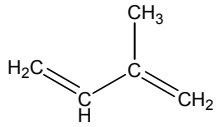
ISOPRENE
CAS No. 78-79-5
First Listed in the *Ninth Report on Carcinogens*



CARCINOGENICITY

Isoprene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of tumor formation at multiple organ sites in multiple species of experimental animals (Melnick *et al.* 1994, NTP 1995, 1997, Placke *et al*. 1996). Inhalation exposure of mice to isoprene vapor induced increased incidences of neoplasms of the lung, liver, harderian gland, forestomach, hematopoietic system, and circulatory system. Inhalation exposure of rats to isoprene vaporsinduced increased incidences of neoplasms of the mammary gland, kidney, and testis (IARC1999).

No adequate human studies of the relationship between exposure to isoprene and human cancer have been reported.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Isoprene is the 2-methyl analog of 1,3-butadiene, an industrial chemical that has been identified as an animal and human carcinogen. Isoprene and butadiene are metabolized to monoepoxide and diepoxide intermediates by liver microsomal cytochrome P450-dependent monooxygenases from several species, including humans. Detoxification of these intermediates may occur by hydrolysis catalyzed by epoxide hydrolase or conjugation with glutathione catalyzed by glutathione-*S*-transferase. The diepoxide intermediates of isoprene and butadiene are mutagenic in *Salmonella typhimurium*, whereas the parent compounds are inactive (Gervasi *et al*. 1985). In mice, isoprene and 1,3-butadiene induced sister chromatid exchanges in bone marrow cells and increased the frequency of micronucleated erythrocytes in peripheral blood (Tice *et al*. 1987, Tice *et al*. 1988). Common sites of neoplasm induction by isoprene and butadiene include the mammary gland and testis in rats, and the liver, lung, harderian gland, forestomach, and circulatory system in mice (NTP 1997). Lung and harderian gland neoplasms induced by isoprene in mice had a high frequency of unique K-*ras* mutations (A to T transversions at codon 61) (Hong *et al*. 1997).

No data were available that would suggest that mechanisms thought to account for tumor induction by isoprene in experimental animals would not also operate in humans.

PROPERTIES

Isoprene is a colorless liquid that is soluble in ethanol and diethyl ether (Budavari 1996, HSDB 2000). Isoprene is highly flammable and is easily ignited by heat, sparks, or flames. Vapors may form highly explosive mixtures with air and may polymerize explosively when

heated. It is highly reactive, with reactions similar to those of 1,3-butadiene. In the absence of inhibitors, isoprene forms peroxides upon air exposure (HSDB 2000, Saltman 1985).

Isoprene is one of the major photochemically reactive hydrocarbons emitted by numerous plant species (Bowling *et al*. 1998). The large quantities of non-methane hydrocarbons (NMHCs) emitted by vegetation, especially in tropical and subtropical regions, influence atmospheric processes. Isoprene and other highly reactive natural alkenes can serve as precursors to formation of photochemical oxidants that contribute to regional-scale air pollution (Hoffman *et al*. 1996). Isoprene, the monoterpenes, and other unsaturated hydrocarbons react with hydroxyl radicals ($HO^{\cdot}$) and tropospheric ozone (O_3) and may act as photochemical smog precursors. The lifetime of atmospheric isoprene has been variably estimated to be 1.3 to 34.0 hours and 1 to 2 hours based on its rates of reactions with ozone and hydroxyl radicals (Altschuller 1983, Guenther *et al*. 1995). In sunlight, ultraviolet irradiation of isoprene, other biogenic NMHCs, and anthropogenic hydrocarbons in the presence of atmospheric nitrogen oxide gives numerous reaction products, including acetaldehyde, acetone, carbon dioxide, carbon monoxide, formaldehyde, formic acid, and peroxyacetyl nitrates (PAN). These products plus methacrolein and methyl vinyl ketone, which are apparently specific to isoprene, represent 30 to 73% of the carbon content of the reacted isoprene (Altschuller 1983).

USE

Approximately 95% of isoprene production is used to produce *cis*-1,4-polyisoprene; 2%, to produce butyl rubber (isobutene-isoprene copolymer); and 3%, to produce thermoplastic, elastomeric co-block (SIS) polymers (Saltman 1985, Taalman 1996).

PRODUCTION

Isoprene is recovered from C_5 streams as a by-product of thermal cracking of naphtha or gas oil. The isoprene yield is approximately 2 to 5% of the ethylene yield (Saltman 1985). U.S. demand for isoprene grew 6.5% annually from 1985 to 1992 (Chem. Mark. Rep. 1994, Chem. Week 1994). In 1994, isoprene production in the United States was approximately 619 million lb (281,000 Mg [metric tons]) (USITC 1995), an increase of almost 29% over production in 1992 (USITC 1994). Estimated isoprene production capacity for 8 facilities was 598 million lb in 1996, based on estimates of isoprene content of product stream available from ethylene production via heavy liquids (SRI 1997). Chem Sources (2001) identified 24 U.S. suppliers of isoprene.

U.S. imports of isoprene (purity of 95% or more by weight) totaled 21.2 million lb in 2000 (ITA 2001). Imports for 1984 were reported to be 11.3 million lb. In 1984, estimated U.S. exports of isoprene (purity of 95% or more by weight) were 12.4 million lb (HSDB 2000). Exports for 2000 increased to 37.2 million lb (ITA 2001).

EXPOSURE

Isoprene is formed endogenously in humans and is generally the major hydrocarbon (up to 70% in human breath) (Gelmont *et al*. 1981). Concentrations in blood range from 15 to 70 nmol/L (1.0 to 4.8 µg/L) (Cailleux *et al*. 1992). Humans produce isoprene endogenously at a rate of 0.15 µmol/kg/h, equivalent to approximately 17 mg/day for a 150-lb (70-kg) person (Taalman 1996). Endogenous production rates reported for rats and mice are 1.9 and 0.4

µmol/kg/h, respectively (Peter *et al*. 1987). Ambient air concentrations of isoprene are generally less than 10 ppb or approximately 0.03 mg isoprene/m^3. Based on estimated human intake of 15 to 20m^3 air per day, ambient air would contribute less than 0.45 to 0.6 mg/day to daily isoprene exposure.

NIOSH collected data on potential exposure to isoprene in the National Occupational Hazard Survey (NOHS) from 1972 to 1974 (NIOSH 1976) and in the National Occupational Exposure Survey (NOES) from 1981 to 1983 (NIOSH 1990). The first survey (NIOSH 1976) indicated that 58,000 employees in over 30 different industries were potentially exposed to isoprene. The more limited later survey of six industries showed that approximately 3,700 workers were potentially exposed to isoprene between 1981 and 1983 (NIOSH 1990).

Isoprene is emitted from plants and trees and is widely present in the environment at low concentrations (Taalman 1996). Isoprene global emissions, estimated at 175 to 503 million Mg per year, represent approximately 44 to 51% of total global natural volatile organic compound emissions (Guenther *et al*. 1995). The average biogenic emission rate factor for isoprene in the United States is approximately 3 mg /m^2/h. Isoprene concentrations in biogenic emissions range from 8% to 91% of total VOCs, with a 58% average. Since isoprene biosynthesis is associated with photosynthesis, isoprene emissions are negligible at night (Guenther *et al*. 1994). The south central and southeastern areas of the United States have the highest biogenic emissions. Summertime isoprene emissions are highest in each region and account for more than 50% of annual biogenic emissions (Lamb *et al*. 1993).

Sources of anthropogenic releases of isoprene to the atmosphere include ethylene production by cracking naphtha, wood pulping, oil fires, wood-burning stoves and fireplaces, other biomass combustion, tobacco smoking (3,100 µg/cigarette), gasoline, and exhaust of turbines and automobiles (HSDB 2000).

Reported U.S. ambient air concentrations of isoprene range from 0.003 to 0.06 mg/m^3 (1 to 21 ppb), with isoprene representing less than 10% of NMHCs (Arnts and Meeks 1980, Altschuller 1983, Lawrimore and Aneja 1997, Hagerman *et al*. 1997). During stagnation conditions, biogenic hydrocarbons may contribute more to total atmospheric hydrocarbons (Altschuller 1983).

Foods of plant origin would be expected to be a source of daily exposure to isoprene since it 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 (IARC 1994). Its occurrence has been reported in the essential oil of oranges, in the fruit of hops, and in the root of carrots (Duke 1992).

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 cafÈ (10 smoking patrons, 10 not smoking) (16.7%) and 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^3 in nonsmoking homes (n = 60), 18.15 µg/m^3 in smoking homes (n = 29), 5.29 µg/m^3 in nonsmoking workplaces (n = 51), and 22.80 µg/m^3 in smoking workplaces (n = 28). Differences in isoprene concentrations in personal air between nonsmoking and smoking sites were highly significant (Heavner *et al*. 1996). Another survey reported median summertime isoprene concentrations of 2.90 µg/m^3 in indoor air (n = 3; no information on whether occupants were smokers or nonsmokers) compared to 0.40 µg/m^3 in outdoor air (n = 1) in the Lower Rio Grande Valley of Texas (Mukerjee *et al*. 1997).

REGULATIONS

EPA regulates isoprene under the Clean Air Act (CAA) and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Under the CAA, it is listed as a regulated flammable substance with a threshold quantity for accidental release prevention of 10,000 lb. Under CERCLA, a final reportable quantity (RQ) of 100 lb (45.4 kg) for the compound has been established.

FDA regulates isoprene as an indirect food additive in paper and paperboard components, in polymers, and in adjuvants, production aids, and sanitizers.

OSHA regulates isoprene under the Hazard Communication Standard and as a hazardous chemical in laboratories. Regulations are summarized in Volume II, Table 99.

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