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Coolants, organic acids, flavourings and other additives that facilitate inhalation of tobacco and nicotine products: implications for regulation

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ABSTRACT

To inform regulatory policy, this article summarises findings on inhalation facilitation from the ninth report of the WHO Study Group on Tobacco Product Regulation. Some additives counteract the harshness and bitterness of tobacco and nicotine product aerosols, making them easier to inhale. Additives that promote inhalability may perpetuate and increase the use of inhaled tobacco and nicotine products, especially by young people. Thus, as a class, additives that facilitate inhalation are an important regulatory target to prevent tobacco and nicotine product uptake. We defined inhalation facilitation as modifications to products during manufacturing that enhance the sensory experience and (potentially) behaviours associated with inhalation (eg, deeper puffs, faster inhalation, larger puff volume, shorter intervals in between puffs and use episodes). Evidence review showed that: (a) menthol and synthetic coolants decrease irritation caused by aerosol constituents by activating sensory perception receptors (eg, cooling receptors) and may promote dependence in inexperienced users; (b) acid additives and sugars, which lower the pH of aerosols and shift nicotine from free-base to protonated salt forms, reduce harshness and increase blood nicotine yield; (c) e-cigarette flavourings perceived as sweet or fruity reduce subjective bitterness, increase attractiveness and may escalate use, although their effects on perceived harshness are inconclusive; (d) sugars in tobacco impart sweet sensations, but limited industry-independent data preclude strong conclusions for sugars' roles in inhalation facilitation. Given these findings, WHO policy recommendations suggest that regulators might consider banning ingredients that facilitate inhalation in all commercial inhaled tobacco and nicotine products.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While it is known that manufacturers use additives to improve flavour, sensory experience and appeal of tobacco and nicotine products, a scientific operationalisation of inhalation facilitation to inform regulation is lacking.

WHAT THIS STUDY ADDS

⇒ This paper provides a conceptual model and definition for inhalation facilitation, and reviews evidence on example additives and their behavioural and biological impacts on inhalation facilitation via three different mechanisms: activating the cooling receptor TRPM-8, lowering pH (nicotine protonation) and enhancing olfactory/orosensory experience.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ According to WHO FCTC Article 9, and in line with several (supra)national legislations, this paper's evidence review and framework indicate that several ingredients that facilitate inhalation meet policy requirements for a ban on tobacco and nicotine product manufacturing. This paper also informs future priorities for regulatory science and policy.

ADDITIVES THAT FACILITATE INHALATION CAN INCREASE ADDICTION LIABILITY

Smoke and other aerosols emitted from tobacco and nicotine products inherently contain constituents that are aversive and difficult to inhale. Internal industry documents show that manufacturers often modify products to improve flavour, sensory experience and appeal.[1–4] More than 100 cigarette additives have been found that mask irritation and other undesirable sensory effects of inhaling smoke, enhance or maintain nicotine delivery, or have other effects that increase use and addictiveness.[2] Additives with such effects have also been found in e-cigarettes, cigars and water pipe products.[5 6] Additives with acute sensory-modifying effects share a common characteristic—they facilitate inhalation of the product's aerosol.

Additives that promote inhalation facilitation may impact health in several ways. For naïve individuals, the aversive sensory attributes of tobacco and nicotine aerosol can cause termination of initial use, limit the amount of aerosol inhaled and nicotine delivered, and deter future use.[7 8] Young people exposed to easily inhaled aerosols with additives that counteract unpleasant sensory experiences may be more inclined to become regular users. Hence, the availability of products with additives that facilitate inhalation could increase overall population use prevalence. In established users, increased inhalability may increase nicotine intake, reinforcement, and promote addiction and long-term, heavy use.[7] Increased inhalability of e-cigarette aerosol may also, however, make them more satisfying nicotine substitutes for some adult smokers and encourage them to quit smoking and switch to e-cigarette use. Policy-makers have identified additives that facilitate inhalation as key determinants of use and therefore potential targets for regulation.[8 9] However, a science-based framework to guide research and inform regulatory policy on inhalation facilitation is lacking.

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This special communication summarises and updates a 2023 WHO Study Group on Tobacco Product Regulation Technical Report paper. It describes a scientific operationalisation of inhalation facilitation and its mechanisms; reviews evidence on exemplary additives that plausibly promote inhalablity; and discusses policy and health impacts of the findings.

BACKGROUND: WHY NICOTINE AND OTHER SENSORY IRRITANTS IN SMOKE/AEROSOL DECREASE INHALABILITY AND SENSORY-MODIFYING ADDITIVES INCREASE USE

Tobacco smoke contains nicotine and other irritants that stimulate chemosensory nerves, causing unpleasant burning and tingling sensations and avoidance reflexes, such as coughing and sneezing.[7 10] Specific receptors, the so-called transient receptor potential (TRP) cation channels mediate local irritation and pain induced by nicotine (eg, cooling receptors (TRPM8) in the oropharynx and larynx).[1 11] Compounds targeting such receptors, including menthol, can modify nicotine-induced oral irritation and pain.[7 11] Other TRP receptors are implicated in nicotine's bitter taste.[12] In addition to nicotine, reactive aldehydes, acids and volatile organic hydrocarbons account for irritation caused by tobacco smoke[7] via the TRPA1 irritant receptor, acid-sensing ion channels and other sensory receptor classes.[7 13] In addition to tobacco smoke, many of these effects extend to aerosol from other inhaled nicotine products, such as e-cigarettes.[11]

Although nicotine elicits oral irritation, pain, bitterness, nausea and dizziness,[11 14] it also has reinforcing central nervous system effects, even at low concentrations.[7 10] Consequently, regular smokers e-cigarette users titrate nicotine intake to experience the reinforcing effects while also tolerating the aversive sensory effects of inhaling smoke/aerosol.[15] The balance of nicotine's reinforcing effects and aversive sensory experience of inhalation are critical during early experiences using tobacco and nicotine products. Early aversive experiences can deter continuation of use and limit the amount of nicotine inhaled and exposure to nicotine's addictive effects. While experienced harshness and bitterness are initially perceived as aversive,[7 16] continued use desensitises users to these effects and causes these sensations to be repeatedly paired with nicotine's reinforcing effects.[1 17] With continued use, sensory cues of (e-)cigarette aerosol become conditioned reinforcers that acquire motivational significance which synergize with nicotine's central nervous system effects and promote tobacco and nicotine-seeking behaviour. Consequently, factors that modify the sensory attributes of smoke/aerosol and increase inhalability are critical to uptake and continuation.

DEFINITION AND EVIDENCE REVIEW OF ADDITIVES THAT FACILITATE INHALATION

We define inhalation facilitation as placing additives or making other product modifications during manufacturing that improve the sensory experience of inhaling the product's aerosol (eg, reduced bitterness and harshness) and may alter inhalation behaviour. Altered aerosol inhalation behaviour could include deeper puffs, faster inhalation, larger puff volume or restoration of breathing patterns that are disturbed by inhaled irritants that shorten intervals between puffs and use episodes. These effects may increase tobacco and nicotine product uptake, persistence, and exposure to nicotine and toxins in aerosol, thereby promoting addiction or other harmful health effects. Such impacts may vary across populations defined by age, smoking status, race and other factors. Additives that potentially facilitate inhalation, and their putative mechanisms are summarised in table 1. Evidence review strategy is described in online supplemental file 1, as well as the conceptual model depicted in figure 1.

Additives with cooling effects

Menthol

Menthol, which naturally occurs in mint (*Mentha* spp), is added to various inhaled products, including those not explicitly marketed as 'menthol flavoured'.[18] Menthol promotes inhalability through anti-irritant, cooling and pain-relieving effects.[19] Menthol interacts with the cooling receptor in cold-sensitive sensory neurons lining the airways and with the sensory irritant receptor.[14] Menthol reduces nicotine's irritating effects through acute cooling effects and through cross-desensitisation, whereby menthol pretreatment suppresses irritation from later nicotine exposures even after its immediate cooling effect dissipates.[11] Menthol counteracts rodents' anti-respiration responses to inhaled irritants, allowing for more frequent breathing, shorter inter-breath intervals and faster respiratory flow rate during inhalational exposure.[7 20] Such changes could reflect rodent analogues of increased puff count, shorter inter-puff intervals and faster puff velocity in humans.

Table 1 Classes of additives implicated in IF: mechanisms and effects

Additive	Key mechanism or characteristic	Reported sensory effects	Comments about evidence base
Menthol	Activating cooling receptor TRPM-8	Increase cooling, reduce harshness of nicotine, minty flavour	Data for both tobacco products and e-cigarettes Increased inhalation behaviour in rodents but inconclusive effects on inhalation behaviour in humans
Wilkinson Sword (WS) compounds, such as WS-3, WS-5, WS-14 and WS-23	Activating cooling receptor TRPM-8	Increase cooling, reduce harshness, reduce bitterness	Data predominately for e-cigarettes Often combined with other flavours in 'ice' hybrid flavours in e-cigarettes
Organic acids and nicotine salts in e-cigarettes	pH lowering	Increase mildness, reduce harshness and irritation	Effects mainly for higher nicotine concentration products Higher blood nicotine levels
Sugars in tobacco	pH lowering	Combust to acids, increase mildness	Mainly industry data
Organic acids in tobacco	pH lowering	Increase mildness, decrease irritation	Mainly industry data
Flavourings with sweet properties	Olfactory and orosensory mechanisms	Increase sweetness, reduce bitterness, partial evidence of increased smoothness and reduced harshness	Data predominately in e-cigarettes, hookahs and cigars
Sugars	Olfactory and orosensory mechanisms	Impart a sweet flavour	Predominately in cigarettes; mainly industry data

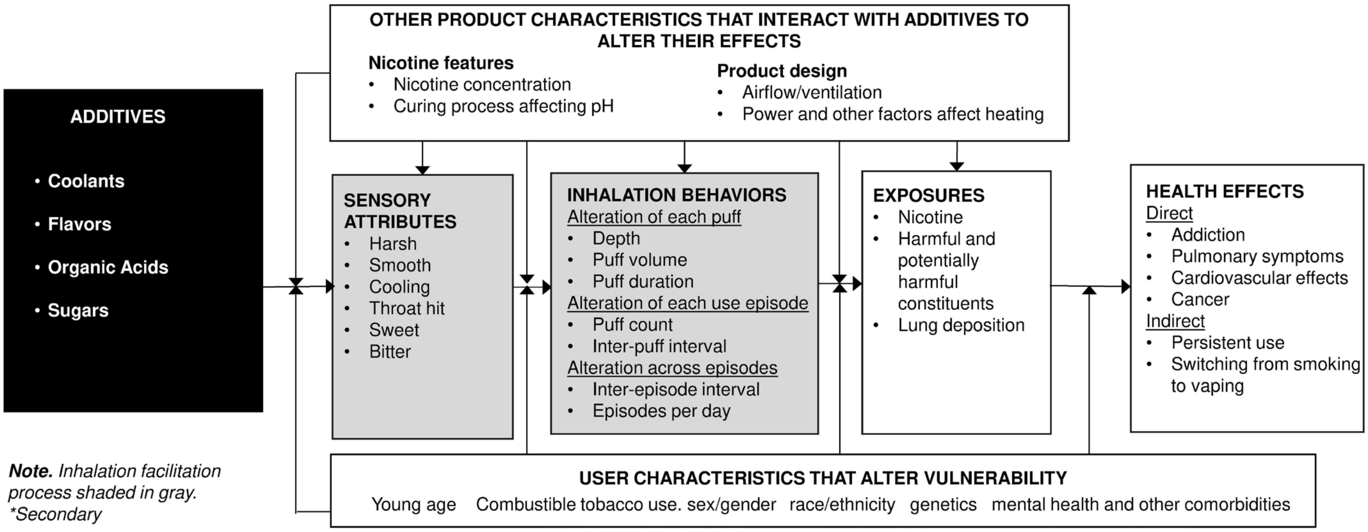

Figure 1 Conceptual model of the effects of additives in facilitating inhalation and of the corresponding effects on health.

For humans, a USFDA review concluded that menthol increases the palatability of cigarettes by masking the harsh taste of smoke and reducing aversive sensory reactions to initial smoking experiences (eg, irritation, coughing), thereby promoting established smoking uptake.[19] The report found the strongest evidence for menthol increasing uptake and dependence in youth, reducing smoking cessation success, and disproportionately impacting black communities, and found mixed evidence for associations of menthol with cigarette dependence or smoking topography measures in adult established smokers.[19] Selection bias complicates interpretation of studies in adult established smokers because menthol cigarettes have been chronically marketed, often disproportionately across populations, creating strong cigarette brand preferences that may impact responses to different flavoured cigarettes.

Clinical laboratory experiments with e-cigarettes find that menthol increases perceived coolness and pleasant taste[21–25] alters some of nicotine's aversive sensory attributes. A study of young adult vapers found that menthol increased measures of e-cigarette appeal (eg, willingness to use the product again), especially in never smokers and nicotine-containing versus nicotine-free e-cigarettes.[23] In an adolescent study, no evidence was found that menthol altered the effects of nicotine levels on e-cigarette appeal, although menthol increased perceived coolness.[21] Menthol did not affect puffing e-cigarette behaviour or short-term nicotine exposure.[21 24]

Synthetic cooling agents

Synthetic coolant additives developed by Wilkinson Sword (WS) and others (eg, compound WS-3 and WS-23) have been detected in cigarettes marketed in Germany[26 27] and the USA.[28 29] Synthetic coolants are added to e-cigarettes marketed in hybrid 'ice' flavours that blend characterising and cooling flavours (eg, 'raspberry ice'),[30 31] which are often used by young people in the USA.[32–34]

Several synthetic coolants are based on menthol's structure. Like menthol, synthetic coolants are pharmacologically active at the cooling receptors lining the airways and oral cavity.[7 20 35 36] Some evidence indicates that cooling agent WS-3 is more active at these receptors than menthol, generates stronger cooling sensations[37 38] and may activate the sensory irritant receptor.[39–41] While menthol is perceived as minty, products with synthetic coolants could produce cooling sensations that mask nicotine's harshness without providing a strong minty flavour.[33]

A clinical-laboratory human study found that administration of fruit, tobacco and mint flavoured e-cigarettes supplemented with WS-23 (vs no cooling agent) additive increased product appeal, smoothness and coolness and reduced bitterness and harshness.[42] Additionally, e-cigarettes with cooling agent WS-23 were perceived as smoother, cooler and less harsh than those with menthol. Cooling agent additive effects did not differ across 2% versus 4% nicotine concentration or smoking status. One observational study found that young adult users of ice-hybrid flavoured e-cigarettes reported more symptoms of nicotine dependence than those using other flavours.[32]

Additives that lower pH

Organic acids and sugars in cigarettes

The tobacco industry has investigated the effects of manipulating pH levels on tolerance to cigarette smoking.[3] The pH of the products' aerosol determines the fraction of protonated versus free-base nicotine depends and can be influenced by adding acidic or basic additives. At pH>7–12, nicotine is present in a free-base state, which permeates membranes more easily than protonated nicotine.[43–45] Free-base nicotine provides a stronger throat hit and is experienced as harsher, and can be aversive especially at high concentrations, because it is absorbed preferentially in the upper respiratory tract.[46] Protonated nicotine is less irritating and hence can be inhaled more deeply, resulting in deposition deeper in the respiratory tract. Cigarette smoke is usually slightly acidic, with a pH of about 6, which makes the smoke less harsh and easier to inhale than smoking products with higher pH, such as cigars.[3 47] Once cigarette smoke reaches the pulmonary alveoli, nicotine leaves the smoke and is readily absorbed through the pulmonary capillaries into the systemic circulation[47] due to the larger absorptive surface of the lung at pH 7.4 and the high local buffering capacity of the lung.[48 49]

Many different acid additives, for example, lactic, citric and tartaric acid, have been used in the production of commercial cigarettes to modify the pH of smoke, increase their smoothness, decrease harshness, bitterness and throat hit and modify flavour.[48 50] Internal tobacco industry documents indicated that laevulinic acid increased nicotine yields while enhancing perceptions of smoothness and mildness.[3] Mechanistically, it reduces the pH of cigarette smoke and desensitises the upper respiratory tract, promoting inhalation of cigarette smoke deeper into the lungs, resulting in significantly increased peak plasma nicotine levels in smokers.

The pH of smoke can also be affected by sugars in tobacco.[50] Addition of sugars to cigarette tobacco has been reported to increase the acidity of smoke,[51–53] as combustion of sugar during smoking results in acids that reduce the pH,[54] thus decreasing the harshness and irritation of the smoke,[55 56] increasing the palatability of the product and facilitating inhalation. Sugars have been referred to by the tobacco industry to '… smooth out harshness and bitterness and/or eliminate pungent aromas from tobaccos'.[57]

Organic acids in e-liquids

In the USA, marketing of JUULs and similar pod-style e-cigarettes increased e-cigarette use among young non-smokers.[58 59] The liquids in these products contain high levels of nicotine in protonated form due to the addition of organic acids such as lactic, salicylic, benzoic, laevulinic, ditartaric and maleic acid.[60 61] As protonated nicotine is less harsh and bitter on inhalation than free-base nicotine, inhaling high amounts of nicotine is more palatable.[5] Furthermore, greater nicotine absorption, with faster, higher peak blood nicotine levels, probably predicts greater abuse liability.[47] Some studies have shown that e-cigarettes with nicotine salt solutions, unlike free-base liquid, result in nicotine blood profiles similar to those of smokers of tobacco cigarettes.[62–65] Smokers who switched to nicotine salt pod-style e-cigarettes maintained their nicotine levels and transferred their dependence, suggesting that these products have a reinforcement potential similar to that of cigarettes.[66] Observational data show that adolescents who use nicotine salt e-liquids experience similar levels of nicotine dependence as adolescent smokers[67] but greater dependence than young users of other e-cigarette products.[68] Thus, nicotine salts increase their addiction potential,[65] and the effect increases with nicotine dose. JUULs containing higher levels (59 mg/mL) of protonated nicotine give rise to significantly higher plasma nicotine levels and relief from craving than lower levels (18–20 mg/mL).[69 70] JUUL with 18 mg/mL, delivered less nicotine and reduced the urge to smoke or vape less strongly than tobacco cigarettes.[71]

A USA clinical trial showed that formulations containing 24 mg/mL nicotine salt had significantly higher ratings than free-base nicotine for appeal, sweetness and smoothness and lower ratings for bitterness and harshness. Nicotine salts improved the sensory experience and thereby the attractiveness of vaping, particularly among never smokers unaccustomed to inhaling free-base nicotine.[72] These findings align with England's observational data indicating that JUUL, which contains nicotine salts, is more commonly used by never smokers than by current smokers, whereas tank devices, which typically include free-base nicotine, are more used by current or former smokers, although other confounders (eg, age) could explain the association.[73] A USA clinical laboratory study found that 29 mg/mL nicotine lactate and benzoate (protonated) e-liquids had greater appeal, smoothness and sweetness and less harshness and bitterness than free-base nicotine. There was some evidence that e-liquids that are highly protonated had stronger effects than e-liquids that are moderately protonated.[74] In the Netherlands, a home use study showed no significant difference in scores for appeal, harshness and topography of nicotine salts at a concentration of 12 mg/mL.[75] Apart from the lower nicotine levels, users in the Dutch study could vape freely, with monitoring of puffing parameters, whereas a set puffing protocol was used in the USA study.[72]

Sweet-flavoured additives and sweeteners

Flavourings with sweet features

Hundreds of flavouring constituents in tobacco and nicotine products give the sensory essence of sweet features (eg, fruit, mint, dessert) that are not sugars or sweeteners, per se.[76 77] Hence, no single biological pathway or set of pathways likely mediate the sensory- and respiratory-altering effects of sweet flavoured additives. Constituents with sweet features appear to improve user experience by olfaction and not by orosensory impact alone.[78 79]

Studies with sweet flavours provide some evidence of possible effects on processes related to inhalation facilitation, but the results for certain outcomes are inconsistent. A review of qualitative studies indicates that sweet flavours in cigars, hookahs, e-cigarettes and cigarettes reduce perceptions of harshness and make the products more tolerable.[80] Flavours with sweet properties in e-cigarettes (eg, fruit) reduce perceived bitterness in clinical experiments.[12 25 81] Effects of sweet flavours in reducing harshness and increasing the smoothness of e-cigarettes are mixed.[25 81–83] Small clinical laboratory studies have found e-cigarettes with fruit compared with non-fruit flavours increased acute puff duration and plasma nicotine but inconsistent effect puff count, with one study finding fruit increased number of puffs and another not showing these effects.[21 84 85] A longitudinal observational study of adolescent e-cigarette users showed that using sweet or fruit compared with menthol, tobacco or mint flavours self-reported more puffs per vaping episode 6 months later, but was not associated with subsequent vaping episodes per day.[86]

Sugars and sweeteners

Sugars and other sweeteners that stimulate orosensory sweet taste receptors are added to e-liquids and tobacco leaves.[87] High-intensity sweeteners like saccharine and glycyrrhizin are also added to the mouthpiece and wrapper of tobacco products such as cigarillos.[88] In addition to their effect on pH, sugars also contribute to the flavour of tobacco and nicotine products[51 56 89–91] and e-cigarettes.[92 93] In combusted products, the sweet taste of caramel flavours generated by the combustion of sugars improves the taste and smell of the tobacco smoke for both users and bystanders.[51 55 94 95] Pyrazines are added to some cigarette products with cocoa, nutty or popcorn-type flavouring features.[17 96] It has been hypothesised that they may reduce noxious sensations such as irritation in the upper airways.[17] It is plausible that orosensory sweeteners lower the cough threshold given evidence that mouth rinsing with sucrose solution modulates sensitivity to the cough reflex.[97]

Evidence from the tobacco industry and some independent sources generally indicate that sugar and other sweetening agent additives increase inhalability. Industry documents indicate that the acceptance of tobacco smoke by users by smokers is proportional to the sugar level in the tobacco, which could be due to their flavour sensations and their effect on pH.[51 90] In e-cigarettes, the addition of sucralose, an artificial sweetener, increased overall flavour and sweetness but had no significant effect on harshness or irritation.[78]

Suggestions for regulation of additives that facilitate inhalation

Regulators ascribing to various (supra)national policies should consider banning all ingredients that facilitate inhalation, as they increase the uptake, dependence and potentially other adverse outcomes related to the use of tobacco and nicotine products. Such regulatory measures should be considered alongside other proven interventions and policies to maximise their potential. It is recommended that policy-makers include a non-limited list of such compounds in legislation to assist surveillance and enforcement. The following constituents and classes of additives merit consideration for this list of banned ingredients for any inhaled commercial tobacco or nicotine product; see also overview table 1 including comments about their evidence base:

- Menthol and both synthetic and natural (eg, geraniol) coolants with similar chemical structure, physiological and sensory effects.
- Acid additives and nicotine salts in e-liquids at nicotine levels >20 mg/mL. While sufficient evidence is not available for nicotine levels <20 mg/mL, regulators might consider banning such additives at any nicotine level as a precaution. Any acid-generating additive should also be considered. Some products may have other additives or modifications that lower pH, such as certain tobacco leaf curing processes or sugar additives. Regulatory restrictions on inhalable tobacco products and e-cigarettes according to a pH threshold or the nicotine protonation state rather than the presence of a particular additive is a pragmatic solution that merits consideration.
- All added flavourings that impart sweet taste or other sensory perceptions of sweetness, including sugars. Regulators could also consider banning sugars and flavourings that are naturally present in tobacco, as they also impart flavour and may facilitate inhalation. For the consumer, it is immaterial whether sugars or flavourings are added or naturally present.
- Additional compounds that promote IF when necessitated by new scientific insights.

These recommendations are supported by the partial guidelines for implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control.[98] For public health, there is no justification for adding ingredients such as flavouring agents that make tobacco and nicotine products more attractive, and the partial guidelines therefore recommend that 'Parties should regulate all tobacco product design features that increase the attractiveness of tobacco products'. Given the WHO definition of attractiveness (ie, factors such as taste, smell and other sensory attributes, ease of use, flexibility of the dosing system, cost, reputation or image, assumed risks and benefits, and other characteristics of a product designed to stimulate use), regulators applying these policies should ban all ingredients that facilitate inhalation and use. Such measures could decrease initiation and overall population use prevalence.

Widescale application of such policies to cigarettes and most other inhaled tobacco products aligns with most countries' regulatory approaches. Legislation on e-cigarettes may depend on each country's circumstances and policy aims. Policy-makers may consider effects at population level and weigh the evidence for whether additives that promote IF could make potentially less harmful inhaled products more satisfying nicotine substitutes for some adult smokers relative to their impacts on appeal, dependence and other adverse outcomes in young people and non-smokers.

The European Tobacco Products Directive (TPD), Article 7.6.d, already stipulates that European Union Member States shall prohibit the placing on the market of tobacco products for smoking and e-cigarettes containing additives that facilitate inhalation or nicotine uptake.[99] The TPD does not, however, provide a definition of IF or nicotine uptake facilitation. Belgium[100] and Germany[101] already prohibit the use of menthol for its IF properties at any level, which is further supported by advice from the European Union Joint Action Tobacco Control,[102] which concluded that all menthol analogues, including geraniol, have a TRPM8-dependent cooling effect and may act cumulatively. Belgium has banned all activators of the TRPM8 thermoreceptor, as also proposed by the Netherlands,[103 104] and Germany has also banned other TRPM8 activators.

Canada does not permit the use of additives with any flavouring properties, sweeteners or several other compounds that increase the attractiveness of tobacco products, although there are a few exceptions (guar gum, alcohol flavours).[105]

The USA has planned Federal product standards that would prohibit all characterising flavours in cigarettes and cigars, including menthol.[8 106] This proposed product standard extends the definition of 'characterising flavour' to 'multisensory experience', including cooling or burning sensations. If finalised, this extended definition will allow regulation of additives that facilitate inhalation, including synthetic cooling agents in cigarettes.[107] The US Tobacco Control Act stipulates that any regulatory decision takes into consideration the impact on the population as a whole. Thus, regulatory restrictions should be designed to minimise tobacco and nicotine product use by young people and non-users and should not deter adult smokers from quitting the use of combustible tobacco products and switching to less harmful inhalable products. To date, the USA has denied applications for numerous e-cigarette products marketed with characterising flavours and sweet features on the basis of sufficient evidence that these flavoured e-cigarettes attract young people and insufficient evidence that they cause adult smokers to switch from smoking to vaping.[108] The USFDA authorised the marketing of several e-cigarette products that contain organic acids and protonated nicotine.[109 110]

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Supplementary file I: Details on Conceptual Model and Evidence Review Strategy

Additives to tobacco and nicotine products (e.g. flavourings, cooling agents, organic acids, sugars) are the focus of this paper. Other factors can affect inhalation facilitation (IF), including extraction of compounds from tobacco, the nicotine concentration and design manipulations (e.g. filter ventilation, airflow, heating element, curing process); however, these factors are not directly addressed.

Processes related to inhalation facilitation

Additives can improve the sensory experience of inhaling aerosol by affecting airway sensations (increased smoothness or coolness, reduced harshness or irritation, and a pleasant "throat hit"), potentially making the aerosol easier to inhale. Olfactory and orosensory features (increased sweetness and decreased bitterness) elicited by additives may peripherally promote IF by increasing the appeal of a product, so that more aerosol is inhaled. IF-related increases in inhalation include instantaneous effects, such as greater inhalation depth, volume, velocity and duration per puff. Such effects may be strongest for nicotine-naive users who are not accustomed to inhaling harsh and bitter aerosols. For inexperienced and younger users, tobacco and nicotine products with desirable sensory features may also shorten the inter-puff interval and increase the number of puffs per use episode (e.g. lighting and then putting out a cigarette), because they may need less time to "recover" from sensory irritation between puffs. This could escalate use and dependence. For established daily users with severe nicotine dependence who are used to maintaining nicotine blood levels and avoiding withdrawal symptoms, additives that promote IF may result in inhalation of more nicotine per puff, which could promote faster satisfaction per puff and reduce the number of puffs necessary to achieve nicotine satiation.

Consequences of inhalation facilitation

Altered inhalation behaviour may increase exposure in two ways. First, changes in inhalation behaviour can directly increase the total quantity of aerosol consumed per puff, per use episode and per day and deeper inhalation. Secondly, increases in inhalation may alter pulmonary deposition, allowing more nicotine absorption and rendering the exposed parts of the lung more vulnerable. A review of the weight of evidence for a causal relation between filter ventilation and lung adenocarcinoma showed that deeper inhalation of cigarette smoke may increase the rate of adenocarcinoma *[1]*. IF-related increases in exposure can have numerous direct health effects, including on the cardiovascular and pulmonary systems and increased risks of various cancers.

Additionally, higher puff volume, shorter inter-puff intervals and deeper inhalation affect the rate and volume of nicotine delivered to the blood, which corresponds directly to the product's reinforcing effects *[2, 3]*. The pleasant sensory attributes of a tobacco product also contribute to its reinforcing effects and increase reinforcement synergistically with nicotine *[4]*. A product's reinforcing effects are directly related to its addiction potential and the likelihood of persistent use. IF is harmful in any inhalable tobacco and nicotine product for youth and adults who are not TNP users, as IF may stimulate uptake and continuation of TNP use. IF in e-cigarettes could, however, be useful for adult smokers who wish to switch to e-cigarettes. Additives that promote IF in e-cigarettes may increase their nicotine yield and reinforcement and thus increase adoption and switching to e-cigarette products and cessation of tobacco smoking. In adults who switch completely from tobacco cigarettes to e-cigarettes, however, such additives might also promote sustained vaping and potentially greater exposure to harmful constituents. Additional data on the net effect at population level are necessary.

Interaction with other products and user characteristics

The quality of a product's sensory attributes that promote IF may depend on user characteristics. On the one hand, youth and never-smokers may be deterred by harsh and bitter tastes, while additives that promote IF would suppress the deterrence. On the other hand, long-term adult smokers who wish to switch to e-cigarettes may seek products to replace the sensory attributes of cigarettes and provide a suitable throat hit and robust tastes. Hence, additives that suppress the bitterness and harshness of e-cigarettes may have less effect in promoting IF among smokers who are already accustomed to inhaling harsh, bitter tobacco smoke. Additional user characteristics (e.g. genetics, mental health, other comorbid conditions, race or ethnicity, sex or gender) may also affect their sensitivity to the sensory attributes of tobacco and nicotine products and their vulnerability to the effects of exposure to nicotine or harmful or potentially harmful constituents. Other product characteristics can interact with additives that promote IF by amplifying their effect on inhalation behaviour and on exposure and outcomes. For instance, additives that suppress the harsh, bitter taste of nicotine may have a particularly strong effect in e-cigarettes with a very high nicotine concentration.

Evidence review strategy

A targeted (non-systematic) search of PubMed and other bibliographic sources with no restrictions on time period, up to September 2022, included terms related to IF processes (e.g. "harshness", "puff duration"), candidate additives (e.g. "menthol") or candidate mechanisms (e.g. "TRPM8 [transient receptor potential cation channel, family 8] receptor"). Inclusion of studies in the review was agreed by consensus by the two authors. We considered primary evidence of IF as that which demonstrated effects of additives on sensory experience and/or inhalation behaviour. Studies of IF-related mechanisms of action and the consequences of IF (biomarkers of exposure and health outcomes) were reviewed to provide supporting evidence for the biological plausibility and health significance of the IF scientific framework.

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