

First draft statement on the bioavailability of nicotine from the use of oral nicotine pouches and assessment of the potential toxicological risk to users

This is a draft statement for discussion.

It does not reflect the final 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 the use of oral nicotine pouches.
2. Papers presenting the publicly available information on the ingredients present in these products and the oral bioavailability of nicotine from their use have been discussed by COT members in May 2021 (TOX/2021/22) and March 2022 (TOX/2022/22).
3. 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).
4. At the COT meeting in March 2022 it was agreed to produce a draft statement concerning the conclusions drawn by members based on the papers presented. The first draft statement is attached at Annex 1 to this paper.

Questions for the Committee

5. The Committee is asked to consider:

- a) Does the Committee have any comments on the general structure and content of this draft statement?
- b) Is the oral bioavailability factor of 0.44 used by EFSA and quoted in paragraph 38 appropriate, given the bioavailability found for other oral products noted in paragraph 21 which may have similar potential for buccal absorption?
- b) Is the Committee content with its conclusions presented within this draft statement?
- c) Does the Committee have any other comments on this draft statement

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TOX/2022/38 Annex 1

Background

1. The Committee has been requested by the Office of Health Improvement and Disparities (OHID) Tobacco teams to consider the toxicological risks from the use of oral nicotine pouches that do not contain tobacco, including ones which may contain up to approximately 120 mg nicotine per pouch (OHID, personal communication).
2. The demand for products that are less damaging to health than conventional cigarettes (CC) is increasing (Fjellner, 2020). Such products include electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes), which have been extensively evaluated by the COT ([COT, 2020](#)), and smokeless tobacco products (STPs) comprising non-combustible products that may be chewed, inhaled or placed in the mouth (ASH, 2020).
3. STPs have been available for many years, with one of the better-known smokeless tobacco products being “snus” which is produced and sold in Sweden as loose powder or in pouches, but has been prohibited for sale elsewhere in the EU since 1992. Today there is a drive towards oral tobacco-derived nicotine (OTDN) products which are tobacco-leaf free and contain tobacco-derived nicotine and food-grade ingredients (Robichaud et al., 2019).

4. 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 available on the market, including in the UK. These are pre-portioned pouches in which the tobacco leaf is replaced with a non-tobacco filler and tobacco-derived or synthetic 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).

5. This statement follows two discussion papers presented in 2021 ([TOX/2021/22](#)) and 2022 ([TOX/2022/22](#)) presenting the publicly available information for the ingredients present in these products and the oral bioavailability of nicotine to support assessment of any potential risks associated with their use.

6. 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 (n = 70), it was not considered necessary to develop more specific search terms and those of relevance are discussed below.

Regulatory framework

7. Oral nicotine pouches do not contain tobacco as defined in the Tobacco and Related Products Regulations (TRPR, 2016), hence they fall outside these regulations. 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 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. The GPSR set out the labelling requirements manufacturers, including importers, need to meet before placing products on the GB market. All manufacturers and importers need to ensure that the packaging and instructions provided with the product clearly communicate all potential risks involved in using them – and what consumers can do to avoid or lessen those safety risks. In the case of nicotine pouches, many suppliers elect to state on their packaging that nicotine has known addictive effects, provide life-stage warnings due to the potential for reproductive and developmental toxicity and display an age limit. In addition there are requirements for products or packaging to have traceability information.

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](#)).

Contents of nicotine pouches

11. Several large tobacco companies currently market oral nicotine pouches. Commercial nicotine pouches are sold with varying nicotine content, with between 4 and 18 mg of nicotine per pouch being typically 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). The British Standards Institution (BSI) has published a publically available specification (PAS) on the composition, manufacture and testing of oral nicotine pouches (PAS 8877:2022), which recommends a maximum nicotine content of 20 mg per pouch.

12. Nicotine pouches are sold in a variety of flavours such as fruit (e.g., black cherry, citrus), peppermint and coffee. Contents typically 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 carbonate
- sodium bicarbonate
- 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 many descriptions are used (indicated above).

13. 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. BfR (2021) reported the presence of tobacco-specific nitrosamines at levels 10 ng/g, determined across four nicotine pouches. During discussions, the COT 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".

14. The 'other ingredients' listed above are standard ingredients that are considered generally safe for use in foods and food products and have not been considered further by COT. However, concern was raised by the Committee regarding differences in exposure for example at the buccal membranes following prolonged exposure with constituents present in nicotine pouches, which would potentially differ from exposures in food.

15. Azzopardi et al. (2021) evaluated the levels of tobacco-related toxicants in nicotine pouches according to the Food and Drug Administration (FDA) smokeless tobacco reporting list (FDA 2012), GothiaTekVR standard compounds (Swedish Match 2016), and the World Health Organization (WHO) Tobacco Product Regulation Group 'TobReg9', with the exception of carbon monoxide. These are commonly used to characterise STPs and the authors compared the levels of toxicants in four types of nicotine pouches with those in snus (three types) and in the nicotine replacement therapies (NRT) lozenge (one type) and gum (one type) 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. 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. Overall, the authors noted that in comparison with CC, the use of nicotine pouches reduced exposure of around 90% of the toxicants measured; this has been stated to be 95% by some manufacturers.

17. 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 ranged between 7.7% and 99.2%, total nicotine between 1.29 and 6.11 mg/pouch, moisture content between 1.12–47.2%, and pH between 6.86–10.1. 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).

Nicotine release and toxicokinetics from oral nicotine pouches

18. There is limited data to evaluate how different factors, such as pouch constituents and usage parameters, affect the delivery of nicotine from pouches into saliva. One study reported cumulative release profiles of nicotine from 35 pouches offered by one manufacturer into artificial saliva maintained at 37°C. Percentage nicotine release was independent of the absolute nicotine level per pouch, and did not vary between flavours. 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 (Aldeek et al., 2021). This was similar to or faster than the nicotine release profiles for traditional pouched smokeless tobacco products that were tested alongside (Aldeek et al., 2021).

19. The toxicokinetics of nicotine were summarised in COT discussion paper [TOX/2019/38](#). Nicotine absorption is pH dependent. Absorption of nicotine from saliva across the buccal mucosa increases with the pH of the saliva, as un-ionised/uncharged forms are transferred more readily due to their higher lipid membrane solubility compared with ionised/charged forms. The proportion of un-ionised/uncharged nicotine present depends on the pH of the medium in which it is found.

20. Following absorption, nicotine is distributed extensively within body tissues, with the highest affinity being 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 which is subsequently metabolised to 3'-hydroxycotinine. Nicotine is excreted by glomerular filtration and tubular secretion, with reabsorption depending on urinary pH (higher reabsorption at higher pH). Plasma nicotine half-life on intravenous (i.v.) infusion is around 2 h, with terminal half-life of 11 h.

21.

1. The bioavailability of nicotine administered as single doses by various routes has been 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%); sub-cutaneous (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%) (Hukkane ADDIN EN.CITE ADDIN EN.CITE.DATA

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3C456E644E6F74653E3C4369746520417574686F72596561723D2231223E3C417574686F
; EFSA, 2009). Gislekog et al. (2020) reported that swallowed nicotine is absorbed in the small intestine but undergoes extensive first-pass metabolism in the liver and has a relatively low (30-40%) bioavailability.

22. Data from the few studies to date that have evaluated the kinetics of nicotine delivery from oral nicotine pouches in comparison with other nicotine-containing products have indicated that use of pouches delivers nicotine to plasma more slowly than CC, but more rapidly than some other oral nicotine-containing products (snus and nicotine gum). The the amount of nicotine delivered appears to be correlated with the total amount of nicotine in the product used as well as product type. The following paragraphs give more

information on specific studies.

23. A study conducted in 20 individuals determined that CC smoking led to a more rapid increase in nicotine plasma level compared with other nicotine-containing products (snus pouches, loose snus, nicotine gum). T_{max} was longest for the snus products (1 h), compared with 45 min for nicotine gum and 7 min for CC. Total nicotine delivery over the study period and maximum achieved plasma nicotine concentration appeared to depend primarily on the amount of nicotine in the product tested and the duration of use, rather than on product type (Digard et al., 2013; study funded by British American Tobacco (Investments) Limited, with some of the authors being current employees).

24. A study conducted in 17 individuals to evaluate single-dose pharmacokinetics of nicotine delivery from pouches (3 or 6 mg) used for 60 min compared with an 8 mg snus product used once indicated that a higher fraction of nicotine was extracted into plasma from the nicotine pouches (56–59%) compared with the snus product (32%). The 6 mg nicotine pouch resulted in significantly higher nicotine levels, area under the plasma concentration time curve from time zero to infinity (AUC_{inf}), area under the plasma concentration time curve from time zero to the last measurable concentration (AUC_{0–t}), area under the plasma concentration time curve at 60 min (AUC_{60 min}), and maximum concentration (C_{max}) compared with the 8 mg snus product. No statistically significant differences were found for the terminal half-life and time to maximum concentration (T_{max}) parameters (Lunell et al., 2020). Another study, conducted in 35 individuals, indicated a longer time to T_{max} for commercially available nicotine pouches (five different brands; 6–10 mg nicotine/pouch, used for 60 min) when compared with a CC (5 min ad libitum use) (McEwan et al., 2021, funded by British American Tobacco (Investments) Limited, with some of the authors being current employees).

Toxicity of nicotine

25. 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.

26. Median lethal dose (LD₅₀) values for nicotine in animals have been reported for oral, dermal, intraperitoneal (i.p.). and i.v. routes of exposure,

ranging from around 3.3 (mouse, oral) to 188 (rat, oral) mg/kg bw (HCN, 2005).

27. Nicotine may 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).

28. 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).

29. 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.

30. Recent evaluations in the literature have noted that evidence for a genotoxic effect of nicotine is mixed. Most studies using the Ames test, chromosomal aberration, 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).

31. 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. Further information on general toxicity of nicotine is available in [TOX/2019/38](#).

32. 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.

33. Data to assess the carcinogenic potential of nicotine pouch use are not available. The COT is aware of the conclusions by IARC and others on smokeless tobacco, but caution should be applied to extrapolation of these conclusions to nicotine itself.

Reference values for nicotine

34. The European Food Safety Authority (EFSA) established an acute reference dose (ARfD) and an acceptable daily intake (ADI) of 0.0008 mg/kg bw/day, based on slight, transient increased heart rate in human CC smokers on i.v. infusion of nicotine (Lindgren et al., 1999).

35. 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).

36. 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 by Woolf et al. (1997), based on clinical signs of toxicity in children exposed dermally.

37. The COT established a health-based guidance value (HBGV) of 2.5 µg/kg bw/day for acute inhalation exposure to nicotine in people switching to ENDS from CC smoking and chronic exposure of ENDS users, based on findings from the

study of Lindgren et al (1999). The COT HBGV 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.

38. 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.

39. Azzopardi et al. (2021) estimated an average consumption of 8.6 nicotine pouches per day in a Swedish population. This would result in an intake of 86 mg nicotine from the use of nicotine pouches containing 10 mg per pouch, equivalent to 1.23 mg/kg bw/day (70 kg adult). This exceeds the COT reference values cited above by 380-fold and > 1000-fold for CC smokers and nicotine-naïve users, respectively.

40. It should be noted that the average daily systemic exposure of nicotine in a group of 22 CC smokers, estimated from blood and urinary nicotine concentration data obtained over 24 h when subjects were smoking CC, was 37.6 ± 17.7 mg, with a wide variation between subjects (10.5–78.6 mg), equivalent to approximately 0.5 mg/kg bw/day for a 70 kg adult (Benowitz and Jacob, 1984). Using an oral bioavailability factor of 0.44, intake of nicotine at a level of 1.23 mg/kg bw/day as suggested by Azzopardi et al. (2021) would result in a systemic nicotine exposure of 0.54 mg/kg bw/day for nicotine pouches, which is similar to the exposure of an average CC smoker.

COT discussion and conclusions

41. COT noted that nicotine pouches provide a pharmacologically active dose of nicotine in both CC smokers and nicotine-naïve users 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 of lower risk than that of CC smoking and if concurrent use of other nicotine-containing products is avoided.

42. It is anticipated that nicotine-related health effects could occur with long-term use of oral nicotine pouches. Risks include effects on a large range of endpoints in users and their offspring.

43. Experienced users may self-titrate nicotine intake. Systemic exposure levels of nicotine equivalent to those from CC smoking can be achieved from use of nicotine pouches. Factors influencing the level of nicotine exposure and retention include the type of pouch used, user profile, usage parameters, nicotine concentration, and the overall formulation of the pouch contents. However, there is potential for the use of nicotine pouches by adults in excess of that recommended by the manufacturers, which would be of concern due to the potential for increased and prolonged nicotine exposure compared to a single source.

44. Individuals who have never been exposed to nicotine and who take up the use of oral nicotine pouches would be at risk from effects of nicotine to which they would not otherwise be exposed. This includes the risk of addiction.

45. Use of nicotine pouches in parallel with other nicotine-containing products (e.g. CC, ENDS) could potentially lead to increased nicotine exposure compared with that from use of a single product-type, and may increase the overall risk of nicotine-related toxicity.

46. While there is limited data on which exposure estimates can be made, the estimated exposure to nicotine from 10 mg pouches as outlined by Azzopardi et al (2021) exceeds the COT reference value. It is very likely that exposures from pouches containing higher levels of nicotine as reported to the Committee by DHSC would be significantly higher, and as such the potential risks would be greater, both for people using these pouches and from accidental ingestion.

47. The Committee considered that accidental exposure of children to nicotine pouches is possible, and that appropriate (i.e. childproof) packaging and labelling is a key safety issue. The appeal and ease of availability of nicotine pouches to individuals under 18 years of age was also highlighted as of potential concern for uptake in this age group.

48. 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. Additionally it was considered that prolonged buccal membrane exposure to food-grade ingredients within the pouches would result in a high local exposure which has not been addressed from a food safety perspective.

49. The Committee expressed concerns over the current regulatory framework for oral nicotine pouch products as they did not fall under specific

regulations. 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.

50. The Committee commented on the apparent variation in how manufacturers present nicotine content and strength across different products, which may be confusing for the consumer. In addition, use of the description ‘tobacco-free’ may be misleading as the nicotine may be derived from tobacco, which raises concerns regarding carry over of toxicologically relevant contaminants (e.g., metals and nitrosamines).

51. An absence of independent data on use/exposure to nicotine pouches was identified, with currently available data being industry sponsored.

Overall conclusion

52. The use of oral nicotine pouches, as recommended by the manufacturer, as a replacement for CC smoking is likely to be associated with a reduction in overall risk of adverse health effects, although the magnitude of the decrease will depend on the effect in question. Use of oral nicotine pouches by nicotine-naïve users is likely to be associated with some adverse health effects to which the user would not otherwise have been subject, as a pharmacologically active dose is delivered. Concurrent use of oral nicotine pouches with CC smoking or other nicotine-containing products could increase and prolong nicotine exposure compared to a single source.

53. The use of oral nicotine pouches results in prolonged exposure of the buccal membrane to the flavouring products and other constituents used in the pouches. The effect of this has not been investigated and is an important data gap. There are large gaps in nicotine exposure data for the use of oral nicotine pouches in humans, which prevents detailed comparison with CC smoking or the use of other smokeless products. It is not currently possible to predict the adverse health effects that could be associated with use of nicotine pouches in the long term, particularly at higher nicotine content levels. As the information and science relating to oral nicotine pouches is changing rapidly, the COT will keep this area under review.

List of Abbreviations and Technical terms

FDA	Food and Drug Administration
FMO	flavin-containing monooxygenase
GPSR	General Product Safety Regulations
HBGV	Health-based guidance value
IARC	International Agency for Research on Cancer
i.p.	intraperitoneal
i.v.	intravenous
LD50	Lethal dose
LOAEL	Lowest observed adverse effect level
MHRA	Medicines and Healthcare products Regulatory Agency*
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
Tmax	Time to maximum concentration
TRPR	Tobacco and Related Products Regulations
UF	Uncertainty factor
WHO	World Health Organization

*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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