ISOPRENE

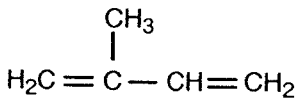
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: *78-79-5*
Deleted CAS Reg. No.: 78006-92-5
Chem. Abstr. Name: 2-Methyl-1,3-butadiene
IUPAC Systematic Name: 2-Methyl-1,3-butadiene
Synonyms: Isopentadiene; β-methylbivinyl; 2-methylbutadiene; 3-methyl-1,3-butadiene

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_5H_8 Relative molecular mass: 68.12

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid or gas with faint aromatic odour (Exxon Chemical Co., 1989; Weitz & Loser, 1989)

(*b*) *Boiling-point*: 34 °C (Lide, 1991)

(*c*) *Melting-point*: –146 °C (Lide, 1991)

(*d*) *Density (liquid)*: 0.6810 at 20 °C/4 °C (Lide, 1991)

(*e*) *Spectroscopy data*: Infrared [prism (688); grating (154)], ultraviolet and mass spectral data have been reported (Weast & Astle, 1985; Sadtler Research Laboratories, 1991; US National Library of Medicine, 1993a).

(*f*) *Solubility*: Insoluble in water (0.029 mol%); soluble in acetone, benzene, diethyl ether and ethanol (Lide, 1991)

(*g*) *Volatility*: Vapour pressure, 60.7 kPa at 20 °C (Weitz & Loser, 1989); relative vapour density (air = 1), 2.35 (Exxon Chemical Co., 1989)

(*h*) *Stability*: Lower explosive limit, 1–1.5% (28–40 g/m^3) (Weitz & Loser, 1989); will ignite readily at ambient temperatures; will polymerize vigorously or decompose with shocks of pressure or temperature (Exxon Chemical Co., 1989)

(*i*) *Octanol–water partition coefficient (P)*: log P, 2.30 (US National Library of Medicine, 1993a)

(*j*) *Conversion factor*: $mg/m^3 = 2.79 \times ppm^a$

1.1.4 *Technical products and impurities*

Isoprene is available commercially at a minimal purity of 99.0%; minor contaminants include acetylenes, cyclopentadiene, peroxides, piperylenes, pentenes and sulfur. It is typically inhibited with *para-tert*-butyl catechol (Exxon Chemical Co., undated). Isoprene feedstock recovered from C_5 hydrocarbon refinery mixtures contains about 20% isoprene (Chevron Chemical Co., undated).

1.1.5 *Analysis*

The US Environmental Protection Agency has proposed methods for the analysis of volatile 'priority pollutants' in water [EPA Method 624] by gas chromatography–mass spectrometry and purge-and-trap techniques. Isoprene, at a detection limit of 3 μg/L, was one of the compounds studied (Spingarn *et al.*, 1982).

A method for the analysis of volatile organic compounds in air samples involves gas chromatography with flame ionization detection and coupled fused silica capillary columns of different polarity and length in order to separate the complex mixtures. Isoprene was detected by this method in atmospheric and alveolar air samples from exposed workers (Clair *et al.*, 1991).

A method for the collection and assay of volatile compounds, including isoprene, in breath involves drawing a sample through a water trap, then through an adsorptive trap of graphitized carbon. The sample is eluted by thermal desorption, concentrated by two-stage cryofocusing, then assayed by gas chromatography with flame ionization and flame photometric detection (Phillips & Greenberg, 1991).

An analytical method for the determination of non-methane hydrocarbons, including isoprene, in air makes use of gas chromatography and simultaneous programming of pressure and temperature on a capillary column. A combination of on-column cryofocusing and gas chromatographic reinjection was used, with a detection limit of 2 pg (Matuška *et al.*, 1986).

1.2 Production and use

1.2.1 *Production*

Isoprene was first isolated in 1860 during the pyrolysis of natural rubber. The reverse reaction, polymerization of isoprene to poly(*cis*-1,4-isoprene), which has a structure corresponding to that of natural rubber, was the subject of intensive effort. The first successful attempts were reported in 1954 and 1955 by the Goodrich Gulf (using an

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[a]Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101.3 kPa)

aluminium–titanium Ziegler catalyst) and Firestone companies (using an alkyl lithium catalyst). Isoprene was commonly prepared on a laboratory scale by thermolysis of turpentine oil (the so-called isoprene lamp). Pyrolysis of dipentene (limonene) was used in the USA early in the Second World War as a commercial source of isoprene (Bibb process). Isoprene itself was of no commercial importance until after the Second World War, when cost-effective methods were developed for obtaining it from petrochemical sources (Weitz & Loser, 1989).

The first commercial synthesis of isoprene, the Goodyear Scientific Design isoprene synthesis, begins with dimerization of propylene to 2-methyl-1-pentene. This is then isomerized to 2-methyl-2-pentene, which is subsequently cracked with loss of methane to give isoprene. The most frequently used synthetic procedure is acid-catalysed addition of formaldehyde to isobutene (Prins reaction). Production facilities of this type are currently in operation in Japan and the former USSR (Weitz & Loser, 1989).

One-step dehydrogenation of isopentane to isoprene can be carried out according to the Houdry–Catadiene procedure (chromic oxide–aluminium oxide catalyst, about 600 °C, and about 7 kPa), with a yield of 52%. Isoprene is prepared commercially in this way in the former USSR. It has been produced by dehydrogenation of methylbutenes in the USA and the Netherlands (Weitz & Loser, 1989).

The primary source of isoprene today is as a by-product in the production of ethylene by naphtha cracking. A solvent extraction process very similar to that for 1,3-butadiene is used. The yield of isoprene is typically 2–5 wt% based on ethylene, although it may be increased by starting with a heavier raw material such as gas oil. With regard to energy consumption, recovery of isoprene from crack fractions is considerably more efficient than synthesizing the compound chemically. Increasingly heavier raw materials are being used in Europe and the USA for ethylene production in crackers, thereby increasing the quantity of isoprene by-product. The most appropriate solvents for production-scale separation of isoprene from other hydrocarbons include *N*-methylpyrrolidone, dimethylformamide and acetonitrile (Weitz & Loser, 1989; Bouton, 1992).

Information available in 1991 indicated that isoprene was produced by five companies in the USA, three in Japan and one each in the Netherlands and the United Kingdom (Chemical Information Services Ltd, 1991). Isoprene is produced in large quantities at several locations in the former USSR, which has a capacity of about 1000 thousand tonnes per year (Weitz & Loser, 1989). Production of isoprene in the USA was 230 thousand tonnes in 1981, 63 thousand tonnes in 1986 and 214 thousand tonnes in 1991 (US International Trade Commission, 1982, 1987, 1993). Production in Japan was 102 thousand tonnes in 1986 and 76 thousand tonnes in 1992. In western Europe, production in 1992 was approximately 15 thousand tonnes (Smith, 1993).

1.2.2 *Use*

Isoprene is used primarily for the synthesis of isoprene rubber, poly(*cis*-1,4-isoprene), which is used mostly for the production of vehicle tyres (Weitz & Loser, 1989). The second largest market for isoprene has been the manufacture of block polymers containing styrene (styrene–isoprene–styrene, or SIS, polymers), which are especially useful as thermoplastic rubbers and as pressure-sensitive or thermosetting adhesives. Smaller amounts of isoprene

are used in the production of butyl rubber (isobutene–isoprene copolymer). The distinctive features of butyl rubber include its low gas permeability, so that it is used in the construction of hoses and as a liner in tubeless tyres (Weitz & Loser, 1989).

The only chemical reaction of isoprene of commercial importance (other than polymerization) is its conversion to terpenes, e.g. citral, linalool, ionones, myrcene, L-menthol, *N,N*-diethylnerylamine, geraniol and nerolidols, which are used extensively in flavours and fragrances (Weitz & Loser, 1989).

1.3 Occurrence

Isoprene occurs widely in nature at low concentrations. It has been estimated that isoprene emissions from plants (associated with photosynthesis) amount to one-half of the total non-methane hydrocarbon emissions from the biosphere (Loreto & Sharkey, 1993). It is present in roasted coffee, in the gas phase of tobacco smoke (Graedel *et al.*, 1986; Löfroth *et al.*, 1989; Weitz & Loser, 1989), in gasoline and turbine automobile exhausts (Katzman & Libby, 1975; Hampton *et al.*, 1983; Stump & Dropkin, 1985; Graedel *et al.*, 1986), and can be regarded as a precursor of polycyclic aromatic compounds (Weitz & Loser, 1989). Isoprene is the basic structural unit of countless natural products, including natural rubber and the terpenes, and of biologically active important substances such as vitamins A and K (Saltman, 1981) and the steroid sex hormones. The biosynthesis of rubber and other natural products containing the isoprene skeleton proceeds not via isoprene itself, but rather via mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) (Stump & Dropkin, 1985).

1.3.1 *Natural occurrence*

Isoprene is the predominant hydrocarbon emitted by a number of deciduous forest species, including oak, poplar, sycamore and willow (Tingey, 1981; Shaw *et al.*, 1983; Lamb *et al.*, 1984; Isidorov *et al.*, 1985; MacKenzie *et al.*, 1991). It is also found in trace amounts in the emissions of coniferous trees and is a component of the volatile emissions of a number of shrubs, ferns, mosses and grasses (Altshuller, 1983; Winer *et al.*, 1989, 1992). Isoprene emission rates from foliage have been found to be in the range of 2.3–45 μg/g per h. Within forest canopies, the concentrations of isoprene and monoterpenes have been reported to range between [10 and 100 ppb carbon (ppbC)], while concentrations outside the canopy range from [1 to 10 ppbC] (Khalil & Rasmussen, 1992). The mean flux of isoprene from an isolated grove of oak trees was determined in two tracer studies to be 6780 and 8110 $\mu g/m^2$ per h (geometric means) (Lamb *et al.*, 1986).

Isoprene is produced endogenously in humans (see section 4.1).

1.3.2 *Occupational exposure*

The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 indicated that 3700 US employees were potentially exposed occupationally to isoprene (US National Institute for Occupational Safety and Health, 1993). Of this number, 93% were estimated to be exposed to isoprene and 7% to be exposed to materials containing isoprene. The estimate is based on a survey of US companies and did not involve measurements of actual exposures.

Exposures to isoprene may occur during the manufacture of synthetic rubber and elastomers. Only two dated reports of occupational exposures to isoprene have been published. Pigolev (1968) reported area samples averaging 40 mg/m^3 in polymerization and rubber separation shops in Russia. The concentration exceeded 40 mg/m^3 in 48 of 140 air samples, with a maximal level of 52 mg/m^3. In an earlier investigation in a Russian synthetic rubber plant, air concentrations of isoprene ranged from 17 to 28 mg/m^3 in a raw materials shop (mean, 19 mg/m^3), from 4 to 37 mg/m^3 in the polymerization department (mean, 22 mg/m^3) and from 3 to 18 mg/m^3 in the rubber separation department (mean, 8 mg/m^3) (Faustov, 1972).

1.3.3 *Air*

Isoprene enters the atmosphere as emissions from vegetation and emissions formed during wood pulping, biomass combustion and rubber abrasion (Graedel *et al.*, 1986). Emission rates and ambient concentrations measured in various field and laboratory studies have been reviewed (Shaw *et al.*, 1983; Graedel *et al.*, 1986; Lamb *et al.*, 1986, 1987).

The global annual emission of isoprene in 1988 was estimated to be 285 million tonnes (Turner *et al.*, 1991). Zimmerman *et al.* (1978) estimated an annual foliar isoprene emission of 350 million tonnes carbon [400 million tonnes isoprene], and Rasmussen and Khalil (1988) estimated a total annual isoprene emission of 450 million tonnes. The annual biogenic emission of isoprene in tropical Australia was estimated to be about 25 million tonnes carbon [28 million tonnes isoprene] (uncertainty range, 6–100 million tonnes carbon) (Ayers & Gillett, 1988). The biogenic isoprene emission rate for the United Kingdom was estimated to be 2000 tonnes per year for the years 1985 and 1989 (Hewitt & Street, 1992). The total rate of emission of isoprene from deciduous forests in the USA has been estimated to be 4.9 million tonnes per year (Lamb *et al.*, 1987), with the greatest emissions in the summer and with the southeast accounting for approximately 48% of the isoprene emitted (Altshuller, 1983). It has been estimated that 15 million tonnes per year of isoprene are emitted from the entire contiguous USA (Altshuller, 1983).

In studies conducted in US cities, the concentrations of isoprene in ambient air ranged from 0.005 to 90 ppbC [0.003–50 μg/m^3] (Lonneman *et al.*, 1979; Arnts & Meeks, 1981; Winer *et al.*, 1981; Khalil & Rasmussen, 1992; US National Library of Medicine, 1993a). Natural isoprene concentrations in Japan during average wet and clear seasons were 0.56 and 1.9 ppbC [0.31 and 1.1 μg/m^3], respectively. The atmospheric concentrations of isoprene at Auch, France, were 0.088–0.675 ppb by volume (ppbv) [0.25–1.9 μg/m^3] at ground level, 0.017 ppbv [0.05 μg/m^3] at 1160 m altitude and 0.160 ppbv [0.45 mg/m^3] at 270 m; it was not detected at 2900 m (Kanakidou *et al.*, 1989).

Isoprene has been detected in emissions from wood stoves and fireplaces at concentrations ranging from 0.003 to 0.130 ppbC/ppm as CO_2 (Edgerton *et al.*, 1986). In another study, it was detected at a concentration of 7 ppb [20.0 μg/m^3] in woodsmoke (Kleindienst *et al.*, 1986). It was detected at a concentration of 0.46 mg/m^3 in an atmospheric grab sample taken near an oil fire (Perry, 1975; US National Library of Medicine, 1993a) and was detected in five of 10 samples of exhaust from turbojet engines at concentrations ranging from 0.05 to 19.8 ppmC [0.028–11 mg/m^3] (Katzman & Libby, 1975). The average airborne yield of isoprene from cigarette smoke has been estimated to be 3.1 mg/cigarette. Isoprene

levels of 85 and 150 μg/m^3 were determined in two studies of tavern air during normal smoking conditions; the corresponding outdoor air concentrations at the time were 2 and < 1 μg/m^3 isoprene (Löfroth *et al.*, 1989).

1.3.4 *Other*

In a pilot study of pollutants in the breast milk of women living in four urban industrial areas in the USA, isoprene was detected in one of eight samples (Pellizzari *et al.*, 1982). In a pilot study of volatile organic compounds in 224 samples of the exhaled breath of 28 non-smoking volunteers, isoprene was detected in about 50% of the samples at concentrations ranging from 0.2 to 0.6 ng/L (Krotoszynski *et al.*, 1977) (see also p. 221).

1.4 Regulations and guidelines

Most countries have not established standards or guidelines for occupational exposures to isoprene (American Conference of Governmental Industrial Hygienists, 1993; ILO, 1993; UNEP, 1993). The short-term exposure limit in Russia is 40 mg/m^3, and the time-weighted average concentration is 100 mg/m^3 in Poland and 10 mg/m^3 in Bulgaria (ILO, 1993; UNEP, 1993; US National Library of Medicine, 1993b).

The US Food and Drug Administration (1993) permits use of isoprene in certain polymeric products in contact with food.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 40 male B6C3F1 mice, six to eight weeks old, were exposed to 0 (control), 70, 220, 700, 2200 or 7000 ppm [194–19 457 mg/m^3] isoprene (purity, > 99%) vapours by inhalation (whole-body exposure) for 6 h per day on five days a week for six months. At the end of the exposure period, 10 mice per group were killed for gross and microscopic examination. The remaining 30 mice per group were maintained for a recovery period of six months without additional exposure to isoprene. Survival at termination of the study (12 months) was 27, 28, 28, 27, 26 and 21 for the control and exposed groups, respectively. Exposure to isoprene was associated with significant increases in the incidences of tumours at four sites, with the following incidences for control and treated groups: alveolar/bronchiolar adenoma or carcinoma: 2, 2, 1, 5, 10 and 9 ($p < 0.001$, logistic regression trend test); Harderian gland adenoma: 2, 6, 4, 14, 13 and 12 ($p < 0.001$, logistic regression trend test);

hepatocellular adenoma or carcinoma: 7, 3, 7, 15, 18 and 17 ($p < 0.001$, logistic regression trend test); forestomach squamous-cell papilloma or carcinoma: 0, 0, 0, 1, 4 and 6 ($p = 0.02$, incidental tumour test). Non-neoplastic lesions related to treatment included forestomach squamous-cell hyperplasia, lung alveolar hyperplasia, nasal olfactory degeneration and spinal cord degeneration (US National Toxicology Program, 1994).

3.1.2 *Rat*

Groups of 40 male Fischer 344/N rats, six to eight weeks old, were exposed to 0 (control), 70, 220, 700, 2200 or 7000 ppm [194–19 457 mg/m^3] isoprene (purity, > 99%) vapours by inhalation (whole-body exposure) for 6 h per day on five days a week for six months. At the end of the six-month exposure period, 10 rats per group were killed. The incidence of interstitial-cell hyperplasia of the testis was significantly increased in the 7000-ppm exposure group ($p < 0.01$) over that in the controls and other exposure groups (1/10, 1/10, 3/10, 1/10, 3/10 and 10/10). The remaining 30 rats per group were maintained for a recovery period of six months without additional exposure to isoprene. There was no treatment-related effect on body weight or survival. Survival at termination of the study (12 months) was 30, 30, 29, 30, 30 and 30 for the control and exposed groups, respectively. In comparison with the incidence in controls, there was a slight increase ($p = 0.02$, Cochran-Armitage trend test) in the incidence of interstitial-cell adenoma of the testis (3/30 controls *versus* 3/30, 4/30, 7/30, 8/30 and 9/30 treated rats). There was no significant treatment-related increase in any other type of tumour (US National Toxicology Program, 1994). [The Working Group noted the short duration of the study and that the design prevented adequate evaluation of carcinogenic potential. It was also noted that the spontaneous incidence of interstitial-cell tumours of the testis in this strain of rat is high at two years.]

4. Other Data Relevant for an Evaluation of Carcinogenicity and Its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Isoprene is formed endogenously, probably from mevalonic acid (Deneris *et al.*, 1984), a precursor of cholesterol biosynthesis. The endogenous production rate of isoprene was calculated to be 0.15 μmol/kg per h (Hartmann & Kessler, 1990). Concentrations in the blood range between 15 and 70 nmol/L (mean, 37 nmol/L [2.5 ng/ml]) (Cailleux *et al.*, 1992). Isoprene is also found in human breath at concentrations in the range of 10–30 nmol/L (Jansson & Larsson, 1969; DeMaster & Nagasawa, 1978; Cailleux & Allain, 1989). The quantity exhaled per day per individual was estimated to be 2–4 mg (Gelmont *et al.*, 1981).

4.1.2 *Experimental systems*

The rate of endogenous production of isoprene was determined to be 1.9 μmol/kg per h in rats and 1.9 μmol/kg per h in mice (Peter *et al.*, 1987).

1,2-Epoxy-2-methyl-3-butene was the major metabolite of isoprene formed by mouse liver microsomes; 3,4-epoxy-2-methyl-1-butene was a minor metabolite (20%) (Del Monte *et al.*, 1985; see Figure 1). 3,4-Epoxy-2-methyl-1-butene, but not 1,2-epoxy-2-methyl-3-butene, can be further metabolized to isoprene diepoxide. Microsomes from mice and Syrian hamsters showed a six-fold higher maximal metabolic velocity (V_{max}) for the latter reaction than those from rats and rabbits: 1.6 *versus* 0.25 nmol diepoxide/mg protein per min. Pretreatment with phenobarbital increased the V_{max} for this reaction by 3–20 times (Longo *et al.*, 1985).

The maximal metabolic elimination rates estimated from experiments in a closed inhalation system were 130 and 400 μmol/kg per h in male Wistar rats and B6C3F1 mice, respectively. The half-lives of isoprene were 6.8 min in rats and 4.4 min in mice. At atmospheric concentrations above 300 ppm [837 mg/m^3], the rate of metabolism was no longer proportional to concentration (Peter *et al.*, 1987).

Male Fischer 344 rats exposed by nose-only inhalation for 6 h to 8, 260, 1480 and 8200 ppm [23, 738, 4200 and 23 268 mg/m^3] [4-^{14}C]isoprene retained 19, 9, 6 and 5% of the inhaled radioactivity, respectively. About 75% of the retained isoprene radioactivity was excreted in urine within 66 h. Liver, blood and, especially, fat were the tissues that contained most isoprene and metabolites. In the inhalation phase, respiratory tract tissues contained concentrations of volatile metabolites substantially out of proportion to their masses relative to liver and blood, which was interpreted to indicate metabolism in the respiratory tract. Most of the radioactivity in blood (> 85%) was associated with material of low volatility, probably mostly conjugates or tetrols. Between 0.031% (at 8 ppm) and 0.002% (at 8200 ppm) of the inhaled 4-^{14}C label was tentatively identified as isoprene diepoxide. Under the assumption that all radioactive material with the volatility of the diepoxide was indeed the diepoxide, blood diepoxide concentrations of 0.37, 7.4, 15 and 17 mmol/L were derived from 6-h exposures to 8, 260, 1480 and 8200 ppm, respectively (Dahl *et al.*, 1987). A species difference was demonstrated in a two-compartment model of isoprene pharmacokinetics. Both rats and mice exhibited saturation kinetics when exposed to isoprene at concentrations above 300 ppm; however, the V_{max} in mice was determined to be 400 μmol/h per kg, or more than three times that in rats (130 μmol/h per kg), implying that mice are sensitive with regard to isoprene metabolism (Peter *et al.*, 1987).

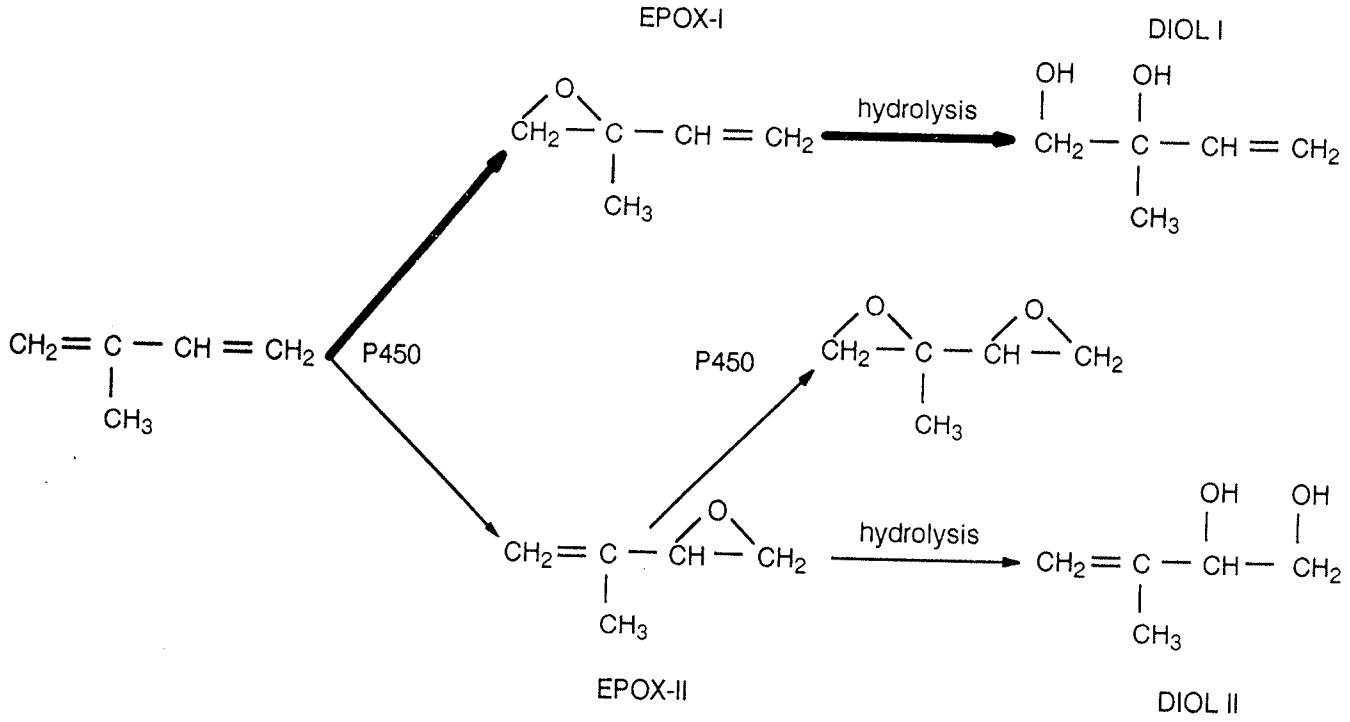
Male B6C3F1 mice exposed to 20, 200 and 2000 ppm [57, 568 and 5675 mg/m^3] ^{14}C-isoprene rapidly reached steady-state levels at which the blood concentrations of isoprene were 24.8, 830 and 6800 ng/ml, respectively (Bond *et al.*, 1991). Radioactivity in haemoglobin, measured 24 h after a single intraperitoneal injection into male Sprague-Dawley rats and male B6C3F1 mice, was linearly related to the administered dose up to 500 μmol/kg and showed the same slope for both species (Sun *et al.*, 1989).

4.2 Toxic effects

4.2.1 *Humans*

Catarrhal inflammation, subtrophic and atrophic processes in the upper respiratory tract, and deterioration of olfaction were noted in isoprene rubber production workers.

Fig. 1. Microsomal metabolic pathways of isoprene



From Gervasi & Longo (1990)
EPOX-I, 1,2-epoxy-2-methyl-3-butene; EPOX-II, 3,4-epoxy-2-methyl-1-butene; P450, cytochrome P450
Major metabolic pathways are indicated by thick arrows and minor pathways by thin arrows.

Prevalence and degree were correlated with increasing length of service (Mitin, 1969; Sandmeyer, 1981).

4.2.2 *Experimental systems*

Exposure of Fischer 344 rats of each sex to 0, 438, 875, 1750, 3500 or 7000 ppm [1222–19 530 mg/m^3] isoprene vapours by inhalation for 6 h a day on five days a week for two weeks had no effect on survival, body weight gain, clinical signs, haematological parameters or clinical chemical measurements and did not produce gross or microscopic lesions. Male B6C3F1 mice, however, had reduced body weight gain, atrophy of the thymus and testis (at 7000 ppm only), olfactory epithelial degeneration (at $\geq$ 1750 ppm), vacuolized liver cytoplasm and forestomach epithelial hyperplasia (at $\geq$ 438 ppm). The last effect was also seen in female mice. In both male and female mice in all exposure groups, there were reductions in erythrocyte numbers, haemoglobin concentrations and volume of packed erythrocytes; the numbers of reticulocytes and polychromatic erythrocytes were not increased (Melnick *et al.*, 1990).

Exposure of male Fischer 344 rats and male B6C3F1 mice to 0, 70, 220, 700, 2200 or 7000 ppm [195–19 530 mg/m^3] isoprene vapours by inhalation for 6 h a day on five days a week for 26 weeks induced exposure-related neoplastic and proliferative lesions in the lung, Harderian gland and forestomach in mice. Interstitial-cell hyperplasia of the testis was induced in rats exposed to 7000 ppm isoprene (US National Toxicology Program, 1994).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

The developmental toxicity of isoprene was reported in abstracts by Mast *et al.* (1989, 1990). Swiss CD-1 mice and Sprague-Dawley rats were exposed to 0, 280, 1400 or 7000 ppm [781–19 530 mg/m^3] isoprene vapour for 6 h per day on seven days per week on days 6–17 (mice) or days 6–19 of gestation (rats). In mice, exposure to 7000 ppm isoprene reduced maternal weight gain, and exposure to any dose reduced fetal body weight. An increase in the incidence of supernumerary ribs was observed at 7000 ppm, but there was no increase in fetal malformations. In rats, there was no adverse effect on the dams or on any reproductive index at any dose level, and there was no increase in the incidence of either fetal malformations or variations, other than reduced ossification of the vertebral centra at 7000 ppm.

4.4 Genetic and related effects (see also Table 1 and Appendices 1 and 2)

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems*

Isoprene did not induce mutation in *Salmonella typhimurium*.

Exposure of male B6C3F1 mice to isoprene by inhalation produced increases in the frequencies of micronuclei in circulating erythrocytes and of sister chromatid exchange in bone-marrow cells, but no chromosomal aberrations were seen.

Neither the major metabolite in mouse liver microsomes, 1,2-epoxy-2-methyl-3-butene, nor an important minor metabolite, 3,4-epoxy-2-methyl-1-butene, was mutagenic to *S. typhimurium* TA98 or TA100. The latter metabolite can be metabolized further to 2-methyl-1,2:3,4-diepoxybutane, which was mutagenic to both strains. This compound may be responsible for the activity of isoprene *in vivo*; it is an analogue of 1,2:3,4-diepoxybutane, which can induce chromosomal aberrations and sister chromatid exchange in mouse bone marrow (Conner *et al.*, 1983; Walk *et al.*, 1987).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Isoprene is produced by dehydrogenation of isopentane or as a by-product in the production of ethylene via naphtha cracking. It is used mainly in the production of isoprene rubber (used in vehicle tyres), block polymers containing styrene (used as thermoplastic rubbers) and pressure-sensitive adhesives and in butyl rubber used for construction of hoses and tyres. Large quantities of isoprene are produced and released into the atmosphere by vegetation. Few data are available on occupational exposure to isoprene.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Isoprene was tested for carcinogenicity in male mice and male rats exposed by inhalation in one-year studies. In mice, exposure to isoprene resulted in increased incidences of benign and malignant tumours of the lung, liver and forestomach and of Harderian gland adenomas. The study by inhalation in rats was inadequate for an assessment of carcinogenicity.

5.4 Other relevant data

Isoprene is formed endogenously and is present in exhaled air from man and rodents. Isoprene concentrations in human blood, from apparently endogenous sources, are approximately one-tenth of the concentrations reached in mouse blood following exposure to 20 ppm [56 mg/m^3] in the atmosphere. At low concentrations, less inhaled isoprene is retained in mice than in rats. Haemoglobin adducts of isoprene can be formed in both mice and rats, but at equal retained doses mice form twice as much haemoglobin adduct as rats. Toxic responses have been observed only in mice. Isoprene can be oxidized sequentially by microsomal enzymes to 2-methyl-1,2:3,4-diepoxybutane.

Table 1. Genetic and related effects of isoprene

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Isoprene				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	680.0000[c]	de Meester *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000.0000	Mortelmans *et al.* (1986)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	0	0.0000	Kushi *et al.* (1985) (abstr.)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	–	–	680.0000[c]	de Meester *et al.* (1981)
SA4, *Salmonella typhimurium* TA104, reverse mutation	–	0	0.0000	Kushi *et al.* (1985) (abstr.)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	680.0000[c]	de Meester *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000.0000	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000.0000	Mortelmans *et al.* (1986)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	680.0000[c]	de Meester *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	680.0000[c]	de Meester *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000.0000	Mortelmans *et al.* (1986)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+		430.0000, inhal. 6 h×12	Tice *et al.* (1988)
MVM, Micronucleus test, mouse peripheral red blood cells *in vivo*	+		430.0000, inhal. 6 h×12	Tice *et al.* (1988)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		6900.0000, inhal. 6 h×12	Tice *et al.* (1988)
Protein binding				
BVP, Binding (covalent) to mouse haemoglobin *in vivo*	+		2.0000×1 ip	Sun *et al.* (1989)
BVP, Binding (covalent) to mouse haemoglobin *in vivo*	+		60.0000, inhal. 6 h	Bond *et al.* (1991)
BVP, Binding (covalent) to rat haemoglobin *in vivo*	+		2.0000×1 ip	Sun *et al.* (1989)
1,2-Epoxy-2-methylbutane				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	0	2600.0000	Gervasi *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	0	2600.0000	Gervasi *et al.* (1985)

Table 1 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
3,4-Epoxy-2-methyl-1-butene				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	0	1300.0000	Gervasi *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	0	1300.0000	Gervasi *et al.* (1985)
2-Methyl-1,2;3,4-diepoxybutane				
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	500.0000	Gervasi *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	0	750.0000	Gervasi *et al.* (1985)

[a] +, positive; –, negative; 0, not tested
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw
[c] Atmospheric concentration

Exposure of mice and rats to isoprene by inhalation had no adverse effect on reproduction.

No data were available on the genetic and related effects of isoprene in humans. Isoprene induced micronuclei in mouse circulating erythrocytes and sister chromatid exchange but not chromosomal aberrations in mouse bone marrow *in vivo*.

Neither isoprene nor its primary metabolites, 3,4-epoxy-2-methyl-1-butene and 1,2-epoxy-2-methyl-3-butene, were mutagenic to bacteria. 2-Methyl-1,2:3,4-diepoxybutane, a metabolite of 3,4-epoxy-2-methyl-1-butene, was mutagenic to *Salmonella typhimurium*.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of isoprene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of isoprene.

Overall evaluation

Isoprene *is possibly carcinogenic to humans (Group 2B).*

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[1]For definition of the italicized terms, see Preamble, pp. 27–30.

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