Evaluation Summary of Benzyl Alcohol for Use as a Cigarette Ingredient

Benzyl alcohol is naturally occurring in many foods and has been used as a food flavoring and fragrance ingredient for over 70 years. Benzyl alcohol is approved by U.S. Food and Drug Administration for use in food as a synthetic flavoring substance or adjuvant (21 CFR § 172.515); as an indirect additive use in adhesives (21 CFR § 175.105); as a coating component of food packaging or food contact surfaces (21 CFR §175.300); as a component of polymers for food container closures or sealing gaskets (21 CFR §177.1210); and as diluent in color additives (21 CFR §73.1001). It is also Generally Recognized As Safe (GRAS) by the Flavor and Extract Manufacturers Association (FEMA No. 2137) for use as a flavoring ingredient.[1] The Council of Europe has approved benzyl alcohol for food use (CoE No. 58).[2]

Benzyl alcohol is relatively non-toxic in acute studies in animals when administered by oral, dermal, intraperitoneal and inhalation routes of exposure. The acute oral and intraperitoneal LD_{50} (the dose administered which kills half the test population) in several species is greater than 1,000 mg/kg.[3-6] No deaths were observed when cats and guinea pigs were treated dermally at doses exceeding 5 g/kg.[4,7] By inhalation, benzyl alcohol is also relatively non-toxic with an LD_{50} of 2,000 ppm with an eight-hour exposure in rats.[5,8]

Benzyl alcohol is slightly to moderately irritating to the skin, depending on the concentration and type of application.[9-13] No reports of food-borne sensitization were found in the literature searches.[14]

In a range finding study conducted by the National Toxicology Program (NTP), repeat oral dosing in mice and rats for three months with benzyl alcohol produced only decreased weight gain in female mice at doses up to 400 mg/kg/day which is considered the lowest-observed-adverse-effect-level.[15] At 200 mg/kg/day, no adverse effects were observed in either species or sex which was considered the no-observed-adverse-effect-level (NOAEL). At a dose of 800 mg/kg/day, body weight gain was less in male and female rats and mice. Histopathological changes were found in several organs/tissues in male rats and in the brain of female rats; no pathology was found in the mice, even at the highest dose. The relative lack of toxicity of benzyl alcohol seen in subchronic feeding studies was confirmed in lifetime bioassays.[15]

The weight of evidence from genetic toxicology testing indicates benzyl alcohol is not genotoxic. Benzyl alcohol was not mutagenic in multiple Ames/Salmonella assays,[16-20] but indirect deoxyribonucleic acid (DNA) damage was reported by other investigators using the *Bacillus subtilis* rec assay.[21,22] Chromosomal aberrations were noted in one report using mammalian cells in culture,[23] but no chromosomal effects were found in another similar assay.[24] Equivocal, non-dose related mutagenicity was reported in mouse lymphoma cells.[25] No increases in micronuclei were found in treated mice.[26]

Developmental toxicity studies in mice by Hardin *et al.*[27] suggest benzyl alcohol is not a developmental toxicant, even at dose levels that induce significant maternal toxicity. The finding of only minimally reduced pup weights in the absence of any other indicator of developmental effects at doses inducing maternal mortality and severe toxicity in the survivors suggests a lack of fetal toxicity. This was confirmed by the absence of adverse developmental effects in a second study conducted at a slightly lower dose.[28]

Currently, benzyl alcohol is used worldwide at levels below 1,000 ppm in selected cigarette brands manufactured and/or distributed by Philip Morris USA Inc.(PM USA) and/or Philip Morris Products SA (PMP SA). Benzyl alcohol is applied directly to the tobacco as an additive, flavoring, flavoring agent, or solvent, and as such, benzyl alcohol may be subject to pyrolysis-type reactions when smoked. Benzyl alcohol 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,[29] benzyl alcohol 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 benzyl alcohol.[30] The results of this analysis suggest that benzyl alcohol would not be pyrolyzed and would be delivered to the smoke mostly intact.

Benzyl alcohol was part of the PM USA ingredient testing program that was designed to evaluate the potential effects of ingredients added to typical commercial blended test cigarettes on selected biological and chemical endpoints. Benzyl alcohol was added to test cigarette tobacco at target concentrations of 500 ppm, 5,000 ppm, or 21,000 ppm, and did not increase the mutagenic response of Salmonella bacteria to smoke condensate preparations.[31] Similarly, at the same target concentrations, the cytotoxic response of mouse embryo cells treated with mainstream smoke condensate preparations was not altered by benzyl alcohol addition.[32] There were also no dose dependent increases for any smoke constituents with the addition of benzyl alcohol.[33] The biological effects of inhaling smoke from benzyl alcohol treated cigarettes was assessed in Sprague-Dawley rats exposed nose-only to smoke for 6 hrs/day, 7 days/week for 13 weeks. The results of the smoke inhalation studies indicated that benzyl alcohol addition to cigarette tobacco at levels up to 21,000 ppm tested did not discernibly alter the biological effects normally associated with smoke exposure in rodents.[34]

The results of this evaluation of benzyl alcohol involving a review of published information and internal studies, suggests that addition of benzyl alcohol 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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