Evaluation Summary of Bergamot Oil for Use as a Cigarette Ingredient

Bergamot oil is used in the food industry as a flavor ingredient. It has been recognized as GRAS (Generally Recognized As Safe) for use in food by U.S. Food and Drug Administration (FDA) (21 CFR §182.20, §582.20) and Flavor Extract Manufacturers Association (FEMA No. 2153)[1] and is approved for use by the Council of Europe (CoE No. 137).[2] Bergamot oil is produced by cold expression of the nearly ripe fruit. The oil represents a complex mixture of over 300 compounds with 5-methoxypsoralen being the most important photoreactive ingredient in bergamot oil.[3] Bergamot oil has a long history of medicinal use, especially in Calabria, Italy.[4,5] In Europe, bergamot oil continues to be prescribed for its antiseptic properties and is part of some over-the-counter drugs.[6,7]

Acute toxicity studies with bergamot oil were performed using various routes of administration. The following acute LD_{50} (the dose administered which kills half the test population) have been reported: oral LD_{50} in rat > 10 g/kg;[8] intraperitoneal LD_{50} in mouse 1.5 to 2 g/kg;[4] and dermal LD_{50} in rabbit > 20 g/kg.[9] Based on these studies, bergamot oil is practically non-toxic. 5-Methoxypsoralen (5-MOP), the most phototoxic constituent of bergamot oil, showed mutagenic activity in bacterial assays and clastogenic effects in mammalian cells in culture when exposed to UV light.[10] Additionally, 5-MOP alone and 5-MOP in bergamot oil had identical effects on cell survival and the induction of reverse mutations and recombination in diploid yeast and on cell survival and the induction of reverse and forward mutations in haploid yeast. In the presence of chemical filters, there is significant protection against the induction of genetic effects from 5-MOP and bergamot oil containing 5-MOP in haploid and diploid cells.[11] Phototoxic effects from topical application of bergamot oil were documented in both animal[12,13] and human studies.[12,14-27] However, it has been shown, in the absence of UVA irradiation, bergamot oil and 5-MOP are virtually devoid of toxicity.[16]

Bergamot oil showed sedative, anticonvulsant and analgesic effects in animals. Cardiovascular testing in animals with the non-volatile total residue of bergamot oil showed significant dilatory action and reduced hyperkinetic ventricular arrhythmias caused by post-ischemic reperfusion.[28]

Currently, bergamot oil is used worldwide at levels below 100 ppm in selected cigarette brands manufactured and/or distributed by Philip Morris USA Inc. (PM USA) and/or Philip Morris Products SA (PMP SA). Bergamot oil is applied directly to the tobacco as an additive, flavoring, flavoring agent, or solvent, and as such, bergamot oil may be subject to pyrolysis-type reactions when smoked. Bergamot oil may also be applied to the filter as a flavoring material where it would not be subjected to pyrolysis temperatures.

As suggested by the purge and trap studies conducted by PM USA, bergamot oil applied to tobacco would be expected to significantly distill intact at 100°C.[29] At the higher temperatures used in pyrolysis studies conducted by PM USA, results suggest that bergamot oil would not be pyrolyzed extensively and would be delivered to the smoke intact. Methoxysalen (8-methoxypsoralen) was identified as a very minor component of the pyrolysis of bergamot oil. This material is a natural component of bergamot oil, and when in the presence of UVA radiation, is considered to be a human carcinogen.[30] 5-Methoxypsoralen was not found in this sample of bergamot oil.[31]

Bergamot oil was a part of a PM USA testing program that was designed to evaluate the potential effects of 333 ingredients added to typical commercial blended test cigarettes on selected biological and chemical endpoints.[32-35] Three pairs of test cigarettes were produced, each containing different groups of ingredients. Bergamot oil was added to one pair at target levels of 6 ppm and 18 ppm on tobacco. No significant effects were noted in cytotoxicity, mutagenic studies or in respiratory tract endpoints in 90-day rat inhalation studies. In addition, smoke chemistry studies from cigarettes containing a mixture of flavors including bergamot oil did not significantly alter the smoke chemistry profile compared to control cigarettes. Based on the results of these studies, the authors concluded that these ingredients (including bergamot oil) added to tobacco do not add significantly to the overall toxicity of cigarettes.

Currently, information is only available for tests utilizing bergamot oil up to target levels of 18 ppm. Studies are ongoing to address the use of bergamot oil as a single ingredient and at higher tobacco application levels. Published studies show there is no meaningful difference in the composition or toxicity of smoke from cigarettes with added ingredients (including bergamot oil) compared to the smoke from cigarettes without added ingredients.[32-37] Based on the best available data, ingredients used in PM USA and/or PMP SA cigarettes do not increase the overall toxicity of cigarette smoke.

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