Hazard Identification and Risk Assessment of Non-Nicotine Ingredients in Oral Nicotine Pouches

Pitegoff, M.E., Haase, V.E., Anderson, C.A. Morgan, R.W.
Altria Client Services LLC, Richmond, VA 23219
Center for Research and Technology
63rd SOT, Poster #137
March 10 – 14, 2024

Abstract

Oral tobacco-derived nicotine pouch products or nicotine pouches (NPs) are a relatively new tobacco product category that do not contain leaf tobacco but typically contain tobacco-derived nicotine and non-tobacco ingredients, principally food-grade flavors, and filler material such as cellulose-based fibers. Toxicants that are typically present in combustible and smokeless tobacco products are substantially lower in NPs, and in most cases, below method limits of quantitation.

We evaluated individual ingredients for potential toxicological risks that may be associated with their use. In the absence of specific guidance outlining acceptable tobacco product ingredients, the processes used to determine ingredient safety in food provide guidance for toxicological assessments including the use of flavors and additives that are generally recognized as safe (GRAS) for foods. However, there are conflicting or incomplete safety data for some flavor compounds, and this raises uncertainty about health risks from long-term exposure. We present a case study of hazard identification and toxicological risk assessment for two flavor compounds, maltol and ethyl maltol, that concludes that they would not present a toxicological risk after a lifetime of exposure.

Product Stewardship for Individual Ingredients

Evaluation of the quality and consistency of incoming materials is integral to the ALCS product stewardship process and provides a foundation upon which the toxicological assessment is built. Prior to hazard identification, we first confirm that the quality of each material and ingredient used in our OTDNs is food grade quality or higher (e.g., U.S. Pharmacopeia (USP), etc.). After ensuring ingredient grade and quality, the toxicological evaluation process for individual ingredients follows 3 key steps:

1. Ingredient hazard identification
2. Ingredient exposure assessment
3. Ingredient risk assessment

Hazard Identification

- Literature databases were searched to locate relevant preclinical and clinical data that characterize the toxicological effects of maltol and ethyl maltol

Electronic Databases Used to Retrieve Literature		
Electronic Database	Date Range	Update Frequency
Adis Clinical Trials Insight	1990 to present	Weekly
AGRICOLA	1970 to present	Monthly
AGRIS	1975 to present	Monthly
Allied & Complimentary Medicine™	1985 to present	Monthly
BIOSIS® Toxicology	1969 to present	Weekly
BIOSIS Previews®	1926 to present	Weekly
CAB ABSTRACTS	1910 to present	Weekly
EMBASE®	1947 to present	Daily
Foodline®: SCIENCE	1972 to present	Twice weekly
FSTA®	1969 to present	Weekly
MEDLINE®	1946 to present	Daily with annual refresh
NTIS: National Technical Information Service	1964 to present	Weekly
ToxFile®	1946 to present	Daily with annual refresh

- Websites of various regulatory agencies and authoritative institutions which provide curated safety and toxicity information, including dose response data that has undergone peer review to establish an acceptable daily intake (ADI) level or derived no effect level (DNEL), were also reviewed and included in the assessment:
  - Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Joint Expert Committee on Food Additives (JECFA), FDA, the European Food Safety Authority (EFSA), and European Chemicals Agency (ECHA)
- Study quality was considered with, for example, good laboratory practice (GLP) studies ranked higher than non-GLP studies

Ingredient	Maltol	Ethyl Maltol
Occurrence	Occurs naturally in a variety of vegetables, dairy products, meat products, alcoholic and nonalcoholic beverages, and nuts; it can also be chemically synthesized	Does not occur naturally, but prepared synthetically, for use as a flavor enhancer in foods and a fragrance in soaps, detergents, creams, and lotions
In-vitro genotoxicity	Mixed (equivocal) in mammalian in-vitro studies, with some positive responses observed in bacterial mutagenicity studies	Mixed (equivocal) in mammalian in-vitro studies, with some positive responses observed in bacterial mutagenicity studies
In-vivo genotoxicity	Negative for genotoxicity in a follow-up in vivo micronucleus assay and considered non-genotoxic by JECFA, EFSA, and ECHA	Negative for genotoxicity in a follow-up in vivo micronucleus assay and considered non-genotoxic by JECFA, EFSA, and ECHA
Carcinogenicity	Not carcinogenic: see in-silico	Not carcinogenic based on chronic toxicity study (Gralla et al. 1969)
In-Silico Predictions	CASE Ultra (statistical) and DEREK Nexus™ (expert rule-based) consensus: no structural basis for concern with respect to in vivo carcinogenicity	N/A; in-vivo study available
Daily Intake	ECHA derived DNEL of 0.667 mg/kg body weight/day	JECFA derived ADI of 2 mg/kg body weight/day

We demonstrate that non-nicotine ingredients in oral nicotine pouches exhibit acceptable levels of toxicological risk

Exposure Assessment

- Daily consumption was set at a conservative exposure level (i.e., 20 pouches per day)
  - Protective of the 95th percentile of consumption estimates based on available actual use data for similar products (e.g., <10 pouches per day)
- An average body weight of 60 kg
- 100% bioavailability of the ingredient by the oral route

$$Daily\ exposure\ to\ ingredient\ \left(\frac{mg}{day}\right) = \frac{\%\ of\ ingredient\ in\ formulation}{100}\ X\ \frac{(X)\ mg}{pouch}\ X\ \frac{(X)\ pouches}{day}$$

$$Daily\ exposure\ to\ ingredient\ on\ a\ per\ kg\ body\ weight\ basis\ \left(\frac{mg}{kg/day}\right) = \frac{Daily\ exposure\ to\ ingredient}{60\ kg}$$

Figure 1: Exposure Assessment Calculation

Ingredient Risk Assessment

Table 1: Margins of Exposure (MOE) for Ethyl Maltol and Maltol

Ingredient	CAS Number	Guidance Value (mg/day)	Guidance Value Reference	MOE
Ethyl Maltol	4940-11-8	120	JECFA ADI	4
Maltol	118-71-8	40	ECHA DNEL	3

- In conjunction with this assessment, a test NP product (i.e., mint NP containing maltol and ethyl maltol) was tested in vitro and in vivo for genotoxicity
  - Studies presented separately: P154 (Farcas et al.; in-vitro) and P212 (Zhang et al.; in-vivo)

Conclusion

- ✓ Maltol and ethyl maltol do not pose concerns for in-vivo genotoxicity or carcinogenicity according to several reviews of the available toxicological data by authoritative bodies
- ✓ Estimated exposures to maltol and ethyl maltol in Test NP products are well below levels that might raise toxicological concerns
- ✓ While NP extracts containing maltol and ethyl maltol might drive in-vitro genotoxicity responses Farcas et al, ref 8), there were no in-vivo sequelae (Zhang et al, ref 11)
- ✓ Maltol and ethyl maltol as used in Test NP have acceptable levels of toxicological risk

References

1. Burdock, G. A. (2010b). Ethyl maltol. In Fenaroli's Handbook of Flavor Ingredients, 6th edition. Boca Raton, FL: CRC Press, Inc.
2. Burdock, G. A. (2010c). Maltol. In Fenaroli's Handbook of Flavor Ingredients, 6th edition (pp. 1114-1115). Boca Raton, FL: CRC Press, Inc.
3. CASE Ultra v.1.9.0.6
4. DEREK v.6.2.1 Nexus™ v.2.5.2; Derek Knowledge Base 2022 v2.0
5. ECHA (2024). European Chemicals Agency, Helsinki, Finland. https://www.echa.europa.eu/
6. EFSA. (2010). Scientific Opinion on Flavouring Group Evaluation 83, Revision 1 (FGE.83Rev1): (question no EFSA-Q-2008-00909, adopted on adopted on 25 November 2009 and published 17 February 2010 by European Food Safety Authority). EFSA J 8(2):1409. [22 pp.]. Retrieved from http://www.efsa.europa.eu/de/efsajournal/pub/1409.htm
7. EFSA. (2015). Scientific Opinion on Flavouring Group Evaluation 213, Revision 2 (FGE.213Rev2): Consideration of genotoxic potential for α, ß-unsaturated alicyclic ketones and precursors from chemical subgroup 2.7 of FGE.19 (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids/CEF) (Question no EFSA-Q-2015-00138, EFSA-Q-2015-00139, adopted: 9 September 2015 by European Food Safety Authority). EFSA J 13(9):4244 [49 pp]. Retrieved from https://www.efsa.europa.eu/en/efsajournal/pub/4244
8. Farcas et al. (2024). SOT 2024. Abstract No. 3052, Poster No. 154: Comparative Toxicity Assessment of Oral Nicotine Pouches to Combustible Cigarettes, Smokeless Tobacco Products and Market Nicotine Pouches Using Regulatory in vitro Cytotoxicity, Mutagenicity, and Genotoxicity Assays. Risk Assessment I, Monday 3/11/24: 2:15-4:15 pm.
9. Gralla et al. 1969. Toxicity studies with ethyl maltol. Toxicology and Applied Pharmacology, Volume 15, Issue 3, Pages 604-613. https://doi.org/10.1016/0041-008X(69)90062-3.
10. JECFA. (2020). Safety evaluation of certain food additives: prepared by the eighty-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Retrieved from https://www.who.int/publications/i/item/9789240004580
11. Zhang et al. (2024). SOT 2024. Abstract No. 3108, Poster No. 212: Evaluation of the in vivo genotoxic potential of an oral nicotine pouch product following ICH S2(R1) guidance. Genotoxicity/DNA Repair, Monday 3/11/24: 11:45-1:45 pm.

Altria Science