

Evaluation Summary of Ethyl Acetate for Use as a Cigarette Ingredient

Ethyl acetate has been approved for addition to food by U.S. Food and Drug Administration (FDA 21 CFR § 182.60), the Flavour and Extract Manufacturers Association (FEMA No. 2414),¹ the Joint FAO/WHO Expert Committee on Food Additives (JECFA)² and the Council of Europe (CoE No. 191).³ Ethyl acetate has been added to foods since at least 1920, and has been reported to occur in nature.⁴⁻¹¹ It is also used as solvent in nail polish, nail polish removers, basecoats and other manicuring preparations.¹²⁻¹⁴

No mutagenic activity of ethyl acetate was detected by Ames test using *Salmonella typhimurium* strains TA92, TA1535, TA1537, TA94, TA98 and for some samples, TA2637, with and without S9 liver microsome fraction.¹⁵⁻¹⁸ Ethyl acetate was nonmutagenic when tested by Rec-assay.¹⁹ However, weakly positive results were obtained in chromosomal aberration test using a Chinese hamster fibroblasts cell line¹⁶ and in mitotic aneuploidy test using *S. cerevisiae*.^{20,21} Chromosomal aberration positives were designated by a value of >10% cells with aberration. The total incidence of cells with aberration in ethyl acetate treated group was only 11%.¹⁶ Hence, based on these results of the single chromosomal aberration assay, it is difficult to interpret that ethyl acetate is mutagenic.²² Single oral or intraperitoneal administration of ethyl acetate did not damage the bone marrow chromosomes of mice or hamster as measured by the micronucleus assay.^{23,24}

Ethyl acetate is rapidly hydrolyzed to ethyl alcohol in rats, rabbits and human blood. *In vivo* ethyl acetate is rapidly metabolized by rats and humans to ethanol and acetic acid, which can then be disposed of by normal metabolic pathways.^{25,26} Ethyl acetate was relatively nontoxic when administered orally, dermally or by inhalation to rats, mice, rabbits and guinea pigs.²⁷⁻³⁶ Vapors of ethyl acetate were irritating to the eyes and respiratory tract of humans and various laboratory animal species.^{27,37-42} In a 90-day inhalation exposure study in male and female rats exposed to 350, 750 and 1500 ppm, a no-observed-effect-level (NOEL) for male rats was not demonstrated. The lowest-observed-effect-level (LOEL) in female rats was 750 ppm, based on reduction in body weight, body weight gain and food efficiency. The demonstrated NOEL in female rats was 350 ppm.⁴³ A NOEL of 900 mg/kg was reported in a subchronic gavage study with Sprague-Dawley rats.⁴⁴ Subchronic exposure of three guinea pigs to 2000 ppm ethyl acetate, 4 hours/day, 6 days/week, for 65 exposures, led to no measurable changes in body weight gains, or in hematological or urinary values.⁴⁵

No carcinogenic effects of ethyl acetate have been reported in humans. Ethyl acetate did not increase the number of lung tumors in mice when administered by the intraperitoneal route in a 24 week carcinogenicity study.⁴⁶

Neither skin irritation nor sensitization was observed in human subjects tested with a nail polish remover containing 16.5% ethyl acetate⁴⁷ or other products containing 97% ethyl acetate.⁴⁸ When tested in humans, at concentrations of up to 10% in petrolatum and cosmetic formulations, ethyl acetate was slight irritant but was not a sensitizer.^{30,39,49-51} In a clinical study, ethyl acetate, at 6.5% in a nail color, did not produce signs of phototoxicity or photoallergenicity.⁵²

Currently, ethyl acetate 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). Ethyl acetate is applied directly to the tobacco as an additive, flavoring, flavoring agent, or solvent, and as such, ethyl acetate may be subject to pyrolysis-type reactions when smoked. Ethyl acetate 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,⁵³ ethyl acetate applied to tobacco would be expected to extensively distill at 100°C. At the higher temperatures used in the pyrolysis studies, the largest peak was identified as ethyl acetate.⁵⁴ The results of this analysis suggest that ethyl acetate would not be pyrolyzed and would be delivered to the smoke mostly intact.

Ethyl acetate 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.⁵⁵⁻⁵⁸ Three pairs of test cigarettes were produced, each containing different groups of ingredients. Ethyl acetate was added to two pairs at target levels of 134 ppm, 172 ppm, 402 ppm and 515 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 ethyl acetate 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 ethyl acetate) added to tobacco do not add significantly to the overall toxicity of cigarettes.

Currently, information is only available for tests utilizing ethyl acetate in a mixture of ingredients applied to cigarette tobacco. Studies are ongoing to address the use of ethyl acetate as a single ingredient. Published studies show there is no meaningful difference in the composition or toxicity of smoke from cigarettes with added ingredients (including ethyl acetate) compared to the smoke from cigarettes without added ingredients.⁵⁵⁻⁶³ Based on the best available data, the addition of ethyl acetate as a cigarette ingredient at the current use levels does not discernibly alter the biological effects normally associated with cigarette smoke.

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