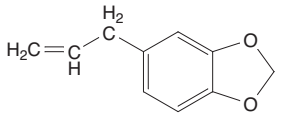
Safrole

CAS No. 94-59-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 5-(2-propenyl)-1,3-benzodioxole



Carcinogenicity

Safrole is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Safrole caused liver tumors in two rodent species and by two different routes of exposure. Dietary administration of safrole caused liver cancer (hepatocellular carcinoma) in male mice and benign or malignant liver tumors (hepatocellular carcinoma or adenoma or cholangiocarcinoma) in rats of both sexes (IARC 1972, 1976). Liver cancer (hepatocellular carcinoma) was also observed in mice of both sexes administered safrole by stomach tube from 7 to 28 days of age, followed by dietary exposure for up to 82 weeks, and in infant male mice administered safrole by subcutaneous injection.

Since safrole was listed in the *Second Annual Report on Carcinogens,* an additional study in mice has been identified. The incidence of liver tumors (adenoma and carcinoma) was increased in male mice exposed during infancy via milk and in adult female mice administered safrole in the diet (Vesselinovitch 1983).

Cancer Studies in Humans

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

Properties

Safrole, a naturally occurring substance, is a derivative of the aromatic phenol ether 1,3-benzodioxole (HSDB 2009). It exists at room temperature as a colorless or pale-yellow oil with an odor of sassafras. It is practically insoluble in water, insoluble in glycerine, slightly soluble in propylene glycol, soluble in alcohol, and miscible with chloroform and ether. Physical and chemical properties of safrole are listed in the following table.

Property	Information
Molecular weight	162.2[a]
Density	1.1 g/cm^3 at 20°C[a]
Melting point	11.2°C[a]
Boiling point	234.5°C[a]
Log K_{ow}	3.45[b]
Water solubility	0.121 g/L at 25°C[b]
Vapor pressure	0.0618 mm Hg at 25°C[b]

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

Use

Safrole has been used as a flavoring agent in drugs and in the manufacture of heliotropin, perfumes, soaps, and piperonyl butoxide (a compound used in a variety of insecticides to enhance the pesticidal properties of other active ingredients) (IARC 1972, 1976, HSDB 2009). Safrole has also been used as a preservative in mucilage and library paste and as a flotation frother. Oil of sassafras, which contains safrole, was formerly used to flavor some soft drinks, such as root beer. However, this use or any other addition of safrole or oil of sassafras to food was banned in the United States in 1960 (IARC 1972, 1976, HSDB 2009). Safrole has also been used in the illicit production of the drug 3,4-methylenedioxymethamphetamine (MDMA, or ecstasy), and the U.S. Drug Enforcement Administration has designated safrole a List I Chemical (DEA 2004, 2009).

Production

Safrole is produced by distillation of oils rich in safrole (IARC 1976). U.S. production of safrole was 257,000 lb in 1969 and 277,000 lb in 1970, but had fallen to 12,000 lb by 1977 (IARC 1976, HSDB 2009). In 2009, safrole was available from 11 U.S. suppliers (ChemSources 2009). The U.S. Environmental Protection Agency (EPA) reported that U.S. production plus imports of safrole totaled 10,000 to 500,000 lb in 1998 (EPA 2004) and less than 500,000 lb in 2006 (EPA 2009); no other reports on production of safrole were found. U.S. imports of safrole from 1980 to 2005 ranged from 11,000 to 132,000 lb (HSDB 2009, USITC 2009), but no imports were reported for 2017 (USITC 2018). U.S. exports of safrole in 2017 were about 30,000 lb (USITC 2018), similar to exports of about 35,000 lb in 1998 (USITC 2009).

Exposure

The potential routes of exposure to safrole are inhalation, ingestion, and dermal contact (HSDB 2009). Safrole may be ingested in edible spices, including sassafras, cinnamon, nutmeg, mace, star anise, ginger, black and white pepper, and from chewing betel quid; all of these substances contain naturally occurring safrole at low levels (IARC 1976, Archer and Jones 2002, HSDB 2009). Safrole is also present in herbal products derived from the sassafras tree, including the creole herb gumbo filé (Carlson and Thompson 1997). The concentration of safrole can be reduced during the cooking process (Farag and Abo-Zeid 1997). Based on common ingestion patterns, the estimated daily intake of safrole is 0.3 mg (Rietjens *et al.* 2005). Safrole was also identified as a minor constituent of bidi cigarettes (mean concentration = 33 µg per cigarette) (Stanfill *et al.* 2006) and regular tobacco cigarettes (median concentration = 5.2 ng/g of tobacco) (Stanfill and Ashley 1999). Safrole may also be a contaminant of MDMA, of which safrole is a major ingredient (Swist *et al.* 2005).

According to EPA's Toxics Release Inventory, relatively small amounts of safrole have been released to the environment since 1988, mostly as air emissions, except in 1999 and 2001, when a large amount of safrole was released to on-site hazardous-waste landfills or off-site non-hazardous-waste landfills. In 2007, two facilities released a total of 1,000 lb of safrole, each facility releasing roughly half the total (TRI 2009); one facility released the waste to air, and the other to an off-site landfill.

Occupational exposure to safrole may occur by inhalation or dermal contact (HSDB 2009). Health professionals, such as pharmacists, physicians, and nurses, could be exposed during formulation, preparation, administration, or clean-up of drugs containing safrole or sassafras. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 6,475 workers, including 5,761 women, potentially were exposed to safrole (NIOSH 1990).

Regulations

Drug Enforcement Administration (Dept. of Justice)

Safrole is listed as a Class I chemical, and manufacturers, distributors, importers and exporters are subject to record-keeping, reporting, and other requirements, as prescribed in 21 CFR 1309, 1310, and 1313.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of safrole = U203.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA, an HHS agency)

Safrole is prohibited from direct addition to food or use as human food.

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