Evaluation Summary of Acetic Acid for Use as a Cigarette Ingredient

Acetic acid is approved by U.S. Food and Drug Administration (21 CFR § 184.1005) and the Flavor and Extracts Manufacturers Association (FEMA No. 2006) as a generally recognized as safe (GRAS) substance for direct addition to food as a flavoring agent [1]. It is also approved for use as a food flavoring agent by the Council of Europe (CoE No.2).[2] Acetic acid and acetate occur ubiquitously and are a normal metabolic intermediate in plants and animal tissues.[3,4] Vinegar (3 – 6% acetic acid) is commonly used in salad dressings, mayonnaise, pickled fruits and vegetables, and in many sauces or ketchups.[5] Acetate salts are frequently added to dialysis and intravenous solutions.[6]

The acute oral LD_{50} of acetic acid in rodents is in the range of 2,500-4,960 mg/kg,[7-9] whereas the inhaled LD_{50} (1 hr) to mice is 5,620 ppm.[10] Some short-term toxicity studies involving rats fed acetic acid (0.5 – 10%) or acetate resulted in reduced weight gain, although these results were not consistent among researchers.[7,11-13] In general, reduced weight gain appeared to be dose-dependent, but may also be due to a decreased palatability of the animal feed with increasing concentrations. The mean acute lethal dose of acetic acid in man has been estimated as 20 ml of pure compound.[14]

The oral administration of 4-10% acetic acid solutions to fasted rats or mice is frequently used in experimental animal models of upper gastrointestinal ulcerations.[15-20] The mechanism of this toxicity is thought to involve nonspecific, acid-induced injury to the mucosa that is followed by an acute inflammatory response.

Acetic acid is considered to be a non-irritant, or have slight irritant effects in animal dermal studies at concentration up to 10%.[21-25] At higher concentrations acetic acid can be severely irritating and corrosive. Ocular irritation studies revealed dose and exposure time dependent corneal damage following the application of 2-10% acetic acid.[26-30] Clinical studies with human volunteers corroborated the results of animal dermal studies and found acetic acid to be a slight dermal irritant at low concentration.[22,23,31] Despite the induction of gastrointestinal ulcers in animals administered acetic acid, one epidemiological study found vinegar consumption to be negatively correlated to mortalities from cancers of the esophagus, stomach, colon, biliary passage and pancreas.[32] However, apple vinegar consumption was strongly correlated to dental erosion.[33]

Acetic acid *per se* is not carcinogenic and could even protect from chemical carcinogens. In animal models of two stage carcinogenicity studies, acetic acid was found to be a weak promoter of tumor formation.[34-36] The weak promoter effect was related to the induction of an inflammatory response and subsequent hyperplasia of exposed tissue.

In vitro studies involving 9 day-old mouse somite stage embryos revealed concentration-dependent increases in malformations when incubated with 3-10 mM acetic acid.[37] However, the oral administration of 1,000 mg/kg/day to pregnant mice resulted in no adverse maternal or neonatal effects.[38]

Ames/Salmonella reverse mutation testing revealed no genotoxic effects of acetic acid.[39-43] Genotoxic effects of acetic acid to cultured mammalian cells were correlated with decreased pH of the culture system and subsequent compromised viability of the cells.[39,44-47]

One epidemiology study and several case reports revealed the irritancy of acute or chronic exposure to acetic acid vapors to the respiratory tract.[10,48,49] In inhalation studies, acute exposure to high levels of acetic acid vapor can potentially lead to reactive airways dysfunction syndrome,[49] whereas chronic exposure to lower levels (approx. 60 ppm in air) induced upper respiratory tract congestion, edema, bronchitis and asthma-like symptoms.[50]

Acetic acid is applied directly to the tobacco as a flavoring material. Acetic acid is currently 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). As such, acetic acid may be subject to pyrolysis-type reactions when smoked. Acetic acid may also be applied to the filter as a flavoring material where it would not be subjected to pyrolysis temperatures.

As suggested by purge and trap studies conducted by PM USA, acetic acid would be expected to extensively distill at 100ºC in front of the burning cone.[51] At the higher temperatures used in the pyrolysis studies conducted by PM USA, the results indicated that if there were to be remaining acetic acid, it would transfer virtually intact.[52]

Acetic acid 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.[53-56] Three pairs of test cigarettes were produced, each containing different groups of ingredients. Acetic acid was added to two pairs at target levels of 28 ppm, 62 ppm, 80 ppm and 186 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 acetic acid 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 acetic acid) added to tobacco do not add significantly to the overall toxicity of cigarettes.

Currently, information is only available for tests utilizing acetic acid in a mixture of ingredients applied to cigarette tobacco. Studies are ongoing to address the use of acetic acid 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 acetic acid) compared to the smoke from cigarettes without added ingredients.[53-61] Based on the best available data, the ingredients used in PM USA and/or PMP SA cigarettes do not increase the overall toxicity of cigarette smoke.

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