ISOPRENE

Document History
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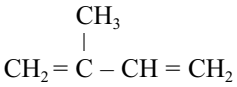
I. IDENTIFICATION

Chemical Name: Isoprene
Synonyms: 2-methyl-1,3-butadiene
CAS Number: 78–79–5
Molecular Formula: C_5H_8
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES

Physical State: Liquid
Molecular Weight: 68.12
Conversion factors: 1 mg/m³ = 0.36 ppm
1 ppm = 2.79 mg/m³
Boiling Point: 34°C (93°F) at 760 mm/Hg
Vapor Pressure: 550 mm Hg at 25°C (77°F)
Saturated Vapor Concentration: 724,000 ppm at 25°C (77°F)
Odor Description and Threshold: Pungent odor; perceptible at less than 5 mg/m³ (1.8 ppm), average approximately 10 mg/m³ (3.6 ppm)
Flammability Limits: 1.5%–8.9%
Flash Point: (Tag Closed Cup): -54C°C (-127°F)[1]
Autoignition Temperature: 395°C (743°F)
Specific Gravity: 0.686 at 15.5°C (60°F)
Vapor Density: 2.35
Solubility in Water: Insoluble
Stability: Unstable; may form explosive peroxides in the presence of oxidizers

III. USES

Isoprene is used in the manufacturing of butyl and synthetic rubber, plastics, and a variety of chemicals.[2]

IV. ANIMAL TOXICITY DATA[2-4]

A. Acute Toxicity

1. *Oral Toxicity*

Rats: LD_{50} greater than 2,000 mg/kg[3] for a distillate cut containing 50% isoprene and 50% 5 paraffins and mono- and diolefins.

Rats: LD_{50} 2043–2210 mg/kg[1]

2. *Eye Toxicity*

Rabbits: slight irritation (approximate Draize score 4/110)[3]

Rabbits: eye irritation score 2.5/110[1]

3. *Skin Toxicity*

a. Irritation

Rabbit: prolonged contact, slight redness; repeated contact, slight chemical burn[3]

Rabbit: irritation score: 3.3/8[1]

b. Absorption

Rabbit: not absorbed in toxic amounts in a 3-day occlusion test[3]

Rabbit: LD_{50} > 7940 mg/kg[1]

c. Sensitization

No data available

4. *Inhalation*

Mice: 2-hr LC_{50}, 139–157 mg/L (50,000–56,500 ppm)[5–7]

Rats: 4-hr LC_{50}, 180 mg/L (64,800 ppm)[5]

Mice: 2-hr, deep CNS depression in 50%, 109 mg/L (39,300 ppm)[7]

Mice: 2-hr LC0 > 20,000 ppm[1]

5. *Other*

No data available

B. Mutagenicity

The National Toxicology Program (NTP) reports negative results for isoprene in the *Salmonella* assay.[8] It also tested negative with and without S-9 activation with the following *Salmonella* strains: TA98, TA100, TA1530, TA1535, TA1538.[9] The monoepoxide metabolites of isoprene were negative in *Salmonella* (strains TA98 and TA100, without S-9). Monoepoxide metabolites of 1,3 butadiene (a structurally similar compound) tested positive (TA100). Diepoxide metabolites of both compounds tested positive in both strains, however, the isoprene diepoxide was formed only via a minor (<20%) metabolic pathway.[10]

Mice exposed to isoprene for 12 days in a 1987 NTP study showed no chromosomal aberrations but did show significant increases in the frequency of sister chromatid exchanges and the number of micronucleated erythrocytes (plateau effect at all doses [440–7000 ppm]).[11] Male mice had no increases in frequency of chromosomal aberrations in bone marrow cells after 12 days of isoprene exposure.[8]

Isoprene did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells with or without exogenous metabolic activation; however, in mice, isoprene induced increases in the frequency of sister chromatid exchanges in bone marrow cells and in the frequency of micronucleated erythrocytes in peripheral blood. The cell cycle duration of proliferating bone marrow cells of mice exposed to 7000 ppm isoprene was significantly lengthened.[8]

Male and female rats exposed to isoprene for 4 weeks showed no increase in the frequency of micronuclei in lung fibroblasts.[8]

C. Metabolism

Dog: Mongrel dogs inhaled 0.4–0.6 µg/mL (144–180 ppm) and retained approximately 65% of the compound after 14 hours.[12]

Rat: Distribution of isoprene following inhalation exposure resulted in the following tissue concentrations: 28.0 mg% spleen, 39.5% mg% brain, 39.6 mg% kidney, 43.3 mg% liver, 178.4 mg% hypodermic fat, and 275.7 mg% perinephric fat.[6] There was a parallel between the toxicity and cerebral concentration.[6,13] Less than 20% of the compound was metabolized via a pathway that could result in the formation of the mutagenic diepoxide in mice.[14] Similar results were seen with rats, rabbits, and hamsters.[15]

D. Developmental/Reproductive Toxicity

Mated female Sprague-Dawley rats (24 to 26 sperm-positive rats/exposure group) and CD-1 Swiss mice (28 to 30 plug-positive mice/exposure group) were exposed to 0, 280, 1400, or 7000 ppm on days 6 through 19 of gestation. No maternal or developmental effects were noted in rats. In mice, male and female fetal body weights decreased with increasing exposure concentration; body weights of male fetuses in the 1400 and 7000-ppm groups and female fetuses in all exposure groups were significantly less than those of controls. An exposure-related increase in the percentage of fetuses per litter with supernumerary ribs was also noted at all dose levels (LOAEL 280 ppm). Table 1 summarizes the reproductive and developmental effects seen in this study.[16]

E. Subacute Toxicity

2 male and 2 female rats exposed to isoprene for 6 hr/day for 15 days at 1670 ppm had no toxic signs, and the necropsy was normal, while another group of 2 male and 2 female rats exposed for 6 hr/day for 6 days at 6000 ppm had lungs that were slightly congested.[17]

F344/N rats and B6C3F_1 mice (10 animals/sex/exposure level) were exposed to isoprene at concentrations of 0, 70, 220, 700, 2200, or 7000 ppm for 6 hours/day for 5 days per week for 12 exposures. No treatment-related changes were observed in survival, body weight gain, clinical

Table 1

Developmental Study NOAELs and LOAELs[16]

Endpoint	Sex and Species	NOAEL/LOAEL
Female (dam) decreased mean body weight	Female mice	280 ppm (LOAEL) All dose groups affected
Female fetus decreased body weights	Female mice	280 ppm (LOAEL) All dose groups affected
Male fetus decreased body weights	Female mice	280 ppm (NOAEL); 1400 ppm (LOAEL)
Fetus increase in # ribs	Male & Female mice	280 ppm (LOAEL) All dose groups affected

signs, hematologic or clinical chemistry parameters, or the incidence of gross or microscopic lesions in rats.

In mice exposed to 0, 70, 220, 700, 1750, 3500, and 7000 ppm, there were no effects on survival. However, the mean body weight of males in the 7000-ppm group was less than that of controls. In addition, exposure of mice to isoprene caused decreases in hematocrit values, hemoglobin concentrations and erythrocyte counts (in all exposure groups), atrophy of the testis and thymus (7000-ppm group), cytoplasmic vacuolization of the liver, olfactory epithelial degeneration in the nasal cavity (1750, 3500 and 7000 ppm, with severity increasing with dose) and epithelial hyperplasia in the forestomach (all levels). Absolute and relative liver weights of male and female mice (all exposure groups) were significantly higher (except males at 438 ppm) and absolute and relative spleen weights were significantly lower (all exposed males, females at 3500 and 7000) when compared to controls. The NOEL for testicular and thymus atrophy in male mice was 3500 ppm, however a NOEL for hematological changes could not be established.[16]

F. Subchronic Toxicity

Rat: Chamber concentration range 0.2–0.6 mg/L (72–216 ppm), 6 hr/day for 6 months: bronchitis; histological changes in lung, liver, heart, and other internal organs.[5]

Rat: Chamber concentration range 2.2–4.9 mg/L (792–1764 ppm) 4 hr/day for 5 months, 11 rats: oxygen consumption decreased.[5]

Mouse and Rabbit: Chamber concentration range 2.2–4.9 mg/L (792–1764 ppm), 4 hr/day for 5 months, 36 mice, 5 rabbits: rabbits exhibited increased leukocytes, slightly decreased erythrocytes, and some increased organ weights (lungs, brain, kidneys).[7]

Rabbit: 0.4 mg/L (144 ppm), 4 hr/day for 4 months: changes in immunological indicators such as lysozyme production and phagocytic activity.[18]

F344/N rats and B6C3F$_1$ mice were exposed to isoprene, 6 hours/day, 5 days/week, for 13 weeks at concentrations of 0, 70, 220, 700, 2200, or 7000 ppm (10 animals/sex/exposure level). No discernible toxicologic effects were seen in rats. In mice, hematologic effects similar to those seen in the 2-week study were seen in all exposed groups. In male mice, absolute and relative testis weights were significantly lower than controls in the 2200 and 7000 ppm groups (NOAEL 700 ppm), absolute and relative liver weights were significantly higher than controls at 7000 ppm (NOAEL 2200 ppm); absolute spleen weights were lower than controls in the 700, 2200 and 7000 ppm groups (NOAEL 220 ppm); relative spleen weights were significantly lower than controls in the 220, 700, 2200, and 7000 ppm exposure groups (NOAEL 70 ppm). In female mice, absolute liver weights were significantly higher than controls at 7000 ppm (NOAEL 2200 ppm); absolute spleen weights were lower than controls in the 700, 2200, and 7000 ppm groups (NOAEL 220 ppm); relative spleen weights were significantly lower than controls at 7000 ppm (NOAEL 2200 ppm).[16]

Microscopic changes were seen in the forestomach, nasal cavity, liver and testis of exposed mice. Epithelial hyperplasia in the forestomach was seen in males and females exposed to 700, 2200, or 7000 ppm (NOAEL 220 ppm); olfactory epithelial

Table 2

Subacute Study NOAELs[16]

Endpoint	Sex and Species	NOAEL
Survival, Body weight gain, clinical signs, hematologic, clinical chemistry, gross or microscopic lesions	Male and female rats	No changes seen (70, 220, 700, 2200, 7000 ppm)
Decreased mean body weight	Male mice	3500 ppm
Testicular Atrophy	Male mice	3500 ppm
Thymus Atrophy	Male and female mice	3500 ppm
Olfactory epithelial degeneration	Male and female mice	700 ppm
Increased liver vacuolization	Male and female mice	700 ppm
Epithelial hyperplasia in forestomach	Male and female mice	All dose groups were affected
Hematological Changes Decreased Hematocrit, Hemoglobin, Erythrocyte counts	Male and female mice	All dose groups were affected

degeneration in the nasal cavity of all males exposed to 7000 ppm; cytoplasmic vacuolization of the liver in males exposed to 2200 or 7000 ppm; and lower epididymal weights, spermatid head counts, sperm concentration and sperm motility in males exposed to 700 or 7000 ppm. Female mice exposed to 7000 ppm had significantly longer estrous cycles than controls.[16]

G. Chronic Toxicity and Carcinogenicity

Isoprene applied to mouse skin 5 times/week for 18 weeks had little or no effect on the number of papillomas in animals treated with a combination of dimethylbenzanthracene and croton resin.[19]

Groups of 50 male and 50 female rats were exposed to 220, 700, or 7000 ppm isoprene by inhalation, 6 hr/day, 5 days/week for 104 weeks. Survival was similar to that of the chamber controls. Mean body weights were similar to those of the chamber controls throughout the study.[8] Exposure-related increases in the incidences of mammary gland fibroadenoma and fibroadenoma or carcinoma (combined) occurred in male rats in all exposed groups. The incidences of mammary gland fibroadenomas in 7000-ppm males and all groups of exposed females were significantly greater than those in the chamber control groups. The incidences of mammary gland fibroadenoma in all exposed groups of males and females and of multiple fibroadenoma in 7000-ppm males and in all groups of exposed females exceeded the historical control ranges. The incidences of renal tubule adenoma in 700 and 7000-ppm males and the incidence of renal tubule hyperplasia in 7000-ppm males were significantly greater than those in the chamber controls. The severity of kidney nephropathy was increased in 7000-ppm males when compared to chamber controls.[8]

An exposure-related increase in the incidences of interstitial cell adenoma of the testis occurred in male rats. The incidences of bilateral interstitial cell adenoma and of unilateral and bilateral interstitial cell adenoma (combined) of the testis in 700- and 7000-ppm males were significantly greater than those in the chamber controls.[8]

Several rare neoplasms including benign astrocytoma, malignant glioma, malignant medulloblastoma, granular cell tumor, and meningeal sarcoma were observed in the brain of exposed female rats, but were not found to be statistically significant. These neoplasms did not occur in chamber controls.[8]

The incidences of splenic fibrosis in 700- and 7000-ppm males were significantly greater than that in the chamber control group.[8]

Male F344/N rats and male B6C3F$_1$ mice were exposed to 0, 70, 220, 700, 2200, or 7000 ppm (40 animals/ dose) for 6 hours/day, 5 days/week, for 6 months. At the end of the exposure period, 10 rats and 10 mice per exposure group were sacrificed and evaluated. The remaining animals

Table 3

Subchronic Study NOAELs in mice[16]

Endpoint	Sex	NOAEL/LOAEL
Increased liver Weights (Absolute and relative)	Male	2200 ppm (NOAEL)
Increased Liver Weights (Absolute)	Female	2200 ppm (NOAEL)
Olfactory epithelial degeneration	Male and female	2200 ppm (NOAEL)
Reproductive: Longer estrous cycles	Female	2200 ppm (NOAEL)
Reproductive Effects (decreased epididymal wts., spermatid head counts, sperm concentration and sperm motility)	Male	220 ppm (NOAEL)
Increased liver vacuolization	Male	700 ppm (NOAEL)
Testicular Atrophy	Male	700 ppm (NOAEL)
Epithelial hyperplasia in forestomach	Male and female	220 ppm (NOAEL)
Decreased spleen weights: (Absolute)	Male	220 ppm (NOAEL)
(Relative)	Male	70 ppm (NOAEL)
Decreased spleen weights: (Absolute)	Female	220 ppm (NOAEL)
(Relative)	Female	2200 ppm (NOAEL); 7000 ppm (LOAEL)
Hematological Changes: Decreased Hematocrit, Hemoglobin, Erythrocyte counts	Male and female	70 ppm (LOAEL) All dose groups were affected

were allowed to recover for an additional 6 months without exposure.[8]

In rats, interstitial cell hyperplasia of the testis was observed in all rats in the 7000-ppm group sacrificed after 6 months of exposure. Following the 6-month recovery period, rats exposed to 700, 2200, or 7000 ppm had slightly greater incidences of interstitial cell adenomas of the testes than the controls, however the authors did not indicate whether the increase followed a dose-response curve.[8]

Exposure of mice to 7000 ppm isoprene for 6 months resulted in decreased survival. After 6 months of exposure and 6 months recovery, mice exposed to 700 ppm or higher had greater incidences of neoplasms of the liver (hepatocellular adenoma, hepatocellular carcinoma), lungs (alveolar and bronchiolar adenomas), forestomach (squamous cell papillomas and carcinomas), and harderian gland (adenoma and carcinoma) than the controls. In addition, in mice exposed to 700 ppm or greater, incidences of multiple neoplasms and/or neoplasms or malignancy were also higher than in controls.[8] Partial hindlimb paralysis in the 7000-ppm group and a dose-related decrease in grip-strength were observed near the end of the 6-month exposure period. Other nonneoplastic effects observed in this group included spinal cord and sciatic nerve degeneration, skeletal muscle atrophy, degeneration of the olfactory epithelium, epithelial hyperplasia of the forestomach, increased estrous cycle length, testicular atrophy and decreased epididymal weight, sperm head count, sperm concentration, and sperm motility. Mild to minimal olfactory degeneration was seen in all mice exposed to 7000 ppm, one at 2200 ppm and one at 700 ppm. There was no evidence of resolution during the recovery period, and some evidence of progression. Atrophy of the seminiferous tubules was seen in five mice exposed to 7000 ppm and 1 mouse exposed to 220 ppm.[8]

At the end of the 6-month exposure period, spinal cord degeneration (minimal severity) was seen in all mice in the 7000-ppm group, and one in the 2200-ppm group. At the end of the recovery period, the incidence of spinal cord degeneration was significantly greater than controls in all exposure groups. Minimal sciatic nerve degeneration was noted in two mice from the 7000 ppm group at the end of the 6-month exposure period; in addition, one mouse each in the 700- and 2200-ppm groups and 3 in the 7000-ppm group had sciatic nerve degeneration. Skeletal muscle atrophy was noted in 4 mice after exposure to 7000 ppm for 6 months, but was not observed at the end of the recovery period.[8]

Table 4

Chronic Study NOAELs and LOAELs[8]

Endpoint	Sex and Species	NOAEL/LOAEL
Interstitial cell hyperplasia of the testis	Male rats	2200 ppm (NOAEL)
Splenic fibrosis	Male rats	220 ppm (NOAEL)
Renal adenomas, hyperplasias, & nephropathies	Male rats	220 ppm (NOAEL)
Interstitial cell adenomas of the testis	Male rats	220 ppm (NOAEL)
Mammary gland fibroadenomas	Female rats	70 ppm (LOAEL)
Skeletal muscle deterioration	Male and female mice	2200 ppm (NOAEL)
Reproductive: Longer estrous cycles	Female mice	2200 ppm (NOAEL)
Increased multiple neoplasms & malignancies (benign astrocytoma, malignant glioma, malignant medulloblastoma, granular cell tumor, and meningeal sarcoma)	Male and female mice	220 ppm (NOAEL)
Neoplasms of the lung, liver and forestomach	Male and female mice	220 ppm (NOAEL)
Spinal cord & Sciatic nerve deterioration	Male and female mice	70 ppm (LOAEL)
Reproductive Effects: (Decreased epididymal wts., spermatid head counts, sperm concentration & Sperm motility)	Male mice	70 ppm (NOAEL)
Decrease in grip strength	Male and female mice	70 ppm (LOAEL)
Hematological Changes:		
Decreased Hematocrit, Hemoglobin, Erythrocyte counts	Male and female mice	70 ppm (LOAEL)
Nonresponsive macrocytic anemia	Male and female mice	70 ppm (LOAEL)

V. HUMAN USE AND EXPERIENCE

Isoprene is the main hydrocarbon in human breath (30%–70%)[20] resulting in nonexposure-related concentrations of 0.6 ppm.[21]

The isoprene moiety is found in various biological systems and may be a building block for steroids, carotenes, and similar molecules. Isoprene also has been detected in the vapor phase of tobacco smoke (approximately 0.15 ppm); the pulmonary retention was 99%.[22]

Studies of employees in the Russian rubber industry found reduced body temperature, increased reflex time, decreased olfactory sensitivity and physiological changes in the nervous and cardiovascular systems (exposure levels not discussed). These employees also were exposed to methanol, formaldehyde, isopentane, dimethyldioxane, and toluene.[23,24] Human volunteers experienced slight irritation of the upper respiratory tract at 160 mg/m^3 (57 ppm), however the duration of exposure was not discussed.[7]

VI. RATIONALE

There was clear evidence of carcinogenicity in mice at concentrations above 220 ppm.[8] Although NOAELs were not established in the 2-year inhalation carcinogenic studies by NTP,[8,16] there was clear evidence of carcinogenic activity of isoprene in rats at exposures above the LOAEL of 200 ppm. A NOAEL for hematological changes could not be established for mice in a subacute study.[16]

In one NTP study, a NOAEL was not found for decreased hindlimb grip-strength or spinal cord and sciatic nerve degeneration in a 6-month study in mice (lowest exposure concentration of 70 ppm) and the neurological effects were dose-related.[8] The spinal cord degeneration (minimal severity) was seen in all mice in the 7000-ppm group and one in the 2200-ppm group, and was significantly greater than controls in all exposure groups. Minimal sciatic nerve degeneration was noted in two mice from the 7000 ppm group at the end of the 6-month exposure period. In addition, one mouse each in the 700- and 2200-ppm groups and 3 in the 7000-ppm group had sciatic nerve degeneration.[8] In a similar 6-month NTP study,[16] no neurological effects were seen behaviorally or pathologically in mice at exposures of 70 to 7000 ppm. Employees in the Russian rubber industry had increased reflex time and physiological changes in the nervous and cardiovascular systems (exposure levels not discussed), however these workers were also exposed to methanol, formaldehyde, isopentane, dimethyldioxane, and toluene.[23,24]

There is no NOEL for the decreased hindlimb grip or spinal cord and sciatic nerve degeneration (LOAEL is 70 ppm), nor are there data to clearly understand the relative sensitivity between animals and the human nervous system, and the spinal cord degeneration is an irreversible lesion. Although the carcinogenicity and hematological endpoints are serious, the NOAEL concentrations (200 or 220 ppm) are above the irreversible neurological endpoints that had LOAEL at 70 ppm. The OEL should be set at 2 ppm based primarily on the neurological effects, further supported by the carcinogenicity effects.

VII. RECOMMENDED OEL

8-hr TWA: 2 ppm (5.6 mg/m^3)

VIII. REFERENCES

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