# QUINOLINE

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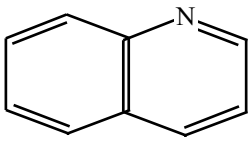
## I. IDENTIFICATION

Chemical Name: Quinoline
Synonyms: chinoline, leukoline, 1-benzazine, benzo[b]pyridine, chinoleine, Leucol, 1-azanaphthalene
CAS Number: 91-22-5
UN Number: 2656
Chemical Family: aza-arenes
Molecular Formula: C9H7N
Structural Formula:




## II. CHEMICAL AND PHYSICAL PROPERTIES [1-11]

### A. Chemical Properties

Weak tertiary base (basic ionization constant 3.2 x $10^{-10}$), forms water-soluble salts with strong acids; hygroscopic (absorbs as much as 22% water); partially soluble in water; completely soluble in alcohol, ether, acetone, benzene, and carbon disulfide; octanol-water partition coefficient (log $P_{ow}$) = 2.06

### B. Physical Properties

Physical State and Appearance: Colorless and highly refractive liquid.

Odor Description: Penetrating, not as offensive as pyridine.

Odor Threshold: 71 ppm

Molecular Weight: 129.15

Conversion Factors: 1 ppm = 5.28 mg/m$^3$

1 mg/m$^3$ = 0.19 ppm

Melting Point: -15.6°C (3.9°F)

Boiling Point: 238°C (460°F)

Vapor Pressure: 0.06 mm Hg at 25°C (77°F)

Saturated Vapor Concentration: 78 ppm at 25°C (77°F)

Explosivity Limits, vol% in air: 1.2-7

Flash Point: 99-105°C (210-221°F)

Autoignition Temperature: 480°C (896°F)

Specific Gravity: 1.0929 at 20°C (68°F)

Solubility in Water: 6g/100 mL at 20°C (68°F), 8.4 g/L at 10°C (50°F); not soluble in cold water, more solubile in warm water; distills in steam.

Other Solubility: Miscible with alcohol, ether, carbon disulfide, acetone, and benzene

Vapor Density: 4.45 (air = 1)

Stability: Turns brown upon exposure to light. Combustible when exposed to heat or flame. Decomposes with heating, emitting $NO_x$.

Reactivity and Incompatibilities: Strong oxidizing agents convert quinoline to 2,3-pyridinedicarboxylic acid. Reacts with maleic anhydride; reacts strongly with metal chlorides and violently with dinitrogen tetraoxide and perchromates. Incompatible with linseed oil + thionyl chloride. Potentially explosive reaction with hydrogen peroxide. Exhibits reactions characteristic of the benzene and pyridine series.

## III. USES AND CONSUMPTION

Quinoline is extracted from coal-tar distillates that have an appreciable concentration of oils boiling in the range 235-240°C[2],or it may be extracted from bone oil.[4,12] It can also be synthesized by a number of different routes.[2] Quinoline is found in significant quantities in polluted air and cigarette smoke.[13] It is a raw material for the manufacture of dyes, fungicides, pesticides, preservatives for anatomical specimens, niacin, pharmaceuticals, and 8-hydroxyquinoline sulfate (used as an antiseptic, antiperspirant, and deodorant).[1] It has also been used in corrosion inhibitors, has been added

to polymers to introduce ion exchange, and has been used in electroplating and metal surface treatments. Many alkaloids are derivatives of quinoline.[2,12] Quinoline is also used as a solvent and a decarboxylation and dehydrohalogenation reagent, and has been used as an antimalarial or antioxidant agent.[1,7,14] Although quinoline dyes were once considered safe for use as food colorants, the use of monosulfonated quinoline yellow is only permitted for use in cosmetics and drugs in the United States. However, other countries permit the use of disulfonated quinoline yellow in foods.[15]

## IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

*1. Oral Toxicity*

Rat $LD_{50}$ 331–460 mg/kg[1,16]

Treated animals exhibited lethargy, respiratory distress, and prostration progressing to coma.[1,4]

*2. Eye Irritation*

Undiluted quinoline causes severe irritation (details unavailable).[16]

Instillation of 0.25 mg quinoline into the eyes of rabbits produced severe ocular irritation (method not described).[3]

*3. Skin Absorption*

Rabbit $LD_{50}$ 540 mL/kg (~0.59 mg/kg).[16]

Treated animals exhibited lethargy, respiratory distress, and prostration progressing to coma.[1,4]

*4. Skin Irritation*

Application of 10 mg quinoline to the skin of rabbits for 24 hr produced mild skin irritation (method not described).[3]

Skin exposure caused moderate to severe irritation in rabbits (method not described).[1]

*5. Skin Sensitization:*

No data found.

*6. Inhalation Toxicity*

Rat: No deaths after inhalation of saturated vapors at room temperature (~78 ppm) for up to 8 hr[4,8,16]; 100% mortality in 5.5 hr after exposure to vapors produced by heating to 100°C (~4000 ppm).[1,4]

*7. Other Toxicity*

Quinoline was systemically toxic to the retina in rabbits after administration of single doses of 200 mg/kg orally, intravenously, or subcutaneously. It caused round white flecks with small reddish rims 3–24 hours post-application. Repeated subcutaneous administration of the tartrate salt at this dose caused degeneration of all layers of the retina. Crystals were identified in retinal tissue similar to those seen with naphthalene poisoning, but unlike naphthalene, no cataracts developed subsequently.[11,17]

B. Subacute Toxicity

Repeated oral administration of 200 mg/kg quinoline to Fischer rats for 28 days caused loose stools, hypoactivity, prone position, soiling in the perioocular or perirhinal region, and reduced body weight gain (also observed at 100 mg/kg). No clinical signs of toxicity were seen at 25 or 50 mg/kg, though genotoxicity was observed at these doses (See Mutagenicity section).[18]

C. Subchronic Toxicity

Male rats fed 0.05, 0.10, or 0.25% quinoline in the diet for 16–40 weeks (equivalent to 25, 50, and 125 mg/kg/day) had lower than normal weight gain, but higher liver weights at all doses. In the 0.25% group, most rats died or became moribund within 40 weeks, due to rupture of vascular liver tumors or general toxic effects. Preneoplastic and neoplastic lesions in the liver were seen at all doses (See Chronic Toxicity/Carcinogenicity section), along with slight-to-moderate oval cell infiltration and fatty degeneration of parenchymal cells in nonneoplastic regions.[19]

D. Chronic Toxicity/Carcinogenicity

Administration of approximately 29 mg quinoline per day (0.2% in the diet; equivalent to 100 mg/kg) to Wistar Kyoto rats for 32 weeks produced hepatic hemangioendothelial sarcomas, often leading to hemorrhaging and death in these animals.[20]

Hepatocellular carcinomas and hemangioendotheliomas were seen in rats fed a diet containing 0.05, 0.10, or 0.25% quinoline (equivalent to 25, 50, or 125 mg/kg/day; 20 rats per dose) for 40 weeks. Tumor incidences among animals surviving to the end of the study were 6/11, 12/16, and 18/19 in the three dose groups, respectively. The incidence of hemagioendotheliomas was higher in low-dose animals, whereas the incidence of hepatocellular carcinomas was higher in high-dose animals. Nodular hyperplasia, a preneoplastic lesion, was also seen in other mid- and high-dose animals, and some animals had metastatic changes in the lung that were histologically similar to the liver malignancies. A NOEL was not identified in this study.[19]

A second study with rats treated for 4–20 weeks with diet containing 0.25% quinoline (equivalent to 125 mg/kg/day) observed that a minimum of 12 weeks of treatment is required in order for hemangioendotheliomas to develop, suggesting that the critical period for tumor development is 12 weeks.[21]

Interspecies comparison of the tumorigenic effects of quinoline found that liver tumors were produced in rats and mice treated with 0.2% quinoline (equivalent to 100 mg/kg/day for rats or 1000 mg/kg/day for mice) for 30 weeks, but not in hamsters or guinea pigs also treated with 0.2% quinoline. However, megalocytosis and oval cell formation were seen in male hamsters.[22]

Quinoline caused hepatic adenomas and hepatomas when given intraperitoneally on the first, eighth, and fifteenth days of life to newborn male CD-1 mice (total dose 1.75 µmol/mouse) that were observed for 52 weeks. Weekly subcutaneous administration of 100 (Weeks 2–7) or 200 (Weeks 1 and 8) µmol/kg quinoline to Sprague-Dawley rats (observation period 78 weeks) caused a high incidence of mortality following the first injection, but no increased incidence of liver tumors.[23]

Quinoline caused hepatic tumors when given intraperitoneally on the first, eighth, and fifteenth days of life to male CD-1 mice (total dose 1.75 µmol/mouse) that were observed for 52 weeks. Leukemia or lymphoma was seen in female newborns, but no liver tumors.[24]

Intraperitoneal administration of quinoline to newborn CD-1 mice at a total dose of 1.75 µmol/mouse on the first, eighth, and fifteenth days of life (observation period 52 weeks) caused hepatic carcinomas, adenomas, and basophilic altered foci in males. It caused basophilic altered foci, but no liver tumors, in female newborn mice. Based on the results of all studies with newborn rats and mice, the authors concluded that newborn mice are exceptionally sensitive to the tumorigenic effects of quinoline and its derivatives.[25]

Quinoline initiated tumors in female SENCAR mice after dermal application of 7.5 mg/animal (male mice were not examined). Its tumor-initiating potential was considered relatively weak, as a similar incidence of tumors was seen following treatment with 0.03 mg benzo[a]pyrene.[36]

E. Reproductive/Developmental Toxicity

There were no available data on *in utero* reproductive/developmental toxicity effects of quinoline in experimental mammalian species. However, a study (presented in an abstract) of one derivative compound, 2-quinoline thioacetamide hydrochloride, reported that digital abnormalities (brachydactylia and oligodactylia) were seen in rats treated with a single oral dose of 200 mg/kg, late in gestation (Day 16) and following the organogenesis period. This finding was attributed to contraction of small blood vessels for at least 6 hr postdosing, leading to ischemia, rupturing of the blood vessels, hemorrhaging, and eventually tissue necrosis. No malformations were observed when the compound was administered during organogenesis (Gestation Days 8–14).[27] No information was located on the potential of thioacetamide alone to cause developmental toxicity or malformations.

F. Genotoxicity/Mutagenicity

Quinoline was mutagenic in the Ames bacterial mutagenicity assay (*S. typhimurium* strains TA98 and TA100) in the presence of metabolic activation only[1,28], and when tested in the CHO/HGPRT mammalian cell assay.[30] Point mutations (DNA base-pair transversions) have also been demonstrated with quinoline in liver cells taken from transgenic mice (intraperitoneal injections of 50 mg/kg for four consecutive days).[13,31] In addition, single intraperitoneal doses of 25–100 mg/kg to mice were shown to cause increased numbers of micronucleated polychromatic erythrocytes in bone marrow cells.[32]

A single oral dose of 200 mg/kg, or 28 consecutive daily doses of 25–200 mg/kg, quinoline given to Fischer rats caused chromosomal aberrations in the liver, increased sister-chromatid exchanges, and increased replicative DNA synthesis.[18] In the single-dose portion of the study, inhibition of mitosis (which increased over time) was also seen. By contrast, single oral doses of 225 and 500 mg/kg quinoline were found to be strongly mitogenic (as shown by increased numbers of liver cells in S-phase) in a second study with Alpk:AP rats.[33]

Mitogenic action was also observed in a follow-up study with C57BL/6J$_f$BL10/Alpk mice at oral doses of 40–225 mg/kg quinoline, but not in Alpk:Dunkin Hartley guinea pigs at doses of 40–100 mg/kg. It was concluded that the mitogenic properties of quinoline correlate closely to its carcinogenic potential, as the compound was positive in both aspects in mice and rats but negative in hamsters and guinea pigs.[34]

Overall, study data suggest that quinoline is mutagenic and genotoxic *in vivo* and *in vitro*, in both bacterial and mammalian cells, although a number of negative and equivocal/inconclusive studies have been published.[33,35–37]

G. Metabolism/Pharmacokinetics

Limited data show that quinoline may be absorbed from the gastrointestinal tract. Following oral administration of 250 mg/kg to large chinchilla rabbits, 3?4% of the dose was detected as quinoline, and 6.7–11% detected as a metabolite, 5,6-dihydroxyquinoline, in a urine sample collected after 24 hours.[38]

Metabolic activation is required to produce the toxic, carcinogenic, and mutagenic effects of quinoline.[19,20] Similar to benzo[a]pyrene, a small amount of quinoline is converted in the liver, via microsomal oxidation of the pyridine moiety, to a reactive epoxide intermediate that alkylates DNA, RNA, and certain polyribonucleotides, initiating carcinogenesis.[39–41] The structure of this intermediate has not been conclusively identified. In one study[39], addition of hydroxy groups at C-5, or C-8 of the quinoline nucleus, or methyl groups at the C-4, C-6, C-7, or C-8 position, did not affect its mutagenic activity in *S. typhimurium* TA100 in the presence of metabolic activation. By contrast, methyl or hydroxyl substitution at C-2 or C-3 eliminated its mutagenicity. The authors of this study suggested that the reactive quinoline metabolite might be quinoline 2,3-epoxide. This is consistent with the results of two additional studies of quinoline bioactivation. In one, 2-chloroquinoline was not shown to not have the same tumorigenic properties as quinoline[19]; in the other, hydrolyzation of quinoline-nucleic acid adducts isolated from liver cells of rats treated intraperitoneally with quinoline resulted in the release of 3-hydroxyquinoline.[42] Other pyridine epoxy and/or dihydro derivatives of quinoline have also been proposed as being its ultimate reactive metabolite.[7,24]

The majority of a dose of quinoline is detoxified *in vivo* either by epoxidation of the benzene moiety or by ring hydroxylation, conjugation, and urinary excretion of the pyridine moiety. It has been proposed that a primary detoxication pathway is epoxidation at the C-5 and C-6 positions to 5,6-dihydroquinoline 5,6-epoxide (which is weakly mutagenic in *S. typhimurium* TA100) and then to 5,6-dihydroquinoline-5,6-diol (quinoline 5,6-diol).[40,43]

Species variability has been found regarding specific metabolic pathways involved in the detoxication of quinoline. In some species, a 1-methyl derivative has also been identified in addition to quinoline 5,6-diol.[38] Moreover, trace quantities of conjugated 6- and 8-hydroxyquinoline (approximately 1–1.5% of the administered dose) were detected along with 5,6-dihydroxyquinoline in the urine of rabbits.[1,7] Quinoline is rapidly and almost completely metabolized and excreted in urine as conjugates in dogs, with 30% of an intravenous dose of 25 mg/kg excreted as conjugated 3-hydroxyquinoline.[1,40,41] Urine has also been identified as the route of elimination of quinoline in rats.[40]

Several cytochrome P450 enzymes involved in quinoline metabolism are common between humans and rats, although they may be present in different relative quantities.[44,45] In particular, CYP 2E1 was shown to be involved in the formation of 3-hydroxyquinoline in both rat and human liver microsomes.[45] The fact that humans and rats share common metabolic enzymes strengthens the relevance of carcinogenic potential observed in rodent studies.[44]

The elimination half life of quinoline in mammals has not been reported.

## V. HUMAN USE AND EXPERIENCE

a. Acute Exposure

Absorption of quinoline into the body (presumably in humans) may lead to nausea, vomiting, gastrointestinal cramps, fever, and a feeling of dizziness, an irregular rapid pulse, and collapse.[1]

Quinoline causes retinitis similar to that caused by naphthalene, but without opacity of the lens.[3] It may also cause permanent corneal injury.[7]

b. Chronic Exposure

A cross-sectional morbidity study on workers in the coal tar products industry, with a broad range of potential exposure histories, found no adverse effects that could be linked to quinoline exposure (study population size not reported).[46]

Primary routes of exposure to quinoline are skin contact with the liquid, or inhalation of vapor or aerosol.[1,4]

## VI. RATIONALE

Quinoline is moderately toxic by ingestion as well as by dermal contact, and is irritating to skin and eyes. It is systemically toxic to the retina. Quinoline is also genotoxic to bacterial and mammalian cells *in vivo* and *in vitro*, and is an initiator/co-initiator of skin tumors in mice. It is a liver carcinogen in rats and mice at high doses, and a quinoline derivative was found to be teratogenic in rats following *in utero* exposure.

Metabolic activation is required to produce the toxic, carcinogenic, and mutagenic effects of quinoline. Metabolic enzymes are similar between rats and

humans, and one known human metabolite of quinoline is a possible intermediate in the production of the ultimate active mutagen. These findings suggest that quinoline may have mutagenic, carcinogenic, or teratogenic potential in human beings. However, no data exist for the effects of chronic exposure to this compound on humans.

Since quinoline is carcinogenic in animals when administered at low doses, this effect is the basis for the OEL. Because a no-observed-effect level (NOEL) was not reported in any available animal studies, the recommended OEL was established by making conservative assumptions when extrapolating from animal data to possible effects in humans.

Using computer-modeling software, the EPA[23] calculated a cancer risk estimate for oral exposure to quinoline. There are significant uncertainties in using this oral cancer potency estimate for assessing occupational cancer risk; therefore it is not used in the quantitative derivation of the OEL. However, as a comparison, based on EPA's estimate, the proposed OEL corresponds to a 2.5:1000 excess cancer risk level. It should be noted that extrapolation from the lowest carcinogenic dose in rats (25 mg/kg) to an occupational setting indicates that an exposure of approximately 170 mg/m$^3$ would result in a similar dose in humans. Extrapolation from the lowest dose associated with non-carcinogenic toxicity (increased mitogenic activity in mice at 40 mg/kg) indicates that an exposure of approximately 275 mg/m$^3$ would result in a similar dose in humans.

A skin notation is also recommended for this OEL because dermal toxicity studies indicate that quinoline may be absorbed through the skin in toxicologically significant amounts.

## VII. RECOMMENDED OEL

8-Hour Time-Weighted Average: 0.001 ppm (0.005 mg/m$^3$), skin.

## VIII. REFERENCES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