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Preliminary health risk assessment of nicotine pouches

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Nicotine pouches are new, tobacco-free products. They contain a white powder made up of nicotine salts and substrates. The BfR has provisionally assessed the health risk of these products based on existing studies and data. It has also started its own experimental studies with nicotine pouches and will present the results in the coming months.

1 Subject of the assessment

Nicotine pouches are new products that were described, e.g. in the USA, United Kingdom and Sweden, in 2019 [1]. In Germany they were, among other things, subject of a Bundestag resolution (Bundestag paper 19/20667 of July 1st, 2020) in 2020.

Nicotine pouches are products that contain nicotine-containing powders. According to the manufacturer, nicotine salts are used, which are mixed with microcrystalline cellulose, various salts (sodium carbonate and hydrogen carbonate), citric acid and aromas [1]. It does not contain any tobacco. According to the literature, the quantities of nicotine in the pouches are between two and eight milligrams [1, 2]. The BfR was asked to produce a preliminary health assessment of the nicotine pouches. These products are sometimes referred to as all-white products.

The BfR asked the German Federal Office for Consumer Protection and Food Safety (BVL) to collect information, among other things, at the level of the state authorities. Nicotine pouches are not subject to tobacco law, so there is no obligation for manufacturers to notify the European registration system EU-CEG. Only “nicotine” is declared on the packaging, there is no information about which nicotine salts are used. The products usually have an ingredient list, although products without an ingredient list have also been reported. The products tested had a weight of 0.38 to 1.1 g/pouch. The following nicotine levels were determined analytically: 0.44 - 3.45 g/100 g or 3.04 - 17.90 mg/pouch. The BfR has currently purchased various products for a research project and determined manufacturer information of up to 50 mg/pouch. This information has not yet been confirmed analytically. One investigation laboratory pointed out the strong aromatisation of all samples examined. Peppermint and menthol were used in particular.

2 Results

Nicotine pouches are new, tobacco-free products that were launched on the German market in 2019. The highest amount of nicotine known to the BfR is 50 mg nicotine/pouch. Pharmacokinetic studies, carried out with nicotine doses of a maximum of 8 mg nicotine per pouch, show that at least half of the nicotine in the pouches can be absorbed systemically through the oral mucosa. Relevant blood levels are achieved, i.e. the nicotine levels are in a range that is also achieved after consuming conventional cigarettes and some e-cigarettes.
A few cases of poisoning via nicotine pouches have been observed, but these did not follow a severe course.

* A new assessment of the BfR of 21 December 2021 is available (https://www.bfr.bund.de/cm/349/health-risk-assessment-of-nicotine-pouches.pdf)

Due to the effects of nicotine and its transfer to breast milk, it is not recommended that pregnant and breastfeeding women consume nicotine pouches. Furthermore, people with cardiovascular diseases, e.g. high blood pressure or coronary artery disease, are discouraged from consuming nicotine. Due to the addictive nature of nicotine and the ability of rapid nicotine absorption from the pouches, it is still not recommended that non-smokers and adolescents consume nicotine pouches. Furthermore, due to the effects of nicotine, it is recommended that nicotine pouches should be stored in containers so that they cannot be accessed by children.

The BfR has started its own experimental studies with nicotine pouches and, as already announced, will present the results in the coming months.

3 Rationale

Nicotine is a natural component of tobacco leaves; cigarette tobacco contains up to 1.5% nicotine [3]. The use of cigarette tobacco, pipe tobacco and chewing tobacco has been known for a long time and is not the subject of the assessment.

In Sweden and some other countries, tobacco is marketed in small pouches that are placed between the upper lip and gums for some time. In most cases, these products are flavoured. In Sweden this form of tobacco is called snus and has been used there for many years. In the EU, snus is not allowed to be sold outside of Sweden. In the US, similar products called "snuff" exist, but these should not be confused with tobacco products consumed via the nose. They are pouches of tobacco placed between the upper lip and gums like snus. In recent years, new products have been introduced in Germany and other European countries that contain no tobacco in the pouches, but rather nicotine salts, substrates and aromas. The health risk assessment of the BfR is limited to the use of nicotine in such pouches. Nicotine is also used as a drug/medical product for replacement therapy among smokers. This documentation makes reference to an oral, nicotine replacement preparation that is available in Germany as a lozenge in strengths of 1 and 2 milligrams. In the following, this assessment also features studies and assessments that deal with oral tobacco products, e.g. Swedish snus. Studies evaluating the health hazards of tobacco smoking were not taken into account here because, as it is well known, many other toxicologically relevant compounds can be found in tobacco smoke in addition to nicotine.

3.1 Risk assessment

3.1.1 Hazard identification

Nicotine is an alkaloid and a weak base with a pK_a value of 8.0 [3]. It stimulates the nicotinic acetylcholine receptors, which are found in both the central nervous system and the autonomic nervous system. Therefore, depending on the dose, nicotine exposure triggers a number of reactions in the organism. Among other things, it causes an increase in blood pressure as well as an increase in heart rate. Mild symptoms of intoxication include nausea and vomiting, with higher exposure symptoms such as diarrhoea, increased salivation and slow heartbeat. Serious poisoning may be characterised by epileptic seizures and respiratory depression [4].

Reproductive toxicity

Various examinations were carried out, including on fertility, as part of the preclinical testing of a nicotine replacement preparation: It has been shown in both humans and animals that nicotine can negatively affect sperm quality. Decreased fertility has been demonstrated in animals [5].

A population-based cohort study was carried out in Sweden to investigate the risk of stillbirth. The investigation included 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, among other things. 7629 women consumed snus, 41488 women were described as light smokers (1 to 9 cigarettes per day) and 17014 women as heavy smokers (at least 10 cigarettes per day). Information on tobacco consumption was missing from 39,734 women. A risk of stillbirth was determined for the tobacco consuming groups compared to women who did not consume tobacco.

Table 1 shows that snus consumption increases the risk of stillbirths during pregnancy. Heavy cigarette smokers had an even higher risk of stillbirth [6].

Table 1: Relationship between tobacco consumption and stillbirths (from [6])

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 ratio" 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

Various *in vitro* and *in vivo* studies were carried out, including on genotoxicity, as part of the preclinical testing of a nicotine replacement preparation [5]: *In vitro* genotoxicity studies gave positive and negative results within the same test system. Standard *in vivo* studies gave negative results for nicotine.

Carcinogenicity

The results of carcinogenicity studies did not provide any clear indication of a tumour-inducing effect for nicotine [5].

3.1.2 Hazard characterisation

Until a few years ago, an oral dose of 60 mg nicotine per person was described as a lethal dose in the pharmacology and toxicology textbooks. In 2014, this assumption was assessed by a pharmacologist who, in view of the confusing sources on the one hand and the descriptions of human poisoning cases on the other, concluded a lethal oral dose of more than 500 milligrams of nicotine per person was applicable [7]. In the assessment of nicotine according to chemical law in 2015, the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) adopted Mayer's assessment of human toxicity [8]. The ECHA assessment reassessed the classifications 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 on rats showed significantly higher LD50 values. The LD50 values for mice were 3.3 and 24 mg/kg body weight and for dogs 9.2 mg/kg body weight [8] and thus in a range that Mayer [7] also calculated in his human toxicity assessment with an LD50 of 6.5 to 13 mg/kg body weight. 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. This recommendation has now been implemented into applicable law with the EU Regulation 2018/1480.

At the meeting of the BfR “Assessment of Intoxications” Committee in December 2020, the representatives of the poison information centres reported on some cases of poisoning from 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 abdominal pain, no further symptoms developed.

Further effects on test persons were also examined [2] in a study that compared nicotine toxicokinetics when using nicotine pouches and Swedish snus (see also 3.1.3). Heart rate “head buzz” were examined in the test subjects. In this context, nicotine pouches (3 mg or 6 mg nicotine per pouch) and snus (8 mg nicotine per pouch) were used for 60 minutes.

Table 2: Effects of nicotine pouches and snus on test subjects (from [2])

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 significantly difference from the group with 3 mg nicotine per pouch ($p < 0.05$), Wilcoxon signed-rank test

The healthy volunteers showed that a single dose of the nicotine-containing pouches was well tolerated. Two cases of dry mouth were assessed as substance-related symptoms. The increases in heart rate (see Table 2) can be easily explained by the effect of nicotine. The effect is 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 as it did significantly higher VAS values than the two nicotine pouch doses [2].

In an earlier study from the USA, the cardiovascular effects of cigarette consumption was compared with the use of American snuff. The subjects were ten healthy smokers. In one test arm a cigarette was smoked with one puff every 45 seconds for twelve puffs, in the other test arm a pouch of American snuff weighing 2.5 grams was placed between the upper lip and gums for 30 minutes. Blood samples were taken at different times and heart rate and blood pressure were measured. The absorbed dose was determined from the 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 increases in blood pressure were 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 [9]. It can be seen from the study that even the consumption of a cigarette or a pouch of American snuff results in a relevant increase in heart rate and blood pressure.

The BfR does not yet have any specific findings on the addiction-inducing effect of the nicotine pouches. However, it is assumed that this form of nicotine use is also addictive.

3.1.3 Exposure assessment

Nicotine can be taken orally, dermally or via inhalation. When using conventional cigarettes or e-cigarettes, inhalation intake is crucial. The essential facts concerning the pharmacokinetics and metabolism of nicotine are summarised in a review article [3]. Accordingly, consumption of a cigarette leads to a systemic intake of between 1 and 1.5 mg of nicotine. In the EU, the upper limit for the nicotine concentration in the smoke of one cigarette is one milligram. After inhaling cigarette smoke, nicotine reaches the brain within 10 to 20 seconds [3]. In the bloodstream, nicotine is approximately 69% ionic and 31% non-ionic at a pH of 7.4. Nicotine can only pass through cell membranes in a non-ionic state. Nicotine accumulates in gastric juice

and saliva as well as in breast milk (milk/plasma ratio = 2.9). Nicotine easily crosses the placental barrier and, at the very least, reaches comparable concentrations in foetal and maternal serum [3].

When using nicotine pouches, nicotine is mainly absorbed through the mucous membrane in the oral cavity. Nicotine pouches are placed between the upper lip and gums for a period of up to 60 minutes and then removed. The pouches are not swallowed.

The toxicokinetics of nicotine from nicotine pouches was investigated in a recent study from Sweden [2]. The authors used three different strengths in two parts of the study (3 and 6 mg nicotine per pouch in the first part of the study and 8 mg nicotine per pouch in the second part of the study).

Table 3: Nicotine release from pouches and snus (from [2])

The results are summarised from two parts of the study featuring different numbers of test subjects. In the first part, the subjects used Swedish snus with 8 mg of nicotine per pouch while, in the second part, two pouches with 8 mg of nicotine were used.

Product	Number of subjects	Nicotine content in mg/pouch	Extracted nicotine in mg/dose	Extracted nicotine 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
Swed. snus	17	8	2.41	32.0
Swed. snus	30	2 x 8	5.04	32.6
Americ. snus	30	18	2.99	18.9

For comparison, snus was examined in the first part of the study. The subjects (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 the pouches were removed, and analysed for nicotine content. The used pouches were examined for the remaining nicotine content. The authors calculated the nicotine extraction from this; it was 56% and 59% for the 3 mg and 6 mg doses, while only 32% of the nicotine was extracted from the snus (see Table 3).

The peak concentrations in the blood for the 3 mg dose were 7.7 ng nicotine/mL and for the 6 mg dose 14.7 ng nicotine/mL; for comparison, snus (8 mg nicotine per pouch) yielded 10.6 ng nicotine/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 were 152 minutes (3 mg dose), 140 minutes (6 mg dose) and 144 minutes (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 test subjects (n = 30) and compared with a Swedish snus. The Swedish snus contains 8 mg of nicotine per pouch; in the second part of the study, the subjects used two pouches simultaneously resulting in an exposure of 16 mg of nicotine. The American product contains 18 mg of nicotine per pouch. Nicotine extraction from the 8 mg nicotine pouches was 50%, from the Swedish snus 33%, and from the American snus 19% (see Table 3). As summarised in Table 4, peak concentrations in the blood were 18.5 ng/mL after 59 minutes for the 8 mg nicotine pouches, 21.2 ng/mL after 63 minutes for the Swedish

snus and 16.9 ng/mL after 65 minutes for the American snus. The half-life here was 109 (nicotine pouches), 114 (Swedish snus) and 115 (American snus) minutes [2].

Table 4: Toxicokinetics of nicotine (from [2])

The results for snus and the nicotine pouches, taken from two parts of the study with different numbers of test subjects, are combined. In the first part, the subjects used Swedish snus with 8 mg of nicotine per pouch while, in the second part, two pouches with 8 mg of nicotine were used. Values are given for conventional cigarettes and for e-cigarettes for comparison.

Product	Nicotine content in mg/unit	C_{max} in ng/ml	T_{max} in minutes	$T_{1/2}$ in minutes
Nicotine pouch	3	7.7	61	152
Nicotine pouch	6	14.7	66	140
Nicotine pouch	8	18.5	59	109
Swed. snus	8	10.6	69	144
Swed. snus	2 x 8	21.2	63	114
Americ. snus	18	16.9	65	115
E-cigarette		8.4	5.1	106
Cigarette		15.0		

The study shows that after 60 minutes of use, at least half of the nicotine contained in a nicotine pouch is absorbed by the body (see Table 3. A substantial part of the nicotine is absorbed directly through the oral mucosa. This portion is not subject to the first pass effect, as the venous blood flows directly to the heart and does not pass through the liver first. This means that the nicotine reaches the central nervous system (CNS) without any loss. The other part is dissolved in the saliva and swallowed. This fraction can be resorbed in the gastrointestinal tract. Different nicotine extraction values were obtained for the two snus products examined. Here the values are between 19% for the American product and 33% for the Swedish product (see Table 3). Some manufacturers of nicotine pouches and snus recommend significantly shorter application times of 20 to 30 minutes. In that case, it may be assumed that less nicotine will be absorbed. On the other hand, pouches containing tobacco (snus) are often used for 60 minutes [10] and it is not unlikely that this usage behaviour would also be adopted for nicotine pouches.

The authors compared the values with the data on e-cigarettes in the literature. It could be seen that peak concentrations of 8.4 ng/mL were measured after 5.1 minutes and the half-life was determined to be 106 minutes [2]. In comparison, in an earlier study, peak values of 15 ng/mL were determined for conventional cigarettes after consumption [9].

It can be seen that consumers ingest significant amounts of nicotine from nicotine pouches. In this study, the nicotine pouches were kept in the oral cavity for 60 minutes. Numerous companies recommend shorter times (in the range of 20 to 30 minutes), but no information is available on how long the consumers really retain the pouches in their mouths. Overall, the values presented here should be viewed somewhat conservatively. The study also shows, however, that increasing nicotine doses lead to increasing nicotine concentrations in the blood. The investigative scope of the study ended at 8 mg of nicotine per nicotine pouch.

According to the German Association of the Tobacco Industry and New Products (BVTE), member companies in Germany offer products with up to 20 mg of nicotine per pouch. According to research by the BVL and the BfR, products are available in Germany that contain up to 50 mg of nicotine per pouch. It must be expected that products with higher nicotine doses will also lead to higher nicotine concentrations in the blood, although it is to be assumed that these increases are not directly proportional. However, considerable uncertainty exists in this respect in view of the absence of experimental data from this high range. The BfR therefore intends to carry out a pharmacokinetic study with higher nicotine concentrations.

In the forensic-toxicological literature, nicotine blood levels are assessed as follows: intended use ("therapeutic") 5 - 30 ng/mL; toxic: 400 ng/mL, comatose-lethal: 1000 – 2000 ng/mL [11].

3.1.4 Risk characterisation

Acute nicotine toxicity can be classified according to CLP regulation, whereby only acute toxicity after oral administration is of interest in this context. On the basis of various animal studies and taking into account human toxicity, the ECHA Risk Assessment Committee has established an estimate of the acute toxicity of 5 mg nicotine/kg body weight. The CLP Regulation (Classification, Labelling and Packaging) specifies the following formula in Appendix 1, Part 3, No. 3.1.3.6.1 for the calculation of mixtures with regard to acute toxicity:

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

The formula is written in terms of c_i.

c_i = concentration of i-th component (% w/w or % v/v)

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

In this specific case, the value of 5 mg/kg body weight is used as the ATE_i; this is the estimated value of acute nicotine toxicity. A value of 300 mg/kg body weight is used for ATE_{mix}, this is the lower limit for category 4 of acute oral toxicity (see also table 3.1.1 of the CLP Regulation) and the formula then results in the following value:

(100 x 5 mg/kg body weight) / 300 mg/kg body weight = 1.67%

For nicotine pouches, this would represent a concentration of 16.7 mg/g of pouch. From the point of view of chemicals law, a pouch with this concentration would only fall within hazard category 4 and does not require labelling with skull and crossbones.

From a toxicological point of view, this limit is easy to understand, as explained under 3.1.2, use of a nicotine pouch containing just 6 mg resulted in a significant increase in heart rate of 10 beats per minute. The concentration suggested here is almost three times higher. Taking into account the effects of nicotine, which has a strong impact on the cardiovascular system, the concentration should be changed from 16.7 mg nicotine/g of pouch to 16.7 mg nicotine per pouch, otherwise larger pouches could be produced, e.g. with a weight of three grams and a nicotine content of 50 mg.

3.2 Framework for action, recommendations for measures

Nicotine has a pronounced pharmacological effect, which also forms the basis of its toxicity. The best-known nicotine-containing products are cigarettes. Cigarettes are subject to restrictions on the nicotine content in cigarette smoke and prohibitions exist on sales to people under the age of 18. E-cigarettes are subject to an upper limit on the nicotine concentration in the liquid of 20 mg nicotine/mL, as well as child-proof closures for the liquid containers and prohibitions on sales to people under the age of 18.

3.3 Other aspects

Snus has been consumed in Sweden for many decades, with men using snus far more often than women. A study from Sweden shows that snus does not encourage people to start smoking cigarettes. Cigarette smokers who start using snus are more likely to quit cigarettes [12]. Sweden enjoys a special position in Europe with regard to tobacco-induced diseases. In an assessment of a WHO report (WHO Global Report: Mortality Attributable to Tobacco, 2012), mortality in the age group 60 – 69 in Sweden was compared with that in other EU member states (see Table 5).

Table 5: Mortality in the age group 60 – 69, which can be attributed to tobacco consumption (from [13])

Comparison of Sweden with other EU countries. Figures in deaths per 100,000 inhabitants. The median value, as well as the minimum and maximum, are given for other EU countries.

	Sweden	EU countries		
		Min	Median	Max
Men				
Lung cancer	87	91	220	399
Misc. cancer	36	41	105	217
Cardiovascular disease	72	107	170	618
All causes	222	378	550	1388
Women				
Lung cancer	61	5	39	127
Misc. cancer	17	1	10	39
Cardiovascular disease	63	5	50	222
All causes	173	14	115	690

In Sweden, snus is mainly consumed by men. Tobacco consumption among Swedish women does not differ much from women in other EU countries. Accordingly, the table shows no particularities for mortality attributed to tobacco in a comparison between women in Sweden and those in other EU countries (Table 5). However, things look different for men: For lung cancer, as well as other cancers and cardiovascular diseases, the mortality of Swedish men attributed to tobacco is lower than the lowest in the rest of the EU [13].

The recent launch of nicotine pouches in Germany and other EU countries represents a new type of product, which is associated with health risks.

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Further information on the topic of tobacco is available from the BfR website:

https://www.bfr.bund.de/en/a-z_index/tobacco-130243.html

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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