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Evaluation of the genotoxic potential of a flavored oral nicotine pouch product using integrated approaches

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Oral nicotine pouch products may aid adult tobacco consumers to switch from cigarettes to potentially reduced-harm, smoke-free products. These nicotine pouch products typically contain flavor ingredients that are “GRAS” (“generally recognized as safe”) in foods. While the GRAS status is not intended to apply to tobacco products, the scientific data supporting the GRAS status including in-silico tools are relevant in characterizing toxicological profiles of the ingredients in the oral nicotine pouch products. In this feasibility study, we used integrated approaches to evaluate the genotoxic potential of a nicotine pouch product containing maltol and ethyl maltol (“maltols”). Maltols, selected as example flavor ingredients, are reported to induce in vitro genotoxicity but do not lead to in vivo sequelae. We first identified maltols as the in vitro activity driver in the in vitro micronuclei assay. We then investigated the dosimetry basis to interpret in vitro versus in vivo genotoxicity and carcinogenicity outcomes for maltols (in vitro-to-in vivo extrapolation, IVIVE). Using open-source PBPK models, we estimated the Cmax in the target tissue (e.g., plasma) under in vivo (rodent) exposure conditions and compared to the in vitro exposure concentrations. These New Approach Methods (NAMs)-based approach was evaluated with the negative in vivo genotoxic responses of the test product based on a combined in vivo micronuclei and comet assay in rats conducted following the ICH S2(R1) guidance. In summary, using maltols as case examples, the integrated approaches utilizing in vitro and in silico methods as well as bioassay outcomes could enable a holistic evaluation of the genotoxic potential of an oral nicotine pouch product, building a case of NAMs-based toxicological assessment without the need for confirmatory in vivo testing.