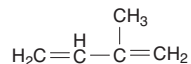


## Isoprene

### CAS No. 78-79-5

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)



### Carcinogenicity

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

#### Cancer Studies in Experimental Animals

Exposure to isoprene by inhalation caused tumors at several different tissue sites in mice and rats. In mice of both sexes, isoprene caused blood-vessel cancer (hemangiosarcoma) and benign or malignant tumors of the Harderian gland (adenoma or carcinoma) and the lung (alveolar/bronchiolar adenoma or carcinoma). In male mice, it also caused cancer of the hematopoietic system (histiocytic sarcoma) and benign or malignant tumors of the liver (hepatocellular adenoma or carcinoma) and forestomach (squamous-cell papilloma or carcinoma). In rats of both sexes, isoprene caused benign or malignant tumors of the mammary gland (fibroadenoma or carcinoma) and kidney (renal-cell adenoma or carcinoma). In male rats, it also caused benign tumors of the testis (adenoma) (NTP 1995, Placke *et al.* 1996, Melnick and Sills 2001).

#### Studies on Mechanisms of Carcinogenesis

Isoprene is the 2-methyl analogue of 1,3-butadiene, an industrial chemical that has been identified as a carcinogen in humans and experimental animals (Gervasi *et al.* 1985, NTP 1999a,b). The isoprene analogue isopentenyl pyrophosphate is a building block of cholesterol synthesis, and levels of exhaled isoprene correlate with cholesterol synthesis (IARC 1994, Rieder *et al.* 2001). Isoprene and butadiene are metabolized to monoepoxide and diepoxide intermediates by liver microsomal cytochrome P450-dependent monooxygenases from several species, including humans (Gervasi *et al.* 1985, IARC 1994, NTP 1999a). These intermediates may be detoxified by hydrolysis (catalyzed by epoxide hydrolase) or conjugation with glutathione (catalyzed by glutathione S-transferase).

The diepoxide intermediates of isoprene and butadiene caused mutations in *Salmonella typhimurium*, whereas the monoepoxides of isoprene and parent compounds did not. In mammalian cells *in vitro*, isoprene did not cause sister chromatid exchange, chromosomal aberrations, or micronucleus formation (NTP 1995, 1999a), but did cause DNA damage in human peripheral-blood mononuclear cells and human leukemia cells when incubated with microsomal enzymes (Fabiani *et al.* 2007). In mice exposed *in vivo*, isoprene and 1,3-butadiene caused sister chromatid exchange in bone-marrow cells and micronucleus formation in peripheral-blood erythrocytes (Tice 1988, Tice *et al.* 1988). Sites at which both isoprene and butadiene caused tumors in rodents include the liver, lung, Harderian gland, forestomach, hematopoietic tissue, and circulatory system in mice and the mammary gland, kidney, and testis in rats (NTP 1999a,b). Harderian-gland tumors caused by isoprene in mice had a high frequency of unique mutations of the *K-ras* protooncogene (A to T transversions at codon 61) (Hong *et al.* 1997).

There is no evidence to suggest that mechanisms by which isoprene causes tumors in experimental animals would not also operate in humans.

#### Cancer Studies in Humans

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

### Properties

Isoprene is structurally similar to 1,3-butadiene and exists as a colorless, volatile liquid at room temperature (NTP 1999a). It occurs frequently in nature and is emitted to the environment by plants and trees. Isoprene is practically insoluble in water, but is soluble in ethanol, diethyl ether, benzene, and acetone. It is stable under normal conditions, but it is very flammable and will polymerize vigorously or decompose with abrupt changes in temperature or pressure (IARC 1994, Akron 2009). Physical and chemical properties of isoprene are listed in the following table.

Property	Information
Molecular weight	68.1
Specific gravity	0.681 at 20°C/4°C
Melting point	-145.95°C
Boiling point	34.07°C at 760 mm Hg
Log $K_{ow}$	2.42
Water solubility	0.642 g/L at 25°C
Vapor pressure	550 mm Hg at 25°C
Vapor density relative to air	2.4

Source: HSDB 2009.

### Use

The majority of isoprene produced commercially is used to make synthetic rubber (*cis*-polyisoprene), most of which is used to produce vehicle tires. The second- and third-largest uses are in the production of styrene-isoprene-styrene block polymers and butyl rubber (isobutene-isoprene copolymer) (IARC 1994).

### Production

Isoprene is recovered as a by-product of thermal cracking of naphtha or gas oil from  $C_5$  streams (IARC 1994, NTP 1999a). The isoprene yield is about 2% to 5% of the ethylene yield. U.S. demand for isoprene grew 6.5% annually from 1985 to 1992 (NTP 1999a). In 1994, isoprene production in the United States was about 619 million pounds, almost 29% more than in 1992. Estimated isoprene production capacity for eight facilities was 598 million pounds in 1996, based on estimates of isoprene content of product stream available from ethylene production via heavy liquids. In 2009, isoprene was produced by 22 manufacturers worldwide, including 12 U.S. producers (SRI 2009), and was available from 23 suppliers, including 12 U.S. suppliers (ChemSources 2009). U.S. imports of isoprene (purity  $\geq$  95% by weight) increased from zero in 1989 to a peak of 144 million pounds in 2003. Imports declined to 19.6 million pounds in 2004, the lowest level since 1992, but remained near 32 million pounds from 2005 through 2008. During this period, U.S. exports of isoprene ranged from 7.9 million to 39.6 million pounds (in 2006) (USITC 2009). Reports filed from 1986 to 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of isoprene totaled 100 million to 500 million pounds (EPA 2004).

### Exposure

Isoprene is formed endogenously in humans at a rate of 0.15  $\mu\text{mol/kg}$  of body weight per hour, equivalent to approximately 2 to 4 mg/kg per

day (Taalman 1996), and is the major hydrocarbon in human breath (accounting for up to 70% of exhaled hydrocarbons) (Gelmont *et al.* 1981). Concentrations in human blood range from 1.0 to 4.8 µg/L (Cailleux *et al.* 1992). Isoprene is produced at higher rates in males than females. The rate of isoprene production increases with age up to the age of 29 (Lechner *et al.* 2006); it is lower in young children than adults by a factor of about 2.4 (Taucher *et al.* 1997). In a study of 30 adult volunteers, the mean isoprene concentration measured in alveolar breath was 118 ppb, with a range of 0 to 474 ppb (Turner *et al.* 2006). After 20 to 30 minutes of exercise, isoprene concentration in exhaled air decreased to a range of 0 to 40 ppb (Senthilmohan *et al.* 2000). Smoking one cigarette increased the concentration of isoprene in exhaled air by 70% (Senthilmohan *et al.* 2001). Isoprene is also produced endogenously by other animals. Production rates reported for rats and mice were 1.9 and 0.4 µmol/kg of body weight per hour, respectively (Peter *et al.* 1987).

Foods of plant origin would be expected to be a source of daily exposure to isoprene, since isoprene is emitted by agricultural crops and is the basic structural unit in countless natural products found in foods, such as terpenes and vitamins A and K (NTP 1999a). Isoprene has been reported to occur in the essential oil of oranges, the fruit of hops, carrot roots, and roasted coffee (Taalman 1996, NTP 1999a).

Isoprene is emitted from plants and trees and is present in the general environment at low concentrations (Taalman 1996). Isoprene emissions from many types of plants have been estimated under various climatic conditions, to evaluate their importance in global climate change (Mayrhofer *et al.* 2004, Parra *et al.* 2004, Schnitzler *et al.* 2004, 2005, Pegoraro *et al.* 2005, Sasaki *et al.* 2005, Sharkey 2005, Moukhtar *et al.* 2006, Simon *et al.* 2006, Tambunan *et al.* 2006). Annual global isoprene emissions, estimated at 175 billion to 503 billion kilograms (386 billion to 1,109 billion pounds), account for an estimated 57% of total global natural volatile organic compound emissions (Guenther *et al.* 1995). The average biogenic emission rate factor for isoprene in U.S. woodlands is 3 mg/m<sup>2</sup> per hour (compared with 5.1 mg/m<sup>2</sup> for total volatile organic compounds) (Guenther *et al.* 1994). Isoprene concentrations in biogenic emissions range from 8% to 91% of total volatile organic compounds, averaging 58%. Because isoprene biosynthesis is associated with photosynthesis, isoprene emissions are negligible at night (Lamb *et al.* 1993). Because isoprene is emitted primarily by deciduous trees, emissions are seasonal, being highest in the summer and lowest in the winter (Guenther *et al.* 1994, Fuentes and Wang 1999). The south central and southeastern areas of the United States have the highest biogenic emissions (Lamb *et al.* 1993, Guenther *et al.* 1994). The half-life of atmospheric isoprene has been estimated at 0.5 hours by reaction with nitric oxide, 4 hours by reaction with hydroxyl radicals, and 19 hours by reaction with ozone (HSDB 2009).

Anthropogenic sources of isoprene in the atmosphere include ethylene production by cracking naphtha, wood pulping, oil fires, wood-burning stoves and fireplaces, other biomass combustion, tobacco smoking (200 to 400 µg per cigarette), gasoline, and exhaust from turbines and automobiles (Adam *et al.* 2006, HSDB 2009). Isoprene has been measured as one of the volatile organic compounds in the ambient air in regions with industrial pollution, and in urban, residential, and rural areas as an indicator of the potential for ozone formation. Thus, isoprene is a key indicator for regional air quality, as well as being a component of the global carbon cycle (Borbon *et al.* 2004, Guo *et al.* 2004, Kuster *et al.* 2004, Warneke *et al.* 2005, Helten *et al.* 2006).

The reported concentration of isoprene in U.S. ambient air ranges from 1 to 21 parts per billion carbon (ppbC) and generally is less than 10 ppbC. Isoprene accounts for less than 10% of non-methane hydro-

carbons in ambient air. Biogenic hydrocarbons may contribute more to total atmospheric hydrocarbons under stagnant atmospheric conditions (Altschuller 1983, Hagerman *et al.* 1997). The major sources of isoprene in ambient air appear to be biogenic emissions at rural sites and vehicular emissions in urban areas (Borbon *et al.* 2001, So and Wang 2004). Where the source is primarily biogenic, the isoprene concentration slowly increases during the day, reaching a peak in the middle of the day, when photosynthesis is greatest. Where vehicular emissions are the primary source, the isoprene concentration peaks during the morning and evening rush hours and is low in the middle of the day (Borbon *et al.* 2002). One study concluded that in summer, at least 80% of the isoprene at a rural site was due to biogenic emissions, but that in winter, more than 90% of residual isoprene was from urban air-mass mixing (Borbon *et al.* 2004). Where industrial emissions are the primary source of isoprene, the concentration may peak at night, or there may be no peak at all (Zhao *et al.* 2004, Chiang *et al.* 2007).

The primary source of isoprene in indoor air is environmental tobacco smoke. Isoprene was found to be the major component of hydrocarbons in the air of a smoky café (10 patrons smoking, 10 not smoking) (16.7%) and in sidestream smoke (29.2%) (Barrefors and Petersson 1993). A monitoring survey in November 1992 in homes and workplaces in the greater Philadelphia area found mean isoprene concentrations in personal air samples of 4.65 µg/m<sup>3</sup> in 60 nonsmoking homes, 18.15 µg/m<sup>3</sup> in 29 homes with smokers, 5.29 µg/m<sup>3</sup> in 51 nonsmoking workplaces, and 22.80 µg/m<sup>3</sup> in 28 workplaces that allowed smoking (Heavner 1996). A survey in the Lower Rio Grande Valley of Texas reported a median summertime isoprene concentration of 2.90 µg/m<sup>3</sup> for three indoor air samples (it was not reported whether the occupants were smokers or nonsmokers), compared with 0.40 µg/m<sup>3</sup> for three outdoor air samples (Mukerjee 1997).

Air-monitoring data were collected at three U.S. facilities that produced isoprene monomers or polymers; 98.5% of the samples showed concentrations of less than 10 ppm, and 91.3% of less than 1 ppm (Leber 2001, Lynch 2001). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 58,000 workers in over 30 industries potentially were exposed to isoprene (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated in a more limited survey that 3,700 workers in four industries, including 578 women, potentially were exposed to isoprene (NIOSH 1990).

## Regulations

### **Coast Guard, Department of Homeland Security**

Minimum requirements have been established for safe transport of isoprene on ships and barges.

### **Department of Transportation (DOT)**

Isoprene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

### **Environmental Protection Agency (EPA)**

#### *Clean Air Act*

*New Source Performance Standards:* Manufacture of isoprene is subject to certain provisions for the control of volatile organic compound emissions.

*Prevention of Accidental Release:* Threshold quantity (TQ) = 10,000 lb.

#### *Clean Water Act*

Isoprene has been designated a hazardous substance.

#### *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.

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