UNIVERSITY OF GRAZ
Institute of Pharmaceutical Sciences
Department of Pharmacology and Toxicology

Humboldtstraße 46/I, A-8010 Graz, Austria

Department Head: O. Univ.-Prof. Dr. Bernhard-Michael Mayer
Tel. +43-316-380-5567 E-Mail: bernhard-michael.mayer@uni-graz.at

Consultatie Nicotineproducten zonder tabak

As a Professor of Pharmacology and Toxicology at the University of Graz, I have been active as a public advocate of alternative nicotine products as efficient tools for reducing the health risks of smoking. Besides many other activities, I have testified as a scientific expert before the Austrian Federal Ministry of Health (2015), the Austrian Constitutional Court (2015), the German Parliament (2016), the German Federal Ministry for Food and Agriculture (2016), and the European Parliament (2018 and 2019). I am financially and ideally independent of the industry and other interest groups.

Summary

1. 1. The harmful effects of smoking are mainly caused by inhaling carcinogenic and otherwise toxic substances present in the smoke of burned tobacco but not by nicotine.
2. The best option for smokers is quitting all nicotine products, but smokers who are unable or unwilling to quit benefit from switching to alternative nicotine products, which do not burn tobacco and expose users to substantially lower levels of toxicants than cigarette smoke.
3. According to the concept of tobacco harm reduction, alternative nicotine products with reduced risk should be available to adult smokers who would otherwise continue to smoke. Youth use of nicotine pouches is non-existent in the Netherlands.
4. The health risk of nicotine pouches is comparable to that of medicinal nicotine products.
5. Sufficiently high nicotine content is essential for former smokers' acceptance and use of alternative products.
6. The suggested maximal content of 0.035 mg of nicotine per pouch is based on an outdated limit established for food, particularly mushrooms, by the EFSA in 2009. This limit cannot be applied to products for intended nicotine consumption.
7. Limiting the nicotine content to 0.035 mg would be absurd, tantamount to a *de facto* ban of nicotine pouches with negative consequences for public health in the Netherlands.

Risk of using nicotine pouches compared to smoking

Nicotine pouches contain high-quality pharmaceutical-grade nicotine, flavorings, humectants to retain moisture content, and additives to ensure product stability but no tobacco [1]. While snus has been on the market for decades, nicotine pouches are relatively new products for which epidemiological data are limited. However, the safety of snus is evident from numerous epidemiological and clinical studies that were published in the last couple of decades (for a recent review, see [2]). It can be assumed that nicotine pouch users are exposed to even lower amounts of harmful and potentially harmful constituents, including 16 established carcinogens [3], partially extracted from unburned tobacco by snus users. Indeed, several recently published studies demonstrate that the health risks of nicotine pouches are by orders of magnitude lower than those posed by smoking and even lower than the minimal health risks posed by snus [4-7], a product that is widely accepted as a reduced risk product compared to continued smoking. In a recent health risk assessment of nicotine pouches [8], the *German Bundesinstitut für Risikobewertung* (BfR) notes that nicotine pouches have a more favorable safety profile than any tobacco products and placed the pouches close to medicinal nicotine patches, which are sold over the counter for smoking cessation.

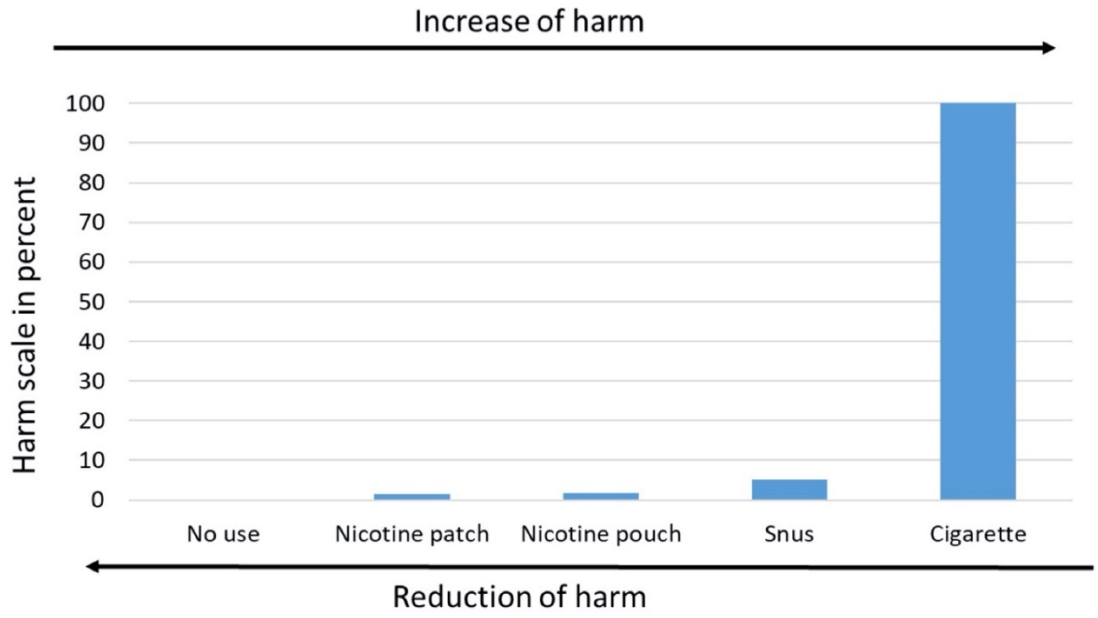


Fig. 1: Continuum of risk posed by nicotine products according to [8] (taken from BfR Opinion No. 042/2021, 21 December 2021,page 13).

Nicotine Biology

Stimulation of nicotinic receptors in sympathetic ganglia and nerve endings provokes a moderate increase in heart rate, systolic blood pressure, and peripheral vasoconstriction. These effects are mild, transient, and well-tolerated. There is scientific consensus that the detrimental effects of smoking, such as the increased risk of cancer, respiratory disease, and

cardiovascular disease, are primarily caused by carcinogenic and otherwise toxic compounds contained in tobacco smoke. Nicotine is not carcinogenic, and according to large clinical studies the rate of serious cardiovascular events is not increased by long-term use of nicotine [9,10]. A meta-analysis recently confirmed these results indicating that replacing tobacco cigarettes with nicotine-containing e-cigarettes incurs no additional cardiovascular risks [11].

Like other well-tolerated stimulants (e.g., caffeine), nicotine causes a release of dopamine in the *nucleus accumbens*, a component of the reward center in the brain that is essentially involved in reinforcing effects that stimulate further use. This effect is thought to be the basis for the addictive potential of nicotine [12]. There is substantial evidence that stimulation of nicotinic receptors in the brain improves cognitive performance, awareness, and memory [13-15], presumably explaining the widespread recreational use of nicotine products in the population. In addition, the anti-inflammatory effects of nicotine in the periphery and the brain protect against several inflammatory diseases, including Parkinson's disease [16,17] and ulcerative colitis [18,19]. Many researchers continue to investigate the properties of nicotine and its potential positive effects on cognition and health.

Adverse effects of nicotine

In recreational use, nicotine-containing products do not cause clinically relevant acute or chronic toxicity. Slight overdosing is readily recognized by dizziness, nausea, and headache, prompting users to stop or reduce nicotine intake. This self-titration with nicotine was reported for smokers [20,21] and users of e-cigarettes [22]. According to Andersson et al. (1995), the same applies to users of oral tobacco, who will also stop nicotine intake upon the occurrence of adverse symptoms [23]. Fatal cases of nicotine poisoning are sporadic and will not occur upon regular use of commercially available nicotine-containing products [24,25].

Application of food law to a product for intended nicotine consumption is absurd

The proposed limit of 0.035 mg of nicotine per pouch is based on the RIVM report [26], in which it has been suggested to limit the nicotine content in pouches according to the *Acute Reference Dose* (ARfD) estimated by the *European Food Safety Authority* (EFSA) as an acceptable limit in food [27]. This proposal reflects a complete misunderstanding of the purpose of nicotine pouches as a much less harmful alternative to combustible tobacco cigarettes used by (former) smokers to reduce their health risks. It is essential to distinguish between the unintended intake of nicotine in food and its intended use as a recreational drug. For example, one may limit the content of alcohol in orange juice to protect consumers from unintended intake of alcohol. However, it would be absurd to apply the same limit to Whiskey.

Overestimation of nicotine toxicity

The EFSA toxicity assessment, published in 2009, assumed a then widely accepted acute lethal dose for nicotine of 60 mg, corresponding to 0.6 - 1.0 mg/kg body weight for a 60 kg adult. Sticking to the outdated EFSA estimate, the RIVM report, and in consequence, the current legal proposition, failed to consider the more recent toxicological assessment of nicotine undertaken by the *European Committee for Risk Assessment* (RAC) [28]. The RAC considered 5 mg per kg body weight as a reasonable LD_{50} for calculating the *Acute Toxicity Estimate* (ATE) value for oral exposure to nicotine. This ATE value is in the same order as my estimate of 0.5-1 g of ingested nicotine as the lower limit for fatal outcomes, which corresponds to an oral LD_{50} of 6.5-13 mg per kg body weight or 390-790 mg of nicotine for a 60 kg adult [24]. Thus, the RIVM overestimated the acute toxicity of nicotine more than 10-fold based on the more recent RAC assessment.

Increased heart rate does not reflect nicotine toxicity

The EFSA defined the endpoint for the *Lowest Observed Adverse Effect Level* (LOAEL) as a detectable increase in heart rate caused by nicotine in humans. However, the slight and rapidly reversible increase in heart rate is a harmless pharmacological effect and not an adverse event with a toxicological meaning. Therefore, the LOAEL assigned by the EFSA to nicotine does not reflect toxicity but the lowest level at which a biological effect is detectable. Moderate exercise and many substances, for example, caffeine, also cause an increase in heart rate, but obviously, these effects do not reflect toxicity. In contrast to the RIVM, the BfR did not consider the EFSA LOAEL and ARfD values as measures for nicotine toxicity and defined 16.67 mg of nicotine per pouch as the upper limit based on a comprehensive study of nicotine effects [8]. Unfortunately, the thorough risk assessment performed by the German federal agency was ignored by the Dutch authorities.

Nicotine addiction

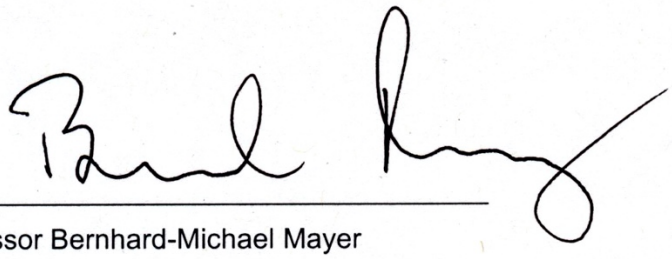
Nicotine contributes to the cigarette dependence of smokers *via* release of dopamine in the brain. The addictive potential of nicotine is strongly enhanced by other constituents of tobacco and tobacco smoke, which inhibit the breakdown of dopamine, resulting in a sustained increase of dopamine levels [29,30]. This combined action of nicotine and other tobacco-related substances is absent when using nicotine pouches, confirming the much lower addictive potential of tobacco-free nicotine products [31]. Moreover, the morbidity and mortality of smokers are caused by inhalation of toxic combustion products but not by their dependence. Therefore, discouraging smokers from using nicotine pouches by warning about nicotine addiction is unwarranted and misleading. The addictive potential of nicotine pouches does not justify the *de facto* ban on these products as proposed by the Dutch government.

Protection of minors

There is general agreement that youth should not consume nicotine and that selling nicotine products to the underaged must be prohibited. A recent study demonstrated that youth use of nicotine pouches is negligible in the Netherlands (0.31 % ever use, 0,00 % current use) [32]. These data demonstrate that the proposed bill would not contribute to youth protection while depriving adult smokers of a low-risk alternative to cigarettes.

Conclusion

Nicotine pouches help adult smokers to transition from harmful smoking to a low-risk alternative to nicotine consumption. Although Youth use of nicotine pouches is non-existent in the Netherlands, selling to minors must be prohibited to avoid potential misuse in the future. The products are not heated and do not contain tobacco, resulting in a safety profile similar to nicotine patches and other medicinal nicotine products recommended for smoking cessation. The proposed limit of 0.035 mg of nicotine per pouch is based on an outdated EFSA nicotine toxicity assessment to protect consumers from unintentional exposure to nicotine by contaminated food. Since (former) smokers use the pouches intentionally to substitute nicotine in cigarettes, the proposed limit is unacceptably low, rendering these products useless. It is strongly recommended that the Dutch government refrains from passing the proposed bill, which would harm public health in the Netherlands.



January 14, 2022

Professor Bernhard-Michael Mayer

References

1. Chapman, F., McDermott, S., Rudd, K., Taverner, V., Stevenson, M., Chaudhary, N., Reichmann, K., Thompson, J., Nahde, T. & O'Connell, G. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic, pharmacodynamic and safety and tolerability profiles of tobacco-free oral nicotine pouches relative to cigarettes. *Psychopharmacology (Berl)* **239**, 2931-2943 (2022) DOI: 10.1007/s00213-022-06178-6
2. Clarke, E., Thompson, K., Weaver, S., Thompson, J. & O'Connell, G. Snus: a compelling harm reduction alternative to cigarettes. *Harm Reduct. J.* **16**, 62 (2019) DOI: 10.1186/s12954-019-0335-1
3. Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. (2010) https://www.ncbi.nlm.nih.gov/books/NBK53010/
4. Bishop, E., East, N., Bozhilova, S., Santopietro, S., Smart, D., Taylor, M., Meredith, S., Baxter, A., Breheny, D., Thorne, D. & Gaca, M. An approach for the extract generation and toxicological assessment of tobacco-free 'modern' oral nicotine pouches. *Food Chem. Toxicol.* **145** (2020) DOI: 10.1016/j.fct.2020.111713
5. 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.*, 1-9 (2021) DOI: 10.1080/01480545.2021.1925691
6. Yu, F., Rudd, K., Pour, S. J., Sticken, E. T., Dethloff, O., Wieczorek, R., Nahde, T., Simms, L., Chapman, F., Czekala, L., Stevenson, M. & O'Connell, G. Preclinical assessment of tobacco-free nicotine pouches demonstrates reduced in vitro toxicity compared with tobacco Snus and combustible cigarette smoke. *Appl. Vitro Toxicol.* **8**, 24-35 (2022) DOI: 10.1089/aivt.2021.0020
7. Miller-Holt, J., Baskerville-Abraham, I., Sakimura, M., Fukushima, T., Puglisi, A. & Gafner, J. In vitro evaluation of mutagenic, cytotoxic, genotoxic and oral irritation potential of nicotine pouch products. *Toxicol. Rep.* **9**, 1316-1324 (2022) DOI: 10.1016/j.toxrep.2022.06.008
8. Bundesinstitut für Risikobewertung (BfR). Health Risk Assessment of Nicotine Pouches - Updated BfR Opinion No. 023/2022 of 7 October 2022. (2022) https://www.bfr.bund.de/cm/349/health-risk-assessment-of-nicotine-pouches.pdf
9. Benowitz, N. L., Pipe, A., West, R., Hays, J. T., Tonstad, S., McRae, T., Lawrence, D., St Aubin, L. & Anthenelli, R. M. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: A randomized clinical trial. *JAMA Intern. Med.* **178**, 622-631 (2018) DOI: 10.1001/jamainternmed.2018.0397
10. Mills, E. J., Thorlund, K., Eapen, S., Wu, P. & Prochaska, J. J. Cardiovascular events associated with smoking cessation pharmacotherapies: A network meta-analysis. *Circulation* **129**, 28-41 (2014) DOI: 10.1161/CIRCULATIONAHA.113.003961
11. La Rosa, G., Vernooij, R., Qureshi, M., Polosa, R. & O'Leary, R. Clinical testing of the cardiovascular effects of e-cigarette substitution for smoking: a living systematic review. *Intern. Emerg. Med.*, (Epub ahead of print) (2023) DOI: 10.1007/s11739-022-03161-z

12. Fagerström, K. Determinants of tobacco use and renaming the FTND to the Fagerström test for cigarette dependence. *Nicotine Tob. Res.* **14**, 75-78 (2012) DOI: 10.1093/ntr/ntr137

13. Beer, A. L. (2016) Nicotine and cognition: Effects of nicotine on attention and memory systems in humans. in *Neuropathology of Drug Addictions and Substance Misuse*. pp 282-290

14. Nop, O., Senft Miller, A., Culver, H., Makarewicz, J. & Dumas, J. A. Nicotine and cognition in cognitively normal older adults. *Front Aging Neurosci* **13**, 640674 (2021) DOI: 10.3389/fnagi.2021.640674

15. Spasova, V., Mehmood, S., Minhas, A., Azhar, R., Anand, S., Abdelaal, S., Sham, S., Chauhan, T. M. & Dragas, D. Impact of nicotine on cognition in patients with schizophrenia: A narrative review. *Cureus* **14**, e24306 (2022) DOI: 10.7759/cureus.24306

16. Quik, M., Zhang, D. H., McGregor, M. & Bordia, T. Alpha7 nicotinic receptors as therapeutic targets for Parkinson's disease. *Biochem. Pharmacol.* **97**, 399-407 (2015) DOI: 10.1016/j.bcp.2015.06.014

17. Ma, C., Liu, Y., Neumann, S. & Gao, X. Nicotine from cigarette smoking and diet and Parkinson disease: A review. *Transl. Neurodegener.* **6**, 18 (2017) DOI: 10.1186/s40035-017-0090-8

18. Pullan, R. D., Rhodes, J., Ganesh, S., Mani, V., Morris, J. S., Williams, G. T., Newcombe, R. G., Russell, M. A. H., Feyerabend, C., Thomas, G. A. O. & Sawe, U. Transdermal nicotine for active ulcerative colitis. *N. Engl. J. Med.* **330**, 811-815 (1994) DOI: 10.1056/nejm199403243301202

19. Hayashi, S., Hamada, T., Zaidi, S. F., Oshiro, M., Lee, J., Yamamoto, T., Ishii, Y., Sasahara, M. & Kadowaki, M. Nicotine suppresses acute colitis and colonic tumorigenesis associated with chronic colitis in mice. *Am. J. Physiol.* **307**, G968-G978 (2014) DOI: 10.1152/ajpgi.00346.2013

20. Ashton, H., Stepney, R. & Thompson, J. W. Self-titration by cigarette smokers. *Br. Med. J.* **2**, 357-360 (1979) DOI: 10.1136/bmj.2.6186.357

21. Ashton, H. & Watson, D. W. Puffing frequency and nicotine intake in cigarette smokers. *Br Med J* **3**, 679-681 (1970) DOI: 10.1136/bmj.3.5724.679

22. Dawkins, L. E., Kimber, C. F., Doig, M., Feyerabend, C. & Corcoran, O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology (Berl)* **233**, 2933-2941 (2016) DOI: 10.1007/s00213-016-4338-2

23. Andersson, G., Axéll, T. & Curvall, M. Reduction in nicotine intake and oral mucosal changes among users of Swedish oral moist snuff after switching to a low-nicotine product. *J. Oral Pathol. Med.* **5**, 229-236 (1976) DOI: 10.1111/j.1600-0714.1976.tb01769.x

24. Mayer, B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. *Arch. Toxicol.* **88**, 5-7 (2014) DOI: 10.1007/s00204-013-1127-0

25. Maessen, G. C., Wijnhoven, A. M., Neijzen, R. L., Paulus, M. C., van Heel, D. A. M., Bomers, B. H. A., Boersma, L. E., Konya, B. & van der Heyden, M. A. G. Nicotine intoxication by e-cigarette liquids: a study of case reports and pathophysiology. *Clin. Toxicol.* **58**, 1-8 (2020) DOI: 10.1080/15563650.2019.1636994

26. RVIM. Nicotineproducten zonder tabak voor recreatief gebruik. (2021) https://www.rivm.nl/en/bibcite/reference/339001

27. EFSA. Potential risks for public health due to the presence of nicotine in wild mushrooms. *EFSA Journal* **RN-286**, 1-47 (2009) DOI: doi.org/10.2903/j.efsa.2009.286r

28. European Chemicals Agency (ECHA) - Committee for Risk Assessment (RAC). Opinion - proposing harmonised classification and labelling at EU level of Nicotine (ISO); 3-[(2S)-1-methylpyrrolidin-2-yl]pyridine. EC Number: 200-193-3 CAS Number: 54-11-5, CLH-O-0000001412-86-68/F. (2015) https://echa.europa.eu/documents/10162/23665416/clh_opinion_nicotine_5579_en.pdf/0103fadb-e945-4839-c4f4-17d20854adf0

29. Guillem, K., Vouillac, C., Azar, M. R., Parsons, L. H., Koob, G. F., Cador, M. & Stinus, L. Monoamine oxidase inhibition dramatically increases the motivation to self-administer nicotine in rats. *J. Neurosci.* **25**, 8593-8600 (2005) DOI: 10.1523/JNEUROSCI.2139-05.2005

30. Hogg, R. C. Contribution of monoamine oxidase inhibition to tobacco dependence: A review of the evidence. *Nicotine Tob. Res.* **18**, 509-523 (2016) DOI: 10.1093/ntr/ntv245

31. Etter, J. F. & Eissenberg, T. Dependence levels in users of electronic cigarettes, nicotine gums and tobacco cigarettes. *Drug Alcohol Depend.* **147**, 68-75 (2015) DOI: 10.1016/j.drugalcdep.2014.12.007

32. Havermans, A., Pennings, J. L. A., Hegger, I., Elling, J. M., de Vries, H., Pauwels, C. G. G. M. & Talhout, R. Awareness, use and perceptions of cigarillos, heated tobacco products and nicotine pouches: A survey among Dutch adolescents and adults. *Drug Alcohol Depend.* **229 (Pt. B)**, 109136 (2021) DOI: 10.1016/j.drugalcdep.2021.109136