Public Health Benefit of Oral, Tobacco-Free Nicotine Pouches

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I have been informed that the Dutch government is considering introducing a ban on oral tobacco-free nicotine products. The proposed ban is a part of the wider strategy to reduce smoking to below 5% in 2040, which is a commendable objective.

According to a report from the Dutch Trimbos Institute 20.6% (amounting to almost 2.9 million people) of the Dutch adult population smoked in 2021 (1), making the objective of reducing smoking to less than 5% in 2040 a very arduous, but nonetheless, a very important objective.

I would therefore kindly like to offer my thoughts of why I believe the proposed ban on nicotine pouches is misguided and will hamper the efforts of reaching the smokefree objective. I sincerely believe that the proposed ban is not likely to promote anti-tobacco efforts but rather the opposite. My conclusions are based on the following facts and scientifically informed considerations:

- Cigarette smoking is by far the most dangerous form of tobacco use. It is associated with increased risks of a broad range of diseases such as lung cancer, oral cancer, pancreatic cancer, myocardial infarction, stroke, and chronic obstructive lung disease. Consequently, about 50 per cent of all daily smokers die prematurely because of their cigarette use.

- It is the combustion products in cigarette smoke that mainly contribute to the mentioned adverse health effects whereas the nicotine exposure *per se* is generally considered unassociated with such effects (2).

- Smoke-free, nicotine delivery alternatives, such as pharmaceutical nicotine replacement products (NRTs), tobacco-based nicotine-delivery pouches for oral use, and nicotine pouches do not entail combustion or inhalation. Therefore, they are associated with vastly lower health risks than cigarette smoking (3).

- Among smoker who want to quit, some manage do so unassisted, but the majority fail to become long-term smoke-free. NRTs and smoke-free tobacco like Swedish snus (which is a commonly used in Scandinavia) increase long-term cessation rates by providing nicotine substitution. Unfortunately, snus is not available outside Sweden and NRTs are often not attractive to or sufficiently effective amongst many smokers. Often, they are also too expensive.

- Tobacco-free nicotine pouches for oral use represent a novel category of nicotine delivery products. They have a toxicant profile similar to NRTs and more favorable to that of Swedish snus (Table 1). This includes the typical, complete absence of carcinogenic nitrosamines and polycyclic hydrocarbons (4, 5). Such compounds have for many decades been considered the most problematic in smoke-free tobacco products. The pouches have a nicotine delivery profile that more closely mimic that of cigarettes compared to NRTs which most likely helps to explain their efficacy for smoking cessation (6). They constitute an important addition to the currently limited range of cessation aids available to the many smokers who want to

quit, but fail to do so unassisted, or who do not want to quit without adequate nicotine replacement (7).

- Tobacco-free nicotine pouches have the potential to benefit public health in the same way that is documented for Swedish snus in Scandinavia, that is, by serving as a low-risk alternative to cigarettes.

- There is no science-based evidence or scientifically grounded reasons to believe that tobacco-free nicotine pouches will have a negative effect on current anti-tobacco efforts.

- Large-scale consumer surveys from the U.S. demonstrate that tobacco-free, nicotine pouches are almost exclusively attractive to current tobacco users. Current non-users expressed little or no interest in such products (8).

- With a smoking rate of 20.6 per cent, the Netherlands should put all energy into finding ways to support smokers to quit or to switch to less harmful products, therefore bans on novel, low risk, nicotine delivery products that have the potential to help cigarette smokers quit long-term should be avoided.

- Instead of a ban, the Netherlands should introduce a stringent product regulation of nicotine pouches and consider even further increasing the constraints on conventional cigarettes.

My background
I am an independent health expert with 50 years of experience relating to tobacco and public health. I have been engaged in the fight against smoking for decades. I developed some of the early pharmaceutical nicotine replacement therapies and have initiated several controlled clinical trials of smoking cessation products. I have published 180 peer reviewed scientific papers in the field of behavioral medicine, including 155 publications on nicotine and tobacco. In 1996 I initiated the European Society for Research on Nicotine and Tobacco (SRNT) and served as its chairman until 2003. In 1999 I received WHO´s Tobacco Free Award for Outstanding Contributions to Public Health.

Underpinning my engagement in the field of tobacco research is the broad acknowledgement in the scientific community that cigarette smoking is the most significant challenge for tobacco control, and that alternative, reduced risk nicotine delivery products play an important role to achieve a smoke-free future.

Tobacco-free nicotine pouches constitute a novel category of low-risk, nicotine delivery products. They typically consist of food-grade constituents and additives (e g fillers, stabilizers, pH adjusters, non-caloric sweeteners, flavorings), and pharma-grade nicotine. The pouch is placed in the mouth between the lip and the gum. The nicotine is delivered to the blood stream via the oral mucosa. This way of consuming nicotine does not involve combustion or inhalation of combustion products which, as mentioned, is the main cause of smoking related morbidity and mortality.

There is substantial scientific evidence from Scandinavia about the vastly reduced health risks associated with use of non-combusted, oral tobacco instead of cigarettes (9). In fact, many independent studies have consistently demonstrated that use of Swedish snus is unassociated with increased cancer risks including, for instance, the risk of lung cancer, oral cancer, and pancreatic cancer. Large-scale epidemiological studies have also consistently demonstrated that snus does not affect the risk of cardiovascular disease (myocardial infarction, stroke). Because oral use does not involve inhalation of toxic and irritating smoke, there is no increased risk of chronic pulmonary diseases with use of such products.

The scientific consensus about Swedish snus, its strict toxicological standards and its reduced risk properties compared to cigarettes, paved the way in 2019 for Swedish snus to be granted the first and, to date, the only Modified Risk Tobacco Product Order (MRTP) by the Food and Drug Administration (FDA) in the U.S. (10). A MRTP order requires determinations by the FDA that use of the product is associated with reduced health risks for the individual consumer compared to smoking, and that marketing of the product is consistent with protection of public health, considering both current users and non-users of tobacco. The FDA order specifically permits marketing of Swedish snus with the following health claims: *"Using … snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis".*

The levels of Harmful or Potentially Harmful Constituents (HPHCs) in nicotine pouches are typically substantially lower than in Swedish snus and comparable to those in NRTs (Table 1).

Nicotine delivery is an important factor for all types of nicotine replacement products in terms of smoking cessation efficacy. In this regard, tobacco-free nicotine pouches are comparable to Swedish snus (6). Both NRTs and snus have a well-documented ability to help some smokers to achieve long-term cessation (11, 12). It is thus reasonable to assume that also non-tobacco nicotine pouches have such a potential and may thus help to lower population smoking prevalence. Therefore, an outright ban is likely to be harmful to public health, particularly in country such as the Netherlands that have a comparatively high smoking prevalence..

There is reason to believe that the levels of highly carcinogenic constituents are substantially higher in some smokeless products with North African or South Asian origin, which are currently marketed in many European countries due to the lack of adequate quality control with the traditional manufacturing methods, and the lack of any constituent regulation in the current European Tobacco Products Directive.

To facilitate cigarette smoking cessation, consumers should be given scientifically based information about the relative health risks of cigarette smoking versus novel, reduced risk smoking cessation aids. Current smokers should also be given access to such reduced-risk products.

Health risks of nicotine?

Nicotine is a vasoactive substance with temporary physiological effects similar to those with caffeine, e. g. constriction of blood vessels, increased heart rate, and increased blood pressure. Exposure to high doses typically result in nausea and vomiting. Nicotine is the constituent that mainly contributes to the addictive potential of tobacco products. In young laboratory animals, nicotine may affect the development of the brain. These circumstances make it reasonable to introduce scientifically informed regulation for all types of nicotine delivery products.

However, there is convincing epidemiological data demonstrating that nicotine *per se* is unassociated with the diseases that make up most of the excess mortality observed among smokers, that is, cancer, cardiovascular disease, and chronic obstructive pulmonary disease (9). It can therefore be concluded that these well-documented adverse effects of smoking are almost exclusively related to the inhalation of combustion products and, thus help to explain the vast difference in health risks between nicotine products that involve combustion and inhalation versus those that are not combusted and are used orally (such as nicotine pouches) (2). A scientifically informed product regulation should take this difference into account.

User profile – what do we know?
Nicotine pouches have been on the European market for only a short time. Consequently, there is scant consumer data from Europe. However, consumer surveys conducted in the U.S. indicate that around 99 per cent of those using the leading brand of nicotine pouches were already established tobacco consumers when they started to use pouches (8). In another study, the content and nature of the pouch was explained to pouch-naïve members of a consumer panel. Only few of current non-users of tobacco expressed an interest in or intention to buy the product compared to those who were current exclusive smokers or dual users of tobacco products. Also data from Rijksinstituut voor Volksgezondheid en Milieu (RIVM) seems to suggest that there are very few users of a product such as nicotine pouches amongst adolescence (13).

Potential public health benefit of nicotine pouches
In Scandinavia the use of Swedish snus, an oral tobacco-based product, has to a large extent replaced cigarettes as the most commonly used tobacco product. In Sweden this has resulted in internationally record low rates of smoking and smoking-related disease, a phenomenon often referred to in the scientific literature as the "Swedish Experience" (12). According Swedish public statistics daily smoking rate is 5.8 per cent and occasional smoking rate is 4.5 per cent, amounted to 10.2 per cent in 2022 (14). According to WHO data, "tobacco-related" mortality is also at internationally record low rates in Sweden (15, 16).

From a consumer perspective, snus and non-tobacco nicotine pouches are similar in terms of how the products are used. Their nicotine delivery profiles are also comparable. Toxicologically, nicotine pouches represent an even lower risk option than snus (Table 1). Against this background there is reason to believe that also nicotine pouches can have significant positive effects on long-term smoking cessation rates and thus benefit public health.

Pragmatic regulation
Instead of banning nicotine pouches it would be appropriate to introduce a scientifically informed regulation of the category. The overarching aim should be to secure a high level of protection of public health, considering both current users and non-users of nicotine products, particularly among young people. It should include marketing restrictions (such as, age limits for purchase), a constituent regulation, and a cap on nicotine content. The cap should be set so that the nicotine exposure is comparable to and does not exceed that with Swedish snus (for instance, a maximum nicotine content of 10-15 mg per consumable).

Table 1:
Levels of selected HPHCs in cigarettes, Swedish snus, nicotine pouches, and a NRT product (lozenge). Note that the toxicity may be different according to the route of exposure. The selected HPHCs are those considered to be particularly relevant by the WHO Advisory Group on Tobacco Product Regulation. Data adapted from the publication by Azzopardi, Liu & Murphy (4).

Exposure/HPHC (type of constituent)	**Cigarette[1] (μg/cig)**	**Snus[2] (μg/pouch)**	**Nicotine pouches[3] (μg/pouch)**	**NRT lozenge (μg/consumable)**
Exposure route	Inhalation	Oral, buccal	Oral, buccal	Oral, buccal, ingestion
HPHC:				
Formaldehyde	94.9, 54.1	<0.7-1.12	0.79	*
Acetaldehyde	1732, 2200	4.83-6.44	*	*
Acrolein	172, 157	*	*	*
NNN (nitrosamine)	0.26, 0.26	0.39-0.45	*	*
NNK (nitrosamine)	0.28, 0,28	0.06-0.14	*	*
Benzo(a)pyrene (PAH)	0.014, 0.0013	*	*	*
1,3-Butadiene (combustion product)	91.8, 108	*	*	*
Benzene	72.9, 78.6	*	*	*
Carbon monoxide (combustion product)	29600, 32000	n.a.	n.a.	n.a.

[1] Based on 10-11 puffs on a scientific reference cigarette. The two values represent results from two separate studies
[2] Range among three commercial brands
[3] Range for four tested products, two of which are market leading
Abbreviations:
* The HPHC concentration was below the level of detection
n.a. Not applicable as the product does not entail combustion

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