Health risk assessment of nicotine pouches

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Nicotine pouches are new, tobacco-free products that contain a powder made up of nicotine salts and filling materials. The German Federal Institute for Risk Assessment (BfR) has assessed the health risks from these products based on existing studies and data. This updated assessment includes an evaluation of experimental studies conducted by the BfR. Pharmacokinetic studies show that at least half of the nicotine in the pouch can be absorbed. Relevant nicotine blood levels were achieved, i.e. levels were within a range that is comparable with conventional cigarettes. Use of high-dose products led to significantly higher nicotine levels than cigarette consumption. The German state authorities classify nicotine pouches as a ‘novel food’.

1 Subject of the assessment

Nicotine pouches are new products, first described in countries such as Sweden, the US and the UK in 2019 [1]. In Germany, these products also formed the subject of a Bundestag resolution (Bundestag paper 19/20667 of 1 July 2020) in 2020.

Nicotine pouches are small pouches that contain nicotine-based powders. According to the manufacturer, nicotine salts are used, which are mixed with microcrystalline cellulose, various other salts (including sodium carbonate and hydrogen carbonate), citric acid and flavourings [1]. These products do not contain tobacco. The BfR was asked to perform a health risk assessment for nicotine pouches. Nicotine pouches are also sometimes referred to as ‘all-white’ products.

In March 2021, the BfR prepared a preliminary health risk assessment that was subsequently discussed by various parties. The BfR also conducted experimental studies on different nicotine pouches; findings from these studies are included in this assessment. This updated version also presents the findings from a pharmacokinetic study conducted by the BfR and the Tobacco Dependence Outpatient Clinic at Ludwig-Maximilians-Universität München (LMU Munich).

2 Results

Nicotine pouches are new, tobacco-free products. The highest nicotine content identified by the BfR was 47.5 mg nicotine/pouch. Investigations by the BfR found tobacco-specific nitrosamines (TSNAs) in some of the nicotine pouches. Pharmacokinetic studies show that at least half of the nicotine in the pouch can be absorbed. Relevant nicotine blood levels are achieved, i.e. nicotine levels are within a range that is also achieved after consuming conventional cigarettes and some e-cigarettes. Use of high-dose products was observed to cause blood levels significantly higher compared with cigarette consumption. The rise in nicotine levels in blood was comparable with the rise following cigarette consumption, which suggests an addictive effect from high-dose nicotine pouches comparable with that known for cigarettes.
A few cases of poisoning from nicotine pouch use have been reported but none with a severe course.

Nicotine is a toxic, biogenic alkaloid. For the oral exposure route, an acute toxicity estimate of 5 mg/kg bodyweight has been defined. Nicotine increases the risk of stillbirth and has strong effects on the cardiovascular system. The long-term effects of using nicotine pouches cannot be assessed on the basis of the limited amount of data available.

Nicotine pouches are currently classified as a ‘novel food’ by the federal state authorities in Germany and are being withdrawn from the market as they exceed the acute reference dose for nicotine.

In terms of effects on health, the BfR defines the following high-risk groups: Children, adolescents and non-smokers, as nicotine is an addictive substance. Pregnant and breastfeeding women, because of the effects of nicotine during pregnancy and its passage into breast milk. People with cardiovascular disease, as nicotine has strong cardiovascular effects.

### 3 Rationale

Nicotine is a natural component of tobacco leaves; the tobacco used in cigarettes contains up to 1.5% nicotine [2]. The use of cigarette tobacco, pipe tobacco and chewing tobacco is well researched and is not the subject of this assessment. Reference to the effects of cigarette consumption is made again at the end of the report. Nicotine is used as a component of liquids for electronic cigarettes (e-cigarettes). In the EU, this use is regulated in the Tobacco Products Directive (2014/40/EU), with e-cigarettes being products that do not contain tobacco. Nicotine is also used in medicines/medical devices for replacement therapy for smoking cessation.

In Sweden and some other countries, tobacco is marketed in small pouches that are placed between the upper lip and gums for a certain period of time. These products are also often flavoured. In Sweden, this form of tobacco is called ‘snus’ and has a long tradition of use in the country. In the EU, the sale of snus is prohibited with the exception of Sweden. In the USA, comparable products are available, which are usually referred to as ‘snuff’ although not technically identical. In the recent years, new products were launched on the market that do not contain tobacco in their pouches, but rather nicotine salts, inactive ingredients, flavourings and other additives. This health risk assessment from BfR focuses only on the use of nicotine in such pouches. In the following sections, this assessment also draws on studies and evaluations that deal with oral tobacco products such as Swedish snus. Studies evaluating the health hazards of tobacco smoking have not been considered here, as it is well known that, alongside nicotine, numerous other toxicologically relevant compounds can be found in tobacco smoke that also contribute to the various harms resulting from smoking tobacco.

In the Netherlands, nicotine pouches containing 0.035 mg or more of nicotine have been banned since 9 November 2021. Denmark is planning to introduce a national register of tobacco-free nicotine pouches.
3.1 Risk assessment

3.1.1 Hazard identification

The BfR carried out its own analyses to gain some initial insights into the chemical composition of nicotine pouches. A total of 44 nicotine pouches were purchased online and then tested for weight, nicotine content and pH. In addition, concentrations of tobacco-specific nitrosamines (TSNAs) were analysed and pack labelling was evaluated [3]. The rate of nicotine release was characterised with the help of in vitro experiments into solubility. The pharmacokinetic study on nicotine absorption following product use by test subjects was completed together with the Tobacco Dependence Outpatient Clinic at LMU Munich. As with e-cigarettes and heated tobacco products, flavourings have a strong impact on the appeal of nicotine pouches. Definitions for flavoured or non-flavoured products, along with potential regulatory schemes, are currently being discussed [4]. Chemical characterisation of the flavourings used is in progress at the BfR.

The median weight per pouch was 0.6 g and the nicotine content per pouch was 9.48 mg. The highest nicotine content was 47.5 mg per pouch and the lowest was 1.79 mg per pouch [3].

In 2020, the Dutch National Institute for Public Health and the Environment (RIVM) published a monograph on nicotine pouches in which pouch weights of 0.25 to 0.8 g were described. Nicotine content was found to be within a range of 1.6 to 32.5 mg per pouch in this monograph [5]. A study from the US CDC (Centers for Disease Control and Prevention) investigated 37 brands from 6 manufacturers, with the highest nicotine content being 6.11 mg per pouch [6]. An investigation of products by one manufacturer revealed a weight of 0.7 g for four products [7]. The nicotine levels of these four products ranged from 4.06 to 11.9 mg per pouch [7]. A study from the USA on snus from northern Europe and from the USA revealed pouch weights ranging from 0.33 to 1.13 g, with nicotine content in the snus samples being between 6.81 and 20.6 mg/g [8].

The median pH for aqueous extracts was 8.8 for the pouches examined by the BfR, with only one product exhibiting an acidic pH. The Henderson-Hasselbalch equation was used to calculate the percentage of uncharged (also known as ‘free-base’) nicotine from the pH values measured. In its uncharged state, nicotine can pass through biomembranes such as the oral mucosa more easily, which leads to improved oral nicotine absorption. The median proportion of free-base nicotine was 86% [3].

In its monograph on nicotine pouches, the RIVM described pH values ranging from 8.8 to 9.9 [5]. The CDC study on 37 brands identified a pH range from 6.94 to 10.1, which was converted into free-base nicotine proportions of 7.7% to 99.2% [6]. The investigation by the above-mentioned manufacturer revealed a pH of 8.5 to 8.7 for the four products [7].

Information about nicotine strength and pack labelling:

Nicotine content, expressed as mg per pouch or per g, was declared clearly on only about a third of the nicotine pouches examined. Instead, most products described the nicotine strength, using either a scale (such as a strength of ‘3 out of 5’) for which no further details were given or figurative language to define the nicotine strength (examples being ‘easy’, ‘medium’, ‘strong’, ‘extra strong’, ‘ultra’, ‘extreme’, ‘danger strong’ or ‘brutal’) [3].
These figurative terms were then compared with the nicotine content per pouch as analysed. Products with a nicotine strength indicated as light had a slightly lower nicotine content than products stating they were of average nicotine strength. For products whose nicotine strength was described within the range ‘medium’ to ‘extra strong’, there was a lot of overlap, rendering a clear differentiation difficult. One reason could be that some manufacturers meant the nicotine content per pouch and others per gram. However, this fact is not apparent to the consumer. Switching between products from different manufacturers can result in nicotine content per pouch doubling even though the nicotine strength of these products is described using the same terms.

For products whose figurative descriptors could be interpreted as indicating a higher nicotine strength than ‘extra strong’ (such as ‘ultra’, ‘extreme’, ‘danger strong’ and ‘brutal’), analysed nicotine content ranged from 12.1 mg per pouch (product described as ‘ultra’) to 47.5 mg per pouch (product described as ‘brutal’) [3].

Almost all products carried a warning advising against consumption by minors. However, Barely one in four products carried a warning about use during pregnancy. Due to the acute toxicity of nicotine, labels for products with a nicotine content of 2.5 mg/g or higher must bear the GHS07 pictogram (exclamation mark, signal word: ‘Warning’) while those exceeding 16.7 mg/g must bear pictogram GHS06 (skull and crossbones, signal word: ‘Danger’) [3].

Release rate of nicotine:

The release kinetics of nicotine were determined for selected nicotine pouches. The aim was to investigate whether the pouches differ in terms of the proportion of nicotine released and the release rate.

Differences were identified both in terms of the proportion of nicotine released in relation to the total nicotine content as well as in terms of the release rate. In four out of 15 samples, more than 70% of the total nicotine content was released in the first 5 minutes. In contrast, seven other samples released less than 60% of the nicotine they contained within the first 10 minutes. In summary, the results can be used to conclude that most of the nicotine pouches released the majority (>80%) of their nicotine content within the period investigated. Accordingly, most of the nicotine is released within 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-butanol (NNK), N'-nitrosoanatabine (NAT) and N'-nitrosoanabasine (NAB). These substances are formed from nicotine and the minor tobacco alkaloids nornicotine, anatabine and anabasine during the fermentation of the tobacco. Therefore, tobacco-based products, especially standard cigarettes but also some types of oral tobacco, contain considerable quantities of TSNAs. As examples, around 1900 ng NNN and 530 ng NNK per cigarette have been found in unburned cigarette tobacco [9]. A more recent comparison of American and Swedish products shows concentrations of less than 1000 ng/g as a sum total of the carcinogens NNN and NNK in most products. In snus, up to 1930 ng NNN and
696 ng NNK have been found per g of snus pouch [8]. Although nicotine pouches do not contain any tobacco, the added nicotine may have been obtained by extracting tobacco leaves and thus may contain trace amounts of TSNAs. TSNAs have also been detected in products that contain tobacco extracts, such as e-liquids for e-cigarettes, in quantities of up to 60 ng NNN and 10 ng NNK per ml [10]. It is conceivable that nicotine pouches also contain TSNAs, possibly as an impurity of the tobacco extract added or via the subsequent conversion of the tobacco alkaloids contained therein.

TSNAs were detected in more than half of the pouches analysed. The highest concentrations found 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 [3]. It should also be noted that TSNAs can also be formed endogenously in the digestive tract, as has been described for NNN in saliva, for example [11].

An investigation by one manufacturer identified TSNA values of <10 ng/g for four products. In the same study, three different snus products were analysed for NNN and NNK, and showed a range of 560 to 640 ng/g for NNN and a range of 89 to 200 ng/g for NNK [7]. The study also investigated the four products for other potential ingredients and contaminants: for carbonyls (formaldehyde, acetaldehyde, acrolein and crotonaldehyde), organic compounds (benzo[a]pyrene, 1,3-butadiene and benzene), elements (arsenic, lead, cadmium, chromium, nickel and mercury) and aflatoxins (B1, B2, G1 and G2) the levels were below the respective limits of detection [7].

### 3.1.2 Hazard characterisation

Nicotine is an alkaloid and a weak base with a pKₐ value of 8.0 [2]. Nicotine stimulates the nicotinic acetylcholine receptors, which are found in both the central nervous system and the autonomic nervous system. Accordingly, nicotine exposure triggers a number of reactions in the organism, depending on the dose. 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 symptoms from higher levels of exposure including diarrhoea, increased salivation and a slowing of the heart rate. Severe poisoning can be characterised by seizures and respiratory depression [12].

Due to their electrophilic properties, nitrosamines cause base modifications in DNA [13]. Nitrosamines are strong genotoxic carcinogens with organ-specific effects. A total of seven TSNAs have so far been detected in smokeless tobacco products. Two of these substances, NNN and NNK, have been classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens (carcinogenic to humans) [14].

Until a few years ago, an oral dose of 60 mg nicotine per person was described as a lethal dose of nicotine in pharmacology and toxicology textbooks. In 2014, this assumption was reviewed by a pharmacologist who, in view of the confusing sources on one hand and the descriptions of human poisoning cases on the other, concluded that the lethal oral dose in humans was more than 0.5 g of nicotine for a single individual [15]. In an assessment of nicotine in terms of chemicals legislation conducted in 2015, the Committee for Risk Assessment (RAC) at the European Chemicals Agency (ECHA) adopted this assessment for toxicity in humans [16]. In this ECHA assessment, the classifications for acute nicotine toxicity were re-evaluated. 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 resulted in significantly higher...
LD$_{50}$ values. The LD$_{50}$ values for mice were 3.3 and 24 mg/kg bodyweight, and 9.2 mg/kg bodyweight for dogs [16]. These values were within the same range calculated in the human toxicity assessment, with an LD$_{50}$ of 6.5 to 13 mg/kg bodyweight. As a consequence, the RAC proposed a classification of nicotine as Acute Tox. 2 (oral), with the hazard warning ‘H300: Fatal if swallowed’ and with an acute toxicity estimate of 5 mg/kg bodyweight. This recommendation has now been taken up into law with the adoption of EU Regulation 2018/1480.

At the December 2020 session of the BfR Committee for the Assessment of Poisonings, representatives from the poison information centres in Germany reported on some cases of poisoning from nicotine pouches. In one case, a pouch with 20 mg nicotine had been swallowed. The affected person was given activated charcoal by the emergency service team but did not develop any symptoms other than stomach pain. In April 2022, several new cases of poisonings involving nicotine pouches were reported. Most of the symptoms reported involved nausea/vomiting and cold sweats.

Further effects on test subjects were also examined in a study, in which a manufacturer also participated, that compared the toxicokinetics of nicotine when using nicotine pouches and when using Swedish snus (see also 3.1.3) [17]. Two aspects investigated in test subjects were heart rate and the subjective feeling of head buzz. In the context of this study, nicotine pouches (3 and 6 mg nicotine per pouch) and snus (8 mg nicotine per pouch) were used for 60 minutes.

<table>
<thead>
<tr>
<th>Product</th>
<th>Max. 'head buzz' VAS (mm)</th>
<th>Max. change in heart rate (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg nicotine</td>
<td>9 (4, 19) 0–59 8.5 (5.5, 14.5) 4.0–18.0</td>
<td></td>
</tr>
<tr>
<td>6 mg nicotine</td>
<td>11 (5, 26) 0–63 10.5* (9.5, 16.5) 4.5–22.5</td>
<td></td>
</tr>
<tr>
<td>Snus (8 mg)</td>
<td>24* (12, 47) 0–62 11.0 (4.0, 15.0) 0.0–22.0</td>
<td></td>
</tr>
</tbody>
</table>

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

A single dose of the pouches containing nicotine was well-tolerated in these healthy test subjects. Two cases of dry mouth were assessed as substance-related. The increase in heart rate (see table 1) is easily explained by the effects of nicotine and these effects are also dose-dependent: the changes in the 6 mg dose group are significantly higher than those in the 3 mg dose group. For the other endpoint, head buzz, the Swedish snus product demonstrated significantly higher VAS values than were recorded for the two nicotine pouch doses [17].

A comparative study from a manufacturer investigated five separate nicotine pouch products with nicotine content ranging from 6 to 10 mg per pouch. A total of 27 adverse events were recorded: of these, 26 were minor and 1 of moderate intensity; 19 of these events were assessed as product-related [18].

Another comparative study from the same manufacturer investigated nicotine pouches, chewing gum and lozenges with a nicotine content of 4 mg per item. A total of 40 adverse events occurred: of these, 29 were assessed as product-related, with 7 occurring after use of nicotine pouches, 9 after using chewing gum and 13 after consumption of the lozenges. Of these 29
adverse events, 28 were minor, with dizziness being most frequently reported, followed by nausea [19].

In a study from another manufacturer, two nicotine pouches with differing nicotine content were investigated, with these doses being 5.8 and 10.1 mg per pouch. Headaches were cited in two cases as relevant adverse events [20].

Together with the Tobacco Dependence Outpatient Clinic at LMU Munich, the BfR conducted a study investigating the pharmacokinetics of nicotine absorption and excretion following the use of nicotine pouches and cigarettes (see 3.1.3). A total of 15 test subjects consumed one of the products under investigation at five study days. On four of these days, a pouch (nicotine-free, 6 mg nicotine, 20 mg nicotine or 30 mg nicotine) was consumed for 20 minutes, while a standard tobacco cigarette was smoked on another day of the study. Over a timeframe of four hours, blood samples were taken at predefined points in time, and parameters such as blood pressure, heart rate, vascular stiffness, changes to oral mucosa, side effects and acute nicotine withdrawal were measured. Heart rate was first measured before consumption, and then after 5, 20 and 30 minutes.

Pouches without nicotine and pouches with 6 mg nicotine did not lead to an increase in heart rate. With the other products, the strongest effect was observed after just five minutes: heart rate increased by 12 beats per minute (bpm) in the 20 mg group, rising to 27 bpm in the cigarette user group. In the cigarette user group, consumption was complete after five minutes, but heart rate was still elevated after 20 and 30 minutes. Nicotine pouches were consumed over 20 minutes, but heart rate declined slightly after 20 minutes compared with the maximum measured at 5 minutes. This decline was more pronounced after 30 minutes.

Other side effects were surveyed at each measurement interval on a 0 to 10-point visual analogue scale. The scores given to the side effects of drowsiness, pounding heart, headache, throat irritation, sweating, dizziness, cold hands and feet, nausea and an urge to vomit were under 3 on average at each measurement interval. While the tobacco cigarette rarely caused irritation to the oral mucosa, all nicotine pouch users reported oral mucosa irritation ranging from moderate (0–20 mg nicotine) to severe (30 mg). The subjective head buzz after consuming the tobacco cigarette and the 30 mg pouch was roughly the same.

In 2009, EFSA established an acute reference dose (ARfD) for nicotine of 0.0008 mg/kg bodyweight, applying an LOAEL of 0.0035 mg/kg bodyweight. The adverse effect here was an increase in heart rate [21]. At that dose, heart rate increased by about 7 beats per minute [22]. The median increase of 8.5 beats when using nicotine pouches with 3 mg nicotine is comparable (see table 1). In the study from the BfR and LMU, an increase in heart rate of 12 beats per minute was observed after using a 20 mg pouch for five minutes. In the same study, an increase in heart rate of 27 beats per minute was recorded after the consumption of one cigarette. It can therefore be concluded that cigarette consumption has an effect on heart rate comparable with that of using 30 mg nicotine pouches. In contrast to the study from Lunell, which demonstrated an increase in heart rate after using 3 mg and 6 mg pouches for 60 minutes, no increase in heart rate following the use of 6 mg pouches for 20 minutes was observable in the BfR and LMU study.

A review article has highlighted the relationship between nicotine and type 2 diabetes [23]. Cigarette smoking is an important risk factor for developing type 2 diabetes. Compared with non-smokers, smokers have increased insulin resistance, although there is no evidence of 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 hormone). On the other hand, nicotine activates a protein kinase that can induce insulin resistance [23].

Reprotoxicity:

Nicotine passes the human placenta throughout pregnancy [24]. Nicotine concentrations in the placenta, amniotic fluid and foetal serum are higher than in maternal serum [24]. Nicotine concentrations in maternal serum and breast milk have been determined after delivery, with the concentration in breast milk found to be 2.9 times higher than in serum [25].

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 data. A total of 7629 women consumed snus, 41,488 women were described as light smokers (1 to 9 cigarettes per day) and 17,014 women were described as heavy smokers (at least 10 cigarettes per day). Data on tobacco consumption were unavailable for 39,734 women. A risk of stillbirth was determined for these groups compared with women who did not consume tobacco.

Table 2 shows that snus consumption increases the risk of a stillbirth during pregnancy. Heavy cigarette smokers had an even higher risk of stillbirth [26].

**Table 2: Relationship between tobacco consumption and stillbirths (from [26])**

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

Genotoxicity:

In its monograph on nicotine pouches, the RIVM found no evidence of mutagenic properties for nicotine [5]. Nicotine has been tested for genotoxic properties in various studies. Several Ames tests gave negative results [27-29] and another study yielded negative results from Ames test and for sister-chromatid exchange (SCE) in cells from Chinese hamster ovaries [30]. Negative results were also obtained from a hypoxanthine phosphoribosyltransferase (HPRT) mutagenicity test conducted on V79 cells [31]. An in vitro micronucleus test was carried out with human lymphocytes, which also yielded negative results [32].

A review article described studies with positive results from SCE tests and chromosome aberration tests in cells from Chinese hamster ovaries. These positive results were confirmed in vitro both for SCE tests and for chromosome aberration tests in human lymphocytes [33]. In
vitro studies on fibroblasts from human gum tissue showed a significant increase in micronuclei formation after treatment with nicotine [34].

An in vivo study of 1 and 2 mg nicotine/kg bodyweight in male mice showed no significant increase in micronuclei formation in bone marrow [35]. In a follow-up study, higher nicotine doses (up to 16 mg/kg bodyweight) and longer treatment times (up to 36 hours) were applied. At high doses of 8 and 16 mg/kg bodyweight, and after 30 and 36 hours, increased micronuclei formation was observed in the bone marrow of female and male mice [36].

In summary, positive and negative results can be observed within the same testing system, in both in vitro and in vivo studies.

Carcinogenicity:

In its monograph on nicotine pouches, the RIVM found no evidence of carcinogenic properties for nicotine [5]. The 2015 review by Sanner and Grimsrud comes to the result that no conclusions can be drawn on the potential carcinogenic effects of long-term treatment with nicotine [33]. A recent publication investigated the carcinogenic effects of an e-cigarette aerosol on mice [37]. The animals (n = 45) were exposed to an e-cigarette aerosol for 54 weeks for 4 hours a day on 5 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 of the 40 mice treated developed lung tumours that were identified as adenocarcinomas. One animal from the filtered air control group developed adenocarcinoma. A statistically significant difference was found when comparing the control groups with the treated group [37]. The study has a number of shortcomings, namely: only one dose was used in the treated group; the group sizes were smaller than those specified in the guidelines for long-term carcinogenicity studies; and an e-cigarette aerosol contains other carcinogenic substances in addition to nicotine. Accordingly, this study does not permit a conclusive assessment of the carcinogenic effect of nicotine.

Addictive effect:

The BfR has not identified any specific findings on the addictive effect of nicotine pouches to date. However, section 3.1.3 also discusses the results from the pharmacokinetic study conducted by the BfR and LMU in terms of potential addiction induction.

3.1.3 Exposure assessment

Nicotine can be taken up orally, dermally or via inhalation. When using conventional cigarettes or e-cigarettes, absorption via inhalation is of most importance. The key facts of nicotine pharmacokinetics and metabolism have been summarised in a review article [2]. According to this article, consumption of one cigarette leads to the systemic absorption of 1 to 1.5 mg of nicotine. In the EU, the upper limit for the nicotine concentration in smoke from one cigarette is one milligram. After inhaling cigarette smoke, nicotine reaches the brain within 10 to 20 seconds [2]. At a pH of 7.4, nicotine is present in the bloodstream in approximately 69% ionic and 31% non-ionic (free-base) proportions. Nicotine can only pass through cell membranes in the non-ionic state.
When using nicotine pouches, nicotine is mainly absorbed via the mucous membranes in the oral cavity. Nicotine pouches are placed between the upper lip and gum for a period of up to 30 minutes, and then removed. The pouches should not be swallowed.

A recent study from Sweden has investigated the pharmacokinetics of nicotine from nicotine pouches [17]. In this study, financed by a manufacturer, three nicotine strengths were investigated in two study arms (3 and 6 mg nicotine per pouch in the first arm and 8 mg nicotine per pouch in the second arm). For comparison, snus was investigated in the first study arm (weight: 1 g per pouch, 8 mg nicotine per pouch). The test subjects (n = 17) placed a pouch between the upper lip and gum and removed the pouch after 60 minutes. Blood samples were taken at the start, at several times during use and up to five hours after the pouches were removed; these samples were then analysed for nicotine concentrations in blood plasma. The discarded pouches were examined for their remaining nicotine content. The authors used these data to calculate nicotine extraction. Nicotine extraction was found to be 56% and 59% for the 3 mg and 6 mg doses, with only 32% of the nicotine being extracted from snus (see table 3).

Table 3: Nicotine release from pouches and snus (from [17])

<table>
<thead>
<tr>
<th>Product</th>
<th>Number of subjects</th>
<th>Nicotine content</th>
<th>Extracted nicotine</th>
<th>Extracted nicotine as % of total content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine pouch</td>
<td>17</td>
<td>3</td>
<td>1.59</td>
<td>55.9</td>
</tr>
<tr>
<td>Nicotine pouch</td>
<td>17</td>
<td>6</td>
<td>3.51</td>
<td>59.1</td>
</tr>
<tr>
<td>Nicotine pouch</td>
<td>30</td>
<td>8</td>
<td>3.79</td>
<td>50.4</td>
</tr>
<tr>
<td>Swedish snus</td>
<td>17</td>
<td>8</td>
<td>2.41</td>
<td>32.0</td>
</tr>
<tr>
<td>Swedish snus</td>
<td>30</td>
<td>2x 8</td>
<td>5.04 (from 2 pouches)</td>
<td>32.6</td>
</tr>
<tr>
<td>American snus</td>
<td>30</td>
<td>18</td>
<td>2.99</td>
<td>18.9</td>
</tr>
</tbody>
</table>

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

The second arm of the Swedish study investigated pharmacokinetics in a larger group of test subjects (n = 30) after consuming pouches of 8 mg nicotine, while also comparing this with Swedish and American snus. The Swedish snus contained 8 mg nicotine per pouch. In the second study arm, the test subjects used two pouches at the same time, leading to a combined nicotine exposure of 16 mg. The American product contained 18 mg nicotine per pouch. Nicotine extraction from the 8 mg nicotine pouches was 50%, while being 33% from the Swedish snus and 19% from the American snus (see table 3). As summarised in table 4, the peak concentrations in blood 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), 140 min (Swedish snus) and 144 min (American snus) [17].
The study by Lunell et al. [17] shows that after 60 minutes of use, at least half of the nicotine contained in the pouch is absorbed by the body (see table 3). The majority of the nicotine is absorbed directly via the oral mucosa. Some of the nicotine may also be dissolved in saliva and then swallowed. This fraction can be reabsorbed in the gastrointestinal tract. Different values for nicotine extraction were obtained for the two snus samples investigated. These values were 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, from which it can be assumed that less nicotine will be absorbed. However, pouches containing tobacco (snus) are often used for 60 min [38] and it is possible that this usage pattern will be carried over to nicotine pouches.

Table 4: Toxicokinetics of nicotine (from [17])

The results for snus and the nicotine pouches are summarised from the two study arms, in which different numbers of test subjects participated. In the first arm, the subjects used Swedish snus with 8 mg of nicotine. In the second arm, two pouches containing 8 mg nicotine were used. [17]. For comparison, values are also given for conventional cigarettes and e-cigarettes.

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

The authors compared the values with e-cigarette data from the literature, in which peak nicotine concentrations of 8.4 ng/ml were measured after 5 minutes and the half-life was found to be 106 min [17]. For comparison, an earlier study found peak values of 15 ng/ml after consumption of conventional cigarettes [39]. As can be seen, consumers absorb significant amounts of nicotine from nicotine pouches. Due to the higher nicotine extraction compared with snus, uptake is higher from pouches despite these having the same nicotine content. Further, the study shows that nicotine concentrations rise in proportion to an increase in the nicotine dose.

A pharmacokinetic study by another manufacturer investigated the pharmacokinetics of six separate products with different flavours, all of which had a nicotine content between 3.30 and 3.82 mg per pouch. All test subjects used all of the flavours provided. In the last part of the study, subjects were allowed to consume their normal brand of cigarettes. The test subjects placed the pouches between the upper lip and the gums for 30 minutes. The peak concentrations (C_{max}) ranged from 9.0 to 11.5 ng/ml for the nicotine pouches and were 16.3 ng/ml for the cigarettes. The peak concentration for cigarettes was reached after 7.5 min, and after 30.1 to 34.9 min for the nicotine pouches. Flavourings used in the pouches had no effect on the pharmacokinetics [40].

A pharmacokinetic study from another manufacturer compared five pouch products from different companies with nicotine contents ranging from 6 to 10 mg per pouch with a cigarette. The
nicotine pouches were placed between the upper lip and the gums for 60 minutes. The cigarette was smoked within a period of five minutes. The peak concentrations ($C_{\text{max}}$) ranged from 11.9 to 17.5 ng/ml for the nicotine pouches and were 13.9 ng/ml for the cigarettes. The peak concentration for cigarettes was reached after 7 min, and after 60 to 65 min for the nicotine pouches [18].

In another pharmacokinetic study from the same manufacturer, a nicotine pouch was compared with two nicotine replacement products (chewing gum and lozenge). All products contained 4 mg nicotine. The nicotine pouch was placed between the upper lip and the gums for 60 minutes. The chewing gum was used for 30 min, while the lozenge was placed in the oral cavity and sucked until it had fully dissolved, which took around ten minutes. The peak concentrations ($C_{\text{max}}$) were 8.5 ng/ml for the nicotine pouch, 4.4 ng/ml for the chewing gum and 8.3 ng/ml for the lozenges. The peak concentrations for lozenge and nicotine pouch use were reached after 60 min, and after only 50 min for the chewing gum [19].

A pharmacokinetic study from another manufacturer investigated two nicotine pouches with different doses and a cigarette product. The products contained either 5.8 mg or 10.1 mg nicotine per pouch. The nicotine pouches were placed between the upper lip and the gums for 20 minutes. For the cigarette, the recommended use was one puff every 30 seconds, with consumption completed in five minutes. The peak concentrations ($C_{\text{max}}$) ranged from 5.2 to 7.9 ng/ml for the nicotine pouches and were 11.6 ng/ml for the cigarettes. The peak concentration for cigarettes was reached after 8.5 min, and after 22 to 26 min for the nicotine pouches [20].

According to the German Federal Association of the Tobacco Industry and Novel Products (BVTE), member companies in Germany offer products containing up to 20 mg of nicotine per pouch. Analyses conducted by the BfR show that products are also available in Germany that contain up to 47.5 mg of nicotine per pouch. Thus, it is possible that products with higher nicotine doses lead to significantly higher nicotine concentrations in the blood. This question was one aspect of the study conducted jointly with the Tobacco Dependence Outpatient Clinic at LMU Munich. This study investigated the pharmacokinetics of nicotine following the use of nicotine pouches and cigarettes. A total of 15 test subjects used one of the products under investigation on five different days. On four of these days, a pouch (nicotine-free, 6 mg nicotine, 20 mg nicotine or 30 mg nicotine) was consumed for 20 minutes, while a standard tobacco cigarette was smoked on another day of the study. Over four hours, blood samples were taken at predefined time points and the nicotine concentration was determined.

The study showed that, within the first five minutes, nicotine absorption from the 30 mg pouches was comparable with that from cigarette consumption. This was not the case for the pouches with $\leq$20 mg nicotine. This rapid rise in nicotine levels is considered to be a critical factor for the addictive effect of cigarette consumption [41, 42]. In this context, the rapid rise in levels from high-dose nicotine pouches suggests that these may also have an addictive effect. After consumption of the 30 mg pouch, the peak concentration in blood was 29.3 ng/ml, higher than after smoking a cigarette (15.1 ng/ml). The very wide range of peak concentrations that were achieved following use of the three separate nicotine pouches is notable. No linear correlation was found between the nicotine content in the pouch and the nicotine concentration in the blood. Since the products were sourced from different manufacturers, variations in the percentage and rate of nicotine release are possible. That products from different manufacturers can differ in terms of their nicotine release has already been shown by an in vitro release study (see section 3.1.1 – ‘Release rate of nicotine’). The results from McEvans et al. also came to similar results. In that study, two products from different manufacturers, each containing 10 mg...
nicotine per pouch, led to peak concentrations of 11.9 and 17.1 ng/ml after 60 minutes of use [18].

Based on the hypothesis that nicotine concentrations in blood derived from products with similar release rates are directly correlated with the nicotine content in the pouch, nicotine blood concentrations were estimated. Based on data for the 30 mg product, the blood concentration that is achievable with a comparably well-reabsorbed 16.6 mg product was calculated. The BfR defined this 16.6 mg/pouch as the applicable upper limit based on the acute toxicity of nicotine. The corresponding calculations resulted in a blood concentration of 16.2 ng/ml. This concentration is comparable with the blood concentration achieved after cigarette consumption.

One should remember that the pouches can be used for longer than 20 minutes: in the manufacturer studies cited above, use durations ranging from 30 minutes to 60 minutes were investigated. This would clearly result in higher levels of nicotine in blood. However, a survey conducted by one manufacturer has shown that most consumers in Germany use their nicotine pouch for between 5 and 20 minutes [43]. It should be kept in mind that two pouches could be used simultaneously, as was shown by Lunell et al [17].

Table 5 summarises the results from the pharmacokinetic studies.
Table 5: Summary of pharmacokinetic studies on nicotine pouches

The first five studies were conducted by manufacturers or with financial support of manufacturers.

<table>
<thead>
<tr>
<th>Authors + year</th>
<th>Nicotine strength</th>
<th>Use duration</th>
<th>$t_{\text{max}}$ (range of average values$^\dagger$ or median values$^\ddagger$)</th>
<th>$C_{\text{max}}$ (range of average values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lunell et al., 2020 [17]</td>
<td>3–8 mg</td>
<td>60 min</td>
<td>59–66 min$^\dagger$</td>
<td>7.7–18.5 ng/ml</td>
</tr>
<tr>
<td>McEwan et al., 2022 [18]</td>
<td>8–10 mg</td>
<td>60 min</td>
<td>60–65 min$^\ddagger$</td>
<td>11.9–18.4 ng/ml</td>
</tr>
<tr>
<td>Rensch et al., 2021 [40]</td>
<td>~4 mg</td>
<td>30 min</td>
<td>32–33 min$^\dagger$</td>
<td>9.1–11.36 ng/ml</td>
</tr>
<tr>
<td>Chapman et al., 2022 [20]</td>
<td>5.8–10.1 mg</td>
<td>20 min</td>
<td>20–30 min$^\ddagger$</td>
<td>5.1–7.9 ng/ml</td>
</tr>
<tr>
<td>Azzopardi et al., 2022 [19]</td>
<td>4 mg</td>
<td>60 min</td>
<td>60 min$^\ddagger$</td>
<td>8.3 ng/ml</td>
</tr>
<tr>
<td>BfR and LMU, 2022</td>
<td>6–30 mg</td>
<td>20 min</td>
<td>15–30 min$^\ddagger$</td>
<td>2.7–29.3 ng/ml</td>
</tr>
</tbody>
</table>

In half of these studies, the nicotine pouches were used for one hour, while pouches were used for 30 minutes in one study and for 20 minutes in two other studies. The study from the BfR and LMU is the only one investigating significantly higher nicotine concentrations than 10 mg per pouch (see table 5).

The influence on acute nicotine craving was also investigated in the study from BfR and LMU Munich. This acute craving for a cigarette was measured using one question (‘On a scale from 1 to 7, how strongly are you feeling the need for a cigarette right now?’) at various points in time after starting nicotine consumption. Nicotine pouches were used for 20 minutes and cigarettes for 5 minutes. In this study approach, even the product without nicotine reduced the need for a cigarette. While the reduction in nicotine withdrawal symptoms was dose-dependent as a trend, differences were not statistically significant between the groups. Craving reduction was strongest following the consumption of the cigarette. After a weaker start, the craving reduction in the 30 mg group achieved values comparable to those after cigarette consumption.

Data on the use of nicotine pouches in the population is sparse. One manufacturer study presents the results of consumer surveys from Sweden, which asked respondents to state their daily consumption of nicotine pouches every three months between Q1 2018 and Q4 2020. Sample sizes ranged from 20 to 99 people in 2018 and 2019, and varied between 190 and 238 people in 2020. On average, respondents consumed 8.6 nicotine pouches per day [7]. In a follow-up study, pouch use was compared between four European countries (Denmark, Germany, Sweden and Switzerland). This involved an online survey of nicotine pouch users, which was completed by 150 respondents in Germany. The most popular use was 10 to 20 minutes, while 15% to 25% of respondents stating they use pouches for 20 to 30 minutes. The most common nicotine content for a pouch was 6 to 15 mg per pouch. 73% of respondents used one to five pouches a day. The most popular flavour was menthol, followed by fruit flavours [43]. In 2021, a nicotine pouch survey was conducted as part of the DEBRA study in Germany. This study surveyed a representative sample in five separate waves (N = 10,135). During the observation period, 0.1% were current users of nicotine pouches. The figure for ‘ever users, reflecting both regular consumption and just trying pouches out, was 0.9%. Just
over a fifth of respondents (21.9%) had heard about nicotine pouches. Among current and former regular users, the median quantity consumed was 8 pouches a day. However, the small sample size (N = 14) does not provide a robust data set [44].

In the USA, tobacco-free nicotine pouches were introduced in 2016 and market share in the smokeless tobacco segment had risen to 4% by 2019 [45]. Analyses of consumer behaviour towards nicotine pouches were also carried out in the USA. Nicotine pouches appealed to only a small proportion of those who had never used tobacco or were former users (11–12%). The product appealed to 36% of active smokers and to 52% of current users of smokeless tobacco. The approval rate was highest (75%) among people who consumed both cigarettes and smokeless tobacco [46]. Sales of tobacco-free nicotine pouches are rising in the USA. In 2021, a representative sample of adult smokers was surveyed in the USA. According to survey responses, 29.2% of this group had already seen or heard about tobacco-free nicotine pouches, 5.6% had already tried them and 16.8% expressed an interest in trying tobacco-free nicotine pouches over the next 6 months [47].

In 2019, a UK survey of current and former users of cigarettes or e-cigarettes found that 4.4% of respondents had used nicotine pouches at least once [48]. Comparable studies for Germany are not yet available.

3.1.4 Risk characterisation

Nicotine is classified under chemicals legislation as acute toxic, although this classification is based only on acute toxicity following oral ingestion. On the basis of various animal studies while also accounting for toxicity in humans, the ECHA Committee for Risk Assessment has established an acute toxicity estimate of 5 mg nicotine/kg bodyweight. The EU CLP Regulation cites the following formula for calculating the acute toxicity of mixtures in Appendix 1, Part 3, No. 3.1.3.6.1:

\[
\frac{100}{ATE_{mix}} = \sum_{i} \frac{C_i}{ATE_i}
\]

The formula is written in terms of \( c_i \).

\[ c_i = \frac{(100 \times ATE_i)}{ATE_{mix}} \]

Here, the value of 5 mg/kg bodyweight is used as the \( ATE_i \), i.e. the acute toxicity estimate for nicotine. For \( ATE_{mix} \), the acute toxicity estimate for mixtures, a value of 300 mg/kg bodyweight
is applied. This is a borderline value between categories 3 and 4 for acute oral toxicity (see table 3.1.1 in the CLP Regulation). The formula then produces the following value:

\[
\frac{(100 \times 5)}{300} = 1.67\%
\]

For nicotine pouches, this would represent a concentration of 16.7 mg per g of pouch leading to a classification in hazard category 4 under chemicals legislation. In this category, labelling with the skull and crossbones pictogram is not required.

This limit is easy to understand from a toxicological perspective. As described in section 3.1.2, the use of a pouch with 6 mg nicotine resulted in a significant increase in heart rate by 10 beats per minute. The concentration proposed here is almost three times higher. From the study by BfR and LMU, the nicotine concentration in blood following 20 minutes of use of a pouch with a 16.6 mg dose is estimated to be equivalent to the level in blood after smoking a cigarette.

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

3.2 Risk management options, recommended measures

Currently, nicotine in pouches is classified as a novel food by the German surveillance authorities. If the ARfD value of 0.0008 mg/kg bodyweight is used, nicotine pouches containing all nicotine quantities presented in this report will be withdrawn from the market. In terms of effects on health, the BfR defines the following high-risk groups: Children, adolescents and non-smokers, as nicotine is an addictive substance. Pregnant and breastfeeding women, because of the effects of nicotine during pregnancy and its passage into breast milk. People with cardiovascular disease, as nicotine has strong effects on the cardiovascular system.

The relevance of variations in strengths for the harmful effects of tobacco or nicotine products have been discussed for some time now. The aim of such discussions is to create options for smokers switching to nicotine products that contain or release a lower concentration of harmful substances [49, 50].

This model has been further developed by Abrams et al. [51]. The harm minimisation continuum described by the authors assumes that nicotine-containing products are not equally harmful, but range from a very low level of harm (e.g. nicotine patches) to a very high level of harm (e.g. cigarettes). The most harmful are cigarettes, whose consumption is held to be responsible for the premature death of around 127,000 people in Germany every year [52] (for the methodology used for this calculation, see [53]). Swedish-style snus is significantly less dangerous. On the other hand, a comparison between non-smokers or non-users of nicotine reveals an increased health risk for snus users. Further evidence for this risk has been provided recently by an aggregated analysis of eight cohort studies on the increased mortality of snus users in Sweden [54]. Nicotine pouches and nicotine replacement medicines such as nicotine
patches do not contain tobacco. However, nicotine patches can also expose patients to TSNAs [55].

For people who have not previously smoked or otherwise consumed nicotine, any form of nicotine consumption represents an increased risk to their health.

Keeping this model of risk minimisation in mind, switching from cigarettes to nicotine pouches could represent a reduction in health risks for a person who smokes. However, measures should be taken to avoid that use of nicotine pouches leads to a higher nicotine intake compared with other products on the market.

In the BfR study, genotoxic and carcinogenic TSNAs were found in some nicotine pouches [3]. The fact that no TSNAs were detected in many products demonstrates that excluding these substances is indeed technically possible. From a toxicological point of view, TSNAs should not be detectable in nicotine pouches. Furthermore, substances contained in nicotine pouches can be swallowed, and are subject to interactions with food components, saliva and gastrointestinal juices. Nitrosamines are formed by the action of nitrosating agents such as nitrite salts, preferably in an acidic environment. This can then lead to the endogenous formation of carcinogenic TSNAs in the human digestive tract [56]. Thus, the measured – and occasionally very high – nicotine content of nicotine pouches is seen to be critical also in this context. In addition to closing the described knowledge gaps, quality control as a result of standardisation and regulatory activities appears to be useful as a means of minimising the risks posed by nicotine pouches.

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 has shown that snus users are not more likely to start smoking cigarettes. On the contrary, cigarette smokers who start using snus are more likely to stop smoking cigarettes [57]. When considering nicotine pouches as an option for smoking cessation, care should be taken to prevent cases of dual use, as often occur with users of e-cigarettes, for example. Alongside market surveillance, independent research is therefore needed to investigate usage patterns within various population subgroups, which should also include non-smokers [58].

In terms of tobacco-induced disease, Sweden is an outlier when compared to other European countries. A 2012 report on cancer incidence and mortality rates in Europe revealed that Sweden was the only country in Europe where lung cancer was not the leading cause of cancer mortality in men [59]. Age-standardised cancer mortality rates were calculated in this study. Sweden had the lowest value of 40 European countries for lung cancer in men, with 26.4 per 100,000 in Sweden compared with 47.0 per 100,000 in Germany [59]. The lung cancer mortality rate for men in Germany is therefore 78% higher. In 2020, an updated report was published, revealing that the lung cancer mortality rate for men in Germany had since climbed to a figure 90% higher than for men in Sweden [60].

These facts are well-known and were recently addressed, for example by the German Behandlungsnetzwerk der Gesellschaft für die Forschung an Nikotin und Tabak [61]. However, whether the effects of the long-term snus use in Sweden indicate a positive effect of nicotine pouches in smoking cessation remains to be shown.
More information on the topic of nicotine and cigarettes

Nicotine
https://www.bfr.bund.de/en/a-z_index/nicotine-130375.html

Cigarettes
https://www.bfr.bund.de/en/a-z_index/cigarettes-130399.html

4 References

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20. Chapman, F., et al., *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), 2022.


35. Adler, I.D. and S.M. Attia, *Nicotine is not clastogenic at doses of 1 or 2 mg/kg body weight given orally to male mice.* Mutat Res., 2003. 542(1-2): p. 139-42. [Mutation research].


**About the BfR**

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

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