

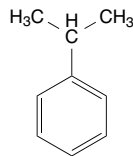
## Cumene

### CAS No. 98-82-8

Reasonably anticipated to be a human carcinogen

First listed in the *Thirteenth Report on Carcinogens* (2014)

Also known as isopropylbenzene, (1-methylethyl)benzene



### Carcinogenicity

Cumene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. Cumene caused tumors at several tissue sites, including lung and liver in mice and kidney in male rats. Several proposed mechanisms of carcinogenesis support the relevance to humans of lung and liver tumors in experimental animals. Specifically, there is evidence that humans and experimental animals metabolize cumene through similar metabolic pathways. There is also evidence that cumene is genotoxic in some tissues, based on findings of DNA damage in rodent lung and liver. Furthermore, mutations of the *K-ras* oncogene and *p53* tumor-suppressor gene observed in cumene-induced lung tumors in mice, along with altered expression of many other genes, resemble molecular alterations found in human lung and other cancers. The relevance of the kidney tumors to cancer in humans is uncertain; there is evidence that a species-specific mechanism not relevant to humans contributes to their induction, but it is possible that other mechanisms relevant to humans, such as genotoxicity, may also contribute to kidney-tumor formation in male rats.

### Cancer Studies in Experimental Animals

Inhalation exposure to cumene caused tumors at several different tissue sites in mice (NTP 2009). In mice of both sexes, cumene caused benign and malignant lung tumors (alveolar/bronchiolar adenoma, carcinoma, and adenoma and carcinoma combined). In female mice, cumene caused dose-related increases in the incidence of benign or malignant liver tumors (hepatocellular adenoma alone or combined with carcinoma).

These findings are supported by observations of dose-related increases in the incidence of benign nasal tumors (adenoma of the respiratory epithelium) in rats of both sexes (NTP 2009). However, this type of nasal tumor typically does not progress to malignancy (Brown 1991). Inhalation exposure to cumene also increased the combined incidence of benign and malignant kidney tumors (renal-tubule adenoma and carcinoma) in male rats. However, the relevance of these kidney tumors to cancer in humans is uncertain (see Studies on Mechanisms of Carcinogenesis). Additional tumors that may have been related to cumene exposure include malignant blood-vessel tumors (hemangiosarcoma, primarily of the spleen) and benign thyroid-gland tumors (follicular-cell adenoma) in male mice and benign tumors of the testes (interstitial-cell adenoma) in male rats.

### Absorption and Metabolism

Cumene is readily absorbed following inhalation or oral exposure, and studies in rats and rabbits showed that cumene is also absorbed through the skin (IPCS 1999, EC 2001, Chen *et al.* 2011). Metabolism of cumene is complex and not fully elucidated; however, there are clear similarities across species, and reactive intermediates of

cumene can be generated by several metabolic pathways. Cumene is extensively metabolized by cytochrome P450 in liver and other tissues, including the lung, but the specific isoforms have not been identified. Thirteen cumene metabolites were identified in rat urine and fifteen metabolites in mouse urine. The most abundant metabolite in rat and mouse urine and rat bile was 2-phenyl-2-propanol glucuronide, and a conjugate or conjugates of 2-phenyl-2-propanol were found in the urine of humans exposed to cumene vapor (Seńczuk and Litewka 1976).

Cumene metabolism proceeds primarily through side-chain oxidation, but ring oxidation also occurs *in vivo*. Metabolism of cumene resulting in side-chain oxidation of  $\alpha$ -methylstyrene to  $\alpha$ -methylstyrene oxide or ring oxidation to arene oxides could potentially cause DNA damage. Arene oxides can form phenols, and when the *para* isomers of methylphenol, ethylphenol, and isopropylphenol were incubated with rat-liver microsomes, reactive quinone methide intermediates were readily formed (Thompson *et al.* 1995).

### Studies on Mechanisms of Carcinogenesis

The mechanisms by which cumene causes cancer in experimental animals are not known. Differences between species in the types of tumors observed may be due, in part, to species differences in metabolism and disposition. Several potential modes of action or molecular alterations associated with carcinogenesis have been identified, including genetic and epigenetic effects, metabolic activation to reactive metabolites, cell proliferation, and  $\alpha_2$ -globulin nephropathy.

Chemical agents that cause cancer at several tissue sites in more than one species frequently are genotoxic carcinogens. Although cumene was not mutagenic or genotoxic in most of the standard *in vitro* and *in vivo* assays, single-cell gel electrophoresis (the comet assay) provided evidence that cumene caused DNA damage in the liver of male rats and the lungs of female mice (NTP 2012). Although  $\alpha$ -methylstyrene was not mutagenic in bacteria (NTP 2007), there is evidence that it causes chromosomal damage in rodents and cultured cells, and its proposed metabolite,  $\alpha$ -methylstyrene oxide, is mutagenic in bacteria. Therefore, some evidence exists for a genotoxic mechanism of action for cumene (presumably via its conversion to  $\alpha$ -methylstyrene or to other metabolites). The extent to which genotoxicity plays a role in causing tumors at various tissue sites is unknown.

### Mouse Lung Tumors

The occurrence of alveolar/bronchiolar neoplasms in mice but not in rats may be partly explained by differences in disposition and metabolism. Following administration of  $^{14}\text{C}$ -labelled cumene,  $^{14}\text{C}$  concentrations in lung tissue were highest in female mice after seven consecutive daily doses, but did not increase with repeated dosing in rats. *In vitro* studies with mouse and rat lung and liver microsomes demonstrated that mouse lung microsomes were the most efficient at metabolizing cumene, which is consistent with the accumulation of cumene metabolites in mouse lung (Chen *et al.* 2011).

Based on a comparison with other compounds that also induced lung tumors in mice but not in rats, including ethylbenzene and styrene, some investigators (Cruzan *et al.* 2009, 2012) proposed that species-specific metabolism by the cytochrome P450 isoform CYP2F2 in the Clara cells of mouse lung results in the production of cytotoxic metabolites that cause tumors. They hypothesized that this mechanism was not relevant to human lung cancer, because humans generate smaller amounts of these cytotoxic metabolites. However, very few data are available to indicate which P450 isoforms are responsible for metabolizing cumene. CYP2E1 and CYP2F2 are likely candidates, based on similarities between cumene and other alkyl-

benzenes, but metabolism of cumene by CYP2F2 in mouse lung has not been demonstrated to date. The orthologous isozyme CYP2F1 is found in human lung. Furthermore, in a two-year carcinogenicity study of cumene (NTP 2009), bronchiolar hyperplasia and alveolar epithelial bronchiolar metaplasia were significantly increased in mice of both sexes, but there was no evidence of cytotoxicity (e.g., necrosis or inflammation) in the lung in the two-year study or in a three-month study.

Cumene-induced mouse lung tumors have more *K-ras* and/or *p53* mutations than do spontaneous lung tumors, and the mutational spectra of *K-ras* and *p53* in lung tumors from mice exposed to cumene differ from those observed in spontaneous lung tumors. These findings suggest the involvement of DNA damage (either direct damage from adduct formation or indirect damage through reactive oxygen species) and genomic instability (Hong *et al.* 2008). The *K-ras* and *p53* mutations observed in cumene-induced lung tumors were accompanied by increased expression of genes involved in alteration of the mitogen-activated kinase signaling pathway, invasion and metastasis, inhibition of apoptosis, increased angiogenesis, and increased metastatic potential (Wakamatsu *et al.* 2008). The molecular alterations in mouse lung tumors resemble molecular alterations found in human lung cancers (Hoenerhoff *et al.* 2009). Therefore, these data support a conclusion that cumene's induction of lung tumors in mice is relevant to human carcinogenicity.

#### Mouse Liver Tumors

No data were identified on the mechanism of liver-tumor formation in mice exposed to cumene. However,  $\alpha$ -methylstyrene, which is produced when cumene is incubated with mammalian microsomes, has been shown to cause liver tumors in mice and rats (NTP 2007). *In vivo* metabolism of  $\alpha$ -methylstyrene is known to form a dihydrodiol product, presumably through the reactive intermediate  $\alpha$ -methylstyrene oxide. These data support the role of  $\alpha$ -methylstyrene in cumene-induced liver cancer.

#### Rat Kidney Tumors

The combined incidence of benign and malignant kidney tumors (renal-tubule adenoma and carcinoma) was increased in male rats exposed to the cumene metabolite  $\alpha$ -methylstyrene by inhalation for two years (NTP 2007), suggesting that this metabolite might play a role in induction of kidney tumors by cumene.

With respect to the relevance of kidney tumors in male rats to human cancer, the major issue is whether the sole mechanism of carcinogenicity is  $\alpha_{2u}$ -globulin nephropathy, which is a recognized mechanism of action associated with kidney tumors in male rats that is not considered relevant to humans. The International Agency for Research on Cancer (IARC 1999) has identified specific criteria for evaluating whether this is the sole mechanism responsible for carcinogenicity. Although the available data are consistent with a role for  $\alpha_{2u}$ -globulin nephropathy in the induction of kidney tumors by cumene, not all of the specific criteria for its being the sole mechanism were met. Criteria for which the evidence is questionable include the following: (1) nongenotoxicity, because there is evidence that cumene is genotoxic in some tissues (liver and lung) and that a metabolite,  $\alpha$ -methylstyrene, can cause chromosomal damage, (2) male-rat specificity for nephropathy, because there is weak evidence of nephropathy in female rats, and (3) evidence of sustained cell proliferation in the renal cortex, because it is not clear from the available data whether cell proliferation occurred in the renal tubules. Overall, the data provide evidence that cumene causes kidney tumors largely via  $\alpha_{2u}$ -globulin nephropathy; however, it cannot be ruled out that other mechanisms, such as genotoxicity, also contribute to kidney-

tumor formation. Although it is likely that genotoxicity plays a role in cumene-induced carcinogenicity at some tissue sites, the strongest evidence for genotoxicity was found for lung and liver tumors, and the extent to which genotoxicity contributes to the formation of kidney tumors is unknown. Thus, the relevance of the kidney tumors in male rats to human cancer is uncertain, and the renal-tumor findings are considered to support, rather than contribute directly to, the sufficiency of the evidence for the carcinogenicity of cumene from studies in experimental animals.

#### Cancer Studies in Humans

No epidemiological studies or case reports were identified that evaluated the relationship between human cancer and exposure specifically to cumene.

#### Properties

Cumene is an alkylated benzene that exists at room temperature as a volatile, colorless liquid with a sharp, penetrating aromatic or gasoline-like odor (NTP 2009). It is a flammable liquid that is stable under normal conditions but may become unstable at high temperatures and pressures. It forms cumene hydroperoxide when exposed to air for long periods and is incompatible with oxidizers, nitric acid, and sulfuric acid. Decomposition of cumene may result in the release of toxic gases and vapors, such as carbon monoxide. Physical and chemical properties of cumene are listed in the following table.

Property	Information
Molecular weight	120.2 <sup>a</sup>
Specific gravity	0.862 at 20°C/4°C <sup>a</sup>
Melting point	–96°C <sup>b</sup>
Boiling point	152.4°C <sup>b</sup>
Log Kow	3.66 <sup>b</sup>
Water solubility	61.3 mg/L at 25°C <sup>b</sup>
Vapor pressure	4.5 mm Hg at 25°C <sup>b</sup>
Vapor density relative to air	4.1 <sup>a</sup>

Sources: <sup>a</sup>HSDB 2005, <sup>b</sup>ChemIDplus 2012.

#### Use

Cumene is used primarily in the manufacture of phenol and acetone (accounting for 98% of all use) and in the manufacture of acetophenone,  $\alpha$ -methylstyrene, diisopropylbenzene, and dicumylperoxide (HSDB 2005). It is used as a constituent of some petroleum-based solvents, such as naphtha; as a catalyst for acrylic and polyester resins; and as a raw material for peroxides and oxidation catalysts (NTP 2009). Other, direct uses are as a thinner for paints, enamels, and lacquers and as a solvent for fats and resins; as such, cumene has been suggested as a replacement for benzene. Cumene is also used as a starting material in the manufacture of aspirin and penicillin (APPE 2012). In addition, cumene has been used in gasoline blending, diesel fuel, and high-octane motor fuels, particularly as an aviation fuel (HSDB 2005, Kolb and Field 2009, NTP 2009).

#### Production

Cumene is a high-production-volume chemical. In 2011, it was manufactured by at least 50 companies worldwide, including at least 8 in the United States (SRI 2011). Demand for cumene from 1986 to 2003 ranged from 3.7 billion to 8.0 billion pounds per year (HSDB 2005). Because the vast majority of cumene is used to make phenol and acetone, demand is strongly tied to the phenol derivatives market. Past growth in global demand for cumene was largely attributed to the rebounding automobile and construction industries (ICIS 2010). U.S. imports and exports of cumene both showed a net increase from 1989 to 2017 (as shown in the table on the next page).

Category	Year	Quantity (lb)
Production + imports <sup>a</sup>	2015	5 billion to 10 billion
U.S. imports <sup>b</sup>	1989	325 million
	2013	2.2 billion
	2017	1.7 billion
U.S. exports <sup>b</sup>	1989	124 million
	2013	20.9 million
	2017	259.8 million

Sources: <sup>a</sup>EPA 2016, <sup>b</sup>USITC 2018.

## Exposure

A significant number of people in the United States are exposed to cumene as a result of its presence in fossil fuels, solvents, and cigarette smoke and in the workplace. Exposure to cumene in the workplace results from its production and use in the chemical industry. The major source of cumene exposure is environmental, via inhalation of ambient air in industrial and urban areas of the United States. Other evidence demonstrating exposure to cumene is its detection in blood, alveolar air, expired air, and urine from people without known occupational exposure to cumene (Perbellini *et al.* 1988, Brugnone *et al.* 1989) and in expired air samples from nonsmoking individuals living in an urban environment (Krotoszynski *et al.* 1977).

Because cumene is a natural component of petroleum (typically 0.1% to 1% by weight in crude oil), its emissions from petroleum-product-related sources, such as combustion of fossil fuels by land transportation vehicles, evaporative losses from gasoline stations, and refuelling losses, are ubiquitous in the environment. From 1990 to 2012, approximately 180 spill incidents involving cumene were reported to the National Response Center (NRC 2012).

Cumene has been measured in the atmosphere in many locations throughout the United States; however, levels are several-fold higher in industrial and urban settings than in rural areas, presumably because of cumene's presence in petroleum emissions. Cumene may also be released from cumene manufacturing and processing. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, reported on- and off-site releases of cumene in 2010 totaled slightly over 1 million pounds from more than 300 facilities across the United States (TRI 2012). Releases to air accounted for 94.1% of total releases, releases to land for 4.4%, off-site disposal for 1.3%, disposal by underground injection for 0.2%, and releases to water for 0.1%. The European Union System for the Evaluation of Substances model indicated that about 97% of total estimated human environmental exposure to cumene is via the air (EC 2001).

The U.S. general population is not likely to be exposed to cumene via ingestion of water. Concentrations of cumene are several-fold lower in surface water and drinking water than in groundwater near industrial sources, in industrial effluents, or in sediments and biota. U.S. drinking water only rarely contains cumene at concentrations above 0.5 mg/L (EPA 1987, IPCS 1999). The main source of soil contamination by cumene is point emissions from garage spills or near gasoline stations (EC 2001).

Cumene has also been detected at low levels in fruits, vegetables, meats, honey, dairy products, wine, and prepared foods (HSDB 2005). In the U.S. Food and Drug Administration Total Diet Study, conducted from 1991–93 through 2003–04, cumene was found at levels ranging from 0.002 to 0.063 ppm in 18 foods, including fruit-flavored popsicles and sherbet, cake doughnuts, sweet rolls and Danish pastries, and raw oranges (FDA 2006). Cumene in food may be from environmental or processing sources or may occur naturally (EPA 1987). Cumene levels in condensates of cigarette smoke were reported to range from 7 to 14 mg/cigarette (IPCS 1999). Cumene

is present at concentrations ranging from 1% to 5% (or not quantified) in several consumer products, including automobile fuel-injector-system cleaners, roof adhesives, some agricultural herbicides, fabric-softener pads, and crib mattresses (Anderson and Anderson 2000a,b, HPDB 2012).

In occupational settings, the main route of exposure to cumene is via inhalation during cumene manufacturing, processing, and use, primarily in the manufacture of phenol and acetone. Dermal exposure to cumene may occur at manufacturing and processing facilities during activities such as cleaning and maintenance. End users of products containing cumene outside of the manufacturing industry (e.g., for painting and car repair) may also be exposed.

## Regulations

### Coast Guard (Dept. of Homeland Security)

Minimum requirements have been established for safe transport of cumene on ships and barges.

### Environmental Protection Agency (EPA)

#### Clean Air Act

*New Source Performance Standards:* Manufacture of cumene is subject to certain provisions for the control of volatile organic compound emissions.

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

*Comprehensive Environmental Response, Compensation, and Liability Act*  
Reportable quantity (RQ) = 5,000 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 cumene = U055.

### U.S. Food and Drug Administration (FDA, an HHS agency)

*Q3C Impurities: Residual Solvents:* Class 2 solvent; permitted daily exposure (PDE) = 0.7 mg; concentration limit = 70 ppm.

### Occupational Safety and Health Administration (OSHA, Dept. of Labor)

This legally enforceable PEL was adopted from the 1968 ACGIH TLV-TWA shortly after OSHA was established. The PEL may not reflect the most recent scientific evidence and may not adequately protect worker health.

Permissible exposure limit (PEL) = 50 ppm.

Potential for dermal absorption.

## Guidelines

### American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 50 ppm.

### Environmental Protection Agency (EPA)

*Acute Exposure Guideline Levels for Hazardous Substances:* AEGL-1 (non-disabling) = 50 ppm; AEGL-2 (disabling) = 130 ppm; AEGL-3 (lethal) = 300 ppm (8-h TWAs).

*Regional Screening Levels* (formerly Preliminary Remediation Goals): residential soil = 1,900 mg/kg; industrial soil = 9,900 mg/kg; residential air = 420 µg/m<sup>3</sup> [0.09 ppm]; industrial air = 1,800 µg/m<sup>3</sup> [0.4 ppm]; tap water = 450 µg/L.

### National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Immediately dangerous to life and health (IDLH) limit = 900 ppm.

Recommended exposure limit (REL) (8-h TWA) = 50 ppm.

Potential for dermal absorption.

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