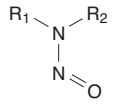
N-Nitrosamines: 15 Listings



Generic *N*-nitrosamine structure

N-Nitrosamines are a class of chemical compounds with the general structure shown above. The essential feature of *N*-nitroso compounds is the N–N=O structure; the R_1 and R_2 groups attached to the amine nitrogen may range from a simple hydrogen (H) atom to more complex chemical substituents (including ring structures that incorporate the nitrogen atom), as shown in the structures of the individual nitrosamines listed below.

Human exposure to nitrosamines can result from formation of *N*-nitroso compounds either in food during storage or preparation or *in vivo*, usually in the stomach (Mirvish 1975). Individual nitrosamines are not found in isolation, but occur in mixtures of various nitrosamines. Nitrosamines or their precursors occur in a wide variety of foods and manufactured and natural products, such as agricultural chemicals, tobacco, detergents, rust inhibitors, cutting fluids, rubber additives, solvents, drugs, plastics, tanned leather products, textiles, and cosmetics (ATSDR 1989). Nitrosamines generally are not intentionally added to foods or consumer products, but are formed from constituents of the foods or products that are either naturally present, such as the amines that are part of the structure of proteins in meat, or added during production (e.g., nitrates or nitrites added to meats as preservatives). Nitrosamines are formed when nitrites, which can be formed from nitrates, react with a secondary or tertiary amine. The concentration of nitrosamines tends to increase over time, and their formation is enhanced by high temperatures, such as occur while frying food, and high acidity, such as in stomach acid. Ascorbic acid or its isomers inhibit the formation of nitrosamines and often are added to food preparations to prevent nitrosamine formation.

Although food and tobacco products are important sources of external exposure to *N*-nitrosamines, exposure also occurs from nitrosamines produced internally in the digestive tract (Hotchkiss 1989). About 5% of ingested nitrates are reduced to nitrites in saliva (NRC 1995). These nitrites can subsequently react in solution with secondary and tertiary amines, as well as N-substituted amides, carbamates, and other related compounds, to form *N*-nitroso compounds within the gastrointestinal tract (Mirvish 1975, Hotchkiss 1989). This internal formation is a major source of human exposure to *N*-nitrosamines.

The listings below are for the individual *N*-nitrosamines and do not constitute a listing for *N*-nitrosamines compounds as a class.

References

ATSDR. 1989. *Toxicological Profile for* N-*Nitrosodimethylamine (Final Report)*. Atlanta, GA: Agency for Toxic Substances and Disease Registry. 132 pp.

Hotchkiss JH. 1989. Preformed *N*-nitroso compounds in foods and beverages. *Cancer Surv* 8(2): 295-321.

Mirvish SS. 1975. Formation of *N*-nitroso compounds: chemistry, kinetics, and *in vivo* occurrence. *Toxicol Appl Pharmacol* 31:325-351.

NRC. 1995. *Nitrate and Nitrite in the Drinking Water*. National Research Council of the National Academies of Science. Washington, DC: National Academies Press. 64 pp.

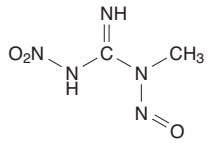
N-Methyl-*N′*-Nitro-*N*-Nitrosoguanidine

CAS No. 70-25-7

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as MNNG or 1-methyl-3-nitro-1-nitrosoguanidine



Carcinogenicity

N-Methyl-*N′*-nitro-*N*-nitrosoguanidine (MNNG) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

MNNG caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It caused tumors primarily at the site of administration, mostly in the gastrointestinal tract, including tumors of the forestomach (papilloma or carcinoma), glandular stomach (adenoma, adenocarcinoma, carcinoma, or sarcoma), small intestine (papilloma, carcinoma, adenocarcinoma, or sarcoma), and large intestine (adenomatous polyps or polypoid carcinoma). Tumors of the forestomach or glandular stomach were observed in rats exposed to MNNG in the drinking water, by stomach tube, and by intraperitoneal injection; in mice exposed by stomach tube; and in male hamsters and dogs exposed via the drinking water. MNNG also caused tumors of the large intestine in rats exposed by intrarectal instillation. It caused tumors of the small intestine in rats exposed via the drinking water, subcutaneous injection, or intraperitoneal injection and in mice exposed by intraperitoneal injection (IARC 1974, 1987).

In addition, MNNG caused tumors of the liver and peritoneum in rats exposed orally (by stomach tube or drinking water) and injection-site tumors (fibrosarcoma and rhabdomyosarcoma) in rats exposed by subcutaneous injection. In mice, MNNG administered by subcutaneous injection caused benign tumors of the liver, lung, and blood vessels (hemangoendothelioma) and by dermal application caused benign and malignant skin tumors (papilloma and carcinoma) (IARC 1974, 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to MNNG. Three deaths from brain tumors (glioma) and one death from colon cancer were reported among workers in a genetics laboratory over a 13-year period. All of the subjects had probably been exposed to MNNG for 6 to 15 years prior to death, but other carcinogens had also been used in the laboratory (IARC 1974, 1987).

Properties

MNNG is an *N*-nitrosamine alkylating agent that exists as a yellow crystal at room temperature and is soluble in water, dimethyl sulfoxide, and polar organic solvents. It reacts violently with water and can explode on heating or high impact. MNNG reacts with various nucleophiles, especially amines (Akron 2009, HSDB 2009). At low pH, it slowly releases nitrous acid, and at high pH in the presence of hydroxyl alkali, it produces the highly toxic gas diazomethane. When MNNG is heated to decomposition, it emits highly toxic fumes of

nitrogen oxides (IARC 1974, HSDB 2009). Physical and chemical properties of MNNG are listed in the following table.

Property	Information
Molecular weight	147.1[a]
Melting point	118°C to 123.5°C (with decomposition)[a]
Log K_{ow}	–0.92[b]
Water solubility	267 g/L at 25°C[b]
Vapor pressure	0.00012 mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

In the 1940s and 1950s, MNNG was used to prepare diazomethane. It currently is used as a research chemical and has no known commercial use (IARC 1974, HSDB 2009).

Production

MNNG is not produced commercially. In 2009, it was available in small quantities for research purposes from seven suppliers worldwide, including five U.S. suppliers (ChemSources 2009).

Exposure

The extent of exposure to MNNG is unknown, but it is probably limited to scientists using it as a research chemical (IARC 1974, HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 523 workers potentially were exposed to MNNG (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of MNNG = U163.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

References

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NIOSH. 1990. *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health. Last updated: 7/1/90. http://www.cdc.gov/noes/noes1/b0070sic.html.

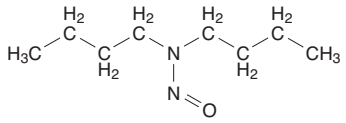
N-Nitrosodi-*n*-butylamine

CAS No. 924-16-3

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as *N*-dibutylnitrosamine



Carcinogenicity

N-Nitrosodi-*n*-butylamine is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosodi-*n*-butylamine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It was carcinogenic after a single dose, and was particularly effective as a urinary-bladder carcinogen, causing benign and/or malignant urinary-bladder tumors (papilloma or squamous- or transitional-cell carcinoma) in mice, rats, hamsters, and guinea pigs exposed orally and in mice, rats, hamsters, and rabbits exposed by subcutaneous injection (IARC 1974, 1978).

N-Nitrosodi-*n*-butylamine also caused tumors of the respiratory tract following oral or prenatal exposure in hamsters; subcutaneous injection in rats, hamsters, and adult and newborn mice; and intraperitoneal injection in hamsters of both sexes. Benign or malignant liver tumors were observed in mice, rats, and guinea pigs exposed orally and in newborn mice exposed by subcutaneous injection. Tumors of the upper digestive tract (pharynx, esophagus, or forestomach) occurred following oral exposure in mice, rats, and hamsters and subcutaneous injection in rats (esophagus) and hamsters (forestomach). Intravenous injection of *N*-nitrosodi-*n*-butylamine caused leukemia in mice of both sexes (IARC 1974, 1978).

Since *N*-nitrosodi-*n*-butylamine was listed in the *Second Annual Report on Carcinogens,* an additional study in rats has been identified. Administration of *N*-nitrosodi-*n*-butylamine to male rats by stomach tube caused cancer of the forestomach (carcinoma), in addition to cancer of the liver (carcinoma) and urinary bladder (transitional-cell carcinoma) (Lijinsky and Reuber 1983).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosodi-*n*-butylamine.

Properties

N-Nitrosodi-*n*-butylamine is a nitrosamine compound that is a yellow oil at room temperature (HSDB 2009). It is slightly soluble in water and soluble in vegetable oils and organic solvents. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet

light (IARC 1978). Physical and chemical properties of *N*-nitrosodi-*n*-butylamine are listed in the following table.

Property	Information
Molecular weight	158.2[a]
Specific gravity	0.9009 at 20°C/4°C[a]
Melting point	< 25°C[b]
Boiling point	116°C at 14 mm Hg[a]
Log K_{ow}	2.63[a]
Water solubility	1.27 g/L at 24°C[b]
Vapor pressure	0.05 mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitrosodi-*n*-butylamine is used primarily as a research chemical (IARC 1974). It has also been used as an intermediate in the synthesis of di-*n*-butylhydrazine.

Production

N-Nitrosodi-*n*-butylamine is not produced commercially in the United States (HSDB 2009). In 2009, it was available in small quantities for research purposes from seven U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to *N*-nitrosodi-*n*-butylamine are ingestion, inhalation, and dermal contact (HSDB 2009). *N*-Nitrosodi-*n*-butylamine has been detected in a variety of products as a result of the nitrosation of amines present in these products. *N*-Nitrosodi-*n*-butylamine may be formed from secondary or tertiary *n*-butylamines and quaternary ammonium salts by reaction with nitrosating agents, such as nitrite, in the stomach or during cooking processes. The degree of this potential exposure is unknown. *N*-Nitrosodi-*n*-butylamine has been measured in soybean oil at a concentration of 290 µg/kg, in cheese at 20 to 30 µg/kg, and in smoked or cured meats at up to 3.9 µg/kg. It has also been detected in tobacco smoke at a concentration of 3 ng per cigarette. *N*-Nitrosamines frequently are produced during rubber processing and may be present as contaminants in the final rubber product. Potential exposure depends on the ability of the nitrosamine to migrate from the product into the body. Nitrosamines present in pacifiers and baby-bottle nipples can migrate into saliva, which could result in ingestion of nitrosamines (IARC 1974, 1978).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, all environmental releases of *N*-nitrosodi-*n*-butylamine since 1998 have been to landfills. Annual releases did not exceed 15 lb from 1998 through 2000 or in 2004, but were 4,510 lb in 2001. In 2007, one facility released 500 lb of *N*-nitrosodi-*n*-butylamine to an off-site hazardous-waste landfill (TRI 2009). The estimated half-life of *N*-nitrosodi-*n*-butylamine in the vapor phase is 2.8 days. *N*-Nitrosodi-*n*-butylamine was detected in the effluent water from a coke facility at a concentration of 0.82 µg/L (IARC 1978).

Occupational exposure potentially could occur among researchers studying the biological effects of *N*-nitrosodi-*n*-butylamine.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0063 µg/L; based on fish or shellfish consumption only = 0.22 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which listing is based wholly or partly on the presence of *N*-nitrosodi-*n*-butylamine = U172.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

References

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Lijinsky W, Reuber MD. 1983. Carcinogenicity of hydroxylated alkylnitrosoureas and of nitrosooxazolidones by mouse skin painting and by gavage in rats. *Cancer Res* 43(1): 214-221.

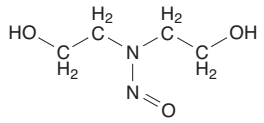
TRI. 2009. *TRI Explorer Chemical Report.* U.S. Environmental Protection Agency. Last updated: 3/19/09. http://www.epa.gov/triexplorer and select *N*-Nitrosodi-*n*-Butylamine.

N-Nitrosodiethanolamine

CAS No. 1116-54-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosodiethanolamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosodiethanolamine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Administration of *N*-nitrosodiethanolamine in the drinking water caused liver cancer (hepatocellular carcinoma) and benign kidney tumors (adenoma) in rats of unspecified sex (IARC 1978). Subcutaneous injection of *N*-nitrosodiethanolamine caused cancer of the nasal cavity (adenocarcinoma) and at the injection site (fibrosarcoma) and benign tumors of the trachea (papilloma) and liver (hepatocellular adenoma) in hamsters of both sexes.

Since *N*-nitrosodiethanolamine was listed in the *Second Annual Report on Carcinogens,* additional studies in rodents have been iden-

tified. Studies in several strains of rats consistently reported that exposure to *N*-nitrosodiethanolamine in the drinking water caused liver cancer (primarily hepatocellular carcinoma, but also cholangiocellular carcinoma) in both sexes; some studies also found increased incidences of nasal-cavity cancer (adenocarcinoma and squamous-cell carcinoma). In female strain A/J mice (a strain with a high spontaneous incidence of lung tumors), administration of *N*-nitrosodiethanolamine in the drinking water increased the incidence of benign lung tumors and the number of tumors per animal. Tumors of the nasal cavity were observed in hamsters of both sexes exposed to *N*-nitrosodiethanolamine in several studies by subcutaneous injection and in one study by swabbing of the oral cavity (IARC 2000).

Cancer Studies in Humans

No epidemiological studies evaluating the relationship between human cancer and exposure specifically to *N*-nitrosodiethanolamine were available when it was listed in the *Second Annual Report on Carcinogens.* Since then, the International Agency for Research on Cancer (IARC 2000) concluded that there was inadequate evidence of the carcinogenicity of *N*-nitrosodiethanolamine from studies in humans. *N*-Nitrosodiethanolamine can be formed from ethanolamines and sodium nitrates, which are additives to soluble and synthetic metalworking fluids. In a review of studies of workers exposed to metalworking fluids, IARC noted increased cancer mortality or incidence among workers using fluids containing ethanolamines and sodium nitrates. One study found that esophageal cancer increased with increasing duration of exposure to nitrosamines as assessed by coexposure to ethanolamines and sodium nitrate; however, the same workers were also exposed to biocides.

Properties

N-Nitrosodiethanolamine is a nitrosamine compound that exists at room temperature as a yellow oil with no distinctive odor (HSDB 2009). It is miscible in water and soluble in polar organic solvents, but insoluble in nonpolar organic solvents. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light (IARC 1978, Akron 2009). Physical and chemical properties of *N*-nitrosodiethanolamine are listed in the following table.

Property	Information
Molecular weight	134.1[a]
Boiling point	114°C at 1.4 mm Hg[a]
Log K_{ow}	–1.28[b]
Water solubility	1,000 g/L[b]
Vapor pressure	0.0005 mm Hg at 20°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitrosodiethanolamine is used primarily as a research chemical and has no known commercial uses (HSDB 2009).

Production

N-Nitrosodiethanolamine is not produced commercially in the United States (HSDB 2009). In 2009, it was available in small quantities for research purposes from 11 suppliers worldwide, including 8 U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to *N*-nitrosodiethanolamine are dermal contact, ingestion, and inhalation (HSDB 2009). *N*-Nitrosodiethanolamine is widespread in the environment. It is a known contaminant of cosmetics, lotions, shampoos, cutting fluids, certain pesticides, antifreeze, and tobacco at concentrations of up to 130 ppm (130,000 ppb) (IARC 2000). Nitrosamines are formed within these products by reactions of precursors (nitrosating agents and primary or secondary amines) or are introduced through the use of contaminated raw materials (Schothorst and Somers 2005).

As of 1980, the U.S. Food and Drug Administration had analyzed over 300 cosmetic products and found that over 40% were contaminated with *N*-nitrosodiethanolamine. It was detected in facial cosmetics at concentrations of 42 to 49,000 µg/kg, in lotions at up to 140 µg/kg, and in shampoos at up to 260 mg/kg (IARC 1978). Cosmetics at least five years old had higher concentrations of *N*-nitrosodiethanolamine than new samples of the same products, indicating that the formation of *N*-nitrosodiethanolamine limits the shelf-life cosmetic products (Matyska *et al.* 2000). *N*-Nitrosodiethanolamine was also measured in 35 of 140 soap and shampoo products at concentrations of 23 to 992 µg/kg (Schothorst and Somers 2005). *N*-Nitrosodiethanolamine was detected in cigarette smoke at concentrations of 24 to 36 ng per cigarette and in smokeless tobacco products at up to 6.8 µg/g (Brunnemann and Hoffmann 1981, Brunnemann *et al.* 1982). The presence of *N*-nitrosodiethanolamine in tobacco is attributed to the use of an herbicide, maleic hydrazide diethanolamine, commonly applied to tobacco (IARC 2000).

Occupational exposure to *N*-nitrosodiethanolamine could occur during the use of synthetic cutting fluids to reduce the temperature of the metal-tool interface during metal cutting or grinding. *N*-Nitrosodiethanolamine is present in most cutting fluids containing triethanolamine and sodium nitrite, at concentrations ranging from 0.02% to 3% (IARC 1978). In addition, an atrazine pesticide formulation emulsified with triethanolamine was reported to contain *N*-nitrosodiethanolamine at a concentration of 0.5 mg/kg (IARC 1978). In 1976, the National Institute for Occupational Safety and Health estimated that 780,000 workers potentially were exposed to cutting fluids during their manufacture and use (NIOSH 1976). In a study of factory workers directly exposed to metalworking fluids, the post-shift concentration of *N*-nitrosodiethanolamine in the urine of workers using the cutting fluids was highly correlated with the concentration of *N*-nitrosodiethanolamine in the cutting fluids; urinary concentrations were up to 277 µg/L in workers using "nitrate-formulated" fluids, compared with 2.7 µg/L in workers using "nitrate-free" fluids. When nitrite concentrations in cutting fluids were less than 20 mg/L, *N*-nitrosodiethanolamine levels in the fluids remained below 5 mg/L (Ducos *et al.* 1999, Ducos and Gaudin 2003).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosodiethanolamine = U173.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

References

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Brunnemann KD, Hoffmann D. 1981. Assessment of the carcinogenic *N*-nitrosodiethanolamine in tobacco products and tobacco smoke. *Carcinogenesis* 2(11): 1123-1127.

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Matyska MT, Pesek JJ, Yang L. 2000. Screening method for determining the presence of *N*-nitrosodiethanolamine in cosmetics by open-tubular capillary electrochromatography. *J Chromatogr A* 887(1-2): 497-503.

NIOSH. 1976. *Current Intelligence Bulletin 15. Nitrosamines in Cutting Fluids*. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/78127_15.html.

Schothorst RC, Somers HHJ. 2005. Determination of *N*-nitrosodiethanolamine in cosmetic products by LC-MS-MS. *Anal Bioanal Chem* 381(3): 681-685.

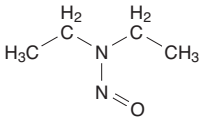
N-Nitrosodiethylamine

CAS No. 55-18-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as diethylnitrosamine



Carcinogenicity

N-Nitrosodiethylamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosodiethylamine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It was carcinogenic in animals exposed perinatally and as adults, causing tumors mainly in the liver, respiratory tract, kidney, and upper digestive tract (IARC 1972, 1978).

Benign and malignant liver tumors occurred in mice, rats, hamsters, guinea pigs, rabbits, dogs, and pigs orally exposed to *N*-nitrosodiethylamine. Liver tumors also occurred in rats following inhalation exposure or rectal administration; in mice, rats, and hamsters following intraperitoneal injection; in hamsters, guinea pigs, gerbils, and hedgehogs following subcutaneous injection; in mice following prenatal exposure; in birds following intramuscular injection; and in fish and frogs exposed to *N*-nitrosodiethylamine in the tank water. In dogs, exposure to *N*-nitrosodiethylamine by stomach tube followed by subcutaneous injection caused cancer of the liver and nasal cavity (squamous-cell carcinoma).

Tumors of the lung and upper respiratory tract occurred in mice, rats, hamsters, dogs, and pigs following oral administration of *N*-nitrosodiethylamine. Inhalation exposure caused tumors of the trachea, bronchi, and lungs in hamsters, and dermal exposure caused tumors of the nasal cavity in mice and hamsters. Subcutaneous injection caused respiratory-tract tumors in adult and newborn mice and hamsters, in pregnant hamsters (benign tracheal tumors), and in adult guinea pigs, gerbils, and hedgehogs. Intraperitoneal injection caused lung tumors in mice and respiratory-tract tumors in hamsters and monkeys, and intravenous injection caused tumors of the nasal cavity in gerbils. Prenatal exposure caused benign lung tumors (adenoma) in mice and hamsters.

Tumors of the kidney occurred in rats following oral, intravenous, or prenatal administration of *N*-nitrosodiethylamine. Oral administration also caused kidney tumors in pigs and tumors of the upper digestive tract in mice, rats, and hamsters. Prenatal exposure caused benign and malignant tumors of the upper digestive tract in mice and tumors of the thymus (thymoma) and benign mammary-gland tumors (adenoma) in rats. One study reported hematopoietic-system tumors in frogs exposed to *N*-nitrosodiethylamine in the tank water.

Since *N*-nitrosodiethylamine was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animals have been identified. As in earlier studies, the most common tumor sites were the liver, kidney, digestive tract, and respiratory tract. However, some of these studies reported that *N*-nitrosodiethylamine caused tumors by additional routes of exposure, in additional species, or at additional tissue sites. Liver tumors were also observed in (1) chickens after intramuscular administration, (2) cats after oral administration (dietary or by stomach tube) (Schmahl *et al.* 1978), and (3) newborn mice after intraperitoneal injection (Lai and Arcos 1980, Vesselinovitch *et al.* 1984). Tumors of the lung or trachea were also observed in (1) hamsters of both sexes after intratracheal administration (Yamamoto *et al.* 1985, Ishinishi *et al.* 1988, Tanaka *et al.* 1988), (2) rabbits after subcutaneous injection (Huntrakoon *et al.* 1989), (3) newborn mice after intraperitoneal injection (Vesselinovitch *et al.* 1984), and (4) snakes after oral exposure (Schmahl and Scherf 1983, 1984). Kidney tumors also were observed in orally exposed snakes. Addition of *N*-nitrosodiethylamine to the tank water increased the incidence of benign or malignant pancreatic tumors (adenoma, cystadenoma, or adenocarcinoma) in larval or juvenile fish (Thiyagarajah and Grizzle 1986) and tumors of the digestive gland and hematopoietic system in mollusks (Khudoley and Syrenko 1978). Benign laryngotracheal tumors (papilloma) were observed in pregnant hamsters exposed by intraperitoneal injection and in the prenatally exposed offspring, and laryngotracheal tumors (neuroendocrine-cell tumors) were observed in the second generation of offspring (Mohr *et al.* 1995).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosodiethylamine.

Properties

N-Nitrosodiethylamine is a nitrosamine compound that is a slightly yellow, volatile liquid at room temperature (HSDB 2009). It is soluble in water, ethanol, ether, organic solvents, and lipids. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet

light. (IARC 1978). Physical and chemical properties of *N*-nitrosodiethylamine are listed in the following table.

Property	Information
Molecular weight	102.1[a]
Specific gravity	0.9422 at 20°C/4°C[a]
Melting point	< 25°C[b]
Boiling point	175°C to 177°C[a]
Log K_{ow}	0.48[a]
Water solubility	106 g/L at 24°C[b]
Vapor pressure	0.86 mm Hg at 20°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitrosodiethylamine is used primarily as a research chemical (HSDB 2009). Previously, it was used as a gasoline and lubricant additive, antioxidant, stabilizer in plastics, fiber-industry solvent, and copolymer softener, and in the synthesis of 1,1-diethylhydrazine. It was also used to increase dielectric constants in condensers (IARC 1972, HSDB 2009).

Production

No commercial producers of *N*-nitrosodiethylamine were identified. In 2009, it was available from 11 U.S. suppliers (ChemSources 2009). No data on U.S. production, imports, or exports of *N*-nitrosodiethylamine were found.

Exposure

The routes of potential human exposure to *N*-nitrosodiethylamine are ingestion, inhalation, and dermal contact. The general population may be exposed to unknown quantities of *N*-nitrosodiethylamine present in foods, beverages, tobacco smoke, drinking water, and industrial pollution (HSDB 2009). Intake from exposure via air, diet, and smoking has been estimated at a few micrograms per day. *N*-Nitrosodiethylamine has been measured in a variety of foods, including cheese at concentrations of 0.5 to 30 µg/kg, soybeans at 0.2 µg/kg, soybean oil at 4 µg/kg, various fish at up to 147 µg/kg, salt-dried fish at 1.2 to 21 mg/kg, cured meats at up to 40 µg/kg, and alcoholic beverages at 0.1 µg/kg. *N*-Nitrosodiethylamine was detected in tobacco-smoke condensate at concentrations of 1.0 to 28 ng per cigarette (IARC 1978). Up to 8.3 ng per cigarette was found in mainstream smoke and 8 to 73 ng in sidestream smoke. *N*-Nitrosodiethylamine was found at concentrations of up to 0.2 ng/L in indoor air polluted with tobacco smoke and at 10 ng/m^3 in the smoking compartment of a train (Brunnemann *et al.* 1977, Brunnemann and Hoffmann 1978).

Nitrosamines frequently are produced during rubber processing and may be present as contaminants in the final rubber product (HSDB 2009). Potential exposure depends on the ability of the nitrosamines to migrate from the product into the body. Nitrosamines present in pacifiers and baby-bottle nipples can migrate into saliva, which could result in ingestion of nitrosamines (IARC 1974, 1978).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, 11,795 lb of waste containing *N*-nitrosodiethylamine was relased by three facilities in 1999; 99.6% was released to land. In 2007, one facility released 500 lb of *N*-nitrosodiethylamine to a hazardous-waste landfill (TRI 2009). *N*-Nitrosodiethylamine is widespread in the environment, but is rapidly decomposed by sunlight and does not usually persist in ambient air or water exposed to sunlight. It was found at concentrations of 0.07 and 0.24 µg/L in wastewater from two chemical plants, 0.010 µg/L in high-nitrate well water for drinking, and 0.33 to 0.83 µg/L in deionized water (HSDB 2009). *N*-Nitrosodiethylamine and other nitrosamines were found at very low concentrations in ion-exchange resins (Gough *et al.* 1977).

There is some potential for occupational exposure of laboratory, copolymer, and lubricant workers to *N*-nitrosodiethylamine (IARC 1972, 1978). No data were found on the numbers of workers potentially exposed.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L; based on fish or shellfish consumption only = 1.24 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosodiethylamine = U174.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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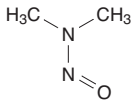
N-Nitrosodimethylamine

CAS No. 62-75-9

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosodimethylamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosodiethylamine caused tumors in numerous species of experimental animals, at several different tissue sites, and by several different routes of exposure. Tumors were observed in all species tested, including mice, rats, hamsters, guinea pigs, multimammate mice (genus *Mastomys*), rabbits, frogs, newts, and various fish. *N*-Nitrosodimethylamine caused tumors primarily of the liver, respiratory tract, kidney, and blood vessels (IARC 1972, 1978). Benign and malignant tumors of the liver (hepatocellular adenoma and carcinoma) or bile duct (cholangioma or cholangiocellular tumors) were observed following (1) oral administration in mice, rats, hamsters, rabbits, guinea pigs, and fish, (2) inhalation exposure in mice, (3) prenatal exposure in mice, (4) subcutaneous administration in hamsters, *Mastomys,* and newborn and suckling mice and rats, (5) intraperitoneal injection in adult and newborn mice and in newts, (6) intramuscular injection in rats, and (7) exposure via tank water in frogs and fish.

Exposure to *N*-nitrosodimethylamine by most of these routes also caused tumors of the respiratory tract: (1) oral exposure caused lung tumors in mice, (2) inhalation exposure caused lung tumors in mice and rats and nasal-cavity tumors in rats, (3) subcutaneous injection caused lung tumors in adult, newborn, and suckling mice and nasal-cavity tumors in adult hamsters, (4) intraperitoneal injection caused lung tumors in adult and newborn mice and nasal-cavity tumors in rats, and (5) prenatal exposure caused lung tumors in mice (IARC 1972, 1978).

N-Nitrosodimethylamine caused kidney tumors in rats and mice exposed orally or by inhalation or intraperitoneal injection and in rats exposed prenatally or by subcutaneous injection. Blood-vessel tumors (hemangioma or hemangiosarcoma) were observed in mice, rats, and hamsters after oral exposure; in hamsters and adult, newborn, and suckling mice after subcutaneous injection; and in mice after intraperitoneal injection. Addition of *N*-nitrosodimethylamine to the tank water of frogs caused tumors of the hematopoietic system (IARC 1972, 1978).

Since *N*-nitrosodimethylamine was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animals have been identified, which reported that *N*-nitrosodimethylamine caused tumors at additional tissue sites and in additional species. Tumors of the digestive gland and hematopoietic system were observed in mollusks exposed to *N*-nitrosodimethylamine in the tank water (Khudoley and Syrenko 1978), and ovarian tumors (granulosa-cell tumors) in female hamsters exposed by subcutaneous injection (Richter-Reichhelm *et al.* 1978). Liver tumors were observed in foxes after dietary exposure (Koppang *et al.* 1981) and in female toads after subcutaneous injection (Sakr *et al.* 1989), and lung and liver tumors were observed in rats after a single intraperitoneal injection (Noronha and Goodall 1983, Sykora *et al.* 1985, Driver and Swann 1987).

Cancer Studies in Humans

No epidemiological studies evaluating the relationship between human cancer and exposure specifically to *N*-nitrosodimethylamine were available when it was listed in the *Second Annual Report on Carcinogens.* Since then, a number of population-based case-control studies or ecological studies of cancer and dietary sources of *N*-nitrosodimethylamine (particularly, for example, cured, salted, or barbecued meat or fish) have been conducted in various countries. These studies focused mainly on cancer of the gastrointestinal tract, and the majority relied on estimated intake from self-reported dietary histories. Several case-control studies reported dose-related associations, some statistically significant, between estimated *N*-nitrosodimethylamine intake and oropharyngeal cancer (De Stefani *et al.* 1994), stomach cancer (Le Vecchia *et al.* 1995, Pobel *et al.* 1995, Larsson *et al.* 2006), esophageal cancer (Lu *et al.* 1987, Rogers *et al.* 1995), or colorectal cancer (Knekt *et al.* 1999). Ecological studies also suggested an association between high dietary *N*-nitrosodimethylamine intake and high rates of esophageal cancer in populations (Siddiqi *et al.* 1988, 1991, Lin *et al.* 2002a,b). A case-control study of lung cancer found a dose-related increase in risk associated with estimated dietary intake of *N*-nitrosodimethylamine among smokers and nonsmokers (De Stefani *et al.* 1996). Several studies adjusted for smoking or alcohol consumption, and interactive effects with these substances were noted in some analyses; however, the results may have been confounded by exposure to these substances or other factors, including other nitrosamines in the diet. No studies of occupational exposure to *N*-nitrosodimethylamine were identified.

Properties

N-Nitrosodimethylamine is a nitrosamine compound that exists at room temperature as a yellow liquid with a faint characteristic odor (Akron 2009). It is very soluble in water, alcohol, and ether, miscible with methylene chloride and vegetable oils, and soluble in lipids, chloroform, and most other organic solvents (HSDB 2009). It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosodimethylamine are listed in the following table.

Property	Information
Molecular weight	74.1[a]
Specific gravity	1.0048 at 20°C/4°C[a]
Melting point	< 25°C[b]
Boiling point	151°C to 153°C[a]
Log K_{ow}	–0.57[a]
Water solubility	1,000 g/L at 24°C[b]
Vapor pressure	2.7 mm Hg at 20°C[b]
Vapor density relative to air	2.56[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitrosodimethylamine is used primarily as a research chemical (HSDB 2009). Before April 1, 1976, it was used as an intermediate in the electrolytic production of 1,1-dimethylhydrazine, a storable liquid rocket fuel containing approximately 0.1% *N*-nitrosodimethylamine as an impurity (IARC 1978). Other former uses of *N*-nitrosodimethylamine include use in control of nematodes, to inhibit nitrification in soil, in active metal anode-electrolyte systems (high-energy batteries), in the preparation of thiocarbonyl fluoride polymers, and as a plasticizer for rubber and acrylonitrile polymers, a solvent in the fiber and plastics industry, an antioxidant, a softener of copolymers, and an additive to lubricants (HSDB 2009).

Production

Commercial production of *N*-nitrosodimethylamine in the United States began in the mid 1950s for use in the manufacture of 1,1-dimethylhydrazine. The last commercial producer of *N*-nitrosodimethylamine closed its plant in 1976 (IARC 1978), and there is no evidence that *N*-nitrosodimethylamine is currently manufactured commercially in the United States (HSDB 2009). In 2009, *N*-nitrosodimethylamine was available from nine U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of *N*-nitrosodimethylamine were found.

Exposure

The routes of potential human exposure to *N*-nitrosodimethylamine are ingestion, inhalation, and dermal contact (HSDB 2009). The general population may be exposed to unknown quantities of *N*-nitrosodimethylamine present in foods and beverages, tobacco smoke, herbicides, pesticides, drinking water, and industrial pollution (IARC 1978, ATSDR 1989). In addition, nitrosamines may be formed from amines reacting with nitrites in the human body as a result of ingestion of these precursors separately in food, water, or air. Intake of *N*-nitrosodimethylamine from exposure via air, diet, and smoking has been estimated at a few micrograms per day. *N*-Nitrosodimethylamine is present in a variety of foods, including cheese, soybean oil, various meat products, bacon, various cured meats, frankfurters, cooked ham, fish and fish products, spices used for meat curing, apple brandy, other alcoholic beverages, and beer. Concentrations in these foodstuffs have been measured at up to 850 µg/kg (in spices used in curing) (IARC 1978).

N-Nitrosodimethylamine has been detected in numerous drugs formulated with aminopyrene, including tablets, suppositories, injections, drops, and syrups, at concentrations ranging from less than 10 to 371 µg/kg. *N*-Nitrosodimethylamine was measured in mainstream cigarette smoke at 13 to 65 ng per cigarette for nonfiltered cigarettes and 5.7 to 43 ng for filtered cigarettes and in sidestream smoke at 680 to 823 ng for nonfiltered cigarettes and 1,040 to 1,770 ng for filtered cigarettes. It was found at concentrations of 90 to 240 ng/m^3 in smoke-filled rooms, such as bars, but at less than 5 ng/m^3 in residences (IARC 1978). Nitrosamines frequently are produced during rubber processing and may be present as contaminants in the final rubber product. Potential exposure depends on the ability of the nitrosamine to migrate from the product into the body. Dimethylamine-formulated pesticides and herbicides contained *N*-nitrosodimethylamine at 190 to 640 mg/L (190,000 to 640,000 µg/L) (ATSDR 1989).

N-Nitrosodimethylamine is widespread in the environment, but it is rapidly decomposed by sunlight and does not usually persist in ambient air or water exposed to sunlight (ATSDR 1989). *N*-Nitrosodimethylamine was found at concentrations of 0.25 µg/L in industrial wastewater from chemical factories, 0.02 to 0.82 µg/L in chlorinated drinking water, less than 0.01 µg/L in high-nitrate well water, and 0.012 to 0.34 µg/L in deionized water. *N*-Nitrosodimethylamine and other nitrosamines were found at very low concentrations in ion-exchange resins (Gough *et al.* 1977). Soil samples taken near industrial plants contained *N*-nitrosodimethylamine at concentrations of up to 15.1 ng/g (IARC 1978).

There is some potential for occupational exposure of laboratory, copolymer, lubricant, and pesticide workers to *N*-nitrosodimethylamine (IARC 1978, HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 747 workers, including 299 women, potentially were exposed to *N*-nitrosodimethylamine (NIOSH 1990). Occupational Safety and Health Administration regulations concerning *N*-nitrosodimethylamine designate strict procedures to avoid worker contact (IARC 1978). Mixtures containing *N*-nitrosodimethylamine at 1.0% or more must be maintained in isolated or closed systems, workers must observe special hygiene rules, and certain procedures must be followed for movement of the material and in case of accidental spills and emergencies.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.00069 µg/L; based on fish or shellfish consumption only = 3.0 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.
Reportable quantity (RQ) = 10 lb.
Threshold planning quantity (TPQ) = 1,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosodimethylamine = P082.
Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

Action levels for *N*-nitrosodimethylamine in barley malt and malt beverages range from 5 to 10 ppb.
The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.
In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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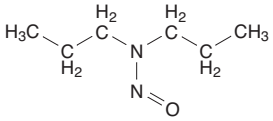
N-Nitrosodi-*n*-propylamine

CAS No. 621-64-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosodi-*n*-propylamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosodi-*n*-propylamine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. In rats, it caused liver cancer (hepatocellular carcinoma) and benign and malignant tumors of the esophagus (papilloma and carcinoma) following administration in the drinking water or subcutaneous injection (IARC 1978). Subcutaneous injection of *N*-nitrosodi-*n*-propylamine also caused tumors of the lung and nasal and paranasal cavities in hamsters and rats, tumors of the laryngobronchial tract in hamsters, and benign and malignant kidney tumors (adenoma and adenocarcinoma) in rats.

Since *N*-nitrosodi-*n*-propylamine was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animal have been identified, which reported that *N*-nitrosodi-*n*-propylamine caused tumors of the liver, esophagus, and respiratory tract by additional routes of exposure or in additional species. Liver tumors were observed in monkeys exposed by intraperitoneal injection (Adamson and Sieber 1979, 1982); cancer (carcinoma) of the liver, esophagus, and nasal cavity in rats exposed by stomach tube (Lijinsky and Reuber 1983); and tracheal tumors in male hamsters exposed by intratracheal instillation (Ishinishi *et al.* 1988). In addition, administration of *N*-nitrosodi-*n*-propylamine in the drinking water caused forestomach tumors in male rats (Lijinsky *et al.* 1981).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosodi-*n*-propylamine.

Properties

N-Nitrosodi-*n*-propylamine is a nitrosamine compound that is a yellow liquid at room temperature (HSDB 2009). It is soluble in water, lipids, and organic solvents. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosodi-*n*-propylamime are listed in the following table.

Property	Information
Molecular weight	130.2[a]
Specific gravity	0.9160 at 20°C/4°C[a]
Boiling point	206°C[b]
Log K_{ow}	1.36[a]
Water solubility	13 g/L at 24°C[b]
Vapor pressure	0.086 mm Hg at 20°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitrosodi-*n*-propylamine is used in small quantities in laboratory research. It has no known commercial use (IARC 1978, ATSDR 1989, HSDB 2009).

Production

N-Nitrosodi-*n*-propylamine was first prepared in 1886, but it has never been produced in commercial quantities (IARC 1978, HSDB 2009). In 2009, it was available in small quantities for research purposes from eight U.S. suppliers (ChemSources 2009).

Exposure

The primary routes of potential human exposure to *N*-nitrosodi-*n*-propylamine are inhalation, ingestion, and dermal contact (HSDB 2009). *N*-Nitrosodi-*n*-propylamine has been detected in extruded rubber products, cheese, and alcoholic beverages, and in the herbicides trifluralin, isopropalin, and oryzalin at low concentrations (17 to 190 ppm) (IARC 1978, ATSDR 1989, HSDB 2009). There is some evidence that *N*-nitrosodi-*n*-propylamine may be formed in the upper gastrointestinal tract following ingestion of foods containing nitrites and secondary amines (ATSDR 1989). It may also occur in cigarette smoke at low levels (about 1 ng per cigarette). *N*-Nitrosodi-*n*-propylamine is not commonly detected in the environment. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, two facilities released a total of 2,379 lb of *N*-nitrosodi-*n*-propylamine to the environment in 1998, and one facility released 5 lb in 1999. Since 2001, releases have ranged from a low of 257 lb in 2002 to a high of 755 lb in 2005. In 2007, 250 lb was released to air and 500 lb to an off-site hazardous-waste landfill (TRI 2009). When released to the environment, *N*-nitrosodi-*n*-propylamine will undergo photochemical and biological degradation and will not persist. *N*-Nitrosodi-*n*-propylamine has been detected in some samples of wastewater from chemical plants (ATSDR 1989).

Occupational exposure to *N*-nitrosodi-*n*-propylamine may occur through inhalation and dermal contact during herbicide application (HSDB 2009) or production of extruded rubber parts (ATSDR 1989). *N*-Nitrosodi-*n*-propylamine was not detected in air samples collected at agricultural fields before, during, or after application of trifluralin. However, at an automobile plant where workers were involved in the production of extruded rubber parts, it was found in air samples at concentrations of 1.3 to 3.3 µg/m^3. In the vulcanization step of tire manufacturing, *N*-Nitrosodi-*n*-propylamine was measured at concentrations of up to 1.086 mg/m^3, resulting in an estimated daily intake of 0.0029 mg/kg of body weight for workers (Durmusoglu 2007). No data were available on the numbers of workers potentially exposed to *N*-nitrosodi-*n*-propylamine.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0050 µg/L; based on fish or shellfish consumption only = 0.51 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosodi-*n*-propylamine = U111.
Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.
In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. http://www.epa.gov/triexplorer and select *N*-Nitrosodi-*n*-Propylamine.

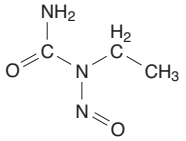
N-Nitroso-*N*-ethylurea

CAS No. 759-73-9

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as *N*-ethyl-*N*-nitrosourea



Carcinogenicity

N-Nitroso-*N*-ethylurea is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitroso-*N*-ethylurea caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It was carcinogenic in animals exposed perinatally and as adults. Perinatal exposure caused primarily nervous-system tumors, whereas tumors occurred at numerous tissue sites in adults, including the kidney and lymphoreticular system.

Tumors of the nervous system (brain, spinal cord, or peripheral nerves) were observed following oral exposure to *N*-nitroso-*N*-ethylurea in suckling rats, a single subcutaneous injection in newborn rats, and prenatal exposure in mice, rats, hamsters, and rabbits. In adult rodents, intraperitoneal injection of *N*-nitroso-*N*-ethylurea caused brain tumors in mice, and intravenous injection caused tumors of the brain and peripheral nerves in rats (IARC 1972, 1978).

Prenatal exposure to *N*-nitroso-*N*-ethylurea also caused benign lung tumors (adenoma), leukemia, and tumors of the liver, Harderian gland, and endocrine glands in mice; benign and malignant kidney tumors (adenoma, adenocarcinoma, and adenocarcinosarcoma) in rabbits; and benign tumors of the sweat glands (adenoma) and skin (papilloma) in pigs. Oral exposure caused leukemia in adult rats, kidney tumors (nephroblastoma) in suckling rats, and tumors of the kidney (nephroblastoma), eye, liver, muscle, and jaw in newborn opossums. Intravenous injection of *N*-nitroso-*N*-ethylurea caused tumors of the kidney, ovary, uterus, and vagina in rats and tumors of the ovary, uterus, bone, skin, and blood vessels in monkeys. Intraperitoneal injection caused thymic lymphoma and myeloid leukemia in rats and lymphoma and tumors of the liver, kidney, ovary, lung, Harderian gland, stomach in mice. In newborn mice, a single subcutaneous injection of *N*-nitroso-*N*-ethylurea caused lymphoma, liver cancer (hepatocellular carcinoma), and benign and malignant lung tumors (adenoma and adenocarcinoma) (IARC 1972, 1978).

Since *N*-nitroso-*N*-ethylurea was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animal have been identified, which confirmed the induction of several tumors types observed in earlier studies and reported that it caused tumors by additional routes of exposure, in additional species, and at additional tissue sites. Tumors were observed for the following additional routes of exposure or additional species:

- Intratracheal administration caused benign tracheal tumors (papilloma and polyps) in male hamsters (Grubbs *et al.* 1981).
- Dermal administration caused skin tumors in mice (Lijinsky 1982, Lijinsky and Reuber 1983).
- Implantation into the mammary gland caused mammary-gland cancer (adenocarcinoma) in female rats (Holtzman *et al.* 1985).
- Intracerebral injection caused brain tumors in adult rats (Druckrey 1973), and a single intracerebral injection caused spinal-cord tumors in newborn rats of both sexes (Pfaffenroth and Das 1979).
- Intravesicular administration caused urinary-bladder tumors in female rats (Lijinsky *et al.* 1992).
- Injection directly into the amniotic sac of pregnant mice caused benign lung tumors (alveologenic adenoma) in the offspring (Rossi *et al.* 1979).
- In fish, exposure in the tank water caused benign skin tumors (papilloma) (Beckwith *et al.* 2000).
- In gerbils, subcutaneous injection caused nervous-system tumors (oligodendroglioma) and skin cancer (melanoma) in newborns of both sexes and benign blood-vessel tumors (hemangioma) in adults of both sexes (Naito *et al.* 1985).

N-nitroso-*N*-ethylurea also caused tumors at the following additional tissue sites:

- Benign forestomach tumors (squamous-cell papilloma) were observed in male hamsters exposed by intraperitoneal injection, as well peripheral-nerve tumors in prenatally exposed hamsters (Likhachey *et al.* 1983, Diwan *et al.* 1996).
- Malignant placental tumors (choriocarcinoma) were observed in pregnant monkeys exposed by intravenous injection (Rice *et al.* 1981).
- Tumors of the lining of the peritoneal cavity (mesothelioma) were observed in orally exposed male rats, as well as mammary-gland tumors in orally exposed female rats (Lijinsky and Kovatch 1989).

Intraperitoneal injection of *N*-nitroso-*N*-ethylurea in rats caused mammary-gland tumors in males, ovarian tumors in females, nervous-system tumors adult males and newborns, and possibly kidney tumors in newborns (Mandybur *et al.* 1978, Stoica and Koestner 1984, Stoica *et al.* 1985, Hasgekar *et al.* 1989). Prenatal exposure of mice to *N*-nitroso-*N*-ethylurea caused benign skin tumors (papilloma and sebaceous adenoma) in nude mice and cancer of the small intestine (adenocarcinoma) in mice of both sexes in other mouse strains (Anderson *et al.* 1982, Oomen *et al.* 1984, 1988, 1989). Prenatal exposure of rabbits caused tumors of the kidney and neural tissue (neurofibroma) (Fox *et al.* 1982).

Oral administration of *N*-nitroso-*N*-ethylurea to rats caused thyroid-gland tumors, forestomach cancer (squamous-cell carcinoma), and benign lung tumors (adenoma) in both sexes; tumors of the colon and skin in males; and ovarian tumors (Sertoli-cell tumors) in females (Maekawa *et al.* 1984, Lijinsky *et al.* 1985, Maekawa *et al.* 1986, Lijinsky and Kovatch 1989, 1996). Administration by stomach tube to hamsters caused benign and malignant forestomach tumors (papilloma and squamous-cell carcinoma) and blood-vessel cancer (hemangiosarcoma) in both sexes (Lijinsky *et al.* 1985).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitroso-*N*-ethylurea.

Properties

N-Nitroso-*N*-ethylurea is a nitrosamine compound that exists as yellow-pink or buff-yellow crystals at room temperature (HSDB 2009). It is soluble in water, chloroform, and other polar organic solvents,

but insoluble in non-polar organic solvents. It decomposes in alkaline solution at a rate that depends on pH (IARC 1978). The pure compound is sensitive to moisture and light and should be stored under refrigeration. Physical and chemical properties of *N*-nitroso-*N*-ethylurea are listed in the following table.

Property	Information
Molecular weight	117.1[a]
Melting point	103°C to 104°C (with decomposition)[a]
Log K_{ow}	0.23[a]
Water solubility	13 g/L at 25°C[b]
Vapor pressure	0.0183 mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitroso-*N*-ethylurea has been used to synthesize diazoethane in the laboratory, and its mutagenic effects have been studied for promoting the growth of various plants (IARC 1978).

Production

N-Nitroso-*N*-ethylurea was first prepared in 1919 but has never been produced in commercial quantities in the United States (IARC 1978). In 2009, it was available in small quantities for research purposes from six U.S. suppliers (ChemSources 2009).

Exposure

The potential for human exposure is limited, because *N*-nitroso-*N*-ethylurea is not produced or used in large quantities in the United States (IARC 1978). Human exposure to *N*-nitroso compounds may occur through absorption from food, water, and air, and from formation in the human body from precursors ingested separately from food or water (IARC 1978). Exposure may also result from the consumption or smoking of tobacco. According to the U.S. Environmental Proection Agency's Toxics Release Inventory, environmental releases of *N*-nitroso-*N*-ethylurea totaled of 169 lb in 1999 and 255 lb in 2001, but only 10 lb in 2005, 2006, and 2007 (TRI 2009). In air, *N*-nitroso-*N*-ethylurea exists solely as vapor and is degraded by reaction with photochemically produced hydroxyl radicals, with an estimated half-life of 3.2 days. It hydrolyzes in water, with a half-life of 1.5 hours at pH 7 at 20°C. Occupational exposure to *N*-nitroso-*N*-ethylurea may occur through inhalation or dermal contact during its use in research (HSDB 2009). No data were found on the numbers of workers potentially exposed to *N*-nitroso-*N*-ethylurea.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitroso-*N*-ethylurea = U176.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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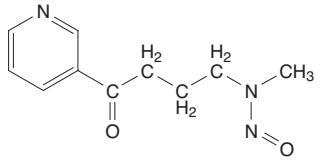
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone

CAS No. 64091-91-4

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as NNK or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone



Carcinogenicity

4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

NNK caused tumors in three rodent species and at several different tissue sites, primarily tumors of the lung and nasal cavity in rats and hamsters. In some studies, NNK caused tumors after a single injection, and dose-response relationships were observed for liver, lung, and nasal-cavity tumors in rats. Subcutaneous injection of NNK caused benign or malignant nasal-cavity tumors (squamous- or transitional-cell papilloma, neuroblastoma, rhabdomyosarcoma, esthesioneuroepithelioma, squamous-cell carcinoma, anaplastic carcinoma, or spindle-cell sarcoma) and lung cancer (squamous-cell carcinoma, adenocarcinoma, and adenosquamous-cell carcinoma) in rats and hamsters of both sexes (IARC 1985). Subcutaneous injection of NNK also caused cancer of the liver (hepatocellular carcinoma) and the blood vessels (hemangiosarcoma) in rats of both sexes and tracheal tumors in hamsters of both sexes after single or multiple injections. In female strain A mice (a strain with a high spontaneous incidence of lung tumors), intraperitoneal injection of NNK caused benign and malignant lung tumors (adenoma and carcinoma).

Since NNK was listed in the *Sixth Annual Report on Carcinogens,* additional studies have been identified in which NNK was carcinogenic by additional routes of exposure or in additional species. The majority of these studies confirmed that NNK primarily caused tumors of the lung, nasal cavity, and liver in rodents:

- Oral administration (by stomach tube or in the drinking water) caused lung tumors in strain A/J mice (Chung 1999, Sugimoto *et al.* 2003, Kim *et al.* 2004, Richie *et al.* 2006) and male rats (Rivenson *et al.* 1988, Lijinsky *et al.* 1991a, Hoffmann *et al.* 1993, Hecht *et al.* 1996), nasal-cavity tumors in rats of both sexes, and liver tumors in male rats (Lijinsky *et al.* 1991a).
- Swabbing of the oral cavity with NNK caused tumors of the lung, nasal cavity, and liver in rats (Prokopczyk *et al.* 1991).
- Administration onto the tongue caused lung tumors in mice (Padma *et al.* 1989).
- Intravesicular instillation caused lung and liver tumors in female rats (Lijinsky *et al.* 1991b).
- Intraperitoneal injection caused lung and liver tumors in newborn mice of both sexes (Anderson *et al.* 1991, Beebe *et al.* 1993).
- Prenatal exposure of hamsters caused nasal-cavity tumors (Correa *et al.* 1990, Schuller *et al.* 1994).
- In female mink, subcutaneous injection caused nasal-cavity tumors (Koppang *et al.* 1997).

NNK also was found to cause tumors at additional tissues sites. Prenatal exposure of hamsters caused adrenal-gland tumors in both sexes (Schuller *et al.* 1993, 1994) and caused tumors of the larynx and trachea, in addition to the nasal cavity (Correa *et al.* 1990). Administration of NNK in the drinking water of male rats also increased the combined incidences of leukemia and lymphoma (Hecht *et al.* 1996) and benign and malignant tumors of the pancreas (exocrine acinar adenoma and adenocarcinoma) (Rivenson *et al.* 1988, Hoffmann *et al.* 1993).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to NNK.

Properties

NNK is a tobacco-specific nitrosamine compound. In its pure form, NNK is a pale-yellow crystalline solid at room temperature (Akron 2009). It is soluble in water (SRC 2009). Physical and chemical properties of NNK are listed in the following table.

Property	Information
Molecular weight	207.2[a]
Melting point	71°C to 73°C[a]
Water solubility	40.5 g/L at 25°C[b]
Dissociation constant (pK_a)	10.57[a]

Sources: [a]Akron 2009, [b]SRC 2009.

Use

NNK has no known use other than as a laboratory chemical; it has been used as a positive-control substance in laboratory carcinogenicity studies (IARC 1985, 2007).

Production

Synthetic NNK is prepared by reacting sodium hydroxide and sodium nitrite with 4-(*N*-methyl)-1-(3-pyridyl)-1-butanone dihydrochloride or by reacting nicotine with sodium nitrite in aqueous solution. NNK is not produced commercially (IARC 1985). In 2009, it was available in small quantities for research purposes from six suppliers worldwide, including four U.S. suppliers (ChemSources 2009).

Exposure

Potential exposure to NNK is widespread among tobacco-product users and people exposed to sidestream smoke. NNK has been measured in tobacco at concentrations of 0.1 to 35 mg/kg. It was found in moist snuff at up to 18 mg/kg (dry weight), in dry snuff at up to 84.4 mg/kg, in leading U.S. brands of snuff at 0.2 to 8.3 mg/kg, in U.S. chewing tobacco products at up to 1.1 mg/kg (dry weight), in U.S. cigarettes at up to 1.27 mg/kg of dry tobacco (IARC 1985, 2007), and in Nigerian or American cigarettes at 55 to 317 ng per cigarette

(Atawodi *et al.* 1995, Harris 2001). NNK was found in the tobacco of bidi cigarettes at concentrations ranging from 0.10 to 0.85 mg/kg, compared with 0.11 to 0.28 mg/kg for U.S. cigarettes (Wu *et al.* 2004).

NNK has been found in mainstream smoke from U.S. cigarettes at concentrations of up to 425 ng per cigarette (IARC 2007). NNK was measured in cigarette and cigar smoke at 0.9 to 7 mg/kg, in mainstream cigarette at 0.02 to 4.2 μg per cigarette, and in sidestream smoke at 0.2 to 15.7 μg per cigarette (IARC 1985). One study found NNK concentrations to be 45% to 73% lower in smoke from filtered than non-filtered cigarettes. NNK was measured in mainstream smoke from bidi cigarettes at 2.13 to 25.9 ng per cigarette and from U.S. cigarettes at 34.3 to 139 ng per cigarette when smoked at an equal rate; however, bidi cigarettes generally are smoked at about twice the rate of U.S. cigarettes, resulting in delivery of about the same total amount of NNK to the smoker (Wu *et al.* 2004).

NNK may also form in the mouth during tobacco chewing or oral snuff use. Concentrations of NNK in the saliva of women who used snuff ranged from 2.1 to 201 ng/g. NNK was detected in pancreatic juices from smokers at a mean concentration of 88.7 ng/mL (compared with 12.4 ng/mL in nonsmokers) and in cervical mucus from smokers at 46.9 ng/g of mucus (Prokopczyk *et al.* 1997, 2002). Metabolites of NNK were found in the urine of newborns whose mothers had smoked during pregnancy, but not in the urine of those born to nonsmoking mothers (Lackmann *et al.* 1999). Children in households with smokers also had significantly elevated urinary concentrations of NNK metabolites; the highest levels were found among African-American children (Sexton *et al.* 2004). The concentration of NNK metabolites was also significantly increased in the urine of nonsmoking hospitality workers on days when they worked in locations where smoking was allowed (Tulunay *et al.* 2005). Reduction of smoking reduced the urinary levels of NNK metabolites, but the reduction was less than expected based on the reduction in the number of cigarettes smoked per day (Hecht *et al.* 2004, Joseph *et al.* 2005).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 μg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 μg/L for nitrosamines.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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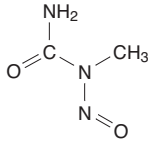
N-Nitroso-*N*-methylurea

CAS No. 684-93-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as nitrosomethylurea or *N*-methyl-*N*-nitrosourea



Carcinogenicity

N-Nitroso-*N*-methylurea is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitroso-*N*-methylurea caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It was carcinogenic in animals exposed perinatally or as adults. Perinatal exposure resulted mainly in nervous-system tumors, whereas tumors occurred at numerous tissue sites in adults, including the respiratory and digestive tracts.

Tumors of the nervous system were observed following prenatal exposure in rats, oral exposure in adult rats (peripheral nerves), and exposure by injection in newborn rats (peripheral nervous system) and adult rats, rabbits, and dogs (peripheral and central nervous system). Prenatal exposure also caused kidney tumors in rats and benign tumors of the lung (adenoma) and liver (hepatocellular adenoma) in mice, and exposed pregnant rats developed mammary-gland tumors (IARC 1972, 1978).

Administration of *N*-nitroso-*N*-methylurea by intratracheal instillation caused cancer of the nasopharyngeal tube, pharynx, larynx, bronchi, esophagus, forestomach, and trachea (epidermoid or large-cell anaplastic carcinoma) in hamsters. Intrarectal administration caused benign or malignant colon tumors (adenoma, adenocarcinoma, or squamous-cell carcinoma) in male rats and female mice and guinea pigs. In female mice, it also caused benign lung tumors (adenoma) and lymphoma. Lung tumors also resulted from exposure by injection in rats. In addition, injection exposure caused (1) digestive-tract tumors in rats, gerbils, and hamsters, (2) tumors of the pancreas, small intestine, and abdominal cavity in guinea pigs, (3) leukemia or lymphoma in newborn and adult mice and lymphoma in adult rats, (4) blood-vessel tumors in guinea pigs, rabbits, and dogs, (5) mammary-gland tumors in rats, and (6) tumors of the heart (sarcoma) and at the injection site in hamsters. Dermal exposure caused leukemia and benign and malignant skin tumors in mice and skin cancer (squamous or basal-cell carcinoma) in rats and hamsters. Intravesicular instillation caused benign and malignant urinary-bladder tumors (transitional-cell papilloma and carcinoma) in female rats (IARC 1972, 1978).

Since *N*-nitroso-*N*-methylurea was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animal have been identified that confirmed the induction of several tumor types previously observed and reported tumors at additional tissue sites, in additional species, and by additional routes of exposure:

- Tumors of the thymus were observed in rats following oral exposure (Lijinsky and Kovatch 1996).
- Tumors of the teeth (odontoma, odontoameloblastoma, and ameloblastoma) were observed in male rats exposed by injection (Smulow *et al.* 1983).
- Female shrews developed uterine and cervical tumors following intrarectal administration (Yang *et al.* 1996).
- In fish, addition of *N*-nitroso-*N*-methylurea to the tank water caused eye tumors (neuroblastoma) (Schwab *et al.* 1979).
- Placement of *N*-nitroso-*N*-methylurea–impregnated sutures in the ovaries of female rats caused benign or malignant ovarian tumors (adenoma or adenocarcinoma) (Tunca *et al.* 1985).
- Implantation of *N*-nitroso-*N*-methylurea, as well as injection, caused mammary-gland cancer (adenocarcinoma) in female rats (Thompson and Meeker 1983, Holtzman *et al.* 1985, Seaborn and Yang 1993, Takahashi *et al.* 1995).
- Administration of *N*-nitroso-*N*-methylurea directly into the stomach via a surgically formed external opening caused cancer of the forestomach (carcinoma) in rats of both sexes (Garcia-Gonzalez *et al.* 2000).

Oral administration, intrarectal administration, and injection of *N*-nitroso-*N*-methylurea in several species (adult monkeys, mice, rats, gerbils, or hamsters) caused tumors of the digestive tract (esophagus, glandular stomach, forestomach, small intestine, or colon) or respiratory tract (oropharynx or lung) (Adamson and Sieber 1979, Zimmerman *et al.* 1982, Eisenberg *et al.* 1983, Likhachey *et al.* 1983, Smulow *et al.* 1983, Yano *et al.* 1984, Wang *et al.* 1985, Verdeal *et al.* 1986, Beland *et al.* 1988, Bosland *et al.* 1992, Furukawa *et al.* 1992, Tatematsu *et al.* 1992, 1993, 1994, 1998, Lijinsky and Kovatch 1996, Tamano *et al.* 1996, Yang *et al.* 1996). Blood-vessel cancer (hemangioendothelial sarcoma) also was reported in mice (Tatematsu *et al.* 1993, 1998) and leukemia and tumors of the prostate, Zymbal gland, uterus, adrenal glands, and blood vessels in rats (Eisenberg *et al.* 1983, Verdeal *et al.* 1986, Bosland *et al.* 1992, Tamano *et al.* 1996).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitroso-*N*-methylurea.

Properties

N-Nitroso-*N*-methylurea is a nitrosamine compound that exists as a colorless to yellow crystal or plate at room temperature (HSDB 2009). It is soluble in water, alcohol, ether, acetone, benzene, chloroform, and other polar organic solvents and insoluble in nonpolar organic solvents. It decomposes in alkaline solution at a rate that depends on pH (IARC 1978). The pure compound is sensitive to moisture and light and should be stored under refrigeration. Physical and chemical properties of *N*-nitroso-*N*-methylurea are listed in the following table.

Property	Information
Molecular weight	103.1[a]
Melting point	124°C (decomposes)[a]
Log K_{ow}	–0.03[a]
Water solubility	14.4 g/L at 24°C[a]
Vapor pressure	0.0293 mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitroso-*N*-methylurea was once widely used to synthesize diazomethane in the laboratory; however, it has been replaced by other reagents for this use (IARC 1972, 1978, HSDB 2009). *N*-Nitroso-*N*-methylurea has been studied as a chemotherapeutic agent in cancer treatment, either alone or in combination with cyclophosphamide. Small quantities are used in research to study its mutagenic effects on plants.

Production

N-Nitroso-*N*-methylurea has never been produced commercially in the United States (IARC 1978, HSDB 2009). In 2009, it was available in small quantities for research purposes from eight U.S. suppliers (ChemSources 2009).

Exposure

The potential for human exposure in the United States is limited, because *N*-nitroso-*N*-methylurea is not produced or used in large quantities (IARC 1978, HSDB 2009). Cancer patients potentially were directly exposed by injection when *N*-nitroso-*N*-methylurea was tested as a chemotherapeutic agent in conjunction with cyclophosphamide; however, no data were found on the frequency or extent of this testing (IARC 1978). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, two facilities released a total of 170 lb of *N*-nitroso-*N*-methylurea to the environment in 1999, 96% of which was from one facility. Releases totaled 260 lb in 2001 and 10 lb in 2005, 2006, and 2007 (TRI 2009). In air, *N*-nitroso-*N*-methylurea exists solely as vapor and is degraded by reaction with photochemically produced hydroxyl radicals, with an estimated half-life of 10 days. In water, it hydrolyzes, with a half-life of 1.2 hours at pH 7 at 20°C.

Occupational exposure to *N*-nitroso-*N*-methylurea may occur through inhalation or dermal contact at facilities where it is used in research (HSDB 2009). During clinical testing for its use as a chemotherapeutic agent, health professionals such as pharmacists, physicians, and nurses could have been exposed during preparation and administration of the drug or during clean-up (IARC 1978).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitroso-*N*-methylurea = U177.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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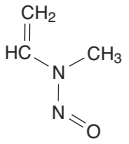
N-Nitrosomethylvinylamine

CAS No. 4549-40-0

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as *N*-methylvinylnitrosoamine



Carcinogenicity

N-Nitrosomethylvinylamine *is reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosomethylvinylamine caused tumors in rats at several different tissue sites and by two different routes of exposure. Administration of *N*-nitrosomethylvinylamine in the drinking water caused cancer (carcinoma) of the tongue and pharynx and benign and malignant tumors of the esophagus (mainly squamous-cell carcinoma), and inhalation exposure caused cancer of the nasal cavity (squamous-cell carcinoma) (IARC 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosomethylvinylamine.

Properties

N-Nitrosomethylvinylamine is a nitrosamine compound that is a yellow liquid at room temperature (HSDB 2009). It is soluble in water, lipids, and organic solvents. It is relatively unstable and decomposes in solution (up to 10% in 24 hours), and it is sensitive to light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosomethylvinylamine are listed in the following table.

Property	Information
Molecular weight	86.1[a]
Boiling point	47°C to 48°C at 30 mm Hg[b]
Log K_{ow}	–0.28[b]
Water solubility	30 g/L[b]
Vapor pressure	8.96 mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-nitrosomethylvinylamine is used as a research chemical; no other uses were identified (IARC 1978, HSDB 2009).

Production

There is no evidence that *N*-nitrosomethylvinylamine has ever been produced commercially in the United States (IARC 1978, HSDB 2009). In 2009, it was available in small quantities for research purposes from one supplier worldwide, in the United States (ChemSources 2009).

Exposure

Exposure to *N*-nitrosomethylvinylamine is limited primarily to the individuals using it in research (HSDB 2009). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of *N*-nitrosomethylvinylamine occurred only in 1999 (157 lb), 2002 (10 lb), and 2003 (26 lb) (TRI 2009).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosomethylvinylamine = P084.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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IARC. 1978. *N*-Nitrosomethylvinylamine. In *Some* N-*nitroso Compounds*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 17. Lyon, France: International Agency for Research on Cancer. pp. 257-261.

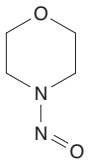
TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. http://www.epa.gov/triexplorer and select *N*-Nitrosomethylvinylamine.

N-Nitrosomorpholine

CAS No. 59-89-2

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosomorpholine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosomorpholine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Tumors of the liver or bile duct were observed in several species and by several routes of exposure. Administration of *N*-nitrosomorpholine in the drinking water caused benign liver tumors (hepatocellular adenoma) in male mice and benign or malignant liver and bile-duct tumors (hepatocellular carcinoma, cholangiofibroma, or cholangiocarcinoma) in rats. Intravenous injection of *N*-nitrosomorpholine caused liver cancer (hepatocellular carcinoma) in rats, and addition of *N*-nitrosomorpholine to the tank water caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in two species of fish (IARC 1978).

Administration of *N*-nitrosomorpholine in the drinking water also caused benign lung tumors (adenoma) in male mice and blood-vessel cancer (hemangiosarcoma and hemangioendothelioma) and kidney tumors (epithelial tumors) in rats. Tumors of the respiratory tract (primarily the nasal cavities and trachea) and upper digestive tract occurred in hamsters of both sexes exposed by subcutaneous injection, and cancer of the nasal cavity in rats exposed by intravenous injection (IARC 1978).

Since *N*-nitrosomorpholine was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animals have been identified, some of which reported induction of tumors by additional routes of exposure or at an additional tissue site:

- Administration of *N*-nitrosomorpholine in the drinking water or by stomach tube caused respiratory- or digestive-tract tumors in hamsters (Ketkar *et al.* 1983, Lijinsky *et al.* 1984, Cardesa *et al.* 1990).
- Inhalation exposure caused forestomach tumors in male rats, tracheal tumors in male hamsters, and liver tumors in female rats and male hamsters (Klein *et al.* 1990).
- Intratracheal instillation caused tracheal tumors in male hamsters (Ishinishi *et al.* 1988).
- Intravesicular instillation caused liver and nasal-cavity tumors in female rats (Lijinsky *et al.* 1991).
- Tumors of the esophagus occurred in female rats exposed to *N*-nitrosomorpholine in the drinking water (Lijinsky *et al.* 1988).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosomorpholine.

Properties

N-Nitrosomorpholine is a nitrosamine compound that exists as yellow crystals at room temperature (HSDB 2009). It is completely miscible with water and soluble in organic solvents. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosomorpholine are listed in the following table.

Property	Information
Molecular weight	116.1[a]
Melting point	29°C[a]
Boiling point	224°C to 224.5°C at 747 mm Hg[a]
Log K_{ow}	–0.44[a]
Water solubility	1,000 g/L at 24°C[b]
Vapor pressure	0.036 mm Hg at 20°C[b]
Dissociation constant (pK_b)	12.41[c]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009, [c]Akron 2009.

Use

N-Nitrosomorpholine is used as a research chemical. Although it was found to be effective as an antimicrobial agent, and patents were issued for its use as a solvent for polyacrylonitrile and as an intermediate in the production of *N*-aminomorpholine, there is no evidence that it is used commercially in the United States (IARC 1978).

Production

There is no evidence that *N*-nitrosomorpholine is produced commercially in the United States. In 2009, it was available in small quantities for research purposes from nine U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to *N*-nitrosomorpholine are dermal contact, ingestion, and inhalation (HSDB 2009). *N*-Nitrosamines are formed by reactions of precursors (nitrosating agents and primary or secondary amines) that are present in industrial processes, foods, or the human body (Schothorst and Somers 2005). *N*-Nitroso compounds have been identified in a variety of vegetables, fruits, cheeses, meats, and alcoholic beverages (Brunnemann *et al.* 1982b). *N*-Nitroso compounds may be formed from amines and quaternary ammonium salts by reaction with nitrosating agents, such as nitrite, in the stomach or during cooking processes. The degree of this potential exposure is unknown, but is assumed to be intermittent and at relatively low levels. *N*-Nitrosomorpholine was found in tobacco snuff at concentrations of 24 to 690 ppb (Brunnemann *et al.* 1982a) and in rubber nipples for baby bottles at 3.0 to 14.1 ppb (HSDB 2009). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, 21 lb of *N*-nitrosomorpholine was released to the environment in 2005, of which 20 lb was released to a hazardous-waste landfill and 1 lb to an off-site hazardous-waste underground injection well (TRI 2009).

Workers in chemical research laboratories and in the rubber and tire manufacturing industry may be exposed to *N*-nitrosomorpholine. *N*-Nitrosomorpholine concentrations in air ranged from 0.07 to 5.1 μg/m^3 in a tire factory and from 0.6 to 27 μg/m^3 in an aircraft tire factory. *N*-Nitrosomorpholine was detected as a contaminant in analytical-grade dichloromethane at 10 to 32 μg/L and in chloroform at 2 to 376 μg/L (IARC 1978).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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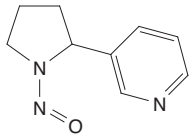
N-Nitrosonornicotine

CAS No. 16543-55-8

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as NNN



Carcinogenicity

N-Nitrosonornicotine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosonornicotine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Administration of *N*-nitrosonornicotine in the drinking water of rats of both sexes caused cancer of the nasal cavity (carcinoma in males and adenocarcinoma in females) and benign and malignant esophageal tumors (papilloma and carcinoma). Subcutaneous injection of *N*-nitrosonornicotine caused benign tracheal tumors (papilloma) in hamsters of both sexes, and intraperitoneal injection caused benign lung tumors (adenoma) in mice of both sexes (IARC 1978).

Since *N*-nitrosonornicotine was listed in the *Second Annual Report on Carcinogens,* additional experimental animal studies have been identified. *N*-Nitrosonornicotine was reported to cause nasal tumors in rodents by the following additional routes of exposure: (1) by stomach tube or dietary exposure in male rats (IARC 1985, Griciute *et al.* 1986), (2) by administration in the drinking water and by intraperitoneal injection in hamsters of both sexes (IARC 1985), and (3) by subcutaneous injection in male rats, male hamsters, and female mink (IARC 1985, Koppang *et al.* 1992, 1997, IARC 2007). The types of nasal tumors varied among the studies, but mainly consisted of the malignant tumor esthesioneuroepithelioma (also known as olfactory neuroblastoma), which arises from the olfactory nerves, and benign tumors (mainly adenoma). In addition, exposure to *N*-nitrosonornicotine by stomach tube or in the diet caused cancer of the esophagus (squamous-cell carcinoma) in male rats (IARC 1985, Griciute *et al.* 1986); subcutaneous injection caused benign lung tumors (adenoma) in rats of both sexes; and intraperitoneal injection caused benign tracheal tumors (papilloma) in male hamsters. *N*-Nitrosonornicotine administered by oral swabbing (of the tongue or cheek pouch) caused tumors of the lung, forestomach, and liver in male mice and in hamsters of both sexes (Padma *et al.* 1989).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosonornicotine.

Properties

N-Nitrosonornicotine is a nitrosamine compound that exists as a yellow oil at room temperature, but solidifies on standing in the cold (HSDB 2009). It is soluble in water (ChemIDplus 2009). Physical and chemical properties of *N*-nitrosonornicotine are listed in the following table.

Property	Information
Molecular weight	177.2[a]
Melting point	47°C[a]
Boiling point	154°C at 0.2 mm Hg[a]
Log K_{ow}	0.32[b]
Water solubility	1,000 g/L at 25°C[b]
Vapor pressure	0.2 mm Hg at 154°C[a]
Dissociation constant (pK_b)	8.84[c]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009, [c]Akron 2009.

Use

The only known use of *N*-nitrosonornicotine is as a research chemical (IARC 1985).

Production

There is no evidence that *N*-nitrosonornicotine has been produced commercially in the United States (IARC 1985). In 2009, it was available in small quantities for research purposes from two U.S. suppliers (ChemSources 2009).

Exposure

N-Nitrosonornicotine has been found in a variety of tobacco products (chewing tobacco, snuff, cigarettes, and cigars) and in mainstream and sidestream smoke from cigars and cigarettes, in the saliva of chewers of betel quid with tobacco, and in the saliva of oral-snuff users (IARC 1978, 1985). Some of the *N*-nitrosonornicotine in saliva appears to be formed endogenously from nitrite in saliva and tobacco alkaloids. Thus, there is widespread exposure to *N*-nitrosonornicotine among users of tobacco products and those exposed to sidestream smoke.

N-Nitrosonornicotine is produced by nitrosation of nicotine during the curing, aging, processing, and smoking of tobacco. About half of the *N*-nitrosonornicotine originates in the unburnt tobacco, whereas the remainder is formed during burning. *N*-Nitrosonornicotine has been found in cigarettes at concentrations of up to 11.9 mg/kg, in snuff products at up to 77.1 mg/kg, and in chewing tobacco at up to 90.6 mg/kg. The differences in *N*-nitrosonornicotine concentrations in tobacco products are largely due to differences in the tobacco types used in a given product, agricultural practices, curing methods, and manufacturing processes. *N*-Nitrosonornicotine is formed primarily from its corresponding secondary amine (nornicotine) in the early stages of tobacco curing and processing. Some *N*-nitrosonornicotine is formed from the tertiary amine (nicotine) at the later stages of tobacco curing and fermentation. Levels of *N*-nitrosonornicotine are consistently higher in Burley than in Bright tobacco, regardless of the curing method. However, flue-curing of Bright tobacco produces nearly three times as much nitrosamine as air-curing of the same tobacco. *N*-Nitrosonornicotine has been found in cigarette smoke at up to 3.7 µg per cigarette (IARC 1978, 1985).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

References

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Koppang N, Rivenson A, Dahle HK, Hoffmann D. 1997. A study of tobacco carcinogenesis, LIII: Carcinogenicity of *N'*-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)1-butanone (NNK) in mink *(Mustala vison)*. *Cancer Lett* 111(1-2): 167-171.

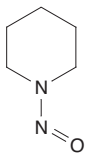
Padma PR, Lalitha VS, Amonkar AJ, Bhide SV. 1989. Carcinogenicity studies on the two tobacco-specific *N*-nitrosamines, *N'*-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. *Carcinogenesis* 10(11): 1997-2002.

N-Nitrosopiperidine

CAS No. 100-75-4

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosopiperidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosopiperidine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Tumor occurred mainly in the respiratory tract, upper digestive tract, and liver (IARC 1978). Benign lung tumors (adenoma) occurred in mice administered *N*-nitrosopiperidine in the diet or drinking water or by intraperitoneal injection. Benign and malignant nasal-cavity tumors (cholesteatoma, esthesioneuroepithelioma, and squamous-cell carcinoma) and cancer of the pharynx (carcinoma) were observed in rats exposed by subcutaneous or intravenous injection. When administered as a single dose to pregnant hamsters, *N*-nitrosopiperidine caused respiratory-tract tumors

at a much higher incidence in the mothers than in the offspring. Upper-digestive-tract tumors caused by *N*-nitrosopiperidine included cancer of the forestomach (squamous-cell carcinoma) and benign esophageal tumors (papilloma) following dietary administration to male mice and benign and malignant esophageal tumors (papilloma and squamous-cell carcinoma) in rats exposed via the drinking water or by subcutaneous or intravenous injection. Benign and/or malignant liver tumors (hepatocellular adenoma or carcinoma) occurred in male mice administered *N*-nitrosopiperidine in the diet and rats and monkeys administered *N*-nitrosopiperidine in the drinking water. Tumors of the respiratory tract, upper digestive tract, and liver also occurred in hamsters administered *N*-nitrosopiperidine by subcutaneous injection. One study reported blood-vessel cancer (hemangioendothelioma) in male mice exposed to *N*-nitrosopiperidine in the diet.

Since *N*-nitrosopiperidine was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animals have been identified. *N*-Nitrosopiperidine administered in the drinking water caused benign and malignant upper-respiratory-tract tumors in hamsters of both sexes (Cardesa *et al.* 1990) and liver cancer (hepatocellular carcinoma) in monkeys exposed by intraperitoneal injection or dietary administration (Adamson and Sieber 1979).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosopiperidine.

Properties

N-Nitrosopiperidine is a nitrosamine compound that exists as a yellow oil at room temperature (HSDB 2009). It is soluble in water, hydrochloric acid, organic liquids, and lipids. Physical and chemical properties of *N*-nitrosopiperidine are listed in the following table.

Property	Information
Molecular weight	114.2[a]
Specific gravity	1.0631 at 18.5°C/4°C[a]
Boiling point	219°C[a]
Log K_{ow}	0.36[a]
Water solubility	76.5 g/L at 24°C[b]
Vapor pressure	0.092 mm Hg at 20°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitrosopiperidine is used as a research chemical (HSDB 2009); no other uses were identified.

Production

N-Nitrosopiperidine was first prepared in 1863 by the action of nitrogen dioxide on piperidine (IARC 1978). Although numerous patents have been issued for the production of *N*-nitrosopiperidine, there is no evidence that it has been manufactured commercially in the United States. In 2009, it was available in small quantities for research purposes from eight U.S. suppliers (ChemSources 2009). No other data on U.S. production, imports, or exports of *N*-nitrosopiperidine were found.

Exposure

Because only small quantities of *N*-nitrosopiperidine are produced for research, potential exposure appears to be limited. The general population may be exposed to low concentrations of *N*-nitrosopiperidine from cigarette smoke and certain foods (IARC 1978). Trace amounts of *N*-nitrosopiperidine were found in cigarettes, but it was not found in all brands of cigarettes tested. *N*-Nitrosopiperidine was found at concentrations of up to 64 µg/kg in meat and fish products such as bacon, bologna, wieners, and smoked cod. The presence of *N*-nitrosopiperidine in meat, cheese, and spices results from the preservative use of sodium nitrite, which reacts with the amines present in meats and cheese to form nitrosamines. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of *N*-nitrosopiperidine were 14,756 lb in 1999 and 19,309 lb in 2001; most was released to on-site hazardous-waste landfills, and a small portion was released to off-site non-hazardous-waste landfills. In 2002 and thereafter, much smaller total quantities (≤ 500 lb) were released to off-site hazardous-waste landfills (TRI 2009).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosopiperidine = U179.
Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.
In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

References

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HSDB. 2009. *Hazardous Substances Data Bank.* National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 10/7/09.

IARC. 1978. *N*-Nitrosopiperidine. In *Some* N-*nitroso compounds*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 17. Lyon, France: International Agency for Research on Cancer. pp. 287-301.

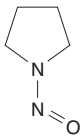
TRI. 2009. *TRI Explorer Chemical Report.* U.S. Environmental Protection Agency. Last updated: 3/19/09. http://www.epa.gov/triexplorer and select *N*-Nitrosopiperidine.

N-Nitrosopyrrolidine

CAS No. 930-55-2

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosopyrrolidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to *N*-nitrosopyrrolidine caused tumors in two rodent species and at two different tissue sites. Administered in the drinking water, it caused liver cancer (hepatocellular carcinoma) in several strains of rats (both sexes) and benign lung tumors (adenoma) in mice of both sexes (IARC 1978).

Since *N*-nitrososPyrrolidine was listed in the *Second Annual Report on Carcinogens,* additional studies in rodents have been identified. Liver tumors were observed in hamsters exposed to *N*-nitrosopyrrolidine in the drinking water; tumor incidence increased with increasing dose (Ketkar *et al.* 1982). *N*-NitrososPyrrolidine administered by intraperitoneal injection to hamsters caused tumors of the larynx or trachea 25 weeks after a single injection and preneoplastic and neoplastic nasal-cavity lesions 25 weeks after two injections. In female strain A/J mice (a strain with a high spontaneous incidence of lung tumors), *N*-nitrosopyrrolidine administered by intraperitoneal injection increased the incidence of benign lung tumors and the number of tumors per animal (Hecht *et al.* 1988, Hoffmann *et al.* 1993).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosopyrrolidine.

Properties

N-Nitrosopyrrolidine is a nitrosamine compound that is a yellow liquid at room temperature (HSDB 2009). It is totally soluble in water, organic liquids, and lipids. It is stable at room temperature in the dark, but is sensitive to light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosopyrrolidine are listed in the following table.

Property	Information
Molecular weight	100.1[a]
Specific gravity	1.1[a]
Boiling point	214°C at 760 mm Hg[a]
Log K_{ow}	–0.19[a]
Water solubility	1,000 g/L at 24°C[b]
Vapor pressure	0.06 at 20°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitrosopyrrolidine is used primarily as a research chemical and is not produced commercially in the United States (IARC 1978, HSDB 2009).

Production

N-Nitrosopyrrolidine was first prepared in 1888 by the reaction of pyrrolidine with potassium nitrate in a weak hydrochloric acid solution (IARC 1978). It is not produced commercially in the United States. In 2009, it was available in small quantities for research purposes from eight U.S. suppliers (ChemSources 2009).

Exposure

N-Nitrosopyrrolidine is produced when foods preserved with or contaminated by nitrite, especially fatty foods, are prepared by heating. Exposure can occur through inhalation of vapors released during cooking or ingestion of food (IARC 1978). In recent years, lower concentrations of sodium nitrite in foods have resulted in lower concentrations of *N*-nitrosopyrrolidine in foods. For example, the *N*-nitrosopyrrolidine content of bacon decreased from approximately 67 µg/kg in 1971 through 1974 to 17 µg/kg in 1975 and 1976; when bacon is fried, an average of 50% of the *N*-nitrosopyrrolidine normally present in the meat is detected in the vapor. Dry premixed cures containing spices and sodium nitrite originally contained *N*-nitrosopyrrolidine at a concentration of 40 µg/kg, but the level increased to 520 µg/kg after six months of storage. *N*-Nitrosopyrrolidine was found in tobacco smoke at concentrations of up to 0.113 µg per cigarette and in pipe-bowl scrapings at up to 1.6 mg/kg of residue. Wastewater from chemical factories was reported to contain *N*-nitrosopyrrolidine at concentrations of 0.09 to 0.20 µg/L.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.016 µg/L; based on fish or shellfish consumption only = 34 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosopyrrolidine = U180.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

References

ChemIDplus. 2009. *ChemIDplus Advanced*. National Library of Medicine. http://chem.sis.nlm.nih.gov/chemidplus and select Registry Number and search on CAS number. Last accessed: 10/7/09.

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Hecht SS, Abbaspour A, Hoffman D. 1988. A study of tobacco carcinogenesis. XLII. Bioassay in A/J mice of some structural analogues of tobacco-specific nitrosamines. *Cancer Lett* 42(1-2): 141-145.

Hoffmann D, Djordjevic MV, Rivenson A, Zang E, Desai D, Amin S. 1993. A study of tobacco carcinogenesis. LI. Relative potencies of tobacco-specific *N*-nitrosamines as inducers of lung tumours in A/J mice. *Cancer Lett* 71(1-3): 25-30.

HSDB. 2009. *Hazardous Substances Data Bank*. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number. Last accessed: 10/7/09.

IARC. 1978. *N*-Nitrosopyrrolidine. In *Some* N-*nitroso compounds*. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, vol. 17. Lyon, France: International Agency for Research on Cancer. pp. 313-326.

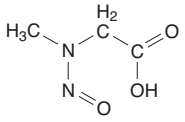
Ketkar MB, Schneider P, Preussmann R, Plass C, Mohr U. 1982. Carcinogenic effect of low doses of nitrosopyrrolidine administered in the drinking water to Syrian golden hamsters. *J Cancer Res Clin Oncol* 104(1-2): 75-79.

N-Nitrososarcosine

CAS No. 13256-22-9

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrososarcosine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrososarcosine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Dietary exposure to *N*-nitrososarcosine caused cancer of the nasal cavity (squamous-cell carcinoma) in mice of both sexes, and administration in the drinking water caused benign and malignant tumors of the esophagus (papilloma and squamous-cell carcinoma) in rats. Intraperitoneal injection of *N*-nitrososarcosine in newborn mice caused liver cancer (hepatocellular carcinoma) in males (IARC 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrososarcosine.

Properties

N-Nitrososarcosine is a nitrosamine compound that is a pale-yellow crystal at room temperature (HSDB 2009). It is soluble in water and polar organic solvents but is unstable in aqueous solution. It is sensitive to light, especially ultraviolet light (Akron 2009). Physical and chemical properties of *N*-nitrososarcosine are listed in the following table.

Property	Information
Molecular weight	118.1[a]
Melting point	66°C to 67°C[a]
Log K_{ow}	–0.78[b]
Water solubility	1,000 g/L at 25°C[b]
Vapor pressure	0.00261 mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

N-Nitrososarcosine is not used commercially in the United States, but has limited use in research (IARC 1978, HSDB 2009).

Production

There is no evidence that *N*-nitrososarcosine has been produced commercially in the United States (IARC 1978, HSDB 2009). In 2009, it was available in small quantities for research purposes from three U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to *N*-nitrososarcosine are inhalation, ingestion, and dermal contact (HSDB 2009). *N*-Nitrososarcosine is formed when nitrite-preserved foods containing primary or secondary amines are prepared by heating. Exposure could occur through inhalation during cooking or through ingestion of the prepared food. *N*-Nitrososarcosine has been detected in foods; in particular, it was found in smoked meat at concentrations of 2 to 56 µg/kg. It was also found in tobacco smoke at concentrations of 22 to 460 ng per cigarette. In air, *N*-nitrososarcosine exists predominantly in the gas phase and degrades by reaction with photochemically produced hydroxyl radicals, with a half-life of 1.9 days (IARC 1978, Tricker *et al.* 1991, HSDB 2009).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

References

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Tricker AR, Ditrich C, Preussmann R. 1991. *N*-Nitroso compounds in cigarette tobacco and their occurrence in mainstream tobacco smoke. *Carcinogenesis* 12(2): 257-261.