Evaluation Summary of Menthol for Use as a Cigarette Ingredient

As a result of a long history of safe use, menthol has been approved in nearly all venues as a food or flavor ingredient. Menthol has been approved for food use by the US Food and Drug Administration (21 CFR § 182.20 and 21 CFR § 172.515), the Joint FAO/WHO Expert Committee on Food Additives (JECFA),¹ and is considered generally recognized as safe (GRAS) by the Flavor and Extract Manufacturers Association (FEMA).²

Menthol has a relatively low order of acute toxicity in rodents.³⁻¹⁴ Subchronic feeding studies in rats and mice indicate a NOEL in both species of 7500 ppm.¹⁵ Long-term feeding studies in rats at concentrations up to 7500 ppm indicated slightly decreased body weights, but no treatment related effects in any tissues examined. This study concluded that menthol was not carcinogenic in rats or mice.¹⁵ Teratology studies found no effect of menthol administration in the mouse, rat, hamster or rabbit at the maximum administered doses of 185, 218, 405 and 425 mg/kg, respectively, or the offspring thereof. These studies indicate that menthol does not possess teratogenic potential.¹⁶

The genotoxicity of menthol has been studied in numerous ways. Negative results have been obtained in the Ames assay,¹⁷⁻²⁰ sister chromatid exchange assay,^{21,22} chromosomal aberration studies,^{19,21,22} replicative DNA synthesis^{5,7} and L5178Y mouse lymphoma cell assays.²³ Positive *in vitro* genotoxicity of menthol is only found at high concentrations where it possesses significant cytotoxicity²⁴ and thus the weight of evidence suggests that menthol is not genotoxic.

Menthol has been used in tobacco products since the 1920's.²⁵ It may be applied to the inner foil of menthol cigarette packages to impart its sensory characteristics to the cigarette. Menthol can also be applied directly to the tobacco during cigarette manufacturing, and as such may be subject to pyrolysis-type reactions when smoked. Menthol may also be applied to the filter as a flavoring material where it would not be subjected to pyrolysis temperatures.

Menthol is currently used worldwide at levels such that the level of menthol in cigarette smoke does not exceed 800 μ g/cig (0.8 mg/cig) in selected cigarette brands manufactured and/or distributed by Philip Morris USA (PM USA) and/or Philip Morris Products SA (PMP SA). After manufacturing, irrespective of how the menthol is applied, the menthol is distributed throughout the product. Transfer of menthol from use on the filler to mainstream cigarette smoke has been shown experimentally to be approximately 30% and the majority of the menthol was found in the particulate phase.^{26,27} However, based on a PM USA production assessment testing for the year 2001,²⁸ the transfer of menthol to mainstream cigarette smoke appears to be less than 10%.

Internal PM USA purge and trap studies conducted at 100°C indicate that menthol is likely to significantly distill from the cigarette prior to the burning cone.²⁹ Furthermore, pyrolysis data indicate that menthol will remain intact and not pyrolyze.³⁰ Jenkins *et al.* found that the pyrolysis of menthol in the burning cone of a cigarette is insignificant. In fact, the major smoke product in mainstream smoke is unchanged menthol (98.9%).²⁶

Menthol 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 ³¹⁻³⁴. Three pairs of test cigarettes were produced, each containing different groups of ingredients. Menthol was added to one pair of test cigarettes at a target level of 18,000 ppm. 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 menthol 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 menthol) added to tobacco do not add significantly to the overall toxicity of cigarettes.

On a separate study performed by the Lorillard Tobacco Co., the effect of menthol (at a target level of 5,000 ppm) as part of a flavor mixture was evaluated on the skin tumor promotion assay ³⁵. The tumor promotion capacity of cigarette smoke condensate obtained from cigarettes containing tobacco with ingredients was not discernibly different from the cigarette smoke condensate obtained from reference cigarettes containing tobacco processed without ingredients.

Studies are ongoing to address the use of menthol as a single ingredient and at higher levels in cigarette smoke. Published studies show there is no meaningful difference in the composition or toxicity of smoke from cigarettes with added ingredients (including menthol) compared to the smoke from cigarettes without added ingredients.^{31-34,36,37}. The results of this evaluation of menthol involving a review of published information and internal studies, suggests that addition of menthol as a cigarette ingredient at current use levels does not discernibly alter the biological effects normally associated with cigarette smoke.

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