

Updated discussion paper on the bioavailability of nicotine and other ingredients from the use of oral nicotine pouches and assessment of risk to users

This is a paper for discussion.

This does not represent the views of the Committee and should not be cited.

Introduction

1. The Committee has been requested by the Office of Health Improvement and Disparities (OHID) Tobacco teams to consider the toxicological risks from tobacco-free oral nicotine pouches.
2. This paper is an updated version of TOX/2021/22 discussed at the May 2021 meeting, providing the additional information requested at that meeting (minutes included in Annex A), namely: a table of pharmacokinetic parameters to allow comparison across nicotine products; a discussion of the International Agency on Cancer (IARC) conclusions on oral tobacco products; identification of health-based guidance values (HBGVs) for nicotine; and consideration of the potential for irritancy or local effects at the site of use. Since May 2021, the OHID has requested an additional risk assessment due to receipt of information that nicotine can be present in pouches at up to approximately 120 mg nicotine per pouch (OHID, personal communication).
3. The demand for tobacco or tobacco-related products that are less damaging to health is increasing as users look for substitutes to conventional cigarettes (CC) (Fjellner, 2020). Such products include electronic nicotine (and non-nicotine) delivery systems (E(N)NDS - e-cigarettes) and the toxicological risks

of E(N)NDS for users and bystanders have been extensively evaluated by the COT ([COT, 2020](#)).

4. Smokeless tobacco products are a further example of CC substitutes. Smokeless tobacco products have been available for many years and comprise non-combustible products that may be chewed, inhaled or placed in the mouth (ASH, 2020). One of the better-known smokeless tobacco products is “snus” which is produced and sold in Sweden as loose powder or in pre-portioned pouches. Snus has been prohibited for sale elsewhere in the EU since 1992.

5. Tobacco-free versions of pre-portioned snus are also available on the Swedish market. These reflect the more modern oral tobacco-derived nicotine (OTDN) products which are tobacco-leaf free and contain tobacco-derived nicotine and food grade ingredients (Robichaud et al., 2019). Commercially available OTDN products available in the UK and EU include lozenges, gums, and dissolving tablets (Choi et al., 2003; West and Shiffman, 2001; O’Connor et al., 2011). More recently, nicotine pouches have emerged as a new category of OTDN products, including on the UK market. These products are pre-portioned pouches, similar to snus pouches, in which the tobacco leaf is replaced with a non-tobacco filler and tobacco-derived nicotine (Aldeek 2021). The pouch is placed between the lip and gum allowing for the dissolution of nicotine to occur in the saliva before being absorbed in the oral cavity and entering the bloodstream (Hukkanen et al., 2005).

6. This paper provides the publicly available information for the ingredients present in these products and in particular focusses on the oral bioavailability of nicotine to support assessment of any potential risks associated with their use. It is noted that nicotine pouches provide a pharmacologically active dose of nicotine and, as such, they are not ‘harmless’ products. However, use of nicotine pouches could be considered as part of a harm reduction strategy, if their use is lower risk than use of CC.

Regulatory framework

7. Oral nicotine pouches are tobacco-free products, hence they fall outside the Tobacco and Related Products Regulations (TRPR, 2016), and as no medicinal claims are made and they are not an obvious alternative to an authorised medicinal product, they are not regulated by the Medicines and Healthcare products Regulatory Agency (MHRA, 2020) - see abbreviations and technical information for a more detailed explanation. The regulatory position on them currently is likely to be under the General Product Safety Regulations (GPSR)

(2005), which generally require less stringent toxicological data to be provided.

8. Under GPSR, the general safety requirement states that “products should only be sold if their compliance with product safety regulations has been demonstrated appropriately”. The GPSR requires all products to be safe in their normal or reasonably foreseeable use and enforcement authorities have powers to take appropriate action when this obligation is not met.

9. Where producers and distributors know that a product poses a risk to the consumer that is incompatible with the general safety requirement, under the GPSR appropriate actions are required to prevent adverse events by informing consumers of the risk that the product presents. In the case of nicotine pouches, nicotine has known addictive effects, and this has to be stated clearly on packaging and an age limit clearly displayed. In addition, due to the potential for reproductive and developmental toxicity, life-stage warnings must be stated.

10. Nicotine has been registered under the EU Registration, Evaluation, Authorisation & restriction of Chemicals (REACH) regulations. It is classified as acutely toxic (category 2) by oral, dermal, and inhalation exposure and has hazard statements H300: fatal if swallowed, H310: fatal in contact with skin, and H330: fatal if inhaled (discussed fully in [TOX/2020/59](#)).

Search strategy

11. A broad-based search of SciFinder and PubMed for publications relating to ‘nicotine pouches’ was conducted on 10/12/2020 and the search of PubMed was briefly updated on 28/01/2021 and again on 28/01/2022. Searches of ‘grey literature’ were also conducted. Due to the low numbers of papers identified it was not considered necessary to develop more specific search terms. Approximately 70 citations were identified and those of relevance are discussed below.

Contents of nicotine pouches

12. Several large tobacco companies currently market tobacco-free nicotine pouches. Commercial nicotine pouches are sold with varying nicotine content, with between 4 and 18 mg of nicotine per pouch being offered across all brands. OHID has provided information that nicotine can be present in pouches up to approximately 120 mg nicotine per pouch (OHID, personal communication). In addition, each of the nicotine content levels has a choice of strength. For

example, a commonly used brand of nicotine pouches used in the UK offers nicotine content of 8, 14 and 16 mg per pouch, with at least two levels of strength (between 1 - 4) available for each of the nicotine contents. The perceived strength of the pouch by the user does not necessarily reflect the actual nicotine content as it is determined by the amount of nicotine released during use, which varies with flavour, the presence of other constituents, moisture content and pH, as well as nicotine content.

13. As with e-cigarette liquids, nicotine pouches are sold in a variety of flavours such as fruit (e.g., black cherry, citrus) and others (e.g., peppermint, coffee). Some of the contents listed on commercially available nicotine pouch products are indicated below, although contents vary between different brands and individual products:

- Nicotine – can be defined as ‘pharmaceutical grade’, ‘synthetic nicotine’, ‘nicotine derived from the tobacco plant’, ‘tobacco-derived nicotine salt’ or simply ‘nicotine
- hydroxypropyl cellulose
- microcrystalline cellulose
- maltitol
- gum, Arabic
- sodium carbonat
- sodium bicarbonat
- acesulfame K
- food-grade flavourings
- water
- salt
- sucralose
- citric acid

It is unclear from the literature whether a ‘standard’ source and purity of nicotine is used in pouches as there appear to be many descriptions used (listed above).

14. It is important, for risk assessment purposes, to identify the presence of potentially toxic impurities in tobacco-derived nicotine, including, for example, tobacco-related nitrosamines, heavy metals and pesticide residues. At the COT meeting in May 2021 (see minutes in Annex A), the Committee considered that “there would be different risks according to the different batches of tobacco used to derive the nicotine, and the extraction process used”. It was recommended that, with respect to extraction of nicotine from tobacco “the possibility of contaminants such as heavy metals, pesticides and nitrosamines should be

considered, and where possible avoided”.

15. The ‘other ingredients’ listed above are standard ingredients that are considered safe for use in foods and food products and are not considered further here. Azzopardi et al. (2021) evaluated the levels of toxicants in nicotine pouches according to the Food and Drug Administration (FDA) smokeless tobacco reporting list (FDA 2012) and GothiaTekVR standard compounds (Swedish Match 2016), which are commonly used to characterise smokeless tobacco products. The authors compared the levels of toxicants in nicotine pouches with those in snus and nicotine replacement therapy (NRT) products to “estimate their position on the tobacco/nicotine product continuums of toxicant delivery and risk”. Note- the “Disclosure Statement’ for this paper states that “All authors are employees of BAT, a company that manufactures tobacco and nicotine products” and the ‘Funding’ statement states that- “BAT funded this study”.

16. A number of products were analysed including: four types of nicotine pouch manufactured by British American Tobacco (BAT) (Lyft Freeze, Lyft Lime Strong, Lyft Berry Frost and Lyft Mint); a BAT snus product (Granit Ice Blue White); two leading non-BAT snus products (Skruf Slim Fresh XStrong Mint and G3 Slim White XStrong Blue Mint); and two leading commercially available NRTs in lozenge (Nicorette 4 mg) and gum (Nicorette 4 mg) format. Each product was analysed for 26 substances including known harmful and potentially harmful constituents (HPHCs) as advised by the FDA, the GothiaTekVR Standard list of toxicants (other than agrochemicals as nicotine pouches are synthetic products), and the World Health Organization (WHO) Tobacco Product Regulation Group ‘TobReg9’, with the exception of carbon monoxide.

17. The four types of nicotine pouches tested contained the toxicants formaldehyde and chromium above the level of quantification, although the amounts detected were close to quantification limits. The authors calculated that, based on the highest mean levels measured and average daily consumption of nicotine pouches ($n = 8.6$ as determined from market surveys in Sweden), the increase in intake of formaldehyde and chromium from the use of nicotine pouches was minimal and not of toxicological concern, when compared with background exposures.

18. In addition, the relevance of the toxicant profiles to relative health risks was estimated for each product, CCs, a tobacco heating product (THP), and e-cigarette (ENDS) vapour by calculating Daily Exposure to Toxicants (DET), with an average determined for each product type, as discussed below (see abbreviations and technical information section for further details):

- When compared with snus, the use of nicotine pouches was associated with lower daily exposure to acetaldehyde (19.7–25.5 mg/day for snus vs not quantified (NQ) for nicotine pouches), N-nitrosornicotine (NNN) (1.5–1.8 mg/day vs NQ), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (0.2–0.6 mg/day vs NQ), dimethyl nitrosamine (NDMA) (NQ–1.0 ng/day vs NQ), cadmium (around 0.2–0.4 mg/day vs NQ), chromium (0.34–0.71 vs <0.18–0.28 mg/day), arsenic (38.6–54.6 ng/day vs NQ), nickel (0.7–1.6 mg/day vs NQ) and lead (79.8–143 ng/day vs NQ), with comparable exposures to formaldehyde (around 3–4 mg/day).
- Compared to NRT products, nicotine pouch use was associated with a higher daily exposure to formaldehyde (NQ for NRT products vs <3.5–4.0 mg/day for nicotine pouches), but lower exposure to cadmium (gum 0.2 mg/day vs NQ), chromium (<0.31–5.83 vs <0.18–0.28 mg/day), nickel (0.5–1.7 mg/day vs NQ) and lead (gum 0.4 mg/day vs NQ).
- In comparison with CC, the use of nicotine pouches reduced exposure for around 90% of the toxicants measured.
- Nicotine pouch use was calculated to be associated with lower levels of daily exposure to formaldehyde (NQ – 3.96 µg/day) and higher levels of exposure to chromium (NQ – 279 ng/day) compared with use of THP (28.8 µg/day and 37.9 ng/day for formaldehyde and chromium, respectively) or exposure to ENDS vapour (19.2 µg/day and 63 ng/day, respectively).

19. The authors concluded that for the majority of the chemicals assessed “on the basis of both the measured toxicant contents and daily exposure estimates, nicotine pouches are likely to fall between snus and NRTs on the toxicant delivery continuum, with substantially less toxicant exposure relative to cigarettes, THPs, snus and even vapor products” (Azzopardi et al., 2021).

20. Stanfil et al. (2021) evaluated the amount of unprotonated nicotine (free or freebase), the form most easily absorbed, from 37 nicotine pouch brands from six manufacturers. Free nicotine content was calculated using total nicotine (protonated and unprotonated), product pH, the appropriate pKa, and the Henderson–Haselbalch equation. Total nicotine content ranged from 1.29 to 6.11 mg/pouch, whilst free nicotine ranged from 0.166 to 6.07 mg/pouch, giving a % free nicotine range between 7.7% and 99.2%. Moisture content and alkalinity were also variable between nicotine pouches, with ranges of 1.12–47.2% and pH 6.86–10.1, respectively, being reported. The authors concluded that nicotine and pH levels in nicotine pouches are similar to those in conventional tobacco products such as moist snuff (pH range 5.54 to 8.61 and free nicotine ranging from 0.01 to 7.8 mg/g) and snus (pH range 5.87 to 9.10 and free nicotine ranging

from 0.08 to 16 mg/g).

Release of nicotine from oral pouches during use

21. There is a general lack of data to evaluate the delivery of nicotine from pouches, i.e. the equivalent of 'puff topography' for E(N)NDS devices. It can be considered that changes to ingredients in nicotine pouches, such as the inclusion of nicotine salts, could affect systemic exposure, but this has not currently been explored.

22. Aldeek et al. (2021) evaluated the release of nicotine from 35 pouches offered by one manufacturer ('on!®' pouches). These pouches are available in seven flavours and five different nicotine levels. Release of nicotine into artificial saliva (pH 6.8 ± 0.1 with buffer capacity of 3.4 mM/1 pH unit; Miller et al., 2020), maintained at 37°C, was monitored at time intervals between 0 and 60 minutes.

23. The authors noted that the cumulative release profiles of nicotine showed a dose-dependent response, with equivalent nicotine release (%) for all flavours across all nicotine levels. Dissolution of nicotine was most rapid between 0 and 20 min (around 80% of release), with approximately 95% of release being achieved within 40 min, then reaching a plateau. The dissolution rate of nicotine from on!® nicotine pouches was compared with that from another type of OTDN pouch (ZYN®) and from smokeless tobacco products. The nicotine release rates (%) of the OTDN products were similar, with differences attributed to individual product characteristics, including pouch paper and the presence of other ingredients. The authors also reported that on!® nicotine pouches had similar or faster nicotine release profiles than the traditional pouched smokeless tobacco products tested (Aldeek et al., 2019).

24. Lunell et al. (2020) carried out a single-dose pharmacokinetic study of nicotine pouches of two strengths (3 and 6 mg) compared with an 8 mg snus product in 17 individuals to determine intra-individual variations in area under the curve (AUC)_{inf}. Several other parameters were also assessed, including: AUC_{60min}; maximum concentration (C_{max}); time to maximum concentration (T_{max}); AUC_{0–t} and terminal half-life; percentage extraction of nicotine *in vivo*; pulse rate and subjective effects (head buzz) after study product administration; and any other adverse events.

25. Volunteers did not eat, drink, chew chewing gum or brush their teeth for a period of 30 min prior to exposure. Pouches were used as per consumers, i.e. placed between the upper lip and the gum for 60 min with no manipulation with

the tongue or lips. Nicotine extraction from the 3 and 6 mg nicotine pouches was reported as 1.5 mg (95% confidence interval [CI]: 1.3–1.8 mg, $p = 0.002$) and 3.5 mg (95% CI: 3.0–4.0 mg, $p = 0.002$), respectively, with 2.4 mg (95% CI: 2.0–2.8 mg) being extracted from the 8 mg snus product. Thus, a higher fraction of nicotine was extracted from the nicotine pouches (56–59%) than from the snus product (32%).

26. The higher extracted fraction of nicotine from 6 mg nicotine pouches resulted in significantly higher nicotine AUC_{inf}, AUC_{0–t}, AUC_{60 min}, and C_{max} compared with the snus (8 mg nicotine) product. No statistically significant differences between the nicotine 6 mg pouch and the snus 8 mg product were found for the terminal half-life and T_{max} parameters. Assessments of the subjective effect of ‘head buzz’, and of heart-rate measurements, were used to indicate systemic nicotine uptake. No correlation was seen between either of these measurements and nicotine levels. The authors concluded that pouches with nicotine content ≥ 6 mg could be used as a smoking reduction/cessation tool as they deliver nicotine as quickly and to a similar concentration as existing smokeless products (Lunell et al., 2020).

Nicotine toxicokinetics

27. The toxicokinetics of nicotine was summarised in COT discussion paper [TOX/2019/38](#). In brief, nicotine is a weak base with pK_a 8.0 and is not well absorbed in the ionised state, in acidic conditions. Absorption of nicotine from saliva across the buccal mucosa increases with the pH of the saliva, which in turn is determined by the relative acid-base buffering capacities of the saliva and nicotine pouch and the pH of the saliva and nicotine pouch before they come into contact. As nicotine absorption is pH dependent, many NRT products (paragraphs 42 to 50) are buffered to pH 7 to enhance absorption.

28. The percentage bioavailability of nicotine administered as single doses by various routes was reported as follows: smoking 1 CC (80-90%); i.v. approximately 5.1 mg (100%); nasal spray 1 mg (60-80%); gum 2-4 mg (55-78%); inhaler 4 mg (51-56%); lozenge 2-4 mg (50-79%); transdermal patch 14-21 mg/24 h (68-100%); s.c. injection 2.4 mg (100%); oral capsule 3-4 mg (44%); oral solution approximately 3 mg (20%); enema approximately 3.5 mg (15- 25%) (Hukkanen et al., 2005; Benowitz et al., 2009; EFSA, 2009). Gislekog et al. (2020) reported that swallowed nicotine is absorbed in the small intestine but undergoes extensive first-pass metabolism by the liver and has a relatively low (30-40%) bioavailability. The variation in time taken to reach maximal nicotine

plasma concentration is due, in part, to differences in administration duration, as well as absorption time that differs with each route of delivery.

29. Following absorption, nicotine is distributed extensively within body tissues, with the highest affinity to liver, kidney, spleen, lung, and brain tissue. Nicotine accumulates in gastric juice, saliva and breast milk, crosses the placental barrier and accumulates in fetal serum and amniotic fluid. Approximately 70-80% of nicotine is metabolised to cotinine (mediated extensively (90%) by hepatic cytochrome P450 (CYP) 2A6). Cotinine is subsequently metabolised to 3'-hydroxycotinine (mediated exclusively by CYP2A6). Nicotine and metabolites are excreted in the urine. The flavin-containing monooxygenase (FMO)3, uridine diphosphate glucuronyl-transferase (UGT)2B10 also plays a minor role in nicotine metabolism. Plasma nicotine half-life on intravenous (i.v.) infusion is around 2 h, with terminal half-life of 11 h.

30. Nicotine is excreted by glomerular filtration and tubular secretion, with reabsorption depending on urinary pH (higher reabsorption at higher pH).

31. Nicotine pouches are designed to be placed inside the mouth between the inner cheek or lip, and gum. Absorption of released nicotine occurs across various oral membranes, including the buccal mucosa (cheek lining) (Ciolino et al. 2001). Transfer across the oral mucosa occurs via passive diffusion. Unionised/uncharged forms are transferred more readily due to their higher lipid membrane solubility compared with ionised/charged forms. The proportion of unionised/uncharged nicotine present depends on the pH of the medium in which it is found (Ciolino et al. 2001).

32. It is possible that some nicotine pouch manufacturers include nicotine in the form of salts. The COT has discussed information relating to whether the inclusion of nicotine salts in ENDS products can modify the level of internal exposure to nicotine that is achieved by use of the product, in comparison with use of ENDS products containing nicotine in the freebase form ([TOX/2020/59](#), discussed at the December 2020 meeting). The Committee agreed that the use of ENDS products containing nicotine salts is likely to be associated with increased bioavailability of nicotine to users. However, it is not currently possible to quantify any effects, given the limited availability of pharmacokinetic data and the additional factor of the role of vaping topology in nicotine exposure.

33. In a randomised, controlled, crossover clinical study involving 35 individuals, nicotine pharmacokinetics and subjective effects of commercially available nicotine pouches (five different brands; 6-10 mg nicotine/pouch) and a

combustible CC were compared (McEwan et al., 2021). Exposure to nicotine pouches was for a 60 min period and for CC a maximum limit of 5 min *ab libitum* smoking was permitted. As detailed in Table 1, nicotine pouches had a longer time to Tmax compared to a CC, meaning a slower increase in nicotine levels in blood plasma following use of nicotine pouches. Although the total amount of nicotine delivered from nicotine pouches (i.e. Cmax and AUC0-6h) was greater or similar to that for CCs, the authors noted that the 60 min exposure period used in the study is higher than the 30 mins recommended by NP manufacturers. Test subjects indicated that “product liking” and “intent-to-use-again” scores were greatest for nicotine pouches with higher nicotine content; however, these scores were lower for all nicotine pouches than for combustible cigarettes. Note: The “Funding” statement for this study states that “The study was supported by British American Tobacco (Investments) Limited, the manufacturer of Lyft and Velo smokeless oral nicotine pouches and the “Competing interests” statement that “All authors are current employees of British American Tobacco (Investments) Limited except JM who is an employee of RAI Services Company and IMF who is a consultant contracted by British American Tobacco (Investments) Limited”.

Exposure to nicotine following use of NRT

34. Although nicotine pouches are not marketed as an NRT product, data to estimate exposure levels following nicotine pouch use have shown similarities with data acquired from NRT studies, for example, Azzopardi et al. (2021). Many NRT products substitute the nicotine from inhaled tobacco products with uptake via other routes, with a number of products being designed for oromucosal (i.e. buccal and sublingual) absorption (Gisleskog et al., 2020).

35. Nicotine gum was the first NRT product, registered in Switzerland in 1978. This was followed by a number of alternative oromucosal absorption products including mouth sprays, lozenges, sublingual tablets and inhalers. Hartmann-Boyce et al. (2018), through the evaluation of data identified in a Cochrane Tobacco Addiction Group trials register, estimated that use of NRT was associated with an increased relative smoking abstinence rate of 50-70% compared with placebo or non-NRT control groups. NRT is considered an important tool in reducing tobacco use and lung cancer incidence (Shields et al., 2016).

36. In a retrospective analysis, Gisleskog et al. (2020) developed population pharmacokinetic models for nicotine, using data from 930 healthy smokers

(46,016 observations) from 29 single- and repeated-dose studies with multiple formulations across intravenous, oral, transdermal and oromucosal routes of administration. The use of oromucosal-route products results in partial delivery of nicotine to the GI tract due to swallowing, with absorption and metabolism as previously discussed (paragraphs 15 to 18). The authors estimated a relatively low bioavailability from this route (30–40%) (Gisleskog et al., 2020).

37. Considered as a group, absorption of nicotine from the buccal cavity was rapid following use of mouth spray, gum, lozenge and inhaler, with peaks occurring shortly after the end of dosing. Many individual profiles showed a second peak of absorption, which was considered by the authors to be due to intestinal absorption of the fraction of the nicotine dose that was swallowed during use. This swallowed fraction of the dose was estimated to be 61%, 67% and 69%, for mouth spray, inhaler and lozenge respectively, and 55% for chewing gum. It was also noted by the authors that increasing doses of nicotine were associated with a higher fraction being swallowed, possibly due to irritant effects of nicotine in the oral cavity resulting in increased saliva production.

38. The acceptability of smokeless tobacco and NRT products to users, including CC smokers who are trying to stop smoking, is considered to be influenced by the ability to achieve rapid absorption of a sufficient dose of nicotine to mimic delivery from CC use. Blood plasma nicotine levels in CC smokers generally range from 10 to 50 ng/mL, with typical daily trough concentrations of 10 to 37 ng/mL and peaks of 19 to 50 ng/mL, and a mean nicotine boost per 1 CC smoked of 10.9 ng/mL. *Ad libitum* use of NRT products generally provides a plasma nicotine concentration approximately one-third to two-thirds of that achieved by CC smoking. Steady-state plasma nicotine concentrations from transdermal patches are in the range of 10–20 ng/mL, with a range of 5–15 ng/mL from gum, inhaler, sublingual tablet, and nasal spray. Systemic doses delivered from different nicotine delivery systems are reported to be as follows: smoking 1 CC, 1–1.5 mg; nicotine gum, 2 mg from one 4-mg gum; transdermal patch, 5–21 mg per day; nasal spray, 0.7 mg per 1-mg dose of 1 spray in each nostril; inhaler, 2 mg for a 4-mg dose released from the 10-mg inhaler; lozenge, 1 mg for a 2 mg lozenge; oral snuff (snus), 3.6 mg for 2.5 g held in the mouth for 30 min; chewing tobacco, 4.5 mg for 7.9 g chewed for 30 min (Hukkanen, et al., 2005; Benowitz et al., 2009).

39. Digard et al. (2013) determined nicotine absorption from snus pouches (1 g portions containing 11 mg of nicotine), loose snus smokeless tobacco products (1 g portion containing 11 mg of nicotine and 2.5g portion containing 27

mg nicotine) in comparison with a CC (14.6 mg nicotine) and an over-the-counter nicotine gum (4.2 mg nicotine) used as directed by the manufacturer. The authors reported that snus users held pouches or portions in the mouth for between 60-70 min, which is longer than directed on the product packaging (typically 20-30 min).

40. As previously widely reported in the literature, Digard et al. (2013) determined that nicotine plasma levels rose more rapidly following the use of a CC compared with other oral nicotine-containing products. However, over the total sampling period (120 min) the systemic exposure to nicotine was higher for the snus products than for nicotine gum or CC. The authors reported that the AUC_{0 - 120} for all six test products were ranked as: loose snus > pouched snus > loose/pouched snus > cigarette > 4.2 mg nicotine gum. C_{max} followed a similar ranking: loose snus > pouched snus > cigarette > loose/pouched snus > nicotine gum. The authors considered that this was due to a higher nicotine content of the snus products and the longer duration of use. In terms of the t_{max}, Digard et al. (2013) determined that this was 1 h for all snus products, equivalent to the time of use specified in the study. For the nicotine gum, time of use was 30 min and the t_{max} was 45 min. The shortest t_{max} of 7 min was measured for CC, which reflected the use time of 5 min. The authors concluded that these findings indicated that nicotine absorption kinetics were dependent on the quantity of tobacco by weight and the total nicotine content, rather than the product form.

41. A summary of toxicokinetic parameters for CC, NRTs and nicotine pouches is given in Table 1.

Table 1 - Toxicokinetic parameters for nicotine-containing products.

Product	Nicotine content (mg)	AUC _{0 - 120} (ng/h/ml)	C _{max} (ng/mL)		Reference
		geometric mean (geometric coefficient of variation %)	geometric mean (geometric coefficient of variation %)	t _{max} (h) Median (min-max)	
Conventional cigarette £	14.6	14.8 (30.4)	12.8 (41.3)	0.117 (0.083-0.517)	Digard et al., 2013

Product	Nicotine content (mg)	AUC0 - 120 (ng/h/ml)	Cmax (ng/mL)	tmax (h)	Reference
		geometric mean (geometric coefficient of variation %)	geometric mean (geometric coefficient of variation %)	Median (min-max)	
Loose snus \$	10.8	16.0 (31.2)	10.8 (34.4)	1.0 (0.75 - 1.5)	Digard et al., 2013
Loose snus \$	27.1	26.9 (23.8)	17.9 (22.8)	1.0 (0.75 - 1.5)	Digard et al., 2013
Pouched snus \$	10.7	16.8 (39.6)	10.8 (41.4)	1.0 (0.33 - 1.5)	Digard et al., 2013
Pouched snus \$	14.7	20.4 (37.6)	13.4 (39.0)	1.0 (0.75 - 1.5)	Digard et al., 2013
Nicotine gum &	4.2	13.1 (28.3)	9.1 (28.6)	0.75 (0.33 - 1.5)	Digard et al., 2013
Snus ^	8.0	45.9 (29.8-62.1)	10.6 (8.9-12.3)	1.15 (1.0-1.3)	Lunell et al., 2020
Nicotine pouches \$	3.0	32.0 (23.3-40.7)	7.7 (6.3-9.0)	1.02 (0.93-1.1)	Lunell et al., 2020
Nicotine pouches \$	6.0	57.7 (43.9-71.6)	14.7 (12.3-17.1)	1.1 (0.98-1.2)	Lunell et al., 2020

Product	Nicotine content (mg)	AUC ₀₋₁₂₀ (ng/h/ml)	C _{max} (ng/mL)		Reference
		geometric mean (geometric coefficient of variation %)	geometric mean (geometric coefficient of variation %)	t _{max} (h) Median (min-max)	
Nicotine pouches, Type 10 mg 1 # ~	10 mg	53.7 (27.2) n=35	17.1 (24.0) n=35	1.0 (0.002-1.3)	McEwan et al., 2021
Nicotine pouches, Type 10 mg 2 # ~	10 mg	35.8 (30.6) n=35	11.9 (26.8) n=35	1.1 (0.75-1.25)	McEwan et al., 2021
Nicotine pouches, Type 9 mg 3 # ~	9 mg	52.8 (30.5) n=35	18.4 (30.1) n=35	1.03 (0.17-2.0)	McEwan et al., 2021
Nicotine pouches, Type 6 mg 4 # ~	6 mg	46.9 (44.2) n=35	17.5 (43.8) n=35	1.08 (0.75-1.25)	McEwan et al., 2021
Nicotine pouches, Type 8 mg 5 # ~	8 mg	39.0 (26.4) n=35	13.0 (20.2) n=35	1.0 (0.05-1.25)	McEwan et al., 2021

£ Smoked according to participants usual smoking behaviour for 5 min

\$ Placed under the upper lip for 60 min with no movement

& Used for 30 min according to the manufacturers guidelines

^ Administration not specified

Placed under the upper lip for 60 min

~ 5 types of commercially available nicotine pouches from different manufacturers were evaluated

Toxicity of nicotine

42. The toxicity of nicotine has been considered by the COT ([TOX/2019/38](#)) for all routes of exposure. The following points are of relevance in relation to oral exposure:

- Nicotine is acutely toxic via all routes of exposure, targeting the central and peripheral nervous systems. In humans, the lethal dose has been estimated as approximately 0.6–1.0 mg/kg bw, although a more recent review has proposed a lethal dose in the range of 6.5–13 mg/kg bw. Poisoning cases mostly relate to accidental or deliberate ingestion or dermal exposure.
- Lethal dose (LD)50 values for nicotine in animals have been reported for oral, dermal, intraperitoneal (i.p.) and i.v. routes of exposure, ranging from around 3 to 188 mg/kg bw (HCN, 2005).
- Nicotine is reported to cause local irritation at the site of administration (e.g. dermal patch, nasal or oral sprays) in humans. A review of nicotine toxicology by the Health Council of the Netherlands concluded that nicotine is a skin irritant and sensitiser (HCN, 2005). The REACH dossier classed nicotine as Category 2 (irritant) and noted that nicotine was not sensitising in a well conducted study *in vivo* (local lymph node assay).
- Nicotine is an agonist to nicotinic receptors, which are located in the autonomic and peripheral nervous system, brain and spinal cord. In humans, as in animals, nicotine has been shown to produce both behavioural stimulation and depression. Pharmacodynamic studies indicate a complex dose-response relationship, due to both the complexity of intrinsic pharmacological actions and the rapid development of tolerance. Nicotine-associated effects depend on the dose, route/type of exposure, and time elapsed since the exposure (BfR, 2009).
- Some evaluations have been made based on data from studies of NRT as an aid to quitting CC smoking. The Lung Health Study reported by Murray et al. (2009) found that NRT use was not a significant predictor for lung, gastrointestinal, or all cancers over 7.5 years of follow-up. Studies relating to cardiovascular disease are generally of inadequate quality to draw clear conclusions but have not shown evidence of serious cardiovascular events. The COT discussion paper, [TOX/2018/45](#), noted that a few studies reported potential associations of NRT prescription or use during pregnancy with adverse birth outcomes, but findings were difficult to evaluate due to factors

including low levels of NRT use and lack of data on levels of continued CC smoking.

- Recent evaluations in the literature have noted that evidence for a genotoxic effect of nicotine is mixed. Most studies using the Ames test, chromosomal aberrations, and sister chromatid exchange assays in Chinese hamster ovary cells, and the bacterial genotoxicity luminescence test, were negative. However, some recent *in vitro* genotoxicity studies, including Comet assay, chromosomal aberration or micronucleus formation assays, produced some positive findings in the concentration range of 160–650 mg/mL. A review by the US Surgeon General noted that although this range is above that of systemic levels of nicotine achieved using NRT, higher levels than this may occur at local sites of entry such as respiratory tract or oral epithelia. Genotoxic effects at lower concentrations (16 ng/mL) were noted in a small number of studies, such as the cytokinesis-block micronucleus assay and chromosomal aberration assay (HHS, 2014). The review by the US Surgeon General concluded that, overall, definitive studies to determine the genotoxic potential of nicotine in users of nicotine delivery systems are missing (HHS, 2014). Experimental studies in animals have suggested that nicotine is not carcinogenic *per se*, but adequate studies of long-term exposure to assess carcinogenicity are not available.

43. The specific effects of nicotine on oral tissues have not been well defined. In a systematic review, Holliday et al. (2019) evaluated evidence from *in vitro* studies of the effect of nicotine on human gingival, periodontal ligament, and oral epithelial cells. Measures of cell viability were consistent between cell lines and indicated that nicotine applied at the levels typically found in the saliva of CC, NRT, and E(N)NDS users was unlikely to cause cytotoxicity to human gingival and periodontal cells. However, the authors reported that saliva levels of nicotine in smokeless tobacco users may be high enough to achieve cytotoxicity.

44. Lee (2011) evaluated the risk of oral cancer due to the use of different tobacco products, including snus; they reported no association of oral cancer with snus use, with relative risk (RR) of 0.97 (95% CI 0.68–1.37). The development of non-neoplastic oral disease and oral mucosal lesions (including leukoplakia), periodontal and gingival diseases, tooth loss and dental caries, were also evaluated. Oral mucosal lesions were defined as “any abnormal change or swelling on the epithelial lining of the mouth, lips or gums, which do not contain any malignant or pre-malignant cells”. The authors cited a review of data by Kallischnigg et al. (2008) which concluded that the use of snus markedly increases the risk of developing oral mucosal lesions, which disappear when snus

use is stopped. Although it is widely reported in the literature that oral leukoplakia is caused by chronic irritation from tobacco, it is unclear which component of tobacco is linked to this effect.

IARC conclusions on smokeless tobacco

45. IARC (2007) evaluated the carcinogenic risks associated with the use of smokeless tobacco, including chewing tobacco and snuff (i.e. not nicotine *per se*) and determined that there was sufficient evidence in humans for the carcinogenicity of smokeless tobacco for oral and pancreatic cancer. With regard to experimental data, there was sufficient evidence in experimental animals for the carcinogenicity of moist snuff. The overall evaluation by IARC was that smokeless tobacco is carcinogenic to humans (i.e. Group 1).

46. A number of studies have identified the use of smokeless tobacco products as a cause of oral cancer (including cancers of the gum and buccal mucosa), with and without the co-consumption of alcoholic beverages, and/or tobacco smoking. Strong associations have also been reported in cross-sectional studies between smokeless tobacco use (after accounting for confounding factors) and precancerous lesions such as oral leukoplakia in a number of countries. A positive association between the use of smokeless tobacco and pancreatic cancer has also been reported in both case-control and cohort studies. An increased risk of pancreatic cancer associated with heavy use of smokeless tobacco was observed in non-smokers or long-term quitters of CC smoking. Data for a relationship between smokeless tobacco use and other cancer sites was inconclusive (IARC, 2007).

Reference values for nicotine

47. A toxicological review of nicotine ([TOX/2019/38](#)) was discussed by COT at the July meeting in 2019, which included a number of reference values.

48. The European Food Safety Authority (EFSA) was asked to consider the possible health risks related to the presence of nicotine in wild mushrooms at concentrations up to 0.5 mg/kg. For this purpose, EFSA established an acute reference dose (ARfD) of 0.0008 mg/kg bw, based on a lowest observed adverse effect level (LOAEL) of 0.0035 mg/kg bw for slight, transient increased heart rate in human CC smokers on i.v. infusion of nicotine, and using an overall uncertainty factor (UF) of 10 and a correction factor of 0.44 for oral bioavailability of nicotine, estimated from a human isotope clearance study delivered as a oral capsule containing 3-4 mg nicotine (Benowitz et al., 1991 as cited in EFSA, 2009;

Hukkanen et al., 2005), see also paragraph 28 above. EFSA considered that given the short biological half-life of nicotine, the fact that it does not accumulate in the body, and that the most sensitive effect was considered to be the pharmacological effect on the cardiovascular system, the value set for the ARfD would be suitable to protect from chronic effects and could also be applied as the acceptable daily intake (ADI). Thus, EFSA established an ADI of 0.0008 mg/kg bw/day but noted some deficiencies in the toxicological database (EFSA, 2009).

49. The German Federal Institute for Risk Assessment also established an ARfD for nicotine of 0.0008 mg/kg bw/day, based on the study of Lindgren et al. (1999) (BfR 2009).

50. A value of 0.0001 mg/kg bw/day was proposed for the ARfD, ADI, and systemic acceptable operator exposure level (AOEL) for nicotine in pesticides. This was based on an estimated lowest observed effect level (LOEL) of 0.01 mg/kg bw/day identified for clinical signs of toxicity in children exposed dermally (Woolf et al., 1997), with an UF of 100 (UK-DAR, 2007). The French Food Safety Agency (AFSSA) endorsed the proposed ADI and ARfD of 0.0001 mg/kg bw/ (AFSSA, 2009). Plant protection products containing nicotine have now been withdrawn from use in the EU (EC, 2008).

51. The COT derived a health-based guidance value (HBGV) for nicotine in people switching to ENDS from CC smoking based on a NOAEL of 7 µg/kg bw for effects on EEG parameters in CC smokers administered nicotine by i.v. infusion (0.0, 3.5, 7.0, 14.0, and 28.0 µg/kg bw, over 10 min), following a 12-h abstinence from smoking. These data were taken from the study of Lindgren et al (1999). Taking the value of 7 µg/kg bw as the point of departure, applying an adjustment of 0.55 for bioavailability (extrapolation from i.v. to inhalation route) and an UF of 5 to account for human variability, produced a HBGV of 2.5 µg/kg bw/day for acute inhalation exposure to nicotine in people switching to ENDS from CC smoking. The Committee reasoned that as nicotine has a short biological half-life in humans, does not accumulate in the body, and the most sensitive effect is considered to be a pharmacological effect (alterations in EEG) after i.v. infusion, the HBGV established for acute effects of nicotine could also be considered to protect against longer term effects; thus the HBGV for chronic exposure of ENDS users would also be 2.5 µg/kg bw/day (see paragraph 50 of the [COT statement on potential toxicological risks E\(N\)NDS](#)).

52. The COT HBGV established for nicotine exposure in people switching to ENDS from CC smoking was not considered suitable for risk assessment for nicotine-naïve ENDS users who, from available evidence, would be expected to be

approximately three-fold more sensitive to the acute effects of nicotine than CC smokers. The UF of 5 was therefore adjusted by an additional factor of 3 (i.e. 15) to account for human variability in nicotine-naïve individuals (see paragraph 53 of the [COT statement on potential toxicological risks E\(N\)NDS](#)).

53. Using the oral bioavailability factor of 0.44, in place of the inhalation value of 0.55 for the COT HBGVs above, would give values of 3.2 µg/kg bw/day for a person switching from CC smoking and 1.1 µg/kg bw/day for a nicotine-naïve user.

COT conclusions on nicotine exposure from ENDS

54. In the [statement](#) regarding the potential toxicological risks from use of E(N)NDS, the COT made the following conclusions with regard to nicotine exposure via inhalation from ENDS, some of which are applicable to nicotine exposure from oral nicotine pouches:

- Experienced users self-titrate nicotine intake from ENDS. Systemic exposure levels of nicotine equivalent to those from CC smoking can be achieved. Factors influencing the level of nicotine exposure and retention include ENDS product type, user profile, usage parameters, e-liquid nicotine concentration, and the overall formulation of the e-liquid.
- For people who switch from CC smoking, the risks associated with nicotine exposure from ENDS would be expected to be similar to those from the same nicotine exposures through use of CC.
- It is thus anticipated that nicotine-related health effects could occur with long-term use of ENDS. Risks include effects on a large range of endpoints in users and their offspring.
- Non-users who have never been exposed to nicotine and who take up vaping would be at risk from effects of nicotine to which they would not otherwise be exposed. This also includes the risk of addiction.
- Use of ENDS while continuing to smoke CC (dual use) could potentially lead to increased nicotine exposure compared with that from CC smoking only and may increase the overall risk.
- Bystanders are likely to be exposed to some nicotine in ambient air where ENDS products are used, which may have some associated effects.

COT concerns raised at the previous discussion to be captured in any future statement

55. During discussions at the COT meeting in May 2021, the Committee noted that accidental exposure of children to nicotine pouches is possible, as previously discussed in TOX/2019/38, and appropriate (i.e. childproof) packaging and labelling is a key safety issue. In addition, there is potential for the use of nicotine pouches by adults in excess of that recommended by the manufacturers, or at the same time as CC or other NRT devices, which would also be of potential concern.

56. The Committee also raised concerns that dual use of these products alongside tobacco products or other nicotine containing products, would be of potential concern due to the potential for increased nicotine exposure compared to a single source.

57. There is an absence of data on the potential influence of co-exposure to food and drink (hot and cold) or the effects of mechanical manipulation on absorption of nicotine from nicotine pouches.

58. Concerns were also noted over the current regulatory framework for these products as they did not fall into any specific category; and it was recommended this be given consideration in the future. It was noted that the different regulatory frameworks for different potential harm reduction products also made it difficult to compare such products, as the data requirements varied.

Questions for the Committee

59. Members are invited to comment on the information provided in this paper and to consider the following questions:

i. Can the Committee draw any conclusions regarding the risks of nicotine pouch use for current CC smokers, CC smokers who switch entirely to nicotine pouches and nicotine-naïve users?

ii. Does the Committee wish to draw any comparisons between exposures and/or risks from the use of nicotine pouches and any NRT products?

iii. Does the Committee have any views on the potential amount of nicotine in nicotine pouches?

IEH-C under contract supporting the PHE COT Secretariat

March 2022

Abbreviations and technical information

ADI	Acceptable daily intake
ADM	Average daily mass of products
AFSSA	French Food Safety Agency
AOEL	acceptable operator exposure level
ARfD	Acute reference dose
AUC	Area under the curve
AUC _{inf}	Area under the plasma concentration time curve from time zero to infinity
BAT	British American Tobacco
CC	Conventional cigarette
CYP	cytochrome P450
DET	Daily Exposure to Toxicants
EFSA	European Food Safety Authority
E(N)NDS	Electronic nicotine (or non-nicotine) delivery system
ENDS	Electronic nicotine delivery system

FDA	Food and Drug Administration
FMO	flavin-containing monooxygenase
GPSR	General Product Safety Regulations
HBGV	Health-based guidance values
HPHC	Harmful and potentially harmful constituents
IARC	International Agency on Cancer
i.p.	intraperitoneal
i.v.	intravenous
LD50	Lethal dose
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MHRA	Medicines and Healthcare products Regulatory Agency
MRH	maximum relative harm
NDMA`	Dimethyl nitrosamine
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosornicotine

NNS	nicotine nasal spray
NQ	Not quantified
NRT	Nicotine replacement therapy
OHID	Office of Health Improvement and Disparities
OTDN	Oral tobacco-derived nicotine
REACH	Registration, Evaluation, Authorisation & restriction of Chemicals
RR	Relative risk
TC	Toxicant content
THP	Tobacco heating product
TRPR	Tobacco and Related Products Regulations
UF	uncertainty factor
UGT	uridine diphosphate glucuronyl-transferase
WHO	World Health Organization

DET (Daily Exposure to Toxicants) was estimated from the toxicant content of the product (TC, mass units) and the oral product exposure factor (EfO), which combines estimates of the fraction of toxicants extracted during individual product use with daily consumption, as follows: $DET = (TC * EfO)$ where $EfO = (fEU * ADM)$; ADM is the average daily mass of products consumed by a user and is calculated from the numbers of products consumed per day and product mass per portion; and fEU is the extraction efficiency (a dimension-less value between

0 and 1), indicating the extent to which compounds are extracted from the product minus losses through events such as expectoration. For the oral products investigated in the present study, little or no expectoration is observed.

MHRA [Guidance Note 8](#) Appendix 4 on Alternatives to tobacco products states: “Products that are sold as alternatives to the use of tobacco products and which do not fall within the definition of a medicinal product will not be regulated by the MHRA. Guidance on the regulation of these products may be obtained from Trading Standards Service. Some products such as electronic cigarettes will now fall within the scope of the Tobacco Products Directive (2014/40/EU). Products may be sold as an alternative to tobacco as a temporary measure such as during periods or in places where smoking is not permitted, or as a longer term regime, perhaps on grounds of comparable costs. Products that do not make any cessation claims but, in the opinion of the MHRA, may be viewed by consumers as an obvious alternative to an authorised medicinal product such as transdermal patches, nicotine gum or mouth sprays, are likely to be regarded as medicinal products.

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TOX/2022/22 Annex A

Updated discussion paper on the bioavailability of nicotine and other ingredients from the use of oral nicotine pouches and assessment of risk to users

Extracts of the minutes of the COT meeting where this topic was discussed.

IEH Consulting under contract supporting the PHE Secretariat

March 2022

Meeting of the Committee at 10:00 on 4th May 2021 on Microsoft Teams

Present

Chair: Prof Alan Boobis

COT Members: Dr Phil Botham

Ms Jane Case

Dr Stella Cochrane

Dr James Coulson

Dr Rene Crevel

Dr Caroline Harris

Professor Gary Hutchison

Dr Sarah Judge

Dr Gunter Kuhnle

Dr David Lovell

Dr Mac Provan

Ms Juliet Rix

Dr Michael Routledge

Dr Cheryl Scudamore

Dr Natalie Thatcher

Professor Mireille Toledano

Professor Philippe Wilson

Prof Paul Haggarty (SACN Liaison)

Prof John O'Brien (Science Council Liaison)

Food Standards Agency

(FSA) Secretariat: Ms Cath Mulholland (FSA Scientific Secretary)

Dr David Gott

Mr Barry Maycock

Ms Claire Potter

Dr Barbara Doerr

Dr Douglas Hedley

Dr Olivia Osborne

Chloe Thomas

Ms Sabrina Thomas

Ms Chara Tsoulli

Ms Frederique Uy

Ms Cleanncy Hoppie

Ms Jocelyn Frimpong-Manso

Public Health England

(PHE) Secretariat: Ms Britta Gadeberg (PHE Scientific Secretary)

Invited Experts and

Contractors: Dr Sarah Bull (IEH)

Dr Ruth Bevan (IEH)

Dr Kate Vassaux (IEH)

Assessors: Prof Tim Gant (PHE)

Ms Frances Hill (BEIS)

Dr Mindy Dulai (BEIS)

Ms Susannah Brown (PHE)

Observers: Dr Simon Wilkinson

Prof Thorhallur Ingi Halldórsson

Prof Shirley Price

Dr Stephen Ruckman (TSG consulting)

FSA and other

Officials: Ms Sophy Wells (FSA)

Ms Aisling Jao (FSA)

Dr Ovnair Sepai (PHE)

Ms Kerry Gribben (FSA NI)

Mr Will Munro (FSS)

Ms Krystle Boss (FSS)

Ms Marianne James (FSS)

Dr Ovnair Sepai (PHE)

Mr Daragh Doyle (DHSC; item 9)

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Item 6: A summary of data on the bioavailability of nicotine and other ingredients from the use of oral nicotine pouches and assessment of risk to users (TOX/2021/22)

36. Professor Alan Boobis declared that he chaired ISO TC126 WG10 on the intense testing regime for CC and is a member of the WHO Study Group on Tobacco Product Regulation. No other interests were declared.

37. The Committee was asked to consider the toxicological risks from tobacco-free oral nicotine pouches by the Department for Health and Social Care (DHSC) and the Public Health England (PHE) Tobacco teams.

38. PHE informed the Committee that these products were being considered as part of the harm reduction approach as an alternative to use of tobacco products.

39. The paper provided the publicly available information for the ingredients present in these products and focussed on the oral bioavailability of nicotine to support assessment of any potential risks associated with their use.

40. The Committee raised concerns that the possible risks to children and adults through non-intended use, e.g. accidental consumption, should be noted. In addition, dual use of these products alongside tobacco products or other nicotine containing products, would be of potential concern due to the increased nicotine exposure compared to a single source.

41. Members noted the toxicological risk profile would be different between oral and inhalation exposure. Risk comparison also changed as the formulation of the different nicotine containing products changed as well as how the consumer was exposed to them e.g. chewed vs inhaled. It was suggested that pharmacokinetic data be presented in tabular form for a future meeting, to enable some comparison across products. The possibility of there being an impact of changing formulation of these tobacco-free oral nicotine pouch products leading to different systemic exposure was also noted.

42. Members considered that within the tobacco-free oral nicotine pouch class of products, there would be different risks according to the different batches of tobacco used to derive the nicotine, and the extraction process used, as well as due to differences in the other ingredients used, and the pouch material itself. With respect to extraction of nicotine from tobacco, the possibility of contaminants such as heavy metals, pesticides and nitrosamines should be considered, and where possible avoided.

43. It was recognised that IARC had made a number of conclusions on oral tobacco products that it would be helpful for the Committee to review. Another aspect that could influence risk was food or beverage consumption as these could influence temperature and/or pH in the mouth which in turn could affect nicotine absorption from the pouches. Potential irritancy or other local effects at the site of use was also raised as a potential issue.

44. The Committee raised concerns over the current regulatory framework for these products as they did not fall into any specific category; and recommended this be given consideration in the future. It was noted that the different regulatory frameworks for different potential harm reduction products also made it difficult to compare such products as the data requirements varied.

45. The Committee concluded that there was limited information available to be able to draw any conclusions regarding the risk of nicotine pouch use. It was

agreed that a future paper would be provided with a summary table on the pharmacokinetics of nicotine in different product types which would allow comparison of exposure and risk in so far as the data were available. Such a paper would also provide the IARC opinions on oral tobacco products.