Isopropylamine
75-31-0

Review of Toxicological Literature
(Update of March 1997 Review)

Prepared for

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EXECUTIVE SUMMARY

Isopropylamine was nominated for testing based on its high production volume, ubiquitous natural occurrence, and the lack of chronic study data.

Isopropylamine can be produced from the corresponding alcohol by reacting with ammonia in the presence of a dehydrating catalyst, from the chloride by reacting with ammonia under pressure, from acetone and ammonia, or from the acetone oxime. In the U.S., about 50,000 tons (45,000 Mg) of isopropylamine are produced annually. U.S. producers include Air Products and Chemicals, Inc. (Pace, Florida and St. Gabriel, Louisiana), Elf Atochem North America, Inc. (Riverview, Michigan), and Hoechst Celanese Corp. (Bucks, Alabama).

Isopropylamine is used as a dehairing agent; as a solvent; as an intermediate in the production of insecticides, herbicides, bactericides, pharmaceuticals, dyes, and rubber accelerators; for the production of surface active agents, including dodecylbenzenesulfonic acid isopropylamine salt; and for the purification of penicillin and streptomycin.

Isopropylamine is present in certain plants, foods, and in white wines. It is released into ambient air from cigarette smoke, effluents, and decomposing animal manure. Isopropylamine exists mainly in protonated form in aquatic environments, and based on its miscibility in water, absorption and bioconcentration are not expected to be important fate processes. It should rapidly degrade in soil and water. Isopropylamine should rapidly evaporate from dry surfaces, but is considered to have only minor atmospheric importance.

Occupational exposure to isopropylamine occurs via dermal contact or inhalation at sites where it is manufactured or used. Atmospheric occupational exposures have also been documented for farm and barnyard workers. The 1983 National Occupational Exposure Survey concluded that the total number of U.S. workers exposed to isopropylamine was 8134 (3173 female workers). Non-occupational exposure to isopropylamine occurs mainly via passive or active inhalation of cigarette smoke. Non-occupational exposures may also occur from ingestion of certain foods (e.g., pork, beef) and white wine, and of drugs that contain a $(CH_3)_2CHN$-moiety. Examples of such drugs are propranolol (a ß-receptor blocking drug, Inderal®) and pindolol (Visken®). The EPA's Occupational Exposure Limit (OEL) and action level for isopropylamine are 12000 µg/m^3 (200 µmol/m^3) and 34 mg/L water (570 µmol/L), respectively.

The acute toxicity of isopropylamine in humans has been evaluated. Brief 10-20 ppm inhalation exposures of humans cause nose and throat irritation. Acute occupational exposures may cause temporary visual disturbances. Liquid isopropylamine can produce eye burns and permanent visual impairment, or skin irritation and dermatitis. The estimated fatal dermal dose for humans is 20 g (3 x 10^5 _ mol).

The absorption, metabolism, and toxicokinetics of isopropylamine are not well evaluated. Isopropylamine is thought to be absorbed from the gut and respiratory tract and through the skin. It is probably oxidized to acetate and ammonia via the action of monoamine oxidases. The half-life of isopropylamine in male Wistar rats after intravenous (i.v.) injection is approximately 2-4 hours, in dogs 2.4 hours. After intraperitoneal (i.p.) administration of isopropylamine hydrochloride, 96.7% is excreted in urine as isopropylamine.

Based on acute toxicity tests, the lowest oral LD_{50} reported for various mammalian species is 68 mg/kg (1.2 mmol/kg) for cats, < 100 mg/kg (2000 mmol/kg) for rats, 680 mg/kg (12 mmol/kg) for rabbits, 2200 mg/kg (37 mmol/kg) for mice, and 2700 mg/kg (46 mmol/kg) for guinea pigs. The 40-minute inhalation LC_{Lo} for mice is 7000 ppm (17200 mg/m^3), while the 4-hour inhalation LC_{50} for rats is 4000 ppm (9800 mg/m^3). The dermal and subcutaneous LD_{50} for rabbits is 380 mg/kg (6.4 mmol/kg) and 550 mg/kg (9.3 mmol/kg), respectively.

Acute and subacute exposure studies in various species by a variety of exposure routes have been conducted. In rats, oral administration causes toxic effects, including ataxia, labored breathing, and convulsions. Inhalation changes respiratory frequency in mice, and causes labored breathing, discharges around the nose, mouth, and eyes, hypoactivity, and eye opacity in rats. Dermal application of isopropylamine to rabbits or guinea pigs causes severe skin irritation, while ocular application to rabbits produces severe irritation. In rats, i.p. injection induces ataxia and unconsciousness. In dogs, i.v. administration causes cardiovascular changes and intraarterial administration causes vascular changes. Rats exposed to isopropylamine by inhalation for one month experienced dose-dependent irritation of the mucous membrane, corneal opacity of the eye, and degenerative changes in the nasal mucous membrane epithelium.

Only very limited data are available on the reproductive and teratogenic effects of isopropylamine. Inhalation exposure of pregnant Sprague-Dawley rats to isopropylamine on days 6-15 of gestation was neither embryotoxic, fetotoxic, nor teratogenic. The dams showed signs of exposure concentration related acute toxicity.

Only a few studies have been conducted to evaluate the genetic toxicity of isopropylamine. Isopropylamine was not mutagenic in *Salmonella typhimurium* in the presence or absence of metabolic activation. *In vitro*, isopropylamine did not induce DNA repair synthesis in cultured rat hepatocytes or chromosomal aberrations in mitogen-stimulated human lymphocytes.

No data on chronic exposure, carcinogenicity, or immunotoxicity were found for isopropylamine.

TABLE OF CONTENTS

TABLES

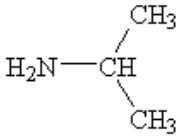
1.0 BASIS FOR NOMINATION

The nomination of isopropylamine for carcinogenicity testing is based on high production volume, ubiquitous natural occurrence, and lack of chronic study data.

2.0 CHEMICAL PROPERTIES

2.1 Chemical Identification

Isopropylamine



Isopropylamine (C_3H_9N, CASRN 75-31-0, mol. wt. = 59.11) is also called:

2-Propanamine (9CI)
2-Amino propane
2-Aminopropane
Isopropylamine, mono
1-Methylethylamine
Monoisopropylamine
Propane, 2-amino-
2-Propylamine
sec-Propylamine
Propylamine (iso-)

Isopropylamine has the designation for shipping UN 1221.

2.2 Physical-Chemical Properties

Property	Information	Reference
Color	Colorless	Budavari (1996)
Physical State	Liquid (Gas above 33°C)	Budavari (1996); Ludwig (1994)
Melting Point, °C	-95.2	Weast and Astle (1980)
Boiling Point, °C	32.4	Weast and Astle (1980)
Density at 20°C, g/mL	0.6891	Weast and Astle (1980)
Odor	Ammonia odor	Budavari (1996)
Odor Threshold, mg/m^3	0.504	HSDB (1996)

Property	Information	Reference
Solubility:		
Water at 20°C	Miscible	Budavari (1996)
Organic Solvents	Miscible in: ethanol and diethyl ether	Budavari (1996); Weast and Astle (1980)
	Soluble in: acetone, benzene, and chloroform	
Vapor pressure, mm Hg, at 25°C	579.6 (7,7270 Pa)	Ludwig (1994); HSDB (1996)
Partition Coefficient, log P_{ow}, at 25°C	-0.03	Verschueren (1983; cited by BASF, 1995)
Auto Flammability, °C, at 1013 kPa	402	Safety Data Sheet Elf Atochem (March 1988; cited by BASF, 1995

Isopropylamine is flammable and reacts with strong acids, strong oxidizers, aldehydes, ketones, and epoxides.

In the vapor state, 1 ppm = 2.46 mg/m^3 air (Ludwig, 1994). It is highly volatile and forms explosive mixtures with air (lower explosive limit 2%, upper explosive limit 10.4%) (OHMTADS, 1972).

3.0 PRODUCTION PROCESSES AND ANALYSES

Isopropylamine can be produced from the corresponding alcohol by reacting with ammonia in the presence of a dehydrating catalyst, or from the chloride by reacting with ammonia under pressure. Isopropylamine can also be produced from acetone and ammonia or from the acetone oxime (HSDB, 1989; cited by Tinsley, 1990).

4.0 PRODUCTION AND IMPORT VOLUMES

Walle et al. (1972) reported Eastman Organic Chemicals (Rochester, NY) as the supplier for the isopropylamine used in their bioassay.

SRI International (1996) listed Air Products and Chemicals, Inc. (Pace, Florida and St. Gabriel, Louisiana), Elf Atochem North America, Inc. (Riverview, Michigan), and Hoechst Celanese Corp. (Bucks, Alabama) as U.S. producers of isopropylamine. About 100 million pounds (50,000 tons; 45,000 Mg) of isopropylamine are produced annually in the U.S. (NIOSH, 1997).

5.0 USES

Isopropylamine is used as a dehairing agent, as a solvent, and as an intermediate in the production of insecticides, herbicides (e.g., prometone, prometryne, propazine, and sancap), bactericides, pharmaceuticals, dyes, and rubber accelerators (Beard and Noe, 1981; HSDB, 1989; cited by Tinsley, 1990). It is used in the paints, lacquers, and varnishes industry (BASF, 1995). In addition, it is used for the production of surface active agents, including dodecylbenzenesulfonic acid and isopropylamine salt, and for the purification of penicillin and streptomycin (HSDB, 1996).

6.0 ENVIRONMENTAL OCCURRENCE

6.1 Occurrence

Isopropylamine occurs naturally in tobacco leaves, soybeans, and corn, and is released during the decomposition of these plants (HSDB, 1966). In addition, it occurs in certain foods (HSDB, 1996), such as pork (Patterson and Mottram, 1974 abstr.) and boiled beef (Golovnya et al., 1979). Small amounts of isopropylamine (0.10 mg/L; 2 μmol/L) have also been detected in white wines, but not in red or rose wines (Busto et al., 1996).

Isopropylamine is released into ambient air from cigarette smoke, and may be released from effluents at sites where it is produced or used as a chemical intermediate or solvent (HSDB, 1996). It is also released from decomposing animal manure (HSDB, 1996) and has been reported to be released from cattle feedyards at concentrations equal to approximately 1% of released ammonia (Mosier et al., 1973; Porter et al., 1975).

6.2 Persistence

Isopropylamine has a dissociation constant (pk_a) of 10.6, so it exists mainly in the protonated form in aquatic environments. It is not expected to volatilize from natural waters, but may do so under extreme alkaline conditions (Henry's Law constant = 1.12×10^{-5} atm m^3/mol) (HSDB, 1996). Based on its miscibility in water (i.e., distribution coefficient [log k_{ow}] = 0.26), adsorption and bioconcentration are not expected to be important fate processes. This is supported by low estimates for the bioconcentration factor (log BCF = 0.43) and soil adsorption coefficient (k_{oc} = 33). However, since cationic molecules generally have a greater affinity for organic carbon and clays than do their neutral forms, isopropylamine may bind to soil and partition from the water column to sediments and suspended solids. Based on a single aerobic screening test in which activated sludge was able to completely degrade isopropylamine within two days, it should degrade rapidly in soil and water (HSDB, 1996).

Based on its vapor pressure (579.6 mm Hg at 25˚C), isopropylamine is expected to rapidly evaporate from dry surfaces, especially when it occurs in high concentrations, as it would in spill situations. In ambient air, isopropylamine exists almost entirely in the vapor phase and is expected to react with photochemically produced hydroxyl radicals (estimated half life = 10 hours). Precipitation and dissolution of isopropylamine from clouds may occur, but the short atmospheric residence time of isopropylamine implies that these processes are only of minor importance (HSDB, 1996).

7.0 HUMAN EXPOSURE

7.1 Occupational Exposure

Occupational exposure to isopropylamine occurs via dermal contact or inhalation at sites where it is manufactured or used. Atmospheric occupational exposures have also been documented for farm and barnyard workers (HSDB, 1996). The 1983 National Occupational Exposure Survey (RTECS, 1996) concluded that the total number of U.S. workers exposed to isopropylamine was 8134 (3173 female workers). Information on the number of U.S. workers exposed to isopropylamine is presented in **Table 7-1** by occupation, and in **Table 7-2** by industry.

Table 1. Exposure to Isopropylamine by Occupation[a]

Occupation	Number of Plants	Number of Employees	Number of Female Employees
Biological Technicians	21	686	300
Chemical Technicians	7	1822	272
Chemists, except Biochemists	17	1769	493
Engineering Technicians	4	51	4
Metal Plating Machine Operators	63	2365	1252
Mixing and Blending Machine Operators	123	245	0
Technicians, N.E.C.	3	1196	852
TOTAL	238	8134	3173

Abbreviations: N.E.C. = not elsewhere classified
[a]NOES, 1983; cited by RTECS, 1996.

Table 2. Exposure to Isopropylamine by Industry[a]

Industry	Number of Plants	Number of Employees	Number of Female Employees
Business Services	24	3591	766
Chemicals and Allied Products	148	983	304
Instruments and Related Products	3	2954	1801
Trucking and Warehousing	61	607	303
TOTAL	236	8135	3174

[a]NOES, 1983; cited by RTECS, 1996
(The inconsistencies in total numbers of plants and employees shown in Table 7-1 and Table 7-2 are due to the cited source.)

7.2 Non-Occupational Exposure

Non-occupational exposure to isopropylamine occurs mainly via passive or active inhalation of cigarette smoke. Non-occupational exposures may also occur from ingestion of certain foods (e.g., pork, beef) and white wine (see **Section 6.1** for references), and of drugs that contain a $(CH_3)_2CHN$-moiety. Examples of such drugs are propranolol (a ß-receptor blocking drug, Inderal®) (Walle et al., 1972; Bakke et al., 1973; Walle et al., 1985) and pindolol (Visken®) (Schwarz, 1982).

8.0 REGULATORY STATUS

Isopropylamine is regulated by the Department of Transporaton (DOT) under 49 CFR 172.101, which states that isopropylamine is classified as a hazard 3 chemical for shipping purposes (RTECS, 1996).

Isopropylamine is produced, either as an intermediate or final product, under process units regulated by the Environmental Protection Agency (EPA) under 40 CFR 60.489, which sets standard of performance for equipment leaks of volatile organic compounds (VOCs) in the synthetic organic chemical manufacturing industry (SOCMI) (HSDB, 1996). All newly constructed, modified, or reconstructed SOCMI units are required to use the best demonstrated system of continuous emission reduction for equipment leaks of VOCs.

The isopropylamine salt of dodecylbenzenesulfonic acid is regulated by the Food and Drug Administration (FDA) under 21 CFR 176 as a defoaming agent used in paper and paperboard components; the isopropylamine salt may be an indirect food additive from this process.

The National Institute of Occupational Safety and Health (NIOSH) recommends a time-weighted average (TWA) of 10 ppm (30 mg/m^3) and a short-term exposure limit (STEL) of 25 ppm (75 mg/m^3) for isopropylamine. The EPA regulates an Occupational Exposure Limit (OEL) of 12000 µg/m^3 (200 µmol/m^3) and an action level of 34 mg/L water (570 µmol/L), for isopropylamine (Eklund et al., 1991). Under 29 CFR 1910.1000, the Occupational Safety and Health Association (OSHA) regulates an 8-hour TWA of 5 ppm (12 mg/m^3) for general industry and a 15-minute STEL of 10 ppm (24 mg/m^3) for isopropylamine. Under 29 CFR 1915.1000, the OSHA-regulated 8-hour TWA for shipyards is also 5 ppm (12 mg/m^3), and 29 CFR 1926.55 mandates the same 8-hour TWA for construction.

9.0 TOXICOLOGICAL DATA

Summary: Brief 10-20 ppm inhalation exposures of humans cause nose and throat irritation. Occupational exposures may cause temporary visual disturbances. Liquid isopropylamine can produce eye burns and permanent visual impairment, or skin irritation and dermatitis. The estimated fatal dermal dose for humans is 20 g (3 x 10^5 _ mol).

Isopropylamine is thought to be absorbed from the gut and respiratory tract and through the skin. It is probably oxidized to acetate and ammonia via the action of monoamine oxidases. The half-life of isopropylamine in male Wistar rats after i.v. injection is approximately 2-4 hours, in dogs 2.4 hours. After i.p. administration of isopropylamine hydrochloride, 96.7% is excreted in urine as isopropylamine.

The lowest oral LD_{50} reported for various mammalian species is 68 mg/kg (1.2 mmol/kg) for cats, < 100 mg/kg (2000 mmol/kg) for rats, 680 mg/kg (12 mmol/kg) for rabbits, 2200 mg/kg (37 mmol/kg) for mice, and 2700 mg/kg (46 mmol/kg) for guinea pigs. The 40-minute inhalation LCLo for mice is 7000 ppm (17200 mg/m^3), while the 4-hour inhalation LC_{50} for rats is 4000 ppm (9800 mg/m^3). The dermal and subcutaneous LD_{50} for rabbits is 380 mg/kg (6.4 mmol/kg) and 550 mg/kg (9.3 mmol/kg), respectively.

In rats, oral administration causes toxic effects, including ataxia, labored breathing, and convulsions. Inhalation changes respiratory frequency in mice, and causes labored breathing, discharges around the nose, mouth, and eyes, hypoactivity, and eye opacity in rats. Dermal application of isopropylamine to rabbits or guinea pigs causes severe skin irritation, while ocular application to rabbits produces severe irritation. In rats, i.p. injection induces ataxia and unconsciousness. In dogs, i.v. administration causes cardiovascular changes and intraarterial administration causes vascular changes.

Rats exposed to isopropylamine by inhalation for one month experienced dose-dependent irritation of the mucous membrane, corneal opacity of the eye, and degenerative changes in the nasal mucous membrane epithelium.

No data were found on the toxic effects from chronic administration of isopropylamine.

Inhalation exposure of pregnant Sprague-Dawley rats to isopropylamine at 5-1000 mg/m^3 (0.8-20 mmol/m^3) on days 6-15 of gestation was not embryotoxic, fetotoxic, or teratogenic. The dams showed signs of exposure concentration related acute toxicity.

No data were found on the carcinogenicity of isopropylamine.

Isopropylamine, at concentrations up to 10,000 µg/plate (169 µmol/plate), was not mutagenic in *Salmonella typhimurium* in the presence or absence of metabolic activation. *In vitro*, isopropylamine, at concentrations up to 3000 µM, did not induce DNA repair synthesis in rat hepatocytes. When tested on mitogen-stimulated human lymphocytes, isopropylamine, at concentrations up to 1000 µg/mL (16,920 µM), did not induce chromosomal aberrations.

No data were found on the immunotoxic effects of isopropylamine.

9.1 Human Data

Irritation of the nose and throat is known to occur after brief inhalation exposures to isopropylamine at 10 to 20 ppm (~25 to 50 mg/m^3). Workers exposed to the vapor for 8 hours have complained of visual disturbances, probably due to mild corneal edema, which usually cleared within 3 to 4 hours. Liquid isopropylamine can produce severe eye burns and permanent visual impairment. It also acts as a skin irritant, possibly causing dermatitis as a result from repeated exposures (HSDB, 1996; Beard and Noe, 1981). The estimated fatal dermal dose is 20 g (3 x 10^5 µmol) (Dreisbach and Robertson, 1987).

9.2 General Toxicology

9.2.1 Chemical Disposition, Metabolism, and Toxicokinetics

Isopropylamine is thought to be readily absorbed from the gut and respiratory tract and is efficiently absorbed through the skin (Beard and Noe 1981; cited by Tinsley, 1990).

Although no in-depth metabolic studies on isopropylamine were located, Tipton et al. (1980; cited by Tinsley, 1990) hypothesized that isopropylamine is oxidized to acetone and ammonia via the action of monoamine oxidases.

In mongrel dogs, isopropylamine was distributed rapidly into tissue compartments after i.v. administration. The tissue/plasma ratios ranged from 1.8 in the atrium to 16.7 in the renal

medulla. A half-life of 2.4 hours was measured in plasma during the elimination phase (Privitera et al., 1982).

The half-life of isopropylamine administered to male Wistar rats by i.v. injection was approximately 2 to 4 hours. Following i.p. injection of a single dose of 0.3 mg ^{14}C-isopropylamine hydrochloride, an average of 96.7% of the administered radioactivity was excreted in urine, 1.2% in feces and 1.0% in expired air. In urine, 100% of the excreted radioactivity was identified as isopropylamine (Bakke et al., 1973).

9.2.2 Acute Exposures

The LD_{50} and LD_{Lo} data for isopropylamine are presented in **Tables 3a** and **3b,** respectively; other acute exposure data are summarized in **Table 4.**

Table 3a. LD_{50} Data for Isopropylamine

Route	Species (sex and strain)	LD_{50}	Reference
oral	mice (sex and strain n.p.)	2200 mg/kg (37 mmol/kg)	Gigiena i Sanitariya (1980; cited by RTECS, 1996)
	rats (sex and strain n.p.)	< 100 mg/kg (< 2 mmol/kg)	Eastman Kodak (1953)
	rats (male, adult Sprague- Dawley)	111 mg/kg (1.88 mmol/kg)	Monsanto (1985a)
	rats (female, adult Sprague-Dawley)	126 mg/kg (2.13 mmol/kg)	Monsanto (1985a)
	rats (sex and strain n.p.)	820 mg/kg (14 mmol/kg)	Union Carbide (1971; cited by RTECS, 1996)
	guinea pigs (sex and strain n.p.)	2700 mg/kg (46 mmol/kg)	Gigiena i Sanitariya (1980; cited by RTECS, 1996)
	rabbits (sex and strain n.p.)	680 mg/kg (12 mmol/kg) killed 2/2	BASF Test (1960, cited by BASF, 1995)
	rabbits (sex and strain n.p.)	820 mg/kg (14 mmol/kg)	Smyth et al. (1951; cited by Beard and Noe, 1981)
	rabbits (sex and strain n.p.)	3200 mg/kg (54 mmol/kg)	Gigiena i Sanitariya (1980; cited by RTECS, 1996)
	cats (sex and strain n.p.)	68-340 mg/kg (1.2-5.8 mmol/kg) killed 2/2	BASF Test (1960, cited by BASF, 1995)
inhalation	rats (strain n.p.)	9800 mg/m^3 (170 mmol/m^3)	Smyth et al. (1951; cited by Beard and Noe, 1981); NCI (1974; cited by RTECS, 1996)
dermal	rat (sex and strain n.p.)	> 400 mg/kg (> 6.77 mmol/kg)	BASF AG (1993 Abteilung Toxikologie 92:360; cited by BASF, 1995)

Route	Species (sex and strain)	LD_{50}	Reference
	guinea pigs (sex and strain n.p.)	< 5 cm^3/kg	Eastman Kodak (1953)
	rabbits (sex and strain n.p.)	0.55 mL/kg (380 mg/kg; 6.4 mmol/kg)	Smyth et al. (1951; cited by Beard and Noe, 1981); NCI (1974; cited by RTECS, 1996)
i.p.	mice (sex and strain n.p.)	34 mg/kg (0.58 mmol/kg)	BASF AG (1960, Abteilung Toxikologie VI:391; cited by BASF, 1995)
	rats (sex and strain n.p.)	< 50 mg/kg (< 800 µmol/kg)	Eastman Kodak (1953)
s.c.	rabbits (sex and strain n.p.)	550 mg/kg (9.3 mmol/kg)	NCI (1974; cited by RTECS, 1996)

Abbreviations: i.p. = intraperitoneal; n.p. = not provided; s.c. = subcutaneous

Table 3b. LD_{Lo} Data for Isopropylamine

Route	Species (sex and strain)	LD_{Lo}	Reference
inhalation	mice (sex and strain n.p.)	17200 mg/m^3 (291 $mmol/m^3$)	Shell Chemical Company (unpublished report; cited by RTECS, 1996)
i.p.	rats (sex and strain n.p.)	50 mg/kg (0.84 mmol/kg)	Farmakologiya i Toksikologiya (1968; cited by RTECS, 1996)

Abbreviations: i.p. = intraperitoneal; LD_{Lo} = lowest lethal dose; n.p. = not provided

9.2.2.1 Oral Administration

In a study reported by Eastman Kodak (1953), death among rats (strain and ages not provided) administered 100-1600 mg isopropylamine/kg (1.69-27.1 mmol/kg) occurred from 3 minutes to 6 days post-exposure, while the symptoms of toxicity included weakness, ataxia, gasping, and convulsions. In another rat acute toxicity study (Monsanto, 1985a), young adult male and female Sprague Dawley rats administered a single dose of isopropylamine at 70, 118, 200, or 338 mg/kg (1.2-5.7 mmol/kg) by gavage and observed over a 15-day period exhibited mild to severe congestion of the stomach non-glandular and/or glandular mucosa. Signs of toxicity included decreased activity, staining around the nose and mouth (at all dose levels), and labored breathing at 118 and 338 mg/kg (2.0 and 5.7 mmol/kg). There were no significant findings, or changes in body weight in any of the dose groups in rats sacrificed after 15 days.

9.2.2.2 Inhalation Exposure

In male Swiss OF_1 mice exposed head-only to isopropylamine vapor at 69-197 ppm (170-490 mg/m^3; 2.9-8.3 mmol/m^3) for 15 minutes, the RD_{50} (the concentration of a sensory irritant responsible for a decrease of 50% in the respiratory frequency) was calculated to be 157 ppm (386 mg/m^3). The respiratory frequency was rapidly affected beginning at approximately 30 to 60 seconds of exposure. The recovery of respiratory frequency was also rapid; a return to pre-exposure levels occurred approximately 1 minute post-exposure (Gagnaire et al., 1989; 1993). The RD_{50} in male Swiss OF_1 mice administered 350-625 ppm (861-1540 mg/m^3; 14.6-26.0 mmol/m^3) isopropylamine for 120 minutes via tracheal cannula was 489 ppm (1200 mg/m^3). Maximal effects on respiratory frequency occurred after 120 minutes of exposure, and little, if any, recovery of respiratory frequency occurred (time period not provided).

In a 4-hour whole-body inhalation exposure study, 7-week-old Sprague-Dawley rats were exposed to isopropylamine at 5.0 or 5.1 mg/L (0.084 or 0.086 mM) and observed for 14 days (Monsanto, 1985b). During the exposure period, signs of toxicity included labored breathing, discharges around the nose and mouth, lacrimation, hypoactivity, and eye opacity (incidences not provided). During the 14-day post-exposure observation period, the incidence and severity of these toxic signs declined, but not completely.

9.2.2.3 Ocular Application

Isopropylamine produced severe irritation when applied to the eyes of rabbits (age and strain not provided) at a dose of 0.05 mg (0.00084 mmol) for 24 hours (Marhold, 1986; cited by RTECS, 1996) or for an unspecified time (AMA Arch. Indust. Hyg. Occup. Med., 1951; cited by RTECS, 1996).

In a study reported by Monsanto (1985a), young adult New Zealand White rabbits were administered a single dose of 0.1 mL (70 mg; 1 mmol) undiluted isopropylamine to the cupped conjunctival sac of the right eye (the left eye served as the control). The rabbits were observed over a 14-day period. Throughout the observation period, all rabbits showed severe redness and swelling of the conjunctivae and maximum corneal opacity. By day 14, all rabbits had developed ulcerations and eschar tissue on the cornea and/or conjunctivae.

Isopropylamine was rated 10 (most severe) on a scale of 1 to 10 for ocular irritation in rabbits. The strain and age of the rabbits, as well as the dose administered, were not provided (Grant, 1986; cited by HSDB, 1996).

9.2.2.4 Dermal Application

In guinea pigs (age and strain not provided) treated by dermal application with isopropylamine in a gauze pad soaked with 5 or 10 mL/kg (3000 or 6900 mg; 60 or 120 mmol/kg), all animals died within 1 day (Eastman Kodak, 1953). At necropsy, the entire dosed area was gray and necrotic.

Guinea pigs were treated intradermally with 0.1 mL isopropylamine (70 mg; 1 mmol) on day 1 (Elf Atochem, 1994; cited by BASF, 1995). On day 8, 0.5 mL (300 mg; 6 mmol) isopropylamine was applied dermally by occlusive dressing for 48 hours. A second dermal application of isopropylamine (0.5 mL) was administered after 12 days of no treatment. No adverse clinical signs, deaths, or cutaneous reactions were noted during the study.

Isopropylamine, administered to rabbits (age and strain not provided) in a dermal patch for 24 hours at 0.75 mg (0.013 mmol) (Marhold, 1986; cited by RTECS, 1996) or on open skin at 10 mg (0.17 mmol) (AMA Arch. Indust. Hyg. Occup. Med., 1951; cited by RTECS, 1996) resulted in severe irritation, while moderate irritation was associated with a dose of 345 mg (5.84 mmol) applied to open skin (exposure duration not provided) (Union Carbide, 1971; cited by RTECS, 1996).

A 24-hour patch application of isopropylamine at 2000 or 5000 mg/kg (33.84 or 84.59 mmol/kg, respectively) to the shaved, intact dorsal skin of young adult New Zealand White rabbits resulted at necropsy 15 days later in the appearance of hardened and thickened skin with a dark discoloration (Monsanto, 1985a). Over the observation period, no significant toxicity or changes in body weight were observed, and no internal changes were detected at necropsy. In the same report (Monsanto, 1985a), the skin of young adult male and female New Zealand White rabbits developed severe erythema and edema following a 4-hour dermal application of 0.5 mL (300 mg; 6 mmol) undiluted isopropylamine to semi-occluded skin and a 24-hour dermal application to fully occluded skin (for occluded skin, a bandage or dressing covers the skin and excludes it from air, preventing loss of the test substance by evaporation). Dark discoloration of semi- and fully occluded sites began 30 minutes post-exposure and persisted for the entire 7-day observation period. Eschar formation (a thick, coagulated scab) was observed in all rabbits at both semi-occluded and fully occluded sites at 24 and 48 hours post-exposure, and persisted throughout the observation period.

9.2.2.5 Intraperitoneal Injection

In rats (strain and age not provided) treated with doses ranging from 50 to 800 mg/kg (0.84-14 mmol/kg), death occurred 2 to 48 hours post-exposure; signs of toxicity included weakness, ataxia, and unconsciousness (Eastman Kodak, 1953).

9.2.2.6 Intravenous Injection

In vagotomized dogs (dogs with cut vagus nerve, age and strain not provided), i.v. administration of isopropylamine at 0.1 to 30 mg/kg (0.002-0.51 mmol/kg) produced a dose-dependent increase in arterial pressure and heart rate (Walle et al., 1972). These effects were reduced by reserpine pretreatment (dose not provided).

In a similar study, Ishizaki et al. (1974) reported that vagotomized dogs treated i.v. with isopropylamine at doses ranging from 0.3 to 30 mg/kg (0.005-0.51 mmol/kg) showed a dose-dependent increase in heart rate, myocardial contractile force, and systemic arterial pressure. The minimal effective dose was 1 mg/kg (0.002 mmol/kg). These effects were completely inhibited by propranolol (a ß-adrenergic blocking agent) administered i.v., while pretreatment with reserpine suppressed the response to the highest dose (30 mg/kg; 0.51 mmol/kg) of isopropylamine only. Ganglionic blockade (induced with a combination of hexamethonium and atropine) suppressed the effects of all doses of isopropylamine except for 30 mg/kg (0.51 mmol/kg).

In a study reported by Privitera et al. (1982), vagotomized mongrel dogs (age not provided) were administered isopropylamine at 0.25, 0.5, or 2.5 mg/kg/min (0.0042-0.042 mmol/kg/min) i.v. for 45 minutes. Mean arterial pressure (MAP) and heart rate were monitored for 2 hours post-exposure. During infusion of the low dose, MAP did not change, but at 30, 60, and 90 minutes post-infusion, MAP was significantly depressed. At the mid-dose, MAP became significantly depressed at the end of the infusion period and remained depressed at 30 minutes post-infusion. The high dose induced a biphasic change in MAP; during infusion, MAP rose significantly, but at 60 and 120 minutes post-infusion, MAP was significantly depressed. Heart rate was not affected by the low and mid doses. However, at the high dose, heart rate increased in 2/3 dogs during infusion and was significantly depressed in all dogs 90 and 120 minutes post-infusion. Treating another group of mongrel dogs i.v. with the high dose (2.5 mg/kg/min; 0.042 mmol/kg/min) only, Privitera et al. (1982) found that MAP peaked between 60 and 120 minutes post-infusion, and was significantly depressed at 210 minutes post-infusion.

In the same report (Privitera et al., 1982), chronotropic (i.e., heart rate) response to cardioaccelerator nerve stimulation (0.3-30 Hz) in mongrel dogs was evaluated before and after i.v. infusion of isopropylamine at 0.5, 1, or 2.5 mg/kg/min (0.008, 0.02, or 0.042 mmol/kg/min, respectively) for 45 minutes. Isopropylamine, at the high dose only, suppressed the increase in heart rate induced by stimulation of preganglionic nerves. Privitera et al. (1982) also demonstrated that isopropylamine administered i.v. at 2.5 mg/kg/min (0.042 mmol/kg/min)

(duration of exposure not provided but probably 45 min) significantly suppressed the depression in heart rate in mongrel dogs induced by electrical stimulation of the right vagus nerve.

9.2.2.7 Intraarterial Injection

In vagotomized dogs (age and strain not provided), a single intraarterial injection of 0.3-10 mg (0.005-0.17 mmol) isopropylamine produced a dose-dependent decrease in hind-leg vascular resistance, measured during constant flow (Walle et al., 1972).

When the denerved hindlegs of mongrel dogs were intraarterially infused with a single dose of isopropylamine at 0.1 to 10 mg (0.002-0.17 mmol), all doses significantly reduced vascular resistance, but these effects generally lasted for less than a minute (Ishizaki et al., 1974).

9.2.3 Short-Term and Subchronic Exposures

The study described in this section is summarized in **Table 5**.

Male and female Sprague-Dawley rats administered isopropylamine by inhalation experienced a dose-dependent irritation of the mucous membrane, corneal opacity of the eye, and degenerative changes in the epithelium of the nasal mucous membrane (BASF, 1995). Rats were dosed with 0.1, 0.5, or 1.35 mg isopropylamine/L air (100, 500, or 1350 mg/m^3; 0.002, 0.009, or 0.0228 mmol/L air) for 6 hours per day, 5 days per week for 4 weeks.

9.2.4 Chronic Exposures

No data were found.

9.3 Reproductive and Teratological Effects

The study described in this section is summarized in **Table 6**.

Embryotoxicity, fetotoxicity, or teratogenicity were not observed in pregnant Sprague-Dawley rats exposed to 50, 500, or 1000 mg isopropylamine/m^3 (0.84, 8.46, or 16.92 mmol/m^3, respectively) for 6 h/day, on days 6 through 15 of gestation (Monsanto, 1986). The exposed rats were sacrificed on day 20 of gestation and the fetuses were removed. In the dams, the high dose was toxic. Signs of toxicity included decreased body weight, rales, labored breathing, vaginal discharge (1 rat), nasal discharge, sneezing, and fur staining/encrustation. The mid dose was slightly toxic. Signs of toxicity included reduced body weight gain, and low incidences of nasal discharge and sneezing. Postmortem evaluation revealed reduced body fat in 9/25 high-dose and 2/25 mid-dose rats. The low dose was not toxic. No unscheduled mortality occurred, and the number of offspring and preimplantation losses were similar in exposed and control rats. Fetal

weights, sex distribution, and incidence of fetal malformations were not different between fetuses of exposed (all doses) and control rats.

9.4 Carcinogenicity

No data were found.

9.5 Genotoxicity

Studies described in this section are summarized in **Table 7.**

9.5.1 Prokaryotic Systems

As reported by Speck et al. (1982), isopropylamine, at concentrations up to 8300 µg/plate (140.4 µmol/plate), was not mutagenic in *S. typhimurium* strains TA98 and TA100 using the pre-incubation method in the presence or absence of metabolic activation.

Zeiger et al. (1987) also reported that isopropylamine was not mutagenic in *S. typhimurium.* Strains TA1535, TA1537, TA98, and TA100 were exposed to concentrations ranging from 10 to 10000 µg/plate (0.17-169 µmol/plate) in the presence or absence of metabolic activation.

9.5.2 *In Vitro* Mammalian DNA Repair

Haas-Jobelius et al. (1991) concluded that isopropylamine did not induce DNA repair synthesis in cultured male Wistar rat hepatocytes treated with 100 to 3000 µM isopropylamine for 4 hours in the presence of BrdUrd and [^{3}H]thymidine. After DNA isolation, repair synthesis was determined using a modified BrdUrd density-shift method, which measured the incorporation of radioactivity in nonreplicated DNA.

9.5.3 *In Vitro* Mammalian Chromosomal Aberrations

Elf Atochem (1994; cited by BASF, 1995) reported that isopropylamine did not induce chromosomal aberrations in mitogen-stimulated human lymphocytes treated with 250, 500, and 1000 µg/mL (4230, 8460, or 16,920 µM) isopropylamine in the presence of S9 or with 30, 100, and 300 µg/mL (510, 1690, or 5080 µM) isopropylamine in the absence of S9.

9.6 Immunotoxicity

No data were found on immunotoxicity.

9.7 Other Toxic Effects

The study described in this section is summarized in **Table 8**.

Surgically removed heart-lungs from mongrel dogs were used to evaluate the *in vitro* cardiovascular effects of isopropylamine infused via a venous inflow cannula at doses of 2, 6, 20, 60, and 200 mg (30-3000 µmol). No effect was seen on heart rate, but myocardial contractile force was increased at doses of 20 mg (300 µmol) and greater (Ishizaka et al., 1974).

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

The ability of 16 aliphatic amines to induce respiratory irritation in male OF_1 mice was evaluated (Gagnaire et al., 1993). The compounds tested included isopropylamine, *n*-propylamine, isobutylamine, diisopropylamine, *n*-butylamine, cyclohexylamine, di-*n*-propylamine, *n*-pentylamine, *tert*-octylamine, *n*-hexylamine, diisobutylamine, di-*n*-butylamine, *n*-heptylamine, *n*-octylamine, allylamine, and diallylamine. Exposures occurred either in chambers (head only) or via tracheal cannulation. For each chemical, the concentration responsible for a 50% decrease in respiratory frequency (RD_{50}) was determined. The RD_{50} value for isopropylamine was 157 ppm (390 mg/m^3) when mice were exposed in chambers and 489 ppm (1200 mg/m^3) when exposed by tracheal cannulation. The RD_{50} values of saturated amines, includinegisopropylamine, were closely related to the *n*-octanol/water partition coefficient, indicating that the more lipophilic amines are more irritating to the upper and lower respiratory tracts.

Table 4. Acute Toxicity of Isopropylamine

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.2.2.1 Oral Administration						
rats (strain and age n.p.)	5 (sex n.p.)	isopropylamine, purity n.p.	100-1600 mg/kg (1.69-27.1 mmol/kg)	n.p.	Deaths occurred 3 min. to 6 days post-exposure. Signs of toxicity included weakness, ataxia, gasping, and convulsions.	Eastman Kodak (1953)
rats (Sprague-Dawley, young adult)	5M, 5F per dose	isopropylamine, purity n.p.	70, 118, 200, or 338 mg/kg (1.2, 2.0, 3.4, or 5.7 mmol/kg) via oral gavage	single dose; 15-day observation period	Signs of toxicity included decreased activity and staining around nose and mouth (observed with all dose levels). Labored breathing was also observed in rats administered 118 and 338 mg/kg. There were no significant changes in body weight in any of the dose groups. There were no remarkable findings in rats sacrificed after 15 days, but mild to severe congestion of the stomach non-glandular and/or glandular mucosa was observed in most rats that died before the end of the study.	Monsanto (1985a)
9.2.2.2 Inhalation Exposure						
mice (Swiss OF_1, age n.p.)	6 M per dose	isopropylamine, purity n.p.	4-6 different exposure concentrations ranging from 69 to 197 ppm (170-490 mg/m^3; 2.9-8.3 mmol/m^3; only the range was given)	15 min. head only exposure; observaton period n.p.	Respiratory frequency was rapidly affected (i.e., after ~ 30 seconds to 1 min. of exposure). Recovery of respiratory frequency also recovered rapidly; a return to pre-exposure levels occurred approximately 1 min. post-exposure. The RD_{50} was 157 ppm (386 mg/m^3) (95% confidence interval, 142-178 ppm) (349-438 mg/m^3). RD_{50} is the concentration of a sensory irritant responsible for a decrease of 50% in the respiratory frequency.	Gagnaire et al. (1989, 1993)
	M (number n.p.)		350-625 ppm (861-1540 mg/m^3; 14.6-26.0 mmol/m^3; only the range was given)	120 min. exposure via tracheal cannulation; observation period n.p.	Maximal effects on respiratory frequency occurred after 120 min. of exposure. Little if any recovery occurred, especially with the highest dose. The tracheal cannula RD_{50} (RD_{50}TC) was 489 ppm (1200 mg/m^3) (95% confidence interval, 464-520 ppm; 1140-1280 mg/m^3).	

Abbreviations: F = female; HD = high dose; i.a. = intra-arterial; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 4. Acute Toxicity of Isopropylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rats (Sprague-Dawley, 7-wk-old)	6 M, 6 F per dose	isopropylamine, purity n.p.	5.0 or 5.1 mg/L (0.084 or 0.086 mM), whole-body inhalation exposure	4 h exposure; 14-day observation period	One HD male died on day 2. During exposure to isopropylamine, signs of toxicity included labored breathing, discharges around the nose and mouth, lacrimation, and hypoactivity (incidences n.p.). Immediately following exposure, all rats (except controls) exhibited labored breathing and red encrustation around the nose. Red encrustation around the eyes (4/6 LD M, 4/6 LD F, 4/6 HD M, 2/6 HD F) and urine-stained fur (4/6 LD M, 4/6 LD F, 6/6 HD M, 4/6 HD F) were also observed immediately following exposure in some animals (none of the controls developed either of these symptoms). At 2 days post-exposure, labored breathing, opacity of eyes, and red encrustation around nose and eyes were observed in some rats. The incidences of these symptoms decreased by 7 days post-exposure. By 14 days post-exposure, toxic symptoms had abated in rats, with the exception of 4/5 HD males and 1/6 LD females that still exhibited eye opacity, 1/6 LD females that had labored breathing, and 1/6 LD females that had red encrustation around the nose (it was n.p. if these symptoms occurred together in the same animals or among different animals).	Monsanto (1985b)
9.2.2.3 Ocular Application						
rabbits (strain and age n.p.)	n.p.	isopropylamine, purity n.p.	0.05 mg (0.00084 mmol)	n.p.	Irritation to eyes was severe. No other details were given.	AMA Arch. Indust. Hyg. Occup. Med. (1950-1954; cited by RTECS, 1996)
rabbits (New Zealand White, young adult)	3 M, 3 F	isopropylamine, purity n.p.	0.1 mL (70 mg; 1 mmol) undiluted isopropylamine applied to cupped conjunctival sac of right eye (left eye served as control)	single dose; 14-day observation period (the study was terminated on day 14 due to the severe, and probably irreversible, nature of ocular irritation)	Rabbits were observed 1 h, and 1, 2, 3, 7, and 14 days after dosing. At all observation times, all rabbits had severe redness and swelling of the conjunctivae and maximum corneal opacity. By day 14, all rabbits developed eschar tissue on the cornea and/or conjunctivae, and corneal ulcerations. In addition, in 1 male and 1 female, scar tissue on the conjunctivae or eyelid was detected on day 14.	Monsanto (1985a)
rabbits (strain and age n.p.)	n.p.	isopropylamine, purity n.p.	0.05 mg (0.00084 mmol)	24 h exposure; observation period n.p.	Irritation to eyes was severe. No other details were given.	Marhold (1986; cited by RTECS, 1996)

Abbreviations: F = female; HD = high dose; i.a. = intra-arterial; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 4. Acute Toxicity of Isopropylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rabbits (strain and age n.p.)	n.p.	isopropylamine, purity n.p.	n.p.	single dose; 24 h observaton period	Isopropylamine rated 10 (most severe) on a scale of 1 to 10 in terms of ocular irritation.	Grant (1986; cited by HSDB, 1996)
9.2.2.4 Dermal Application						
guinea pigs (strain and age n.p.)	2 (sex n.p.)	isopropylamine, purity n.p.	5 or 10 mL/kg (3000 or 6900 mg/kg; 60 or 120 mmol/kg) applied in a gauze pad under a rubber cuff	n.p.	Both animals died on day 1. At necropsy, the entire dosed area was gray and necrotic.	Eastman Kodak (1953)
guinea pigs (strain and age n.p.)	n.p.	isopropylamine, purity n.p.	0.1 mL (70 mg; 1 mmol) intradermally on day 1; 0.5 mL (300 mg; 6 mmol) applied by occlusive dressing for 48 hours on day 8; after 12 days of no treatment, a 2nd dermal dose of 0.5 mL (300 mg; 6 mmol)	see dose for exposure; observation period n.p.	The dose was not lethal. No adverse clinical signs or cutaneous reactions were observed.	Elf Atochem (1994; cited by BASF, 1995)
rabbits (strain and age n.p.)	n.p.	isopropylamine, purity n.p.	10 mg (0.17 mmol) on open skin	24 h exposure; observation period n.p.	Irritation was severe. Additional details were n.p.	AMA Arch. Indust. Hyg. Occup. Med. (1950-1954; cited by RTECS, 1996)
rabbits (strain and age n.p.)	n.p.	isopropylamine, purity n.p.	345 mg (5.84 mmol) on open skin	n.p.	Irritation was moderate. Additional details were n.p.	Union Carbide, 1971; cited by RTECS, 1996
rabbits (New Zealand White, young adult)	5 M, 5 F per dose	isopropylamine, purity n.p.	2000 or 5000 mg/kg (33.84 or 84.59 mmol/kg) applied by patch to shaved, intact dorsal skin	24-h exposure; 15-day observation period	1/5 HD females died on day 2. There were no significant changes in body weight and no observable pharmacotoxicity. Although no internal changes were detected at necropsy, the skin of all rabbits was hardened, thickened, and had a dark discoloration.	Monsanto (1985a)

Abbreviations: F = female; HD = high dose; i.a. = intra-arterial; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 4. Acute Toxicity of Isopropylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
	3 M, 3 F		0.5 mL undiluted (300 mg; 6 mmol) isopropylamine applied by patch to 2 sites on each rabbit (1 site was semi-occluded; the other site was fully occluded)	4 h (semi-occluded site) or 24 h (fully occluded site) exposure; the observation period was terminated on day 7 due to the severe and irreversible nature of skin irritation	Rabbits were observed approximately 30 min., 24, 48, and 72 hours (semi-occluded sites only), and on day 7 post-exposure. All rabbits developed severe erythema and edema, and dark discoloration of semi- and fully occluded sites beginning 30 min. post-exposure and persisting for the entire observation period. Eschar formation (a thick, coagulated scab) was observed in all rabbits at both sites 24 and 48 h post-exposure and persisted throughout the observation period.	
rabbits (strain and age n.p.)	n.p.	isopropylamine, purity n.p.	0.75 mg (0.013 mmol) by dermal patch	24 h exposure; observation period n.p.	Irritation was severe. Additional details were n.p.	Marhold (1986; cited by RTECS, 1996)
9.2.2.5 Intraperitoneal Injection						
rats (strain and age n.p.)	5 (sex n.p.)	isopropylamine, purity n.p.	50-800 mg/kg (0.84-14 mmol/kg)	n.p.	Death occurred 2 to 48 hours post-exposure. Symptoms of toxicity included weakness, ataxia, and unconsciousness	Eastman Kodak (1953)
9.2.2.6 Intravenous Injection						
vagotomized dogs (strain and age n.p.)	n.p.	isopropylamine, purity n.p.	0.1-30 mg/kg (0.002-0.51 mmol/kg)	n.p.	Arterial pressure and heart rate were increased in a dose-dependent manner. These effects were reduced by reserpine pretreatment (data n.p.).	Walle et al. (1972)
vagotomized dogs (mongrel, age n.p.)	6 (sex n.p.)	isopropylamine, 97.5% pure (containing 0.5% acetone, but no other amines)	0.3-30 mg/kg (0.005-0.51 mmol/kg)	n.p.	Heart rate, myocardial contractile force, and systemic arterial pressure increased in a dose-response manner. The minimal effective dose was 1 mg (0.002 mmol/kg). When dogs were injected i.v. with propranolol (a β-adrenergic blockade), these effects of isopropylamine were completely inhibited. Pretreatment of the dogs with reserpine suppressed the responses to 30 mg/kg (0.51 mmol/kg) isopropylamine. Ganglionic blockade (induced with a combination of hexamethonium and atropine) of the dogs suppressed the effects of all doses of isopropylamine except at 30 mg/kg (0.51 mmol/kg).	Ishizaki et al. (1974)

Abbreviations: F = female; HD = high dose; i.a. = intra-arterial; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 4. Acute Toxicity of Isopropylamine (continued)

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
vagotomized dogs (mongrel, age n.p.)	n.p.	isopropylamine, purity n.p.	0.25, 0.5, or 2.5 mg/kg/min (0.0042, 0.008, or 0.042 mmol/kg/min)	45 min. exposure; dogs were monitored for 2 h after cessation of treatment	**Mean Arterial Pressure (MAP):** During infusion of the LD, MAP did not change, but at 30, 60, and 90 min. post-infusion, MAP was significantly depressed ($p < 0.05$). With the MD, MAP became significantly depressed at the end of the infusion period and remained depressed at 30 min. post-infusion ($p < 0.05$). The HD induced a biphasic change in MAP. During infusion of the HD, MAP increased significantly; 60 and 120 min. post-infusion, MAP was significantly depressed. **Heart Rate:** Heart rate was not affected by the LD and MD. With the HD, heart rate increased in 2/3 dogs during infusion, and was significantly depressed in all dogs 90 and 120 min. post-infusion.	Privitera et al. (1982)
			2.5 mg/kg/min (0.042 mmol/kg/ min)	30 min. exposure; dogs were monitored for 3.5 h after cessation of treatment	**Mean Arterial Pressure (MAP):** MAP peaked between 60 and 120 min. post-infusion, and was significantly depressed at 210 min. post-infusion.	
			0.5, 1, or 2.5 mg/kg/min (0.008, 0.02, or 0.042 mmol/kg/min)	45 min. exposure; observation period n.p.	Chronotropic (i.e., heart rate) response to cardioaccelerator nerve stimulation (0.3-30 Hz) was evaluated before and after infusion of isopropylamine. **Heart Rate:** Isopropylamine at the HD only suppressed the chronotropic response to stimulation of preganglionic nerves.	
vagotomized dogs (mongrel, age n.p.)	n.p.	isopropylamine, purity n.p.	2.5 mg/kg/min (0.042 mmol/kg/ min)	n.p.	The depression in heart rate caused by electrical stimulation of the right vagus nerve was measured before and after infusion of isopropylamine. **Heart Rate:** The decrease in heart rate induced by electrical stimulation of the right vagus nerve was significantly suppressed by infusion of isopropylamine.	Privitera et al. (1982)
9.2.2.7 Intraarterial Injection						
vagotomized dogs (strain and age n.p.)	n.p.	isopropylamine, purity n.p.	0.3-10 mg (0.005-0.17 mmol)	n.p.	Hind-leg vascular resistance, measured during constant flow, was decreased in a dose-dependent manner.	Walle et al. (1972)
denerved hindlegs of dogs (mongrel, age n.p.)	n.p.	isopropylamine, 97.5% pure (containing 0.5% acetone, but no other amines)	0.1-10 mg (0.002-0.17 mmol)	n.p.	All doses of isopropylamine significantly reduced vascular resistance, but these effects generally lasted less than a minute. I.v. administration of propranolol had no effect on the vascular response to isopropylamine. Pretreatment with atropine sulfate or diphenyldramine also did not affect the vascular response to isopropylamine.	Ishizaki et al. (1974)

Abbreviations: F = female; HD = high dose; i.a. = intra-arterial; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 5. Short-Term and Subchronic Exposure to Isopropylamine

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rats (Sprague-Dawley, age n.p.)	15 M, 15 F per dose	isopropylamine, purity n.p.	0.1, 0.5, or 1.35 mg/L air (100, 500, or 1350 mg/m^3; 0.002, 0.009, or 0.0228 mmol/L air) 6 hours/day, 5 days/week for 4 weeks	see dose for exposure period; observation period n.p.	Dose-dependent irritation of mucous membranes, corneal opacity of the eyes, and degenerative changes in the epithelium of the nasal mucous membrane were observed.	BASF (1995)

Table 6. Reproductive and Teratological Effects of Isopropylamine

Species, Strain, Age	Number and Sex of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rats (pregnant Sprague-Dawley, age n.p.)	25 F per dose	isopropylamine, 99.77% pure	50, 500, or 1000 mg/m^3 (0.84, 8.46, or 16.92 mmol/m^3) 6 h/day, on days 6-15 of gestation.	10 days; pregnant rats were sacrificed on day 20 of gestation and fetuses were removed	No deaths of dams occurred. Number of offspring and preimplantation losses were similar in dosed and control rats. **Dams:** The HD was toxic; signs of toxicity included decreased body weight, rales, labored breathing, vaginal discharge (1 rat), nasal discharge, sneezing, and fur staining/encrustation. The MD was slightly toxic; signs of toxicity included reduced body weight gain, and low incidences of nasal discharge and sneezing. Postmortem, reduced body fat was observed in 9/25 HD and 2/25 MD rats. The LD was not toxic. **Offspring:** None of the doses were embryotoxic, fetotoxic, or teratogenic. Fetal weights, sex distribution and incidence of fetal malformations were similar in dosed and control groups.	Monsanto (1986)

Abbreviations: F = female; HD = high dose; i.a. = intra-arterial; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

Table 7. Genotoxicity of Isopropylamine

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
9.5.1 Prokaryotic Systems							
Salmonella typhimurium strains TA98 and TA100	*his* reverse gene mutations	-/+	isopropylamine, >99% pure	up to 8300 µg/plate (140.4 µmol/plate)	negative	The pre-incubation method was used; no other experimental details were given.	Speck et al. (1982)
S. typhimuriu strains TA1535, TA1537, TA98, and TA100	*his* reverse gene mutations	-/+	isopropylamine, purity n.p.	10 to 10000 µg/plate (0.17-169 µmol/plate)	negative	The pre-incubation method was used.	Zeiger et al. (1987)
9.5.2 *In Vitro* Mammalian DNA Repair							
male Wistar rat hepatocytes	DNA repair as measured by the incorporation of [^{3}H]thymidine using a modified BrdUrd density-shift method)	NA	isopropylamine, purity n.p.	100 to 3000 µM for 4 h in the presence of BrdUrd and [^{3}H]thymidine	negative	After DNA isolation, repair synthesis was determined by measuring the incorporation of radioactivity in unreplicated DNA.	Haas-Jobelius et al. (1991)
9.5.3 ***In Vitro* Mammalian Chromosomal Aberrations**							
human lymphocytes	chromosomal aberrations	+	isopropylamine, purity n.p.	250, 500, or 1000 µg/mL (4230, 8460, or 16,920 µM)	negative	The length of exposure was n.p.	ELF ATOCHEM (1994; cited by BASF, 1995)
		-		30, 100, or 300 µg/mL (510, 1690, or 5080 µM)	negative		

Table 8. Other Toxic Effects

Test System	Biological Endpoint	Chemical Form, Purity	Dose	Endpoint Response	Results/Comments	Reference
heart-lung organ preparations from mongrel dogs	Change in myocardial contractile force	isopropylamine, 97.5% pure (containing 0.5% acetone, but no other amines)	2, 6, 20, 60, and 200 mg (30-3000 µmol), injected via venous inflow cannula	positive (increased force)	Minimal effective dose was 20 mg (300 µmol). Heart rate was not affected at any dose tested.	Ishizaki et al. (1974)

Abbreviations: F = female; HD = high dose; i.a. = intra-arterial; i.p. = intraperitoneal; i.v. = intravenous; LD = low dose; M = male; MD = mid dose; n.p. = not provided

11.0 ONLINE DATABASES AND SECONDARY REFERENCES SEARCHED

11.1 Online Databases

Chemical Information System Files

ISHOW (Information System for Hazardous Organics in Water)
SANSS (Structure and Nomenclature Search System)
TSCAPP (Toxic Substances Control Act Plant and Production)
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

359 Chemical Economics Handbook

Internet Databases

Code of Federal Regulations full text. 1996 versions of various titles via GPO Gate, a gateway by the Libraries of the University of California to the GPO Access service of the Government Printing Office, Washington, DC. Internet URL http://www.gpo.ucop.edu/

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

BIOSIS (Biological Abstracts)
CA File (Chemical Abstracts)
CANCERLIT
CEN (Chemical & Engineering News)
CIN (Chemical Industry Notes)
CSNB (Chemical Safety News Base)
EMBASE (Excerpta Medica)
HSDB (Hazardous Substances Data Bank)
IPA (International Pharmaceutical Abstracts)
MEDLINE (Index Medicus)
PROMT (Predicasts Overview of Markets and Technology)
RTECS (Registry of Toxic Effects of Chemical Substances)
TOXLINE
TOXLIT

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicology Research Projects	CRISP
NIOSHTIC7	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

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