ISOPRENE

Data were last evaluated in IARC (1994).

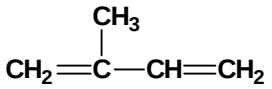
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 78-79-5
Chem. Abstr. Name: 2-Methyl-1,3-butadiene
IUPAC Systematic Name: Isoprene
Synonym: Isopentadiene

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, volatile liquid (Budavari, 1996)
(*b*) *Boiling-point*: 34.0°C (Lide, 1997)
(*c*) *Melting-point*: –149.5°C (Lide, 1997)
(*d*) *Solubility*: Practically insoluble in water; miscible with ethanol and diethyl ether (Budavari, 1996)
(*e*) *Vapour pressure*: 66 kPa at 20°C; relative vapour density (air = 1), 2.35 (Verschueren, 1996)
(*f*) *Flash-point*: –48°C (Lewis, 1993)
(*g*) *Conversion factor:* $mg/m^3 = 2.79 \times ppm$

1.2 Production and use

Production of isoprene in the United States in 1993 was reported to be 276 841 tonnes (United States International Trade Commission, 1994). Production capacities for isoprene in 1987 were estimated to be (thousand tonnes): United States, 199; the Netherlands, 25; Republic of South Africa, 45; Japan, 105; and the former Soviet Union, about 800 (Weitz & Loser, 1989). In 1992, isoprene monomer reportedly was produced in Brazil, the Netherlands, Japan, Romania, countries of the former Soviet Union and the United States (Lybarger, 1995).

Almost all isoprene produced is used in the preparation of polymers and copolymers. cis-Polyisoprene, primarily for vehicle tyres, is the largest application, with styrene–isoprene–styrene (SIS) block polymers being a rapidly growing secondary application. Butyl rubber is a significant third application. World demand for isoprene for monomer use in 1992 was (thousand tonnes): polyisoprene, 827; SIS, 95; butyl rubber, 25; and other uses, 10 (Weitz & Loser, 1989; Lybarger, 1995).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES) in the United States (NOES, 1997), approximately 4000 workers in the United States were potentially exposed to isoprene (see General Remarks). Occupational exposures to isoprene occur mainly in the production of the monomer and of synthetic rubbers.

1.3.2 *Environmental occurrence*

Isoprene occurs in the environment as emissions from vegetation, particularly from deciduous forests, and as a by-product in the production of ethylene by naphtha cracking. In the United States, the total emission rate of isoprene from deciduous forests has been estimated at 4.9 tonnes per year, with greatest emissions in the summer. The global annual emission of isoprene in 1988 was estimated to be 285 000 thousand tonnes. Isoprene is produced endogenously in humans. It has also been found in tobacco smoke, gasoline, turbine and automobile exhaust, and in emissions from wood pulping, biomass combustion and rubber abrasion (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not proposed any occupational exposure limits for isoprene in workplace air. Poland has an 8-h time-weighted average threshold limit value of 100 mg/m^3 and Russia has a short-term exposure limit of 40 mg/m^3 for exposure in workplace air (International Labour Office, 1991)

No international guideline for isoprene in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Isoprene was tested for carcinogenicity in male mice and in male rats by inhalation exposure in one-year studies. In mice, exposure to isoprene resulted in increased incidence 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 (IARC, 1994).

3.1 Inhalation

3.1.1 *Mouse*

Groups of 50 male B6C3F_1 mice [age unspecified] were exposed to isoprene by whole-body inhalation at concentrations of 0, 10, 70, 140, 280, 700 or 2200 ppm [0, 28, 200, 400, 800, 2000 or 6160 mg/m^3] for 4 or 8 h per day on five days per week for 20, 40 or 80 weeks, followed by holding periods until termination of the experiment at 96 or 104 weeks. The isoprene was > 99% pure, containing less than 1% limonene and less than 100 ppm *tert*-butyl catechol. Similar groups of female mice were exposed to 0, 10 or 70 ppm for 80 weeks and held until 104 weeks. All animals received a complete gross necropsy and major tissues and organs were examined histologically. Survival of groups exposed to 280 ppm for 80 weeks or to higher concentrations was less than that of controls and less than 50%. As shown in Table 1, increases in tumour incidence were found in the lung, liver, heart, spleen and Harderian gland in males. In female mice, increased incidence of Harderian gland adenomas (2/49 controls, 3/49 10-ppm and 8/49 ($p < 005$) 70-ppm) and pituitary adenomas (1/49 controls, 6/46 10-ppm and 9/49 ($p < 0.05$) 70-ppm) was seen at the high dose (Cox *et al.*, 1996; Placke *et al.*, 1996).

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, six weeks of age, were exposed to isoprene (> 99% pure) by whole-body inhalation at concentrations 0, 220, 700 or 7000 ppm [0, 614, 1953 or 19 530 mg/m^3] for 6 h per day on five days per week for 104 weeks. Animals received a complete gross examination and major tissues and organs were evaluated histologically. Survival of exposed rats was similar to that of controls (males: control, 18/50; low-dose, 16/50; mid-dose, 15/50; high-dose, 15/50; females: 29/50, 30/50, 28/50, 27/50), and weight gain was not affected by the exposures. Exposed males and females had increased incidences of mammary fibroadenomas (males: control, 2/50; low-dose, 4/50; mid-dose, 6/50; high-dose, 21/50; females, 19/50, 35/50, 32/50, 32/50). The incidence of renal tubule adenomas was increased in treated males (2/50, 4/50, 8/50, 15/50). Some animals also had a renal carcinoma. Treated males also had increased incidence of interstitial-cell adenomas of the testis (33/50, 37/50, 44/50, 48/50) (United States National Toxicology Program, 1997).

Table 1. Summary of isoprene exposure-related neoplasms in male B6C3F$_1$ mice

Group	1	2	3	4	5	6	7	8	9	10	11	12
ppm/weeks	0/80	10/80	70/40	70/80	140/40	280/20	280/80	700/80	2200/20	2200/80	2200/40	2200/80
ppm × weeks[a]	0	800	2800	5600	5600	5600	22 400	5600	22 000	77 000	88 000	176 000
Alveolar/bronchiolar												
Adenoma	11/50	16/50	8/50	4/50	10/50	16/50	13/50	23/50*	14/50	15/50	29/49*	30/50*
Carcinoma	0	1	0	2	1	3	1	7*	2	3	3	7*
Hepatocellular												
Adenoma	11/50	12/50	14/49	15/50	22/50*	18/49	24/50*	27/48*	22/50*	21/50*	28/47*	30/50*
Carcinoma	9	6	11	9	10	12	16	17	12	15	18*	16
Harderian gland												
Adenoma	4/47	4/49	13/48	9/50	12/50*	16/49*	17/50*	26/49*	19/49*	28/50*	31/49*	35/50*
Carcinoma	0	0	0	0	2	3	1	3	1	2	0	2
Haemangiosarcoma												
Heart	0/49	0/50	0/49	0/50	0/50	0/50	2/50	1/50	4/50	1/50	1/49	1/50
Spleen	1/49	3/48	1/47	2/50	3/50	2/47	1/50	2/48	2/48	2/50	0/47	1/49
Histiocytic sarcoma[b]	0/50	2/50	2/50	2/50	1/59	8/50*	4/50	2/50	5/50*	7/50*	7/50*	2/50

From Placke *et al*. (1996) and Cox *et al*. (1996)

[a] Groups 9 and 10 were exposed for 4 h per day instead of 8 h per day

[b] Found in kidney, lung, liver, lymph nodes, bone marrow and spleen

* Incidence significantly greater than in the control group ($p < 0.05$, Fisher's exact test).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Isoprene is formed endogenously at the rate of 0.15 μmol/kg per hour in man. No further data were available to the Working Group (IARC, 1994).

4.1.2 *Experimental systems*

Isoprene is formed endogenously at the rate of 1.9 μmol/kg per hour in both rats and mice. 1,2-Epoxy-2-methyl-3-butene (80%) and 3,4-epoxy-2-methyl-1-butene (20%) are two major metabolites in mouse liver microsomes. The 3,4-epoxide can be further metabolized to isoprene diepoxide. Both rats and mice exhibited saturation kinetics when exposed to isoprene at concentrations above 300 ppm [837 mg/m^3]. The maximal rate of metabolism *in vivo* is more than three times greater in mice than in rats (IARC, 1994).

The most important enzyme converting isoprene to both monoepoxides and also to the diepoxide is CYP2E1, as shown by both recombinant expressed enzymes and in human liver microsomes (Bogaards *et al*., 1996).

Both rat and mouse liver microsomes are able to catalyse the formation of isoprene monoepoxides (Bogaards *et al*., 1996).

4.1.3 *Comparison of human and rodent data*

The intrinsic rates of formation of monoepoxides in human, rat and mouse liver microsomes are roughly similar, when epoxide hydrolase is inhibited, whereas the amount of monoepoxides at the end of incubation is two and even 15 times higher in mouse liver microsomes than in rat and human liver microsomes, respectively (Bogaards *et al*., 1996). Thus, differences in epoxide hydrolase activity between different species may be of importance for toxicological outcomes.

A physiological toxicokinetic model has been developed for inhaled isoprene in mouse, rat and humans, taking into account published or assumed kinetic parameters (Filser *et al*., 1996). On the basis of this model, at human exposure conditions (up to 50 ppm [140 mg/m^3]), rates of metabolism are about 14 times faster in mice and about eight times faster in rats than in humans.

4.2 Toxic effects

4.2.1 *Humans*

Increasing duration of employment of isoprene rubber production workers showed a correlation with the prevalence and degree of various effects (IARC, 1994). Effects noted in these workers were subtrophic and atrophic processes in the upper respiratory tract, catarrhal inflammation, and degeneration of the olfactory tract.

4.2.2 *Experimental systems*

Inhalation exposure to isoprene (0, 438, 875, 1750, 3500 or 7000 ppm [1222–19 530 mg/m^3]) for 6 h per day on five days per week for two weeks did not affect survival, body weight gain, clinical signs or haematological parameters in male or female Fischer 344 rats. However, both male and female B6C3F$_1$ mice exposed under identical conditions had reduced erythrocyte numbers, haemoglobin concentrations and volume of packed erythrocytes, without increases in reticulocytes and polychromatic erythrocytes. In addition, both male and female mice exhibited forestomach epithelial hyperplasia at exposures ≥ 438 ppm. Male B6C3F$_1$ mice exposed to ≥ 1750 ppm had degeneration of the olfactory epithelium, and 7000 ppm isoprene caused reduced body weight gain and atrophy of the thymus and testis in these mice (Melnick *et al*., 1990).

Male Fischer 344 rats and B6C3F$_1$ mice were exposed by inhalation to 0, 70, 220, 700, 2200 or 7000 ppm [195–19 530 mg/m^3] isoprene for 6 h per day on five days per week for 26 weeks and were monitored for a further 26 weeks post-exposure. All exposure doses induced neoplastic and proliferative lesions in the liver, lung, Harderian gland and forestomach of mice. Exposure to 7000 ppm reduced survival in mice. There was an increase in altered hepatocellular foci and incidence of forestomach hyperplasia at doses ≥ 700 ppm [1950 mg/m^3]. At the end of the 26-week recovery period, alveolar epithelial hyperplasia was increased in the 700 ppm and higher-dose groups, alveolar/bronchiolar neoplasms were increased in the ≥ 2200-ppm and 7000-ppm groups and spinal cord degeneration was evident in all dose groups. Rats exposed to ≥ 700 ppm isoprene developed interstitial-cell hyperplasia of the testis (Melnick *et al*., 1994, 1996).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Sprague-Dawley rats and Swiss CD-1 mice were exposed by inhalation to 0, 280, 1400 or 7000 ppm [800–19 530 mg/m^3] isoprene for 6 h per day on seven days per week on gestational days 6–19 (rats) or 6–17 (mice) (IARC, 1994). There was no adverse effect on rat dams or other reproductive index at any dose level. The only fetal malformation observed in rats was reduced ossification of the vertebral centra, which occurred at 7000 ppm isoprene. In mice, there was reduced fetal body weight at all dose levels and decreased maternal weight gain in the 7000-ppm group. Also in the 7000-ppm group, there was an increased incidence of supernumerary ribs but no increase in fetal malformations.

B6C3F$_1$ mice were exposed by inhalation to 0, 70, 220, 700, 2200 or 7000 ppm [200–19 530 mg/m^3] isoprene for 6 h per day on five days per week for 13 weeks. Effects observed in the males were reduction of testicular weight by 35% in the animals exposed to 7000 ppm, seminiferous tubular atrophy in 20% of animals studied, reduced epididymal weights, lower spermatid headcounts and concentrations, and reduced sperm

motility in the 700- and 7000-ppm groups. Female mice in the 7000-ppm group had significantly longer average oestrous cycles (Melnick *et al*., 1994).

Isoprene [7.34 mmol/kg bw by intraperitoneal injection] affected ovarian follicles in 21-day-old $B6C3F_1$ mice. Small (primordial) follicle counts were reduced by 76 ± 5%; while growing (primary to pre-antral) follicle counts were reduced by 46% ± 8% when compared with the respective sesame seed oil controls (Doerr *et al*., 1995).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 2 for references)

Isoprene did not induce mutations in bacteria or, in single studies, either sister chromatid exchangess or chromosomal aberrations in cultures of Chinese hamster ovary cells. An inhalation study with mice demonstrated that isoprene could induce sister chromatid exchanges and micronuclei in bone-marrow cells. No increase in the incidence of chromosomal aberrations was observed in the same study.

Isoprene can be metabolized by mouse liver microsomes to oxirane intermediates, the main metabolite being 1,2-epoxy-2-methyl-3-butene. Neither this metabolite nor 3,4-epoxy-2-methyl-1-butene was mutagenic to *Salmonella typhimurium* TA100 or TA98 when tested up to lethal concentrations (30 mM), whereas another possible minor metabolite, 2-methyl-1,2,3,4-diepoxybutane was mutagenic in *S. typhimurium* TA100. The diepoxide had a high rate of nicotinamide alkylation (Gervasi *et al*., 1985). Isoprene has been shown to bind covalently to haemoglobin in rat and mice *in vivo*.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to isoprene occurs in the production of the monomer and in the production of synthetic rubbers. Isoprene occurs in the environment due to emissions from vegetation and the production of ethylene by naphtha cracking.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Isoprene was tested for carcinogenicity in mice and rats by inhalation exposure. In two studies in mice, exposure to isoprene resulted in increased combined incidences of benign and malignant tumours of the lung and liver and of Harderian gland adenomas. In one study, haemangiosarcomas of the heart and spleen and histiocytic sarcomas were also found in male mice, as well as increased incidences of pituitary adenomas and Harderian

Table 2. Genetic and related effects of isoprene

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	680	de Meester *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	5000	Mortelmans *et al*. (1986)
SA3, *Salmonella typhimurium* TA1530, reverse mutation			680	de Meester *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	680	de Meester *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	5000	Mortelmans *et al*. (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	5000	Mortelmans *et al*. (1986)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	680	de Meester *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	680	de Meester *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000	Mortelmans *et al*. (1986)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	–	–	5000	US National Toxicology Program (1995)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	–	5000	US National Toxicology Program (1995)
SVA, Sister chromatid exchange, B6C3F_1 mouse bone-marrow cells *in vivo*	+		430 inh 6 h/d × 12	Tice *et al*. (1988)
MVM, Micronucleus test, B6C3F_1 mouse bone-marrow cells *in vivo*	+		430 inh 6 h/d × 12	Tice *et al*. (1988)
CBA, Chromosomal aberrations, B6C3F_1 mouse bone-marrow cells *in vivo*	–		6900 inh 6 h/d × 12	Tice *et al*. (1988)
BVP, Binding (covalent) male B6C3F_1 mouse haemoglobin *in vivo*	+		2 ip × 1	Sun *et al*. (1989)
BVP, Binding (covalent) male Sprague-Dawley rat haemoglobin *in vivo*	+		2 ip × 1	Sun *et al*. (1989)
BVP, Binding (covalent) B6C3F_1 mouse haemoglobin *in vivo*	+		60 inh 6 h	Bond *et al*. (1991)

[a] +, positive;–, negative

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw /day; inh, inhalation; ip, intraperitoneal

gland adenomas in female mice. In one adequate study with rats, increased incidences were observed for benign neoplasms in the mammary gland in males and females and in the kidney and testis in males.

5.4 Other relevant data

Both rats and mice exhibited saturation kinetics when exposed to concentrations above 300 ppm [840 mg/m^3]. The maximal rate of metabolism *in vivo*, which occurs via monoepoxides and diepoxide and subsequent epoxide hydration, is more than three times greater in mice than in rats. In-vitro studies and a physiological toxicokinetic model suggest that the rates of metabolism in humans is lower.

At high inhalation exposures, proliferative lesions in olfactory epithelium and lung were observed. Forestomach epithelial hyperplasia was detected at lower exposure levels in rats and mice. Adverse effects in reproductive organs of male and female mice were detected after high inhalation doses.

Isoprene did not induce mutations in bacteria or sister chromatid exchanges or chromosomal aberrations in animal cells *in vitro*. Isoprene induced sister chromatid exchanges and micronuclei in bone-marrow cells after inhalation exposure of mice.

Isoprene binds covalently to haemoglobin *in vivo.*

5.5 Evaluation

No epidemiological data relevant to the carcinogenicity of isoprene were available.

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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