## **Evaluation Summary of 4'-Methylacetophenone for Use as a Cigarette Ingredient**

4'-Methylacetophenone is a monoterpene ketone with a fruity floral odor and sweet flavor used in food as a flavoring agent and adjuvant. It is present naturally in several foods including sour cherry, guava, peach, fresh blackberry, stalks of celery, and baked potato as well as in essential oils from the wood of *Myrocarpus* and bois de rose. 4'-Methylacetophenone has a history of natural occurrence and consumption and is approved for food use by United States Food and Drug Administration (FDA) (21CFR§172.515), the Flavour and Extract Manufacturers Association (FEMA, No. 2677),<sup>1</sup> the Joint FAO/WHO Expert Committee on Food Additives (JECFA),<sup>2</sup> and the Council of Europe (CoE No. 156).<sup>3</sup> It has been in public use since 1920.

4'-Methylacetophenone is used as a flavoring agent in several food products including baked goods, frozen dairy, gelatin, pudding, chewing gum, hard candy, soft candy, alcoholic and nonalcoholic beverages. Acetophenone and its derivatives, including 4'-methylacetophenone, are important in perfumery because of their good smell and their usefulness as raw materials in the manufacture of other perfumery synthetics.<sup>4</sup> It can be found in soaps and lotions as well as perfumes.<sup>5,6</sup>

The acute oral toxicity  $(LD_{50})$  in rats and the acute dermal toxicity  $(LD_{50})$  in rabbits of 4'methylacetophenone was reported as 1.4 g/kg and >2 g/kg of body weight, respectively.<sup>7</sup> Application of full strength 4'-methylacetophenone to intact or abraded rabbit skin for 24 hours under occlusion was slightly irritating.<sup>7</sup> In humans, the sensitization potential of 4'methylacetophenone using the maximization test in 25 normal volunteers was investigated and no sensitization reactions were observed when tested at a concentration of 6% in petrolatum.<sup>8</sup> In a 24 hour patch test, 4'-methylacetophenone tested at full strength in 15 subjects produced one irritation reaction.<sup>9</sup>

The genotoxic and cytotoxic properties of 4'-methylacetophenone (in addition to several other compounds) were studied as it was derived from cigarette smoke condensate. 4'- Methylacetophenone was contained in the semivolatile neutral fraction of the cigarette smoke condensate. This fraction induced sister chromatid exchange while no mutagenic activity was demonstrated in the Ames assay.<sup>10</sup> In a separate study, the degree of membrane damage of human diploid embryonic lung fibroblasts measured by the release of nucleotide in the presence of substances derived from tobacco and tobacco smoke was evaluated. 4'-Methylacetophenone released 16% nucleotide where nil is considered <15% and moderate is 45-70%.<sup>11</sup>

Acetophenone, the parent compound of 4'-methylacetophenone, was found to be not mutagenic in several strains of *Salmonella typhimurium* while it caused breaks in DNA from *E. coli*.<sup>12,13</sup> In a subchronic study, acetophenone was studied for its toxic effects in rats. In the results of this study a NOAEL (no observable advese effect level) of 500 mg/kg/day was found.<sup>14</sup> Based on the results of this study, EPA developed a NOAEL of 423 mg/kg/day with a reference dose of 0.1 mg/kg/day.<sup>14,15</sup>

4'-Methylacetophenone is currently used worldwide at levels below 5 ppm in selected cigarette brands manufactured and/or distributed by Philip Morris USA Inc. (PM USA) and/or Philip Morris Products SA (PMP SA). 4'-Methylacetophenone is applied directly to the tobacco as a flavoring material and as such, 4'-methylacetophenone may be subject to pyrolysis-type

reactions when smoked. 4'-Methylacetophenone may also be applied to the filter as a flavoring material where it would not be subjected to pyrolysis temperatures.

Purge and trap studies performed at 100°C, conducted by PM USA, suggest that 4'methylacetophenone would distill in front of the burning cone.<sup>16</sup> At the higher temperatures used in pyrolysis studies conducted by PM USA, results showed that remaining 4'methylacetophenone would remain completely intact with some appearance of 3methylacetophenone.<sup>17</sup>

4'-methylacetophenone was 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.<sup>18-21</sup> Three pairs of test cigarettes were produced, each containing different groups of ingredients. 4'-Methylacetophenone was added to one pair at target levels of 12 ppm and 39 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 4'- methylacetophenone 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 4'-methylacetophenone) added to tobacco do not add significantly to the overall toxicity of cigarettes.

The results of this evaluation of 4'-methylacetophenone, involving a review of published information and internal studies, suggest that addition of 4'-methylacetophenone as a cigarette ingredient at the current use levels does not discernibly alter the biological effects normally associated with cigarette smoke.

## References

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