CHAPTER TWENTY-SEVEN

Aliphatic Hydrocarbons

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Aliphatic hydrocarbons are open-chain compounds that may be saturated or unsaturated. The saturated compounds, known as *paraffin hydrocarbons* or *alkanes*, include methane and its homologs having the empirical formula C_nH_{2n+2}. The unsaturated compounds fall into a number of homologous series: (*1*) those containing one double bond (ethylene and its homologs) and having the formula C_nH_{2n} are known as *olefins* or *alkenes*; (*2*) those containing one triple bond (acetylene and its homologs) are called *acetylenes* or *alkynes* and have the formula C_nH_{2n-2}; (*3*) those having two double bonds (allene, 1,3-butadiene, and 1,4-pentadiene represent three types) are *diolefins* or *alkadienes* and also have the formula C_nH_{2n-2}; (*4*) those having a large number of double or triple bonds or both double and triple bonds are named in analogous fashion as *alkatrienes*, *alkatetraenes*, *alkadiynes*, *alkenynes*, and *alkadienynes*.

Aliphatic hydrocarbons are asphyxiants and central nervous system (CNS) depressants. Serious toxic effects of aliphatic hydrocarbons include asphyxia and chemical pneumonitis for many paraffins, axonal neuropathy for *n*-hexane, and cancer for 1,3-butadiene.

ALKANES (SATURATED HYDROCARBONS, PARAFFINS)

The alkanes have the generic formula of C_nH_{2n+2}. All the carbons have single covalent bonds between them. They are also called *saturated hydrocarbons*, which means that all the carbons have the maximum number of bonds (four). The alkane series is composed of gases (methane, ethane, propane, and butanes), liquids from pentanes (C5–C16 compounds), and longer chain solids (1).

The toxicity of the alkanes is generally related to vapor pressure, viscosity, surface tension, and lipid solubility. Physical properties of saturated aliphatic hydrocarbons are listed in Table 27.1.

In general, the saturated hydrocarbons from propane through the octanes show increasingly narcotic properties. The onset of narcosis is above the lower flammability point for methane, ethane, and propane, at the lower flammability limit for butanes, and generally below the lower flammability limit for higher order saturated hydrocarbons (2). The margin between narcosis and lethal depression of vital centers is too narrow, and because of their explosive characteristics, these compounds are not used as surgical anesthetics. Narcotic effects may be accompanied by exhilaration, dizziness, and headache (1).

Virtually all paraffins will cause nausea, vomiting, abdominal pain, and occasionally diarrhea when ingested (3–5). Dermatitis, CNS depression, anesthesia, and cardiac sensitization have also been noted for many paraffins. Acutely, the most common toxic effects are CNS depression, asphyxia, or ventricular tachycardia following inhalation and chemical pneumonitis after the aspiration of ingested alkanes. Asphyxia occurs when the oxygen in air is displaced by high concentrations of a gas or vapor. When the oxygen concentration is lowered from ambient levels to $\leq$10%, hypoxia results and the body is starved for oxygen. At this level of oxygen deprivation, death occurs swiftly. Ventricular tachycardia occurs due to the sensitization of the heart to epinephrine following saturated alkane exposure. The mechanism of this cardiac sensitization is not well understood and most research on epinephrine-induced tachycardia after exposure to volatile chemicals has focused on halocarbons, not saturated alkanes (6, 7). Whether saturated alkanes work through similar or different mechanisms is not known.

Patty's Toxicology, Sixth Edition. Volume 2, Edited by Eula Bingham and Barbara Cohrssen.

Dermal irritation and CNS depression are common problems with liquid aliphatic hydrocarbons in chronic exposures. Dermal irritation occurs in workers repeatedly exposed to liquid hydrocarbons as solvents. The paraffins are lipid solvents and dissolve or extract the fats from the skin, resulting in painful drying and cracking of the skin, that is, chronic eczematoid dermatitis, with itching and inflammation.

CNS depression occurs as the inhaled vapor or gas crosses the alveolar–capillary membrane to be absorbed into the bloodstream. At levels that cause CNS depression, the lung itself is spared injury (3–5). The CNS depressant properties of some alkanes have led to substance abuse in the form of "glue sniffing," usually toluene or *n*-hexane. Other abusers have utilized gasoline; paints containing solvents such as xylene, methyl ethyl ketone, acetone, ethyl acetate, ethyl benzene, and isobutyl acetate; typewriter correction fluids; aerosol can propellants, including propane, butane, and isobutane; and exhaust emissions. Abusers often exhibit a drunken appearance and suffer from learning or memory impairment, personality disorders, seizures, neuropsychological disorders, and tachycardia (3–5).

In general, branched-chain derivatives are less toxic than the corresponding parent straight-chain alkanes. Odorant properties increase whereas analgesic properties decrease with the increasing chain length. Both dermal and pulmonary irritant properties increase with increasing chain length up to C14 derivatives (8).

1.0 Methane

1.0.1 CAS Number

[*74–82-8*]

1.0.2 Synonyms

Methyl hydride; fire damp; marsh gas; biogas; natural gas; fire damp; r 50 (refrigerant); methane, various grades

1.0.3 Trade Names

NA

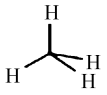
1.0.4 Molecular Weight

16.042

1.0.5 Molecular Formula

CH_4

1.0.6 Molecular Structure



1.1 Chemical and Physical Properties

1.1.1 General

Methane, CH_4, is a colorless, extremely flammable, and explosive gas that occurs in natural gas (9). Its specific gravity is 0.72, and its vapor pressure is 760 Torr. Measurements of the partition coefficient of methane between olive oil and air (a measure of the solubility of a gas in blood) at 37°C range between 0.31 and 0.89 (2, 10). Selected physical and chemical properties are presented in Table 27.1.

1.1.2 Odor and Warning Properties

Methane has a sweet, oil-like odor (11). An odor threshold of 200 ppm has been reported (12).

1.2 Production and Use

Methane is the end product of anaerobic decay. It is the major constituent of natural gas, present at concentrations between 600,000 and 800,000 ppm 60 to 80% of natural gas. Methane collects in coal mines or geologically similar earth deposit sites, evolves as marsh gas, and forms during certain fermentation and sludge degradation processes. Methane is also produced by decomposition in municipal landfills; concentrations can be as high as 250,000 ppm. It is often accompanied by other low molecular weight hydrocarbons (11).

Major uses of methane include power generation and chemical production. Methane gas is used as a power source in sewage treatment plants. Methane is used in the manufacture of methanol, hydrogen, hydrogen cyanide, halogenated hydrocarbons, ammonia, and acetylene. Methane is a source of petrochemicals by conversion to hydrogen and carbon monoxide and a starting material for the manufacture of synthetic proteins (13–15).

Methane is a major constituent of natural gas, which is used for power generation, chemical feedstocks, cooking and residential heating. Residential and commercial use of natural gas comprises nearly half the total sales. The second most common use of natural gas is petroleum and polymer intermediate production (11).

1.3 Exposure Assessment

1.3.1 Air

Headspace gas chromatography is used to determine the concentration of methane in the atmosphere. Detector tubes using a colorimetric assay and direct reading instruments (e.g., flame ionization detection, catalytic combustion, and thermal conductivity detection) are also used to determine methane concentrations in the air (13). A hydrocarbon fast-response gas sensor has been developed to measure methane in liquefied natural-gas spills (16).

Table 27.1. Physicochemical Properties of Alkanes

Compound	Molecular Formula	Molecular Weight	Boiling Point (°C)	Melting Point (°C)	Density (mg/cm^3) (at °C)	Refractive Index (n_D)	Solubility	Flash Point (°C)	Flammability Limits (%)
Methane	CH_4	16.042	−161.5	−182.5	0.4228 (−162)	–	w 3, al 3, et 3, ac 2	−187.8 (open cup)	5.0–15.0
Ethane	C_2H_6	30.07	−88.63	−183.23	0.5446 (−89)	–	bz 4	−135	3.0–12.5
Propane	C_3H_8	44.09	−42.1	−187.7	0.493 (25)	–	w 3, al 3, et 4, ac 2	−104.0	2.1–9.5
Butane	C_4H_{10}	58.12	−0.5	−138.35	0.573 (25)	1.3326 (20)	w 3, al 4, et 4, ch 4	−60.0 (closed cup)	1.9–8.5
2-Methylpropane	C_4H_{10}	58.12	−11.7	−159.6	0.5510 (25)	1.3518 (−25)	w 2, al 3, et 3, ch 3	−82.8 (closed cup)	1.8–8.4
Pentane	C_5H_{12}	72.15	36.1	−129.8	0.6262 (20)	1.3575 (20)	w 2, al 5, et 5, ac 5	−49.0	1.4–8.0
2-Methylbutane	C_5H_{12}	72.15	27.8	−159.8	0.6201 (20)	1.3537 (20)	w 1, al 5, et 5	−51.0	1.4–7.6
2,2-Dimethylbutane	C_6H_{14}	86.177	49.7	−100	0.6444 (25)	1.3688 (20)	w 1, al 3, et 3, ac 4	−48.0	1.2–7.0
2,3-Dimethylbutane	C_6H_{14}	86.177	58	−128.5	0.6616 (20)	1.3750 (20)	w 1, al 3, et 3, ac 4	−29.0	1.2–7.0
2,2-Dimethylpropane	C_5H_{12}	72.15	9.5	−16.6	0.5258 (25)	1.3476 (6)	w 1, al 3, et 3, ct 3	−6.67	1.4–7.5
Hexane	C_6H_{14}	86.10	68.95	−95	0.6548 (25)	1.3749 (20)	w 1, al 4, et 3, ch 3	−22.0 (closed cup)	1.1–7.5
2-Methylpentane	C_6H_{14}	86.177	62	−154	0.650 (25)	1.3715 (20)	w 1, al 3, et 3, ac 5	−23.0	1.0–7.0
3-Methylpentane	C_6H_{14}	86.177	64	−118.0	0.6598 (25)	1.3765 (20)	w 1, al 3, et 5, ac 5	−6.0	1.2–7.0
Heptane	C_7H_{16}	100.20	98.4	−90.7	0.6837 (20)	1.3878 (20)	w 1, al 4, et 5, ac 5	−4.4 (closed cup)	1.05–6.7
2-Methylhexane	C_7H_{16}	100.20	90.0	−118.2	0.6787 (20)	1.3848 (20)	w 1, al 3, et 5, ac 5	−1.0	1.0–6.0
3-Methylhexane	C_7H_{16}	100.20	92.0	−119.0	0.6860 (20)	1.3887 (20)	w 1, al 3, et 5, ac 5	−4.0	–
Octane	C_8H_{18}	114.22	125.7	−56.8	0.6986 (25)	1.3974 (20)	w 1, al 3, et 3, ac 5	−13.0 (closed cup) 22 (open cup)	1.0–6.5
2,5-Dimethylhexane	C_8H_{18}	114.23	109.1	−91.0	0.6901 (25)	1.3925 (20)	w 1, al 5, et 3, ac 5	–	–
2,2,4-Trimethylpentane	C_8H_{18}	114.22	99.2	−116	0.6877 (25)	1.3915 (20)	w 1, al 5, et 3, ac 5	−12.0	–
2,3,4-Trimethylpentane	C_8H_{18}	114.23	113.5	−109.2	0.7191 (20)	1.4042 (20)	w 1, al 4, et 5, ac 5	−12.0	–
Nonane	C_9H_{20}	128.26	150.8	−53.5	0.7176 (20)	1.4054 (20)	w 1, al 4, et 4, ac 5	31.0	0.8–2.9
2,2,5-Trimethylhexane	C_9H_{20}	128.26	124.0	−105.7	0.7072 (20)	1.3997 (20)	w 1, al 4, et 4, ac 4	13.0	–
Decane	$C_{10}H_{22}$	142.28	174.1	−29.7	0.7300 (20)	1.4102 (20)	w 1, al 5, et 3, ct 2	46	0.8–5.4
2,7-Dimethyloctane	$C_{10}H_{22}$	142.28	159.9	−54.9	0.7202 (25)	1.4086 (20)	et 3, aa 3	–	–
Undecane	$C_{11}H_{24}$	156.31	195.9	−25.59	0.7402 (20)	1.4398 (20)	w 1, al 5, et 5	60.0	–
Dodecane	$C_{12}H_{26}$	170.34	216.3	−9.6	0.7487 (20)	1.4216 (20)	w 1, al 4, et 4, ac 4	71.0	0.6–?
Tridecane	$C_{13}H_{28}$	184.36	235.4	−5.5	0.7564 (20)	1.4256 (20)	w 1, al 4, et 4, ct 3	79.0	–
Tetradecane	$C_{14}H_{30}$	198.39	253.7	5.89	0.7628 (20)	1.4290 (20)	w 1, al 4, et 4, ct 3	99	0.5–?
Pentadecane	$C_{15}H_{32}$	212.42	270.63	9.9	0.7685 (20)	1.4315 (20)	w 1, al 4, et 4	132	–
Hexadecane	$C_{16}H_{34}$	226.44	287	18.17	0.7733 (20)	1.4345 (20)	w 1, al 2, et 5, ct 3	135	–
Heptadecane	$C_{17}H_{36}$	240.47	302.0	22.0	0.7780 (20)	1.4369 (20)	w 1, al 2, et 3, ct 2	–	–
Octadecane	$C_{18}H_{38}$	254.50	316.3	28.2	0.7768 (28)	1.4390 (20)	w 1, al 2, et 3, ac 3	> 100.0	–
Nonadecane	$C_{19}H_{40}$	268.53	329.9	32.1	0.7855 (20)	1.4409 (20)	w 1, al 2, et 3, ac 3	–	–
Pristane	$C_{19}H_{40}$	268.53	296.0	–	0.783 (20)	1.4379 (20)	et 4, bz 4, ch 4, pe 4	–	–
Eicosane	$C_{20}H_{42}$	282.55	343.0	36.8	0.7886 (20)	1.4425 (20)	w 1, et 3, ac 4, bz 3	> 100.0	–

Molecular formula, in Hill notation; molecular weight, relative molar mass; density, mass per unit volume in g/cm^3 at the temperature indicated in parentheses; refractive index, at the temperature indicated in parentheses, unless otherwise indicated, all values refer to a wavelength of 589 nm; solubility, solubility in common solvents (w, water; al, ethanol; et, ethyl ether; ac, acetone; bz, benzene; ch, chloroform; ct, carbon tetrachloride; aa, acetic acid; pe, petroleum ether; os, organic solvents) on a relative scale: 1 = insoluble, 2 = slightly soluble, 3 = soluble, 4 = very soluble, 5 = miscible, 6 = decomposes; flammability limits, explosive limits (in percent by volume) at ambient temperature and pressure.

1.3.2 Background Levels

NA

1.3.3 Workplace Methods

NA

1.3.4 Community Methods

NA

1.3.5 Biomonitoring/Biomarkers

Because of its volatility, methane concentrations are determined in blood and tissues using headspace gas chromatography techniques (13).

1.4 Toxic Effects

1.4.1 Experimental Studies

1.4.1.1 Acute Toxicity. A concentration of 87% methane has caused asphyxiation in mice. Respiratory arrest occurred in mice at 90% (900,000 ppm) methane concentration (17). Cats were anesthetized at an 87% (870,000 ppm) methane concentration in air; the LC_{50} for cats was an atmosphere of 90% (900,000 ppm) methane (18).

Using the Drummond model for estimating the flammability, asphyxiant, and narcotic properties of light hydrocarbon gases place the lower explosive limit for methane at 50,000 ppm and the onset of narcosis at 300,000 ppm (2). An olive oil/air partition coefficient between 0.31 and 0.89 indicates that methane is relatively insoluble in blood, and rapid onset of narcosis (2, 11).

1.4.1.2 Chronic and Subchronic Toxicity. NA

1.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Methane is absorbed through the lungs in mammals (19, 20). When inhaled, the majority of the absorbed dose is exhaled unchanged. A small amount of methane is converted to methanol and ultimately to carbon dioxide (13). Uptake in humans is less rapid than that in the rat (19, 20).

1.4.1.4 Reproductive and Developmental. Pregnant mice were exposed on gestation day 8 for 1 h to 5–8% concentration of fuel gas. In addition to 85% methane, most natural gases contain small amounts of ethane, propane, and butane. Abnormalities of the fetal brains were found to result in brain hernia and hydrocephalus (21).

1.4.2 Human Experience

1.4.2.1 General Information. Methane displaces oxygen in air at concentrations greater than 14% (140,000 ppm) and is considered a simple asphyxiant (i.e., it displaces oxygen from the breathing atmosphere primarily in enclosed spaces, resulting in hypoxia) (11, 22). Methane is narcotic in high concentrations in the absence of oxygen. Methane concentrations of 300,000 ppm in air are predicted to induce CNS effects in humans using a model for the potency of anesthetic gases (2). When heated to decomposition, it emits toxic fumes of carbon monoxide, carbon dioxide, and various hydrocarbons (23). Methane is not irritating to the skin, eyes, nose, throat, or lungs; however, it may cause frostbite on skin contact (11).

1.5 Standards, Regulations, or Guidelines of Exposure

Methane is on the Environmental Protection Agency Toxic Substances Control Act (U.S. EPA TSCA), Chemical Inventory, and the Test Submission Data Base (23). The ACGIH previously considered methane a simple asphyxiant (11). Drummond's modeling of the narcotic and flammability of methane suggests that regulation as a simple asphyxiant provides adequate protection for workers (2). Because of possible synergistic effects with other hydrocarbons, ACGIH has developed a time-weighted average (TWA) level for methane, ethane, propane, *n*-butane, 2-methylpropane, and any combination of these gases (9). The California Division of Occupational Safety and Health (Cal/OSHA) regulates methane as a simple asphyxiant and does not provide a concentration for a PEL [California Division of Occupational Safety and Health (Cal/OSHA), (24)]. Methane is also considered an asphyxiant by Australia, Belgium, Hungary, The Netherlands, and the United Kingdom (25). The occupational exposure limit in Switzerland is 10,000 ppm (6700 mg/m^3) TWA (25).

2.0 Ethane

2.0.1 CAS Number

[*74–84-0*]

2.0.2 Synonyms

Bimethyl, dimethyl, ethyl hydride, methylmethane; ethane, CP-grade, 90%, ethane, CP-grade 99%

2.0.3 Trade Names

NA

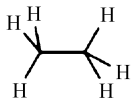
2.0.4 Molecular Weight

30.07

2.0.5 Molecular Formula

CH_3CH_3

2.0.6 Molecular Structure



2.1 Chemical and Physical Properties

2.1.1 General

Ethane, C_2H_6, is a flammable, colorless gas that occurs in the paraffin fraction of crude oil and natural gas (22). Ethane occurs in natural gas in concentrations between 5 and 9% (26). It is released in the exhaust of diesel and gasoline engines, from municipal incinerators, and from the combustion of natural gas, gasoline, and polypropylene. The partition coefficient of ethane between olive oil and air at 37°C is 2.1 using the method described by Sato and Nakajima and Perbellini et al. (27, 28). The lower explosive limit is 30,000 ppm in air. Selected physical properties of ethane are listed in Table 27.1.

2.1.2 Odor and Warning Properties

The odor of ethane has been described as mild and sweet (15). Ethane can be detected between 185 and 1106 mg/m^3 (29).

2.2 Production and Use

Ethane can be prepared by fractionating low molecular weight gases recovered during the refining of crude oil. It is produced as a catabolic product of lipid peroxidation in rats (30). Ethane is used in the production of ethylene by high temperature thermal cracking, as a feedstock in the production of vinyl chloride, in the synthesis of chlorinated hydrocarbons, as a refrigerant, and as a component of fuel gas (31).

2.3 Exposure Assessment

2.3.1 Air

Headspace gas chromatography may be used to determine ethane concentrations in the air (32). A highly efficient gas chromatography separation column has been described (33). Methods used to determine methane in the atmosphere may also be used for ethane determination. A procedure for measuring ethane in liquefied natural gas spills using a hydrocarbon fast response gas sensor has been developed (16). Ethane may also be measured in the air using direct-reading devices (flame ionization meter or portable thermal conductivity gas chromatography) (34).

2.3.2 Background Levels

NA

2.3.3 Workplace Methods

NA

2.3.4 Community Methods

NA

2.3.5 Biomonitoring/Biomarkers

Ethane concentrations in blood and tissues may be measured by headspace gas chromatography (27). Analysis of ethane metabolites has not been reported, partly because ethane undergoes very little metabolism to ethanol.

2.4 Toxic Effects

2.4.1 Experimental Studies

2.4.1.1 Acute Toxicity. Ethane does not have anesthetic properties. Using the Drummond model for estimating the flammability, asphyxiant, and narcotic properties of light hydrocarbon gases place the lower explosive limit for ethane at 30,000 ppm and the onset of narcosis at 130,000 ppm. Drummond concludes that control as an asphyxiant is marginal for ethane (2).

Guinea pigs exposed to 2.2–5.5% ethane (22,000–55,000 ppm) for 2 h showed slight signs of irregular respiration, which is readily reversible on cessation of the exposure (35). Ethane is considered a "weak" cardiac sensitizer in animals (6). At concentrations of 15–90%, ethane sensitized the canine myocardium to cardiac arrhythmias induced by epinephrine in two of four test animals (36).

2.4.1.2 Chronic and Subchronic Toxicity. NA

2.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. The metabolism of ethane to ethanol does not occur significantly in rat liver microsomal preparations, perhaps because ethane is a poor substrate for the cytochrome P450 enzyme system (37). Lipid peroxidation processes can generate ethane as the end product of degradation (32, 38). Absorption of ethane occurs primarily through the lungs. Ethane appears to be mainly eliminated unchanged in expired air. The elimination half-life of ethane has been reported to be 0.95 h. In rats, over a concentration range of 0.5–5000 ppm, ethane displayed linear pharmacokinetics, indicating that there is no saturation of elimination processes even at high concentrations (32, 38).

2.4.1.4 Reproductive and Developmental. Pregnant mice were exposed on gestation day 8 for 1 h to 5–8% concentration of fuel gas. In addition to 85% methane, most natural gases contain small amounts of ethane, propane, and butane. Abnormalities of the fetal brains were found to result in brain hernia and hydrocephalus (21).

2.4.1.5 Carcinogenesis. Syrian hamster embryo cells were exposed *in vitro* to ethane gas. After exposure, the cells were removed and assayed for viability and increased sensitivity to viral transformation. Ethane was determined to be inactive (39).

2.4.2 Human Experience

2.4.2.1 General Information. At high concentrations, ethane causes CNS depression (15, 26). The Drummond model predicts that ethane is a fast-acting agent inducing narcosis at concentrations above 130,000 ppm (2). Ethane sensitized the heart to cardiac arrhythmias induced by epinephrine at 150,000–190,000 ppm (26). At higher concentrations, ethane displaces oxygen from the air (26). The liquid causes severe frostbite (12).

2.5 Standards, Regulations, or Guidelines of Exposure

Ethane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (22). Industrially, ethane is handled similarly to methane. The ACGIH previously considered ethane a simple asphyxiant (26). Drummond's modeling of the narcotic and flammability of ethane suggests that regulation as a simple asphyxiant provides marginal protection for workers (2). Because of possible synergistic effects with other hydrocarbons and concurrent exposures, ACGIH currently recommends a time-weighted average level for methane, ethane, propane, *n*-butane, 2-methylpropane, and any combination of these gases (9). Both OSHA and the California Division of Occupational Safety and Health (Cal/OSHA) regulate ethane as a simple asphyxiant and do not provide concentrations for a PEL (24, 25). Ethane is considered an asphyxiant in Australia and New Zealand (25). Argentina, Bulgaria, Colombia, Jordan, Singapore, and Vietnam use the recommended 1000 ppm TWA (25). The occupational exposure limit in Switzerland is 10,000 ppm (12,500 mg/m^3) TWA (25).

3.0 Propane

3.0.1 CAS Number

[*74–98-6*]

3.0.2 Synonyms

Dimethylmethane; *n*-propane; propane, various grades; liquefied petroleum gas; propyl hydride

3.0.3 Trade Names

NA

3.0.4 Molecular Weight

44.09

3.0.5 Molecular Formula

$CH_3CH_2CH_3$

3.0.6 Molecular Structure

3.1 Chemical and Physical Properties

3.1.1 General

Propane, C_3H_8, is a colorless, highly flammable gas. It is a constituent in the paraffin fraction of crude oil and natural gas (22). The partition coefficient of propane between olive oil and air at 37°C is 5.9 using the method described by Sato and Nakajima and Perbellini et al. (2, 27, 28). The lower explosive limit is 21,200 ppm in air. Its specific gravity is 1.55. Selected physical data are presented in Table 27.1.

3.1.2 Odor and Warning Properties

Propane is odorless when pure; a foul smelling odorant is often added when propane is used for fuel purposes (40, 41). The odor of propane can be detected between 1,800 and 36,000 mg/m^3 (29).

3.2 Production and Use

Propane is emitted into the atmosphere from furnaces, automobile exhausts, and natural gas sources and from the combustion of polyethylene and phenolic resins. Propane is used as a component of liquid petroleum gas; in colder climates, liquid petroleum gas is predominantly propane. Residential and commercial uses comprise half of all commercial liquid petroleum gas sales (42). Propane is also used as a feedstock in thermal cracking processes, to manufacture ethylene and propylene; as a basic material in chemical synthesis, for oxidation, alkylation, nitration, and chlorination; as an aerosol propellant, to replace the chlorofluorocarbons; as a refrigerant in chemical refining and gas processing operations; as a fuel in welding and cutting operations; and as a solvent and extractant in deasphalting and degreasing of crude oils (43).

Propane is also used recreationally, termed "inhaling" or "huffing," to become intoxicated—either alone or in combination with butane. Propane-containing products are abused because they are widely available to adolescents, and provides a rapid, short lasting euphoria, usually with minimal "hangover" symptoms (44). From 2002 to 2007, inhalants comprised 14.5–19.6% of first illegal drug use among adolescents. Propane, butane, or a propane–butane mix were 7.1–9.9% of all inhalants used in the past year (45).

3.3 Exposure Assessment

3.3.1 Air

Propane may be determined in the air using a colorimetric assay and direct-reading devices (flame ionization meter or portable thermal conductivity gas chromatography) (34). Propane concentrations are also determined using headspace gas chromatography methods (46, 47). A hydrocarbon fast-response gas sensor has been developed to measure propane in liquefied natural gas spills (16).

3.3.2 Background Levels

NA

3.3.3 Workplace Methods

NA

3.3.4 Community Methods

NA

3.3.5 Biomonitoring/Biomarkers

Propane has been measured in blood and expired air samples using gas chromatography (42). Propane in tissues has been determined using headspace gas chromatography techniques with either a 1,1,2-trichlorotrifluoroethane or pentane/isobutanol internal standards (48, 49).

3.4 Toxic Effects

3.4.1 Experimental Studies

3.4.1.1 Acute Toxicity. Guinea pigs exposed to 24,000–29,000 ppm for 5–120 min showed irregular breathing. At a concentration of 47,000–55,000 ppm tremors occurred during the first 5 min of exposure. Stupor was observed in all animals exposed for $\leq$2 h. The effect was rapidly reversible on cessation of exposure (36). In cats, 93% propane is mildly anesthetic (50).

Using the Drummond model for estimating the flammability, asphyxiant and narcotic properties of light hydrocarbon gases, the lower explosive limit for propane is 21,200 ppm. A concentration of 47,000 ppm is the estimated concentration for the onset of narcosis (2).

3.4.1.2 Chronic and Subchronic Toxicity. Subchronic inhalation studies were conducted in monkeys exposed to 750 ppm for 90 consecutive days with no toxicity observed (51). In an inhalation study in monkeys exposed to an aerosol spray deodorant containing a mixture of propane and isobutane of 65% by weight, all animals survived and showed no changes in body weight, behavior, hematology, blood chemistry, urinalysis, and electrocardiogram and pulmonary function. No organ toxicity was found (52).

3.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. In mice exposed to a liquid–gas mixture containing propane, butane, and isobutane (17, 31, and 52%, respectively), death occurred within 15 s of exposure. Concentrations of the compound were maximal within 1 h of death and decreased thereafter. No residues or only traces were detected by day 15 postmortem. Maximum concentrations were observed in the adipose tissue 4 days after death, and the compound was still detectable by day 15 (53).

Exposure to domestic cooking gas (a mixture of butane, propane, and their resultant alkenes) resulted in a dose-dependent increase γ-glutamyl transferase and alkaline phosphatase activity in mice serum and livers (54).

3.4.1.4 Reproductive and Developmental. Pregnant mice were exposed on gestation day 8 for 1 h to a 5–8% concentration of fuel gas. In addition to 85% methane, most natural gases contain small amounts of ethane, propane, and butane. Abnormalities of the fetal brains were found to result in brain hernia and hydrocephalus (21).

3.4.1.5 Carcinogenesis. NA

3.4.1.6 Genetic and Related Cellular Effects Studies. Propane was not mutagenic when tested using the Ames *Salmonella typhimurium* system at various vapor concentrations with and without metabolic activation (51).

Mice exposed to domestic cooking gas had significantly increased micronucleated polychromatic erythrocytes (PCEs). The relationship between gas exposure and PCE levels was dose dependent. This may indicate that propane or a propane–butane mixture causes chromosome breaks and interferes with spindle formation (54).

3.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Propane is considered a "weak" cardiac sensitizer in animals (6). At concentrations of 15–90%, propane sensitized the canine myocardium to cardiac arrhythmias induced by epinephrine in three of three test animals (36). In dogs, 1% propane causes hemodynamic changes, whereas 3.3% decreases inotropism of the heart; a decrease in mean aortic pressure, stroke volume, and cardiac output; and increase in pulmonary vascular resistance (55). Exposure to 5.0% propane for 5 min followed by epinephrine challenge did not induce cardiac arrhythmia in any test dogs; 10% propane-induced cardiac arrhythmia in 2 of 12 test dogs, and 20% propane-induced cardiac arrhythmia in all 7 of 12 test dogs and ventricular fibrillation in 1 (6). In other studies, 10% propane in the mouse and 15% in the dog produced no arrhythmia but weak cardiac sensitization (36, 56).

In primates, 10% induces some myocardial effects, whereas exposure to 20% causes aggravation of these parameters and respiratory depression (55, 57).

Propane is moderately irritating to the skin of rabbits, but not to the skin of mice (51).

3.4.2 Human Experience

3.4.2.1 General Information. Propane is an anesthetic and is nonirritating to the eyes, nose, or throat (12). Direct skin or mucous membrane contact with liquefied propane causes burns and frostbite (42). At air concentration levels below 1000 ppm, propane exerts very little physiological action (58). At very high levels, propane has CNS depressant and asphyxiating properties; its target organ is the central nervous system (41).

3.4.2.2 Clinical Cases

3.4.2.2.1 Acute toxicity. There are multiple reports of sudden death after exposure to propane or propane–butane mixtures. A 19 year old man found dead holding a liquid petroleum gas (LPG) hose to his cheek. Propane concentrations ranged from 0.19 μL/mL in urine to 70.63 μL/g in the liver (59). A 19 year old male was found dead after inhalation of propane and butane from a "Kisag Gas" cartridge. Propane concentrations in tissues on autopsy ranged from 0.07 mg/kg (blood) to 1.1 mg/kg (fat tissue). Death was attributed to ventricular fibrillation (60).

Two industrial LPG accidents have been reported (61). The first involved a 28 year old male and a 41 year old male found unconscious at the bottom of a hole installing pipe fittings. The 41 year old male died 12 h after admission to the hospital; the 28 year old died 2 days after admission. Petechial hemorrhages were observed on the left eye and pleural surfaces. Severe edema was found in the lungs and the brain and the cerebellum showed "respirator brain" with total necrosis on autopsy of the 41 year old male. Cause of death was determined to be anoxia. A 34 year old male was installing a pipe fitting when overcome by LPG gas. Resuscitation was not successful. Petechial hemorrhages were observed in both eyes, thymus, epicardium, and both lungs. There was marked edema on the lungs. The cause of death was attributed to LPG poisoning.

The development of rhabdomyolysis, the breakdown of muscle and the release of muscle fiber into the bloodstream, has been observed after exposure to LPG with a 20% propane and 80% butane mix for 8 h (62). A 30 year old female presented with a diffuse dull pain that was not localized and did not have associated swelling. The patient could walk with difficulty if given support. Creatine phosphokinase at admission was 11,370 IU/dL. The patient did not develop complications and was discharged 9 days after admission.

There is one reported case of a man exposed to propane (concentration was not reported) from a leaking tank in an automobile. He exhibited colicky pains; became stupefied, disoriented, and excited; pupils of his eyes narrowed; and he exhibited marked salivation. The man recovered, but suffered from retrograde amnesia (63). Five female workers were exposed to propane when the gas escaped through improper pipe fittings. Headache, numbness, a "chilly feeling," and vomiting were reported (63).

3.4.2.2.2 Chronic and subchronic toxicity. A 28 year old male was admitted to the hospital complaining of nausea, malaise, and generalized lower limb weakness. Alanine aminotransferase and aspartate aminotransferase were significantly elevated at admission. Viral and other drug screens were negative. The patient worked in confined spaces fixing butane and propane cylinders. He was diagnosed with acute hepatitis, likely due to chronic propane and butane exposure. Symptoms resolved themselves after 10 days of hospitalization (64).

3.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. A death involving asphyxiation by propane inhalation has been reported. The presence of propane was determined in blood, brain, kidney, liver, and lung by gas chromatography. The brain of the deceased showed the highest level of propane, whereas the kidney exhibited the lowest level (65). Twenty cases of "sudden death" have been reported in which propane and propylene were quantified in blood, urine, and cerebrospinal fluid (8). Traces of propane have been measured in human expired air (66).

3.4.2.3 Epidemiology Studies

3.4.2.3.1 Acute toxicity. Eight adult volunteers of both sexes were exposed to isobutane, propane, or mixtures of both gases (250–1000 ppm for 1, 5, and 10 min, and 1, 2, and 8 h/day for 1 day or 2 weeks) in a controlled environmental chamber for the purpose of monitoring their physiological responses. No abnormal physiological responses, cardiac abnormalities, or pulmonary function abnormalities were observed in any volunteer (67). Acute exposures of volunteers to 250, 500, or 1000 ppm for periods of 1 min to 8 h did not produce any physiological effects as determined by serial electrocardiograms or modified V5 by telemetry during exposure (68).

3.4.2.3.2 Chronic and subchronic toxicity. NA

3.4.2.3.3 Pharmacokinetics, metabolism, and mechanisms. Inhalation represents the major route by which propane is absorbed systemically. A study on human volunteers showed that blood levels of propane could be detected after exposure to 250–1000 ppm. Compared to respiratory absorption, dermal penetration of propane can be considered to be very low (67). The distribution of propane in tissues can be expected to follow the same pattern observed for butane (69).

Table 27.2. Occupational Exposure Limits for Propane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH Exposure Limit	ACGIH TLV
Time-weighted average	1000 ppm (1800 mg/m^3)	1000 ppm (1800 mg/m^3)	A TLV–TWA has been developed by ACGIH
Short-term exposure limit	–	–	–
Ceiling limit	–	–	–

[a] OSHA and ACGIH, 8 h TWA; NIOSH, 10 h TWA.

From Ref. 25.

3.4.2.3.4 Reproductive and developmental. NA

3.4.2.3.5 Carcinogenesis. NA

3.4.2.3.6 Genetic and related cellular effects studies. NA

3.4.2.3.7 Other: neurological, pulmonary, and skin sensitization. Propane, used as an aerosol propellant with isobutane in deodorant and antiperspirant products (65–70% by weight), did not cause skin irritation in 125 volunteers who applied the aerosol products twice a day for 12 weeks (52).

3.5 Standards, Regulations, or Guidelines of Exposure

Propane is on the EPA TSCA Chemical Inventory and Test Submission Data Base (63). The immediately dangerous to life or health (IDLH) concentration established by NIOSH is 2100 ppm, based on 10% of the lower explosion limit for safety considerations, even though the relevant toxicological data indicate that irreversible health effects or impairment of escape exist only at higher concentrations (41). The ACGIH previously considered propane a simple asphyxiant (42). Drummond's modeling of the narcotic and flammability of propane suggests that regulation as a simple asphyxiant provides marginal protection for workers (2). Because of possible synergistic effects with other hydrocarbons and concurrent exposures, ACGIH recommends a time-weighted average for methane, ethane, propane, *n*-butane, 2-methylpropane, and any combination of these gases (9).

Table 27.3. Occupational Exposure Limits for Propane in Different Countries

Country	Exposure Limit
Australia	Asphyxiant
Belgium	Asphyxiant
Denmark	TWA 1000 ppm (1800 mg/m^3)
Finland	TWA 800 ppm (1100 mg/m^3)
Germany	TWA 1000 ppm (1800 mg/m^3)
Hungary	Asphyxiant
The Netherlands	Asphyxiant
The Philippines	TWA 1000 ppm (1800 mg/m^3)
Switzerland	TWA 1000 ppm (1800 mg/m^3)
United Kingdom	Asphyxiant

From Ref. 25.

The exposure limits for propane in the United States are listed in Table 27.2. Argentina, Bulgaria, Colombia, Jordan, Singapore, and Vietnam all use the recommended TWA of 1000 ppm (25); additional international occupational limits are presented in Table 27.3.

4.0 *n*-Butane

4.0.1 CAS Number

[*106–97-8*]

4.0.2 Synonyms

Diethyl, methylethyl methane; butane, methylethylmethane, butyl hydride, pyrofax

4.0.3 Trade Names

NA

4.0.4 Molecular Weight

58.12

4.0.5 Molecular Formula

$CH_3(CH_2)_2CH_3$

4.0.6 Molecular Structure

4.1 Chemical and Physical Properties

4.1.1 General

Butane, C_4H_{10}, is a flammable, colorless, and explosive gas, with specific gravity 0.6011. Butane occurs in natural gas and in the ambient urban air, in small concentrations. It has been detected in the exhaust of gasoline engines and in air above landfills and disposal sites (70, 71). The partition coefficient of propane between olive oil and air at 37°C is 17 using the method described by Sato and Nakajima and Perbellini et al. (2, 27, 28). The lower explosive limit is 18,600 ppm in air. Selected physical properties are listed in Table 27.1.

4.1.2 Odor and Warning Properties

Butane's odor can be detected between 2.9 and 14.6 mg/m^3 and in water at 6.2 ppm (29, 72).

4.2 Production and Use

Butane and isobutane are produced from raw natural gas and from petroleum streams by catalytic cracking, catalytic reforming, and other refining processes. Liquid butane is recovered from the feedstock gas through a process involving refrigeration, adsorption, expansion, compression, fractionation, and other cryogenic steps (73). Butane is used in the production of ethylene and 1,3-butadiene; in the blending of gasoline or motor fuel; in the synthesis of high octane blend stocks of motor fuel; in the synthesis of acetic acid, maleic anhydride, isobutane, and other chemicals. Butane is a major constituent in liquefied natural gas and substitute natural gas; in warmer climates, liquid petroleum gas is predominantly butane. Residential and commercial uses comprise half of all commercial liquid petroleum gas sales (74). Butane is also used as a refrigerant and aerosol propellant, the fuel in cigarette lighters and as a solvent in the liquid–liquid extraction of heavy oils in deasphalting processes (73).

Butane is also used recreationally, either alone or in combination with propane and/or isobutane. Users, generally adolescents, will inhale high concentrations to become intoxicated. Butane-containing products are abused because they are widely available to adolescents, and provides a rapid, short lasting euphoria, usually with minimal "hangover" symptoms (44). From 2002 to 2007, inhalants comprised 14.5–19.6% of first illegal drug use among adolescents. Propane, butane, or a propane–butane mix were 7.1–9.9% of all inhalants used in the past year (45). Almost 10% of nearly 1 million inhalant users used butane; another 26% used lighter fluid that included butane (45).

4.3 Exposure Assessment

4.3.1 Air

Butane has been measured in the atmosphere using gas chromatography and headspace techniques (46). A gas chromatography–mass spectrometric method has been described for the survey and determination of trace components in air, including butane (75). The determination of hydrocarbons, including butane, in the parts per billion range, is accomplished using glass capillary columns coated with aluminum oxide (33). In addition, colorimetric detection tubes, permeation tubes, and direct reading gas analyzers have been employed to quantitate the levels of butane in the air (34).

4.3.2 Background Levels

NA

4.3.3 Workplace Methods

NA

4.3.4 Community Methods

NA

4.3.5 Biomonitoring/Biomarkers

Detection and quantification of butane in tissues of rats and mice, such as brain, liver, kidney, spleen, and perinephric fat, have been conducted by gas chromatography methods (69). Gas chromatography is used to quantify butane levels in human blood, urine, and other tissues (59).

4.4 Toxic Effects

4.4.1 Experimental Studies

4.4.1.1 Acute Toxicity. The 4 h lethal concentration 50% kill (LC_{50}) for the rat is 658 mg/L, and the 2 h LC_{50} for the mouse is 680 mg/L (69). Butane is anesthetic to mice at 13% in 25 min and at 22% in 1 min. Respiratory exposure to mice to 27% for 2 h caused death in 40% of the animals and 31% caused 60% mortality; surviving mice recovered rapidly (1–5 min) (76). In dogs, lethality was observed at concentrations of 20–25%; anesthesia and relaxation preceded death (76). There was only a small margin of safety between anesthetic and lethal concentrations. Mixing butane and isobutylene has an additive CNS depressant effect in rats (77). The mechanism concerning the anesthetic properties of butane is similar to that of ethane and propane.

4.4.1.2 Chronic and Subchronic Toxicity. NA

4.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Butane is partially absorbed in the rat lung and is translocated to the brain, kidney, liver, spleen, and perinephric fat (69). In both rats and mice, the brain levels of butane correlated with the degree of CNS depression and narcosis (69). Hydroxylation of butane occurs in rat liver microsomes to produce 2-butanol as the major metabolite (37). Butane is the lowest molecular weight alkane demonstrated to substrate-bind with cytochrome P450. If 2-butanol is the major metabolite formed in animals, it would be expected to be eliminated in expired air (78). 2-Butanol may also be conjugated with glucuronic acid or be oxidized to methyl ethyl ketone, which, in turn, is expired (73). Because of its volatile nature, elimination of butane by exhalation can be anticipated (73). Its elimination half-life is 0.13 h at nonsaturating concentrations (32).

Baboon studies show that butane is quickly taken up by the brain. Maximum uptake was 1.5 min after inhalation. Brain–blood ratios reached 5.7, 20 min after inhalation. However, the uptake to the neural system is highly inefficient, and large

quantities need to be inhaled to achieve neurological effects (79). PET scans of primates exposed to [^{11}C]-butane showed rapid transfer from the blood to lipid-rich regions of the brain (80).

Exposure to domestic cooking gas (a mixture of butane, propane, and their resultant alkenes) resulted in a dose-dependent increase γ-glutamyl transferase and alkaline phosphatase activity in mice serum and livers (54).

4.4.1.4 Reproductive and Developmental. NA

4.4.1.5 Carcinogenesis. NA

4.4.1.6 Genetic and Related Cellular Effects Studies.

The mutagenic potential of butane was evaluated *in vitro* at several concentrations using the Ames *S. typhimurium* microsome assay. Butane was not mutagenic (81). Butane was negative in *Drosophila melanogaster* sex-linked recessive lethal/reciprocal translocation tests (74).

Mice exposed to domestic cooking gas had significantly increased micronucleated polychromatic erythrocytes. The relationship between gas exposure and PCE levels was dose dependent. This may indicate that butane or a propane–butane mixture causes chromosome breaks and interferes with spindle formation (54).

4.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization.

Using the Drummond model for estimating the flammability, asphyxiant, and narcotic properties of light hydrocarbon gases, narcosis is possible at butane concentrations greater than 17,000 ppm (2).

Butane is considered a "weak" cardiac sensitizer in animals (6). At concentrations of 15–90%, butane sensitized the canine myocardium to cardiac arrhythmias induced by epinephrine in two of two test animals (36). Concentrations of 5000 ppm in the anesthetized dog may cause hemodynamic changes, such as decreases in cardiac output, left ventricular pressure and stroke volume, myocardial contractility, and aortic pressure (82). Butane does not cause respiratory or eye irritation in rabbits, and it appears to be mildly to moderately irritating to the rabbit skin (51).

4.4.2 Human Experience

4.4.2.1 General Information.

On direct contact, liquefied butane may cause burns or frostbite to the eyes, skin, or mucous membranes. The inhalation of 10,000 ppm for 10 min may result in CNS depression but produces no systemic effects (58). It can cause blurred vision and can be aspirated resulting in pneumonitis.

4.4.2.2 Clinical Cases.

At present, there are no epidemiological studies of the human health risks of inhaling butane; to date, all human butane toxicity studies are case reports. The majority of clinical reports of human butane exposure involve recreational use. Because intoxication requires inhalation of high concentration, it is difficult to determine if a given effect is the result of the most recent high-concentration exposure, or repeated exposures to high concentrations. Therefore, human health effects are presented by symptoms.

4.4.2.2.1 Death. There are numerous case reports of death resulting from inhalation of large concentrations of butane (59–61). Most fatal butane exposure patients are found dead. A 19 year old and a 14 year old adolescent who inhaled butane (24 empty cooking gas containers and 13 empty cigarette lighters, respectively) collapsed and died after sustained exertion (59). A nonfatal ventricular fibrillation was reported in a 15 year old healthy schoolgirl who collapsed after inhaling butane while fleeing from police (83). Blood butane levels in cases of fatal butane exposure range from 0.11 μg/mL to 129 mg/L (60).

Inhalation of butane from cigarette lighter refills causes burns to throat and lungs. This results in mucosal edema and laryngospasm, potentially causing both hypoxia and vagal stimulation, resulting in brachycardia and cardiac arrest (84). Butane also lowers the threshold for arrhythmia and overly sensitizes the myocardium to epinephrine and endogenous catecholamines. Stimulation (such as fright or exercise) after exposure to butane results in ventricular fibrillation and often death (85). Butane can induce fatal heart arrhythmia at concentrations between 0.5 and 15% in the air (59). Patients suffering from butane-induced cardiac arrest are usually very difficult to resuscitate (86).

4.4.2.2.2 Fetal brain injury. There are two case reports of brain injury in fetuses exposed to butane *in utero*. Hydranencephaly was described in an infant after maternal exposure to butane gas during pregnancy (87). A pregnant 34 year old mother was discovered unconscious after butane exposure in the 27th week of pregnancy. She required mechanical ventilation for 5 h and recovered from consciousness after 48 h. An interuterine ultrasound at the 39th week of pregnancy showed an almost complete absence of brain tissue in the fetus. At 7 days of age, electroencephalograms showed slow and low-voltage activity. Cranial CT scans revealed two fluid-filled cavities and only a small portion of the left occipital lobe was present. Some cerebral remnants persisted in the thalamic regions and the posterior fossa structures appeared to survive. Angiograms showed little to no blood vessel development in the brain, except for the circle of Willis and the vertebrobasilar system. Hydranencephaly is often associated with (or develops from) multicystic encephalomalacia. Brain damage was also reported in an infant exposed to butane gas *in utero* at 30 weeks of development (87, 88). The infant was born at 36 weeks of development and died 11 h after birth. Extensive

multicystic encephalomalacia was identified on autopsy; hydranencephaly that may have developed had the exposure happened earlier or the infant lived longer. Both of these case reports suggest that butane exposure to pregnant women can cause significant neurodevelopmental damage to the fetus.

4.4.2.2.3 Adult/adolescent brain injury. Six case reports show butane-related brain injury. A 600 mg brain edema was discovered on autopsy in a fatal case of propane–butane poisoning in a 19 year old baker's apprentice exposed to two "Kisag Gas" cartridges (60). The development of encephalopathy was reported within 24 h of hospitalization of a long-term butane user (5–10 cans over 3 years) for abdominal pain. CT scans showed severe cerebral edema and evidence of coning. These findings were confirmed on autopsy (89).

The development of severe brain damage was described in a 15 year old girl with a 4 week history of butane abuse (90). She was discovered after inhaling butane from lighter refill cans. After hospitalization, neurological complications developed. MRI scans revealed disintegrating gray matter, cerebral atrophy, and the destruction of the basal ganglia. There was diminished basal activity on an EEG scan. Six additional neurological cases were identified after butane exposure from German Toxicological Emergency Information Centers from 1996 to 2001. Of the six, four suffered hypoxic brain damage resulting in comas, one developed seizures, and one was somnolent (90).

The hospitalization of a 13 year old girl after inhalation of two commercial deodorant cans containing butane and hydrofluorocarbon 152A has been reported (91). On admission her Glasgow Coma Score as 10/15. The patient was alert 24 h after admission, and unable to stand for the first 3 days. A magnetic resonance image (MRI) performed 4 days after admission showed no abnormalities; the electroencephalogram showed abnormal delta and theta waveforms consistent with drug-induced encephalopathy.

A 16 year old male was admitted 2 days after inhaling 300 mL of butane (92). Family reported the patient was confused and lethargic 1 day before admission, with visual hallucinations. The patient was nonverbal on examination, with masked facies, and difficulties in coordination. Encephalogram reported intermittent front bilateral delta waves, and abnormal arousal response pattern consistent with encephalopathy. An MRI showed markedly abnormal increased signal in the thalami bilaterally. Increased diffusion coefficient values on diffusion-weighted imaging showed edema in the thalami. The conclusion was that butane may cause specific toxic damage to the thalamus and not just brain damage due to anoxia.

A 2 year old girl developed seizures, hypotension, and recurrent ventricular tachycardia after unintentional exposure to a spray can containing butane, isobutane, and propane (93).

4.4.2.2.4 Psychotic disorders. A 16 year old girl used butane as an abuse drug. She inhaled it for a year, and during the 3 months prior to the report, she inhaled about 22 canisters (232 mL). She used the cover of the canister as the mask for the abuse. She suffered from visual hallucinations during initial abuse and became increasingly irritable. Gradual deterioration in social functioning led to social isolation with very little contact with her peer group. Physical examination was unremarkable (94).

A 17 year old male was hospitalized for persistent visual, auditory, and somatic hallucinations and delusions of persecution (95). He began inhaling butane gas cylinders two and a half years before admission, inhaling the contents of one or two gas cylinders daily. When intoxicated, he experienced severe visual and auditory hallucinations. Hallucinations continued and became progressively worse after the patient stopped inhaling butane.

4.4.2.2.5 Hepatic failure. A 17 year old male presented with a 10 h history of abdominal pain and vomiting. Patient developed hepatomegaly (enlarged liver), polyuria, and jaundice. Patient admitted taking a proprietary engine/carburetor cleaner 2 days prior to admission; patient had a history of abusing 5–10 aerosol cans of butane daily for 3 years. On autopsy, the liver showed extensive necrosis of zones 2 and 3; these findings were typical of toxin-induced fulminant hepatic failure. Abuse of butane might either directly cause hepatic damage, or sensitize the liver to damage by other hepatotoxins (89).

4.4.2.2.6 Hemiparesis. A 15 year old boy with no previous symptoms was admitted 10 h after inhaling half a can of butane after falling and complaining that his leg felt "dead." He denied any long-term history of butane inhalation. Upon examination, a right-sided hemiparesis was identified. The patient had grade 1/5 in both the right arm and the right leg, flaccid tone, and an extensor (Babinski) plantar reflex. Brain CT scans were normal. Power began to return (grade 3/5) after 24 h. The patient still had pronounced upper limb weakness and a hemiplegic gait at discharge, 5 days after admission (96).

4.4.2.2.7 Rhabdomyolysis. The development of rhabdomyolysis after accidental exposure to butane has been reported (97). A 24 year old female was discovered unconscious 12 h after a butane gas leak. Examination revealed diffuse myalgias, swelling with marked muscle tension, and motor deficit in the peroneal nerve area internally and externally. Rhabdomyolysis was confirmed by a positive reaction to myoglobin by orthotoluidine strips and elevated creatine phosphokinase (3340 UI/L). Muscle tension and edema resolved after a week, but distal weakness persisted. Electromyography performed 25 days after exposure showed persistent myogenic muscle damage to the right side of the body.

A 50 year old male was admitted to the hospital after 5 h of exposure to butane through a gas leak in the bathroom. The

Table 27.4. Occupational Exposure Limits for Butane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH Recommended Exposure Limit	ACGIH TLV
Time-weighted average	–	800 ppm (1900 mg/m^3)	A TLV–TWA has been developed by ACGIH
Short-term exposure limit	–	–	–
Ceiling limit	–	–	–

[a] ACGIH, 8 h TWA; NIOSH, 10 h TWA.

From Ref. 25.

patient presented with myalgia and significant swelling of the legs. Peripheral pulse was present in both legs. Creatine phosphokinase was significantly elevated (37,450 UI/L). The patient developed anuric renal failure, requiring dialysis. Renal function, muscle tension, and creatinine phosphokinase gradually returned to normal 15 days after admission. The patient was released from the hospital after 1 month.

The development of rhabdomyolysis, the breakdown of muscle and the release of muscle fiber into the bloodstream, was observed after exposure to LPG with a 20% propane and 80% butane mix for 8 h (62). A 30 year old female presented with a diffuse dull pain that was not localized and did not have associated swelling. The patient could walk with difficulty if given support. Creatine phosphokinase at admission was 11,370 IU/dL. The patient did not develop complications and was discharged 9 days after admission.

4.4.2.2.8 Occupational hepatitis. A 28 year old male was admitted to the hospital complaining of nausea, malaise, and generalized lower limb weakness. ALT and AST were significantly elevated at admission. Viral and other drug screens were negative. The patient worked in confined spaces fixing butane and propane cylinders. He was diagnosed with acute hepatitis, likely due to chronic propane and butane exposure. Symptoms resolved themselves after 10 days of hospitalization (64).

4.4.2.2.9 Eye injury. A case report indicated that a spray on the eye (preignition) repeatedly caused transient blurring of vision (98).

Table 27.5. Occupational Exposure Limits for Butane in Different Countries

Country	Exposure Limit
Australia	TWA 800 ppm (1900 mg/m^3)
Austria	TWA 1000 ppm (2300 mg/m^3)
Belgium	TWA 800 ppm (1900 mg/m^3)
Denmark	TWA 500 ppm (1200 mg/m^3)
Finland	TWA 800 ppm (1900 mg/m^3); STEL 1000 ppm (2350 mg/m^3)
France	TWA 800 ppm (1900 mg/m^3)
Germany	TWA 1000 ppm (2350 mg/m^3)
Hungary	TWA 300 ppm; STEL 900 ppm
India	TWA 800 ppm (1900 mg/m^3)
Ireland	TWA 600 ppm (1430 mg/m^3); STEL 750 ppm (1780 mg/m^3)
Japan	TWA 500 ppm (1200 mg/m^3)
The Netherlands	TWA 600 ppm (1430 mg/m^3)
Poland	TWA 1900 mg/m^3; STEL 3000 mg/m^3
Russia	TWA 500 ppm; STEL 300 ppm
Switzerland	TWA 800 ppm (1900 mg/m^3)
United Kingdom	TWA 600 ppm (1450 mg/m^3); STEL 750 ppm (1810 mg/m^3)

From Ref. 25.

4.5 Standards, Regulations, or Guidelines of Exposure

Butane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). The ACGIH previously considered butane a simple asphyxiant (74). Drummond's modeling of the narcotic and flammability of butane suggests that regulation as a simple asphyxiant provides marginal protection for workers (2). Because of possible synergistic effects with other hydrocarbons and concurrent exposures, ACGIH recommends a time-weighted average for methane, ethane, propane, *n*-butane, 2-methylpropane, and any combination of these gases (9). Table 27.4 shows the occupational exposure limits for butane in the United States. Argentina, Bulgaria, Colombia, Jordan, Singapore, and Vietnam all use the recommended TWA of 1000 ppm (25); additional international limits are shown in Table 27.5.

5.0 2-Methylpropane

5.0.1 CAS Number

[*75–28-5*]

5.0.2 Synonyms

Isobutane, various grades; 1,1-dimethylethane; trimethylmethane

5.0.3 Trade Names

NA

5.0.4 Molecular Weight

58.12

5.0.5 Molecular Formula

$CH(CH_3)_3$

5.0.6 Molecular Structure

5.1 Chemical and Physical Properties

5.1.1 General

2-Methylpropane (isobutane), C_4H_{10}, a flammable gas, occurs in small quantities in natural gas and crude oil. It has been detected in urban atmospheres at concentrations of 44–74 ppb (99, 100). It also evolves from natural sources and has been measured in diesel exhaust at 1.4–11 ppm (101, 102) and in cigarette smoke at 10 ppm (103). The partition coefficient of propane between olive oil and air at 37°C is 12 using the method described by Sato and Nakajima and Perbellini et al. (2, 27, 28). The lower explosive limit is 18,000 ppm in air. Selected physical properties are listed in Table 27.1.

5.1.2 Odor and Warning Properties

Isobutane has a gasoline-like or natural gas odor (41).

5.2 Production and Use

Isobutane is produced in petroleum refining processes and from raw natural gas (104). Manufacturing generally occurs in closed systems to contain the gas and protect workers (105).

Isobutane is used as a component of gasoline, in the blending of motor fuels and in the production of high-octane blend stocks. It is used as an aerosol propellant in food products, cosmetics, and other consumer products. Isobutane comprises 10–16% of frying pan lubricants; manufacturers limit isobutane to 16% to avoid flammability hazards of higher concentrations (105). Isobutane is a constituent of aviation fuel, liquefied natural gas, substitute natural gas, industrial carrier gases, blowing agents, solvents, and refrigerants. The chemical industry uses isobutane in the synthesis of other chemicals, including propylene glycols, oxides, polyurethane foams, and polyurethane resins (105).

Isobutane is also used recreationally, either alone or in combination with propane and/or butane. Users, generally adolescents, will inhale high concentrations to become intoxicated. Isobutane-containing products are abused because they are widely available to adolescents, and provides a rapid, short lasting euphoria, usually with minimal "hangover" symptoms (44). From 2002 to 2007, inhalants comprised 14.5–19.6% of first illegal drug use among adolescents. Propane, butane, or a propane–butane mix were 7.1–9.9% of all inhalants used in the past year (45).

5.3 Exposure Assessment

5.3.1 Air

Headspace gas chromatography and infrared absorption spectroscopy have been used to measure isobutane concentrations in exposure chamber atmospheres (106). A gas chromatographic method for identification of propellants and aerating agents in aerosol whipped toppings and antistick pan coatings has been developed (107).

5.3.2 Background Levels

NA

5.3.3 Workplace Methods

NA

5.3.4 Community Methods

NA

5.3.5 Biomonitoring/Biomarkers

Isobutane has been determined in blood and expired air of human volunteers by headspace gas chromatography (106).

5.4 Toxic Effects

5.4.1 Experimental Studies

5.4.1.1 Acute Toxicity. The 1 h LC_{50} for the mouse is 52 mg/L (103). At concentrations in the range of the LC_{50}, mice exhibit CNS depression, rapid and shallow respiration, and apnea (8). In another study, 2 h exposures of mice to 41 mg/L caused death in 60% of the exposed animals, whereas exposure to 52 mg/L was lethal to 100% of the animals within an average of 28 min (76). The onset of anesthesia in mice exposed to 15, 20, and 23% isobutane by volume was 60, 17, and 26 min, respectively (76).

The 4 h LC_{50} for the rat is greater than 32.21 mg/L; this was the highest concentration tested due to explosive hazard and no rats died at this concentration. Albino Sprague–Dawley rats exposed to isobutane concentrations up to 32.21 mg/L did not present symptoms of intoxication and appeared normal for the 14 day observation period. Weight was decreased in male rats 2–3 days postexposure, and in female rats for the entire 14 day observation period (105). In dogs, 55 mg/L were fatal, and 45 mg/L caused anesthesia (105).

5.4.1.2 Chronic and Subchronic Toxicity. Subchronic toxicity studies of exposure to mixtures containing isobutane are summarized in Table 27.6 (51, 108, 109).

5.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Rats exposed to 1000–5000 ppm by inhalation only absorbed 5.4% through their lungs (105). Isobutane is oxidatively metabolized by rat liver microsomes to its parent alcohol (37). Butanol cannot be oxidized to a ketone product, and it may be either conjugated with glucuronic acid or excreted unchanged in the expired air or urine (111).

5.4.1.4 Reproductive and Developmental. NA

5.4.1.5 Carcinogenesis. NA

5.4.1.6 Genetic and Related Cellular Effects Studies. Isobutane tested negative in the Ames *Salmonella* mutagenicity assay (81).

5.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Using the Drummond model for estimating the flammability, asphyxiant, and narcotic properties of light hydrocarbon gases, narcosis is possible at isobutane concentrations greater than 24,000 ppm (2).

Isobutane is a weak cardiac sensitizer (6). At high concentrations, a decrease in pulmonary compliance and tidal volume has been noted in the rat (112). No effects were noted in anesthetized dogs at concentrations of $\leq$2%, but decreased myocardial contractility was noted at 2.5%; exaggerated effects, at 5%, with a decrease in ventricular and aortic pressure; and at 10%, decreased left ventricular pressure, mean arterial flow, and stroke volume, with increased pulmonary vascular resistance. At concentrations of 15–90%, isobutane sensitized the canine myocardium to cardiac arrhythmias induced by epinephrine in two of two test animals (36). Exposure to 2.5% isobutane for 5 min followed by epinephrine challenge did not induce cardiac arrhythmia in any test dogs; 5% isobutane induced cardiac arrhythmia in 4 of 12 test dogs, and 10–20% isobutane-induced cardiac arrhythmia in all 6 test dogs and ventricular fibrillation in 1 (6). Swiss male mice exposed to 20% isobutane for 2 min followed by epinephrine challenge induced arrhythmia (56). Rats exposed to 27% isobutane for 15 min suffered cardiac arrest (112).

Isobutane is a CNS depressant in the mouse at 15% in 60 min, and at 23% in 26 min (76). Mice exposed to 35% isobutane by volume lost postural control an average of 25 min of exposure; mice exposed at higher concentrations (41 and 52% by volume) lost postural control almost immediately (2–3 min after exposure, respectively). Mice exposed at these concentrations recovered within 3–4 min (76).

Studies in rabbits exposed in the eyes to undiluted hairspray containing 22% isobutane, showed that irritation of the eye was immediately evident with transient iritis and mild conjunctivitis (103).

5.4.2 Human Experience

5.4.2.1 General Information. Isobutane is a simple asphyxiant. Acute exposures may cause tachypnea and tachycardia. In severe cases, hypotension, apnea, and cardiac arrest develop. Direct contact with the liquid produces chemical burns. Toxicologically, the vapor exerts no effect on skin and eyes (8).

5.4.2.2 Clinical Cases. A 2 year old girl suffered ventricular tachycardia, tonoclonic seizure, and hypokalemia after exposure to a deodorant containing butane, isobutane, and propane. Exposure and endogenous epinephrine is thought to have induced the tachycardia. Hypokalemia may have been due to increased endogenous catecholamine levels (113).

Two fatal cases of isobutane exposure have been described (114). The first case was a 13 year old male who collapsed after sniffing the contents of a cigarette lighter via a plastic bag; he was reported to be laughing after the first exposure and collapsed after the second. The second case was a 20 year old male found dead with a cigarette lighter refill. On autopsy, the lungs of both cases had massive hemorrhagic edema with activated macrophages. Both cases also had distinct myocardial fibrosis, an accumulation of fibronectin and a reduction in troponin C. These cardiac changes may have been caused by a chronic isobutane exposure at high levels consistent with repeated isobutane abuse.

5.4.2.3 Epidemiology Studies

5.4.2.3.1 Acute toxicity. Human volunteers exposed to 250–1000 ppm for 1 min to 8 h and 500 ppm for 1–8 h/day for 10 days to isobutane showed no adverse effects or abnormal physiological responses (cardiac and pulmonary function) (68, 106).

5.4.2.3.2 Pharmacokinetics, metabolism, and mechanisms. Human volunteers were exposed to 100 ppm of isobutane by inhalation absorbed 14% of the exposed gas through the lungs (105).

5.4.2.3.3 Other: neurological, pulmonary, and skin sensitization. Seventy-five human volunteers from 18 to 60 years old were dermally exposed to a deodorant with a 64.5% mix of isobutane and propane twice a day for 12 weeks, and 50 human volunteers from 18 to 60 years old were exposed to an antiperspirant with a 70% mix of isobutane and propane. Participants developed slight, transient erythema; these reactions were considered negligible (52).

5.5 Standards, Regulations, or Guidelines of Exposure

Isobutane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). Isobutane is generally

Table 27.6. Summary of Subchronic Toxicity Studies in Animals Exposed to Mixtures Containing 2-Methylpropane

Species	Exposure Route	Chemical Mixture	Approximate Dose	Treatment Regimen	Observed Effect	References
Fischer rats	Inhalation	50–50 (wt%) *n*-butane:*n*-pentane	1000, 4500 ppm	6 h/day, 5 days/week, 13 weeks	Mild–transient kidney effects not exposure-related	(109)
		50–50 (wt %) isobutane:isopentane	1000, 4500 ppm	6 h/day, 5 days/week, 13 weeks	Mild–transient kidney effects not exposure-related	
Sprague–Dawley rats	Inhalation	25 (wt%) *n*-butane, *n*-pentane, isobutane, isopentane	0, 44, 432, 4437 ppm	6 h/day, 5 days/week, 3 weeks	No clinical signs of toxicity and no nephrotoxicity observed	(110)
Rabbits	Inhalation	Hairspray with 22% isobutane	2 daily, 30 s aerosol bursts	3 days/week, 90 days	No changes in body weight, hematology, clinical chemistry, and urinalysis	(51)

Table 27.7. Occupational Exposure Limits for 2-Methylpropane in Different Countries

Country	Exposure Limit
Germany	TWA 1000 ppm (2350 mg/m^3)
Switzerland	TWA 800 ppm (1900 mg/m^3)
United Kingdom	TWA 600 ppm (1430 mg/m^3); STEL 750 ppm

From Ref. 25.

recognized as safe by the FDA for use as a food ingredient (105). Drummond's modeling of the narcotic and flammability of butane suggests that regulation as a simple asphyxiant provides marginal protection for workers (2). Because of possible synergistic effects with other hydrocarbons and concurrent exposures, ACGIH recommends a time-weighted average for methane, ethane, propane, *n*-butane, 2-methylpropane, and any combination of these gases (9). There is no OSHA PEL. The NIOSH 10 h TWA is 800 ppm (1900 mg/m^3) (44). Argentina, Bulgaria, Colombia, Jordan, Singapore, and Vietnam all use the recommended TWA of 1000 ppm (25); additional occupational exposure limits for isobutane in different countries are shown in Table 27.7.

6.0 *n*-Pentane

6.0.1 CAS Number

[*109–66-0*]

6.0.2 Synonyms

Amyl hydride, skellysolve A, normal pentane.

6.0.3 Trade Names

NA

6.0.4 Molecular Weight

72.15

6.0.5 Molecular Formula

$CH_3(CH_2)_3CH_3$

6.0.6 Molecular Structure

6.1 Chemical and Physical Properties

6.1.1 General

Pentane, C_5H_{12}, is a colorless, highly volatile, and flammable liquid, with specific gravity 0.626 and vapor pressure 400 Torr at 18.5°C. It has been detected in the urban atmosphere from combustion exhausts and natural sources (115). Selected physical properties are given in Table 27.1.

6.1.2 Odor and Warning Properties

The odor threshold for pentane is between 6.6 and 3000 mg/m^3. Pentane exhibits a moderate odor intensity at 5000 ppm (29, 58) and has a gasoline-like odor (29).

6.2 Production and Use

Pentane is produced by fractional distillation of natural gas liquids and crude oil. It is also produced by the catalytic crackdown of naphtha (116). Pentane is used as a constituent in motor and aviation fuel; in solvent extraction processes, as a general laboratory solvent, and as a medium solvent for polymerization reactions; and as a raw material in the synthesis of olefins and other industrial chemicals like amyl chloride (116). Pentane is used in the manufacture of ice and low-temperature thermometers (117).

6.3 Exposure Assessment

6.3.1 Air

Determination of pentane has been conducted by adsorption on Tenax and subsequent thermal desorption into a gas chromatograph (118). Other methods to determine pentane in air include headspace gas chromatography and infrared absorption spectrometry (32).

6.3.2 Background Levels

NA

6.3.3 Workplace Methods

NIOSH method 1500 describes an air monitoring procedure for pentane and other hydrocarbons (119). Samples are collected on charcoal, desorbed with carbon disulfide, and quantified by gas chromatography with a flame ionization detector. Passive vapor monitors have also been used and correlate satisfactorily with charcoal sampling (120).

6.3.4 Community Methods

NA

6.3.5 Biomonitoring/Biomarkers

Pentane has been measured in human blood and tissues (liver, kidney, brain, fat, muscle, heart, and lung) by headspace gas chromatography (27).

6.4 Toxic Effects

6.4.1 Experimental Studies

6.4.1.1 Acute Toxicity. The intravenous LD_{50} of pentane is 446 mg/kg and the 2 h LC_{50} is 325 mg/m^3 (63). Pentane is anesthetic to mice at 7% concentration in 10 min and 9% concentration in 1.3 min (76). A concentration of 128,000 ppm caused deep anesthesia in mice, whereas 9–12% concentration for 5–60 min resulted in CNS depression, and 12.8% for 37 min resulted in death (121). Doses of 40% resulted in death of mice, which showed collapsed lungs on autopsy (122). Generally, death is preceded by loss of reflexes and prostration (116). Concentrations of 200–300 mg/L caused incoordination and inhibition of the righting reflex of mice (123). Air concentrations of 10.4, 50.9, and 94.7 mg/m^3 showed histological changes in the developing cerebral cortex of the rat (124).

6.4.1.2 Chronic and Subchronic Toxicity. Studies in rats exposed to 3000 ppm (12 h/day, 7 days/week for 16 weeks) found no signs of abnormal neurobehavioral effects (normal motor activity and no evidence of peripheral neuropathy). No particular changes in the nerve fibers and the peripheral nerve or alteration of motor conduction velocity were observed (125, 126). Thirty-week inhalation studies in rats exposed to 3000 ppm pentane (9 h/day, 5 days/week) showed no evidence of neurotoxicity. Nerve tissues examined histologically showed no "giant axonal degeneration," but a decrease in body weight was observed in exposed rats (127).

6.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Absorption of pentane via the lungs is the most likely mean of exposure. Under occluded conditions, pentane penetrates through full-thickness rat skin at a rate of 2.2 µg/cm^2 per h (128). Pentane distributes into the human tissues and blood. In the tissues studied, the highest solubility was found in adipose tissue, followed by brain, liver, muscle, kidney, lung, and heart (27). The elimination half-life of pentane is about 13 h (32). Pentane is metabolized by hydroxylation to pentanol, conjugated with glucuronate, and subsequently excreted in urine or expired air (37, 129). The metabolism of pentane is saturable (32).

6.4.1.4 Reproductive and Developmental. NA

6.4.1.5 Carcinogenesis. NA

6.4.1.6 Genetic and Related Cellular Effects Studies. Pentane is not mutagenic in the Ames *Salmonella* system (81).

6.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Pentane is a weak cardiac sensitizer of the dog heart to epinephrine (6, 36). It is a dermal irritant; however, inhalation of 5000 ppm (0.5%) pentane for 10 min was not irritating to mucous membranes and did not produce local or systemic effects (8). Pentane had a slow inhibitory action on the myelin sheath of the peripheral nerve tissue in the rat (130). A nerve impulse blockage has been demonstrated in the squid axon and in the frog sciatic nerve (131) that could be verified for pentane and hexane (132). Pure pentane does not cause axonopathy (125). Some isolated systemic effects indicate local affinity and destruction of the myelin sheath of peripheral nerve tissue (130). Subcutaneous injections of pentane produce temporary impairment of the liver function in rats (133).

6.4.2 Human Experience

6.4.2.1 General Information

Pentane is a CNS depressant, but is not as effective as the C1–C4 gases. The intensity of CNS depression appears generally to decrease with increasing molecular weight, but increases for the highly symmetrical compounds (134). Only a small increment in dose separates CNS depression and lethality (8). The aspiration hazard of pentane is considerably less than that of kerosene, octane, nonane, or decane (135).

6.4.2.2 Clinical Cases

6.4.2.2.1 Acute toxicity. Five cases of polyneuropathy occurred among employees of a belt manufacturing shop. The solvent believed responsible contained 80% pentane, 14% heptane, and 5% hexane. The symptoms in three of the cases consisted of anorexia, asthenia, paresthesis, fatigue, and bilateral symmetrical muscle failure. Electromyographic and nerve conduction studies revealed peripheral nerve changes. Hexane, however, is believed to be responsible for the toxicity (136).

6.4.2.2.2 Chronic and subchronic toxicity. Chronic exposure to pentane has resulted in anoxia (137).

6.4.2.3 Epidemiology Studies

6.4.2.3.1 Acute toxicity. Volunteers exposed to 5000 ppm pentane for 10 min showed no mucous membrane irritation or other symptoms (58).

6.4.2.3.2 Chronic and subchronic toxicity. NA

6.4.2.3.3 Pharmacokinetics, metabolism, and mechanisms. NA

6.4.2.3.4 Reproductive and developmental. NA

6.4.2.3.5 Carcinogenesis. NA

Table 27.8. Occupational Exposure Limits for Pentane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH Exposure Limit	ACGIH TLV
Time-weighted average	1000 ppm (2950 mg/m^3)	120 ppm (350 mg/m^3)	A TLV–TWA has been developed by ACGIH
Short-term exposure limit	750 ppm (2250 mg/m^3)	610 ppm (1800 mg/m^3)	–
Ceiling limit	–	–	–

[a] OSHA and ACGIH, 8 h TWA; NIOSH, 10 h TWA.

From Ref. 25.

6.4.2.3.6 Genetic and related cellular effects studies. NA

6.4.2.3.7 Other: neurological, pulmonary, and skin sensitization. Dermal effects of pentane vapors applied to the skin of five volunteers were studied. Erythema, hyperemia, swelling, and pigmentation were observed after dermal exposure. The volunteers complained of a constant burning sensation accompanied by itching and blisters after 5 h of exposure. There was no evidence of anesthetic effects on the skin. When pentane was removed after 5 h, pain continued for 15 min (138).

6.5 Standards, Regulations, or Guidelines of Exposure

Pentane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (84). The IDLH concentration determined by NIOSH is 1500 ppm (based on 10% of the lower explosive limit) (41). The occupational exposure limits for pentane in the United States are listed in Table 27.8, and the international standards are presented in Table 27.9.

7.0 2-Methylbutane

7.0.1 CAS Number

[*78–78-4*]

7.0.2 Synonyms

Isopentane, ethyldimethylmethane, isoamylhydride, 1,1,2-trimethylbutane, 1,1,2-trimethylethane, 1-pentane, isopropentane

7.0.3 Trade Names

NA

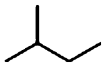
7.0.4 Molecular Weight

72.15

7.0.5 Molecular Formula

$(CH_3)_2CHCH_2CH_3$

7.0.6 Molecular Structure



7.1 Chemical and Physical Properties

7.1.1 General

2-Methylbutane (isopentane), C_5H_{12}, is a flammable liquid and exhibits physical properties very similar to those of pentane. It has a specific gravity of 0.619 and a vapor pressure of 595 Torr at 21.1°C. It has been detected in urban air (99, 100, 102). Selected physical data are given in Table 27.1.

Table 27.9. Occupational Exposure Limits for Pentane in Different Countries[b]

Country	Exposure Limit
Australia	TWA 600 ppm (1800 mg/m^3); STEL 750 ppm (2250 mg/m^3)
Belgium	TWA 600 ppm (1770 mg/m^3); STEL 750 ppm (2210 mg/m^3)
Denmark	TWA 500 ppm (1500 mg/m^3)
Finland	TWA 500 ppm (1500 mg/m^3); STEL 625 ppm (1800 mg/m^3)
France	TWA 600 ppm (1800 mg/m^3)
Germany	TWA 1000 ppm (3000 mg/m^3)
Hungary	TWA 500 mg/m^3; STEL 1500 mg/m^3
Ireland	TWA 600 ppm (1800 mg/m^3); STEL 750 ppm (2250 mg/m^3)
Japan	TWA 300 ppm (880 mg/m^3)
The Netherlands	TWA 600 ppm (1800 mg/m^3)
The Philippines	TWA 1000 ppm (2950 mg/m^3)
Poland	TWA 1800 mg/m^3; STEL 2300 mg/m^3
Russia	TWA 300 ppm; STEL 300 mg/m^3
Sweden	TWA 600 ppm (1800 mg/m^3); STEL 750 ppm (2000 mg/m^3)
Switzerland	TWA 600 ppm (1800 mg/m^3)
Turkey	TWA 1000 ppm (2950 mg/m^3)
United Kingdom	TWA 600 ppm (1800 mg/m^3); STEL 750 ppm

From Ref. 25.

7.1.2 Odor and Warning Properties

Isopentane exhibits a gasoline-like odor (63).

7.2 Production and Use

Isopentane is produced by fractional distillation of natural gas liquids and crude oil (139). It is used as a solvent, as a blowing agent for polystyrene and other polymers, and in the synthesis of organic chemicals (e.g., chlorinated hydrocarbons) (139). As an anesthetic, isopentane is less potent than the shorter-chain alkanes; however, it appears more active metabolically (76).

7.3 Exposure Assessment

7.3.1 Air

Atmospheric concentrations of isopentane may be determined by a gas chromatographic system equipped with a flame ionization detector (71). Other methods to determine isopentane in air include headspace gas chromatography, infrared absorption spectrometry, and gas chromatography/mass spectrometry (32, 140).

7.3.2 Background Levels

NA

7.3.3 Workplace Methods

Monitoring of worker exposures to gasoline vapors using charcoal tubes yields excellent results if sample flow rate is adjusted properly with regard to absolute humidity (141).

7.3.4 Community Methods

NA

7.3.5 Biomonitoring/Biomarkers

Isopentane can be measured in human blood and tissues by headspace gas chromatography (139).

7.4 Toxic Effects

7.4.1 Experimental Studies

7.4.1.1 Acute Toxicity. The 1 h LC_{50} in the mouse is estimated to be 1000 mg/L. Isopentane is lethal to dogs at levels of 150,000–170,000 ppm (76). Mice exposed to 90,000 isopentane for 11 min showed light anesthesia. At higher concentrations (110,000 and 120,000 ppm), the narcotic effect appeared within 4 and 2 min, respectively. In dogs, 120,000 ppm was required to induce light anesthesia (76).

7.4.1.2 Chronic and Subchronic Toxicity. NA

7.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Male rats exposed to 10 ppm isopentane for 10 min for five consecutive days showed an uptake of 1.6 $\pm$ 0.2 nmol/kg/min (142). Isopentane is metabolized by hydroxylation to 2-methyl-2-butanol as the major metabolite, and 3-methyl-2-butanol, 2-methyl-1-butanol, and 3-methyl-1-butanol as minor metabolites in rat, mouse, rabbit, and guinea pig liver microsomes (37).

7.4.1.4 Reproductive and Developmental. NA

7.4.1.5 Carcinogenesis. NA

7.4.1.6 Genetic and Related Cellular Effects Studies. The mutagenic activity of isopentane has been assayed using the Ames test. At concentrations of 100,000 ppm, it was not mutagenic in the presence and absence of a metabolic activating system (81).

7.4.2 Human Experience

7.4.2.1 General Information. Very little is known about the toxicity of isopentane.

7.4.2.2 Clinical Cases

7.4.2.2.1 Acute toxicity. Inhalation of $\leq$500 ppm isopentane appears to have no effect on humans (80). In confined spaces, high concentrations capable of causing unconsciousness or death have been known to occur (143).

7.4.2.2.2 Chronic and subchronic toxicity. NA

7.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. NA

7.4.2.2.4 Reproductive and developmental. NA

7.4.2.2.5 Carcinogenesis. NA

7.4.2.2.6 Genetic and related cellular effects studies. NA

7.4.2.2.7 Other: neurological, pulmonary, skin sensitization, and so on. Isopentane causes CNS depression between 270 and 400 mg/L (18), and is a weak cardiac sensitizer (36). High vapor concentrations are irritating to the skin and eyes.

7.5 Standards, Regulations, or Guidelines of Exposure

Isopentane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA and NIOSH have not established exposure limits. ACGIH recommends a combined time-weighted average for all pentane isomers (117). Argentina, Bulgaria, Colombia, Jordan, Singapore, and Vietnam all

use a recommended TWA of 600 ppm. Belgium and Sweden have a TWA of 600 ppm and a STEL of 750 ppm. Denmark has a TWA of 500 ppm. The European Community and Germany use a TWA of 1000 ppm. Switzerland has a MAK-week limit of 600 ppm and a KZG-week limit of 1200 ppm (25).

8.0 2,2-Dimethylbutane

8.0.1 CAS Number

[*75–83-2*]

8.0.2 Synonyms

Neohexane, neohexane (2,2-dimethylbutane)

8.0.3 Trade Names

NA

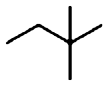
8.0.4 Molecular Weight

86.177

8.0.5 Molecular Formula

$CH_3CH(CH_3)_2CH_2CH_3$

8.0.6 Molecular Structure



8.1 Chemical and Physical Properties

8.1.1 General

2,2-Dimethylbutane, C_6H_{14}, is a colorless and flammable liquid with a specific gravity of 0.6444. Selected physical and chemical properties are listed in Table 27.1.

8.1.2 Odor and Warning Properties

2,2-Dimethylbutane has a mild gasoline-like odor (23).

8.2 Production and Use

2,2-Dimethylbutane is produced from crude oil, natural liquid gases, and petroleum refining processes. It is used as a component of high-octane motor and aviation fuels; and as an intermediate in agricultural chemistry (144).

8.3 Exposure Assessment

8.3.1 Air/Water

2,2-Dimethylbutane samples have been analyzed by gas chromatography using a cryogenic trapping technique (63). Headspace gas chromatographic techniques may also be used (27). A modified purge-and-trap gas chromatographic analysis has been used to measure 2,2-dimethylbutane in water (145).

8.3.2 Background Levels

NA

8.3.3 Workplace Methods

2,2-Dimethylbutane air samples may be collected using charcoal tubes, passive vapor samplers, stainless-steel canisters, and Tenax tubes (63, 120).

8.3.4 Community Methods

NA

8.3.5 Biomonitoring/Biomarkers

Headspace gas chromatography methods have been used to measure the concentrations of 2,2-dimethylbutane in human blood and tissues (27). A purge-and-trap method with gas chromatography/mass spectrometry has also been used to measure blood levels in humans (146).

8.4 Toxic Effects

8.4.1 Experimental Studies

Relatively little toxicity data on 2,2-dimethylbutane are available.

8.4.1.1 Acute Toxicity. NA

8.4.1.2 Chronic and Subchronic Toxicity. NA

8.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. NA

8.4.1.4 Reproductive and Developmental. NA

8.4.1.5 Carcinogenesis. NA

8.4.1.6 Genetic and Related Cellular Effects Studies. 2,2-Dimethylbutane tested negative for mutagenicity in the Ames *S. typhimurium* assay, both with and without metabolic activation (147).

8.4.1.7 Other: Neurological, Pulmonary, Skin Sensitization, and so on. 2,2-Dimethylbutane at concentrations of 100,000–250,000 ppm sensitizes the myocardium in dogs to epinephrine-induced cardiac arrhythmias (36).

8.4.2 Human Experience

8.4.2.1 General Information. Very little is known about the health effects of 2,2-dimethylbutane in humans. It may be narcotic in high concentrations.

8.4.2.2 Clinical Cases

8.4.2.2.1 Acute toxicity. NA

8.4.2.2.2 Chronic and subchronic toxicity. NA

8.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. 2,2-Dimethylbutane is distributed in human tissues in the same manner as pentane and hexane; adipose tissue has a high affinity for all the C6–alkanes (27).

8.5 Standards, Regulations, or Guidelines of Exposure

OSHA has not established exposure limits (41). A TLV–TWA has been developed by ACGIH (148). The Cal/OSHA PEL for all hexane isomers other than *n*-hexane is 500 ppm (1800 mg/m^3); the STEL is 1000 ppm (3600 mg/m^3) (24). The NIOSH REL is 100 ppm (350 mg/m^3) TWA, with 510 ppm (1800 mg/m^3) ceiling limit for hexane isomers other than *n*-hexane (41).

9.0 2,3-Dimethylbutane

9.0.1 CAS Number

[*79–29-8*]

9.0.2 Synonyms

Diisopropyl, 1,1,2,2-tetramethylethane

9.0.2 Trade Names

NA

9.0.3 Molecular Weight

86.177

9.0.4 Molecular Formula

$(CH_3)_2CHCH(CH_3)_2$

9.0.5 Molecular Structure

9.1 Chemical and Physical Properties

9.1.1 General

2,3-Dimethylbutane, C_6H_{14}, is a flammable liquid with a specific gravity of 0.66164. It is released into the atmosphere from automobile, biomass combustion, and gasoline vapor emissions. Selected physical and chemical properties are listed in Table 27.1.

9.1.2 Odor and Warning Properties

2,3-Dimethylbutane has a mild gasoline-like odor (23).

9.1.3 Production and Use

2,3-Dimethylbutane is produced from crude oil, natural liquid gases, and petroleum refining processes (144). It is used in high-octane fuels and in organic synthesis (63).

9.2 Exposure Assessment

9.2.1 Air/Water

Gas chromatography using a low-volume photoionization detector and a standard flame ionization detector in tandem has been used to detect trace hydrocarbons in atmospheric samples, including 2,3-dimethylbutane (149). A modified variant of the purge-and-trap gas chromatographic analysis can be used to detect 2,3-dimethylbutane in water (145). Headspace gas chromatographic techniques may also be used (27).

9.3 Toxic Effects

9.3.1 Experimental Studies

Little toxicity data on 2,3-dimethylbutane are available.

9.3.1.1 Acute Toxicity. NA

9.3.1.2 Chronic and Subchronic Toxicity. Subchronic toxicity was evaluated in two groups of 10 male rats receiving 0.5 or 2.0 g/kg 2,3-dimethylbutane once daily by oral gavage, 5 days/week for 4 weeks. Mortality was observed in the low-dose group (two rats) and in the high-dose group (three rats) during the test. Terminal body weights were significantly lower in the high-dose group, and mean kidney weights were significantly higher in both groups compared to the control group. Histopathological kidney examination showed signs of nephrotoxicity (63).

9.3.1.3 Pharmacokinetics, Metabolism, and Mechanisms. NA

9.3.1.4 Reproductive and Developmental. NA

9.3.1.5 Carcinogenesis. NA

9.3.1.6 Genetic and Related Cellular Effects Studies. 2,3-Dimethylbutane tested negative for mutagenicity in the Ames *S. typhimurium* assay, with and without metabolic activation (147).

9.4 Standards, Regulations, or Guidelines of Exposure

2,3-Dimethylbutane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (22). OSHA has not established exposure limits (NIOSH Pocket Guide). A TLV–TWA has been developed by ACGIH (148). The Cal/OSHA PEL for all hexane isomers other than *n*-hexane is 500 ppm (1800 mg/m^3); the STEL is 1000 ppm (3600 mg/m^3) (24). The NIOSH REL is 100 ppm (350 mg/m^3) TWA, with 510 ppm (1800 mg/m^3) ceiling limit for hexane isomers other than *n*-hexane (41).

10.0 2,2-Dimethylpropane

10.0.1 CAS Number

[*463–82-1*]

10.0.2 Synonyms

Neopentane, *tert*-pentane, neopentane (in cylinder without valve), tetramethylmethane, 1,1,1-trimethylethane

10.0.3 Trade Names

NA

10.0.4 Molecular Weight

72.15

10.0.5 Molecular Formula

$C(CH_3)_4$

10.0.6 Molecular Structure

10.1 Chemical and Physical Properties

10.1.1 General

2,2-Dimethylpropane, C_5H_{12}, is a flammable liquid and is physically similar to butane. It is an important component of petroleum fuel mixtures. It has a specific gravity of 0.591 and a vapor pressure of 1100 Torr at 21.8°C. Selected physical properties are shown in Table 27.1.

10.2 Production and Use

2,2-Dimethylpropane is manufactured by petroleum refining operations. It is used as a chemical intermediate for agricultural chemicals, and as a component of high-octane motor and aviation fuels (63).

10.3 Exposure Assessment

10.3.1 Air

2,2-Dimethylpropane may be quantified by headspace gas chromatography and by infrared absorption spectrometry (139).

10.3.2 Background Levels

NA

10.3.3 Workplace Methods

NA

10.3.4 Community Methods

NA

10.3.5 Biomonitoring/Biomarkers

Headspace gas chromatography may be used to measure 2,2-dimethylpropane in blood and tissues (139).

10.4 Toxic Effects

10.4.1 Experimental Studies

10.4.1.1 Acute Toxicity. The lethal dose 50% kill (LD_{50}) for 2,2-dimethylpropane in mouse is 100 mg/kg (150). At concentrations of 340,000 ppm, it is lethal to 40% of mice exposed for 2 h. At 200,000–270,000 ppm, no deaths were observed. Comparatively, it is less toxic than isopentane and pentane (76). Thirty-minute exposures to 200 ppm 2,2-dimethylpropane are required before light anesthesia is seen in mice (76).

10.4.1.2 Chronic and Subchronic Toxicity. NA

10.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. 2,2-Dimethylpropane is hydroxylated to 2,2-dimethylpropanol by rat liver microsomes (37).

10.4.1.4 Reproductive and Developmental. NA

10.4.1.5 Carcinogenesis. NA

10.4.1.6 Genetic and Related Cellular Effects Studies. NA

10.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization,. 2,2-Dimethylpropane is likely to sensitize the myocardium at high exposure levels (139).

10.5 Standards, Regulations, or Guidelines of Exposure

2,2-Dimethylpropane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA and NIOSH have not established exposure limits. A TLV–TWA has been developed by ACGIH (117). The occupational exposure limit in Denmark is 500 ppm (1500 mg/m^3) TWA (25).

11.0 n-Hexane

11.0.1 CAS Number

[*110–54-3*]

11.0.1 Synonyms

Hexyl hydride, hexane, hex, normal hexane, dipropyl, skellysolve B, gettysolve b

11.0.2 Trade Names

NA

11.0.3 Molecular Weight

86.10

11.0.4 Molecular Formula

$CH_3(CH_2)_4CH_3$

11.0.5 Molecular Structure

11.1 Chemical and Physical Properties

11.1.1 General

n-Hexane, C_6H_{14}, is a flammable liquid. Its vapor pressure is 124 Torr at 20°C and 145 Torr at 25°C, and its specific gravity is 0.660 at 20°C. It is a constituent in the paraffin fraction of crude oil and natural gas, and is released to the environment via the manufacture, use, and disposal of many products associated with the petroleum (63). Selected physical properties are given in Table 27.1.

11.1.2 Odor and Warning Properties

Hexane has a gasoline-like odor that is irritating at 1800 mg/m^3 (29).

11.2 Production and Use

Hexane is isolated from natural gas and crude oil (151). It is used pure or as commercial-grade solvent in the extraction of oil seeds; as the reaction medium in the manufacture of polyolefins, elastomers, and pharmaceuticals; formulated in a variety of products (glues, stains, varnishes, cleaning agents, and printing inks); as a laboratory reagent; and as a denaturant for alcohol (151, 152).

11.3 Exposure Assessment

11.3.1 Air

Hexane may be detected in air by gas chromatography or extractive Fourier transform infrared spectrometry (41).

11.3.2 Water

Hexane may be detected in water by gas chromatography with flame ionization detection (153, 154).

11.3.3 Background Levels

NA

11.3.4 Workplace Methods

NIOSH method 1500 has been used to determine air concentrations for hexane and other hydrocarbons (119). Samples are collected on charcoal, desorbed with carbon disulfide, and quantified by gas chromatography with a flame ionization detector. Samples may also be collected using passive samplers in which individual chemicals simply diffuse from the atmosphere into the sampler at a fixed rate. The sampler consists of a polypropylene/polyester assembly with tubular sampling channels and a coconut charcoal wafer (155). NIOSH method 3800 can be used to determine hexane concentrations in ambient air (41).

11.3.5 Community Methods

NA

11.3.6 Biomonitoring/Biomarkers

Hexane has been determined in blood and urine by headspace gas chromatography (156, 157). It has been measured in milk and expired air by gas chromatography/mass spectrometry (158, 159). 2,5-Hexanedione, a metabolite of hexane, is measured in urine for toxicokinetic studies and biological monitoring of occupational exposure to hexane. The ACGIH developed a BEI for 2,5-hexanedione, measured at the end of a shift (152). Two analytical methods are commonly used: one of them is based on derivatization, followed by gas chromatography and electron capture detection; the second one involves direct extraction of 2,5-hexanedione followed

by gas chromatography and flame ionization detection (160). Human polymorphonuclear leukocytes chemotaxis has been used as biomarker of early effect to exposure to low levels of hexane (161). Suppression in the serum immunoglobulin (IgG, IgM, and IgA), has also been used as a marker of the immune function in workers exposed to hexane (162).

11.4 Toxic Effects

11.4.1 Experimental Studies

11.4.1.1 Acute Toxicity. Hexane is three times more toxic than pentane to mice; concentrations of 30,000 ppm produce narcosis within 30–60 min, and convulsions and death occur from inhalation of 35,000–40,000 ppm (121). The oral LD_{50} in rats is 28.7 mg/kg (163), and the inhalation 4 h LC_{50} in rats is 48,000 ppm (164). Dermal application of 2–5 mL/kg for 4 h to rabbits resulted in ataxia and restlessness (165). No deaths occurred at 2 mL/kg, but lethality was noted at 5 mL/kg. Inhalation of 1,000–64,000 ppm for 5 min in the mouse resulted in irritation of the respiratory tract and anesthesia (121), 30,000 ppm produced CNS depression (135), and 34,000–42,000 ppm was lethal (166).

11.4.1.2 Chronic and Subchronic Toxicity. Subchronic toxicity studies of exposure to hexane are summarized in Table 27.10 (128, 167–173).

11.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Hexane is absorbed by respiratory or percutaneous routes, and reaches peak blood levels in less than 1 h (174). It is actively absorbed by mammals and accumulates in tissues proportional to the lipid content (175). Significant levels of hexane and its metabolites are seen in the fetus (176). It is metabolized to hydroxy derivatives by a cytochrome P450-containing mixed-function oxidase system before being converted to keto forms (170). The metabolites 5-hydroxy-2-hexanone and 2,5-hexanedione, also common to other neurotoxic hexacarbons, have been identified (177). Some normal hydroxylated intermediates are excreted as the glucuronides (129). Hexane activates various enzyme systems, including UDP-glucuronyl transferase (178). The straight-chain hexacarbons have an affinity to nerve tissue, where they affect the blockage of nerve impulses in the frog (131). Jurkat T-cells exposed to *n*-hexane for 48 h *in vitro* showed significantly elevated formation of reactive oxygen species, followed by reduced resazurin reduction and increased membrane permeability indicated by LDH leakage (179).

11.4.1.4 Reproductive and Developmental. Adult male rats exposed to 1000 ppm hexane (61 day inhalation exposure) developed permanent testicular damage, characterized by total loss of the germ-cell line. Simultaneous administration of 1000 ppm hexane and 1000 ppm toluene, or 1000 ppm hexane and 1000 ppm xylene, did not cause germ-cell line alterations or testicular atrophy. Toluene and xylene were thus found to protect from hexane-induced testicular atrophy (180). Hexane does not appear to be a teratogen. Different studies of pregnant rats and mice exposed to concentrations of $\leq$5000 ppm during gestation failed to show fetal malformations even at maternally toxic doses (181–183). Rats exposed to 72% toluene and 18% *n*-hexane daily from P2 to P21 exhibited reduced brain weight and markedly arrested basal dendritic growth (184).

11.4.1.5 Carcinogenesis. Male rabbits exposed to 3000 ppm hexane (8 h/day, 6 days/week for 24 weeks) developed papillary proliferation of nonciliated bronchiolar cells (173). No tumors were found in mice painted with hexane and croton oil as cocarcinogen, presumably for the lifetime of each animal (185). Hexane is inactive as a tumor-promoting agent (186).

11.4.1.6 Genetic and Related Cellular Effects Studies. Hexane was found to be negative when tested for mutagenicity using the *Salmonella* microsome preincubation assay in either the presence or the absence of rat and hamster liver S9 (187). A hexane preparation in dimethyl sulfoxide was not mutagenic in *S. typhimurium* (188). No mutagenic activity was reported in a microsuspension fluctuation assay with *S. typhimurium* (189). No evidence of mutagenic activity was found using hexane in dimethyl sulfoxide in a $TK^{+/-}$ mouse lymphoma forward mutation assay (190).

Incubation of a Chinese hamster fibroblast cell line with 330 μg/mL hexane for 48 h, induced an increase in polyploidy, but not an increase in structural aberrations (188). Rats exposed to 150–600 ppm hexane (6 h/day for 5 days) experienced an increase in the incidence of bone marrow cells with chromatid breaks (190). In male rats exposed to 5000 ppm hexane vapor (16 h/day, 6 days/week for 2–4 weeks), chromosomal changes in the germ cells were observed (191). No increase in unscheduled DNA synthesis was reported in human lymphocytes exposed to hexane *in vitro*, either with or without metabolic activation with rat liver S9 mix (192).

11.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Hexane is a neurotoxic chemical, and causes axonal swellings of the axon, and degeneration of the distal axon in the longest peripheral nerves. Smaller species, such as mice, are less vulnerable than larger species to the neurotoxic effect of hexane, apparently a reflection of axonal length and diameter (151).

Intramuscular injection of hexane in rabbits causes edema and hemorrhaging of the lungs and tissues, with polymorphonuclear leukocytic reactions. Hexane is an irritant to the skin. Following subcutaneous injections, hexane produces pathological changes in mice (193). Epicutaneous

Table 27.10. Summary of Subchronic Toxicity Studies in Animals Exposed to Hexane

Species	Exposure Route	Chemical	Approximate Dose (ppm)	Treatment Regimen	Observed Effect	References
Fischer rat	Inhalation	Hexane	0; 3,000; 6,500; 10,000	6 h/day, 5 days/week, 13 weeks	Depression of body weight gain, lower brain weight, and axonopathy in males	(167)
B6C3F$_1$ mice	Inhalation	Hexane	0; 500; 1,000; 4,000; 10,000	6 h/day, 5 days/week, 13 weeks	No effect in survival	(168)
			0; 500; 1,000; 4,000; 10,000	6 h/day, 5 days/week, 13 weeks	Morphological alterations in the respiratory tract	
			1,000	22 h/day, 5 days/week, 13 weeks	Paranodal axonal swelling in the tibial nerve	
SM-A male mice	Inhalation	Commercial-grade hexane	0; 100; 250; 500; 1,000; 2,000	6 days/week, 1 year	Peripheral neuropathy by electromyographic analysis	(169)
Sprague–Dawley rats	Inhalation	Hexane	0; 6; 26; 129	6 h/day, 5 days/week, 26 weeks	No signs of nervous system degeneration	(170)
			0; 5; 27; 126	21 h/day, 7 days/week, 26 weeks	No signs of nervous system degeneration	
Sprague–Dawley rats	Inhalation	Hexane	0; 126; 502	22 h/day, 7 days/week, 6 month	Abnormal gait, axonal degeneration, myelin vacuolization	(171)
		Hexane + hexane mixtures	125 + 125; 375; 1,375	22 h/day, 7 days/week, 6 month	No neuropathic/myopathic alterations	
Wistar male rats	Inhalation	Hexane	0; 500; 1,200; 3,000	12 h/day, 7 days/week, 16 weeks	Dose-dependent peripheral neurotoxicity and body weight decrease	(172)
Sprague–Dawley rats	Inhalation	Hexane	0; 500; 1,500; 5,000	9 h/day, 5 days/week, 14–30 weeks	Decrease in weight gain, axonal degeneration, swelling of axons	(128)
			2,500	10 h/day, 6 days/week, 14–30 weeks	Axonal degeneration, swelling of axons	
Rabbits	Inhalation	Hexane	3,000	8 h/day, 5 days/week, 24 weeks	Ocular and upper respiratory tract irritation, respiratory difficulties	(173)

administration of hexane to guinea pigs caused progressing nuclear pyknosis and junctional separation between the basement membrane and the basal cells of the skin (194). Respiratory tract lesions have been observed in rabbits following exposure to hexane (173).

11.4.2 Human Experience

11.4.2.1 General Information. Hexane may be the most highly toxic member of the alkanes. It is an anesthetic (131, 132, 195). When ingested, it causes nausea, vertigo, bronchial and general intestinal irritation, and CNS depression. Concentrations of ~50 g may be fatal to humans (8).

11.4.2.2 Clinical Cases

11.4.2.2.1 Acute toxicity. Acute inhalation effects of hexane are euphoria, dizziness, and numbness of limbs (196). Occupational exposures to hexane concentrations of 1,000–25,500 ppm for 30–60 min caused drowsiness (197). Two workers at a hexane extraction facility reported transient paraesthesia following excessive acute exposure to hexane (198).

11.4.2.2.2 Chronic and subchronic toxicity. Chronic inhalation of hexane produces a progressive sensorimotor neuropathy. When exposure is stopped, progression of neuropathy continues for several months, followed by slow recovery. The prognosis for total recovery is good for most patients with hexane-induced axonopathy (199). Populations at risk are "glue sniffers" and workers in shoe and furniture industries, where hexane is employed as a glue solvent (151). Chronic effects from glue sniffing over a period of 5–15 months have been described as distal symmetrical motor sensory polyneuropathy (200–202). Degeneration of axons and nerve terminals has also been observed as a result of glue sniffing (203). Eleven workers in the shoe industry exposed to hexane and other solvents (168–204 mg/m^3 over at least 3 years) had significantly elevated activation of soluble guanylate cyclase by nitric oxide in lymphocytes (204)). "Blurred vision," without explanation for its basis, and without further characterization has been mentioned in association with hexane polyneuropathy in numerous case reports (98). A report listed 7 cases of "constriction of visual field," 2 cases of "optic nerve atrophy" and 1 case of "retrobulbar neuritis" that were "mild" among 39 patients with hexane peripheral neuropathy (205). Fifteen workers exposed industrially to hexane for an average of 12 years had normal visual acuity and visual fields (they did not have hexane peripheral neuropathy). However, only three appeared to have normal color discrimination. Eleven of the workers had vague disturbances in the appearance of the macula and others had minor abnormalities in the retina. The authors suggested that these lesions were developed in the cerebral part of the visual pathway (206). Twenty-six workers with hexane neuropathy had significantly elevated mean total error scores for color differentiation compared to 50 unexposed controls on the FM-100 Hue test of color discrimination; indicating solvent-induced color vision defects due to neural damage (207). Hexane caused eye lesions in the macula of 11 of 15 workers exposed for 5–21 years in an adhesive bandage factory (208).

11.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. Hexane has been detected in mothers' breast milk, and in expired air from humans (158, 159). The metabolism of hexane in humans is qualitatively similar to that in the rat (209). Hexane is metabolized by hepatic cytochrome P450 to α-, β-, γ-, and δ-diketones. Only the γ-diketones (including 2,5-heptanedione, 6,6-octanedione, and 2,5-hexanedione) have neurotoxic effects (172). 2,5-Hexanedione, 2,5-dimethylfuran, *y*-valerolactone, and 2-hexanol have been identified in urine samples of workers exposed to hexane (210–212). 2,5-Hexanedione has also been detected in urine of people apparently not exposed to hexane. It has been speculated that hexane may be produced in the body via lipid peroxidation (213).

11.4.2.2.4 Reproductive and developmental. NA

11.4.2.2.5 Carcinogenesis. NA

11.4.2.2.6 Genetic and related cellular effects studies. NA

11.4.2.2.7 Other: neurological, pulmonary, and skin sensitization. Hexane peripheral neuropathy is characterized by symmetrical paraesthesia and weakness. The lower extremities are affected first. Other symptoms include headache, anorexia, and dizziness (205). A "stocking and glove" anesthesia that results in sensory impairment and muscular weakness in the feet and hands usually develops (209). Nerve biopsies show morphological changes of neurofilament-filled axonal swellings and degeneration of the distal axon (151). Biopsied nerve samples show degeneration of both the axon and myelin (172). There is a marked reduction in conduction velocity in sensory and motor nerves (209). Symptoms usually worsen for 2–5 months after exposure ceases, with maximum muscle strength deterioration and sensory deficit at 2–3 months after exposure. Recovery for mild-to-moderate cases usually takes 1–3 years. In severe cases, drop foot, claw hand, and spastic gait may persist (172). Table 27.11 shows a summary of the studies of neurotoxic effects of exposure to hexane in humans (198, 208, 214–219).

11.4.2.3 Epidemiologic/Controlled Exposure Studies

11.4.2.3.1 Acute toxicity. In studies in human volunteers, exposure to 2000 ppm was without effect, whereas exposure

Table 27.11. Summary of Neurotoxicity Studies in Human Exposed to Hexane

Type of Facility/ Population	Mixture Composition	Exposure Levels	Persons Affected	Findings	References
Laminating plant	Solvents containing 65–95% hexane	500–2,000 ppm	17 cases	Polyneuritis	(198)
Vinyl sandal manufacture	Glues containing 70% hexane	500–25,007 ppm, 48 h/week	93 of 296	Progressive polyneuropathy, symmetrical sensorimotor disorder, no deaths	(214)
Shoe industry	Hexane and other solvents	196 ppm, 1–25 years	15 studied	Reductions in maximal motor and distal sensory nerve conduction velocities Changes in somatosensory-evoked potentials	(215)
Press proofing workers	Solvents containing hexane	190 ppm	15 of 59 studied	Overt peripheral neuropathy, CNS malfunction, residual abnormalities after exposure removal; no neuropathy at $<$100 ppm	(216–218)
Tungsten carbide milling	Tungsten carbide + hexane or acetone	58 ppm 8 h TWA/2 years	14 + 5 past exposed	No signs of neuropathy; headaches, hyperaesthesia of limbs, and muscle weakness	(219)
Printers and spray painters	Solvents containing hexane	1–39 ppm, 6 years	16% of 240 exposed	Not clinically significant signs of peripheral neuropathy	(208)

to 5000 ppm for 10 min caused marked vertigo and nausea (58).

11.4.2.3.2 Chronic and subchronic toxicity. NA

11.4.2.3.3 Pharmacokinetics, metabolism, and mechanisms. Respiratory uptake of hexane (87–122 ppm) in man averages $27.8 \pm 5.3\%$, and some is exhaled following cessation of exposure (220). Four volunteers were exposed to a mean concentration of 49.5 ppm hexane both at rest and under varying workload conditions. Hexane concentrations in exhaled air increased between 7 and 20% with increasing workload intensity (221). PBTK modeling of hexane exposures predict urinary 2,5-hexanedione increased 35% with increasing workload in the same hexane exposure (222). Steady-state levels of hexane in blood were linearly dose dependent following inhalation of up to 200 ppm. Near-plateau levels were obtained within 15 min, in both resting volunteers and those undergoing physical exercise (223). No hexane was detected in the blood or exhaled air of a volunteer who immersed one hand in hexane for 1 min (224).

11.4.2.3.4 Reproductive and developmental. NA

11.4.2.3.5 Carcinogenesis. NA

11.4.2.3.6 Genetic and related cellular effects studies. NA

11.4.2.3.7 Other: neurological, pulmonary, and skin sensitization. Volunteers exposed to 500 ppm hexane vapor for 3–5 min did not show eye irritation (196). Application of 1.5 mL hexane (analytical grade) for 5 min, caused a stinging and burning sensation and transient erythema (225). In another study, 0.1 mL hexane rubbed into the forearm skin for 18 days did not produce erythema or edema (226). Skin sensitization was not induced with hexane applied undiluted for induction and as a 25% solution for challenge (227).

In a study of kidney function, workers exposed to hydrocarbon mixtures including hexane (mean air concentration: 71 ppm) were compared to an undefined control group. No effects on mean total urinary protein, albumin, β-glucuronidase, or muramidase levels were reported (228). Kidney function was also studied in a group of shoe workers exposed on a number of occasions to more than 100 ppm hexane, a group of unexposed workers, and a group of historically exposed workers who had left the factory during the previous 5 years. The mean total urinary protein was significantly higher in the exposed workers than in any control group. Some workers also experienced abnormally high urinary lysozyme activity or increased β-glucuronidase activity. There were no effects on urinary albumin or serum creatinine levels (229, 230).

11.5 Standards, Regulations, or Guidelines of Exposure

Hexane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). Table 27.12 shows the

Table 27.12. Occupational Exposure Limits for Hexane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	500 ppm (1800 mg/m^3)	50 ppm (180 mg/m^3)	A TLV–TWA has been developed by ACGIH
Short-term exposure limit	–	–	–
Ceiling limit	–	–	–

[a] OSHA and ACGIH, 8 h TWA; NIOSH, 10 h TWA.

From Ref. 25.

occupational exposure limits for hexane in the United States. The IDLH concentration determined by NIOSH is 1100 ppm (based on 10% of the lower explosive limit) (41). A TLV–TWA and BEI have been developed by ACGIH (152). Measurement of *n*-hexane in exhaled air has been recommended as a screening test (152). Argentina, Bulgaria, Colombia, Jordan, Singapore, and Vietnam all use a recommended TWA for skin (25); additional international exposure limits for hexane are shown in Table 27.13.

12.0 2-Methylpentane

12.0.1 CAS Number

[*107–83-5*]

12.0.2 Synonyms

1,1-Dimethylbutane, isohexane, dimethylpropylmethane

Table 27.13. Occupational Exposure Limits for Hexane in Different Countries

Country	Exposure Limit
Australia	TWA 50 ppm (180 mg/m^3)
Belgium	TWA 50 ppm (180 mg/m^3)
Denmark	TWA 50 ppm (180 mg/m^3)
Finland	TWA 50 ppm (180 mg/m^3); STEL 150 ppm (530 mg/m^3)
France	TWA 50 ppm (180 mg/m^3)
Germany	TWA 50 ppm (180 mg/m^3)
Hungary	TWA 100 mg/m^3; STEL 200 mg/m^3
Ireland	TWA 20 ppm (70 mg/m^3)
Japan	TWA 40 ppm (140 mg/m^3)
The Netherlands	TWA 25 ppm (90 mg/m^3)
The Philippines	TWA 500 ppm (1800 mg/m^3)
Poland	TWA 100 mg/m^3; STEL 400 mg/m^3
Russia	TWA 40 ppm; STEL 300 mg/m^3
Sweden	TWA 25 ppm (90 mg/m^3); STEL 50 ppm (180 mg/m^3)
Switzerland	TWA 50 ppm (180 mg/m^3); STEL 100 ppm (360 mg/m^3)
Turkey	TWA 500 ppm (1800 mg/m^3)
United Kingdom	TWA 20 ppm (72 mg/m^3)

From Ref 25.

12.0.3 Trade Names

NA

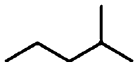
12.0.4 Molecular Weight

86.177

12.0.5 Molecular Formula

$(CH_3)_2CH(CH_2)_2CH_3$

12.0.6 Molecular Structure



12.1 Chemical and Physical Properties

12.1.1 General

2-Methylpentane (isohexane), C_6H_{14}, is a flammable liquid with a specific gravity of 0.653. It occurs naturally in petroleum and gas and as a plant volatile. It is found in sources associated with petroleum products such as petroleum manufacture, natural gas, turbines, and automobiles. Selected physical properties are listed in Table 27.1.

12.1.2 Odor and Warning Properties

The odor threshold for isohexane is 0.29 mg/m^3 (29).

12.2 Production and Use

Isohexane is manufactured by fractional distillation of gasoline derived from crude oil or liquid product derived from natural gas (63). It is a component of commercial hexane (144). Isohexane is used in organic synthesis and as a solvent for extracting oil for seeds.

12.3 Exposure Assessment

12.3.1 Air

Atmospheric concentrations of isohexane have been measured by headspace gas chromatographic techniques (210).

Purge-and-trap gas chromatography has been used to measure volatile organic compounds in water, including isohexane (145).

12.3.2 Background Levels

NA

12.3.3 Workplace Methods

Sampling procedures in the workplace include charcoal tubes and passive vapor monitors (120).

12.3.4 Community Methods

NA

12.3.5 Biomonitoring/Biomarkers

Isohexane has been measured in blood and tissues using headspace gas chromatography (27). The alcohol metabolite of isohexane has been determined in urine of humans and rats using gas chromatography (210). A purge-and-trap method with gas chromatography/mass spectrometry (GC-MS) was used to measure isohexane blood levels in humans (146). It has been detected in breath samples by thermal desorption and purging by helium into a liquid nitrogen-cooled nickel capillary cryogenic trap, followed by high-resolution GC-MS (231). 2-Methyl-2-pentanol and 2-methylpentane-2,4-diol may be measured by gas chromatography in urine as biomarkers of occupational exposure to isohexane (232).

12.4 Toxic Effects

12.4.1 Experimental Studies

12.4.1.1 Acute Toxicity

NA

12.4.1.2 Chronic and Subchronic Toxicity. NA

12.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. The rate of dermal absorption of isohexane using *in vitro* percutaneous techniques is 0.11 µg/cm^2/h (128). Skin absorption of the C6 isomers appears to be minor in contrast to respiratory absorption (144). Isohexane appears to distribute in human tissues in the same manner as pentane and hexane (27). In rats exposed to 1500 ppm isohexane for 14 weeks, 2-methyl-2-pentanol was detected in urine (127).

12.4.1.4 Reproductive and Developmental. NA

12.4.1.5 Carcinogenesis. NA

12.4.1.6 Genetic and Related Cellular Effects Studies. NA

12.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. A comparative toxicity study in rats exposed to hexane and hexane isomers, including isohexane, was conducted. The chemicals were orally administered daily for 8 weeks. The results revealed that the neurotoxicity of the isohexane was not as severe as that of hexane (233).

12.4.2 Human Experience

12.4.2.1 General Information. Little information is available on isohexane. No physiological data are available. However, it is expected to be skin, eye, and mucous membrane irritant and to have a low oral toxicity. Isohexane is predicted to be CNS depressant and cardiac sensitizer, but is not expected to have neurotoxic properties (36).

12.4.2.2 Clinical Cases

12.4.2.2.1 Acute toxicity. NA

12.4.2.2.2 Chronic and subchronic toxicity. NA

12.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. 2-Methyl-2-pentanol was one of the metabolites found in connection to isohexane (48 ppm) exposure at a shoe factory (210). Isohexane was detected in 3 of 12 breath samples collected during a pilot broad-spectrum analysis of exposure to chemicals (231).

12.5 Standards, Regulations, or Guidelines of Exposure

Isohexane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). The NIOSH REL is 100 ppm (350 mg/m^3) TWA, 510 ppm (1800 mg/m^3) ceiling limit for hexane isomers other than *n*-hexane (41). A TLV–TWA has been developed by ACGIH (148). The Cal/OSHA PEL for all hexane isomers other than *n*-hexane is 500 ppm (1800 mg/m^3); the STEL is 1000 ppm (3600 mg/m^3) (24).

13.0 3-Methylpentane

13.0.1 CAS Number

[*96–14-0*]

13.0.2 Synonyms

Diethylmethylmethane

13.0.3 Trade Names

NA

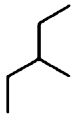
13.0.4 Molecular Weight

86.177

13.0.5 Molecular Formula

$CH_3CH_2CHCH_3CH_2CH_3$

13.0.6 Molecular Structure



13.1 Chemical and Physical Properties

13.1.1 General

3-Methylpentane, C_6H_{14}, is a colorless, flammable liquid with specific gravity 0.664. It occurs in petroleum and natural gas, and may be released to the environment in evaporative losses, wastewater, spills, and combustion exhaust. Physical and chemical properties are listed in Table 27.1.

13.2 Production and Use

3-Methylpentane is a component of three typical commercial hexanes, obtained from the fractionation of natural gas liquids, a refinery operation involving hydrogenation, and a stream meeting polymerization (63). Other than for fuel, it is used in extraction of oil from seeds and as a solvent and reaction medium in the manufacture of polyolefins, synthetic rubbers, and some pharmaceuticals (63).

13.3 Exposure Assessment

13.3.1 Air/Water

3-Methylpentane has been determined in air by headspace gas chromatography (210). A modified variant of the purge-and-trap gas chromatographic method has been used to measure 3-methylpentane in water (145).

13.3.2 Background Levels

NA

13.3.3 Workplace Methods

NA

13.3.4 Community Methods

NA

13.3.5 Biomonitoring/Biomarkers

A headspace gas chromatography method has been used to measure the concentration of 3-methylpentane in human blood and tissues (27). A purge-and-trap method using GC-MS was employed to measure blood levels in humans (146). It has also been analyzed in breath samples by thermal desorption followed by high-resolution GC-MS (231). 3-Methyl-2-pentanol may be measured by GC in urine as a biomarker of occupational exposure to 3-methylpentane (232).

13.4 Toxic Effects

13.4.1 Experimental Studies

13.4.1.1 Acute Toxicity. Sprague–Dawley rats of both sexes were exposed to commercial hexane solvent containing 3-methylpentane, only nose, to concentrations of 900–9000 ppm for 6 h. Increased lacrimation was the only overt sign of toxicity (234).

13.4.1.2 Chronic and Subchronic Toxicity. NA

13.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Skin absorption of the C6 isomers appears to be minor in contrast to respiratory absorption (144). It has been demonstrated that 3-methylpentane distributes in human tissues in the same manner as pentane and hexane (27). In rats exposed to 1500 ppm isohexane for 14 weeks, 3-methyl-2-pentanol and 3-methyl-3-pentanol were detected in urine (127).

13.4.1.4 Reproductive and Developmental. NA

13.4.1.5 Carcinogenesis. NA

13.4.1.6 Genetic and Related Cellular Effects Studies. Chinese hamster ovary cells were exposed to commercial hexane containing 3-methylpentane at concentrations ranging from 5.0×10^{-4} to 5.0 µg/dL. The highest doses tested produced overt cellular toxicity and corresponding reductions in mitotic indices. Cell cycle kinetics was also delayed at the higher concentrations; however, no chromosome alterations were evident in any group tested (234). Rats exposed to commercial hexane and sacrificed showed no increase in chromosomal damage to bone marrow at the concentrations tested (900–9000 ppm for 6 h) (234).

13.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Rat neurotoxicity from chronic oral administration of 3-methylpentane is not as severe as that from hexane (233).

13.4.2 Human Experience

13.4.2.1 General Information. Very little is known about the health effects of 3-methylpentane.

13.4.2.2 Clinical Cases

13.4.2.2.1 Acute toxicity. NA

13.4.2.2.2 Chronic and subchronic toxicity. NA

13.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. 3-Methyl-2-pentanol was one of the metabolites found in connection to 3-methylpentane exposure (39 ppm) at a shoe factory (210). 3-Methylpentane has been detected in the expired air of human subjects (158).

13.5 Standards, Regulations, or Guidelines of Exposure

The NIOSH REL is 100 ppm (350 mg/m^3) TWA, 510 ppm (1800 mg/m^3) ceiling limit for hexane isomers other than *n*-hexane (41). A TLV–TWA has been developed by ACGIH (148). The Cal/OSHA PEL for all hexane isomers other than *n*-hexane is 500 ppm (1800 mg/m^3); the STEL is 1000 ppm (3600 mg/m^3) (24).

14.0 *n*-Heptane

14.0.1 CAS Number

[*142–82-5*]

14.0.2 Synonyms

Dipropylmethane, heptane, gettysolve-C, heptyl hydride, normal heptane

14.0.3 Trade Names

NA

14.0.4 Molecular Weight

100.20

14.0.5 Molecular Formula

$CH_3(CH_2)_5CH_3$

14.0.6 Molecular Structure

14.1 Chemical and Physical Properties

14.1.1 General

n-Heptane, C_7H_{16}, is a volatile, flammable liquid, and occurs in natural gas, crude oil, and pine extracts. Its vapor pressure is 47.7 Torr at 25°C, and its specific gravity is 0.673–0.698. Selected physical properties are given in Table 27.1.

14.1.1.1 Heptane Isomers. 2-Methylhexane and 3-methylhexane are flammable liquids, often used in fuel mixtures. Physiologically, 2-methylhexane is somewhat less active than hexane. It is a CNS depressant at 0.8–1.1% (123). For 2-methylhexane, the loss of the righting reflex in mice occurred at concentrations of 50 mg/L, whereas the loss was observed at 40 mg/L for heptane (123). Thus, the isomer appears somewhat less toxic and is not a neurotoxin. 3-Methylhexane is expected to have toxic properties similar to those of heptane. Selected physical data on these chemicals are given in Table 27.1.

14.1.2 Odor and Warning Properties

The odor threshold for heptane is between 200 and 1280 mg/m^3. It has a gasoline-like odor (29).

14.2 Production and Use

Heptane is produced in refining processes. Highly purified heptane is produced by adsorption of commercial heptane on molecular sieves (235). It is used as an industrial solvent; as automotive starter fluid and paraffinic naphtha and as a gasoline knock-testing standard.

14.3 Exposure Assessment

14.3.1 Air/Water

Continuous monitoring by direct headspace sampling and gas chromatography with flame ionization detector has been used to measure heptane in controlled atmospheres (235). Heptane has been concentrated in water using reverse-phase C18 minicolumns and detected using a gas chromatograph with a flame ionization detector (153).

14.3.2 Background Levels

NA

14.3.3 Workplace Methods

NIOSH method 1500 has been used to determine air concentrations for heptane and other hydrocarbons (119). Samples are collected on charcoal, desorbed with carbon disulfide, and quantified by gas chromatography with a flame ionization detector. Samples may also be collected using passive samplers in which individual chemicals simply

diffuse from the atmosphere into the sampler at a fixed rate. The sampler consists of a polypropylene/polyester assembly with tubular sampling channels and a coconut charcoal wafer (155).

14.3.4 Community Methods

NA

14.3.5 Biomonitoring/Biomarkers

Heptane has been measured in brain and adipose tissue by gas chromatography using a backflush technique (236). Headspace gas chromatography has also been used to measure heptane in human blood and tissues (27). Ion-selective monitoring GC-MS spectrometry may also add sensitivity to heptane measurement in tissues (235). Urinary metabolites of heptane have been analyzed by GC-MS (237).

14.4 Toxic Effects

14.4.1 Experimental Studies

14.4.1.1 Acute Toxicity. The 4 h LC_{50} in mice by inhalation is 103 g/m^3 (63). Inhalation exposures of mice to 10,000–15,000 ppm heptane produced CNS depression in mice within 30–60 min. At higher concentrations ($\leq$20,000 ppm), 30–60 min exposures caused convulsions and death in mice; 48,000 ppm caused respiratory arrest in three of the four exposed mice in 3 min (121). A concentration of 40 mg/L affected the righting reflexes of mice, and 70 mg/L was lethal (123).

14.4.1.2 Chronic and Subchronic Toxicity. In a study in rats exposed to 400 and 3000 ppm heptane (6 h/day, 5 days/week for 26 weeks), no evidence of neurological alterations or organ toxicity was found. Only female rats showed a significant increase in serum alkaline phosphatase levels at the higher dose, but no liver, hematological, or renal abnormalities were found (238). A study in rats exposed to heptane vapors (100–1500 ppm) for 2 weeks, minor biochemical changes were observed but were reversed 2 weeks after exposure was terminated (236).

14.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Studies in rats suggest that heptane enters the organism mainly by inhalation, and to a minor degree by dermal absorption (128, 237). Heptane is metabolized to its parent alcohols (mainly 2-heptanol and 3-heptanol, and to a minor extent 1-heptanol and 4-heptanol). The heptanol metabolites are conjugated by glucuronates or sulfates, and subsequently excreted in urine (237). Heptane is further metabolized at relatively high rates by hydroxylation before being converted to the corresponding keto forms. Diketone metabolic products, believed to be responsible for neurotoxicity, are produced to a lower extent compared to hexane in agreement with the finding that heptane is less neurotoxic (125). *In vitro* studies have shown that at least three cytochrome P450 isozymes are involved in the liver metabolism of heptane (239).

14.4.1.4 Reproductive and Developmental. NA

14.4.1.5 Carcinogenesis. NA

14.4.1.6 Genetic and Related Cellular Effects Studies. Rats exposed to 400 and 3000 ppm heptane vapors for 26 weeks showed no changes in blood parameters (hemoglobin, hematocrit, erythrocyte count, leukocyte count, and clotting time) (238). Heptane has not been shown to cause detrimental effects to bone marrow (235). Heptane is not mutagenic in the Ames *S. typhimurium* system (240).

14.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Aside from its narcotic effects, rats exposed to heptane vapors did not show any clinical signs of neuropathy (236). High concentrations of heptane ($>$32,000 ppm) cause respiratory irritation and breathing irregularities in mice (121). Liver dysfunction in rats occurs at high levels of exposure (235).

14.4.2 Human Experience

14.4.2.1 General Information. The target organs for heptane are the skin, the respiratory system, and the central nervous system (41).

14.4.2.2 Clinical Cases

14.4.2.2.1 Acute toxicity. Concentrations of 4.8% heptane caused respiratory arrest within 3 min. Survivors showed marked vertigo and incoordination requiring 30 min for recovery; they also exhibited mucous membrane irritation, slight nausea, and lassitude (121). A narrow margin exists between the onset of CNS depression or convulsions and cardiac sensitization and recovery or death (8). The fatal concentration of heptane in humans has been reported as 16,000 ppm (241).

14.4.2.2.2 Chronic and subchronic toxicity. Numerous cases of polyneuritis have been reported, following prolonged exposure to a petroleum fraction containing various isomers of heptane as major ingredients (241).

14.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. NA

14.4.2.2.4 Reproductive and developmental. NA

14.4.2.2.5 Carcinogenesis. NA

Table 27.14. Occupational Exposure Limits for Heptane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	500 ppm (2000 mg/m^3)	85 ppm (350 mg/m^3)	A TLV–TWA has been developed by ACGIH
Short-term exposure limit	–	440 ppm (1800 mg/m^3)	A TLV–TWA has been developed by ACGIH
Ceiling limit	–	–	–

[a] OSHA and ACGIH, 8 h TWA; NIOSH, 10 h TWA.

From Ref. 25.

14.4.2.2.6 Genetic and related cellular effects studies. Hematological effects in workers exposed to heptane in a rubber tire factory have been reported. These include slight anemia, slight leukopenia, and slight neutropenia (235).

14.4.2.2.7 Other: neurological, pulmonary, and skin sensitization. Direct skin contact with heptane may cause pain, burning, and itching. The time for symptom reversal is longer than for pentane or hexane (8). Heptane is a weak cardiac sensitizer (6). In workers exposed to solvent mixtures containing pentane, hexane, and heptane, polyneuropathy was observed, including signs of anorexia, asthenia, paresthesia, fatigue, and bilateral symmetrical muscle paralysis in the legs (136).

14.4.2.3 Epidemiology Studies

14.4.2.3.1 Acute toxicity. Human volunteers exposed to 0.1% heptane exhibited slight vertigo in 6 min; to 0.2%, vertigo in 4 min; and to 0.5%, CNS depression in 7 min (58). The lingering taste of gasoline for several hours after exposure has also been reported.

14.4.2.3.2 Chronic and subchronic toxicity. NA

14.4.2.3.3 Pharmacokinetics, metabolism, and mechanisms. NA

14.4.2.3.4 Reproductive and developmental. NA

14.4.2.3.5 Carcinogenesis. NA

14.4.2.3.6 Genetic and related cellular effects studies. NA

14.4.2.3.7 Other: neurological, pulmonary, and skin sensitization. Volunteers exposed dermally to liquid heptane for 1 h experienced erythema, itching, pigmentation, swelling, and a painful sensation in the skin (138).

14.5 Standards, Regulations, or Guidelines of Exposure

Heptane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). The IDLH concentration determined by NIOSH is 750 ppm (41). Table 27.14 shows the occupational exposure limits for hexane in the United States. Argentina, Bulgaria, Colombia, Jordan, Singapore, and Vietnam all use the recommended TWA of 50 ppm for skin (25); additional international exposure limits are shown in Table 27.15.

15.0 *n*-Octane

15.0.1 CAS Number

[*111–65-9*]

15.0.2 Synonyms

Octane, normal octane, alkane C8

Table 27.15. Occupational Exposure Limits for Heptane in Different Countries

Country	Exposure Limit
Australia	TWA 400 ppm (1600 mg/m^3); STEL 500 ppm (2000 mg/m^3)
Belgium	TWA 400 ppm (1640 mg/m^3); STEL 500 ppm (2050 mg/m^3)
Denmark	TWA 400 ppm (1600 mg/m^3)
Finland	TWA 300 ppm (1200 mg/m^3); STEL 500 ppm (2000 mg/m^3)
France	TWA 400 ppm (1600 mg/m^3)
Ireland	TWA 400 ppm (1600 mg/m^3); STEL 500 ppm (2000 mg/m^3)
Germany	TWA 500 ppm (2100 mg/m^3)
Japan	TWA 200 ppm (820 mg/m^3)
The Netherlands	TWA 300 ppm (1200 mg/m^3); STEL 400 ppm (1600 mg/m^3)
The Philippines	TWA 500 ppm (2000 mg/m^3)
Poland	TWA 1200 mg/m^3; STEL 2000 mg/m^3
Russia	TWA 200 ppm
Sweden	TWA 200 ppm (800 mg/m^3); STEL 300 ppm (1250 mg/m^3)
Switzerland	TWA 400 ppm (1600 mg/m^3); STEL 800 ppm
Turkey	TWA 500 ppm (2000 mg/m^3)
United Kingdom	TWA 400 ppm (1600 mg/m^3); STEL 500 ppm

From Ref. 25.

15.0.3 Trade Names

NA

15.0.4 Molecular Weight

114.22

15.0.5 Molecular Formula

$CH_3(CH_2)_6CH_3$

15.0.6 Molecular Structure

15.1 Chemical and Physical Properties

15.1.1 General

Octane, C_8H_{18}, is a colorless, flammable liquid, and is a component of natural gas and crude oil (63). Its vapor pressure is 10.0 Torr at 19°C, and its specific gravity is 0.7025. It is released to the environment via the manufacture, use, and disposal of many products associated with the petroleum and gasoline industries. Selected physical properties are given in Table 27.1.

15.1.2 Odor and Warning Properties

Octane has a gasoline-like odor. It has an odor threshold between 725 and 1208 mg/m^3 and is irritating at 1450 mg/m^3 (29).

15.2 Production and Use

Octane is produced from the fractional distillation and refining of petroleum (242). It is used as a solvent, a chemical raw material, and an important chemical agent in the petroleum industry. Octane offers desirable blending values that achieve certain antiknock and combustion qualities for high compression engine fuels.

15.3 Exposure Assessment

15.3.1 Air/Water

Headspace gas chromatography and infrared absorption spectroscopy have been used to measure octane in inhalation chambers (242, 243). Octane has been concentrated in water using reverse-phase C18 minicolumns and detected using a gas chromatograph with a flame ionization detector (153).

15.3.2 Background Levels

NA

15.3.3 Workplace Methods

NIOSH method 1500 has been used to determine air concentrations for octane and other hydrocarbons (119). Samples are collected on charcoal, desorbed with carbon disulfide, and quantified by gas chromatography with a flame ionization detector. Another collection procedure for octane in air involves the use of passive vapor monitors (120).

15.3.4 Community Methods

NA

15.3.5 Biomonitoring/Biomarkers

Headspace gas chromatography methods have been used to measure octane in blood, brain, fat, liver, kidney, lung, and muscle tissues (244). Octane metabolites may be measured in urine by GC-MS (242).

15.4 Toxic Effects

15.4.1 Experimental Studies

15.4.1.1 Acute Toxicity. The 4 h LC_{50} by inhalation in rats is 118 g/m^3 (63). The inhalation of 0.2 mL octane caused convulsions and death in rats within a few seconds. If the material is aspirated into the lungs, it may cause rapid death due to cardiac arrest, respiratory paralysis, or asphyxiation (135). Narcosis is produced in 30–90 min in mice exposed at 6,600–13,700 ppm octane in air (245). Respiratory arrest occurred in one of four mice within 5 min at 16,000 ppm and in four of four mice within 3 min at 32,000 ppm (121). Orally, octane may be more toxic than its lower homologs (8).

15.4.1.2 Chronic and Subchronic Toxicity. Rats exposed daily to intraperitoneal injections of 1.0 mL/kg octane for 7 days manifested a decrease in body weight, liver enlargement, and diminished drug-metabolizing activity of the liver (246).

15.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Inhalation is the major route of absorption of octane (242). *In vitro* percutaneous methods have shown that octane is poorly absorbed through the skin (128). As for most alkanes, the greatest affinity for octane is in the adipose tissue (244, 247). Octane is metabolized to hydroxy derivatives via a cytochrome P450 oxidase system, but it may not occur as extensively as for shorter chain alkenes (248). The 1-octanol formed is conjugated with glucuronic acid or undergoes further oxidation to octanoic acid (242).

15.4.1.4 Reproductive and Developmental. NA

15.4.1.5 Carcinogenesis. The promoting activity of octane in skin carcinogenesis, including its physical effect on

micellar models of biological membranes, was tested. Octane proved to have significant promoting activity when tested as a 75% solution in cyclohexane (249).

15.4.1.6 Genetic and Related Cellular Effects Studies. Octane does not enhance the mitogenic response of the murine spleen lymphocytes to the lectin phytohemagglutinin (250).

15.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. The CNS depressant potential of octane is approximately that of heptane, but does not appear to exhibit other CNS effects seen in lower homologs. Octane does not cause axonopathy (245). A concentration of 35 mg/L resulted in the loss of righting reflexes in mice and 50 mg/L caused a total loss of reflexes (123). A concentration of 9.5% causes loss of reflexes in mice in 125 min; however, $\leq$1.9% is easily tolerated for 143 min, and the effects are reversible (245). Octane is also a dermal irritant (237).

15.4.2 Human Experience

15.4.2.1 General Information. Octane has not been shown to be associated with the type of peripheral neuropathy caused by hexane (242). The health effects of octane are expected to be similar to those of heptane; octane is about 1.2–2 times more toxic than heptane (250).

15.4.2.2 Clinical Cases

15.4.2.2.1 Acute toxicity. The narcotic concentration of octane in humans has been estimated at 10,000 (58). Other authors have estimated the narcotic concentration at 8000 ppm and the fatal concentration at 13,500 ppm (250).

15.4.2.3 Epidemiology Studies

15.4.2.3.1 Acute toxicity. NA

15.4.2.3.2 Chronic and subchronic toxicity. NA

15.4.2.3.3 Pharmacokinetics, metabolism, and mechanisms. NA

15.4.2.3.4 Reproductive and developmental. NA

15.4.2.3.5 Carcinogenesis. NA

15.4.2.3.6 Genetic and related cellular effects studies. NA

15.4.2.3.7 Other: neurological, pulmonary, and skin sensitization,. Volunteers administered liquid octane to the forearm for 1 h and the thigh for 5 h showed hyperemia, inflammation, and pigmentation. A burning and itching sensation in the skin also developed at the site of application (138).

15.5 Standards, Regulations, or Guidelines of Exposure

Octane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). The ILDH concentration determined by NIOSH is 1000 ppm (based on 10% of the lower explosive limit) (41). The occupational exposure limits for octane in the United States are listed in Table 27.16. Argentina, Bulgaria, Colombia, Jordan, Singapore, and Vietnam all use a recommended TWA of 300 ppm (25); additional international standards are presented in Table 27.17.

16.0 2,2,4-Trimethylpentane

16.0.1 CAS Number

[*540–84-1*]

16.0.2 Synonyms

Isobutyltrimethylmethane, isooctane, 2,4,4-trimethylpentane

16.0.3 Trade Names

NA

16.0.4 Molecular Weight

114.22

16.0.5 Molecular Formula

$CH_3CH(CH_3)_2CH_2CH(CH_3)_2$

Table 27.16. Occupational Exposure Limits for Octane in the United States[a]

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	500 ppm (2350 mg/m^3)	75 ppm (350 mg/m^3)	A TLV–TWA has been developed by ACGIH
Short-term exposure limit	–	–	A TLV–TWA has been developed by ACGIH
Ceiling limit	–	385 ppm (1800 mg/m^3)	–

[a] OSHA and ACGIH, 8 h TWA; NIOSH, 10 h TWA.

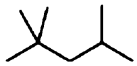
From Ref. 25.

Table 27.17. Occupational Exposure Limits for Octane in Different Countries

Country	Exposure Limit
Australia	TWA 300 ppm (1450 mg/m^3); STEL 375 ppm (1800 mg/m^3)
Belgium	TWA 300 ppm (1400 mg/m^3); STEL 375 ppm (1750 mg/m^3)
Denmark	TWA 300 ppm (1450 mg/m^3)
Finland	TWA 300 ppm (1400 mg/m^3); STEL 375 ppm (1750 mg/m^3)
France	TWA 300 ppm (1450 mg/m^3)
Germany	TWA 500 ppm (2400 mg/m^3)
Hungary	TWA 500 mg/m^3; STEL 1500 mg/m^3
Ireland	TWA 300 ppm (1450 mg/m^3); STEL 375 ppm (1800 mg/m^3)
Japan	TWA 300 ppm (1400 mg/m^3)
The Netherlands	TWA 300 ppm (1450 mg/m^3)
The Philippines	TWA 500 ppm (2350 mg/m^3)
Poland	TWA 1000 mg/m^3; STEL 1800 mg/m^3
Russia	TWA 300 ppm
Sweden	TWA 200 ppm (900 mg/m^3); STEL 300 ppm (1400 mg/m^3)
Switzerland	TWA 300 ppm (1400 mg/m^3); STEL 600 ppm
Turkey	TWA 400 ppm (1900 mg/m^3)
United Kingdom	TWA 300 ppm (1450 mg/m^3); STEL 375 ppm

From Ref 25.

16.0.6 Molecular Structure



16.1 Chemical and Physical Properties

16.1.1 General

2,2,4-Trimethylpentane (isooctane), C_8H_{18}, is a colorless liquid naturally found in crude petroleum and in small amounts in natural gas. Its vapor pressure is 40.6 Torr at 21°C, and its specific gravity is 0.6919. It is released to the environment by the petroleum industries, by automotive exhausts and emissions, and from hazardous-waste sites, landfills, and emissions from wood combustion (63). Selected physical properties are given in Table 27.1.

16.1.1.1 Other Octane Isomers. There are 17 compounds besides *n*-octane with molecular formula C_8H_{18}. Selected physical data for 2,5-dimethylhexane, 2,2,4-trimethylpentane, and 2,3,4-trimethylpentane are given in Table 27.1. 2,5-Dimethylhexane and 2,3,4-trimethylpentane are blended with lower alkane homologs to form preignition additives for high-compression engine fuel (251). 2,5-Dimethylhexane causes CNS depression at 70–80 mg/L for the mouse, but is not as effective as octane (123). 2,3,4-Trimethylpentane is more nephrotoxic than 2,2,4-trimethylpentane, based on the magnitude of changes observed for four urine parameters in rats (252).

16.1.2 Odor and Warning Properties

Isooctane has the odor of gasoline (63).

16.2 Production and Use

Isooctane is produced from the fractional distillation of petroleum fractions and naphthas. It is also produced from the alkylation of 2-methylpropene with isobutane (253). Isooctane is economically important because it adds "high octane" or antiknock qualities to gasoline, motor, and aviation fuel (253). It is also used as solvent and thinner, in spectrophotometric analysis, and in organic synthesis (63).

16.3 Exposure Assessment

16.3.1 Air

Headspace gas chromatography, gas chromatography with a flame ionization detector, and infrared absorption spectroscopy may be used to measure isooctane in the atmosphere (253).

16.3.2 Background Levels

NA

16.3.3 Workplace Methods

Isooctane may be sampled on charcoal tubes or using passive vapor monitors (254).

16.3.4 Community Methods

NA

16.3.5 Biomonitoring/Biomarkers

Headspace gas chromatography methods may be used to measure isooctane in blood and tissues (253).

16.4 Toxic Effects

16.4.1 Experimental Studies

16.4.1.1 Acute Toxicity. Isooctane is highly irritating to mice after 1000 ppm exposure for 5 min. It causes respiratory arrest at 16,000 in 25% of mice after 6 min, and arrest in all animals at 32,000 ppm after 3–4 min (121). The narcotic effect of isooctane probably occurs within

8,000–10,000 ppm (253). Following intramuscular injection into rabbits, isooctane produces hemorrhage, edema, and polymorphonuclear leukocytic reactions in the pulmonary tract (8). Specifically, angiitis, interstitial pneumonitis, abscess formation, thrombosis, and fibrosis were noted (8).

16.4.1.2 Chronic and Subchronic Toxicity. Oral administration of isooctane at doses of 2–50 mg/kg/day for 21 days caused proliferation of renal epithelial cells (255). It has been hypothesized that increased cell proliferation due to α2u-globulin accumulation can promote renal neoplasia (256).

16.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. The most likely route of absorption of isooctane is respiration, although its respiratory uptake has not been determined. Dermal absorption would be expected to be minor (253). Oral absorption occurs to the extent of 86% in male rats (257). Rats exposed orally to radiolabeled isooctane showed selective retention of the label in the kidneys of males; the kidney to plasma ratio was greater at lower doses (258). A study in rats showed that isooctane was eliminated exclusively via the kidneys over the whole postexposure period ($\leq$70 h), whereas octane was eliminated about equally in urine and exhaled after 10–20 h (259). Male and female rats metabolize isooctane via the same pathway and at a similar rate; the major metabolite in the male kidney was 2,2,4-trimethyl-2-pentanol, but it was absent in the female rat kidney. Females excrete more conjugates of 2,2,4-trimethyl-2-pentanol than male rats (258).

16.4.1.4 Reproductive and Developmental. NA

16.4.1.5 Carcinogenesis. Male and female rats were initiated with 170 ppm *N*-ethyl-*N*-hydroxyethylnitrosamine for 2 weeks and subsequently exposed to isooctane for $\leq$61 weeks. An increase in atypical cell foci (a preneoplastic lesion) was observed in male but not female rats promoted with the high dose (260).

16.4.1.6 Genetic and Related Cellular Effects Studies. Unscheduled DNA synthesis (UDS) as an indicator of genotoxic activity and replicative DNA synthesis (RDS) as an indicator of cell proliferation were measured in rat and mouse hepatocytes following *in vivo* and *in vitro* exposures to unleaded gasoline and isooctane. No UDS was induced in rat hepatocytes treated *in vivo* or *in vitro* with isooctane. Twenty- and fourfold increases in the percentage of S-phase cells (RDS induction) were observed 24 h after treatment with isooctane in male and female mice, respectively, as compared to a fivefold increase in male rats (261).

16.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Oral administration of isooctane can induce renal toxicity, specifically in the male rat. The nephrotoxicity is characterized by hyaline droplet accumulation in the cells of the tubules, and tubule dilation. Hepatotoxic properties have also been reported, such as centrilobular and confluent necrosis, hydropic degeneration, and vacuolation of hepatocytes (262).

16.4.2 Human Experience

16.4.2.1 General Information. Little information is available on the health effects of isooctane in humans. It is not known whether isooctane can induce nephrotoxic effects similar to those seen in male rats. This is unlikely because there is no evidence that humans have α2u globulin, whose alteration is necessary for isooctane nephrotoxicity (256).

16.4.2.2 Clinical Cases

16.4.2.2.1 Acute toxicity. A serious hand injury resulted from the unpacking of an HPLC column filled with silicon dioxide by pumping isooctane into the column. A mixture of silicon dioxide and isooctane was discharged so violently that some isooctane penetrated the skin, causing necrosis (263).

16.4.2.2.2 Chronic and subchronic toxicity. NA

16.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. NA

16.4.2.2.4 Reproductive and developmental. NA

16.4.2.2.5 Carcinogenesis. NA

16.4.2.2.6 Genetic and related cellular effects studies. The ability of isooctane to induce genotoxic effects in human cells *in vitro* was investigated. TK6 human lymphoblastoid cells were used, with and without rat liver homogenate metabolizing system. Isooctane did not induce mutation at the thymidine kinase locus or sister chromatid exchanges (SCEs) (264).

16.5 Standards, Regulations, or Guidelines of Exposure

Isooctane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA and NIOSH have not established exposure limits. ACGIH has developed a TWA for all octane isomers (265).

17.0 *n*-Nonane

17.0.1 CAS Number

[*111–84-2*]

17.0.2 Synonyms

Nonyl hydride, shellsol 140, nonane

17.0.3 Trade Names

NA

17.0.4 Molecular Weight

128.26

17.0.5 Molecular Formula

$CH_3(CH_2)_7CH_3$

17.0.6 Molecular Structure

17.1 Chemical and Physical Properties

17.1.1 General

n-Nonane, C_9H_{20}, is a colorless, highly flammable liquid. Its vapor pressure is 10 Torr at 38°C, and its specific gravity is 0.7176. Nonane is a constituent in the paraffin fraction of crude oil and natural gas. It is released to the environment via the manufacture, use, and disposal of many products associated with the petroleum and gasoline industries. Selected physical data are given in Table 27.1.

17.1.1.1 Nonane Isomer. 2,2,5-Trimethylhexane (neononane), $(CH_3)_3C(CH_2)_2CH(CH_3)_2$, is a flammable liquid and a component of gasoline (22). Selected physical data are given in Table 27.1. Little toxicological information is available. By extrapolation, 2,2,5-trimethylhexane is expected to be less toxic than nonane. 2,2,5-Trimethylhexane is nephrotoxic in rats orally exposed at doses of 10 g/kg for 4 weeks (108).

17.1.2 Odor and Warning Properties

Nonane has a gasoline-like odor. The odor threshold for nonane is 3412 mg/m^3 (29).

17.2 Production and Use

Nonane is obtained from the fractional distillation of petroleum (266). It is a component of gasoline and jet fuels, and is used in organic synthesis, as a solvent, in the manufacture of paraffin products, and in the synthesis of biodegradable detergents (266, 267).

17.3 Exposure Assessment

17.3.1 Air

Atmospheric nonane may be collected using passive samplers that consist of a polypropylene/polyester assembly with tubular sampling channels and a coconut charcoal wafer. Samples may be analyzed by gas chromatography with a flame ionization detector (155). Headspace gas chromatography and infrared absorption spectroscopy may be used to measure nonane in the atmosphere (266).

17.3.2 Background Levels

NA

17.3.3 Workplace Methods

NA

17.3.4 Community Methods

NA

17.3.5 Biomonitoring/Biomarkers

Nonane may be measured in blood and tissues by gas chromatographic methods (266).

17.4 Toxic Effects

17.4.1 Experimental Studies

17.4.1.1 Acute Toxicity. The 4 h LC_{50} by inhalation in rats is 3200 ppm (17 mg/L) (268), and the intravenous LD_{50} in mice is 218 mg/kg (195). Nonane is considered to be more toxic than octane and heptane (267).

17.4.1.2 Chronic and Subchronic Toxicity. No-effect levels of 1.9 and 3.2 mg/L were noted for rats exposed 6 h/day, 5 days/week for 13 weeks. A concentration of 8.1 mg/L (1500 ppm) resulted in mild tremors, slight coordination loss, and low irritation of the eyes and extremities (268). Chronic inhalation of nonane vapors may cause altered neutrophils, but no pulmonary lesions were noted (269). There is no indication that nonane causes axonopathy (266).

17.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. The major route of absorption of nonane is respiratory, and dermal absorption is expected to be very low (266). Distribution studies have not been conducted for nonane, but it is expected to have the greatest affinity for adipose tissue, liver, and brain (244). Nonane is metabolized in the rat to hydroxyl derivatives prior to conversion into the corresponding keto form, using a cytochrome P450-containing mixed-function oxidase system (248). Repeated intraperitoneal injections of nonane in rats (10 mL/kg/day for 7 days)

cause a decrease in the drug metabolizing activity of the liver (246).

17.4.2 Human Experience

17.4.2.1 General Information. Nonane is a CNS depressant in high concentrations (14). It is a primary skin irritant similar to other liquid paraffin hydrocarbons (143).

17.5 Standards, Regulations, or Guidelines of Exposure

Nonane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (22). The NIOSH REL is 200 ppm (1050 mg/m^3) (41). OSHA has not established exposure values. Argentina, Bulgaria, Colombia, Jordan, Singapore, and Vietnam all use a recommended TWA. A TLV–TWA has been developed by ACGIH (25); additional international occupational standards are presented in Table 27.18.

18.0 *n*-Decane

18.0.1 CAS Number

[*124–18-5*]

18.0.2 Synonyms

Decyl hydride, decane, alkane C(10)

18.0.3 Trade Names

NA

18.0.4 Molecular Weight

142.28

18.0.5 Molecular Formula

$CH_3(CH_2)_8CH_3$

Table 27.18. Occupational Exposure Limits for Nonane in Different Countries

Country	Exposure Limit
Denmark	TWA 200 ppm (1050 mg/m^3)
Finland	TWA 200 ppm (1050 mg/m^3); STEL 250 ppm (1315 mg/m^3)
France	TWA 200 ppm (1050 mg/m^3)
Ireland	TWA 200 ppm (1050 mg/m^3)
Japan	TWA 200 ppm (1050 mg/m^3)
The Netherlands	TWA 200 ppm (1050 mg/m^3)
Switzerland	TWA 200 ppm (1050 mg/m^3)

From Ref. 25.

18.0.6 Molecular Structure

18.1 Chemical and Physical Properties

18.1.1 General

Decane, $C_{10}H_{22}$, is a flammable liquid (22) with specific gravity 0.73. Selected physical and chemical properties are given in Table 27.1. Decane is a constituent in the paraffin fraction of crude oil and natural gas. It is released to the environment via the manufacture, use, and disposal of many products associated with the petroleum, gasoline, and plastics industries (22).

18.1.1.1 Decane Isomer. 2,7-Dimethyloctane (diisoamyl), $(CH_3)_2CH(CH_2)_4CH(CH_3)_2$, does not cause CNS depression (123). Selected chemical and physical data are given in Table 27.1.

18.1.2 Odor and Warning Properties

The odor threshold for decane is 11.3 mg/m^3 (270).

18.2 Production and Use

Decane is obtained mainly from the refining of petroleum. It is a component of engine fuel and is used in organic synthesis, as a solvent, as a standardized hydrocarbon, and in jet fuel research (22, 251).

18.3 Exposure Assessment

18.3.1 Air/Water

Atmospheric decane may be collected on charcoal tubes and analyzed by gas chromatographic methods (271). Infrared absorbance has also been used to measure C10–C11 paraffinic hydrocarbons in inhalation chambers (272). Decane may also be concentrated in water using reverse-phase C18 minicolumns and detected using a gas chromatograph with a flame ionization detector (153). EPA Method 1625 is used to measure semivolatile organic compounds, including decane, in water by isotope dilution gas chromatography–mass spectrometry (273).

18.3.2 Background Levels

NA

18.3.3 Workplace Methods

Passive diffusion samplers to collect decane in indoor air have been developed (274).

18.3.4 Community Methods

NA

18.3.5 Biomonitoring/Biomarkers

Headspace gas chromatography appears to be the method of choice for the analysis of decane in blood and tissues (271).

18.4 Toxic Effects

18.4.1 Experimental Studies

18.4.1.1 Acute Toxicity. Rats exposed to 0.2 mL of decane by inhalation died within 24 h by pulmonary edema and hemorrhaging. Decane is highly lipid-soluble and causes pulmonary pneumonitis when aspirated. Animals showed signs of dyspnea, tachypnea, and cyanosis (135). The 2 h LC_{50} in mice is 72.3 mg/L (63).

18.4.1.2 Chronic and Subchronic Toxicity. Exposure of rats to 540 ppm of decane 18 h/day, 7 days/week for 57 days stimulated weight gains and decreased the total white blood count, but no bone marrow changes or other organ changes were noted (275). Male rats were exposed by inhalation to 0, 400 (2.29 mg/L), or 800 ppm (4.58 mg/L) of dearomatized white spirit containing *n*-decane for 6 h/day, 5 days/week up to 3 weeks. One week of exposure at 800 ppm caused a statistically significant increase in whole brain dopamine concentration while the noradrenaline concentration was unaffected. Exposure at both exposure levels for 1 week caused a statistically significantly decreased concentration of 5-hydroxytryptamine in the whole brain. These changes in neurotransmitter concentrations were normalized after 2 and 3 weeks' exposure (276).

18.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Absorption of decane occurs mainly by inhalation. Dermal absorption of alkanes with more than eight carbons (octane) occurs very slowly. The distribution of the C10–C12 aliphatics would likely follow the same pattern reported for *n*-octane (271). Male rats were exposed by inhalation to 0, 400 (2.29 mg/L), or 800 ppm (4.58 mg/L) of dearomatized white spirit, 6 h/day, 5 days/week up to 3 weeks. After 3 weeks of exposure, the concentration of total white spirit was 1.5 and 5.6 mg/kg in blood; 7.1 and 17.1 mg/kg in brain; 432 and 1452 mg/kg in fat tissue at the exposure levels of 400 and 800 ppm, respectively. The concentrations of nonane, decane, undecane, and total white spirit in blood and brain were not affected by the duration of exposure. Two hours after the end of exposure, the decane concentration decreased to about 25% in blood and 50% in brain. A similar pattern of elimination was also observed for nonane, undecane, and total white spirit in blood and brain. In fat tissue, the concentrations of nonane, decane, undecane, and total white spirit increased during the 3 weeks of exposure. The time to reach steady-state concentrations is longer than 3 weeks. After the 3 weeks' exposure the fat tissue concentration of nonane, decane, undecane, and total white spirit decreased very slowly compared with the rate of decrease in blood and brain suggesting that long-lasting redistribution from fat to brain may occur (276).

Decane is metabolized in rats to hydroxy derivatives before being converted to the respective keto form, using a cytochrome P450–microsomal oxidase mixed function (248). Decane hydroxylation has been observed in liver microsomal fractions obtained from mice, rats, rabbits, cows, pigeons, and chick embryos (277). In rats, hydroxylation takes place not only in liver but also in other organs and microsomes isolated from the kidney and lungs (277).

18.4.1.4 Reproductive and Developmental. NA

18.4.1.5 Carcinogenesis. Mice treated with decane developed tumors on the backs, after exposure to ultraviolet radiation at wavelengths longer than 350 nm, generally considered noncarcinogenic (278). A series of 21 tobacco smoke components and related compounds were applied to mouse skin (50 female ICR/Ha Swiss mice/group) three times weekly with 5 mug/application of benzo[*a*]pyrene (B[*a*]P). The test compounds were of five classes: aliphatic hydrocarbons, aromatic hydrocarbons, phenols, and long-chain acids and alcohols. Decane was among the compounds that enhanced remarkably the carcinogenicity of B[*a*]P. and also acted as tumor promoter in two-stage carcinogenesis (279).

18.4.1.6 Genetic and Related Cellular Effects Studies. NA

18.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Dermal application of undiluted decane to mice (0.1–0.15 g per mouse, three times a week for 50 weeks) caused fibrosis of the dermis, pigmentation, and some ulceration. Some animals also showed kidney effects and lung hemorrhaging (275). Rats exposed to decane vapor have been examined for lens opacities, but no cataracts were found (280).

18.4.2 Human Experience

18.4.2.1 General Information. Decane is a simple asphyxiant and causes CNS depression in high concentrations (14).

18.4.2.2 Clinical Cases

18.4.2.2.1 Acute toxicity. A dose–response study of human reactions to decane was performed in a climate chamber.

Sixty-three healthy subjects, randomly selected from the normal population, were exposed to pure decane concentrations of 0, 10, 35, or 100 µL/L for 6 h in a controlled, double blind study. Dose-dependent changes in irritation of mucous membranes, increased sensation of odor intensity, and reduced air quality were observed. Adaptation was seen at the highest exposure levels, but not at the levels relevant for a nonindustrial environment. The physiological measurements showed decreased tear film stability at all exposure concentrations. The number of conjunctival polymorphonuclear leucocytes increased in a dose-related manner (281).

18.5 Standards, Regulations, or Guidelines of Exposure

Decane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA, ACGIH, and NIOSH have not established exposure standards for decane.

19.0 Undecane

19.0.1 CAS Number

[*1120–21-4*]

19.0.2 Synonyms

Hendecane, *n*-hendecane, *n*-undecane

19.0.3 Trade Names

NA

19.0.4 Molecular Weight

195.9

19.0.5 Molecular Formula

$CH_3(CH_2)_9CH_3$

19.0.6 Molecular Structure

19.1 Chemical and Physical Properties

19.1.1 General

Undecane, $C_{11}H_{24}$, is a flammable, colorless liquid with specific gravity 0.74. Physical data are given in Table 27.1.

19.2 Production and Use

Undecane is obtained from the refining of petroleum (271). Paraffins are isolated by selective adsorption followed by fractional distillation to produce the desired mix of *n*-paraffins (63). Undecane is a component of gasoline and is used in petroleum research, in organic synthesis, and as a distillation chaser (63).

19.3 Exposure Assessment

19.3.1 Air/Water

Infrared absorbance has been used to measure C10–C11 paraffinic hydrocarbons in inhalation chambers (272). Atmospheric decane may be collected on charcoal tubes and analyzed by gas chromatographic methods (271). Undecane has been measured in water by a modified variant of a purge-and-trap gas chromatographic method (145).

19.3.2 Background Levels

NA

19.3.3 Workplace Methods

NIOSH Method 1500, Issue 3 uses gas chromatography with a flame ionization detector to measure undecane and other hydrocarbons in air. The detection limit is 0.06 µg/sample (119).

19.3.4 Community Methods

NA

19.3.5 Biomonitoring/Biomarkers

Headspace gas chromatography may be used to measure undecane in blood and tissues (271).

19.4 Toxic Effects

19.4.1 Experimental Studies

Few toxicological studies have been conducted for the individual undecane, except as part of mixtures such as dearomatized white spirit and C10–C11 isoparaffins (272, 282). In an *in vitro* study, undecane induced the production of interleukin 8, a proinflammatory cytokine, in normal human epidermal keratinocytes (283).

19.4.1.1 Acute Toxicity. The LD_{50} for undecane administered intravenously to mice is 517 mg/kg (195).

19.4.1.2 Chronic and Subchronic Toxicity. NA

19.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Absorption of undecane occurs mainly by inhalation (271). Inhaled *undecane* is rapidly distributed from the blood to different organs and tissues, especially those with high lipid content. The concentrations of *undecane* in the brains and blood of rats exposed at 100 ppm, 12 h/day for

3 days were 47.7 and 13.7 µmol/kg (284). Male rats were exposed by inhalation to 0, 400 (2.29 mg/L), or 800 ppm (4.58 mg/L) of dearomatized white spirit, 6 h/day, 5 days/week up to 3 weeks. After 3 weeks of exposure, the concentration of total white spirit was 1.5 and 5.6 mg/kg in blood; 7.1 and 17.1 mg/kg in brain; 432 and 1452 mg/kg in fat tissue at the exposure levels of 400 and 800 ppm, respectively. The concentrations of nonane, decane, undecane, and total white spirit in blood and brain were not affected by the duration of exposure. Two hours after the end of exposure, the decane concentration decreased to about 25% in blood and 50% in brain. A similar pattern of elimination was also observed for nonane, undecane, and total white spirit in blood and brain. In fat tissue, the concentrations of nonane, decane, undecane, and total white spirit increased during the 3 weeks of exposure. The time to reach steady-state concentrations is longer than 3 weeks. After the 3 weeks' exposure the fat tissue concentration of nonane, decane, undecane, and total white spirit decreased very slowly compared with the rate of decrease in blood and brain suggesting that long-lasting redistribution from fat to brain may occur (276). Metabolism of undecane is likely to occur by hydroxylation to yield the corresponding alcohol (248, 277).

19.4.1.4 Reproductive and Developmental. NA

19.4.1.5 Carcinogenesis. Undecane (25 mg) and benzo[*a*]pyrene (B[*a*]P) (5 µg) were applied to the skin of female ICR/Ha Swiss mice for 3/week for 440 days, inducing papillomas in 41 of 50 animals. B[*a*]P alone induced tumors in 12 of 50 animals in the same time, while undecane alone did not produce tumors (279).

19.4.1.6 Genetic and Related Cellular Effects Studies. Undecane mutagenicity tested negative using the Ames *S. typhimurium* assay, with and without metabolic activation (285).

19.4.2 Human Experience

19.4.2.1 General Information. Undecane, in solutions as strong as 30%, produced no skin irritation in human subjects when applied for 24 h (286).

19.4.2.2 Clinical Cases

19.4.2.2.1 Acute toxicity. Undecane may be linked to the development of neurological impairment associated with acute exposure to a high level of JP-4 jet fuel (287). Minor neurological effects (dizziness, changes in simple reaction time, and visual-motor coordination) have also been reported in humans from short-term exposure to Stoddard solvent. Similarly, minor neurobehavioral changes were seen in subjects exposed to other white spirits (288).

19.4.2.2.2 Chronic and subchronic toxicity. Severe neurological changes have been described from chronic exposure to Stoddard solvent, white spirits, and other similar solvents; although a cause–effect relationship has not been established (289).

19.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. NA

19.4.2.2.4 Reproductive and developmental. NA

19.4.2.2.5 Carcinogenesis. NA

19.4.2.2.6 Genetic and related cellular effects studies. NA

19.4.2.2.7 Other: neurological, pulmonary, and skin sensitization. A man who was exposed to Stoddard solvent by direct dermal contact and inhalation for 1 year developed glomerulonephritis (289).

19.5 Standards, Regulations, or Guidelines of Exposure

Undecane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA, ACGIH, and NIOSH have not established exposure standards for undecane.

20.0 Dodecane

20.0.1 CAS Number

[*112–40-3*]

20.0.2 Synonyms

Duodecane, bihexyl, adakane 12, *n*-dodecane, alkane C(12)

20.0.3 Trade Names

NA

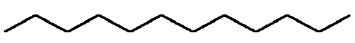
20.0.4 Molecular Weight

170.34

20.0.5 Molecular Formula

$CH_3(CH_2)_{10}CH_3$

20.0.6 Molecular Structure



20.1 Chemical and Physical Properties

20.1.1 General

Dodecane, $C_{12}H_{26}$, is a flammable, colorless liquid with specific gravity 0.749. It occurs in the paraffin fraction of

petroleum. Dodecane is released to the environment by wastewater and spills from laboratory and general use of paraffins, petroleum oils, and tars (63). Selected physical and chemical properties are given in Table 27.1.

20.1.2 Odor and Warning Properties

The odor threshold for dodecane is 37 mg/m^3 (270).

20.1.3 Production and Use

Dodecane is isolated from the kerosene and gas oil fractions of crude oil by selective adsorption and subsequent desorption to yield mixtures of paraffins that can be separated by fractional distillation (63). Dodecane is a component of gasoline and is used as solvent, in organic synthesis, in jet fuel research, as a distillation chaser, and in the rubber and paper processing industries (63, 251).

20.2 Exposure Assessment

20.2.1 Air/Water

Dodecane may be measured in air by gas chromatographic methods under programmed temperature conditions (171, 290). It has been measured in water by gas chromatography, including headspace gas analysis (291).

20.2.2 Background Levels

NA

20.2.3 Workplace Methods

NIOSH Method 1500, Issue 3 uses gas chromatography with a flame ionization detector to measure dodecane and other hydrocarbons in air. The detection limit is 0.05 µg/sample (119).

20.2.4 Community Methods

NA

20.2.5 Biomonitoring/Biomarkers

Headspace gas chromatography appears to be the preferred method for the analysis of dodecane in blood and tissues (271). It has been detected in mother's milk by a purge-and-trap method to recover volatile compounds, and measured by GC-MS (159).

20.3 Toxic Effects

20.3.1 Experimental Studies

20.3.1.1 Acute Toxicity. Rats exposed by inhalation to 0.2 mL dodecane died within 24 h of progressive edema and hemorrhaging (135). In a study that evaluated the acute inhalation toxicity of *n*-alkanes from C9 to C13, dodecane did not show effects at high concentrations (above 3500 ppm) in rats exposed for 8 h, including no central nervous system depression, when rats were similarly exposed at their saturated vapor concentrations (292).

20.3.1.2 Chronic and Subchronic Toxicity. NA

20.3.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Absorption of dodecane occurs mainly by inhalation (271). It has been detected in mother's milk (159). Dodecane is hydroxylated to yield the corresponding primary alcohol. It is metabolized by the rat liver microsomal mixed-function oxidase system (248). Dodecane induces the metabolism of benzo[*a*]pyrene in the lung (293).

20.3.1.4 Reproductive and Developmental. Dodecane, applied topically to progeny of rats treated with benzo[*a*]pyrene, chrysene, or benzo[*b*]triphenylene on gestation day 17, produced tumors in offspring (294).

20.3.1.5 Carcinogenesis. Dodecane has been shown to be a promoter of skin carcinogenesis for benzo[*a*]pyrene and ultraviolet radiation (278, 295).

20.3.1.6 Genetic and Related Cellular Effects Studies. Dodecane is able to enhance mutagenesis induced by methylazoxymethanol acetate at the ouabain resistance locus (296).

20.3.2 Human Experience

20.3.2.1 General Information. Acute eye contact to dodecane may cause irritation. Skin contact may cause irritation or burns. Dodecane may be harmful if inhaled, swallowed, or absorbed through the skin. It can be irritating to mucous membranes. The effects of chronic exposure in humans are unknown (297).

20.4 Standards, Regulations, or Guidelines of Exposure

Dodecane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA, ACGIH, and NIOSH have not established exposure standards.

21.0 Tridecane

21.0.1 CAS Number

[*629–50-5*]

21.0.2 Synonyms

n-Tridecane

21.0.3 Trade Names

NA

21.0.4 Molecular Weight

184.36

21.0.5 Molecular Formula

$CH_3(CH_2)_{11}CH_3$

21.0.6 Molecular Structure

21.1 Chemical and Physical Properties

21.1.1 General

Tridecane, $C_{13}H_{28}$, is a colorless, combustible liquid with specific gravity 0.756. Selected physical and chemical properties are given in Table 27.1.

21.2 Production and Use

Tridecane is isolated from kerosene and gas oil fractions by fractional distillation (63). It is used in organic synthesis, as a solvent, and as a distillation chaser (63).

21.3 Exposure Assessment

21.3.1 Air/Sediment

Atmospheric tridecane may be collected on charcoal and determined by gas chromatography (63). Mass fragmentography has been used to analyze emissions from factories that contain tridecane (298). Tridecane has been isolated from sediment by steam distillation and analyzed by gas chromatography–flame ionization (299).

21.3.2 Background Levels

NA

21.3.3 Workplace Methods

NA

21.3.4 Community Methods

NA

21.3.5 Biomonitoring/Biomarkers

Tridecane has been determined in tissues by gas chromatography and GC-MS (300, 301).

21.4 Toxic Effects

Little information is available on the toxic effects of tridecane.

21.4.1 Experimental Studies

21.4.1.1 Acute Toxicity. The intravenous LD_{50} for tridecane in mice is 1161 mg/kg (195). When aspirated into the lungs, tridecane is an asphyxiant similar to the C6–C10 members. It can cause death more slowly and chemical pneumonitis (135).

21.4.1.2 Chronic and Subchronic Toxicity. NA

21.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. The main route of entry of tridecane to the organism is by inhalation. Tridecane is distributed to the liver, heart, kidneys, muscle, milk, and adipose tissues (159, 300).

21.4.1.4 Reproductive and Developmental. NA

21.4.1.5 Carcinogenesis. Mice treated with tridecane developed tumors on their backs, after exposure to ultraviolet radiation at wavelengths longer than 350 nm, generally considered noncarcinogenic (278).

21.4.2 Human Experience

21.4.2.1 General Information. Tridecane may be harmful by inhalation, ingestion, or skin absorption during industrial use. Vapor or mist is irritating to the eyes, mucous membranes, and upper respiratory tract. It causes skin irritation (297).

21.5 Standards, Regulations, or Guidelines of Exposure

Tridecane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA, ACGIH, and NIOSH have not established exposure standards.

22.0 Tetradecane

22.0.1 CAS Number

[*629–59-4*]

22.0.2 Synonyms

n-Tetradecane

22.0.3 Trade Names

NA

22.0.4 Molecular Weight

184.39

22.0.5 Molecular Formula

$CH_3(CH_2)_{12}CH_3$

22.0.6 Molecular Structure

22.1 Chemical and Physical Properties

22.1.1 General

Tetradecane, $C_{14}H_{30}$, is a colorless liquid with moderate explosive potential and specific gravity 0.763. Selected physical and chemical properties are given in Table 27.1. It occurs naturally in crude oil and in chickpea seeds, nectarines, and kiwi-fruit flowers (63). It may be released to the environment during its production and use, in the exhaust of motor vehicles, and in the effluent of landfills and industrial processes (63).

22.2 Production and Use

Tetradecane is isolated from kerosene and gas oil fractions of crude oil by selective adsorption followed by fractional distillation (63). Tetradecane, often as a mixture with other straight-chain alkanes, is used as building block for detergents and animal feeds, and as a solvent and distillation chaser (14).

22.3 Exposure Assessment

22.3.1 Air/Water

Tetradecane has been detected in air samples collected on activated charcoal, desorbed with trichlorofluoromethane and analyzed by GC-MS (302). It has also been detected in water by the isotope dilution capillary column GC-MS method (EPA method 1625) (273).

22.3.2 Background Levels

NA

22.3.3 Workplace Methods

Tetradecane has been detected in air collected with passive samplers, and identified using standard GC-MS procedures (303).

22.3.4 Community Methods

NA

22.3.5 Biomonitoring/Biomarkers

Tetradecane has been detected in mother's milk by thermal desorption/glass capillary gas chromatography/electron impact mass spectrometry (159). It has been measured in muscle, blubber, liver, and kidney tissue by gas–liquid chromatography and gas–liquid chromatography/mass spectrometry (G/LC-MS) (304, 305).

22.4 Toxic Effects

22.4.1 Experimental Studies

22.4.1.1 Acute Toxicity. Intravenous injection of tetradecane in mice is lethal at 5800 mg/kg. Animals presented altered sleep time, including change in righting reflex (306). Tetradecane, when aspirated into the lungs, is an asphyxiant similar to the C6–C10 alkanes. These alkanes cause death more slowly and can cause chemical pneumonitis (135).

22.4.1.2 Chronic and Subchronic Toxicity. NA

22.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. The main route of entry of tetradecane to the organism is by inhalation. It has been detected in the muscle of fish samples (305). Tetradecane can be metabolized by the cytochrome P450-containing mixed-function oxidase system (248).

22.4.1.4 Reproductive and Developmental. NA

22.4.1.5 Carcinogenesis. Tetradecane is a cocarcinogen and tumor promoter in two-stage experiments of benzo[*a*]pyrene carcinogenicity in mice (279).

22.4.1.6 Genetic and Related Cellular Effects Studies. Tetradecane enhances the mitogenic response of murine spleen lymphocytes to the lectin phytohemagglutinin (250).

22.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Tetradecane administered topically in a rabbit model caused a marked hyperplasia of sebaceous glands, epidermis, and follicular epithelium (307).

22.4.2 Human Experience

22.4.2.1 General Information. Little information is available about the toxic effects of tetradecane in humans. During industrial use, tetradecane may be harmful by inhalation, ingestion, or skin absorption. Vapor or mist is irritating to the eyes, mucous membranes, and upper respiratory tract. It causes skin irritation (297).

22.4.2.2 Clinical Cases

22.4.2.2.1 Acute toxicity. NA

22.4.2.2.2 Chronic and subchronic toxicity. NA

22.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. Tetradecane was detected in samples of mother's milk obtained from residents of urban centers (308). It has also been detected in breath samples of subjects (231).

22.5 Standards, Regulations, or Guidelines of Exposure

Tetradecane is on the EPA TSCA Chemical Inventory and the Test Submission DataBase (63). OSHA, ACGIH, and NIOSH have not set exposure standards.

23.0 Pentadecane

23.0.1 CAS Number

[*629–62-9*]

23.0.2 Synonyms

n-Pentadecane, pentadecane (*n*), pentadecane-d32

23.0.3 Trade Names

NA

23.0.4 Molecular Weight

212.42

23.0.5 Molecular Formula

$CH_3(CH_2)_{13}CH_3$

23.0.6 Molecular Structure

23.1 Chemical and Physical Properties

23.1.1 General

Pentadecane, $C_{15}H_{32}$, is a colorless liquid with specific gravity 0.768. Selected physical and chemical properties are given in Table 27.1.

23.2 Production and Use

Pentadecane is produced by isolation of *n*-paraffins (C9–C17) from kerosene and gas oil fractions of crude oil by selective adsorption and fractional distillation (63). It is used in organic synthesis and as solvent (63).

23.3 Exposure Assessment

23.3.1 Air

Pentadecane in air may be collected on charcoal and analyzed by gas chromatographic methods (309).

23.3.2 Background Levels

NA

23.3.3 Workplace Methods

NA

23.3.4 Community Methods

NA

23.3.5 Biomonitoring/Biomarkers

Pentadecane has been measured in liver, kidney, fat, and brain tissues by gas–liquid chromatography and by G/LC-MS (301, 304).

23.4 Toxic Effects

23.4.1 Experimental Studies

23.4.1.1 Acute Toxicity. The LD_{50} for pentadecane administered intravenously to mice is 3494 mg/kg (310). Pentadecane, when aspirated into the lungs, is an asphyxiant similar to the C6–C10 alkanes (135).

23.4.1.2 Chronic and Subchronic Toxicity. NA

23.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. NA

23.4.1.4 Reproductive and Developmental. Fertile duck eggs were treated with mixtures of aromatic and aliphatic hydrocarbons, including pentadecane. The aliphatic mixture had a minimal effect on embryo survival (311).

23.4.1.5 Carcinogenesis. NA

23.4.1.6 Genetic and Related Cellular Effects Studies. NA

23.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Pentadecane incubated *in vitro* with 10–160 µg/mg rabbit heart mitochondrial protein did not cause significant effects on respiration and oxidative phosphorylation of the heart mitochondria (312).

23.4.2 Human Experience

23.4.2.1 General Information. Little information is available on the health effects of pentadecane in humans. Pentadecane may be harmful by inhalation, ingestion, or skin absorption during industrial use. It may cause eye and skin irritation. It may also cause central nervous system depression and liver damage (313).

23.5 Standards, Regulations, or Guidelines of Exposure

Pentadecane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA, ACGIH, and NIOSH have not established exposure standards.

24.0 Hexadecane

24.0.1 CAS Number

[*544–76-3*]

24.0.2 Synonyms

Cetane, *n*-cetane, *n*-hexadecane

24.0.3 Trade Names

NA

24.0.4 Molecular Weight

226.44

24.0.5 Molecular Formula

$CH_3(CH_2)_{14}CH_3$

24.0.6 Molecular Structure

24.1 Chemical and Physical Properties

24.1.1 General

Hexadecane, $C_{16}H_{34}$, is a colorless, combustible liquid with specific gravity 0.773. It is a constituent in paraffin fraction of petroleum, and occurs naturally in volatile components of certain plants (63). It is released to the environment from gasoline- and diesel-powered vehicles, rubber manufacture, shale oil production, coal combustion, biomass combustion, and tobacco smoke (63). Selected physical and chemical properties are given in Table 27.1.

24.2 Production and Use

Hexadecane is a component of gasoline, and is used as a solvent, organic intermediate, ignition standard for diesel fuels, and as stock for hydrocracking processes (63).

24.3 Exposure Assessment

24.3.1 Air/Water

Hexadecane in the atmosphere has been collected on activated charcoal, desorbed with trichlorofluoromethane, and analyzed by GC-MS (302, 314). It may be measured in water by isotope dilution GC-MS (EPA method 1625) (273).

24.3.2 Background Levels

NA

24.3.3 Workplace Methods

NA

24.3.4 Community Methods

NA

24.3.5 Biomonitoring/Biomarkers

Hexadecane has been measured in animal tissues by gas–liquid chromatography and G/LC-MS (301, 304).

24.4 Toxic Effects

24.4.1 Experimental Studies

24.4.1.1 Acute Toxicity. Exposure of mussel larvae (*Mytilus edulis*) to 10 and 50 ppm hexadecane caused a slight reduction of growth rate; an increase in growth rate was observed at 100 ppm (270). Hexadecane, when aspirated into the lungs, is an asphyxiant similar to the C6–C10 members (135). Hexadecane in combination with 2-butanone or cyclohexane potentiates local anesthetics (315).

24.4.1.2 Chronic and Subchronic Toxicity. NA

24.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. NA

24.4.1.4 Reproductive and Developmental. NA

24.4.1.5 Carcinogenesis. NA

24.4.1.6 Genetic and Related Cellular Effects Studies. NA

24.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Topical applications of hexadecane to the female albino guinea pig skin caused erythema at 24 h after application and edema at 48 h. Epidermal thickness and number of cell nuclei were significantly increased after application (316).

24.4.2 Human Experience

24.4.2.1 General Information. Hexadecane is a mild eye and mucous membrane irritant, primary skin irritant, and CNS depressant. Acute exposure by industrial use to hexadecane causes irritation, narcosis, and GI tract irritation (317). Toxicity information in humans is inadequate.

24.4.2.2 Clinical Cases

24.4.2.1.1 Acute toxicity. NA

24.4.2.1.2 Chronic and subchronic toxicity. NA

24.4.2.1.3 Pharmacokinetics, metabolism, and mechanisms. Hexadecane has been identified in two human atherosclerotic aortas at concentrations of 40 and 60 ng/g (318).

24.5 Standards, Regulations, or Guidelines of Exposure

Hexadecane is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA, ACGIH, and NIOSH have not set exposure standards.

Other Higher Alkane Homologs

Heptadecane (C17) is in the physical form of hexagonal leaves; *octadecane* (C18) is a colorless liquid; *nonadecane* (C19) is wax; *pristane* (2,6,10,14-tetramethylpentadecane) (C19) is a colorless liquid; and *eicosane* (didecyl) (C20) is a white crystalline solid (63, 319). Selected physical and chemical properties are given in Table 27.1 for heptadecane, octadecane, nonadecane, pristane, and eicosane. Heptadecane and other higher homologs are used as stock for hydrocracking processes (320). Octadecane is used as a solvent, in organic synthesis, and as a calibration standard (8). Pristane is used as a lubricant and transformer oil (8). Pristane is also used as an adjuvant for inducing human-type diseases in rodent models (321–324) and to precondition the peritoneal cavity of mice, prior to the induction of ascites fluid with myeloma cells for production of monoclonal antibodies (325). The alkanes to C17 can be collected on charcoal and the higher members as particulate matter on filters, desorbed with carbon disulfide, and quantified using gas chromatography (309).

Little is known about the toxicological properties of higher alkanes. Following oral gavage of 1 g to rats, heptadecane was found in concentrations of 0.7%, 1.4%, 1.2%, and 0.2% in the intestinal wall, liver, intestinal content, and feces, respectively (8). In rats fed a diet of 25% *Spirulina* algae, heptadecane accumulated in adipose tissue at 80.2 and 272.0 mg/g in males and females and in lung and muscle at ~10–20 mg/kg, respectively (326). Dietary concentrations of 52 ppm fed to pigs for 12 months resulted in the excretion of some heptadecane in milk during lactation (326). Higher alkanes may be harmful by inhalation, ingestion, or skin absorption during industrial use. They may cause eye and skin irritation (317). High concentrations of pristane are extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes, and skin (319). The cocarcinogenic activity may be common to many C12–C30 aliphatic hydrocarbons (327).

3 ALKENES (OLEFINS)

Alkenes differ from alkanes in the presence of a double covalent bond in the carbon chain. They have the generic formula C_nH_{2n}. They represent the simplest of the *unsaturated hydrocarbons*.

Alkenes are chemically more reactive than alkanes, primarily through addition reactions across the double bonds (8). When heated or in the presence of catalysts, most olefins will polymerize. They have higher boiling points than the parent paraffins as shown in Table 27.19.

Alkenes, except for butadiene, are only slightly more toxic than alkanes. Ethene, propene, butene, and isobutene are weak anesthetics and simple asphyxiants. Pentene has been used for surgical anesthesia. Because of increasing mucous membrane irritancy and cardiac effects with increasing chain length, the hexylenes and higher members are unsuitable as anesthetic agents. The higher members may cause CNS depression, but are not sufficiently volatile to be considered vapor hazards at room temperature (328). Branching decreases the toxicity of C3 alkenes, does not appreciably affect the C4 and C5 alkenes, and increases the toxicity of C6–C18 alkenes. Unlike the hexanes, the olefins do not produce axonopathy. Repeated exposure to high concentrations of the lower members of the alkenes results in hepatic damage and hyperplasia of the bone marrow in animals. However, no corresponding effects have been noted in humans. Alpha olefins are more reactive and toxic than beta isomers. The alkadienes are more irritant and generally more toxic than the corresponding alkanes (329).

1,3-Butadiene is probably the most toxic member of the alkene family. The toxicological properties of butadiene have been studied extensively in both experimental animals and humans. Epidemiological studies on cancer among people exposed to butadiene have suggested increased risks for leukemia and lymphoma (330).

25.0 Ethene

25.0.1 CAS Number

[*74–85-1*]

25.0.2 Synonyms

Ethylene, acetene, bicarburretted hydrogen, elayl, ethylene-d3 (gas), olefiant gas

Table 27.19. Physicochemical Properties of Alkanes

Compound	Molecular Formula	Molecular Weight	Boiling Point (°C)	Melting Point (°C)	Density (mg/cm^3) (at °C)	Refractive Index n_D	Solubility	Flash Point (°C)	Flammability Limits (%)
Ethene	C_2H_4	28.0	−103.7	−169.2	0.5678 (−104)	1.363 (100)	w 1, al 2, et 3, ac 2	−130 (closed cup)	2.7–3.6
Propene	C_3H_6	42.08	−47.4	−185.24	0.505 (25)	1.3567 (−70)	w 4, al 4, aa 4	−108	2.0–11.1
1-Butene	C_4H_8	56.107	−6.1	−185.3	0.588 (25)	1.3962 (20)	w 1, al 4, et 4, bz 3	–	1.6–10.0
cis-2-Butene	C_4H_8	56.107	3.7		0.616 (25)	1.3931 (−25)	w 1, al 4, et 4, bz 3	–	1.7–9.0
trans-2-Butene	C_4H_8	56.107	0.88		0.599 (25)	1.3848 (−25)	bz 3	–	1.8–9.7
2-Methylpropene	C_4H_8	56.107	−6.9	−140.3	0.589 (25)	1.3926 (−25)	w 1, al 4, et 4, bz 3	–	1.8–9.6
1-Pentene	C_5H_{10}	70.134	30	−165	0.6405 (20)	1.3715 (20)	w 1, al 5, et 5, bz 3	−28	1.5–8.7
cis-2-Pentene	C_5H_{10}	70.13	36.9	−151.4	0.6556 (20)	1.3830 (20)	w 1, al 5, et 5, bz 3	<−20.0	–
trans-2-Pentene	C_5H_{10}	70.13	36.3	−140.2	0.6431 (25)	1.3793 (20)	w 1, al 5, et 5, bz 3	< −20.0	–
3-Methyl-1-butene	C_5H_{10}	70.13	20.1	−168.5	0.6213 (25)	1.3643 (20)	w 1, al 5, et 5, bz 3	−7.0	1.5–9.1
1-Hexene	C_6H_{12}	84.16	63.3	−139.8	0.6731 (20)	1.3837 (20)	al 4, et 4, bz 4, pe 4	15 (closed cup)	1.2–6.9
cis-2-Hexene	C_6H_{12}	84.16	68.8	−141.1	0.6869 (20)	1.3979 (20)	w 1, al 3, et 3, bz 3	−21.0	–
trans-2-Hexene	C_6H_{12}	84.16	67.9	−133.0	0.6732 (25)	1.3936 (20)	w 1, al 3, et 3, bz 3	–	–
2-Methyl-2-pentene	C_6H_{12}	84.16	67.3	−135.0	0.6863 (20)	1.4004 (20)	w 1, al 3, bz 3, ct 3	<−7.0	–
1-Heptene	C_7H_{14}	98.188	93.3	−119	0.6970 (20)	1.3998 (20)	w 1, al 3, et 3, ct 2		–
1-Octene	C_8H_{16}	112.22	121.2	−101.7	0.7149 (20)	1.4087 (20)	w 1, al 5, et 3, ac 3	21.0	–
2-Methyl-2-heptene	C_8H_{16}	112.22	122.6	–	0.7200 (25)	1.4170 (20)	w 1, et 3, bz 3, ct 3	–	–
1-Nonene	C_9H_{18}	126.24	146.9	−81.3	0.7253 (25)	1.4257 (20)	–	26.0	–
Propadiene	C_3H_4	40.06	−34.4	−136.2	0.584 (25)	1.4168 (20)	bz 4, pe 4	–	2.1–12.5
1,3-Butadiene	C_4H_6	54.09	−4.4	−108.9	0.6149 (25)	1.4292 (−25)	w 1, al 3, et 3, ac 4	−76	2.0–12.0
2-Methyl-1,3-butadiene	C_5H_8	68.118	34.0	−120	0.679 (20)	1.4219 (20)	w 1, al 5, et 5, ac 5	−48	1.5–8.9
cis-1,3-Hexadiene	C_6H_{10}	82.15	73.1	–	0.7033 (25)	1.4379 (20)	–	–	–
trans-1,3-Hexadiene	C_6H_{10}	82.15	73.2	−102.4	0.6995 (25)	1.4406 (20)	–	–	–
1,4-Hexadiene	C_6H_{10}	82.15	65.0	–	0.7000 (20)	1.4150 (20)	w 1, et 4	−21.0	2.0–6.1
1,5-Hexadiene	C_6H_{10}	82.15	59.4	−140.7	0.6878 (25)	1.4042 (20)	w 1, al 3, et 3, bz 3	–	–
1,7-Octadiene	C_8H_{14}	110.20	115.5	–	0.734 (20)	1.4245 (20)	–	9.0	–
Squalene	$C_{30}H_{50}$	410.73	280.0	<−20.0	0.8584 (20)	1.4990 (20)	w 1, al 2, et 3, ac 3	–	–
Lycopene	$C_{40}H_{56}$	536.88	–	175.0	–	–	al 2, et 3, bz 4, ch 4	–	–
β-Carotene	$C_{40}H_{56}$	536.88	–	183.0	1.00 (20)	–	w 1, al 2, et 3, ac 3	–	–

Molecular formula, in Hill notation; molecular weight, relative molar mass; density, mass per unit volume in g/cm^3 at the temperature indicated in parentheses; refractive index, at the temperature indicated in parentheses, unless otherwise indicated, all values refer to a wavelength of 589 nm; solubility, solubility in common solvents (w, water; al, ethanol; et, ethyl ether; ac, acetone; bz, benzene; ch, chloroform; ct, carbon tetrachloride; aa, acetic acid; pe, petroleum ether; os, organic solvents) on a relative scale: 1 = insoluble, 2 = slightly soluble, 3 = soluble, 4 = very soluble, 5 = miscible, 6 = decomposes; flammability limits, explosive limits (in percent by volume) at ambient temperature and pressure.

25.0.3 Trade Names

NA

25.0.4 Molecular Weight

28.0

25.0.5 Molecular Formula

$CH_2{:}CH_2$

25.0.6 Molecular Structure

25.1 Chemical and Physical Properties

25.1.1 General

Ethene, C_2H_4, is a colorless, flammable, explosive gas, and is strikingly reactive (12). Its specific gravity is 0.6 at 0°C. It is produced by all plant tissues in significant amounts and acts as an endogenous plant growth regulator; it is also produced by soil microorganisms. Ethene is released in emissions from acrylonitrile, chemical and petroleum manufacture, automotive and diesel exhaust, wood and polyethylene combustion, foundries, sewage treatment plants, turbine engines, veneer drying, wood pulping, tobacco smoke, and some solvents (63). Selected physical and chemical properties are given in Table 27.19.

25.1.2 Odor and Warning Properties

Ethene has an olefinic and hedonic odor (270). The odor of ethene can be detected between 299 and 4600 mg/m^3 (29).

25.2 Production and Use

Ethene is prepared by cracking of ethane and propane and other petroleum gases, and by catalytic dehydration of ethanol (320). Ethene is one of the most important industrial raw materials for a variety of chemicals, petrochemicals, polymers, and resins. It is used as a fruit and vegetable-ripening agent, and was formerly used as a surgical anesthetic (63, 331).

25.3 Exposure Assessment

25.3.1 Air/Water

Methods for detecting ethene in air include infrared spectrophotometry, gas chromatography with flame ionization detection, and gas chromatography combined with mass spectrometry (63, 332). Ethene has also been determined in water by gas chromatography (333).

25.3.2 Background Levels

NA

25.3.3 Workplace Methods

NA

25.3.4 Community Methods

NA

25.3.5 Biomonitoring/Biomarkers

Ethene has been measured in exhaled air by GC-MS (66). The hemoglobin adduct of the metabolite ethylene oxide [*N*-(2-hydroxyethyl)valine], has been used as a biomarker of occupational exposure to ethene. It can be measured by GC-MS (334) and gas chromatography with electron capture detection (335).

25.4 Toxic Effects

25.4.1 Experimental Studies

25.4.1.1 Acute Toxicity. Male rats exposed to 10,000, 25,000, or 57,000 ppm ethene for 4 h exhibited increased serum pyruvate levels and liver weights (336). The liver mitochondrial volume increased in rats treated with ethene (337). Rats exposed to 90% ethene and 10% oxygen are anesthetized in about 20 min and exhibit slight nervous symptoms (338). Deep anesthesia occurs in a few seconds with 95% ethene and 5% oxygen, accompanied by marked cyanosis and depression with a slow fall in blood pressure (336). In dogs, ethene at a concentration of 1.4% is a rapidly acting anesthetic (331). Exposure to 700,000–900,000 ppm causes changes in the EEG activity and decrease in stomach emptying time (339, 340). Rats treated with up to 500,000 ppm ethene for 5 h showed no effects; however, if the rats were pretreated with 500 mg/kg of Arochlor and exposed at 100,000 ppm ethane, an increased serum glutamicpyruvic transaminase (SGPT) activity and centrolobular necrosis were observed. Similar effects were not evident with other enzyme inducers such as phenobarbital and 3-methyl cholanthrene (341).

25.4.1.2 Chronic and Subchronic Toxicity. Rats exposed to ethene by inhalation, to concentrations of 300–10,000 ppm, 6 h/day, 5 days/week for 14 weeks showed no toxic effects (342). Nor were any effects seen at doses of 300–3000 ppm for 6 h/day, 5 days/week for 106 weeks (343). Inhalation exposure to 600,000 ppm continuously for 90 days in rats caused reduced food uptake and activity, peripheral

leucopenia, decreased thrombocyte and erythrocyte count, and decrease in bone marrow cellularity (344). In a chronic study, 1 day old and adult rats continuously exposed to 3 mg/m^3 per day for 90 days exhibited hypertension, disruption of the subordination chronaxy, and decreased cholinesterase activity (345).

25.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Inhalation is the major route of entry of ethene to the organism (346). Only a small portion of ethene is taken up by tissues, and most is expired unchanged or as CO_2, or excreted in urine and feces. Ethene equilibrated in alveolar, arterial, brain, and muscle tissue in 2–8.2 min, even more rapidly than ethyl ether (331). Ethene is metabolized by the cytochrome P450 system into its corresponding oxide (347). Evidence suggests that ethene oxide is further metabolized by glutathione *S*-transferases but not by the epoxide hydrolase enzyme system (346). Rat liver microsomal monooxygenases also transform ethene to oxirane (348). The metabolism and disposition of ethene in rats is altered by pretreatment with Aroclor 1254 (341).

25.4.1.4 Reproductive and Developmental. Rats were exposed to ethene for 2 weeks prior to pairing, during the pairing period and until the day prior to necropsy for males (minimum 28 days) or until day 20 of gestation. Ten males and 10 females per group were held in rodent restraint tubes and exposed by head-only to ethene in concentrations of 0 (air control), 200, 1000, or 5000 ppm for 6 h/day. There were no deaths attributable to ethene and treatment did not adversely affect weight gain or food intake of males or females. All females became pregnant and there was no effect of treatment on fertility, fecundity, litter size, sex ratio, mean pup weight, pup growth, or clinical condition. Macroscopic findings and histopathologic examination (including staging of the spermatogenic cycle) of parental animals revealed no treatment-related effects. Comparison of unrestrained, nonexposed animals, and control animals revealed no evidence of adverse effects (349).

25.4.1.5 Carcinogenesis. Female and male rats exposed to concentrations of 300–3000 ppm ethene for 6 h/day, 5 days/week for 106 weeks showed no evidence of oncogenicity (343). Rats exposed to 10,000 ppm ethene (8 h/day, 5 days/week for 3 weeks) and Clophen A50 as a promoting agent, were examined for ATPase-deficient foci in the liver. The number of ATPase-deficient foci in the rats exposed to ethene did not exceed the control values (350).

25.4.1.6 Genetic and Related Cellular Effects Studies. Ethene is not mutagenic in the Ames *S. typhimurium* assay, with or without metabolic activation (343). Rats and mice exposed 6 h/day 5 days/week for 4 weeks to 40–3000 ppm ethene did not have a significant increase in the frequency of micronucleated polychromatic erythrocytes in the bone marrow, when compared to the control group (351). Rats exposed 6 h/day, 5 days/week for 4 weeks at 40, 1000, or 3000 ppm ethene showed no significant increase in peripheral lymphocyte *Hprt* mutant frequencies compared to unexposed controls, while exposure at 200 ppm ethylene oxide increased mutant frequencies five- to sixfold. The authors concluded that too little endogenous ethylene oxide arises from exogenous ethene exposure to produce positive results in this mutagenicity assay (352).

25.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Ethene is not a cardiac sensitizer in the dog (36). Mice repeatedly exposed at concentrations causing CNS depression showed no histopathological changes in kidneys, adrenals, hearts, or lungs (8). Acute, subchronic, and chronic exposure to ethene does not have hepatotoxic effects in rats; however, under the same exposure conditions, pretreatment with Aroclor 1254 resulted in hepatic injury (336). Ethene is nonirritating to the skin and eyes (18). Conversely, ethene has speeded up the wound healing process in muscle injuries of mice (353).

25.4.2 Human Experience

25.4.2.1 General Information. Concentrations of $\leq$2.5% ethene are systemically inert. However, very high concentrations may cause CNS depression, unconsciousness, and asphyxia due to oxygen displacement (12, 63). Ethene was formerly used as an anesthetic agent. Its advantages over comparable human anesthetics are rapid onset and recovery time after exposure termination with little or no effect on cardiac and pulmonary functions (331). Respiration, blood pressure, and pulse rates are rarely changed, even under anesthetic conditions. Cardiac arrhythmias occur infrequently, and ethene has little effect on renal and hepatic functions; however, cyanosis often occurs (331, 354). The disadvantages as an anesthetic are its explosion and flammability properties.

25.4.2.2 Clinical Cases

25.4.2.2.1 Acute toxicity. Humans exposed to ethene may experience subtle signs of intoxication, resulting in prolonged reaction time (355). Exposure at 37.5% for 15 min resulted in marked memory disturbances (8). Humans exposed to as much as 50% ethene in air, whereby the oxygen availability is decreased to 10%, experience loss of consciousness. Prolonged inhalation of 85% ethene in air is slightly toxic, whereas 94% in oxygen is fatal. Death is certain at 8% oxygen (143).

25.4.2.2.2 Chronic and subchronic toxicity. In workers chronically exposed, ethene has been associated with a

decrease in maximum arterial pressure, slower pulse, lengthened later period of the visual-motor response, increased thresholds of olfaction and hearing, and in the tension of the thermoregulatory apparatus (356).

25.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. In humans, ethene is metabolized to ethylene oxide, a human carcinogen. Six subjects were exposed at 5 and 50 ppm ethene in a chamber for 2 h and measured ethene uptake and exhalation of endogenously produced ethene. Only 2% of the inhaled ethene was absorbed and metabolized (98% exhaled unchanged). The rate of endogenous production was calculated as 32 nmol/h, a level three times higher than in rats. The measured value of hydroxyethyl valine hemoglobin adduct in unexposed control subjects was 0.02 pmol adduct/mg hemoglobin (20 pmol/g), which was in good agreement with the value predicted from a two-compartment physiologically based pharmacokinetic model (0.018 pmol adduct/mg hemoglobin or 18 pmol/g) (357). A multicompartment model for human data was also developed, including endogenous ethene and ethylene oxide formation. The model predicted that an exposure at 45 ppm ethene was equivalent to 1 ppm ethylene oxide exposure. The model was also able to predict hemoglobin adduct values that were 86% of measured values in available human studies (358). Hydroxyethylvaline hemoglobin adducts have been measured in fruit store workers exposed at approximately 0.3 ppm ethene (range, 0.02–3.35 ppm). Unexposed nonsmokers had mean hemoglobin adduct levels of 0.02 pmol adduct/mg hemoglobin (20 pmol/g). Exposed workers had mean hemoglobin adduct levels of 0.043 pmol adduct/mg hemoglobin (43 pmol/g). It was estimated that 3% (uncertainty range, 1–10%) of inhaled ethene was converted to ethylene oxide (359).

Measurable levels of hemoglobin adducts were detected in workers exposed to 1 ppm ethene (335). In the plastics industry, a study found that workers exposed at 3.5 ppm ethene had mean hemoglobin adduct values of 0.101 pmol adduct/mg hemoglobin (101 pmol/g) (360). In a subsequent study, the authors found that workers exposed at 3.8 ppm had mean hemoglobin adduct levels of 0.110 pmol adduct/mg hemoglobin (110 pmol/g). Control hemoglobin adduct levels were 0.015 pmol adduct/mg hemoglobin (15 pmol/g). The researchers calculated the percent conversion of ethene to ethylene oxide as 0.5% from a physiologically based pharmacokinetic model (361).

25.4.2.2.4 Reproductive and developmental. NA

25.4.2.2.5 Carcinogenesis. A case-control study of brain cancer among Texas petrochemical workers reported increased risks associated with exposure to multiple chemicals, including ethene (362, 363). The findings were not statistically significant. The risks for ethene have not been shown to increase with increasing duration of employment. The observed increases could not be attributed to specific chemical exposures.

25.4.2.2.6 Genetic and related cellular effects studies. In eight people not occupationally exposed to ethene, the DNA adduct 7-(2-hydroxyethyl)guanine was detected at a background level of 8.5 ± 5.7 nmol/g of DNA in peripheral lymphocytes (364). Possible sources for this DNA adduct are not indicated.

25.4.2.2.7 Other: neurological, pulmonary, and skin sensitization. In fatal intoxication, ethene affects the respiratory center of the brain and kills by suffocation. Postmortem analysis has revealed that the right side of the heart is full of blood, while the left side is empty (365).

25.5 Standards, Regulations, or Guidelines of Exposure

A TLV–TWA has been developed by ACGIH (366). OSHA and NIOSH have not established exposure limits for ethene. The German MAK Commission has assigned ethene a carcinogenicity classification of 3B, "a substance for which *in vitro* or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories." The Commission developed the following biological tolerance value (BAT) as an indicator of exposure at 50 mg/m^3 (27.75 ppm) ethene in air: an erythrocyte hydroxyethylvaline level of 90 µg/L blood that is equivalent to the technical exposure limit of 2 mg/m^3 (1 ppm) for ethylene oxide (367). IARC found inadequate evidence in humans and experimental animals for the carcinogenicity of ethene and concluded that it is "not classifiable as to its carcinogenicity to humans (Group 3)" (332).

26.0 Propene

26.0.1 CAS Number

[*115–07-1*]

26.0.2 Synonyms

Methylethene; methylethylene; propylene; 1-propylene; 1-propene; propylene, various grades

26.0.3 Trade Names

NA

26.0.4 Molecular Weight

42.08

26.0.5 Molecular Formula

CH_2:$CHCH_3$

26.0.6 Molecular Structure

26.1 Chemical and Physical Properties

26.1.1 General

Propene, C_3H_6, is a colorless, flammable, practically odorless gas. Propene occurs in refined petroleum products (63). It has been identified as a natural product from vegetation (368). Propene is released to the atmosphere in emissions from the combustion of gasoline, coal, wood, cigarettes, and refuse (63). Selected physical properties are given in Table 27.19.

26.1.2 Odor and Warning Properties

The odor threshold for propene is between 39.6 and 116.27 mg/m^3, and the odor is described as aromatic (29).

26.2 Production and Use

Propene is produced in the petroleum cracking process (251). Commercially, it is available in liquefied form with trace impurities of lower alkanes and alkenes (369). Propene is highly reactive and is utilized as a raw material for a variety of processes, including plastics manufacture (251, 369). It is a common feedstock for the production of gasoline and is used as an aerosol propellant (251, 370). Early investigations indicated its possible use as an anesthetic, and it was found to be twice as potent as ethene (371).

26.3 Exposure Assessment

26.3.1 Air/Water

Gas chromatography combined with gas spectrometry has been used to determine propene in gaseous mixtures and hydrocarbon oils. It can also be detected by capillary column gas chromatography and a flame ionization detector (332). Propene has also been detected by measuring its reaction with ozone or with active nitrogen (372). Air may be preconcentrated on silica gel at dry ice temperature (373). Infrared spectrophotometry of cryogenically cooled gaseous mixtures can also be used to detect propene (372). It may also be measured in water by gas chromatography (372).

26.3.2 Background Levels

NA

26.3.3 Workplace Methods

NA

26.3.4 Community Methods

NA

26.3.5 Biomonitoring/Biomarkers

Propene has been measured in mother's milk by thermal desorption/gas chromatography/mass spectrometry (159). Exposure to propene can be measured through the analysis of adducts to N-terminal valine in hemoglobin using gas chromatography and electron capture detection or GC-MS (335).

26.4 Toxic Effects

26.4.1 Experimental Studies

26.4.1.1 Acute Toxicity. A concentration of 40% inhaled propene produced light anesthesia in rats, but no toxic symptoms within 6 h. Exposure to 55% for 3–6 min, 65% for 2–5 min, or 70% for 1–3 min resulted in deep anesthesia with no CNS signs or symptoms (338). Inhaled propene was not toxic to rats exposed for 4 h to 50,000 ppm, but it was hepatotoxic in animals exposed to the same concentration and pretreated with Aroclor 1254 (374). Cats do not exhibit any toxic signs when anesthesia is induced with propene concentrations of 20–31%. Subtle effects occur from exposure to 40–50%, blood pressure decrease and rapid pulse at 70%, and the unusual ventricular ectopic beat at 50–80% (8).

26.4.1.2 Chronic and Subchronic Toxicity. Rats and mice of both sexes exposed to propene at concentrations ranging from 625 to 10,000 ppm for 6 h/day, 5 days/week for 14 days, 14 weeks and 103 weeks, showed no significantly different survival and mean body weights than those of controls (375). In a 90 day inhalation study on Fischer 344 rats, two test groups of 20 males and 10 females were administered 1017 ppm and 4489 ppm propene, respectively. A negative control group of 40 males and 20 female received no treatment. There were no deaths, and no other significant toxicological effects were found. Serial sacrifices of 10 male and 5 female animals were made after 28 days. The male animals showed mild but significant characteristics of light hydrocarbon nephropathy. However, at 90 days the animals showed no evidence of kidney effects (376).

26.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. In rats exposed to 50,000 ppm propene, about one-sixth of the inhaled material is absorbed, almost one-half of which is exhaled again, unchanged. The remainder is eliminated metabolically (332). Propene oxide was the principal metabolite of propene in mice that inhaled 0–30,000 ppm [^{14}C]propene for 6 h (377). It appears that propene is metabolized by the cytochrome P450-dependent

mixed-function oxidase system (370). Glutathione does not play a major role in the detoxification of propene or its metabolites (374).

26.4.1.4 Reproductive and Developmental. Twenty-five female Wistar rats per test group were exposed to dynamic atmospheres of propene for 6 h/day on days 6 through 19 postcoitum at concentrations of 200, 1,000, and 10,000 ppm. A concurrent control group was exposed to clean air. There were no differences of toxicological relevance between the control and the propane-exposed groups on the gestational parameters, that is, in conception rate; mean number of corpora lutea; total implantations; resorptions and live fetuses; fetal sex; ratio or in the values calculated for the pre- and the postimplantation losses. No propene-related differences were recorded for placental and fetal body weights. The external, soft tissue, and/or skeletal examinations of the fetuses revealed no toxicologically relevant differences between the control and the propene-exposed groups. Under the conditions of the study, the inhalation exposure of pregnant Wistar rats to propene from implantation to 1 day prior to the expected day of parturition (days 6–19 postcoitum) elicited no maternal toxicity, prenatal or developmental toxicity, or teratogenicity at all tested concentrations up to 10,000 ppm (378).

26.4.1.5 Carcinogenesis. Exposure of rats and mice to 200, 1000, or 5000 ppm propene 7 h/day, 5 days/week for 18–24 months did not reveal any carcinogenic effects in either species (379). In another study with exposures of 5,000 and 10,000 ppm, rats exhibited non-neoplastic lesions in the nasal cavity. These consisted of hyperplasia in female rats exposed to the high concentrations, and squamous metaplasia in female rats exposed to both concentrations and in male rats exposed to the low concentration. Inflammatory changes occurred also in male rats of both exposure groups (375, 380).

26.4.1.6 Genetic and Related Cellular Effects Studies. Propene is not mutagenic in *Escherichia coli* and protects against mutation (381). It is not cytotoxic or mutagenic in cultures of mouse lymphoma cells in either presence or absence of a hepatic microsomal activating system (382). In mouse peripheral tissues and hemoglobin, propene is six times less potent an alkylating agent than propene oxide (377). Six week old male F344 rats were exposed to 0, 200, 2,000, or 10,000 ppm propene by inhalation for 4 weeks (6 h/day, 5 days/week), and mutant frequencies were determined in the Hprt gene of splenic T-lymphocytes. Hprt mutant frequencies in propene-exposed rats were not significantly increased over background (383).

26.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Propene is a cardiac sensitizer in the dog (36). Chronic exposure of mice to concentrations causing CNS depression resulted in moderate to very slight fatty degeneration of the liver, but somewhat less than caused by ethene (384). Rats pretreated with Aroclor 1254 and exposed to 50,000 ppm propene, exhibited hepatotoxicity (374). These results suggest that Aroclor alters the disposition and/or metabolism of propene (370).

26.4.2 Human Experience

26.4.2.1 General Information

Propene is of generally low toxicity and acts as a simple asphyxiant and mild anesthetic (15, 371). The vapor is nonirritating to the skin, but the liquefied product may cause burns from direct contact (12).

26.4.2.2 Clinical Cases

26.4.2.2.1 Acute toxicity. Propene has been used in dental surgery as a temporary anesthetic (385). At a concentration of 6.4% for 2.25 min, mild intoxication, paresthesias, and inability to concentrate were noted (181). At 12.8% in 1 min, symptoms were markedly accentuated and at 24% and 33%, unconsciousness followed in 3 min (181, 386). Human exposure to 23% propene for 3–4 min did not result in unconsciousness (8). Two subjects exposed to 35% and 40% propene vomited during or after the exposure and one complained of vertigo (372). Exposure to 40%, 50%, or 75% for a few minutes caused initial reddening of the eyelids, flushing of the face, lacrimation, coughing, and sometimes flexing of the legs (385). No variations in respiratory or pulse rates or electrocardiograms were noted (385). A concentration of 50% prompted anesthesia in 2 min, followed by complete recovery (8).

26.4.2.2.2 Chronic and subchronic toxicity. NA

26.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. The most probable route of human exposure to propene is by inhalation (63). Propene has been detected in breast milk of women (159).

26.4.2.2.4 Reproductive and developmental. NA

26.4.2.2.5 Carcinogenesis. NA

26.4.2.2.6 Genetic and related cellular effects studies. NA

26.4.2.2.7 Other: neurological, pulmonary, and skin sensitization. A light sensitivity to the eyes following exposure to approximately 1 mg/m^3 has been reported (8). The concentration for onset of narcosis (loss of judgment, disorientation, dizziness, and lightheadedness) from propene exposure in humans has been estimated at 46,000 ppm, based

on a model for anesthetic potency and oil/water partition coefficients. The model was validated using human experience with diving (nitrogen narcosis) and workplace exposure to toluene. The recommendation is made that in addition to an 8 h time-weighted average exposure limit (1000 ppm, set on a basis of good industrial hygiene practice) for all C1–C3 hydrocarbons, a maximum exposure limit of 10% of the lower explosive limit is necessary, on the basis of avoidance of narcosis and recognition of the explosive hazards of the gases (2).

26.4.2.3 Epidemiology Studies

26.4.2.3.1 Acute toxicity. NA

26.4.2.3.2 Chronic and subchronic toxicity. NA

26.4.2.3.3 Pharmacokinetics, metabolism, and mechanisms. NA

26.4.2.3.4 Reproductive and developmental. NA

26.4.2.3.5 Carcinogenesis. After an observation of an apparent cluster of colorectal cancers in a polypropylene manufacturing plant, a cohort study of men working in the plant was conducted. Seven incident colorectal cancers were ascertained (1.3 expected) (387). In a subsequent case-control study of adenomatous polyps and carcinoma *in situ* of the large bowel, cases tended to have higher exposure to pre-extrusion polymer plus additives [odds ratio (OR) = 2.6, 90% confidence interval (CI) 1.1–6.3] and higher exposure to certain finishing additives (OR = 4.8, 90% CI 1.5–15.3) (388). Propene was handled in the plant, along with various other chemicals, but neither of the reports classified subjects according to propene exposure.

26.5 Standards, Regulations, or Guidelines of Exposure

Propene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). A TLV–TWA has been developed by ACGIH (378). OSHA and NIOSH have not established occupational exposure limits for propene. It has been classified as a simple asphyxiant in Australia, Belgium, Hungary, The Netherlands, and the United Kingdom (25). The occupational limit in Russia is 100 mg/m^3 STEL, and in Switzerland is 10,000 ppm (17,500 mg/m^3) TWA (25).

27.0 1-Butene

27.0.1 CAS Number

[*106–98-9*]

27.0.2 Synonyms

Butylene; *n*-butene; α-butylene, ethylethylene; but-1-ene; butene-1; 1-butene, various grades

27.0.3 Trade Names

NA

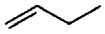
27.0.4 Molecular Weight

56.107

27.0.5 Molecular Formula

$CH_2{:}CHCH_2CH_3$

27.0.6 Molecular Structure



27.1 Chemical and Physical Properties

27.1.1 General

1-Butene, C_4H_8, is a colorless, flammable gas. Butene occurs as a petroleum-refining by-product and has been detected in diesel exhaust (101, 251). It is not detected in the urban atmosphere, probably because of its chemical reactivity (101). When thermally reacted, butene pyrolizes to C1 and C2 alkanes, toluene, and several C5 and C6 cyclanes, or cyclenes (320). Selected physical data are given in Table 27.19.

27.1.2 Odor and Warning Properties

Butene has a gassy, slightly aromatic odor (310). The odor threshold for butene is 54.96 mg/m^3 (29).

27.2 Production and Use

Butene is produced by cracking of petroleum products; it is also a by-product of ethene production from gas oils and naphthas (63). It is used in the production of a wide variety of chemicals in gasoline and rubber processing industries (63). It is very reactive and readily undergoes addition reactions (389).

27.3 Exposure Assessment

27.3.1 Analytic Laboratory Methods

Chemical identification of butene by spectral methods is available (309).

27.3.2 Background Levels

NA

27.3.3 Workplace Methods

NA

27.3.4 Community Methods

NA

27.3.5 Biomonitoring/Biomarkers

A multistage cryogenic trapping system has been used to sample and concentrate butene in expired breath. Chemical analysis was conducted by GC-MS (66).

27.4 Toxic Effects

27.4.1 Experimental Studies

27.4.1.1 Acute Toxicity. Exposure of mice to concentrations of 15% butene resulted in reversible signs of incoordination, confusion, and hyperexcitability; at 20% deep anesthesia in 8–15 min, with subsequent respiratory failure in 2 h; and at 30% in 2–4 min and 40 min, respectively. A concentration of 40% resulted in profound anesthesia in 30 s, with no CNS symptoms but with death in 10–15 min (338).

27.4.1.2 Chronic and Subchronic Toxicity. NA

27.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Butene is metabolized slowly through its 1-hydroxy derivative (390). Conjugation with glutathione appears to be an important excretion route for butene metabolites (391). Butene is liberated from tetra- and tributyl-lead or tin during oxidative dealkylation by hepatic microsomes (392).

27.4.1.4 Reproductive and Developmental. NA

27.4.1.5 Carcinogenesis. NA

27.4.1.6 Genetic and Related Cellular Effects Studies. Butene is not mutagenic in *S. typhimurium* and *E. coli* assays, with or without metabolic activation (393).

27.4.2 Human Experience

27.4.2.1 General Information. Butene is a simple asphyxiant and classified as nontoxic (8). At concentrations above the flammability range, it is an anesthetic (394). It has a low acute toxicity and is mildly irritating to the eye. On direct eye and skin contact liquid butene can cause burns and frostbite. As an anesthetic, it is 4.5 times more potent than ethene (181).

27.5 Standards, Regulations, or Guidelines of Exposure

Butene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA, NIOSH, and ACGIH have not established exposure levels for butene.

28.0 2-Butene

28.0.1 CAS Number

[*624–64-6*] (*trans*-2-butene); [*590–18-1*] (*cis*-2-butene)

28.0.2 Synonyms

β-Butylene, pseudobutylene, 2-butylene, dimethylethylene; *trans*-2-butene; 2-butene-(*E*); (*E*)-butene; *trans*-but-2-ene; *E*-but-2-ene; *trans*-2-butene, various grades; *cis*-2-butene; (*Z*)-2-butene; *cis*-but-2-ene; *Z*-but-2-ene; *cis*-2-butene, various grades

28.0.3 Trade Names

NA

28.0.4 Molecular Weight

56.107

28.0.5 Molecular Formula

$CH_3CH{:}CHCH_3$

28.0.6 Molecular Structure

trans

cis

28.1 Chemical and Physical Properties

28.1.1 General

2-Butene, C_4H_8, can occur in *trans* or *cis* conformation; the former is the more stable form. It is a colorless, extremely flammable gas. 2-Butene occurs in coal gas and has been detected in diesel exhaust (101). The more highly reactive *trans*-2-butene occurs at much lower concentrations in the atmosphere than other comparable hydrocarbons (395). Selected physical properties are given in Table 27.19.

28.1.2 Odor and Warning Properties

The odor threshold for 2-butene is generally 0.05–0.059 mg/L, and specifically is 4.8 mg/m^3 for the *trans*-2 isomer (72).

28.2 Production and Use

2-Butene has been recovered from refining gases or produced by petroleum cracking (251). It is a component in the production of gasolines, butadiene, and a variety of other chemicals (251).

28.3 Exposure Assessment

28.3.1 Air

Chemiluminescence monitors, and both Teflon and Tedlar bags have been used to sample atmospheric 2-butene (63, 396). Gas chromatography with flame ionization detector and GC-MS have been used for identification of alkenes, including *cis*-2-butene and *trans*-2-butene (63, 396).

28.4 Toxic Effects

28.4.1 Experimental Studies

28.4.1.1 Acute Toxicity. The LC_{50} by inhalation in mice is 425 ppm (25). Concentrations of 13–13.5% (300–400 mg/L) cause deep CNS depression in mice and about 19% (120–420 mg/L) is fatal (181).

28.4.1.2 Chronic and Subchronic Toxicity. NA

28.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. NA

28.4.1.4 Reproductive and Developmental. NA

28.4.1.5 Carcinogenesis. NA

28.4.1.6 Genetic and Related Cellular Effects Studies. 2-Butene is not mutagenic in *S. typhimurium* or *E. coli*, with or without metabolic activation (393).

28.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. 2-Butene is a mild mucous membrane irritant (181). It is a cardiac sensitizer in dogs (36).

28.4.2 Human Experience

28.4.2.1 General Information. Rapid evaporation of the 2-butene (in its *cis* or *trans* form, or as a mixture of both) may cause frostbite. The substance may cause effects on the central nervous system. Exposure may result in unconsciousness (397).

28.4.2.2 Clinical Cases

28.4.2.2.1 Acute toxicity. NA

28.4.2.2.2 Chronic and subchronic toxicity. NA

28.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. 2-Butene has been detected in exhaled air. In the majority of subjects, concentrations of the *cis* form were greater than those for the *trans* isomer (66).

28.5 Standards, Regulations, or Guidelines of Exposure

2-Butene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA, NIOSH, and ACGIH have not established exposure levels for 2-butene.

29.0 2-Methylpropene

29.0.1 CAS Number

[*115–11-7*]

29.0.2 Synonyms

1,1-Dimethylethene; 1,1-dimethylethylene; γ-butylene; isobutene; isobutylene; isopropylidenemethylene; 2-methylpropylene; 2-methyl-1-propene; methylpropene; unsymmetrical dimethylethylene; isobutylene, various grades

29.0.3 Trade Names

NA

29.0.4 Molecular Weight

56.107

29.0.5 Molecular Formula

$CH_2{:}C(CH_3)_2$

29.0.6 Molecular Structure

29.1 Chemical and Physical Properties

29.1.1 General

2-Methylpropene (isobutene), C_4H_8, is a highly volatile, flammable liquid (398). It reacts easily with numerous materials, and polymerizes easily (14, 310). Selected physical properties are given in Table 27.19. Isobutene is a

component of natural gas. It has been detected in the urban atmosphere at low concentrations (100).

29.1.2 Odor and Warning Properties

Isobutene has a gassy odor that can be detected at 45.8 mg/m^3 (29).

29.2 Production and Use

Isobutene is produced in refinery streams by absorption on 65% H_2SO_4 at about 15°C, or by reacting with an aliphatic primary alcohol and then hydrolyzing the resulting ether (15). It is used as a monomer or the formation of a copolymer for the production of synthetic rubber and various plastics, and to produce antioxidants for food or food packaging and for plastics (15, 310).

29.3 Exposure Assessment

29.3.1 Air

A colorimetric method for the determination of isobutene in air, without interference by ethene or propene, has been developed (399).

29.3.2 Background Levels

NA

29.3.3 Workplace Methods

NA

29.3.4 Community Methods

NA

29.3.5 Biomonitoring/Biomarkers

Gas chromatography has been used to measure isobutene in mouse and rat body tissues (400).

29.4 Toxic Effects

29.4.1 Experimental Studies

29.4.1.1 Acute Toxicity. Isobutene, at 30%, produces no CNS depression in mice, and excitement and CNS depression in 7–8 min at 40%, but immediate CNS depression in 2–2.25 min at 50%, or in 50–60 s at 60–70% (40). The 2 h LC_{50} in the mouse is 415 mg/L and the 4 h LC_{50} in the rat is 620 mg/L (77).

29.4.1.2 Chronic and Subchronic Toxicity. NA

29.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. In metabolic studies on rats and mice, inhaled isobutene levels in the brain and parenchymatous organs were similar, but the level in the fatty tissue was significantly higher than in the brain, liver, kidneys, or spleen (69). The epoxidation of isobutene was studied *in vitro* in rat lung tissue in comparison with the rat liver. Pulmonary tissue appears to be less exposed to the toxic epoxide metabolite than is the case for hepatic tissue. The results are correlated with the low capacity of the mixed function oxidase system, expressed by means of the cytochrome P450 content and the 7-ethoxycoumarin *O*-deethylase activity, to form reactive intermediates. The activities of the principal epoxide detoxifying enzymes glutathione *S*-transferase and epoxide hydrolase represent only 5–10% of the values measured in the rat liver (401).

It has been shown both *in vivo* and *in vitro* that isobutene is metabolized to the primary metabolite 2-methyl-1,2-epoxypropane by rodent and human liver tissue. The formation of this reactive epoxide intermediate is catalyzed by CYP2E1, while epoxide hydrolase and glutathione *S*-transferase appear to be involved in its inactivation. In rats, the capacity to absorb and metabolize isobutene is saturable. Isobutene is oxidized to compounds that are mainly excreted in urine. Data indicate that rodents can tolerate low levels of isobutene without apparent toxicity. The primary metabolite 2-methyl-1,2-epoxypropane, however, is able to produce genetic damage in both prokaryotic and eukaryotic cells *in vitro* (402).

29.4.1.4 Reproductive and Developmental. NA

29.4.1.5 Carcinogenesis. Groups of 50 male and 50 female F344/N rats were exposed to isobutene at concentrations of 0, 500, 2000, or 8000 ppm 6 h/day 5 days/week for 105 weeks. Groups of 50 male and 50 female B6C3F1 mice were exposed to isobutene at concentrations of 0, 500, 2000, or 8000 ppm 6 h/day, 5 days/week for 105 weeks. Under the conditions of these 2 year inhalation studies, there was some evidence of the carcinogenic activity of isobutene in male F344/N rats based on an increased incidence of follicular cell carcinoma of the thyroid gland. There was no evidence of the carcinogenic activity of isobutene in female F344/N rats or male or female B6C3F1 mice exposed to 500, 2000, or 8000 ppm (403).

29.4.1.6 Genetic and Related Cellular Effects Studies. Isobutene was negative when tested for mutagenicity in *E. coli*, the Ames *S. typhimurium* assay, and a modified *Salmonella* assay, with and without metabolic activation (393, 404, 405).

29.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Isobutene is a simple asphyxiant and causes CNS depression at higher concentrations. There is a linear relationship between the degree of CNS depression and the cerebral concentrations (69, 400).

29.4.2 Human Experience

29.4.2.1 General Information. Isobutene is nonhazardous below the lower flammability limit. Except for asphyxia at high concentrations for prolonged periods, no untoward effects of isobutene on the health of workers have been reported.

29.4.2.2 Clinical Cases

29.4.2.2.1 Acute toxicity. NA

29.4.2.2.2 Chronic and subchronic toxicity. NA

29.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. The biotransformation of isobutene was investigated *in vitro* in liver tissue of rats, mice, and humans. Interspecies comparison revealed that the lowest levels of the primary epoxide metabolite were detected in incubations of isobutene with human liver homogenate, followed by rat and mouse, respectively. Among the human liver samples, important interindividual variations were observed. Out of the 16 samples analyzed, only 2 contained measurable epoxide amounts, while in the other samples only traces were detectable. The involvement of rat liver cytochrome P450 2E1 in the activation of isobutene to its epoxide 2-methyl-1,2-epoxypropane has been established. The lower capacity of the mixed function oxidase system in human liver samples compared to rodents is confirmed. Concerning epoxide-detoxifying enzymes, a high microsomal epoxide hydrolase activity was observed in human liver tissue and an intermediate in rat liver, while a low activity was measured in mouse liver. These findings were inversely correlated with the epoxide levels measured *in vitro* in liver tissue of the three species studied. Although, the same biotransformation pathways are involved, marked quantitative differences in epoxide levels were observed. The results indicate that human liver tissue is exposed *in vitro* to smaller concentrations of the primary metabolite 2-methyl-1,2-epoxypropane than rodent liver (406).

29.5 Standards, Regulations, or Guidelines of Exposure

Isobutene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). OSHA, NIOSH, and ACGIH have not established exposure standards for isobutene. The STEL in Russia is 100 mg/m^3 (25).

30.0 1-Pentene

30.0.1 CAS Number

[*109–67-1*]

30.0.2 Synonyms

Amylene, pentylene, α-amylene, α-*N*-amylene, propylethylene, pent-1-ene

30.0.3 Trade Names

NA

30.0.4 Molecular Weight

70.134

30.0.5 Molecular Formula

CH_2:$CH(CH_2)_2CH_3$

30.0.6 Molecular Structure

30.1 Chemical and Physical Properties

30.1.1 General

1-Pentene, C_5H_{10}, is a flammable liquid with specific gravity 0.641. It occurs in coal tar and in petroleum cracking mixtures, and polymerizes on extended periods of storage (15, 320). Selected physical properties are given in Table 27.19.

30.1.1.1 Other Pentene Isomers. 2-*Pentene*, CH_3CH:$CHCH_2CH_3$, is produced by petroleum cracking and is a component of high octane fuel (320). The odor threshold is 0.54–6.6 mg/m^3 (72). 3-*Methyl-1-butene* (1-isopentene, -isoamylene), CH_2:$CHCH(CH_3)_2$, is a colorless liquid or gas with a disagreeable odor. It is a product of petroleum cracking and a component of refinery gas, used as a chemical intermediate for petroleum resins, and hydrocarbon solvent. Selected properties for both compounds are given in Table 27.19.

The toxicological properties of 2-pentene and isopentene have not been thoroughly investigated. During industrial use, *cis*-2-pentene is an irritant and may be harmful by inhalation, ingestion, or skin absorption (63). *trans*-2-Pentene may also be harmful if inhaled or swallowed. Vapor or mist is irritating to the eyes, mucous membranes, skin, and upper respiratory tract. Symptoms of exposure to *trans*-2-pentene may include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, nausea, and vomiting (63). Inhalation or contact with isopentene may irritate or burn skin and eyes. Vapors may cause dizziness or suffocation (12). Exposure standards have not been established for pentene isomers.

30.1.2 Odor and Warning Properties

1-Pentene has a highly disagreeable odor (310). The odor threshold for 1-pentene is 0.19 ppm (72).

30.2 Production and Use

1-Pentene is prepared from allyl bromide and ethyl magnesium bromide in ether or in dipropyl ether (63). It is used in organic synthesis, and as a blending agent for high-octane motor fuel (310).

30.3 Exposure Assessment

30.3.1 Air

Gas chromatography has been used for the determination of 1-pentene in air (407).

30.4 Toxic Effects

30.4.1 Experimental Studies

NA

30.4.1.1 Acute Toxicity. NA

30.4.1.2 Chronic and Subchronic Toxicity. NA

30.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. 1-Pentene is probably absorbed by inhalation and excreted by exhalation (408). Pentene is oxidized at the double bond and excreted as the alcohol or its conjugate (181).

30.4.1.4 Reproductive and Developmental. NA

30.4.1.5 Carcinogenesis. NA

30.4.1.6 Genetic and Related Cellular Effects Studies. NA

30.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. In animals, pentene causes respiratory and cardiac depression (181).

30.4.2 Human Experience

30.4.2.1 General Information. 1-Pentene is harmful if inhaled or swallowed. Its vapor or mist is irritant to the eyes, mucous membranes, and upper respiratory tract. It causes skin irritation. Symptoms of exposure to 1-pentene during industrial use may include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, nausea, and vomiting (63).

30.4.2.2 Clinical Cases

30.4.2.2.1 Acute toxicity. The anesthetic action of pentene appeared about 15 times more potent than that of ethene. However, at CNS depression levels, it causes more severe primary excitement (8). It produces anesthesia at 6% in 15–20 min. At one time it was used without success as a human anesthetic but produced better results in dentistry (338).

30.4.2.2.2 Chronic and subchronic toxicity. NA

30.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. NA

30.4.2.2.4 Reproductive and developmental. NA

30.4.2.2.5 Carcinogenesis. NA

30.4.2.2.6 Genetic and related cellular effects studies. NA

30.4.2.2.7 Other: neurological, pulmonary, and skin sensitization. 1-Pentene is more cardiotoxic than the lower homologs (181).

30.5 Standards, Regulations, or Guidelines of Exposure

Occupational exposure standards have not been established for 1-pentene. It is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63).

31.0 1-Hexene

31.0.1 CAS Number

[*592–41-6*]

31.0.2 Synonyms

Butylethylene, hexene, hexylene, 1-*n*-hexene, hexene-1, hex-1-ene

31.0.3 Trade Names

NA

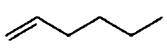
31.0.4 Molecular Weight

84.16

31.0.5 Molecular Formula

$CH_2{:}CH(CH_2)_3CH_3$

31.0.6 Molecular Structure



31.1 Chemical and Physical Properties

31.1.1 General

1-Hexene, C_6H_{12}, is a colorless liquid, which is highly volatile and flammable. Hexene is a component of refinery gas and coffee aroma (63, 409). Selected physical properties are given in Table 27.19.

31.1.1.1 Other Hexene Isomers. *2-Hexene* (β-hexylene, 2-hexylene, or methylpropylethylene), $CH_3CH{:}CH(CH_2)_2CH_3$, is a highly flammable liquid and vapor (410). Its toxicity resembles that of 1-hexene. *2-Methyl-2-pentene* (isohexene, β-isohexylene, or 2-methylpent-2-ene), $(CH_3)_2C{:}CHCH_2CH_3$, is a component of cigarette smoke and is classified as a cilia toxin to the respiratory tract (411). Selected physical properties are given in Table 27.19.

Very little toxicological information is available for 2-hexene and isohexene. During industrial use, both chemicals can cause eye and skin irritation and can be irritating to mucous membranes if swallowed (410). Exposure standards have not been established for hexene isomers.

31.2 Production and Use

Hexene is produced by olefin cracking (320). It is used in fuels and in the synthesis of flavors, perfumes, dyes, resins, and polymer modifiers (63).

31.3 Exposure Assessment

31.3.1 Air

Gas chromatographic separation on a capillary column connected to a flame ionization detector or a mass spectrometer has been used to detect hexene in air (412).

31.4 Toxic Effects

31.4.1 Experimental Studies

31.4.1.1 Acute Toxicity. The minimal concentration of hexene causing CNS depression in mice was 2.9% or 29,100 ppm, and the minimal fatal concentration was 4.08% or 40,800 ppm (123).

31.4.1.2 Chronic and Subchronic Toxicity. A 13 week inhalation exposure study was conducted among 40 male and 40 female Fischer 344 rats, in which 10 rats of each sex were exposed to 1-hexene 6 h/day 5 day/week at 0, 300, 1000, or 3000 ppm. No macroscopic or histopathological lesions were observed in any organ system at any exposure level. There was no difference in the neuromuscular function at any exposure level. Serum phosphorus was the only clinical chemistry value that was statistically associated with exposure in a dose-related fashion in both sexes (413).

31.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. *In vitro* testing of 1-hexene caused autocatalytic destruction of cytochrome P-450 and heme in hepatic microsomes from phenobarbital-pretreated rats. The destructive process was time dependent, saturable, and required nicotinamide adenine dinucleotide phosphate (NADP) (414). Rat and human liver microsomal preparations metabolized 1-hexene to 1-hexen-3-ol, which was then catalyzed to 1-hexen-3-one (415).

31.4.1.4 Reproductive and Developmental. In an inhalation exposure study conducted among male Fischer 344 rats, testicular effects did not persist to 13 weeks at exposures up to 3000 ppm (413). In a study of Sprague–Dawley rats, exposure to 1-hexene was provided orally in a corn oil vehicle at 0, 100, 500, or 1000 mg/kg/day. Males were exposed for 28 days prior to mating and females for 14 days prior to mating, during mating, gestation, and lactation until lactation day 4. No effects on fertility, gestation, reproductive organ toxicity, offspring viability, or pup weights were reported. The F2 generation was not studied (416).

31.4.1.5 Carcinogenesis. NA

31.4.1.6 Genetic and Related Cellular Effects Studies. There was no evidence of genetic toxicity for 1-hexene in *S. typhimurium* tester strains TA98, TA100, TA1535, TA1537, or TA1538 or in cultured Chinese hamster ovary cells in the presence or absence of exogenous metabolic activation. There was no evidence for unscheduled DNA synthesis when 1-hexene was added to cultured primary rat hepatocytes and no evidence of genotoxicity in cultured mouse lymphoma L51784 cells or in cultured human lymphocytes treated with up to 125 mg/mL in the presence or absence of a rodent microsomal (S9) activating system. When Crl:CD-1 mice inhaled 1-hexene up to 25,000 ppm, 6 h/day for 2 days, there was no evidence of clastogenicity in bone marrow smears (414).

31.4.2 Human Experience

31.4.2.1 General Information. Hexene is a low to moderate irritant to the skin and eyes. When ingested, it presents a moderate aspiration hazard (135). When inhaled, it produces CNS depression in humans at a concentration of about 0.1%, with accompanying mucous membrane irritation, vertigo, vomiting, and cyanosis (8).

31.5 Standards, Regulations, or Guidelines of Exposure

Hexene is on the EPA TSCA Chemical Inventory and Test Submission Data Base (63). A TLV–TWA has been developed by ACGIH (417). Neither OSHA nor NIOSH have limits for this substance.

32.0 1-Heptene

32.0.1 CAS Number

[*592–76-7*]

32.0.2 Synonyms

n-Heptene, α-heptilene

32.0.3 Trade Names

NA

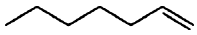
32.0.4 Molecular Weight

98.188

32.0.5 Molecular Formula

CH_2:$CH(CH_2)_4CH_3$

32.0.6 Molecular Structure



32.1 Chemical and Physical Properties

32.1.1 General

1-Heptene, C_7H_{14}, is a colorless, highly flammable liquid with specific gravity 0.697. Selected physical properties are given in Table 27.19.

32.2 Production and Use

Heptene is produced in a process involving the oligomerization of ethene in the presence of aluminum alkyls. It is used in the organic synthesis of flavors, perfumes, pharmaceuticals, dyes, oils, and resins (63).

32.3 Exposure Assessment

32.3.1 Air

Atmospheric heptene has been measured by a combined gas chromatographic–infrared spectrometric system (418). Volatile organic compounds such as heptene may be measured using Tenax adsorption and GC-MS (419).

32.4 Toxic Effects

32.4.1 Experimental Studies

32.4.1.1 Acute Toxicity. The general toxicity of the heptenes is somewhat lower than that of the hexenes in rats, except that its aspiration hazard is increased (135). In mice, concentrations of 60 mg/L cause loss of the righting reflex (123). CNS depression and lethality have been noted at 60 and >200 mg/L, respectively (181).

32.4.1.2 Chronic and Subchronic Toxicity. NA

32.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. NA

32.4.1.4 Reproductive and Developmental. NA

32.4.1.5 Carcinogenesis. NA

32.4.1.6 Genetic and Related Cellular Effects Studies. NA

32.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Heptene is a liver toxin and destroys microsomal cytochrome P450 in phenobarbital treated rats, in the presence of NADPH (420).

32.4.2 Human Experience

32.4.2.1 General Information. Inhalation of or contact with heptene may irritate or burn skin and eyes.

32.5 Standards, Regulations, or Guidelines of Exposure

Heptene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). Occupational exposure standards have not been established.

32.6 Octenes and Higher Alkenes

1-Octene (octylene, caprylene), CH_2:$CH(CH_2)_5CH_3$; *2-methyl-2-heptene* (isooctene), $(CH_3)_2C$:$CH(CH_2)_3CH_3$; and *2-ethyl-1-hexene*, CH_2:$C(C_2H_5)(CH_2)_3CH_3$, are flammable liquids. 1-Octene is produced by oligomerization of ethene. The odor threshold for 1-octene is 2.0 ppm, and it is used as a chemical intermediate and in organic synthesis (63, 72). Selected physical properties are given in Table 27.19.

Octenes may be more irritant to mucous membranes, skin, and eyes than the lower homologs. Octenes, when ingested, may rapidly be aspirated into the lungs and may act as simple asphyxiants (8, 12, 14). The intraperitoneal LD_{50} in the mouse is 100 mg/kg for 2-ethyl-1-hexene (25). All octenes are metabolically hydroxylated, conjugated, and excreted from the mammalian system (181).

1-Nonene (tripropylene), CH_2:$CH(CH_2)_6CH_3$, is a colorless, flammable liquid. It is produced by polymerization of a petroleum stream and is used as a chemical intermediate (63). *1-Decene* (*n*-decylene), CH_2:$CH(CH_2)_7CH_3$, is a colorless, flammable liquid. The odor of decene is pleasant and its odor threshold in air is 7 ppm (12, 72). It is produced by

oligomerization of ethene and is used in organic synthesis of flavors, perfumes, pharmaceuticals, dyes, oils, and resins (63). Selected physical properties are given in Table 27.19.

Nonene is an aspiration hazard when ingested (135). It is irritating to the skin, eyes, nose, and throat, and at high concentrations, it is an anesthetic (12, 339). Decene is irritating to the eyes and respiratory tract and has CNS depressant properties (12, 310). Decene and dodecene also may present an aspiration hazard when ingested (135). Exposure standards have not been established for the higher alkenes.

33.0 1,3-Butadiene

33.0.1 CAS Number

[*106–99-0*]

33.0.2 Synonyms

Biethylene; butadiene; α-butadiene; divinyl; erythrene; 1-methylallene; vinylethylene; pyrrolylene; buta-1,3-diene; bivinyl; α, γ-butadiene; erythrene; 1,3-butadiene, various grades

33.0.3 Trade Names

NA

33.0.4 Molecular Weight

54.09

33.0.5 Molecular Formula

CH_2:CHCH:CH_2

33.0.6 Molecular Structure

33.1 Chemical and Physical Properties

33.1.1 General

Butadiene, C_4H_6, is a colorless, flammable gas with specific gravity 0.65 at −6°C (liquid). It is potentially explosive when mixed with air and has a characteristic aromatic odor (369). Handling procedures should be strictly followed, because its boiling point is 23.54°F. The greatest danger exists when it is mixed with air to the explosive limit of 2%. The use of protective garments and equipment is required. Selected physical properties are given in Table 27.19. Butadiene does not occur naturally and exposure is due to inhalation of ambient air, especially in urban and suburban areas; in addition, air close to and inside the manufacturing plants that produce or use butadiene may contain significant amounts of this chemical (421). The highest exposures to butadiene occur in occupational settings. Industrial activities with potential for exposure include: petroleum refining and related operations, production of purified butadiene monomer, production of various butadiene-based rubber and plastics polymers, and manufacture of rubber and plastics products (422). Butadiene has also been measured in automobile fuel, automotive emissions, and exhaust of diesel engines (330). Butadiene has been detected as a component of cigarette smoke (423).

33.1.2 Odor and Warning Properties

Butadiene has a mild aromatic or gasoline-like odor (41). The odor threshold for butadiene is between 0.352 and 2.86 mg/m^3 (29). An odor threshold of 0.0014 ppm for butadiene in water has been reported (29, 424). The authors state that this solution lacks enough persistence for this value to be used for reference purposes.

33.2 Production and Use

Except for a small amount of butadiene produced by the oxydehydrogenation of *n*-butane, most of butadiene is produced commercially as a by-product of ethylene production during the steam cracking of hydrocarbon streams. It is separated and purificated from other components by extractive distillation, using acetonitrile and dimethylformamide as solvents (63, 425, 426). Butadiene is used in the production of resins and plastics, including butadiene rubber, styrene–butadiene rubber, adiponitrile, polychloroprene, nitrile rubber, styrene–butadiene latex, and acrylonitrile–butadiene–styrene. In 2000, these uses accounted for about 89% of butadiene consumed in the United States (426). Automobile tires are the major end use product (330). Butadiene is highly reactive, dimerizes to form 4-vinylcyclohexene, and polymerizes easily. Therefore, polymerization inhibitors have to be added for its storage and transport (369).

33.3 Exposure Assessment

33.3.1 Air/Water

Infrared and gas chromatographic analytical methods have been adapted for monitoring the concentration and distribution of butadiene in exposure chambers, and for analysis of known impurities in atmospheres generated for inhalation tests (427). Butadiene and other volatile organic compounds have been analyzed in ambient air samples using EPA Methods TO-14A and TO-15 (419, 428). Method TO-14A uses a cryogenic concentration procedure in which a large volume of air is collected in a specially designed sampling

container and volatile compounds are concentrated at low temperatures. The sample is further separated into its components by gas chromatography. Variations of this method have been described (429, 430). An analytical procedure has been developed for the analysis of butadiene in the gas phase of cigarette smoke and environmental tobacco smoke utilizing cryogenic gas chromatography–mass selective detection (431). A toxic gas detector system for on-the-spot readings can be used to determine the concentration in air. A color stain is produced in the detector tube, whose length provides the concentration of the sample being measured (369). Butadiene has been measured in water by a modified variant of a purge-and-trap gas chromatographic method (145).

33.3.2 Background Levels

Butadiene is widely detected at low ppb levels in urban air samples. The U.S. EPA estimated that the average background concentration of butadiene in the air of the United States is 0.13 $\mu g/m^3$ (432). No data were located on the concentration of butadiene in soil or drinking water (330).

33.3.3 Workplace Methods

NIOSH method 1024 has been used to determine air concentrations for butadiene. Samples are collected with low flow air-sampling pumps on tandem solid sorbent tubes (activated coconut shell charcoal), desorbed with methylene chloride, and quantified by gas chromatography with a flame ionization detector (119). In OSHA method 56, air samples are collected using sampling tubes containing charcoal adsorbent coated with 4-*tert*-butylcatechol. The samples are desorbed with carbon disulfide and then analyzed by gas chromatography with a flame ionization detector (433).

33.3.4 Community Methods

NA

33.3.5 Biomonitoring/Biomarkers

Urinary biomarkers and hemoglobin adducts have been proposed as indicators of exposure to butadiene. The ACGIH has developed a BEI for 1,2-dihydroxy-4-(*N*-acetylcysteinyl)-butane (DHAB) in a urine sample obtained at the end of the work shift as a biomarker of exposure to butadiene (434). The ACGIH also recommends a certain concentration of hemoglobin (Hb) of *N*-1 and *N*-2-(hydroxylbutenyl)valine (MHBVal) hemoglobin adducts in a blood sample obtained after at least 120 days of exposure as a biomarker of butadiene. They indicate that sample time is not critical (434). Measurement of unmetabolized butadiene in blood and urine may be preferable for measuring very low levels of exposure (435).

Urinary metabolites of butadiene, 1,2-dihydroxy-4-(*N*-acetylcysteinyl-*S*-)-butane (M-I) and 1-hydroxy-2-(*N*-acetylcysteinyl-*S*-)-3-butene (M-II), have been measured using an assay based on isotope dilution GC-MS (436). Butadiene, butadiene monoxide, and butadiene dioxide have also been measured in blood by a method based on vacuum distillation of tissues followed by analysis of the distillates using multidimensional GC-MS (437).

Adducts formed by the reaction of a butadiene metabolite with the *N*-terminal valine of hemoglobin have been investigated as biomarkers of exposure to low doses of butadiene. The hemoglobin adducts of 1,2-epoxybutene, *N*-(2-hydroxy-3-buten-1-yl)valine and *N*-(1-hydroxy-3-buten-2-yl)valine, were determined as the pentaflurophenylthiohydantoin derivatives using the modified Edman degradation procedure and gas chromatography with negative-ion chemical ionization mass spectrometry (438). In another method, the pentaflurophenylthiohydantoin derivatives of the alkylated valines were analyzed by mass/mass spectrometry (439).

DNA adducts of butadiene may be used as biomarkers of exposure to butadiene, but as their formation may result from the metabolism, distribution, and reaction of the chemical to DNA, they may be considered effect biomarkers as well. A number of adenine and guanine DNA adducts of 1,2-epoxybutene, 1,2:3,4-diepoxybutane, and 3,4-epoxy-1,2-butanediol, the reactive metabolites of butadiene, have been identified by different assays. A widely used method, the ^{32}P-postlabeling assay, includes the enzymatic digestion of DNA to nucleotides, 5' labeling of these nucleotides with an isotopically labeled phosphate group, and the resolution and detection of the labeled products, generally by thin-layer chromatography or high-performance liquid chromatography (HPLC) (440–446). Other methods used to detect and measure DNA adducts of butadiene include liquid chromatography in combination with tandem mass spectrometry (447), and HPLC separation and analysis of adducts by UV spectrophotometry, electrospray ionization mass spectrometry, nuclear magnetic resonance (NMR), and/or fast-atom-bombardment mass spectrometry (448–450).

Biomarkers of effect resulting from butadiene exposure have been explored. These include gene mutation and chromosomal changes; but no clear associations have been observed (451, 452).

33.4 Toxic Effects

33.4.1 Experimental Studies

33.4.1.1 Acute Toxicity. The 4 h inhalation LC_{50} in rats is 285,000 mg/m^3, and the 2 h LC_{50} in mice is 270,000 mg/m^3 (69). The acute oral LD_{50} is 5.48 and 3.21 g/kg, in rats and mice, respectively. The acute inhalation LC_{50} is 285,000 mg/m^3 per 4 h in rats, and 270,000 mg/m^3 per 2 h in mice (63). In mice exposed to concentrations of 10%, butadiene caused

no symptoms; of 15%, light CNS depression; of 20%, some excitement and CNS depression in 6–12 min, and of 30–40%, excitement with twitching in 1–1.2 min and 40–60 s; respectively (181). As a CNS depressant, butadiene is more potent than propadiene, but only half as potent as butene. In rabbits exposed to 25% (250,000 ppm), butadiene exhibited light, relaxed anesthesia in 1.6 min, followed by loss of various reflexes, CNS effects, and death in 23 min (453)

33.4.1.2 Chronic and Subchronic Toxicity. Five groups of rats were exposed to butadiene gas at atmospheric concentrations of 1000, 2000, 4000, and 8000 ppm v/v, respectively, 6 h/day, 5 days/week for 13 weeks. No effects attributable to exposure were produced, except for a moderately increased salivation at higher concentrations of butadiene (454). Rats and guinea pigs exposed by inhalation to concentrations of 6700 ppm 7.5 h/day, 6 days/week for 8 months experienced a slightly reduced body weight gain compared to controls. No significant effects were noted in animals exposed at concentrations of 600 or 2300 ppm (453). In rats exposed to atmospheres containing 1000 or 8000 ppm butadiene for 6 h/day, 5 days/week no effects in respiratory tract were observed. Liver weights at both doses were increased in both sexes with no associated pathological change, and kidney weight was increased in males at the high dose, together with an increase in the severity of nephrosis. No effects were observed for cardiovascular, gastrointestinal, hematological, liver, skin, and eye (455).

33.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Studies on the metabolism and pharmacokinetics of butadiene have been conducted in rats and mice to investigate differences in organ site specificity and carcinogenic potencies. Metabolism is probably an important factor in the carcinogenicity of butadiene. Butadiene metabolism presumably involves cytochrome P450-mediated oxidations to three different epoxides (1,2-epoxy-3-butene, 1,2:3,4-diepoxybutane, and 3,4-epoxybutane-1,2-diol). The epoxide intermediates are detoxified by conjugation with glutathione via glutathione *S*-transferase or by hydrolysis via epoxide hydrolase (456). Figure 27.1 shows the main pathways involved in the metabolism of butadiene.

Butadiene is substrate for at least two isozymes of the cytochrome P450 monooxygenases, CYP2E1 and CYP2A6 (457, 458). CYP2E1 appears to be the principal enzyme responsible for the metabolism of butadiene to epoxybutene and epoxybutene to diepoxybutane at low-exposure concentrations of butadiene (459). Epoxybutene has been measured as a major metabolite of butadiene in exhaled breath, in the blood of mice, rats, and monkeys and in the liver and lungs of rats and mice (436, 460–464). In addition to cytochrome P450, two other enzymes appear to play major roles in the metabolism of epoxybutene:

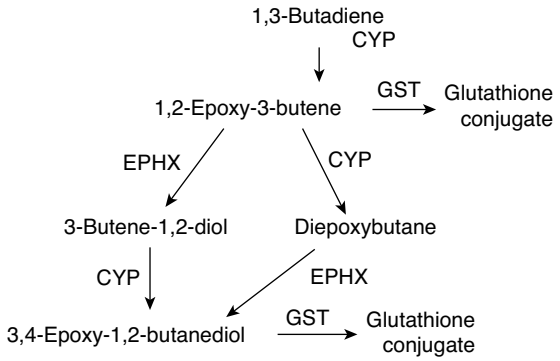


Figure 27.1. Key pathways in butadiene metabolism (CYP, cytochrome P450; GST, glutathione *S*-transferase; EPHX, epoxide hydrolase). (Modified from Ref. (421).)

glutathione *S*-transferase (GST) and epoxide hydrolase. GST mediates the conjugation of epoxybutene with glutathione (GSH), and this reaction occurs almost exclusively in the cytosol. Thus, three potential mutagenic epoxides may be generated during butadiene biotransformation.

The metabolism of butadiene has been quantified *in vitro* using incubation systems that contain microsomal and cytosolic preparations of livers and lungs obtained from rats and mice. These studies have shown that the rate of epoxybutene formation is higher in mice than in rats, and that the elimination of epoxybutene and diepoxybutane by GSH conjugation appears to be faster for mice than rats (457, 459, 465, 466). *In vivo* data substantiate the *in vitro* metabolism studies showing the existence of species differences in butadiene metabolism and disposition (463, 467). These studies showed that peak concentrations of epoxybutene in mice, compared to those in rats, were 4- to 8-fold higher in blood, 13- to 15-fold higher in lung, and 5- to 8-fold higher in liver following inhalation of 62.5, 625, 1250, or 8000 (rats only) ppm butadiene for up to 6 h. The concentration of diepoxybutane was greatest in the lungs of mice, but it could not be detected in the livers of mice or lungs and livers of rats. The production and disposition of epoxybutene and diepoxybutane in blood and other tissues of rats and mice during and following inhalation exposures to a concentration of 62.5 ppm butadiene for 4 h were examined. Concentrations of epoxybutene were 3–74 times greater in tissues of mice compared with rats, and levels of diepoxybutane in blood and tissues of mice were 40–163 times higher than in corresponding rat tissues. The high concentrations of diepoxybutane in target organs suggest that this compound may be particularly important in butadiene-induced carcinogenesis (464).

Inhalation exposure of rats and mice to butadiene revealed significant GSH depletion in lung, liver, and heart (463, 468, 469). GSH depletion was greater in various tissues of mice than rats for similar exposures, and was dependent on the concentration and duration of butadiene exposure (463).

Butadiene also induces cytochrome P450 metabolism in liver and lung microsomes of rats and mice (470, 471).

Various physiologically based pharmacokinetic (PBPK) models have been developed for butadiene (472–477). Some models describe the disposition of butadiene as well as its epoxide metabolites. Some models have attempted to account for differences in butadiene disposition in rats, mice, and humans. They have also intended to describe butadiene disposition in animals coexposed to styrene. The number of compartments (e.g., blood, liver, lung, fat, GI tract) and subcompartments vary from one model to another, and the values assigned to the kinetics of various reactions and the parameters describing ventilation, perfusion, metabolism, and chemical partitioning also differ among models. The earlier PBPK models tried to predict internal concentrations of butadiene and formation of epoxybutene. The current models link together a sequential pathway of metabolism from butadiene to epoxybutene to diepoxybutane, but initial simulations overestimate epoxybutene blood concentrations (421). To correct for this problem, alternate model structures that adjust the kinetic, physiological, and biochemical parameters have been proposed, but experimental data are required to fully validate these models.

33.4.1.4 Reproductive and Developmental. Male and female rats exposed to 600, 2300, or 6700 ppm butadiene for 7.5 h/day, 6 days/week for 8 months produced smaller litters than did the control group, although litter sizes slightly exceeded the expected number of pups per litter (453). Breeding tests conducted in the offspring of the higher exposure groups suggested reduced fecundity, but it was not determined whether the deficit was attributed to the males or the females. Mating studies were also performed in guinea pigs and rabbits, but no significant effect on reproductive capability was observed.

The developmental toxicity of butadiene was investigated in female rats exposed to 200, 1000, or 8000 ppm butadiene for 6 h/day during gestation days 6–15 (478). A significant suppression of maternal body weight gain was observed in animals exposed to the two highest concentrations. Reproductive measurements such as pregnancy rate, gravid uterus weight, number of implantation sites, number of fetuses per dam, and preimplantation loss were unaffected. The mortality of postimplantation embryos was increased in the highest exposure group. Body weights and crown–rump lengths of fetuses in the 8000 ppm exposure group were decreased significantly compared with control fetuses. Other fetal effects observed include hematomas, skeletal defects, lens opacities, and irregularities of ossification.

The National Toxicology Program conducted teratology studies in rats and mice, a spermhead morphology assay in mice, and a dominant lethal study in mice (479). In the teratology studies, pregnant mice and rats were exposed to 40, 200, or 1000 ppm butadiene for 6 h/day on gestation days 6–15. In the rat study, the only toxicity observed was in animals at the highest exposure level, in the form of a decrease in maternal body weight gain on gestation days 6–11 and decreased extragestational body weight. No fetal toxicity was observed in rats. In the mice study, maternal toxicity was observed at 200 and 1000 ppm concentrations; reductions in body weight gain and extragestational weight gain were evident. Mice showed developmental toxicity and fetal anomalies (supernumerary ribs, reduced ossification) at the two highest concentrations. Furthermore, decreased fetal body weights were observed in mice exposed to 40 ppm butadiene in the absence of maternal toxicity.

For the spermhead morphology assay, mice were exposed to 200, 1000, or 5000 ppm butadiene for 6 h/day for 5 days. Sperm showed a significant increased percentage of abnormal spermheads in the 1000 and 5000 ppm exposure groups at 5 weeks after treatment. The percentage of abnormalities increased proportionally with exposure concentration (479).

For the dominant lethal study, male mice were exposed to 200, 1000, or 5000 ppm butadiene for 6 h/day for 5 days. After exposure, mice were mated with unexposed females (two females per week for each male for 8 weeks). Females mated with males exposed to 1000 ppm butadiene showed a statistically significant increase in the percentage of dead implants 1 week following exposure. There were significant increases in the percentage of females with two or more dead implantations in all exposure groups. During the second week after exposure, the number of dead implantations per pregnancy increased in both the 200 and 1000 ppm groups, but not in the 5000 ppm group. No significant increases were observed in weeks 3–8 (479).

A study of untreated female mice with males exposed to 12.5 ppm butadiene for 6 h/day for 5 days/week for 10 weeks resulted in fetal toxicity of the offspring. The effects observed included an increase in late fetal death, exencephaly, and skull abnormalities. Early fetal death was observed in the offspring of untreated female mice mated to males exposed to 6.5 ppm butadiene for 6 h/day for 5 days/week for 4 weeks (480).

33.4.1.5 Carcinogenesis. Butadiene is carcinogenic in laboratory animals exposed chronically by inhalation. A summary of the carcinogenicity studies and the tumors developed is presented in Table 27.20. Two long-term inhalation exposure studies in mice were conducted by the National Toxicology Program. The first study, designed to last for 103 weeks, was terminated after 60–61 weeks because of reduced survival at both exposure concentrations, due to malignant neoplasms in both sexes (481). The second study was performed over an expanded range of exposure concentrations and lasted for 2 years (482). The results of both studies show that butadiene is a potent multiorgan carcinogen in mice. Male and female mice had tumors of

Table 27.20. Summary of Carcinogenicity Studies and Tumors Developed in Animals Exposed to 1,3-Butadiene

Species	Gender	Exposure Route	Approximate Dose (ppm)	Treatment Regimen	Neoplasm	References
Sprague–Dawley rats	Female	Inhalation	0, 1000, 8000	6 h/day, 5 days/week, 105 weeks	Mammary gland adenoma and carcinoma Thyroid follicular cell adenoma Uterine sarcoma Zymbal gland carcinoma	(455)
Sprague–Dawley rats	Male	Inhalation	0, 1000, 8000	6 h/day, 5 days/week, 111 weeks	Pancreatic exocrine adenoma Testicular Leydig cell tumors	(455)
$B6C3F_1$ mice	Female	Inhalation	0, 625, 1250	6 h/day, 5 days/week, 60–61 weeks	Lethal thymic lymphomas Acinar cell carcinomas of the mammary gland Granulosa cell neoplasms of the ovary Hepatocellular neoplasms Heart hemangiosarcomas Malignant lymphomas Alveolar–bronchiolar neoplasms Squamous-cell neoplasms of the forestomach	(481)
$B6C3F_1$ mice	Male	Inhalation	0, 625, 1250	6 h/day, 5 days/week, 60–61 weeks	Lethal thymic lymphomas Heart hemangiosarcomas Alveolar–bronchiolar neoplasms Squamous-cell neoplasms of the forestomach	(481)
$B6C3F_1$ mice	Female	Inhalation	0, 6.25, 20, 62.5, 200, 625	6 h/day, 5 days/week, 104 weeks	Lethal thymic lymphomas Heart hemangiosarcomas Alveolar–bronchiolar neoplasms Hepatocellular neoplasms Harderian gland adenoma and carcinoma Granulosa cell neoplasms of the ovary Mammary gland carcinomas Squamous-cell neoplasms of the forestomach	(482)
$B6C3F_1$ mice	Male	Inhalation	0, 6.25, 20, 62.5, 200, 625	6 h/day, 5 days/week, 104 weeks	Lethal thymic lymphomas Alveolar–bronchiolar neoplasms Harderian gland adenoma and carcinoma Heart hemangiosarcomas Hepatocellular neoplasms Squamous-cell neoplasms of the forestomach Preputial gland adenoma or carcinoma	(482)

similar tissues, but for the most part females developed tumors at lower exposure concentrations. In general, the development of tumors followed a linear or supralinear dose–response curve (483).

The National Toxicology Program also conducted stop-exposure studies to evaluate the relationship between exposure level and duration of exposure. Groups of male mice were exposed to equivalent concentrations of

8000 ppm/week (200 ppm for 40 weeks versus 625 ppm for 13 weeks, 6 h/day, 5 days/week) and 16,000 ppm/week (312 ppm for 52 weeks versus 625 ppm for 26 weeks, 6 h/day, 5 days/week). These studies showed that, at comparable total exposures, the concentration of butadiene is a greater contributing factor than is the duration of exposure for the development of lymphomas and forestomach neoplasms (421, 483, 484).

The International Institute of Synthetic Rubber Producers conducted a carcinogenicity study in rats (455). The results of this study are also summarized in Table 27.20. Rats developed tumors from exposures to butadiene that were as much as three orders of magnitude higher than those that caused tumors in mice. Unlike the response in mice, cancers in rats developed in a different spectrum of tissues.

33.4.1.6 Genetic and Related Cellular Effects Studies. Butadiene is mutagenic in the *S. typhimurium* assay in the presence of metabolic activation (393, 485–487). Butadiene is a weak inducer of sister chromatid exchanges in Chinese hamster ovary cells, but only in the presence of S9 mix (488). Gaseous butadiene did not induce SCEs in cultured human lymphocytes with or without metabolic activation (485); however, when administered in cooled, liquid form, it produced a weak increase in SCEs both with and without S9 mix (489).

Genotoxicity studies *in vivo* have been conducted in mice and rats. In the bone marrow of mice exposed by inhalation, butadiene produced chromosomal aberrations (1250 ppm for 6 h or 625 ppm for 10 days), SCEs (6.25–625 ppm for 10 days), and micronuclei (6.25–625 ppm for 10 days, 6.25–625 ppm for 13 weeks, or 1250 ppm for 3–24 weeks) but not aneuploidy (1250 ppm for 6 h) (490–493). In rats exposed by inhalation, no SCEs or micronuclei were induced in bone marrow, and no chromosomal aberrations were found in lymphocytes (100–1000 ppm for 2 day) (490). No micronuclei were found in bone marrow of rats (250–1000 ppm for 2 week), but SCEs were weakly induced in lymphocytes and primary lung cells (494). Exposure of mice and rats to 50, 200, 500, or 1300 ppm butadiene (7 h/day for 5 days) resulted in significant increases in the frequency of micronuclei (in blood and bone marrow) in mice at 50 ppm and up to a ninefold at 500–1300 ppm, but no effects were observed in rats (495, 496).

Epoxybutene and diepoxybutane, two reactive metabolites of butadiene, are genotoxic in a wide variety of test organisms, including bacteria, yeasts, *Drosophila*, and mammalian cells in culture (including human cells) (421, 488, 489, 497, 498). Alkali labile sites following inhalation exposure to 2000 ppm butadiene (7 h/day for 7 days) have been demonstrated in liver DNA isolated from mice and rats, whereas DNA crosslinking was detected only in mice (499). The formation of alkali labile sites has been attributed to the action of epoxybutene, and DNA crosslinks have been attributed to the presence of significant levels of diepoxybutane in mice but not in rats (421).

The induction of *in vivo* gene mutations at marker genes (*lacI* and *lacZ*) in the tissues of transgenic mice and at the *hprt* locus in T lymphocytes has been examined. Results are shown in Table 27.21 (498, 500–504). These data indicate that exposure of mice to butadiene results in an increased frequency of gene mutations. Mutational spectra analyses in these target genes indicate an increased frequency of point

Table 27.21. Summary of Mutation Induction Studies in Transgenic Animals Exposed to 1,3-Butadiene

Species	Exposure Route	Approximate Dose (ppm)	Treatment	Gene Mutation	References
$CD2F_1$ transgenic mice	Inhalation	625	6 h/day, 5 days/week, 1 week	Increased mutant frequency of the *lacZ* transgene from the lung, no increase in bone marrow and liver	(500)
$B6C3F_1$ mice	Inhalation	625	6 h/day, 5 days/week, 2 weeks	Increased frequency of *hprt* mutant T lymphocytes	(498)
$(102/E_1$ X C3H/E1)F_1 mice	Inhalation	200, 500, 1300	6 h/day, 5 days/week, 1 week	Increased frequency of *hprt* mutant T lymphocytes at higher dose	(502)
$B6C3F_1$ transgenic mice	Inhalation	62.5, 625, 1250	6 h/day, 5 days/week, 4 weeks	Concentration-dependent increase in bone marrow *lacI* mutant frequency	(501)
$B6C3F_1$ transgenic mice	Inhalation	62.5, 625, 1250	6 h/day, 5 days/week, 4 weeks	Increase in bone marrow *lacI* mutant frequency at all levels of exposure	(503)
$B6C3F_1$ mice	Inhalation	20, 62.5, 625	6 h/day, 5 days/week, 4 weeks	Increased frequency of *hprt* mutant T lymphocytes	(504)
F344 rats	Inhalation	20, 62.5, 625	6 h/day, 5 days/week, 4 weeks	Increased frequency of *hprt* mutant T lymphocytes, rate of mutation accumulation greater in rats	(504)

mutations occurring at A:T base pairs (498, 501, 505). Epoxybutene and diepoxybutane are also mutagenic to B6C3F1 mice, and induce an increased frequency of *hprt* mutant T lymphocytes. DNA sequence analysis revealed point mutations at both G:C and A:T base pairs (498).

Lymphomas and lung and liver tumors induced in mice exposed to 6.25 and 625 ppm butadiene (6 h/day, 5 days/week for $\leq$2 years), were examined for the presence of activated proto-oncogenes. A mutation in codon 13 was detected in six of six lung tumors, two of three liver tumors, and one of two lymphomas with activated K-*ras* (506). Twenty-three adenomas and six adenocarcinomas of the Harderian gland were analyzed for mutations in the K-*ras* and the H-*ras* genes. Activation of *ras* was also examined in 16 spontaneously occurring Harderian gland adenomas and 1 adenocarcinoma. Only 1 butadiene-induced tumor contained the K-*ras* codon 13 mutation previously detected in lymphomas and lung and liver tumors; however, 16 of 29 tumors from the treated mice contained mutations in H-*ras* codon 61. The spectrum of mutations observed did not differ from that in spontaneously occurring tumors (507). Mice showed losses of heterozygosity on chromosome 11 at several loci surrounding the p53 tumor-suppressor gene in 12 of 17 mammary tumors and 2 of 8 lung tumors induced by exposure to butadiene (20–625 ppm, 6 h/day, 5 days/week for $\leq$2 years). Losses of heterozygosity were also detected at the *Rb-1* tumor-suppressor gene in seven mammary tumors and one lung tumor (508).

33.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. Dogs and rabbits exposed experimentally to as much as 6700 ppm butadiene, 7.5 h/day for 8 months, developed no histologically demonstrable abnormality in any part of the eyes (98). When exposed to photo-oxidation with ozone and nitrogen dioxide (as in smog formation), butadiene is a potent precursor of products that are irritating to the human eye, such as formaldehyde and acrolein (98). Chronic inhalation of butadiene caused liver necrosis and nephrosis in mice exposed to high doses. No such changes were found after chronic exposure in rats (455).

Immune function assays were performed in mice exposed to 1250 ppm butadiene by inhalation 6 h/day, 5 days/week for 6 or 12 weeks. Significant extramedullary hematopoiesis and depression of cellularity were observed in spleens from exposed mice. Overall, no persistent immunological defects were detectable (509). Exposure to 1250 ppm butadiene (6 h/day for 6 weeks) induces macrocytic–megablastic anemia in mice (510, 511). The toxicity of butadiene to bone marrow was studied using the spleen colony formation unit CFU-S assay. Exposure to 1250 ppm butadiene for 6 weeks resulted in no demonstrable alteration in the frequency of CFU-S; however, colonies derived from treated animals were smaller than those from controls. After a 30–31 week exposure to butadiene, a significant decrease in the number of CFU-S was observed (512). Other studies suggest that epoxybutene (an epoxide metabolite of butadiene) adversely affects cytokine-mediated cell differentiation in bone marrow in mice (513).

To study the effect of butadiene on arteriosclerosis development, cockerels were exposed by inhalation to 20 ppm butadiene (6 h/day for 80 days). Arteriosclerotic plaque frequency or location was no different from those in the control group; however, plaque sizes were significantly larger in butadiene-treated cockerels than in controls (514).

33.4.2 Human Experience

33.4.2.1 General Information. Inhalation is the primary route of potential exposure to butadiene for the general population. Some exposure may occur from ingesting contaminated food or water or dermal (skin) contact; however, these types of exposures are unlikely in most circumstances. This chemical is not a common contaminant of water supplies, and, although some food packaging contains residual butadiene, the available data indicate that it does not usually migrate to the food (515). Certain cooking oils, such as rapeseed oil, release butadiene when heated (516).

33.4.2.2 Clinical Cases

33.4.2.2.1 Acute toxicity. The acute toxicity of butadiene is of low order and is not cumulative. It has anesthetic action and at very high concentrations causes CNS depression, respiratory paralysis, and death. Respiratory paralysis is likely to occur after exposure to concentrations higher than 10,000 ppm. Rubber manufacturing workers exposed to butadiene gas reported irritation of eyes, nasal passages, throat, and lungs; some workers developed symptoms such as coughing, fatigue, and drowsiness. These physiological responses dissipated on removal from the area where butadiene had accumulated (517).

33.4.2.2.2 Chronic and subchronic toxicity. NA

33.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. NA

33.4.2.2.4 Reproductive and developmental. NA

33.4.2.2.5 Carcinogenesis. NA

33.4.2.2.6 Genetic and related cellular effects studies. NA

33.4.2.2.7 Other: neurological, pulmonary, and skin sensitization. Dermatitis among butadiene workers appears to represent a secondary effect of additives, accelerators, or inhibitors (1). On direct dermal contact, the liquefied product causes burns and frostbite (41). Persons chronically exposed

to petroleum derivatives, including butadiene, showed a statistically significant decrease in lacrimal secretion, as well as shortening of lacrimal film breakup time, when compared with an unexposed control group (518).

33.4.2.3 Epidemiologic Studies

33.4.2.3.1 Acute toxicity. Butadiene causes slight irritation to the skin and eyes. Humans exposed to 1000 ppm showed no irritant effects, whereas 2000–4000 ppm during 6–7 h resulted in mild irritation of the eyes and difficulty in focusing on instrument scales. Exposure of two volunteers to 8000 ppm for 8 h resulted in slight eye and upper respiratory tract irritation, blurred vision, coughing, and drowsiness (453).

33.4.2.3.2 Chronic and subchronic toxicity. NA

33.4.2.3.3 Pharmacokinetics, metabolism, and mechanisms. Butadiene metabolism in humans has been investigated using *in vitro* studies. In general, results have shown that mice have a faster rate of GSH conjugation with epoxybutene in lung cytosol and liver microsomes than rats and humans, and that humans have faster rates of epoxybutene and diepoxybutane hydrolysis by epoxide hydrolase compared with rats or mice (421). Results also indicate that the rate of cytochrome P450-mediated epoxidation of epoxybutene to diepoxybutane is higher in mice and rats, and that the rate in humans is highly variable (421).

The excretion of urinary butadiene metabolites [1,2-dihydroxy-4-(*N*-acetylcysteinyl-*S*-)-butane (M-I) and 1-hydroxy-2-(*N*-acetylcysteinyl-*S*-)-3-butene (M-II)] in humans exposed to butadiene in a production plant was investigated. M-I, but not M-II, could be readily identified and quantitated in the urine samples at levels frequently greater than 1 μg/mL. This finding was consistent with a higher rate of epoxide hydrolase activity in the livers of humans compared with rats and mice (436).

Interindividual variability in the enzymes that metabolize butadiene may arise from genetic polymorphisms that affect enzyme expression. Depending on the enzyme, there may be one or several mutant alleles that produce enzyme variants with reduced or increased efficiency in comparison with the wild-type form, whereas in other cases, the functional enzyme is completely missing. Polymorphic variants of the genes that code for the enzymes that metabolize butadiene—cytochrome P450, glutathione *S*-transferase, and epoxide hydrolase—have been identified (519–522).

The contribution of glutathione *S*-transferase genetic polymorphisms in determining genotoxic response after exposure to butadiene has been studied. Sister chromatid exchanges were induced after a 48 h treatment of epoxybutene (50 and 250 μmol) and analyzed in cultured lymphocytes of glutathione *S*-transferase μ1 (*GSTM1*) donors: six *GSTM1*-null (gene deleted) and six *GSTM1*-positive (gene present). Epoxybutene produced a higher level of SCEs among the *GSTM1*-null than *GSTM1*-positive samples (523). Sister chromatid exchanges were induced by a 48 h treatment with diepoxybutane (2 and 5 μmol) in whole-blood lymphocyte cultures of 20 human donors with known genotypes of two polymorphic glutathione *S*-transferases, *GSTT1* and *GSTM1*. The mean frequency of SCEs/cell was 1.6 times higher among *GSTT1*-null donors than *GSTT1*-positive donors at both concentrations; all diepoxybutane-sensitive individuals were of the *GSTT1*-null genotype, whereas all diepoxybutane-resistant persons had a detectable *GSTT1* gene. No influence on diepoxybutane-induced SCEs or cytotoxic effects was observed for the *GSTM1* genotype (524). The frequency of SCEs was analyzed in human lymphocytes treated with 125 and 250 μmol epoxybutene for 48 h. Whole-blood lymphocytes were obtained from 18 donors, representing both *GSTT1*-positive and *GSTT1*-null genotypes. Individual mean frequencies of SCEs induced by the 250-μmol concentration were higher in the *GSTT1*-null group than in the *GSTT1*-positive group (525). In a similar study with lymphocytes exposed to butadienediol epoxide, no differences in induced SCEs could be associated with the *GSTM1* and *GSTT1* genotypes either separately or in combination (526).

In vivo cytogenetic studies on a possible genotype effect among butadiene-exposed workers have been conducted. Baseline frequencies of SCEs, diepoxybutane-induced SCEs frequencies, and *GSTT1* deletion status were assessed in 40 butadiene production workers in the United States. Of the 40 workers, 6 were *GSTT1*-null; however, *GSTT1* genotype was not associated with elevations in diepoxybutane-induced SCEs frequency (527). Cytogenetic parameters (chromosomal aberrations, SCEs frequency, and micronuclei in peripheral blood lymphocytes) were analyzed in 99 workers (53 exposed, 46 controls) involved in butadiene production and styrene–butadiene polymerization in Portugal and the Czech Republic. *GSTT1*-null genotype was observed among 17.2% of workers, and *GSTM1*-null was present in 57.6%. Chromosomal aberrations (gaps excluded) were significantly increased among the workers lacking the *GSTT1* gene as compared to the *GSTT1*-positive workers; the other polymorphic *GSTM1* gene showed no association with the cytogenetic parameters (528). In a study of 19 butadiene production workers and 19 controls of the Czech Republic, chromosomal aberrations, SCEs, micronuclei, and comet assay parameters were analyzed. Butadiene exposure significantly increased the percentage of cells with chromosomal aberrations in exposed versus control groups and the frequency of SCEs per cell. The *GSTM1* genotype affected chromosomal aberrations in the exposed group, whereas the *GSTT1* genotype affected chromosomal aberrations in controls (529).

A study was conducted among 27 butadiene-exposed workers and 37 controls using different biomarkers of genotoxic effect. Study participants were assigned to different groups, based on the epoxide hydrolase activity predicted by their genotype (low, intermediate, high). The studied biomarkers did not allow for discrimination between exposed and nonexposed individuals, but smoking habits affected the frequency of sister chromatid exchanges (530).

33.4.2.3.4 Reproductive and developmental. NA

33.4.2.3.5 Carcinogenesis. Epidemiological studies have been conducted among workers involved in the production of butadiene monomer and among workers exposed to butadiene in the manufacture of styrene–butadiene rubber and latex. The results of these studies as well as their strengths and limitations have been reviewed (531). The characteristics of these studies and the main results are summarized in Table 27.22.

A group of styrene–butadiene rubber production workers was studied by the National Institute of Occupational Safety and Health (NIOSH) in a two-plant complex in Ohio. This study found an elevated, although not statistically significant, mortality for lymphatic and hematopoietic neoplasms at one of two plants studied [standardized mortality ratio (SMR) = 1.5], in particular lymphosarcoma and reticulosarcoma (SMR = 1.8) and leukemia (SMR = 2.0) (532, 542). An analysis of the subgroup with 2 year exposure in a plant where process and operational changes occurred, revealed a nonsignificant increase in mortality for leukemia (SMR = 2.8) (532).

A cohort study was conducted in a butadiene production plant, where worker mortality was evaluated by duration of employment (534, 543–545). The most recent update reported a significantly increased SMR of 1.5 for lymphatic and hematopoietic cancers, due to increased mortality for lymphosarcoma and reticulosarcoma, Hodgkin's disease, and other lymphatic cancers. Leukemia mortality rate for these workers was comparable to U.S. rates (534).

A retrospective cohort study conducted in eight styrene–-butadiene rubber plants in the United States and Canada found no significant increase in mortality from lymphatic or hematopoietic cancer, or any other cancer site. A nonsignificant excess risk of "other lymphatic cancer" (SMR = 2.0) was noted among production workers (546). In an update of this study, there was no significant increase in lymphatic or hematopoietic cancer, or any other cancer site. Production workers had a significant excess of "other lymphatic cancer"

Table 27.22. Summary of Epidemiological Studies in Human Exposed to 1,3-Butadiene

Study Design	Industry	Workers (*N*)	Study Period	Main Result, SMR (95% CI) Unless Indicated	References
Cohort	SBR	2,756	1943–1976	All LHC: 1.3 (0.9–1.4) Leukemia: 1.7 (0.8–1.5) Lymphosarcoma: 1.7 (0.7–1.7)	(532, 533)
Cohort	BDM	2,795	1943–1994	All LHC: 1.5 (1.1–2.0) Leukemia: 1.1 (0.6–1.9) Lymphosarcoma: 1.9 (0.9–3.6)	(534)
Cohort	SBR	12,110	1943–1982	All LHC: 1.0 (0.9–1.4) Leukemia: 1.0 (0.8–1.5) Lymphosarcoma: 0.6 (0.7–1.7)	(535)
Case-control	SBR 193 (controls)	59 (LHC cases)	1943–1982	OR (95% CI) All LHC: 2.3 (1.1–4.7) Leukemia: 9.4 (2.1–22.9) Lymphosarcoma: 0.5 (0.1–4.2)	(536)
Case-control	SBR	59 (LHC cases) 1,242 (controls)	1943–1982	OR (95% CI) at 1 ppm butadiene Leukemia: 1.5 (1.1–2.1)	(537)
Cohort	SBR	15,649	1943–1991	All LHC: 1.1 (0.9–1.3) Leukemia: 1.3 (1.0–1.7) Lymphosarcoma: 0.8 (0.4–1.4)	(538)
Cohort	SBL	420	1947–1986	All LHC: 1 obs, 2.2 exp Leukemia: 1 obs, 0.9 exp	(539)
Cohort	BDM	614	1948–1989	All LHC: 0 obs, 1.2 exp	(540)
Cohort	BDM	364	1943–1970	All LHC: 1.7 (0.7–3.6) Leukemia: 1.2 (0.2–4.4) Lymphosarcoma: 5.8 (1.6–14.8)	(541)

Key: ABS, acrylonitrile–butadiene–styrene plastic; BDM, butadiene monomer; CI, confidence integral; exp., expected; LHC, lymphohematopoietic cancer; obs, observed; OR, odds ratio; SBL, styrene–butadiene latex; SBR, styrene–butadiene rubber; SMR, standardized mortality ratio.

(SMR = 2.6), and a significant excess of all lymphopoietic cancers was noted for black workers (SMR = 5.1) (535). A nested case-control study of lymphopoietic cancer was conducted within this cohort. Each worker was assigned an exposure index calculated as the sum of the product of exposure rank for butadiene and styrene assigned to each job multiplied by the time in months spent in that job. A strong association between leukemia and butadiene was reported; no significant associations were found between butadiene exposure and lymphosarcoma, other lymphatic cancers, and Hodgkin's disease. When both butadiene and styrene were included in the logistic regression model for leukemia, the odds ratio for butadiene remained high [OR = 7.6, 95% confidence integral (CI) 1.6–35.6] (536). A further study of these cases and a larger number of controls used butadiene and styrene exposure measurements. Cumulative exposures and TWA exposures were calculated using job- and plant-specific exposure levels and the job histories of cases and controls. This study showed a significant increase in the risk of leukemia for each unit increase in the average measured levels of butadiene (OR at 1 ppm = 1.5, 95% CI 1.1–2.1) (537).

A cohort study was conducted in eight styrene–butadiene rubber plants in North America, all of which were previously studied by other researchers (532, 535). Results for the total cohort are shown in Table 27.22. Mortality rates were slightly elevated for leukemia, but not for lymphosarcoma or other lymphatic cancers. The SMR for leukemia increased for workers employed at least 10 years with 20 or more years follow-up (SMR = 2.2, 95% CI 1.5–3.2), and for hourly workers (SMR = 1.4, 95% CI 1.0–1.9) (538). Leukemia increases greater than twofold occurred among workers in polymerization, coagulation, maintenance labor, and laboratories. An analysis using retrospective quantitative estimates of exposure to butadiene and styrene expanded these results. The resulting estimates were linked with the subjects' work histories to obtain cumulative exposure indices for individual workers. Leukemia SMRs and mortality rate ratios adjusted by race, age, and cumulative exposure to styrene increased with cumulative butadiene exposure categories. These results suggest that butadiene produces a dose-related increase in the occurrence of leukemia among exposed workers (547). In the most recent follow-up of the cohort, the exposure assessment to butadiene and to possible confounding coexposures was revised and refined. Mortality from leukemia showed a consistently positive association with increasing exposure to butadiene and to styrene. Exposure to dimethyldithiocarbamate also showed consistently increased relative rates, but with no monotonic trend (548–550). Results for a case series comprised of chronic lymphocytic leukemia and non-Hodgkin lymphoma combined were similar to those for non-Hodgkin lymphoma alone (551).

Three cohort studies that include relatively few subjects have been reported. The description and main results are presented in Table 27.22. A cohort mortality study was conducted in workers engaged in the development or production of styrene-based products. Mortality from lymphatic and hematopoietic cancer was not excessive for a subgroup of workers involved in the production of styrene–butadiene latex (539).

Mortality rates were evaluated in a butadiene production plant located in a petrochemical complex. Men entered the study if they had been employed for at least 5 years in jobs with potential exposure to butadiene. There were no deaths due to cancer of the lymphatic and hematopoietic tissue (540). In the most recent follow-up, three deaths due to cancer of the lymphatic and hematopoietic tissues were observed (SMR = 1.1; 95% CI, 0.3–1.5), and no deaths from leukemia were observed, whereas one death was expected (552).

A cohort study was conducted in two facilities that produced butadiene and a wide variety of chemical substances. Workers were identified from departments where butadiene was a primary product and neither benzene nor ethylene oxide was present. An excess mortality from lymphosarcoma and reticulosarcoma among workers employed in butadiene production processes was found (SMR = 5.8, 95% CI 1.6–14.8). Mortality for leukemia and other lymphatic cancers was less than or equal to U.S. rates (541).

According to the Health Review Committee of the Health Effects Institute, the apparent discrepancies among the results of the epidemiologic studies discussed above may reflect (*1*) the lower TWA butadiene concentrations in the monomer facilities, (*2*) the smaller number of monomer workers included in the analysis, or (*3*) the presence of styrene or some other confounding substance such as the stopping agent dimethyldithiocarbamate in the rubber-production facilities (551). The Committee concluded that the study in the styrene–butadiene plants strengthens the epidemiologic evidence for the carcinogenicity of butadiene.

The mortality of women in the eight styrene–butadiene rubber plants was evaluated. No increased risks were found for leukemia or lymphoma, but other cancers had statistically significant increased risks (SMR = 1.6, 95% CI 1.2–2.1 for lung cancer and SMR = 3.3, 95% CI 1.2–7.2 for bladder cancer) (553). No trend of increasing SMRs for lung cancer with increased duration of employment was observed. The authors conclude that the excess risks observed may be attributable to nonoccupational factors.

In the most recent study of this cohort, the lung cancer risk among men and women was reported. Among men, there was no indication of an increased risk for lung cancer and no evidence for an internal dose–response. Among women there was evidence of increased risk of lung cancer, but there was no evidence for a dose–response effect in the exposed group (554).

A population-based case-control study in Montreal, Canada evaluated the association between renal-cell

carcinoma and a large number of occupational exposures among men aged 35–70 years between 1979 and 1985. Cases were identified at all large hospitals in the area and two sets of controls were used. The odds ratio for exposure to "styrene–butadiene rubber" was 2.1 (95% CI, 1.1–4.2) after controlling for age, family income, tobacco smoke, and body mass index and 1.8 (95% CI, 0.9–3.7) after controlling for other occupational exposures (555), and a cohort study of students at a high school adjacent to a styrene–butadiene rubber production plant in the United States (556).

The association between childhood leukemia and proximity to sources of butadiene has been evaluated in ecological studies. A study reported an increased risk of childhood cancer among children who were born within 1.0 km of hot spots of industrial butadiene emissions in Great Britain (557). In another study, an increased risk of childhood cancers was associated with birth proximity to roads, railways, waterways, and bus, ferry, or train stations. The effects were evident at ranges down to 100 m, and decayed rapidly with an increasing distance. The author concluded that butadiene was the most probable causal agent (558). A study in California evaluated the relationship between childhood cancer rates and exposure scores for potentially carcinogenic pollutants (including butadiene) emitted from mobile, area, and point sources and from all sources combined. Elevated childhood leukemia rate ratios and a significant trend with increasing exposure level were reported in tracts ranked highest for exposure to the combined group of agents (RR = 1.21; 95% CI 1.03–1.42) and in tracts ranked highest for point-source exposure (RR = 1.32; 95% CI 1.11–1.57) (559). A similar analysis in Southeastern Texas reported the following risks among census tracts with the highest butadiene levels: RR = 1.40 (95% CI, 1.07–1.81) for all leukemia, RR = 1.68 (95% CI, 0.84–3.35) for acute myeloid leukemia, and 1.32 (95% CI, 0.98–1.77) for acute lymphocytic leukemia (560). The risk for lymphatic and hematopoietic cancers was evaluated among students of a high school in Texas that was adjacent to facilities that had produced synthetic styrene–butadiene rubber since 1943. The SMR for all lymphatic and hematopoietic cancer was 1.64 (95% CI 0.85–2.87) for men and 0.47 (95% CI 0.06–1.70) for women. The slight male excess in lymphatic and hematopoietic cancers was stronger among men who attended school for 2 years or less (556). Together, these studies suggest a role of butadiene in the development of childhood leukemia, since exposures were not measured, no causality can be established.

33.4.2.3.6 Genetic and related cellular effects studies. In a pilot study at a butadiene production plant in the United States, the frequency of mutations at the hypoxanthine–guanine phosphoribosyl transferase (*hprt*) locus in peripheral blood lymphocytes of workers was evaluated (561). An increase in *hprt* variant (mutant) frequency (V_f) was detected in workers in the butadiene production area, compared with workers in other areas of the plant and outside facility controls. A correlation between an increase in the *hprt* V_f and increased levels of a butadiene metabolite in urine was observed. In a subsequent study, workers from higher (production units), intermediate (rovers and tank farm), and lower (control center and utilities) exposure groups were evaluated, as well as workers from a styrene–butadiene rubber plant (562). A significant increase in *hprt* V_f was observed in personnel from the areas of higher exposure when compared to workers from lower exposure areas or nonexposed subjects. The frequency of *hprt* mutation (*hprt* M_f) was assessed in workers at a polybutadiene rubber production plant in China. After adjustment by multiple regression for mean age, sex, and cloning efficiency, the adjusted mean *hprt* M_f was not significantly increased in exposed workers compared with unexposed workers (563). In another study in China, a higher but not statistically significant increase in *hprt* mutation frequencies was observed among petrochemical workers exposed to mean levels of butadiene of 10 ppm. In addition, the frequency of exon deletions in butadiene-exposed workers was significantly higher than that in control subjects (564).

A cytogenetic assay was used to determine chromosome aberration frequencies in 10 exposed workers and 10 unexposed controls in a butadiene production facility. The exposed group had a higher frequency of cells with chromosome aberrations and higher chromatid breaks per 100 cells compared with the control, but the difference was not statistically significant (565). In the same study, lymphocytes were irradiated *in vitro*, and the exposed group had a significant increase in the frequency of chromosomal aberrations compared to the controls. In addition, the dicentric frequencies from workers were significantly correlated with the presence of a butadiene metabolite in urine. In a study of 40 exposed workers and 30 controls from two butadiene production plants, peripheral blood lymphocytes were evaluated for chromosomal damage (chromosomal aberrations, micronuclei, and SCEs). No exposure-related effects were seen in any of the three cytogenetic endpoints in either of the butadiene production plants (566).

A study in butadiene polymer workers in a Southeast Texas facility with current exposure to butadiene levels below the OSHA permissible exposure limit of 1000 ppb, showed no association of *hprt* mutation frequency with current exposure or age. However, for workers with 30 or more years of employment, a significant but weak association was observed. This result suggests that chronic and/or past, high-level exposures might leave a mutagenic signature that is revealed by the *hprt* assay, possibly through the retention of mutant, long-term memory T-cells (567).

The reasons for inconsistent findings in lymphocyte *hprt* gene mutation and butadiene exposure among workers are not clear, but may be explained by methodological

Table 27.23. Occupational Exposure Limits for 1,3-Butadiene in the United States[a]

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	1 ppm (2.2 mg/m^3)	Lowest feasible concentration	A TLV–TWA has been developed by ACGIH
Short-term exposure limit	5 ppp (11 mg/m^3)	–	–
Ceiling limit	–	–	–

[a] OSHA and ACGIH, 8 h TWA; NIOSH, 10 h TWA. From Ref. (25)

differences in exposure assessment of mutation analysis (330). Longevity of the workers, as suggested by the study described above, may be another explanation (567).

33.4.2.3.7 Other: neurological, pulmonary, and skin sensitization. A cross-sectional survey of hematological parameters in workers at a styrene–butadiene synthetic rubber plant was conducted. Slightly lower levels of red blood cell counts, hemoglobin concentrations, and packed red cell volumes, with higher mean corpuscular red cell volumes, were observed in tank farm workers compared to workers in other departments with lower butadiene exposures (568). Hematological data available for 429 workers involved in butadiene production were compared with results for subjects working in other parts of a chemical complex. Hematological outcomes studied include red cell count, hemoglobin concentration, mean corpuscular volume, platelet count, white blood cell count, neutrophil count, and lymphocyte count. No significant differences occurred between the mean values of each of these variables, adjusted for the effects of age and smoking, for both groups (540).

33.5 Standards, Regulations, or Guidelines of Exposure

Butadiene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). It has been classified as a human carcinogen by IARC (Group 1) on the basis of sufficient evidence in humans and in experimental animals. The U.S. Environmental Protection Agency (EPA) has classified butadiene as a B2 carcinogen (probable human carcinogen), based on inadequate human data and sufficient rodent (mouse and rat) studies in which exposure to airborne concentrations of butadiene caused multiple tumors and tumor types. The EPA inhalation carcinogenic unit risk for butadiene is 2.8×10^{-4} per μg/m^3 (25). Butadiene has been categorized as a suspected human carcinogen based on available carcinogenicity information in experimental animals and epidemiological studies available but insufficient to confirm an increase in cancer. The IDLH concentration established by NIOSH is 2000 ppm, based on health considerations and acute toxicity data in humans and animals (41). A review of the animal, human, and genotoxicity evidence has led to recognition by the Occupational Safety and Health Administration (OSHA) of the carcinogenic potential of butadiene in humans. OSHA has issued an occupational permissible exposure limit (PEL) of 1 ppm of butadiene in air as an 8 h TWA (569). Table 27.23 lists the occupational exposure limits for butadiene in the United States, and the international standards are presented in Table 27.24.

33.6 Lower Alkadyenes

Propadiene (allene, dimethylenemethane,1,2-propadiene), CH_2:C:CH_2, is a colorless, flammable, and unstable gas with a sweetish odor. Propadiene is produced in small quantities in petroleum cracking processes. It is used as a chemical intermediate in the production of its isomer, propyne (63). Selected physical properties are given in Table 27.19.

Propadiene is of low general toxicity, but may cause CNS depression at very high concentrations (406). In mice, concentrations of 20% caused restlessness and CNS depression in 11 min, 30% caused CNS depression in 3 min, and 40% in 1–2 min (181). For industrial use, propadiene vapors may cause dizziness or asphyxiation without warning; some may be toxic if inhaled at high concentrations. Contact with

Table 27.24. Occupational Exposure Limits for 1,3-Butadiene in Different Countries

Country	Exposure Limit
Australia	TWA 10 ppm (22 mg/m^3); carcinogen
Belgium	TWA 10 ppm (22 mg/m^3); carcinogen
Denmark	TWA 10 ppm (22 mg/m^3); carcinogen
Finland	TWA 50 ppm (73 mg/m^3); carcinogen
France	TWA 10 ppm (22 mg/m^3)
Germany	Carcinogen
Hungary	STEL 10 mg/m^3; carcinogen
Ireland	TWA 10 ppm (22 mg/m^3); carcinogen
The Netherlands	TWA 21 ppm (46.2 mg/m^3)
The Philippines	TWA 1000 ppm (2200 mg/m^3)
Poland	TWA 10 mg/m^3; STEL 40 mg/m^3; carcinogen
Russia	STEL 100 mg/m^3
Sweden	TWA 10 ppm (22 mg/m^3); STEL 20 ppm (40 mg/m^3); carcinogen
Switzerland	TWA 5 ppm (11 mg/m^3); carcinogen
Turkey	TWA 1000 ppm (2200 mg/m^3)
United Kingdom	TWA 10 ppm (22 mg/m^3)

From Ref. 25.

propadiene gas or liquefied gas may cause burns, severe injury, and/or frostbite (12).

34.0 2-Methyl-1,3-Butadiene

34.0.1 CAS Number

[*78–79-5*]

34.0.2 Synonyms

Isoprene, β-methylbivinil; 2-methylbutadiene; *2-methyl-1,3-butadiene*; 2-methylbutadiene; 3-methyl-1,3-butadiene; isopentadiene; methyl bivinyl; hemiterpene; 2-methylbuta-1,3-diene; isoprene, stabilized with 100 ppm 4-*tert*-butylcatechol

34.0.3 Trade Names

NA

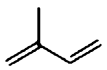
34.0.4 Molecular Weight

68.118

34.0.5 Molecular Formula

CH_2:C(CH_3)CH:CH_2

34.0.6 Molecular Structure



34.1 Chemical and Physical Properties

34.1.1 General

2-Methyl-1,3-butadiene (isoprene), C_5H_8, is a colorless, volatile, flammable liquid with specific gravity 0.6758. It is highly reactive, usually occurs as its dimer (570), and unless inhibited undergoes explosive polymerization (571). Isoprene naturally occurs in the environment as emissions from vegetation (572). It may be released to the environment as emissions during wood pulping, biomass combustion, and rubber abrasion; through tobacco smoke, gasoline, turbine, and automobile exhaust (332). In tobacco smoke, isoprene has been determined to be the precursor of a number of polycyclic aromatics, as demonstrated by thermal condensations in the range of 450–700°C (573). Selected physical properties are given in Table 27.19.

34.1.2 Odor and Warning Properties

The odor threshold of isoprene is 5 mg/m^3 (72). It has a faint aromatic odor (332).

34.2 Production and Use

Industrially, isoprene is produced by dehydrogenation in the *oxo* process from isopentene, by the acid-catalyzed addition of formaldehyde to isobutene, or by high temperature thermal cracking of petroleum oil, gas oils, and naphthas (251, 332). It is used in the manufacture of butyl and synthetic rubber, plastics, and a variety of other chemicals (251). Isoprene possesses two reactive centers and can combine linearly or three-dimensionally to form polyenes, cyclics, aromatics, and diverse polymers. Much literature is available on its di- and polymerization to farnesene (C10), squalene (C30), and a variety of C40 compounds, such as the lycopenes and carotenes. The isoprene unit was the most important building block for lipids, steroids, terpenoids, and a wide variety of natural products, including latex, the raw material for natural rubber, but it has been replaced as a source of hydrocarbons for the chemical industry by a more economical starting material (425).

34.3 Exposure Assessment

34.3.1 Air/Water

Air samples containing isoprene may be collected on charcoal tubes (309). Methods of analysis of air samples include gas chromatography in combination with photoionization, electron capture and flame ionization detection (574), gas chromatography and a combination of on-column cryofocusing and gas chromatography reinjection (575), and gas chromatography with flame ionization detection and coupled fused-silica capillary columns (576). GC-MS and purge-and-trap techniques have also been used to measure isoprene in water (577).

34.3.2 Background Levels

NA

34.3.3 Workplace Methods

NA

34.3.4 Community Methods

NA

34.3.5 Biomonitoring/Biomarkers

Isoprene in expired breath has been concentrated using a multistage cryogenic trapping system and GC-MS (66). Another method of analysis of expired air involves gas chromatography with flame ionization detection and coupled fused-silica capillary columns (576). Isoprene has been measured in mother's milk by thermal desorption/GC-MS (159).

34.4 Toxic Effects

34.4.1 Experimental Studies

34.4.1.1 Acute Toxicity. Acute inhalation studies have shown a no-effect level of 20,000 ppm in mice. Deep CNS depression was seen at 35,000–45,000 ppm, and death was noted at 50,000 ppm (8). Similar results showed loss of the righting and total reflexes in the mouse at 120 mg/L but no deaths at 200 mg/L (123). The 2 h LC_{50} values are 148 mg/L for the female and 139 mg/L for the male mouse. The 4 h LC_{50} in rats is 180 mg/L (63).

34.4.1.2 Chronic and Subchronic Toxicity. Rats exposed to 0, 438, 875, 1750, 3500, or 7000 isoprene vapors by inhalation for 6 h/day, 5 days/week for 2 weeks showed no effect on survival, body weight gain, clinical signs, clinical chemistry parameters, or gross or microscopic lesions. The same dose regimen in mice did not produce mortalities and only caused a decrease in body weight gain in the higher exposure group of males; however, hematological changes and microscopic lesions, including testicular atrophy, olfactory epithelial degeneration, and forestomach epithelial hyperplasia, were observed in isoprene-exposed mice (578). Mice and rabbits repeatedly exposed to 2.2–4.9 mg/L, 4 h/day for 4 months, and rats for 5 months, showed no weight differential from the control. However, after the third month, oxygen consumption in rats decreased. In rabbits, there were increased numbers of leukocytes, decreased numbers of erythrocytes, and some increased organ weights (579).

34.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms. Low atmospheric concentrations of isoprene inhaled by rats and mice do not accumulate in the body, and only small amounts are exhaled as unchanged substance. At higher concentrations, the rate of metabolism does not increase, indicating limited production of possible monoepoxides of isoprene (580). Liver microsomes of mouse, rat, rabbit, and hamster metabolize isoprene to 3,4-epoxy-3-methyl-1-butene, the major metabolite, and 3,4-epoxy-2-methyl-1-butene, a minor metabolite. 3,4-Epoxy-2-methyl-1-butene, but not 3,4-epoxy-3-methyl-1-butene, can be further metabolized to isoprene diepoxide, a known mutagen (581). Differences in epoxide hydrolase activity between species may be of crucial importance for the toxicity of isoprene (582). Furthermore, pharmacokinetic studies have demonstrated species differences in the maximum metabolic elimination rate; in mice, this was determined to be at least three times higher in mice than in rats (583). Body fat appears to be a reservoir for both isoprene metabolites and isoprene itself. The appearance of metabolites in the respiratory tract after short exposures together with low blood concentrations of isoprene indicates that substantial metabolism of inhaled isoprene in the respiratory tract may occur (584).

34.4.1.4 Reproductive and Developmental. Rodents were exposed to isoprene (280, 1400, and 7000 ppm for 6 h/day, 7 days/week) during gestation (days 6–17 in mice, days 6–19 in rats). In mice, exposure to 7000 ppm reduced maternal weight gain, and all doses caused reduction in fetal body weight. At 7000 ppm, an increase in supernumerary ribs, but no increase in fetal malformations, was observed. In rats, no adverse effects on the dams or on any reproductive index and no increase in the incidence of fetal malformations were observed (332).

34.4.1.5 Carcinogenesis. Male rats exposed to isoprene by inhalation at concentrations of $\leq$7000 ppm (6 h/day, 5 days/week for 6 months) showed a slight increase in the incidence of interstitial-cell carcinoma of the testis, but no increase in any other type of tumor (585). B6C3F1 mice were exposed to isoprene for 8 h/day, 5 days/week as follows (ppm–weeks): 0–80, 10–80, 70–40, 70–80, 140–40, 280–20, 280–80, 700–80, 2200–40, 2200–80. Two groups were exposed for 4 h/day: 2200–20, 2200–80. Groups were held until 96 or 105 weeks on study. There was an exposure-related increased incidence of liver, lung, Harderian gland and forestomach tumors, and hemangiosarcomas and histiocytic sarcomas. These results were similar to the profile of tumors seen in butadiene-exposed mice without the early onset of T-cell lymphoma as seen with butadiene. Isoprene appears to be about one order of magnitude less potent than butadiene in mice (586).

34.4.1.6 Genetic and Related Cellular Effects Studies. Isoprene tested negative for mutagenicity in the *Salmonella*/microsome preincubation assay in the presence and absence of rat or hamster liver S9 (187). Mice exposed to isoprene (438–7000 ppm) for 6 h/day for 12 days showed significant increases in SCE frequency in bone marrow cells and in the levels of micronucleated polychromatic erythrocytes and of micronucleated normochromatic erythrocytes in peripheral blood. In addition, a significant lengthening of the bone marrow average generation time and a significant decrease in the percentage of circulating PCE was detected (587). Mice exposed to 438–7000 ppm isoprene for 6 h/day on 12 days had SCEs and micronuclei in bone marrow cells (588). Isoprene exposure in rats and mice induces hemoglobin adduct formation, in a linear fashion, up to 500 μmol/kg (589).

34.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. In rabbits, exposure to 0.19–0.75 mg/L isoprene caused an increased respiratory rate. At 109 mg/L for 2 h, rats lost the righting reflex. At 24 h postexposure, survivors in both groups exhibited improved swimming time.

Enlarged lungs were found in mice that died during the study (579). When applied to mouse skin, isoprene reduced the number of papillomas, but at a much lower rate than retinyl acetate (590).

34.4.2 Human Experience

34.4.2.1 General Information. The toxicity of isoprene is similar to that of butadiene and butene, although it is more irritating than comparable alkenes or alkanes of similar volatility (1, 329). At low concentrations, except as a result of cigarette smoking and in some occupational connections, few toxic effects have been documented, although at high concentrations it is a CNS depressant and asphyxiant (394).

34.4.2.2 Clinical Cases

34.4.2.2.1 Acute toxicity. NA

34.4.2.2.2 Chronic and subchronic toxicity. NA

34.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. Isoprene is formed endogenously, probably from mevalonic acid, a precursor of cholesterol biosynthesis (591). It has been detected in human expired air at 15–390 mg/h in smokers and 40–250 mg/h in nonsmokers (66). Twenty percent of inhaled isoprene was absorbed in the upper respiratory tract, and a total of 70–99% was retained in the lungs (592, 593). Isoprene has been detected in the milk of women living in urban industrial areas (159).

The relative toxicity and inflammatory gene expression induced by exposure of A549 cells to 1,3-butadiene, isoprene, and their photochemical degradation products was determined in the presence of nitric oxide. Gas chromatography and mass spectrometry analyses indicate the initial and major photochemical products produced during these experiments for butadiene are acrolein, acetaldehyde, and formaldehyde, and products for isoprene are methacrolein, methyl vinyl ketone, and formaldehyde; both formed $<$200 ppb of ozone. After exposure the cells were examined for cytotoxicity and interleukin-8 (IL-8) gene expression, as a marker for inflammation. These results indicate that although butadiene and isoprene alone caused similar cytotoxicity and IL-8 responses compared with the air control, their photochemical products significantly enhanced cytotoxicity and IL-8 gene expression and suggests that once they are released into the environment, reactions occurring in the atmosphere transform these hydrocarbons into products that induce potentially greater adverse health effects than the emitted hydrocarbons by themselves (594).

34.4.2.2.4 Reproductive and developmental. NA

34.4.2.2.5 Carcinogenesis. NA

34.4.2.2.6 Genetic and related cellular effects studies. In the single-cell gel electrophoresis assay (SCGE or comet assay), isoprene was able to induce DNA damage in peripheral blood mononuclear cells (PBMCs) in the presence of metabolic activation. In addition, treatment of cells with the main isoprene monoepoxide induced time- and dose-dependent DNA damage in both PBMCs and human leukemia cells. The inclusion of S9 fractions from noninduced or phenobarbital-induced rats resulted in a statistically significant enhancement of isoprene genotoxicity. A different pattern was obtained by the addition of ethanol-induced S9, which appeared highly genotoxic by itself even in the absence of isoprene. Reducing the concentration of ethanol-induced S9 resulted in a considerable enhancement of isoprene genotoxicity (595).

34.4.2.2.7 Other: neurological, pulmonary, and skin sensitization. Catarrhal inflammation, subtrophic and atrophic processes in the upper respiratory tract, and deterioration of olfaction have been noted in isoprene rubber production workers. Prevalence and degree of symptoms were correlated with increased length of service (596). Occupational exposures to concentrations above the maximum permissible concentrations have allegedly resulted in CNS and cardiac alterations and subtle immunological changes (597, 598). However, these signs and symptoms may be due to a variety of other materials utilized and produced in the isoprene rubber industry (599).

34.4.2.3 Epidemiology Studies

34.4.2.3.1 Acute toxicity. NA

34.4.2.3.2 Chronic and subchronic toxicity. NA

34.4.2.3.3 Pharmacokinetics, metabolism, and mechanisms. NA

34.4.2.3.4 Reproductive and developmental. NA

34.4.2.3.5 Carcinogenesis. NA

34.4.2.3.6 Genetic and related cellular effects studies. NA

34.4.2.3.7 Other: neurological, pulmonary, and skin sensitization. In human volunteers, the average odor threshold for isoprene occurred at 10 mg/m^3, and slight irritation of the upper respiratory mucosa, larynx, and pharynx was noted at 160 mg/m^3 (579). Isoprene is also effective in reducing the tracheal mucous flow (600).

34.5 Standards, Regulations, or Guidelines of Exposure

Isoprene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). The IARC has classified

isoprene in group 2B: possibly carcinogenic to animals, based on inadequate evidence in humans and sufficient evidence in animals (332). No exposure standards have been established by OSHA or NIOSH. The occupational exposure limit in Poland is 100 mg/m^3 STEL 200 mg/m^3 TWA, and the limit in Russia is 40 mg/m^3 STEL (143).

34.6 Higher Alkadienes and Polyenes

1,3-Hexadiene (ethylbutadiene), CH_2:CHCH:$CHCH_2CH_3$, is a flammable liquid with an odor threshold of 2.0 ppm (72). *1,4-Hexadiene* (allyl allene), CH_2:$CHCH_2CH$:$CHCH_3$ and *1,5-hexadiene* (diallyl), (CH_2:$CHCH_2$)$_2$ are colorless, flammable liquids. *1,7-Octadiene* (CH_2:CH(CH_2)$_2$)$_2$, is a yellow liquid (600). Selected physical properties are given in Table 27.19.

There is very little information on the toxicologic properties of higher alkadienes. The oral LD_{50} for 1,4-hexadiene in the mouse is 150 mg/kg. Exposure of mice by inhalation to 500 ppm, 6 h/day for 2 days is able to induce micronuclei in bone marrow cells (25). For 1,7-octadiene, the oral LD_{50} in the rat is 19.7 mL/kg; the dermal LD_{50} is 14.1 mL/kg, and the saturated vapor causes death in 15 min. It is moderately irritating to the rabbit skin and produces low corneal injury (601).

The alkatrienes or triolefins are also named *cumulenes*, after *cumulene*, which is the simplest compound of the series. Higher homologues of this class are *squalene* ($C_{30}H_{48}$), *lycopene*, and *carotenes* ($C_{40}H_{60}$). Selected physical properties are given in Table 27.19.

The alkatrienes occur naturally in animals, plants, and lower organisms (63). Therefore, their toxicity at low concentrations is negligible. The oral LD_{50} for squalene in mice is 5 g/kg, and the intravenous LD_{50} is 1800 mg/kg (25). The cocarcinogenic properties of squalene have been investigated. Squalene showed only borderline cocarcinogenic activity in mice exposed to 7,12-dimethylbenz[*a*]anthracene, and inhibited benzo[*a*]pyrene carcinogenicity completely in mice (279, 295). No case reports of excess carotene intake associated with congenital defects have been found; symptoms of hypervitaminosis A with excess carotene intake have not been found (602).

ALKYNES

The presence of a triple covalent bond in the carbon chain gives rise to the compounds called *alkynes*. They have the generic formula C_nH_{2n-2}. Physical properties for selected alkynes are listed in Table 27.25.

The alkynes do not exert any acute local toxicity. The lower members are anesthetics and cause CNS depression. They are practically nonirritating to the skin, but cause pulmonary irritation and edema at very high concentrations. The higher molecular weight members can be aspirated into the lungs when ingested (8).

35.0 Acetylene

35.0.1 CAS Number

[*74–86-2*]

35.0.2 Synonyms

Ethyne, narcylen, narcilene, ethine, ethenylene, welding gas

35.0.3 Trade Names

NA

Table 27.25. Physicochemical Properties of Alkanes

Compound	Molecular Formula	Molecular Weight	Boiling Point (°C)	Melting Point (°C)	Density (mg/cm^3) (at °C)	Refractive Index n_D	Solubility	Flash Point (°C)	Flammability Limits (%)
Acetylene	C_2H_2	26.02	−84 (subl. pt.)	−80.8 (trip. pt.)	0.337 (25)	–	w 2, al 2, ac 3, bz 3	−17.7 (closed cup)	2.5–100.0
Propyne	C_3H_4	40.07	−23.2	−103	0.607 (25)	1.3863 (−40)	w 2, al 4, bz 3, ch 3	–	2.1–12.5
3-Methylbutyne	C_5H_8	68.12	26.3	−89.7	0.6660 (20)	1.3723 (20)	w 1, al 5, et 5	–	–
1-Buten-3-yne	C_4H_4	52.08	5.1	–	0.7094 (0)	1.4161 (1)	w 1, bz 3	–	21.0–100.0
1,6-Heptadiyne	C_7H_8	92.14	112.0	−85.0	0.8164 (17)	1.4510 (17)	w 1, bz 3, aa 3	–	–
1-Decyne	$C_{10}H_{18}$	138.25	174.0	−44.0	0.7655 (20)	1.4265 (20)	w 1, al 3, et 3, os 3	–	–

Molecular formula, in Hill notation; molecular weight, relative molar mass; density, mass per unit volume in g/cm^3 at the temperature indicated in parentheses; refractive index, at the temperature indicated in parentheses, unless otherwise indicated, all values refer to a wavelength of 589 nm; solubility, solubility in common solvents (w, water; al, ethanol; et, ethyl ether; ac, acetone; bz, benzene; ch, chloroform; ct, carbon tetrachloride; aa, acetic acid; pe, petroleum ether; os, organic solvents) on a relative scale: 1 = insoluble, 2 = slightly soluble, 3 = soluble, 4 = very soluble, 5 = miscible, 6 = decomposes; flammability limits, explosive limits (in percent by volume) at ambient temperature and pressure; subl. pt., sublimation point; trip. pt., triple point.

35.0.4 Molecular Weight

26.02

35.0.5 Molecular Formula

$CH_3{:}CH_3$

35.0.6 Molecular Structure

35.1 Chemical and Physical Properties

35.1.1 General

Acetylene, C_2H_2, is a colorless, highly flammable, and explosive gas. Its vapor pressure is 3.04×10^4 Torr at 16.8°C, and its specific gravity is 0.65. Acetylene has been detected in the air near industrial, urban, and suburban areas (8, 99). Selected physical properties are given in Table 27.25.

35.1.2 Odor and Warning Properties

Acetylene has a faint, ethereal odor; commercial-grade acetylene has a garlic-like odor (46). The odor threshold for acetylene is 657.2 mg/m^3 (29).

35.2 Production and Use

Acetylene is produced by thermal cracking of hydrocarbons. The most widely used method for producing acetylene is from calcium carbide and occasionally contains phosphine and arsine as impurities (354). These impurities account for the etheral to garlic-like odor and its secondary toxic effects (603, 604). Acetylene is highly reactive and forms explosive mixtures with oxygen, chlorine, and fluorine. When heated, it undergoes explosive, exothermic reactions (143). An important industrial raw material, acetylene is used to produce solvents and alkenes, which, in turn, serve as monomers in plastic production (251). It is also utilized in brazing, cutting, flame scarfing, and metallurgical heating and hardening, and in the glass industry (603). In optometry, it is a component in contact lens coatings (605). Like ethylene, acetylene is used to ripen fruit and mature trees or flowers (606). In the early 1920s, acetylene was used as an anesthetic (607).

35.3 Exposure Assessment

35.3.1 Air

Gas chromatography equipped with a flame ionization detector may be used to detect acetylene in the atmosphere (608). A toxic gas detector system for on-the-spot readings can be used to determine the concentration in air. A color stain is produced in the detector tube, whose length provides the concentration of the sample being measured (369).

35.4 Toxic Effects

35.4.1 Experimental Studies

35.4.1.1 Acute Toxicity. Mammals have shown tolerance to acetylene at 10%, intoxication at 25%, and death at 50% in 5–10 min (609). Rodents exposed to 25%, 50%, or 80% acetylene in oxygen for 1–2 h daily, up to 93 h, showed no organ weight changes or cellular injuries (610). Rats exposed to a 900,000 ppm acetylene concentration developed respiratory failure after 2 h of administration (355). Exposure to 500,000 ppm acetylene in oxygen has a rapid anesthetic effect in dogs; exposure levels of 700,000–800,000 ppm slightly increase blood sugar (611, 612). It has also been shown that the anesthetic effect in dogs has a rapid recovery and no after effects (613).

35.4.1.2 Chronic and Subchronic Toxicity. NA

35.4.1.3 Pharmacokinetics, Metabolism, and Mechanisms NA

35.4.1.4 Reproductive and Developmental. NA

35.4.1.5 Carcinogenesis. NA

35.4.1.6 Genetic and Related Cellular Effects Studies NA

35.4.1.7 Other: Neurological, Pulmonary, and Skin Sensitization. A rise in blood pressure was noted in cats exposed to an 80% acetylene–oxygen mixture (614). Exposure of rats, mice, guinea pigs, rabbits, and dogs to anesthetic concentrations of acetylene showed no evidence of cellular injury to the parenchymatous cells of the heart, lungs, liver, kidneys, or spleen (615).

35.4.2 Human Experience

35.4.2.1 General Information. Acetylene is nontoxic below its lower explosive limit of 2.5%. It produces varying degrees of temporary and reversible narcosis when administered with oxygen in concentrations of $\geq$100,000 ppm, and at higher levels it is a simple asphyxiant (609, 610). Acetylene was used as an anesthetic, because it afforded immediate recovery without aftereffects (355). However, due to its explosive characteristics, it now finds only limited application as an anesthetic. It causes CNS depression at slightly higher concentrations than for ethylene (355).

35.4.2.2 Clinical Cases

35.4.2.2.1 Acute toxicity. Humans can tolerate an exposure of 100 mg/L for 30–60 min (369). Marked intoxication occurs at 20%, incoordination at 30%, and unconsciousness at 35% in 5 min. There is no evidence that tolerable levels have any deleterious effects on health (8, 610), although two deaths and a near-fatality at 40% have been recorded, which occurred during acetylene manufacturing using calcium carbide (394, 616, 617). The intoxications have been attributed to the phosphine and arsine impurities in crude acetylene (143). In another case, a 17 year old high school student inhaled 100% acetylene, and experienced nausea and bilateral lower limb numbness several hours later. In the evening his symptoms worsened, dyspnea followed. On admission chest radiography and CT scanning revealed peripheral ground-glass opacity, patchy infiltrate and Kerley's B line in the right lung fields, and bilateral pleural effusion. The case was diagnosed as acute eosinophilic pneumonia (AEP) (618).

35.4.2.2.2 Chronic and subchronic toxicity. NA

35.4.2.2.3 Pharmacokinetics, metabolism, and mechanisms. NA

35.4.2.2.4 Reproductive and developmental. In an epidemiological study conducted in Russia, the health status of an unknown number of pregnant women chemists who produced acetylene-vinyl acetate from 1972 to 1975 was compared to that of 84 pregnant women that did not work with chemicals. Twenty percent of the chemists were "sick," compared to 8% of the controls ($p < 0.001$). The nature of the illnesses was not mentioned; however, they were listed as being associated with temporary disability to work related to pathology of the pregnancy. No chemicals were identified in the study other than acetylene-vinyl acetate (619).

35.4.2.2.5 Carcinogenesis. A link between use of acetylene and cancer has not been established. Acetylene exposure did not appear to be a risk factor for mortality from lung cancer in a case-referent study in which exposure to chemicals in an acetylene and phthalic anhydride plant accounted for one third of the total number of lung cancer deaths (620). In a study conducted on 370 workers involved in acetylene cylinder manufacture between 1935 and 1975, an excess of deaths from lung cancer, and cancer of the stomach and pancreas was observed. However, an association between exposure to acetylene and lung cancer was not identified (621).

35.4.2.2.6 Genetic and related cellular effects studies. In an Ames test employing three strains of *S. typhimurium* (TA97, TA98, TA100), acetylene did not induce mutations in both the absence and presence of metabolic activation (622).

35.4.2.2.7 Other: neurological, pulmonary, and skin sensitization. An acetylene–oxygen mixture administered as an anesthetic at an initial concentration of 70% (700,000 ppm) did not appear to have any effect on either the liver or the kidney (623). Acetylene produced no untoward hematological effects when administered in anesthetic concentrations (624). It has not been shown to cause any abnormal effects on heart function (623), although acetylene–oxygen mixtures (750,000–800,000 ppm) produced an increase in blood pressure during anesthesia (625). A case of a welder who developed urticaria and asthma while welding a railroad rod with an acetylene torch has been reported. Symptoms appeared after 15 min of exposure to acetylene welding. The lesions lasted for 6 h and dyspnea lasted for 1 h after cessation of exposure (626).

35.5 Standards, Regulations, or Guidelines of Exposure

Acetylene is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). The NIOSH REL for acetylene is 2500 ppm (2662 mg/m^3) as a ceiling (608), whereas OSHA treats acetylene as a simple asphyxiant. The presence of contaminants in acetylene is an important consideration because they may pose a greater threat to human health than acetylene alone. A TLV–TWA has been developed by ACGIH (607). Acetylene is considered an asphyxiant in Australia, Belgium, Hungary, The Netherlands, and the United Kingdom (25). The occupational exposure limit in the Arab Republic of Egypt is 1 ppm (14 mg/m^3) TWA, and 1000 ppm (1080 mg/m^3) TWA in Switzerland (25).

36.0 Propyne

36.0.1 CAS Number

[*74–99-7*]

36.0.2 Synonyms

Methylacetylene, allylene, 1-propyne, methyl acetylene (propyne)

36.0.3 Trade Names

NA

36.0.4 Molecular Weight

40.07

36.0.5 Molecular Formula

$CH_3C...CH$

36.0.6 Molecular Structure

36.1 Chemical and Physical Properties

36.1.1 General

Propyne, C_3H_4, is a colorless, highly flammable, and explosive gas. Its vapor pressure is 3800 Torr at 20°C, and its specific gravity is 0.7062. Sources of propyne emissions to the atmosphere include automobile and turbine exhaust, biomass and polymer combustion, petroleum manufacturing, and tobacco smoke (63). Selected physical data are given in Table 27.25.

36.1.2 Odor and Warning Properties

Propyne has a sweet odor (41).

36.1.3 Production and Use

Propyne is produced by thermal or catalytic pyrolysis of propene. Like acetylene, propyne is used as a welding torch fuel, as a specialty fuel, and chemical intermediate (63).

36.2 Exposure Assessment

36.2.1 Air

NA

36.2.2 Background Levels

NA

36.2.3 Workplace Methods

Propyne may be collected in a gas-sampling bag and analyzed by gas chromatography with flame ionization detector (627).

36.2.4 Community Methods

NA

36.2.5 Biomonitoring/Biomarkers

Gas chromatography/mass spectrometry has been used to measure propyne in exhaled air (66).

36.3 Toxic Effects

36.3.1 Experimental Studies

36.3.1.1 Acute Toxicity. Rats exposed to 42,000 ppm propyne became hyperactive and within 7 min were lethargic and ataxic, and after 95 min the animals were completely anesthetized. When the exposure was terminated at the end of 5 h, most of the animals recovered completely within 40 min. Death occurred after 6 h of exposure. Edema and alveolar hemorrhage were observed in animals killed at termination of the single exposure, and rats sacrificed 9 days postexposure showed bronchiolitis and pneumonitis (628).

36.3.1.2 Chronic and Subchronic Toxicity. Rats and dogs were exposed to an average concentration of 28,700 ppm propyne for 6 h/day, 5 days/week for 6 months. Mortality was observed in rats, but no dogs died. Signs of toxicity were excitement, ataxia salivation, mydriasis, and tremors. The dogs experienced convulsions three times during the period of exposure. Weight gain was reduced in animals of both species, and pathology indicated pulmonary irritation (628).

36.3.1.3 Pharmacokinetics, Metabolism, and Mechanisms. NA

36.3.1.4 Reproductive and Developmental. NA

36.3.1.5 Carcinogenesis. NA

36.3.1.6 Genetic and Related Cellular Effects Studies. Propyne is mutagenic in *S. typhimurium* and *E. coli* using a gas exposure method (393).

36.3.2 Human Experience

36.3.2.1 General Information. Propyne is 18 times as potent as acetylene in causing CNS depression (355). It is a simple anesthetic and in high concentrations is an asphyxiant (14).

36.3.2.2 Clinical Cases

36.3.2.2.1 Acute toxicity. A 33 year old man died after intentionally inhaling a gaseous mix of propyne and propadiene (allene) commonly known as MAPP. A comprehensive toxicological analysis revealed only a trace of diphenhydramine in the liver and 0.02 mg/L of morphine in the urine. Analysis of blood by headspace gas chromatography (HS-GC) detected two unknown peaks. These were determined to be the components of MAPP gas (629).

36.3.2.2.2 Chronic and subchronic toxicity. NA

36.3.2.2.3 Pharmacokinetics, metabolism, and mechanisms. Propyne has been detected in exhaled air at 0.81 mg/h in nonsmokers, and at 1.1 and 2.3 mg/h in smokers (66).

Table 27.26. Occupational Exposure Limits for Propyne in the United States[a]

Exposure Limits	OSHA PEL	NIOSH REL	ACGIH TLV
Time-weighted average	1000 ppm (1650 mg/m^3)	1000 ppm (1650 mg/m^3)	A TLV–TWA has been developed by ACGIH
Short-term exposure limit	–	–	–
Ceiling limit	–	–	–

[a] OSHA and ACGIH, 8 h TWA; NIOSH, 10 h TWA.

From Ref. (25).

Table 27.27. Occupational Exposure Limits for Propyne in Different Countries

Country	Exposure Limit
Australia	TWA 1000 ppm (1650 mg/m^3); STEL 1250 ppm
Belgium	TWA 1000 ppm (1650 mg/m^3); STEL 1250 ppm (2050 mg/m^3)
Denmark	TWA 1000 ppm (1650 mg/m^3)
Finland	TWA 1000 ppm (1650 mg/m^3); STEL 1250 ppm (2065 mg/m^3)
France	TWA 1000 ppm (1650 mg/m^3)
Germany	TWA 1000 ppm (1650 mg/m^3)
Ireland	TWA 1000 ppm (1650 mg/m^3)
The Netherlands	TWA 1000 ppm (1650 mg/m^3)
The Philippines	TWA 1000 ppm (1650 mg/m^3)
Poland	TWA 1500 mg/m^3; STEL 2000 mg/m^3
Switzerland	TWA 1000 ppm (1650 mg/m^3)
Turkey	TWA 1000 ppm (1650 mg/m^3)

From Ref. (25).

36.4 Standards, Regulations, or Guidelines of Exposure

Propyne is on the EPA TSCA Chemical Inventory and the Test Submission Data Base (63). The IDLH concentration determined by NIOSH is 1700 ppm (based on 10% of the lower explosive limit) (41). The occupational exposure limits for propyne in the United States are listed in Table 27.26, and the international standards are presented in Table 27.27.

36.5 Higher Alkynes

Practically no toxicity data are available on butynes and above. Selected physical properties are given in Table 27.25 for *3-methylbutyne*, *1-buten-3-yne*, *1,6-heptadiyne*, and *1-decyne*.

3-Methylbutyne (isopentyne), $(CH_3)_2CHC{:}CH$, causes loss of righting reflexes in mice at 150 mg/L and is fatal at 250 mg/L (123, 181). The C6–C10 alkynes, when ingested, may present aspiration hazards (153). The taste threshold of 1-decyne is 0.1 ppm, and odor recognition occurs at 4 ppm in air (72). 1-Buten-3-yne, $CH_2{:}CHC{:}CH$, is a colorless gas or liquid used as an intermediate in the manufacture of neoprene and for various organic syntheses (63). The 2 h LC_{50} in mice by inhalation is 97,200 mg/m^3 (25). For 1,6-heptadiyne, $CH{:}C(CH_2)C{:}CH$, the oral LD_{50} is 2300 mg/kg in the rat, 2620 mg/kg in the rabbit, and 3830 mg/kg in the dog (630).

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