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.

References

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[2] Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol* 2009;**49**:57-71.
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[4] Chaudhri N, Caggiula AR, Donny EC, *et al.* Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. *Psychopharmacology (Berl)* 2006;**184**(3-4):353-366.