## **Evaluation Summary of Linalool for Use as a Cigarette Ingredient**

Linalool 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 §182.60), Joint FAO/WHO Expert Committee on Food Additives (JECFA, No. 356)<sup>1,2</sup> and Flavor Extract Manufacturers' Association (FEMA, No. 2635)<sup>3</sup> and is approved for use by the Council of Europe (CoE, No. 61)<sup>4</sup>. It occurs widely in nature and is present in many unprocessed foods as well as processed foods. Linalool has been in use since the mid-1800s for its taste (food) and aromatic (perfumery) characteristics.<sup>5-7</sup> It is also used in the manufacture of other flavor ingredients, as well as, in the manufacture of Vitamins A and E.<sup>5,8</sup>

Linalool is a terpene alcohol that is rapidly absorbed, but neither widely nor extensively distributed throughout the body. Rather, it is rapidly excreted in urine, air and feces. Linalool is metabolized by multiple enzymatic pathways that include conjugation and oxidation.<sup>9-12</sup> The acute, subchronic, genotoxicity, cytotoxicity and immunotoxicity effects of linalool were reported in the literature. The oral and dermal LD<sub>50</sub> (the dose administered which kills half the test population) in rats and rabbits are 2.79 and 5.61 g/kg, indicating that linalool is of slight acute toxic potential.<sup>13-15</sup> A short-term carcinogenicity study suggests that linalool is non-carcinogenic<sup>16</sup> and numerous *in vitro* genotoxicity studies indicate it is non-genotoxic.<sup>17-23</sup> Linalool is also reported to be non-immunotoxic (*in vivo*)<sup>24</sup> and its cytotoxic (*in vitro*) effects are equivocal<sup>25-27</sup>. At high concentrations, linalool is reported to produce moderate irritation in experimental animal studies<sup>14,25,28</sup>, and as shown in human studies is non-irritating when diluted.<sup>29,30</sup> Further, experimental human studies did not reveal linalool to be a sensitizing substance.<sup>25,29,31,32</sup> Although human studies that included large numbers of subjects do report some individuals to be allergic to linalool, the incidence of allergenicity to linalool indicates that it is a rare occurrence.<sup>33-37</sup>

Currently, linalool is 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). Linalool is applied directly to the tobacco as an additive, flavoring, flavoring agent, or solvent, and as such, linalool may be subject to pyrolysis-type reactions when smoked. Linalool 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, linalool applied to tobacco would be expected to significantly distill intact at 100°C.<sup>38</sup> At the higher temperatures used in the pyrolysis studies, the largest peak identified was linalool, with the next largest peak identified as beta-Pinene, a starting material for linalool synthesis. The results of this analysis suggest that linalool would not be pyrolyzed extensively and would remain intact.<sup>39</sup>

Linalool was a part of a 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>40-43</sup> Three pairs of test cigarettes were produced, each containing different groups of ingredients. Linalool was added as part of the ingredient mixture to one pair at target levels of below 1 ppm and 3 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 linalool 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 linalool) added to tobacco do not add significantly to the overall toxicity of cigarettes.

The results of this evaluation of linalool, involving a review of current published information and internal studies, suggest that the addition of linalool as a cigarette ingredient at current use levels would not be expected to discernibly alter the biological effects normally associated with cigarette smoke exposure.

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