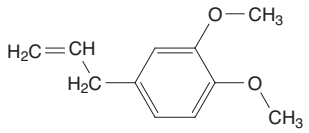
Methyleugenol

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.

Cancer Studies in Experimental Animals

Oral exposure to methyleugenol caused tumors in two rodent species and at several different tissue sites. Methyleugenol administered by stomach tube caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in rats and mice of both sexes. In rats, methyleugenol also caused benign or malignant stomach tumors (neuroendocrine tumors) in both sexes and tumors of the kidney (renal-tubule adenoma), mammary gland (fibroadenoma), and skin (fibroma or fibrosarcoma) in males. Malignant neuroendocrine tumors of the stomach in male mice also were considered to be related to methyleugenol exposure (NTP 2000). Earlier studies found that methyleugenol and two structurally related allylbenzenes, safrole and estragole, caused liver tumors in mice when administered by 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 the International Agency for Research on Cancer as possibly carcinogenic to humans.

Studies on Mechanisms of Carcinogenesis

Mechanistic studies 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 (Boberg *et al.* 1983, Miller *et al.* 1983, Randerath *et al.* 1984, Gardner *et al.* 1996, NTP 2000).

Methyleugenol, safrole, and estragole caused unscheduled DNA synthesis in rat hepatocytes, and their corresponding 1′-hydroxy metabolites were more potent genotoxic agents than were the parent compounds (Howes *et al.* 1990, Chan and Caldwell 1992). Methyleugenol caused morphological transformation of Syrian hamster embryo cells (Kerckaert *et al.* 1996), sister chromatid exchange in Chinese hamster ovary (CHO) cells (NTP 2000), intrachromosomal recombination in yeast (Schiestl *et al.* 1989), and DNA repair in *Bacillus subtilis* (Sekizawa and Shibamoto 1982). It did not cause mutations in *Salmonella typhimurium* (NTP 2000) or *Escherichia coli* (Sekizawa and Shibamoto 1982), chromosomal aberrations in CHO cells (NTP 2000), or micronucleus formation in the peripheral-blood erythrocytes of mice (NTP 2000). A higher frequency of β-catenin mutations was observed in liver tumors from mice exposed to methyleugenol than in spontaneous liver tumors from unexposed 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.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to methyleugenol.

Properties

Methyleugenol is an allyl-chain-substituted guaiacol that structurally resembles safrole (NTP 2000). It is a colorless to pale yellow, oily liquid with an odor of cloves and carnations. It is insoluble in water, glycol, and propylene glycol and soluble in ethanol, ethyl ether, chloroform, and many other organic solvents. Methyleugenol is unstable at room temperature; it darkens and thickens when exposed to air and readily evaporates at room temperature (NTP 2000). Physical and chemical properties of methyleugenol are listed in the following table.

Property	Information
Molecular weight	178.2[a]
Specific gravity	1.0396 at 20°C/4°C[a]
Melting point	–4°C[a]
Boiling point	254.7°C at 760 mm Hg[a]
Log K_{ow}	3.03[b]
Water solubility	0.500 g/L at 25°C[b]
Vapor pressure	1 mm Hg at 85.0°C[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Methyleugenol is used in fragrances and as a flavoring agent in jellies, baked goods, nonalcoholic beverages, chewing gum, candy, pudding, relish, and ice cream. It is also used as an insect attractant in combination with insecticides and has been used as an anesthetic in rodents (NTP 2000, HSDB 2009).

Production

Annual production of methyleugenol in the United States in 1990 was estimated at 25,000 lb (NTP 2000). No current production data were found.

Exposure

The general population may be exposed to methyleugenol through ingestion of foods or inhalation of fragrances containing the compound (HSDB 2009). Methyleugenol is a naturally occurring substance, present in many essential oils, including the oils of rose, pimento, basil, hyacinth, citronella, anise, nutmeg, mace, cinnamon leaves, pixuri seeds, and laurel fruits and leaves. It has also been found in blackberry essence, bananas, black pepper, and bilberries (NTP 2000). Methyleugenol is used in commercial products as a flavorant at concentrations of 5 to 52 ppm and in fragrances at concentrations of 0.002% to 0.3% (HSDB 2009). 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 food was estimated by the World Health Organization to be 0.073 mg (WHO 1981) and, more recently, 0.26 mg/kg of body weight (Strofberg and Grundschober 1987, NAS 1989).

Although methyleugenol has been identified in various natural substances, no quantitative studies were found that assessed environmental (nondietary) exposure to methyleugenol. In air, methyleugenol exists as a vapor; it reacts with photochemically produced hydroxyl radicals and degrades with an estimated half-life of 5 hours (HSDB 2009). Methyleugenol has been detected in wastewater effluent from a paper mill (NTP 2000).

Occupational exposure to methyleugenol may occur through dermal contact, inhalation, and ingestion. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 12,682 workers, including 9,413 women, potentially were exposed to methyleugenol (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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