerations. World Health Organ Tech Rep Ser. 2023;1047:35–60.
31. Jacob P 3rd, Benowitz NL, Copeland JR, Risner ME, Cone EJ. Disposition kinetics of nicotine and cotinine enantiomers in rabbits and beagle

dogs. J Pharm Sci. 1988 May;77(5):396–400. http://dx.doi.org/10.1002/jps.2600770508.
32. Ikushima S, Muramatsu I, Sakakibara Y, Yokotani K, Fujiwara M. The effects of d-nicotine and l-isomer on nicotinic receptors. J Pharmacol Exp Ther. 1982 Aug;222(2):463–70.
33. Nwosu CG, Godin CS, Houdi AA, Damani LA, Crooks PA. Enantioselective metabolism during continuous administration of S-(-)- and R-(+)-nicotine isomers to guinea-pigs. J Pharm Pharmacol. 1988 Dec;40(12):862–9. http://dx.doi.org/10.1111/j.2042-7158.1988.tb06289.x.
34. Krüsemann EJ, Boesveldt S, de Graaf K, Talhout R. An E-Liquid Flavor Wheel: A Shared Vocabulary Based on Systematically Reviewing E-Liquid Flavor Classifications in Literature. Nicotine Tob Res. 2019 Sep;21(10):1310–9. http://dx.doi.org/10.1093/ntr/nty101.
35. US Food and Drug Administration. FDA finalizes enforcement policy on unauthorized flavored cartridge-based e-cigarettes that appeal to children, including fruit and mint. 2020; Available from: https://www.fda.gov/news-events/press-announcements/fda-finalizes-enforcement-policy-unauthorized-flavored-cartridge-based-e-cigarettes-appeal-children
36. Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P, Stewart JH, et al. Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes. Environ Health Perspect. 2016 Jun;124(6):733–9. http://dx.doi.org/10.1289/ehp.1510185.
37. Fujioka K, Shibamoto T. Determination of toxic carbonyl compounds in cigarette smoke. Environ Toxicol. 2006 Feb;21(1):47–54. http://dx.doi.org/10.1002/tox.20153.
38. White AV, Wambui DW, Pokhrel LR. Risk assessment of inhaled diacetyl from electronic cigarette use among teens and adults. Sci Total Environ. 2021 Jun;772:145486. http://dx.doi.org/10.1016/j.scitotenv.2021.145486.
39. Kosmider L, Sobczak A, Prokopowicz A, Kurek J, Zaciera M, Knysak J, et al. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. Thorax. 2016 Apr;71(4):376–7. http://dx.doi.org/10.1136/thoraxjnl-2015-207895.
40. Effah F, Taiwo B, Baines D, Bailey A, Marczylo T. Pulmonary effects of e-liquid flavors: a systematic review. J Toxicol Environ Health B Crit Rev. 2022 Oct;25(7):343–71. http://dx.doi.org/10.1080/10937404.2022.2124563.
41. Erythropel HC, Jabba SV, DeWinter TM, Mendizabal M, Anastas PT, Jordt SE, et al. Formation of flavorant-propylene Glycol Adducts With Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids. Nicotine Tob Res. 2019 Aug;21(9):1248–58. http://dx.doi.org/10.1093/ntr/nty192.
42. Zervas E, Matsouki N, Kyriakopoulos G, Poulopoulos S, Ioannides T, Katsaounou P. Transfer of metals in the liquids of electronic cigarettes. Inhal Toxicol. 2020 May;32(6):240–8. http://dx.doi.org/10.1080/08958378.2020.1776801.
43. Meza R, Jimenez-Mendoza E, Levy DT. Trends in Tobacco Use Among Adolescents by Grade, Sex, and Race, 1991-2019. JAMA Netw Open. 2020 Dec;3(12):e2027465. http://dx.doi.org/10.1001/jamanetworkopen.2020.27465.
44. Pierce JP, Luo M, McMenamin SB, Stone MD, Leas EC, Strong D, et al. Declines in cigarette smoking among US adolescents and young adults: indications of independence from e-cigarette vaping surge. Tob Control. 2023 Nov8:tc-2022–057907. http://dx.doi.org/10.1136/tc-2022-057907.
45. Hajek P, Pittaccio K, Pesola F, Myers Smith K, Phillips-Waller A, Przulj D. Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. Addiction. 2020 Jun;115(6):1141–8. http://dx.doi.org/10.1111/add.14936.
46. O'Connell G, Pritchard JD, Prue C, Thompson J, Verron T, Graff D, et al. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. Intern Emerg Med. 2019 Sep;14(6):853–61. http://dx.doi.org/10.1007/s11739-019-02025-3.
47. St Helen G, Havel C, Dempsey DA, Jacob P 3rd, Benowitz NL. Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes. Addiction. 2016 Mar;111(3):535–44. http://dx.doi.org/10.1111/add.13183.
48. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. N Engl J Med. 2019 Feb;380(7):629–37. http://dx.doi.org/10.1056/NEJMoa1808779.
49. Auer R, Schoeni A, Humair JP, Jacot-Sadowski I, Berlin I, Stuber MJ, et al. Electronic Nicotine-Delivery Systems for Smoking Cessation. N Engl J Med. 2024 Feb;390(7):601–10. http://dx.doi.org/10.1056/NEJMoa2308815.
50. Warner KE, Benowitz NL, McNeill A, Rigotti NA. Nicotine e-cigarettes as a tool for smoking cessation. Nat Med. 2023 Mar;29(3):520–4. http://dx.doi.org/10.1038/s41591-022-02201-7.
51. Caponnetto P, Campagna D, Ahluwalia JS, Russell C, Maglia M, Riela PM, et al. Varenicline and counseling for vaping cessation: a double-blind, randomized, parallel-group, placebo-controlled trial. BMC Med. 2023 Jul;21(1):220. http://dx.doi.org/10.1186/s12916-023-02919-2.
52. Rigotti NA, Benowitz NL, Prochaska JJ, Cain DF, Ball J, Clarke A, et al. Cytisinicline for Vaping Cessation in Adults Using Nicotine E-Cigarettes: The ORCA-V1 Randomized Clinical Trial. JAMA Intern Med. 2024 Aug;184(8):922–30. http://dx.doi.org/10.1001/jamainternmed.2024.1313.
53. Graham AL, Amato MS, Cha S, Jacobs MA, Bottcher MM, Papandonatos GD. Effectiveness of a Vaping Cessation Text Message Program Among Young Adult e-Cigarette Users: A Randomized Clinical Trial. JAMA Intern Med. 2021 Jul;181(7):923–30. http://dx.doi.org/10.1001/jamainternmed.2021.1793.
54. Kundu A, Kouzoukas E, Zawertailo L, Fougere C, Dragonetti R, Selby P, et al. Scoping review of guidance on cessation interventions for electronic cigarettes and dual electronic and combustible cigarettes use. CMAJ Open. 2023 Apr;11(2):E336–44. http://dx.doi.org/10.9778/cmajo.20210325.
55. Leung LW, Davies GA. Smoking Cessation Strategies in Pregnancy. J Obstet Gynaecol Can. 2015 Sep;37(9):791–7. http://dx.doi.org/10.1016/S1701-2163(15)30149-3.
56. Fahy SJ, Cooper S, Coleman T, Naughton F, Bauld L. Provision of smoking cessation support for pregnant women in England: results from an online survey of NHS Stop Smoking Services for Pregnant Women. BMC Health Serv Res. 2014 Mar;14(1):107. http://dx.doi.org/10.1186/1472-6963-14-107.
57. Przulj D, Pesola F, Myers Smith K, McRobbie H, Coleman T, Lewis S, et al. Helping pregnant smokers quit: a multi-centre randomised controlled trial of electronic cigarettes versus nicotine replacement therapy. Health Technol Assess. 2023 Jul;27(13):1–53. http://dx.doi.org/10.3310/AGTH6901.
58. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: implications for electronic cigarette use. Trends Cardiovasc Med. 2016 Aug;26(6):515–23. http://dx.doi.org/10.1016/j.tcm.2016.03.001.
59. Chen C, Huo C, Mattey-Mora PP, Bidulescu A, Parker MA. Assessing the association between e-cigarette use and cardiovascular disease: A meta-analysis of exclusive and dual use with combustible cigarettes. Addict Behav. 2024 Oct;157:108086. http://dx.doi.org/10.1016/j.addbeh.2024.108086.
60. National Institute for Health and Care Excellence (NICE), Tobacco: preventing uptake, promoting quitting and treating dependence. 2023.
61. Tabuchi T, Gallus S, Shinozaki T, Nakaya T, Kunugita N, Colwell B. Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. Tob Control. 2018 Jul;27 e1:e25–33. http://dx.doi.org/10.1136/tobaccocontrol-2017-053947.
62. Cohen JE, Gartner C, Edwards R, Hammond D. Australia tightens its prescription-only regulation of e-cigarettes. BMJ. 2023 Jun;381:1216. http://dx.doi.org/10.1136/bmj.p1216.
63. Federal Department of Home Affairs FDHA. E-Zigaretten Politik in den Kantonen. 2023; Available from: https://www.bag.admin.ch/bag/de/home/strategie-und-politik/politische-auftraege-und-aktionsplaene/politische-auftraege-zur-tabakpraevention/tabakpolitik-kantone/e-zigarette.html
64. Bundesamt für Gesundheit BAG. Neues Tabakproduktegesetz. 2024; Available from: https://www.bag.admin.ch/bag/de/home/strategie-und-politik/politische-auftraege-und-aktionsplaene/politische-auftraege-zur-tabakpraevention/tabakpolitik-schweiz/tabpg.html
65. Ruggia L. Novel nicotine products in Switzerland: A major threat to public health. Tob Prev Cessat. 2022 Nov;8(November):40. http://dx.doi.org/10.18332/tpc/155938.
66. Mendelsohn C, Wodak A, Hall W. How should nicotine vaping be regulated in Australia? Drug Alcohol Rev. 2023 Jul;42(5):1288–94. http://dx.doi.org/10.1111/dar.13663.
67. Saffer H, Dench D, Grossman M, Dave D. E-Cigarettes and Adult Smoking: evidence from Minnesota. J Risk Uncertain. 2020 Jun;60(3):207–28. http://dx.doi.org/10.1007/s11166-020-09326-5.
68. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. 2018 Jan;360:j5855. http://dx.doi.org/10.1136/bmj.j5855.
69. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study.

Ann Intern Med. 2017 Mar;166(6):390–400. http://dx.doi.org/10.7326/M16-1107.
70. Merz L, Puhan MA. Taxation options for nicotine and tobacco products in Switzerland - a review of tax policies. Swiss Med Wkly. 2021 Dec;151(5152):w30083. http://dx.doi.org/10.4414/SMW.2021.w30083.
71. Odani S, Tabuchi T. Prevalence and denial of current tobacco product use: combustible and heated tobacco products, Japan, 2022. Prev Med Rep. 2022 Oct;30:102031. http://dx.doi.org/10.1016/j.pmedr.2022.102031.
72. Sun T, Anandan A, Lim CC, East K, Xu SS, Quah AC, et al. Global prevalence of heated tobacco product use, 2015-22: A systematic review and meta-analysis. Addiction. 2023 Aug;118(8):1430–44. http://dx.doi.org/10.1111/add.16199.
73. Stoklosa M, Cahn Z, Liber A, Nargis N, Drope J. Effect of IQOS introduction on cigarette sales: evidence of decline and replacement. Tob Control. 2020 Jul;29(4):381–7.
74. Cummings KM, Nahhas GJ, Sweanor DT. What Is Accounting for the Rapid Decline in Cigarette Sales in Japan? Int J Environ Res Public Health. 2020 May;17(10):3570. http://dx.doi.org/10.3390/ijerph17103570.
75. Odani S, Tsuno K, Agaku IT, Tabuchi T. Heated tobacco products do not help smokers quit or prevent relapse: a longitudinal study in Japan. Tob Control. 2023 Feb;33(4):472–80. http://dx.doi.org/10.1136/tc-2022-057613.
76. Gallus S, Borroni E, Odone A, van den Brandt PA, Gorini G, Spizzichino L, et al.; The Role of Novel. The Role of Novel (Tobacco) Products on Tobacco Control in Italy. Int J Environ Res Public Health. 2021 Feb;18(4):1895. http://dx.doi.org/10.3390/ijerph18041895.
77. US Food and Drug Administration. FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information. 2020; Available from: https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information
78. St Helen G, Jacob Iii P, Nardone N, Benowitz NL. IQOS: examination of Philip Morris International's claim of reduced exposure. Tob Control. 2018 Nov;27 Suppl 1:s30–6. http://dx.doi.org/10.1136/tobaccocontrol-2018-054321.
79. Sutanto E, Miller CR, Smith DM, O'Connor RJ, Gravely S, Hammond D, et al. Perceived relative harm of heated tobacco products (IQOS), e-cigarettes, and cigarettes among adults in Canada: findings from the ITC Project. Tob Induc Dis. 2020 Sep;18(September):81. http://dx.doi.org/10.18332/tid/127233.
80. Glantz SA. Heated tobacco products: the example of IQOS. Tob Control. 2018 Nov;27 Suppl 1:s1–6. http://dx.doi.org/10.1136/tobaccocontrol-2018-054601.
81. Drovandi A, Salem S, Barker D, Booth D, Kairuz T. Human Biomarker Exposure From Cigarettes Versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis. Nicotine Tob Res. 2020 Jun;22(7):1077–85. http://dx.doi.org/10.1093/ntr/ntz200.
82. National Cancer Institute and Centers for Disease Control and Prevention, Smokeless Tobacco and Public Health: A Global Perspective. 2014.
83. Rutqvist LE, Curvall M, Hassler T, Ringberger T, Wahlberg I. Swedish snus and the GothiaTek® standard. Harm Reduct J. 2011 May;8(1):11. http://dx.doi.org/10.1186/1477-7517-8-11.
84. Robichaud MO, Seidenberg AB, Byron MJ. Tobacco companies introduce 'tobacco-free' nicotine pouches. Tob Control. 2020 Dec;29 e1:e145–6.
85. Clarke E, Thompson K, Weaver S, Thompson J, O'Connell G. Snus: a compelling harm reduction alternative to cigarettes. Harm Reduct J. 2019 Nov;16(1):62. http://dx.doi.org/10.1186/s12954-019-0335-1.
86. Bundesamt für Gesundheit BAG, Informationsschreiben: Das Verbot von Tabakerzeugnissen zum oralen Gebrauch (Art. 5 TabV) ist nicht mehr anzuwenden 2019.
87. Tobacco Tactics University of Bath. Nicotine Pouches. 2024; Available from: https://tobaccotactics.org/article/nicotine-pouches/
88. Official Statistics of Sweden, National public health survey. 2022.
89. Patel M, Kierstead EC, Kreslake J, Schillo BA. Patterns of oral nicotine pouch use among U.S. adolescents and young adults. Prev Med Rep. 2023 May;34:102239. http://dx.doi.org/10.1016/j.pmedr.2023.102239.
90. Statistics Norway. Almost twice as many daily users of snus as daily smokders. 2022; Available from: https://www.ssb.no/en/helse/helseforhold-og-levevaner/statistikk/royk-alkohol-og-andre-rusmidler/tobacco-alcohol-and-other-drugs/almost-twice-as-many-daily-users-of-snus-as-daily-smokers
91. US Food and Drug Administration. FDA authorizes modified risk tobacco products. 2020; Available from: https://www.fda.gov/tobacco-products/advertising-and-promotion/fda-authorizes-modified-risk-tobacco-products
92. Duren M, Atella L, Welding K, Kennedy RD. Nicotine pouches: a summary of regulatory approaches across 67 countries. Tob Control. 2023 Feb;33 e1:e32–40. http://dx.doi.org/10.1136/tc-2022-057734.
93. Lunell E, Fagerström K, Hughes J, Pendrill R. Pharmacokinetic Comparison of a Novel Non-tobacco-Based Nicotine Pouch (ZYN) With Conventional, Tobacco-Based Swedish Snus and American Moist Snuff. Nicotine Tob Res. 2020 Oct;22(10):1757–63. http://dx.doi.org/10.1093/ntr/ntaa068.
94. McAdam KG, Kimpton H, Faizi A, Porter A, Rodu B. The composition of contemporary American and Swedish smokeless tobacco products. BMC Chem. 2019 Mar;13(1):31. http://dx.doi.org/10.1186/s13065-019-0548-0.
95. Digard H, Proctor C, Kulasekaran A, Malmqvist U, Richter A. Determination of nicotine absorption from multiple tobacco products and nicotine gum. Nicotine Tob Res. 2013 Jan;15(1):255–61. http://dx.doi.org/10.1093/ntr/nts123.
96. McEwan M, Azzopardi D, Gale N, Camacho OM, Hardie G, Fearon IM, et al. A Randomised Study to Investigate the Nicotine Pharmacokinetics of Oral Nicotine Pouches and a Combustible Cigarette. Eur J Drug Metab Pharmacokinet. 2022 Mar;47(2):211–21. http://dx.doi.org/10.1007/s13318-021-00742-9.
97. Vansickel A, Baxter S, Sherwood N, Kong M, Campbell L. Human Abuse Liability Assessment of Tobacco and Nicotine Products: Approaches for Meeting Current Regulatory Recommendations. Nicotine Tob Res. 2022 Feb;24(3):295–305. http://dx.doi.org/10.1093/ntr/ntab183.
98. Digard H, Errington G, Richter A, McAdam K. Patterns and behaviors of snus consumption in Sweden. Nicotine Tob Res. 2009 Oct;11(10):1175–81. http://dx.doi.org/10.1093/ntr/ntp118.
99. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol. 2009;49(1):57–71. http://dx.doi.org/10.1146/annurev.pharmtox.48.113006.094742.
100. Hecht SS. Smokeless tobacco and its constituents. In: Baan RA, Stewart BW, Straif K, editors. Tumour Site Concordance and Mechanisms of Carcinogenesis. Lyon, FR; 2019.
101. Lawler TS, Stanfill SB, Tran HT, Lee GE, Chen PX, Kimbrell JB, et al. Chemical analysis of snus products from the United States and northern Europe. PLoS One. 2020 Jan;15(1):e0227837. http://dx.doi.org/10.1371/journal.pone.0227837.
102. Osterdahl BG, Jansson C, Paccou A. Decreased levels of tobacco-specific N-nitrosamines in moist snuff on the Swedish market. J Agric Food Chem. 2004 Aug;52(16):5085–8. http://dx.doi.org/10.1021/jf049931a.
103. Wyss AB, Hashibe M, Lee YA, Chuang SC, Muscat J, Chen C, et al. Smokeless Tobacco Use and the Risk of Head and Neck Cancer: Pooled Analysis of US Studies in the INHANCE Consortium. Am J Epidemiol. 2016 Nov;184(10):703–16. http://dx.doi.org/10.1093/aje/kww075.
104. Rostron BL, Chang JT, Anic GM, Tanwar M, Chang CM, Corey CG. Smokeless tobacco use and circulatory disease risk: a systematic review and meta-analysis. Open Heart. 2018 Oct;5(2):e000846. http://dx.doi.org/10.1136/openhrt-2018-000846.
105. Hajat C, Stein E, Ramstrom L, Shantikumar S, Polosa R. The health impact of smokeless tobacco products: a systematic review. Harm Reduct J. 2021 Dec;18(1):123. http://dx.doi.org/10.1186/s12954-021-00557-6.
106. Lee PN. Summary of the epidemiological evidence relating snus to health. Regul Toxicol Pharmacol. 2011 Mar;59(2):197–214. http://dx.doi.org/10.1016/j.yrtph.2010.12.002.
107. Valen H, Becher R, Vist GE, Holme JA, Mdala I, Elvsaas IØ, et al. A systematic review of cancer risk among users of smokeless tobacco (Swedish snus) exclusively, compared with no use of tobacco. Int J Cancer. 2023 Dec;153(12):1942–53. http://dx.doi.org/10.1002/ijc.34643.
108. Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, et al. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. Eur J Epidemiol. 2012 Oct;27(10):771–9. http://dx.doi.org/10.1007/s10654-012-9704-8.
109. Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, et al. Snus (Swedish smokeless tobacco) use and risk of stroke: pooled analyses of incidence and survival. J Intern Med. 2014 Jul;276(1):87–95. http://dx.doi.org/10.1111/joim.12219.
110. Titova OE, Baron JA, Michaëlsson K, Larsson SC. Swedish snuff (snus) and risk of cardiovascular disease and mortality: prospective cohort study of middle-aged and older individuals. BMC Med. 2021 May;19(1):111. http://dx.doi.org/10.1186/s12916-021-01979-6.
111. Arefalk G, Hambraeus K, Lind L, Michaëlsson K, Lindahl B, Sundström J. Discontinuation of smokeless tobacco and mortality risk after

myocardial infarction. Circulation. 2014 Jul;130(4):325–32. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.007252.
112. Byhamre ML, Araghi M, Alfredsson L, Bellocco R, Engström G, Eriksson M, et al. Swedish snus use is associated with mortality: a pooled analysis of eight prospective studies. Int J Epidemiol. 2021 Jan;49(6):2041–50. http://dx.doi.org/10.1093/ije/dyaa197.
113. Norwegian Institute of Public Health, Health risks of Scandinavian snus consumption (English summary). 2014.
114. velo. Available from: velo.com/ch
115. Ling PM, Hrywna M, Talbot EM, Lewis MJ. Tobacco-Derived Nicotine Pouch Brands and Marketing Messages on Internet and Traditional Media: content Analysis. JMIR Form Res. 2023 Feb;7:e39146. http://dx.doi.org/10.2196/39146.
116. Azzopardi D, Liu C, Murphy J. Chemical characterization of tobacco-free "modern" oral nicotine pouches and their position on the toxicant and risk continuums. Drug Chem Toxicol. 2022 Sep;45(5):2246–54. http://dx.doi.org/10.1080/01480545.2021.1925691.
117. Azzopardi D, Haswell LE, Frosina J, McEwan M, Gale N, Thissen J, et al. Assessment of biomarkers of exposure and potential harm, and physiological and subjective health measures in exclusive users of nicotine pouches and current, former and never smokers. Biomarkers. 2023 Feb;28(1):118–29. http://dx.doi.org/10.1080/1354750X.2022.2148747.
118. Ebbert JO, Elrashidi MY, Stead LF. Interventions for smokeless tobacco use cessation. Cochrane Database Syst Rev. 2015 Oct;2015(10):CD004306.
119. Hendlin YH, Elias J, Ling PM. The Pharmaceuticalization of the Tobacco Industry. Ann Intern Med. 2017 Aug;167(4):278–80. http://dx.doi.org/10.7326/M17-0759.
120. Dubrosa F, Sangiuolo K, Franco J Jr, Milanaik RL. Quick nic: novel smokeless nicotine products and pediatric trends. Curr Opin Pediatr. 2023 Aug;35(4):500–12. http://dx.doi.org/10.1097/MOP.0000000000001270.
121. Etter JF. Addiction to the nicotine gum in never smokers. BMC Public Health. 2007 Jul;7(1):159. http://dx.doi.org/10.1186/1471-2458-7-159.
122. Borowiecki M, Emery SL, Kostygina G. New recreational nicotine lozenges, tablets, gummies and gum proliferate on the US market. Tob Control. 2024 Apr;33(3):414–6. http://dx.doi.org/10.1136/tc-2022-057673.
123. King BA, Toll BA. Commentary on Wackowski et al.: Opportunities and Considerations for Addressing Misperceptions About the Relative Risks of Tobacco Products among Adult Smokers. Addiction. 2023 Oct;118(10):1892–4. http://dx.doi.org/10.1111/add.16296.