

## Summary of the salient content of the GRAS determination of caffeine in chewing gum

Mars Wrigley Confectionery conducted a generally recognized as safe (GRAS) determination following the requirements set forth in the Final Rule on Food Ingredients that are "Generally Recognized as Safe" <https://www.federalregister.gov/documents/2016/08/17/2016-19164/substances-generally-recognized-as-safe>. Independent qualified experts in the U.S. in caffeine safety and epidemiology were enrolled in the GRAS panel, which concluded that the use of caffeine in chewing gum is GRAS at up to 52 mg per 1 piece serving. To highlight the salient components of the GRAS dossier:

- **Absorption, Distribution, Metabolism, and Excretion (ADME) data on caffeine, in chewing gum.** In addition to the well-established literature on the pharmacokinetics of caffeine, an open-label, randomized, 2-way crossover study showed the pharmacokinetics of caffeine delivered via caffeinated chewing gum was very similar to that of caffeine from coffee in healthy adult volunteers. This study is under peer review by Journal of Caffeine Research (anticipated online publication date is late October to early November).
- **Thorough and detailed discussions of preclinical toxicological studies and human safety endpoints.** Preclinical toxicological studies reviewed included acute toxicity, subchronic/chronic toxicity, developmental/reproductive toxicity, and genotoxicity/mutagenicity potential. Thorough and detailed discussions of the acute toxic effects, cardiovascular effects, potential effects on fertility, pregnancy, and fetal outcomes, potential effects on mood, anxiety, and sleep, potential to induce seizures, relationship between caffeine intake and neurological disorders, potential to induce physical dependence, potential to alter fluid homeostasis, potential effect on glucose tolerance and insulin sensitivity, potential effect on calcium balance, potential association with cancer, potential adverse effects in children and adolescents, use of caffeine during physical exertion, combination of caffeine with alcohol, and the adverse effects of caffeine in energy drinks were included. Overall there is an established body of literature on caffeine safety.
- **Summary of expert evaluations of caffeine safety.** Most notably, safety assessments conducted by the European Food Safety Authority (EFSA, 2015) and the ILSI North America commissioned systematic review of the literature published since the Health Canada assessment (from 2001 to June 2015) (Wikoff et al., 2017) were included in the 2017 GRAS determination.
- **Cumulative intake assessment.** The cumulative intake of caffeine from the background diet and dietary supplements was calculated using data from the U.S. National Health and Nutrition Examination Surveys (NHANES) 2013-2014. Total population estimated intakes of caffeine from the intended use in chewing gum, background dietary sources, and dietary supplements are below the intake of 400 mg/day in healthy adults, which is a value that is not associated with adverse effects (Nawrot *et al.*, 2003; EFSA, 2015; Wikoff *et al.*, 2017). Although Alert Caffeinated Gum is not intended for use by children or adolescents under the age of 18, these population groups were included in the exposure assessment for completeness. The estimated intakes of caffeine in children and teenagers were below the level of 2.5 mg/kg body weight/day, which is considered the level below which there is no safety concern (Nawrot et al., 2003; EFSA, 2015; Wikoff et al., 2017).

- **Evaluation and mitigation of the potential risk to vulnerable population groups.** Vulnerable population groups include children, adolescents and pregnant/nursing women – therefore children, adolescents and women of childbearing age – were included in the exposure assessments. While the exposure assessment supports safety, the Alert gum packaging and marketing materials provide an advisory statement to the effect of *“Not recommended for those under the age of 18, pregnant and nursing women, or people sensitive to caffeine”*. The product label further informs consumers that *“One serving (1 piece) contains 40 mg of caffeine, or about as much caffeine as ½ cup of coffee”*. And in addition, a consumer education website is available to additionally assist consumers in moderating their caffeine intake.

Over 1,000 published scientific journals and public references, as well as data from the U.S. National Health and Nutrition Examination Surveys (NHANES) 2013-2014 were reviewed and referenced in the GRAS dossier. By critically evaluating the data and information deemed pertinent to the safety of the proposed use and use level of caffeine in chewing gum, the independent GRAS panel comprised of qualified experts concluded that caffeine in our Alert chewing gum is GRAS.