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Health Risk Assessment of Nicotine Pouches

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Nicotine pouches are new, tobacco-free products, currently emerging on the consumer market of certain countries. They contain a powder made up of nicotine salts and fillers. The BfR has assessed these products with regard to possible health effects based on existing studies and data. Experimental studies by the BfR were included in the current assessment. These studies have not yet been completed, thus a comprehensive assessment is not possible at the moment. The German state authorities classify nicotine pouches as a novel food product.

1 Subject of the Assessment

Nicotine pouches are new products that were described, e.g. in the USA, Great Britain and Sweden, in 2019 [1]. In Germany, they were among the subjects in focus of a so-called Bundestag resolution (Bundestag paper 19/20667 of July 1st, 2020) in 2020.

Nicotine pouches are small pouches that contain powders with nicotine. According to the manufacturer, nicotine salts are used, which are mixed with microcrystalline cellulose, various salts (e.g. sodium carbonate and hydrogen carbonate), citric acid and aroma compounds [1]. They do not contain tobacco though. The BfR was requested to provide a health-based assessment of nicotine pouches. These products are sometimes also referred to as all-white products.

The BfR prepared a preliminary health assessment in March 2021, which was discussed in various meetings. Furthermore, experimental studies with different nicotine pouches were carried out at the BfR, the results of which are included in this assessment.

2 Results

Nicotine pouches are new, tobacco-free products. The highest amount of nicotine, according to the knowledge of BfR, is 47.5 mg nicotine/pouch. Based upon own analyses, tobacco-specific nitrosamines (TSNA) were detected in some of the nicotine pouches. Pharmacokinetic tests revealed that at least half of the nicotine in the pouch can be absorbed, albeit these tests were carried out with nicotine doses of a maximum of 8 mg nicotine per pouch only. Relevant blood levels can be reached, i.e. with nicotine levels being in a comparable range as found after consuming conventional cigarettes or certain brands of e-cigarettes.

A few cases of poisoning with nicotine pouches have been observed. However, none of them can be categorised as severe.

Nicotine is a biogenic yet non-physiological compound in the human body. At certain levels it can be acutely toxic; an estimated acute toxicity value of 5 mg/kg bodyweight has been defined for oral exposure. Depending on the dose incorporated, nicotine increases the number of stillbirths and may affect the cardiovascular system. Nevertheless, the long-term effects of consuming nicotine pouches cannot be reliably assessed based on the limited amount of data available at the moment.

Nicotine pouches are currently being classified as novel food products by the Federal State authorities in Germany and are being withdrawn from the market due to the lack of approval.

Despite all limitations in the data sets available, the BfR is concerned of health risks that likely may affect – due to its addictive potential – vulnerable subgroups in the human population, such as children, adolescents and non-smokers. Further concern relates to pregnant and breastfeeding women (embryotoxicity, developmental toxicity, transfer of nicotine into breast milk), and people who suffer from cardiovascular diseases.

3 Rationale

Nicotine is a natural component of tobacco leaves; cigarette tobacco contains up to 1.5 % nicotine [2]. The use of cigarette tobacco, pipe tobacco and chewing tobacco has been known for a long time and is not the subject of this assessment. Reference is made again to the effects of cigarette consumption at the end of the report. Nicotine is used as a component of liquids applied in e-cigarettes. In the EU, this kind of use is regulated in the Tobacco Product Directive 2014/40/EU, although e-cigarettes do not contain tobacco. Nicotine is also used in pharmaceutical products for replacement therapy in smokers.

In Sweden and some other countries, tobacco is marketed in small pouches that are placed between the upper lip and the gums for a certain time. These products often contain flavouring compounds. In Sweden, this form of tobacco is called “snus” and has now been used for many years. In the EU, snus may not be sold outside of Sweden. In the USA there are comparable products available at the market. Although these are usually called “snuff”, they are actually not being snuffed but also placed between the upper lip and the gums. Already for some years now, similar products became available that do not contain tobacco in the pouches, but rather fillers with nicotine salts aroma compounds and other additives.

This health-based assessment of the BfR only addresses such pouches that contain nicotine. For this we also considered data of studies that looked into oral tobacco products, e.g. Swedish snus. Conversely, studies evaluating the health hazards of tobacco smoking were excluded, as it is well known that, in addition to nicotine, numerous other toxicologically relevant compounds can be found in tobacco smoke which also contribute to the danger associated with this source.

3.1 Risk assessment

3.1.1 Hazard identification

In order to gain initial insights into the chemical composition of nicotine pouches, the BfR carried out own analyses. 44 nicotine pouches were purchased online and then tested for weight, nicotine content and pH value. The content of tobacco-specific nitrosamines (TSNAs) was also analysed. In addition, the labels on the packages were evaluated. The rate of nicotine release was characterised with in vitro dissolution experiments. A pharmacokinetics study on nicotine uptake during product use is currently being carried out in cooperation with a clinical department. Chemical characterisation of the flavouring substances present in these products is still in progress at the BfR. The detailed results of the investigations will be published in the peer reviewed literature later on.

The median weight and nicotine content per pouch was 0.6 g and 9.48 mg, respectively. The highest nicotine content measured in one pouch was 47.5 mg, and the lowest 1.79 mg.

The Dutch National Institute for Public Health and the Environment (RIVM) published a monograph on nicotine pouches in 2020, describing pouch weights of 0.25 to

0.8 g. In terms of nicotine, a range of 1.6 to 32.5 mg per pouch has been reported [3]. In a study of the US Centers for Disease Control and Prevention (CDC), 37 brands from six manufacturers were examined; the highest nicotine content reported was 6.11 mg per pouch [4]. An investigation by a manufacturer showed a weight of 0.7 g for four products [5]. The nicotine levels of the four products were found between 4.06 and 11.9 mg per pouch [5]. A study from the USA on snus from Northern Europe and from the USA revealed pouch weights in the range of 0.33 to 1.13 g per pouch, while the nicotine contents in the snus samples were between 6.81 and 20.6 mg/g [6] .

The median pH values of the aqueous extracts of the pouches examined by the BfR were 8.8. Only one product extract had a pH value in the acidic range. The Henderson-Hasselbalch equation was used to calculate the percentage of uncharged nicotine, also known as free-base nicotine. In the free-base form, nicotine can easily migrate through biomembranes such as the oral mucosa, which leads to a higher oral nicotine uptake. The median proportion of free-base was 86%.

In its monograph on nicotine pouches, the RIVM described pH values between 8.8 and 9.9 [3]. A study conducted by the US CDC on 37 brands showed a pH range of 6.94 to 10.1. This was converted into proportions of 7.7% to 99.2% of free-base nicotine [4]. An investigation by a manufacturer showed a pH range of 8.5 to 8.7 in four products [5].

Information on nicotine strength and labelling on the packaging:

The nicotine content was sufficiently declared in mg per pouch or per g only in about a third of the nicotine pouches examined. Most products were labelled with a statement according to their “nicotine strength”, either in a rather non-specified way (for example as strength 3 out of 5), or by using a qualitative measure such as “easy”, “medium”, “strong”, “extra strong”, “ultra”, “extreme”, “danger strong”, or “brutal”.

This conceptual information on the nicotine strengths was compared with the nicotine contents measured. Products with a nicotine strength indicated as being rather light had a slightly lower nicotine content than products that offered a medium nicotine strength. Products with nicotine strengths described as “medium” to “extra strong”, were not always in line with the respective nicotine contents measured. This makes a clear distinction between nicotine strengths difficult. One explanation could be that some manufacturers refer to the nicotine content per pouch and others per gram. However, this remains unclear to the consumer. Switching products between different manufacturers may therefore result in the doubling of the nicotine content per pouch even though the products are labelled with similar conceptual nicotine strength.

For products with descriptors that indicate a higher nicotine strength than “extra strong” (e.g. “ultra”, “extreme”, “danger strong” and “brutal”), the range of analysed nicotine contents was between 12.1 mg per pouch (product declared with “ultra”) and 47.5 mg per pouch (product declared with “brutal”).

Almost all products carried a warning sign advising against consumption by minors, only every fourth concerning the use during pregnancy. Due to the acute toxicity of nicotine, products with a nicotine content of 2.5 mg/g or more must be labelled with the GHS pictogram 07 (exclamation mark, signal word: Warning) and products starting at 16.7 mg/g with the GHS pictogram 06 (skull and crossbones, signal word: Danger).

Release rate of nicotine:

The release kinetics of nicotine were determined for selected nicotine pouches. It was investigated whether the pouches differ in the released proportion of nicotine and in the rate of nicotine release.

Between the different pouches, differences in the proportion of nicotine released in relation to the total nicotine content in the pouch and differences in the release rates were found. In four samples, over 70% of the nicotine content was released within the first 5 minutes. In contrast, seven other samples released less than 60% of the nicotine content within the first 10 minutes. In summary, it can be concluded that most of the nicotine pouches released the majority (> 80%) of their nicotine content within the time period studied (60 min), with the highest quantity in the first 20 minutes.

Tobacco-specific nitrosamines in nicotine pouches:

Tobacco-specific nitrosamines (TSNAs) include the four substances *N´*-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), *N´*-nitrosoanatabine (NAT) and *N´*-nitrosoanabasine (NAB). These compounds are formed from nicotine and the minor tobacco alkaloids nornicotine, anatabine and anabasine during fermentation of the tobacco leaves. Therefore, tobacco-based products, especially cigarettes, but also some oral tobacco products, contain considerable amounts of TSNAs. In unburned cigarette tobacco, for example, around 1900 ng NNN and 530 ng NNK per cigarette were found [7]. A recent comparison of American and Swedish oral tobacco products revealed concentrations of less than 1000 ng/g for the sum of the carcinogens NNN and NNK in most products. Up to 1930 ng NNN and 696 ng NNK per g were found in snus pouches [6]. Nicotine pouches do not contain any tobacco, but the added nicotine may have been isolated through extraction of tobacco leaves and thus may contain traces of TSNAs. In products that contain tobacco extracts, for example e-liquids, TSNAs were also detected at levels up to 60 ng NNN and 10 ng NNK per ml of e-liquid [8]. Therefore it seems possible that nicotine pouches may also contain TSNAs, e.g. due to the addition of tobacco extracts or the conversion of tobacco alkaloids that may be contained.

TSNAs were detected in more than half of the pouches analysed. The highest levels determined were 13 ng per pouch for NNN, 5.4 ng per pouch for NNK, 2.5 ng per pouch for NAT and 5.6 ng per pouch for NAB. It should be taken into account that TSNAs can also be formed endogenously in the digestive tract, e.g. as described for NNN in saliva [9].

In an investigation of a manufacturer TSNA levels of <10 ng/g were found in four products. In the same study, three different snus products revealed concentrations of 560 to 640 ng/g and 89 to 200 ng/g for NNN and NNK, respectively [5]. The study also examined the levels of other possible ingredients and contaminants belonging to the following four categories: carbonyl compounds (i.e., formaldehyde, acetaldehyde, acrolein and crotonaldehyde), organic compounds (i.e., benzo[*a*]pyrene, 1,3-butadiene and benzene), elements (i.e., arsenic, lead, cadmium, chromium, nickel and mercury), and aflatoxins (i.e., AFB1, B2, G1 and G2). However, all levels were below the respective detection limits [5].

3.1.2 Hazard characterisation

Nicotine is an alkaloid and a weak base with a pK_a value of 8.0 [2]. It stimulates nicotinic acetylcholine receptors, which are present in both the central nervous system and the autonomic nervous system. Depending on the dose applied, nicotine exposure may trigger a number of different reactions in the organism. Among other physiological reactions, it also may cause increases in blood pressure and heart rate. Mild symptoms of intoxication include nausea and vomiting, with higher exposure symptoms such as diarrhoea, increased salivation and slowing of the heartbeat. Severe poisoning can be characterised by seizures and respiratory depression [10].

Due to their electrophilic properties, nitrosamines may cause base modifications of the DNA [11]. Certain representatives of these compounds are strongly genotoxic carcinogens with organ-specific effects. A total of seven TSNAs have so far been detected in smokeless tobacco products. Two of the substances, NNN and NNK, have been classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens (carcinogenic to humans) [12].

Until a few years ago, and as stated in pharmacology and toxicology textbooks, an oral dose of 60 mg nicotine per person was assumed to be potentially lethal. In 2014, this assumption was assessed by a pharmacologist who, in view of the confusing sources on the one hand and human poisoning case studies on the other, suggested a lethal oral dose of more than 500 mg of nicotine per person [13]. In the assessment of nicotine according to chemical law in 2015, the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) adopted this assessment of human toxicity [14]. The ECHA reassessed the classification for acute nicotine toxicity. The RAC came to the conclusion that only the studies on acute oral toxicity in mice and dogs are relevant for classification, since the studies in rats showed significantly higher LD50 values. The LD50 values for mice were 3.3 and 24 mg/kg bodyweight and for dogs 9.2 mg/kg bodyweight [14] and thus in a comparable range as calculated for human toxicity with an LD50 of 6.5 to 13 mg/kg bodyweight. As a consequence, the RAC proposed a classification of nicotine as Acute Toxicity 2 (oral) with the hazard warning “H300: Fatal if swallowed” and with an estimated acute toxicity value of 5 mg/kg body weight. According to EU Regulation 2018/1480, this recommendation has now been implemented into applicable law.

At the meeting of the “Poisoning Commission of the BfR” in December 2020, the representatives of the German speaking poison information centres reported on some cases of poisoning associated with the (mis-)use of nicotine pouches. In one case a pouch of 20 mg nicotine was swallowed. The affected person received activated charcoal from the rescue service. Except for stomach pain, this patient did not develop any severe symptoms.

Further effects on test persons were also examined [15]. In this study data of one manufacturer reporting on the differences between nicotine toxicokinetics of nicotine pouches and Swedish snus were included (see also 3.1.3). Heart rates and the perception of light intoxication symptoms (“head buzz”) were examined in the test subjects. For this purpose, nicotine pouches (3 mg or 6 mg nicotine per pouch) and snus (8 mg nicotine per pouch) were used for 60 minutes.

Table 1: Effects of nicotine pouch and snus consumption in volunteers (from [15])

Heart rate (beats per minute - bpm) and "head buzz" were examined with the help of a visual analogue scale (VAS) during the 60-minute use of nicotine pouches or Swedish snus with 8 mg nicotine per pouch.

	Max. "head buzz" VAS (mm)		Max. change in heart rate (bpm)	
Product	Median (Q1;Q3)	Range	Median (Q1;Q3)	Range
3 mg of nicotine	9 (4;19)	0 - 59	8.5 (5.5; 14.5)	4.0 – 18.0
6 mg nicotine	11 (5; 26)	0 - 63	10.5*(9.5; 16.5)	4.5 – 22.5
Snus (8 mg)	24* (12; 47)	0 - 62	11.0 (4.0; 15.0)	0.0 – 22.0

* Statistically significant difference to the group with 3 mg nicotine per pouch ($p < 0.05$), Wilcoxon signed-rank test

The healthy participants showed that a single dose of the nicotine-containing pouches was well tolerated. Two cases of dry mouth were assessed as substance-related. The increase in heart rate (see Table 1) can be easily explained by the physiological effects of nicotine. This effect was also dose-dependent: the changes in the 6 mg dose group are significantly higher than in the 3 mg dose group. For the other endpoint, "head buzz", the Swedish snus product stood out, demonstrating significantly higher visual analogue scale (VAS) values than the two nicotine pouch doses [15].

In 2009, EFSA established an acute reference dose (ARfD) for nicotine of 0.0008 mg/kg bodyweight by using the lowest observed adverse effect level (LOAEL) of 0.0035 mg/kg bodyweight. The adverse effect noticed was an increase in the heart rate [16]. At that dose, the heart rate increased by about 7 beats per minute [17]. The median increase of 8.5 beats when using nicotine pouches with 3 mg nicotine is comparable (see Table 1).

In an earlier US study, the cardiovascular effects of cigarette consumption were compared with the use of American "snuff" in ten healthy smokers. In one study part, a cigarette was smoked with one puff every 45 seconds for twelve puffs, in the other study part, a pouch of American "snuff" weighing 2.5 g was placed between the upper lip and the gum for 30 min. Blood samples were taken at different time points and heart rate and blood pressure were measured. The absorbed dose was calculated based on nicotine measurements; it was 1.8 mg nicotine for cigarette consumption and 3.6 mg nicotine for snuff consumption. The heart rate increased by 26 beats per minute after cigarette consumption and by 18.2 beats per minute after snuff consumption. The blood pressure increased by 18.6 mm (systolic) and 12.2 mm (diastolic) for cigarette consumption and 15.6 mm (systolic) and 11.4 mm (diastolic) for snuff consumption [18]. The study shows that the consumption of a cigarette or a pouch of American "snuff" leads to a relevant increase in the heart rate and blood pressure.

In a review article, the relationship between nicotine and type 2 diabetes is pointed out [19]. Cigarette smoking is an important risk factor for developing type 2 diabetes. Compared to non-smokers, smokers show an increased insulin resistance, but there is no evidence for an effect on insulin secretion. On the one hand, nicotine can increase insulin resistance by increasing the levels of insulin antagonists (catecholamines, cortisol and growth hormones). On the other hand, nicotine activates a protein kinase that can induce insulin resistance [19].

Reproductive toxicity:

Nicotine crosses the human placenta throughout pregnancy [20]. Nicotine concentrations are higher in the placenta, amniotic fluid and foetal serum than in maternal serum [20]. Nicotine concentrations were determined in maternal serum and breast milk after childbirth; the concentration in breast milk was 2.9 times higher than in serum [21].

A population-based cohort study was carried out in Sweden to investigate the risk of stillbirth. The investigation consisted of an analysis of the birth register for the years 1999 to 2006 (n = 610,879). The birth register also contains information on the mother's tobacco consumption. 7629 women consumed snus, 41,488 women were described as light smokers (1 to 9 cigarettes per day) and 17,014 women as heavy smokers (at least 10 cigarettes per day). Information on tobacco consumption was missing in the case of 39,734 women. A risk of stillbirth was determined for these groups compared to women who did not consume tobacco.

Table 2 shows that snus consumption increases the risk of stillbirths during pregnancy. Heavy cigarette smokers had an even higher risk of stillbirth [22].

Table 2: Relationship between tobacco consumption and stillbirths (from [22])

Tobacco consumption is subdivided on the basis of cigarette consumption per day or snus consumption. The stillbirths (cases), the conversion to cases per thousand pregnant women and the adjusted odds ratios are given.

Tobacco consumption	Cases	Quota (1/1000)	Adj. OR	(95% CI)
None	1386	2.7	1.00	
Snus	40	5.2	1.60	1.13 – 2.29
Cigarettes				
1 – 9	172	4.1	1.40	1.17 – 1.67
≥10	120	7.1	2.42	1.96 – 2.99

Genotoxicity:

In their monograph on nicotine pouches, the RIVM reported no evidence for mutagenic activity of nicotine [3]. Nicotine has been tested for genotoxic properties in various studies. The Ames test always gave negative results [23-25]. Another study revealed negative results in both an Ames test and for sister-chromatid exchange (SCE) in cells of Chinese hamster ovaries [26]. A hypoxanthine phosphoribosyltransferase (HPRT) mutagenicity test was carried out in V79 cells, which was also negative [27], the same as an in vitro micronucleus test in human lymphocytes [28].

Conversely, positive results in SCE and chromosome aberration tests in cells from Chinese hamster ovaries were compiled in a review article. The positive results were confirmed in human lymphocytes in vitro [29]. Similarly, fibroblasts from human gums showed a significant increase in micronucleus formation after treatment with nicotine [30].

By contrast, treatment of male mice with 1 or 2 mg nicotine/kg body weight nicotine lacked any micronucleus formation in the bone marrow when compared to control mice [31]. In a follow-up study, higher nicotine doses (up to 16 mg/kg body weight) and longer treatment times (up to 36 hours) were applied. At the highest doses of 8 and 16 mg/kg body weight increased micronucleus formation in the bone marrow of female and male mice was observed after 30 and 36 hours, respectively [32].

In summary, negative as well as positive results can be observed both in vitro and in vivo, depending on the doses and incubation times applied.

Carcinogenicity:

In their monograph on nicotine pouches, the RIVM reported that there is no evidence of carcinogenic properties of nicotine [3]. In another review article from 2015, Sanner & Grimsrud stated that no conclusions can be drawn about possible tumour-inducing effects of long-term treatment with nicotine [29]. A recent publication examined tumour-inducing effects of e-cigarette aerosol in mice [33]. The animals (n = 45) were exposed to the aerosol of e-cigarettes for 54 weeks, 4 hours a day and five days a week; the liquid used had a nicotine concentration of 36 mg per ml. Five animals from the treatment group died or required euthanasia. The control groups were exposed either to the vehicle (n = 20) or to filtered air (n = 20). Nine out of 40 treated mice developed lung tumours that were identified as adenocarcinomas. One animal from the control group with filtered air developed adenocarcinoma. A statistically significant difference was found when the two control groups were compared with the treated group [33]. It should be noted that only one dose was used in the treatment group, the group sizes were smaller than those specified in the guidelines for long-term carcinogenicity studies, and that the aerosol of e-cigarettes may contain many additional potentially carcinogenic substances besides nicotine. A conclusive assessment of the carcinogenic effects of nicotine based on this study is thus not possible.

Addictiveness:

The BfR does not yet have any specific data on possible addiction-inducing effects of nicotine pouches. However, it seems likely that this form of nicotine application is also prone to induce addictiveness in the consumer.

3.1.3 Exposure assessment

The relevant routes for the uptake of nicotine into the body are ingestion (orally), through the skin (dermally), or inhalation. Most relevant data on the pharmacokinetics and metabolism of nicotine are summarised in the review article of Benowitz et al. [2]. Consumption of a cigarette leads to a systemic intake of 1 to 1.5 mg nicotine. In the EU, the upper limit of nicotine in the smoke of one cigarette is one milligram. After inhaling cigarette smoke, nicotine reaches the brain within 10 to 20 seconds [2]. At the physiological pH of blood (7.4), approximately 69% of nicotine becomes protonated (ionic form), and the remaining 31% stays non-ionic, the latter also termed as free-base nicotine. Nicotine easily migrates through cell membranes only in its non-ionic form.

When using nicotine pouches, nicotine is mainly absorbed through the mucosal epithelium in the oral cavity. The nicotine pouches are placed between the upper lip and the gums for a period of up to 30 minutes. The pouches should not be swallowed.

The pharmacokinetics of nicotine in nicotine pouches was recently investigated [15]. In this study financed by a manufacturer, three different nicotine strengths were used in two parts of the study (3 and 6 mg nicotine per pouch in the first part and 8 mg nicotine per pouch in the second part). For comparison, snus was examined in the first part of the study (weight: One gram per pouch, 8 mg nicotine per pouch). The participants (n = 17) placed a pouch between the upper lip and the gum and removed it after 60 minutes. Blood samples were taken at the beginning, at various times during use, and up to five hours after removal of the pouch and then analysed for the respective nicotine concentrations in the plasma. After use, the pouches were examined for the remaining nicotine contents. The authors used these data to calculate the nicotine extraction. While nicotine extraction for the 3 mg and 6 mg pouches was 56% and 59%, respectively, only 32% of the nicotine was extracted from snus (see Table 3).

Table 3: Nicotine release from pouches and snus (from [15])

The results are from both parts of the study with different numbers of participants. In the first part, the participants used Swedish snus with 8 mg nicotine per pouch. In the second two pouches with 8 mg nicotine.

	Number of participants	Nicotine content	Extracted nicotine	Extracted nicotine
Product		in mg/pouch	in mg/pouch	in % of the total amount
Nicotine pouch	17	3	1.59	55.9
Nicotine pouch	17	6	3.51	59.1
Nicotine pouch	30	8	3.79	50.4
Swedish snus	17	8	2.41	32.0
Swedish snus	30	2 x 8	5.04 (with 2 pouches)	32.6
American snus	30	18	2.99	18.9

The peak concentrations measured in the blood after application of 3 mg and 6 mg were 7.7 ng/ml and 14.7 ng/ml, respectively. For comparison, snus (8 mg nicotine per pouch) yielded 10.6 ng/ml (see Table 4). These concentrations were determined 61 (3 mg dose), 66 (6 mg dose) and 69 (snus) minutes after application. The half-lives calculated were 152 min (3 mg dose), 140 min (6 mg dose) and 144 min (snus) (see Table 4).

In the second part of the Swedish study, the kinetics after consuming pouches of 8 mg nicotine were investigated with a larger group of participants (n = 30) and again compared with Swedish and US-American snus. The Swedish snus contained 8 mg nicotine per pouch. In the second part of the study, the subjects used two snus pouches at the same time, thus leading to a nicotine exposure of 16 mg. The American product contained 18 mg of nicotine per pouch. The nicotine extraction from the 8 mg nicotine pouches was 50%, from Swedish snus 33%, and from the American snus 19% (see Table 3). As summarised in Table 4, the peak blood concentrations were 18.5 ng/ml after 59 min for the 8 mg nicotine pouch, 21.2 ng/ml after 63 min for the Swedish snus and 16.9 ng/ml after 65 min for the American snus. The half-lives were 109 min (nicotine pouch), 114 min (Swedish snus) and 115 min (American snus), respectively [15].

Overall this study shows that after 60 minutes of use, at least half of the nicotine in the pouch is being extracted and taken up by the body (see Table 3). The majority of the nicotine is absorbed directly through the oral mucosa. Some of the nicotine might also be dissolved in saliva and then swallowed. This fraction can then be absorbed in the intestine. Different levels of nicotine extraction were found for the two snus samples examined. The

values were between 19% for the American product and 33% for the Swedish product (see Table 3). However, some manufacturers of nicotine pouches and snus recommend significantly shorter application times of 20 to 30 minutes. It therefore seems reasonable to assume that less nicotine is being absorbed. On the other hand, it is also reported that pouches containing tobacco (snus) might be used for up to 60 min [34], and it is possible that this consumption behaviour would also be adopted for nicotine pouches.

Table 4: Toxicokinetics of nicotine (from [15])

The results for snus and nicotine pouches taken from two parts of the study with different numbers of participants are combined. In the first part, the participants used Swedish snus with 8 mg nicotine per pouch. In the second two pouches with 8 mg of nicotine [15]. Values for conventional cigarettes and for e-cigarettes are provided for comparison.

	Nicotine content	C_{max}	T_{max}	$T_{1/2}$
Product	in mg/pouch	in ng/ml	in min	in min
Nicotine pouch	3	7.7	61	152
Nicotine pouch	6	14.7	66	140
Nicotine pouch	8	18.5	59	109
Swedish snus	8	10.6	69	144
Swedish snus	2 x 8	21.2	63	114
American snus	18	16.9	65	115
E-cigarette	Not applicable	8.4	5	106
Cigarette	Not applicable	15.0	No data	No data

The authors compared the values with data on e-cigarettes in the literature, in which nicotine peak concentrations of 8.4 ng/ml were measured after 5 minutes and the half-life was determined to be 106 minutes [15]. In comparison, in an earlier study peak values of 15 ng/ml were determined for conventional cigarettes after consumption [18]. In light of these data it can be stated that consumers of nicotine pouches incorporate significant amounts of nicotine as well. Due to the higher level of nicotine extraction compared to snus, consumer exposure is even higher in the case of nicotine pouches despite similar contents of nicotine. The study also confirms that increasing nicotine doses in the product lead to increasing nicotine concentrations in the blood. The nicotine content investigated in this study was no higher than 8 mg per pouch. Due to the lack of experimental data, no conclusions can yet be made about the blood concentrations that may occur at higher nicotine strengths.

Another pharmacokinetics study by a manufacturer examined the kinetics of six different products with different flavours, all of which had a nicotine content between 3.30 and 3.82 mg per pouch. All participants used all flavours. In the last part of the study, they were allowed to consume the brand of cigarettes they normally use. The test subjects placed the pouch between the upper lip and the gums for 30 minutes. The peak concentrations (C_{max}) measured were between 9.0 and 11.5 ng/ml for nicotine pouches and 16.3 ng/ml for cigarettes. The peak concentration for cigarettes was reached after 7.5 minutes, in the case of nicotine pouches this was not before 30.1 to 34.9 minutes. The flavouring of the pouches had no effect on the pharmacokinetics of nicotine [35].

The pharmacokinetics behaviour of nicotine present in nicotine pouches is currently being investigated by the BfR in cooperation with a clinical department at the medical university of Munich.

According to the German Association of the Tobacco Industry and New Products (BVTE), their member companies offer products that contain up to 20 mg nicotine per pouch.

However, analyses of the BfR revealed that products of up to 47.5 mg nicotine per pouch are also available at the German market. In the absence of experimental data for nicotine pouches that contain more than 8 mg nicotine, there remains some uncertainty. Nevertheless it is likely that higher nicotine doses in the product will also lead to higher nicotine concentrations in the blood of consumers. Exactly this issue is currently being addressed in the BfR study mentioned above.

There is also no sufficient data available on the dimension of nicotine pouch consumption in the general population. In a manufacturer study, the results of consumer surveys in Sweden were presented. Here the daily consumption of nicotine pouches every three months between the 1st quarter of 2018 and the 4th quarter of 2020 was investigated. In 2018 and 2019, the sample size remained between 20 and 99 people, while there were between 190 and 238 attendees in 2020. Based on the results of this study, an average of 8.6 nicotine pouches was consumed per day [5].

Tobacco-free nicotine pouches were introduced in the USA in 2016, and the market share in the smokeless tobacco segment rose to 4% by 2019 [36]. Analyses of consumer behaviour towards nicotine pouches were also carried out in the USA. The nicotine pouches only appealed to a small proportion of never and former tobacco users (11-12%). For active smokers, the product appealed to a share of 36%, while it appealed to 52% of smokeless tobacco users. The appeal was with 75% highest among people who consumed both cigarettes and smokeless tobacco [37].

In the UK in 2019, a survey among current and former users of cigarettes or e-cigarettes found that 4.4% had used nicotine pouches at least once [38]. Comparable studies for Germany are not yet available.

3.1.4 Risk characterisation

According to chemical law, classification of acute toxicity of nicotine is available. However, in this context only oral administration is being considered. On the basis of various animal studies and by considering human toxicity data, the ECHA Risk Assessment Committee has established an estimate of 5 mg nicotine/kg body weight for the acute toxicity of nicotine. The CLP Regulation specifies the following formula in Appendix 1, Part 3, No. 3.1.3.6.1 for calculating the acute toxicity of mixtures:

$$\frac{100}{\mathrm{ATE_{mix}}} = \sum_{n} \frac{\mathrm{C_i}}{\mathrm{ATE_i}}$$

The formula is rearranged in terms of c_i.

$$c_i = (100 \times \mathrm{ATE_i}) / \mathrm{ATE_{mix}}$$

In this specific case, the value of 5 mg/kg body weight is used as ATE_i (acute toxicity estimate). A value of 300 mg/kg body weight is used for ATE_{mix} (acute toxicity estimate for mixtures). This is the limit between categories 3 and 4 of acute oral toxicity (see also table 3.1.1 of the CLP Regulation). The formula then results in the following value:

$$(100 \times 5)/300 = 1.67\ \%$$

For nicotine pouches, this percentage would translate into a maximum concentration of 16.7 mg/g. Products with concentrations higher than 16.6 mg/g would therefore require classification according to hazard category 3 under chemical law and would thus need to be labelled with a skull and crossbones symbol.

From a toxicological point of view, this limit is easy to justify. As described under the section 3.1.2, the use of a pouch with only 6 mg nicotine resulted in a significant increase in the heart rate of 10 beats per minute. The concentration suggested here is even almost three times higher.

NNN and NNK are genotoxic carcinogens for which no threshold values can be defined. Thus, the concentrations of TSNAs in nicotine pouches should remain below the detection limit.

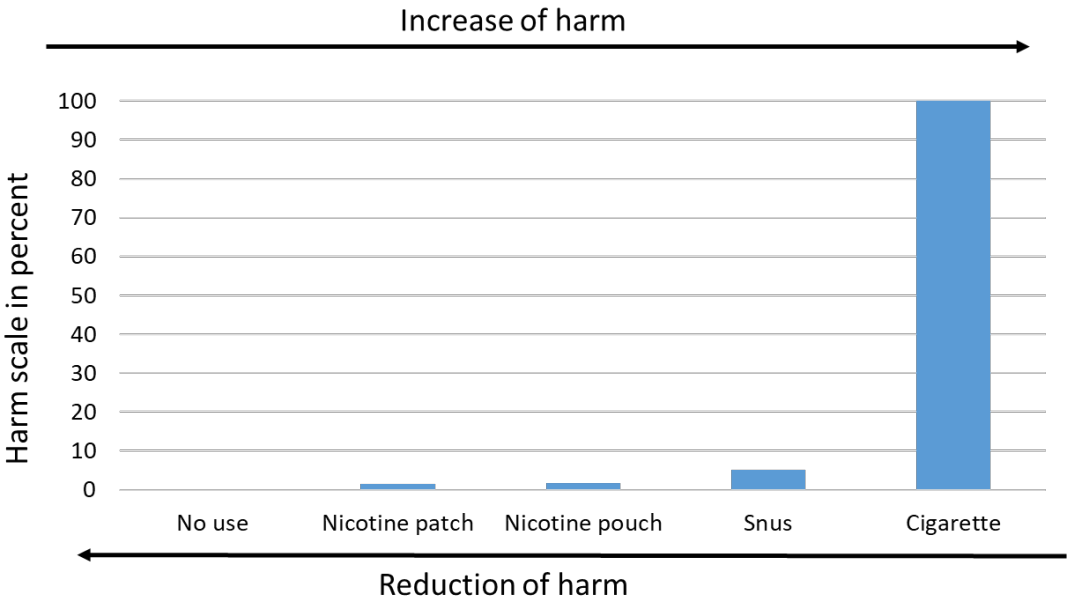
3.2 Framework for action, recommendations for measures

Currently, nicotine pouches are classified as a novel food product by German Federal State authorities. Using the ARfD value of 0.0008 mg/kg bodyweight, nicotine pouches containing the nicotine quantities presented in this report are to be withdrawn from the market. The BfR expects health risks in particular for the following vulnerable subpopulations: Children, adolescents and non-smokers, as nicotine is addictive. Pregnant and breastfeeding women, because of the effects of nicotine during pregnancy and because of the transfer of nicotine into breast milk. People with cardiovascular diseases, as nicotine has strong cardiovascular effects.

For now several years, the harmful effects of tobacco or nicotine products have been discussed. These discussion were mainly focussed on the option to switch to nicotine products that still contain or release harmful substances albeit to a lesser extent [39, 40].

This idea was further developed into a concept published by Abrams and colleagues; see Figure 1 [41].

Figure 1. Products along the harm minimisation continuum (modified from [41]).



The harm minimisation continuum assumes that nicotine-containing products are not equally harmful, but range from very low harmfulness (e.g. nicotine patches) to very high harmfulness (e.g. cigarettes). Figure 1 shows a selection of nicotine-containing products according to the study of Abrams et al. [41]. Most harmful are cigarettes, the consumption of which is responsible for the death of around 127,000 people in Germany each year [42]. Swedish-style snus is suggested to be much less harmful. On the other hand, the comparison between non-smokers and non-users of nicotine, who are summarised in the figure under “no use”, shows an increased risk for snus users. This assumption can be substantiated by an aggregated analysis of eight cohort studies in Sweden that have shown an increased mortality among snus users [43]. Nicotine pouches and nicotine replacement therapy such as nicotine patches do not contain tobacco. Still, nicotine patches can also lead to an exposure against TSNAs [44].

Figure 1 also emphasises that any form of nicotine consumption leads an increase in the health risks of people who have not previously smoked or consumed nicotine in any other kind.

With this concept in mind, switching from cigarettes to nicotine pouches might certainly represent a risk reduction step in smokers. However, there are still considerable uncertainties. As explained above, no data are yet available on the nicotine levels that will be reached in the blood after consumption of pouches with nicotine contents beyond 8 mg. It should be unwanted that consumption of nicotine pouches results in a higher nicotine uptake compared to other products available on the market. In the BfR study, genotoxic and carcinogenic TSNAs were found in some nicotine pouches. The fact that no TSNAs were detectable in several other pouch products demonstrates that it will be technologically feasible to produce such products without these hazardous compounds. From a toxicological point of view, genotoxic TSNAs should certainly not be detectable in nicotine pouches. Furthermore, the fraction of substances which is being swallowed, might also interact with food components, saliva, gastric and intestinal juice.

The formation of nitrosamines is known to occur in the presence of nitrosating agents, e.g. nitrite salts, preferably in an acidic environment. Therefore endogenous formation of carcinogenic TSNAs might occur in the human digestive tract [45]. Potential formation of TSNAs represents another critical issue that adds to the issue of very high nicotine contents measured in some of the nicotine pouches investigated. Altogether, it appears to be necessary to close existing knowledge gaps and to minimise the potential harm caused by nicotine pouches through standardization and regulation and by quality control measures.

3.3 Other aspects

Snus has been consumed in Sweden for many decades, with men using snus far more often than women. A recent study shows that snus does not facilitate the beginning of cigarette smoking. Furthermore, cigarette smokers who start using snus are more likely to quit cigarettes [46]. It is not yet possible to estimate whether a similar situation exists with nicotine pouches though.

With regard to tobacco-induced diseases, Sweden has a special position in Europe. An evaluation of cancer incidences and mortality rates in Europe in 2012 showed that Sweden was the only country in Europe where lung cancer was not at the top of cancer mortality rates in men [47]. Age-standardised cancer incidences were also calculated in the study. Among men, Sweden had the lowest value for lung cancer among the 40 countries in Europe investigated (28.8 per 100,000). In comparison, Germany had an incidence of 57.3 per 100,000, twice as high as in Sweden [47].

These data are also currently recognised, e.g. by the treatment network of the Society for Research on Nicotine and Tobacco [48]. However, it currently remains unclear whether these effects observed in the case of snus can be also transferred to the situation in the field of nicotine pouches.

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About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. The BfR advises the Federal Government and the States (‘Laender’) on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.

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