Evaluation Summary of Licorice Extract for Use as a Cigarette Ingredient

Licorice (or ‘liquorice’) is a plant of ancient origin and steeped in history. The genus name Glycyrrhiza is derived from the ancient Greek work for ‘sweet root’. The two principal forms in commerce are licorice root (Liquiriti radix) and the extract (Glycyrrhizae extractum crudum or Succus liquiritiae). Licorice root contains about 20% of water-soluble extractives, and much of this is composed of glycyrrhizin, a mixture of potassium and calcium salts of glycyrrhizic acid. Glycyrrhizin constitutes 10-25% of the extract and is considered the primary ingredient.

Although licorice root is regarded as a food, licorice extract (including glycyrrhizin and its salts) are food ingredients and are regulated as such (21 CFR § 184.1408). Licorice extract and its derivatives are also approved for use in some over-the-counter drugs (21 CFR § 310.528, § 310.544, § 310.545, § 582.10, and § 582.20). Licorice and its derivatives are also generally recognized as safe (GRAS) by the Flavor and Extract Manufacturers’ Association (FEMA No. 2628), and are used in a variety of foods, and in both traditional and herbal medicine.

In vitro tests have shown that glycyrrhizic acid is non-genotoxic and may have anti-genotoxic properties. The mechanism of this anti-genotoxicity appears to be through the induction of the bacterial adaptive response as opposed to a desmutagenic effect. Whether glycyrrhizic acid is anti-genotoxic in mammalian systems is not known.

The acute oral toxicities of glycyrrhizic acid and licorice extract are low. In mice and rats the LD50 (lethal dose to 50% of the test population) is in the gram/kg range. Consumption of glycyrrhizic acid by mice for 96 weeks did not elicit carcinogenic or chronic toxic effects. Teratological studies revealed that glycyrrhizic acid is not a teratogen, does not induce heritable chromosomal defects in rats or mice, and is likely not toxic to the developing rodent fetus.

Glycyrrhizin compounds act by the inhibition of 11β-hydroxysteroid dehydrogenase, and evidence suggests that mineralocorticoid receptor binding activity may also play a role in its physiologic effects. Short-term studies in both animals and humans have clearly defined the hypermineralocordism effects of glycyrrhizic consumption. Hypertension, hypokalemia, edema, and loss of plasma renin activity appear to be the most common clinical signs of glycyrrhizin toxicity. Full recovery occurs over several days to weeks following abstinence from the causative agent. Interestingly, not all subjects appear to be susceptible to the detrimental effects of glycyrrhizic acid. The reasons for this are not understood and unfortunately, have not been well investigated.

Immunological studies have indicated that glycyrrhizic acid can induce the production of γ-interferon. Additional immunostimulatory properties of licorice extract have been speculated upon, but there is little data to substantiate these claims.

Reports of glycyrrhizin toxicity in humans are difficult to interpret, as they are anecdotal, single case reports with little patient history and little follow-up. Further, by the very nature of these reports, each represents either an extreme over-consumption or an exquisite sensitivity to glycyrrhizin and often involves patients with concurrent chronic disease and who are often taking several medications. For these reasons, no “toxic dose” may be derived from these reports.
Although the toxic effects of glycyrrhizin may be insidious in onset and highly probable in cases of an abnormally high consumption (pica), licorice and its extracts have been safely consumed for many hundreds of years and do not represent a hazard at normal levels of consumption.4

Licorice extract is currently used worldwide at levels below 1.4% (14,000 ppm, total weight tobacco) in selected cigarette brands manufactured and/or distributed by Philip Morris USA Inc. (PM USA) and/or Philip Morris Products SA (PMP SA). Licorice is applied to cigarette tobacco both as a flavor and casing material. It enhances and harmonizes the flavor characteristics of smoke, improves moisture holding characteristics of tobacco, thus increasing stability and shelf life, and acts as a surface active agent during the spraying process of casing ingredients, thus improving the rate of absorption of flavors uniformly and evenly into tobacco. Applied as such, licorice may be subject to pyrolysis-type reactions during the smoking process.

As suggested by purge and trap studies conducted by PM USA at 100°C, licorice extract applied to cigarette tobacco would not be expected to distill in front of the burning cone.6 At the higher temperatures used in the pyrolysis studies conducted by PM USA, licorice extract produced a number of individual chemical entities, including pyrolysis products such as benzene and acetaldehyde.62 The formation of small amounts of these materials is expected, since pyrolysis of organic materials may lead to formation of these compounds. Therefore, the results of these analyses suggest that licorice extract applied to cigarette tobacco would not distill in front of the burning cone, but would be pyrolyzed extensively and would not be delivered in the smoke intact.

Licorice extract was part of the PM USA ingredient testing program that was designed to evaluate the potential effects of ingredients added to typical commercial blended test cigarettes on selected biological and chemical endpoints. Licorice extract was added to test cigarette tobacco at target concentrations of 12,500, 37,500, or 125,000 ppm, and did not increase the mutagenic response of Salmonella bacteria to smoke condensate preparations.63 Similarly, at the same target concentrations, the cytotoxic response of mouse embryo cells treated with mainstream smoke condensate preparations was not altered by licorice extract addition.64 When licorice extract was applied to tobacco at exaggerated concentrations far in excess of the normal use level, there was an increased concentration of some smoke constituents (phenol and formaldehyde). However, lower levels approximating normal use conditions did not significantly alter the smoke chemistry profile compared to control cigarettes.65 The biological effects of inhaling smoke from cigarettes with licorice extract was assessed in Sprague-Dawley rats exposed nose-only to smoke for 6 hrs/day, 7 days/week for 13 weeks. The results of the smoke inhalation studies indicated that the addition of licorice extract to cigarette tobacco at levels up to 125,000 ppm did not discernibly alter the biological effects normally associated with smoke exposure in rodents.66

The results of this evaluation of licorice extract involving a review of published information and internal studies, suggests that addition of licorice extract as a cigarette ingredient at current use levels does not discernibly alter the biological effects normally associated with cigarette smoke.
References


