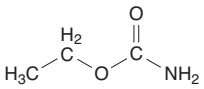
Urethane

CAS No. 51-79-6

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as ethyl carbamate or carbamic acid ethyl ester



Carcinogenicity

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

Cancer Studies in Experimental Animals

Urethane caused tumors in several rodent species at several different tissue sites and by several different routes of exposure. It was carcinogenic following administration of a single dose and by prenatal exposure, and neonatal or infant mice generally were more susceptible than adult mice. Malignant and/or benign tumors of the lung, liver, and blood vessels were seen in many studies, along with lymphoma, leukemia, or melanoma (Guyer and Claus 1947, IARC 1974).

Urethane caused benign and/or malignant lung tumors (adenoma or squamous-cell carcinoma) in (1) mice exposed orally (by stomach tube or via the drinking water), by inhalation or intratracheal administration, by intraperitoneal injection, by dermal administration, prenatally, or by lactation, (2) newborn mice exposed by subcutaneous or intraperitoneal injection, (3) hamsters exposed orally or by subcutaneous injection, and (4) newborn hamsters exposed by subcutaneous injection. Urethane caused liver cancer (hepatocellular carcinoma) in (1) adult and newborn mice exposed orally (by stomach tube), by intraperitoneal injection, by subcutaneous injection, and/or prenatally, (2) newborn rats exposed by intraperitoneal injection, (3) female rats exposed orally, and (4) hamsters exposed orally.

Benign and/or malignant blood-vessel tumors (hemangioma or hemangiosarcoma of the liver, spleen, uterus, or unspecified sites) resulted from exposure to urethane via the drinking water in mice and hamsters of both sexes and in female rats. Malignant lymphoma (in some cases of thymic origin) or leukemia resulted from (1) oral exposure (by stomach tube or via the drinking water) in mice and hamsters of both sexes and in female rats and (2) exposure by intraperitoneal injection or subcutaneous injection in newborn mice. In hamsters, melanoma (primarily of the skin) occurred in adults exposed via the drinking water or by subcutaneous injection and in newborns exposed by intraperitoneal or subcutaneous injection. Other types of skin tumors were observed in mice following dermal or oral administration of urethane. In addition, urethane caused tumors at the following tissue sites:

- The mammary gland in female mice, rats, and hamsters exposed orally, female mice exposed dermally, and female rats exposed by intraperitoneal injection.
- The Harderian gland in mice exposed dermally and in newborn mice exposed by intraperitoneal or subcutaneous injection; some tumors were also observed following oral exposure.
- The forestomach in adult hamsters exposed orally and in adult and newborn hamsters exposed by subcutaneous injection.

Tumors were found less consistently in rodents at other tissue sites, including the ovary, Zymbal gland, adrenal cortex of the kidney, and gastrointestinal tract.

Since urethane was listed in the *Third Annual Report on Carcinogens,* additional studies in rodents have been identified. Many of these studies confirmed the findings of the earlier studies or found that urethane caused similar tumors by additional routes of exposure or in additional species. Administration of urethane in the drinking water caused benign and/or malignant tumors of the blood vessels, liver, lung, and Harderian gland in mice of both sexes, the ovary and mammary gland in female mice, and the forestomach and skin in male mice (NTP 2004, Beland 2005). Urethane administered to mice by intraperitoneal injection caused tumors of the thymus (thymoma) in both sexes and the blood vessels in females, in addition to liver and lung tumors, as observed in earlier studies (Dahl *et al.* 1980, Ward *et al.* 1986).

Cancer Studies in Humans

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

Properties

Urethane is an ester of carbamic acid that exists at room temperature as a colorless or white, almost odorless crystalline solid. It is soluble in water, benzene, alcohol, ether, chloroform, glycerol, and olive oil. Urethane is stable under normal temperatures and pressures (Akron 2009, HSDB 2009). Physical and chemical properties of urethane are listed in the following table.

Property	Information
Molecular weight	89.1[a]
Specific gravity	0.9813[a]
Melting point	49°C[a]
Boiling point	185°C[a]
Log K_{ow}	–0.15[a]
Water solubility	480 g/L at 15°C[b]
Vapor pressure	0.262 mm Hg at 25°C[a]
Vapor density relative to air	3.07[a]

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

The name "urethane" is sometimes applied to high-molecular-weight polyurethanes used as foams, elastomers, and coatings. Such products are not made from the chemical urethane and do not generate it upon decomposition.

Use

The primary use of urethane has been as a chemical intermediate in preparation of amino resins (IARC 1974). The process involves a reaction with formaldehyde to give hydroxymethyl derivatives that are used as cross-linking agents in permanent-press textile treatments designed to impart wash-and-wear properties to fabrics. Urethane is also used as a solubilizer and co-solvent in the manufacture of pesticides, fumigants, and cosmetics, as an intermediate in the manufacture of pharmaceuticals, and in biochemical research (HSDB 2009). Urethane was formerly used as an active ingredient in drugs prescribed for the treatment of neoplastic diseases, as a sclerosing solution for varicose veins, as a hypnotic, and as a topical bactericide. It is also used in veterinary medicine as an anesthetic (IARC 1974). Urethane is produced naturally during many fermentation processes (Zimmerli and Schlatter 1991).

Production

Urethane has been produced commercially in the United States since 1945 (IARC 1974). In 2009, urethane was produced by one manufacturer worldwide, in the United States (SRI 2009), and was available from 21 suppliers, including 13 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule in 1986 indicated that U.S. production plus imports of urethane totaled 10,000 to 50,000 lb; no inventory update reports have been filed since 1986 (EPA 2004). No data were found on U.S. imports or exports of urethane in 2009.

Exposure

The routes of potential human exposure to urethane are inhalation, ingestion, and dermal contact. Urethane is a naturally occurring substance that is formed during many fermentation processes (Zimmerli and Schlatter 1991). The general population is exposed primarily through ingestion of yeast breads and alcoholic beverages. Measured concentrations of urethane in wine ranged from 8 ng/mL in white table wine to 111 ng/mL in sake (Jagerdeo *et al.* 2002), and urethane concentrations in stone-fruit brandies ranged from 100 to 20,000 µg/kg (ppb) (Zimmerli and Schlatter 1991, Lachenmeier *et al.* 2005). Other alcoholic beverages may contain more urethane than table wine (3 to 9 ppb), including port (16 to 60 ppb), sherry (32 to 242 ppb), and whiskey (68 to 389 ppb) (Brumley *et al.* 1988). Urethane has also been found in dimethyl pyrocarbonate–treated beverages and in beer, orange juice, and some soft drinks (IARC 1974). Other foods with measurable concentrations of urethane include soy sauce, yogurt, and cheese (Zimmerli and Schlatter 1991). Assuming that bread is the major source of urethane intake, the estimated mean intake of urethane in adults is 10 to 20 ng/kg of body weight. Toasting bread increases its urethane concentration 2- to 3-fold. Adding a cup (200 to 300 mL) of table wine to the daily diet could as much as triple urethane intake, and drinking one ounce of cherry or plum brandy could increase daily intake 60 fold over the baseline intake from other food sources. Urethane is also a natural constituent of tobacco and is present in tobacco smoke. Consumers were also potentially exposed to urethane residues in urethane-treated textiles (IARC 1974).

In the 1940s and 1950s, patients with leukemia, multiple myeloma, and mycosis fungoides were treated with urethane, and urethane was measured in the blood of two leukemia patients at concentrations ranging from 4 to 38 mg/100 mL (Archer *et al.* 1948, Kennedy *et al.* 1950, Skipper *et al.* 1951, Seibert *et al.* 1966). Individuals potentially were exposed to urethane in other pharmaceutical products administered by injection (HSDB 2009). Certain patients with epilepsy potentially were exposed to urethane as a contaminant in the anticonvulsant drugs trimethadione and paramethadione. Although one product containing trimethadione is still approved by the U.S. Food and Drug Administration, all three products containing paramethadione have been discontinued (FDA 2009).

According to EPA's Toxics Release Inventory, environmental releases of urethane decreased from 146,500 lb in 1988 to 500 lb in 1997, increasing to 128,000 lb in 2003. In 2007, eight facilities released about 95,000 lb of urethane. Since 1997, most releases of urethane have been to landfills (TRI 2009). In the atmosphere, urethane will exist in the vapor state and react with photochemically produced hydroxyl radicals, with an estimated half-life of 17 hours. If released to soil or water, urethane is expected to adsorb weakly to soil and primarily to leach to groundwater. (HSDB 2009).

Occupational exposure to urethane may occur during its production or its use in medical research. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 9,459 workers, including 5,050 women, potentially were exposed to urethane (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

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

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 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 urethane = U238.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Urethane has been withdrawn from the market as a pharmaceutical because it was found to be unsafe or not effective, and it cannot be compounded.

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