COT evaluations - 2023

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Oral nicotine pouches

1.1 The COT was requested by the Office of Health Improvement and Disparities (OHID) Tobacco team to consider the toxicological risks from the use of oral nicotine pouches that do not contain tobacco, including ones that may contain up to approximately 120 mg nicotine per pouch.

1.2 Oral nicotine pouches contain tobacco-derived nicotine and food grade ingredients and are placed between the lip and gum to release the nicotine into the saliva so it can be absorbed within the mouth before entering the blood stream.

1.3 The Committee considered the available information on ingredients present in the products and reviewed the oral bioavailability of nicotine to assess any potential risks associated with use of oral nicotine pouches.

1.4 The COT noted that oral nicotine pouches provide a pharmacologically active dose of nicotine in both conventional cigarette (CC) smokers and nicotine-naïve users and, as such, they are not ‘harmless’ products. However, use of oral 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.

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

1.6 Experienced users may self-titrate nicotine intake. Systemic exposure levels of nicotine equivalent to those from CC smoking can be achieved from use of oral 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 oral nicotine pouches by adults in excess of that recommended by the manufacturers, which could be of concern due to the

potential for increased and prolonged nicotine exposure.

1.7 The health risks from other constituents of CC smoke or oral nicotine pouches have not been fully assessed. However, it is plausible that use of oral nicotine pouches, produced according to appropriate manufacturing standards and used as recommended, as a replacement for CC smoking, would 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.

1.8 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.

1.9 Use of oral 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.

1.10 While there are 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.

1.11 The Committee considered that accidental exposure of children to oral 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 oral nicotine pouches to individuals under 18 years of age was also highlighted as of potential concern for uptake in this age group.

1.12 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 (e.g., sucking or chewing) on absorption of nicotine from oral 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.

1.13 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.

1.14 The Committee commented on the 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).

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

1.16 Overall, the COT considered that the use of oral nicotine pouches, as recommended by the manufacturer, as a replacement for CC smoking was 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 was likely to be associated with some adverse health effects to which the user would not otherwise have been subject, as a pharmacologically active dose of nicotine 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.

1.17 The use of oral nicotine pouches could result in prolonged exposure of the buccal membrane to the flavouring products and other constituents used in the pouches. The effect of this had 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 prevent 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 oral 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.

1.18 The full COT statement can be found at: Statement on the bioavailability of nicotine from the use of oral nicotine pouches and assessment of the potential toxicological risk to users .

Interim position on per- and polyfluoroalkyl substances

1.19 The COT had considered per- and poly-fluoroalkyl substances (PFAS) on a number of previous occasions and published a statement in 2022 on the European Food Safety Authority (EFSA) opinion in which the scientific basis of their new tolerable weekly intake (TWI) for the sum of four PFAS was reviewed. The Committee was subsequently asked to consider what further guidance can be provided to support human health risk assessments undertaken by UK Government Departments and Agencies.

1.20 The Committee considered there were a number of uncertainties with regards to the critical endpoint of decreased vaccine response in children, used as a basis for the EFSA TWI and draft US EPA RfDs for PFOA and PFOS, with respect to the biological significance of the response and reservations concerning the critical studies (Abraham et al. (2020) and Grandjean et al. (2012)). In the statement on the EFSA TWI the COT expressed a number of reservations with respect to some of the modelling undertaken to determine the TWI.

1.21 In considering the wider evidence base, the Committee noted that a number of different approaches had been adopted by other authoritative bodies in deriving their HBGVs due to differences in the critical study and endpoint selected, resulting in a range of available HBGVs for a number of different PFAS.

1.22 The Committee noted other challenges regarding the risk assessment of PFAS including the lack of data for most PFAS and consequently HBGVs only being established for a small number and the uncertainty over how best to assess all detected PFAS, such as by summing all PFAS present or grouping similar substances.

1.23 Due to the uncertainties noted and the need for more guidance to support UK Government Departments and Agencies undertaking risk assessments for PFAS, the COT decided to undertake its own consideration of the evidence base and risk assessment.

1.24 Future COT work to be undertaken by a subgroup of Members would include:

- An independent review of toxicological and epidemiological data, focusing on a number of critical endpoints, and considering the biological relevance of

the endpoints assessed.

- Consideration of the toxicokinetics of PFAS.
- Whether and how different PFAS can be grouped for assessment.
- Establishing a HBGV or a number of HBGVs as the data allow.

1.25 The Committee acknowledged that a further review of PFAS would be an extensive and lengthy undertaking. In the meantime, consideration should be given to the available HBGVs for the specific compounds identified, recognising the uncertainties with respect to the critical effects and modelling approaches adopted.

1.26 The full COT position paper can be found at: Interim Position Paper on Per- and Polyfluoroalkyl Substances.

Statement paper on the guidance levels for the fortificants in the Bread and Flour Regulations

1.27 The Bread and Flour Regulations (BFR) stipulate the levels of calcium carbonate, iron, thiamin (also known as vitamin B1) and nicotinic acid that must be present in flour. In 2022, the Department for Environment, Food and Rural Affairs (Defra) held a consultation on the BFR 1998 review and asked whether the consultees agreed with the proposal to raise the minimum levels of calcium carbonate, iron and niacin added in non-wholemeal wheat flour to 15% of the nutrient reference values (NRV) supplied by 100g of flour as stated in point 1 of Part A of Annex XIII of regulation EC No. 1169/2011. NRVs are established guidelines for the recommended daily energy and nutrient consumption. The minimum amount of thiamin required to be present in non-wholemeal wheat flour will remain the same at 19% of the NRV.

1.28 The COT were asked by DHSC to provide a risk assessment on the dietary exposure of calcium carbonate, iron, nicotinic acid and thiamin at the current and proposed fortification levels to identify whether there were any potential adverse health effects.

1.29 High calcium intakes (around 4 g per day) can cause milk-alkali syndrome in people with peptic ulcers. Milk-alkali syndrome is characterised by hypercalcemia (a condition where calcium blood levels are above normal), alkalosis (a condition where the blood becomes too alkaline, i.e., has a PH >7) and impaired kidney function, symptoms of high blood pressure, problems

affecting the brain, abdominal pain, and a build-up of calcium in tissues of the body. In individuals at risk of colonic polyps, calcium at levels of 1.6 g or greater per day can lead to ill-health effects that include problems in the gastrointestinal system (i.e., mouth, throat, oesophagus, stomach, small intestine, large intestine, rectum, and anus). Hight calcium diets can also affect how other minerals such as iron, zinc, magnesium, and phosphorus can be absorbed by the body (via the intestine).

1.30 High intakes of iron in infants of around 20 mg per kg of body weight can result in irritation to the gastrointestinal system. Lethal doses in children are between 200 and 300 mg per kg bodyweight. High intakes of iron in adults between 50 and 220 mg per day can cause constipation, nausea, and vomiting. It can also cause inflammation and perforation (formation of holes) of the gastrointestinal tract, has effects on the metabolism of cells, central nervous system, liver, and heart. For adults the lethal dose is 1.4 g per kg bodyweight. Excessive levels of iron can also result in increased levels of bilirubin and enzymes indicative of damage to the liver (alkaline phosphates and aminotransferase) in the blood. Other side effects may include anorexia, ophthalmological effects (effects on the eye), darkening of the skin and incipient psychosis.

1.31 High intakes of niacin can cause flushing (redness of the skin), itchy skin, nausea, vomiting, diarrhoea, and constipation. Long term intakes of 3 g per kg of body weight or more can cause jaundice, hyperglycaemia (high blood sugar levels) and abdominal pain.

1.32 Thiamin is generally of very low toxicity, with symptoms such as headache, nausea, irritability, insomnia, rapid pulse and weakness being seen at high oral doses of ≥7,000 mg thiamin hydrochloride per day. There have been a small number of reports of effects such as muscle tremors, rapid pulse and nerve hyperirritability at daily doses as low as of 17 mg per day and there have been one or two cases indicative on allergic reaction at doses as low as 100 mg per day.

1.33 A tolerable upper level (TUL) or safe upper level has not been established for calcium, iron, nicotinic acid and thamin by the UK Expert Group on Vitamins and Minerals although they did provide levels for guidance, below which the risk of adverse effects was considered low (EVM, 2003). The EVM reported that intakes of 1,500 mg per day of calcium in supplemental form were not expected to result in any adverse effects. For iron, intakes of 17 mg per day would not be expected to produce any adverse effects. However, this level does

not apply to individuals with increased susceptibility (i.e. genetic predisposition) to iron overload. For nicotinic acid in supplemental form, the EVM reported intakes of 17 mg per day would not be expected to produce any adverse effects. This level does not apply to sustained release preparations of nicotinic acid. Whilst the EVM did not set an UL for nicotinic acid, the Scientific Committee on Food (SCF, 2003) did set an UL of 10 mg per day. For thamin, the EVM proposed a guidance level of 100 mg per day.

1.34 Exposure assessments were performed using data from the Diet and Nutrition Survey of Infants and Young Children (DNSIYC) and National Diet and Nutrition Survey (NDNS) to estimate intakes of these minerals to the UK population from food sources. In the absence of any published data, various online sources were used to estimate the intakes of these minerals from supplements. The assessment determined how much exposure there was to the above minerals from:

a) non-wholemeal flour (i.e., wheat flour without grain wheat),

b) all food groups in the entire diet,

c) supplements.

1.35 Acute (short-term) intakes for all nutrients (calcium, iron niacin and thamin) at the current and proposed fortification level in food did not exceed levels considered to be acutely toxic and are therefore not a health concern.

1.36 Chronic (long term) intakes of calcium, iron, niacin, and thiamin at the current and proposed fortification levels in food did not exceed their guidance levels. Therefore, chronic intakes of calcium, iron, niacin, and thiamin from fortified non-wholemeal flour are not of concern to health.

1.37 Intakes of calcium from supplements alone did not exceed the guidance level. However, daily intakes of iron, niacin and thamin from supplements alone may result in exceedance of their guidance levels when higher dosage supplements are consumed. However, it is important to note that not all of the population consume supplements. Therefore, potential risks to health apply only to members of the population who consume high dosage iron, niacin, and thiamin supplements.

1.38 Intakes of calcium from both food and supplements will not result in exceedance of the guidance level of calcium. However, intakes of iron, niacin and thamin from food and supplements combined can lead to exceedances of their

guidance levels. Given that the exceedance of the guidance levels is evident from supplement consumption alone, the exceedances of iron, niacin and thiamin here would only be of toxicological concern to individuals that consume high dosage of iron, niacin, and thiamin through supplements.

1.39 The COT concluded that the proposed increase in the fortification level of calcium, iron and niacin in non-wholemeal flour would not result in any excess risk. However, there would be a possible exceedance in individuals that consume supplemental iron, niacin and thiamin alongside food containing and/or fortified with these minerals.

1.40 The full statement can be accessed at Statement on the guidance levels for the fortificants in the Bread and Flour Regulations.