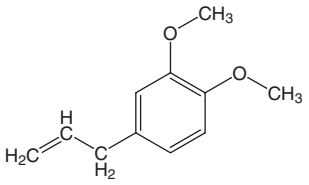
Methyleugenol
CAS No. 93-15-2

Reasonably anticipated to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)



Carcinogenicity

Methyleugenol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or combination of malignant and benign tumors at multiple tissue sites in multiple species of experimental animals. In animal studies, methyleugenol given orally to rats induced liver and stomach tumors in both sexes and kidney, mammary gland, and skin tumors in males. Methyleugenol given orally to mice induced benign and malignant tumors of the liver. Tumors of the stomach in male mice also were considered related to exposure to methyleugenol (NTP 1998). Earlier studies found that methyleugenol and two similar compounds, the structurally related allylbenzenes, safrole and estragole, induced liver tumors in mice after intraperitoneal injection (IARC 1976, Miller *et al.* 1983). Safrole is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* and by IARC as *possibly carcinogenic to humans* (Group 2B).

No adequate human studies of the relationship between exposure to methyleugenol and human cancer were found.

Additional Information Relevant to Carcinogenicity

Mechanistic data indicate that liver tumors induced by methyleugenol and structurally related allylbenzenes result from metabolism of these compounds to DNA-reactive intermediates. Methyleugenol may be bioactivated by three different pathways: (1) hydroxylation at the 1′ position of the allylic side chain to yield 1′-hydroxymethyleugenol, followed by sulfation of this intermediate to form 1′-hydroxymethyleugenol sulfate, (2) oxidation of the 2′,3′-double bond of the allylic side chain to form methyleugenol-2,3-oxide, and (3) *O*-demethylation followed by spontaneous rearrangement to form eugenol quinone methide. Formation of protein adducts and DNA adducts in the livers of animals (and in cultured human hepatocytes) exposed to allylbenzenes and induction of liver tumors by these compounds in animals have been attributed to activation via the hydroxylation pathway, because similar effects were produced by the 1′-hydroxy metabolites and because these effects were inhibited by pretreatment with sulfotransferase inhibitors (Miller *et al.* 1983, Boberg *et al.* 1983, Randerath *et al.* 1984, Gardner *et al.* 1996, NTP 1998).

Methyleugenol, safrole, and estragole induce unscheduled DNA synthesis in rat hepatocytes, and their corresponding 1′-hydroxy metabolites are more potent genotoxic agents than are the parent compounds (Howes *et al.* 1990, Chan and Caldwell 1992). Methyleugenol induces morphological transformations in Syrian hamster embryo cells (Kerckaert *et al.* 1996), sister chromatid exchange in Chinese hamster ovary (CHO) cells (NTP 1998), intrachromosomal recombination in yeast (Schiestl *et al.* 1989), and DNA repair in *Bacillus subtilis* (Sekizawa and Shibamoto 1982). Methyleugenol does not induce mutations in *Salmonella typhimurium* (NTP 1998) or *Escherichia coli* (Sekizawa and Shibamoto 1982), chromosomal aberrations in CHO cells (NTP 1998), or micronucleated erythrocytes in peripheral blood of mice (NTP 1998). A higher frequency of β-*catenin* mutations was observed in liver tumors from mice treated with methyleugenol than in spontaneous liver tumors from control mice (Devereux *et al.* 1999). Methyleugenol's lack of mutagenicity in bacteria may be due to the need for sulfation in the metabolic activation of methyleugenol to its ultimate mutagenic or carcinogenic form.

Properties

Methyleugenol is a colorless to pale yellow oily liquid with a boiling point of 254.7°C and a melting point of -4°C. It has a delicate clove-carnation odor and a bitter burning taste. It forms azeotropic mixtures with ethylene glycol, eugenol, and benzoic acid. It slowly darkens and thickens when exposed to air and readily evaporates at room temperature (Lide 1998). It is soluble in water, ether, ethanol, and chloroform and insoluble in glycol and propylene glycol (HSDB 2001).

Use

Methyleugenol is used as a flavoring agent in jellies, baked goods, nonalcoholic beverages, chewing gum, candy, pudding, relish, and ice cream. Methyleugenol has been used as an anesthetic in rodents. It also is used as an insect attractant in combination with insecticides (NTP 2000).

Production

Annual production of methyleugenol in the United States in 1990 was estimated at 25,000 lb (NTP 1998). No current production data were available for methyleugenol.

Exposure

Methyleugenol is a naturally occurring substance, present in many essential oils, including rose, pimento, basil, hyacinth, citronella, anise, nutmeg, mace, cinnamon leaves, pixuri seeds, and laurel fruits and leaves. It also has been found in blackberry essence, bananas, black pepper, and bilberries (NTP 2000). Methyleugenol is used in commercial products as a flavorant at concentrations from 5 to 52 ppm and as a fragrance at concentrations from 0.002% to 0.3%. Methyleugenol has been detected in the wastewater effluent from a paper mill (NTP 2000). Although methyleugenol has been identified in various natural substances, no quantitative studies have assessed environmental (nondietary) exposure to methyleugenol. Methyleugenol exists as a vapor in the ambient atmosphere. Vapor-phase methyleugenol reacts with photochemically produced hydroxyl radicals and degrades with an estimated half-life of five hours (HSDB 2001).

The general population is exposed to methyleugenol through ingestion of foodstuffs or inhalation of fragrances containing the compound (HSDB 2001). In a subset of serum samples from adults participating in the third National Health and Nutrition Examination Survey, methyleugenol was detected in 98% of the 206 samples analyzed. The average methyleugenol concentration was 24 pg/g, and the highest concentration was 390 pg/g (Barr *et al.* 2000).

Daily per capita consumption of methyleugenol in foods was estimated by the World Health Organization to be 0.073 mg (WHO 1981) and, more recently, 0.26 mg/kg body weight (Strofberg and Grundschober 1987, NAS 1989). Occupational exposure to methyleugenol occurs through dermal contact, inhalation, and ingestion. The National Occupational Exposure Survey conducted by NIOSH between 1981 and 1983 estimated that 2,824 workers, including 877 women, potentially were exposed to methyeugenol (NIOSH 1990).

Regulations and Guidelines

No specific regulations or guidelines relevant to reduction of exposure to methyleugenol were identified.

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