IRIS SUMMARY

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Quinoline; CASRN 91-22-5; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Quinoline

File First On-Line 00/00/00

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	discussion	00/00/00
Inhalation RfC Assessment (I.B.)	discussion	00/00/00
Carcinogenicity Assessment (II.)	on-line	00/00/00

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Quinoline
CASRN -- 91-22-5
Last Revised -- 00/00/00

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg/day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the

noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An oral RfD for quinoline is not available at this time. No human studies pertaining to subchronic or chronic toxicity or carcinogenicity of quinoline were identified. Limited information from the studies summarized below regarding the oral toxicity of quinoline in animals following subchronic exposures was available from carcinogenicity bioassays. However, only one dose was used in the experiments reported by Hasegawa et.al. (1989) and Shinohara et al. (1977), and most of the experiments reported by Shinohara et al. did not employ a control group. Exposure durations ranged from just 4-20 weeks in the Hasegawa et.al. (1989) study to 30 weeks in the Shinohara et al. (1977) study. A study by Hirao et al. (1976) included a control and three dose groups of Sprague-Dawley rats fed quinoline in their diets for up to 40 weeks, but did not provide adequate dose-response information for noncarcinogenic endpoints.

These three studies have reported mild hepatic effects including increased liver weight, increased SGOT and alkaline phosphatase (ALP) activities, and histological changes in the liver such as fatty change, bile duct proliferation, oval cells, megalocytosis, endothelial dysplasias and nodular hyperplasia in rats and mice (Hasegawa et al. 1989; Hirao et al. 1976; Shinohara et al. 1977). Early mortality and decreased body weight gains were also noted. Hamsters exhibited oval cells and megalocytosis (both changes graded as trace severity); no histological effects in the livers of guinea pigs were detected (Shinohara et al. 1977). The animal data suggest the liver as a target organ for quinoline.

The observed hepatic changes, body weight loss and early mortalities were considered by the various study authors and EPA (1985) to be related to the hepatocarcinogenic effects of quinoline. In support of this hypothesis, Hasegawa et. al. point out that increase in ALP levels coincided with increased tumor size in the groups they exposed for longer duration (16 and 20 weeks). Effects such as megalocytosis, endothelial displasia and nodular hyperplasia also appeared to be strongly correlated with increased tumor size and incidence. The relationships of the reported body and liver weight changes and histopathology in nonneoplastic regions of the liver (oval cell infiltration, proliferation of bile ducts and fatty degeneration of parenchymal cells) to tumor formation are not as clear. However, it is likely that the weight changes, and possibly the histopathological changes, were at least confounded by the formation of tumors. In any case, none of these oral exposure data were reported in a manner that would allow for a meaningful quantitative dose-response assessment. In addition, no human or animal inhalation toxicity data were available for consideration of an RfC. Thus, in accordance with minimum data base requirements outlined in EPA methods (EPA, 1994), neither an RfD nor an RfC were derived.

___I.A.1. ORAL RfD SUMMARY

Not applicable.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Not applicable.

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

Not applicable.

___I.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

Not applicable.

___I.A.5. CONFIDENCE IN THE ORAL RfD

Not applicable.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- U.S. EPA, 2000

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in the finalization of this IRIS summary. A record of these comments is included as an appendix to the Toxicological Review for Quinoline.

Agency Consensus Date -- 00/00/00

___I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (fax) or RIH.IRIS@EPAMAIL.EPA.GOV (Internet address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Quinoline

No human or animal inhalation toxicity data were available for consideration of an RfC. In accordance with minimum data base requirements outlined in EPA methods (EPA, 1994) an RfC was not derived. See sections I.A. and II for a discussion of the available toxicity data from other routes of exposure, including information on EPA support documents, reviews and contacts associated with this assessment.

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Quinoline
CASRN -- 91-22-5
Last Revised -- 00/00/00

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per $\mu g/m^3$ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

No reliable human epidemiological studies are available that address the potential carcinogenicity of quinoline. As is discussed below, quinoline has been shown to be a hepatocarcinogen in male Sprague-Dawley and SHR rats and both sexes of ddY mice and Wistar rats following oral exposure. Quinoline has also been found to be a hepatocarcinogen in female SENCAR mice following dermal exposure (LaVoie et al., 1984) and newborn mice following intraperitoneal and subcutaneous routes of exposure (LaVoie et al. 1987; LaVoie et al., 1988;

Weyland et al., 1993). Two important aspects of the carcinogenicity of quinoline are the relatively short latency period (as low as 12 weeks) for tumor formation, and the fact that one of the tumor types observed, hemangioendotheliomas, is uncommon in rats and mice. In addition, evidence of the mitogenicity and mutagenicity of quinoline has been demonstrated in both *in vitro* and *in vivo* studies (U.S. EPA, 1985; Hamoud et al. 1989; LaVoie et al. 1991; Lefevre and Ashby 1992; Asakura et al., 1997).

U.S. EPA (1985) previously classified quinoline as Group C carcinogen (i.e., possible human carcinogen). However, in accordance with existing EPA cancer guidelines (U.S. EPA, 1986), quinoline is a Group B2 "*probable human carcinogen*," with sufficient evidence of carcinogenicity involving an unusual type of tumor in multiple species and strains of animals from multiple experiments using different doses and routes of exposure, but no reliable data from human studies. In addition, because quinoline has been shown to increase the incidence of rarely observed, early onset vascular tumors of the liver in both sexes of two rodent species from multiple exposure routes, it is considered "likely to be carcinogenic in humans" in accordance with the proposed EPA carcinogen risk assessment guidelines (U.S. EPA 1996).

___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Human data are inadequate for assessment of the potential human carcinogenicity of quinoline. No reliable human epidemiological studies are available that address the potential carcinogenicity of quinoline, though Reigh et al. (1996) have identified human and rat cytochrome P450 enzymes that mediate metabolic activity which may have implications for the mutagenicity of quinoline in both species.

___II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Several animal studies report hepatocarcinogenicity (hepatocellular carcinomas and hemangioendotheliomas or hemangiosarcomas, a vascular tumor) in rats and mice following oral dosing with quinoline (Futakuchi et al. 1996; Hasegawa et al. 1989; Hirao et al. 1976; Shinohara et al. 1977). Limitations of these studies include small sample size, examination of only one sex in some cases, early mortality, the lack of statistical analyses, the lack of clear distinction between hemangioendotheliomas and hemangiosarcomas and/or short duration of exposure.

Hirao et al. (1976) fed groups of 20 male Sprague-Dawley rats a diet containing 0.05% (low-dose), 0.10% (mid-dose), or 0.25% (high-dose) quinoline for approximately 16–40 weeks. A control group consisting of six rats was also included. Early mortality due to rupture of vascular tumors of the liver was observed in treated animals at all dose levels. Absolute and relative liver weights were significantly increased in all treatment groups, and the difference between initial and final mean body weights decreased with increasing dose. Histological

examination of the liver revealed fatty change, bile duct proliferation, and oval cells in treated animals. Also, nodular hyperplasia was seen in the mid- and high-dose animals. The activities of serum glutamic oxalocetic transaminase (SGOT) and alkaline phosphatase were slightly increased in the low-dose animals; these parameters were not measured in the mid- and high-dose animals.

Tumors were evaluated for all rats after 40 weeks of treatment. Rats that died within the first 16 weeks were excluded. Mortality was observed in the mid- and high-dose groups; the mean survival period was 27.3 weeks in the mid-dose group and 20 weeks in the high-dose group. An increased incidence of hepatic tumors and nodular hyperplasia was noted in treated rats. Hirao et al. (1976) stated that the liver tumors induced by quinoline were classified histologically as hemangioendotheliomas (or hemangiosarcomas) and trabecular hepatocellular carcinomas. Hirao et al. (1976) did not make a clear distinction between hemangioendotheliomas (benign tumors) and hemangiosarcomas (malignant tumors). The incidence of hemangioendotheliomas (or hemangiosarcomas) in the control, low-dose, mid-dose, and high-dose groups were 0/6, 6/11, 12/16, and 18/19, respectively. Metastatic changes, arising from these tumors, were detected in the lungs of some of the rats. The incidences of hepatocellular carcinomas in the control, low-dose, mid-dose, and high-dose groups were 0/6, 3/11, 3/16, and 0/19, respectively. The incidences of nodular hyperplasia in these dose groups were 0/6, 6/11, 4/16, and 0/19, respectively. The decreased incidence of hepatocellular carcinomas and nodular hyperplasia in the high-dose group might be reflective of early mortality. Limitations of this study include its small sample size, the fact that only males were examined, the limited toxicity parameters examined, early deaths, and the lack of statistical analyses.

Shinohara et al. (1977) studied sex and species differences in susceptibility to quinoline-induced histological lesions and tumors. Male and female ddY mice, Wistar rats, Syrian golden hamsters, and Hartley guinea pigs were examined in the first series of experiments, while only male Sprague-Dawley rats were examined in the second series of experiments. In the first series of experiments, animals were given basal diet containing 0.2% quinoline for 30 weeks. A control group was not included. Animals that died prior to 26 weeks were excluded from the study. Examinations were limited to the liver, kidneys, and spleen.

For the first series of experiments, body weight changes for all species tested were reported but are difficult to evaluate without corresponding controls. Further complicating the evaluation of this first experiment was the fact that half of the male and half of the female mice died of pneumonia within the first 6 weeks of the experiment. Liver weight, as a percentage of body weight, increased in all species tested. Liver hepatic changes (graded as trace in severity) in the mouse included oval cells, bile duct proliferation, and megalocytosis. These same hepatic changes were observed in the rat, however, the severity was graded as slight. Rats also exhibited fatty changes (trace severity). Nodular hyperplasia was observed in both rats (58% in males; 64% in females) and mice (10% in males; 20% in females). Only trace oval cell and megalotcytosis lesions were observed in the livers of hamsters (males only) and no lesions were

observed in guinea pigs. The incidences of hemangioendotheliomas, hepatocellular carcinomas, and nodular hyperplasia in rats were 11/15, 2/15, and 7/15, respectively, in males, and 7/22, 2/22 and 14/22, in females. The incidences of hemangioendotheliomas, hepatocellular carcinomas, and nodular hyperplasia in mice were 8/10, 1/10, and 1/10, respectively, in males, and 8/10, 0/10 and 2/10, in females. Some of the rats had hemorrhagic metastatic foci in the lungs. There were no tumors in hamsters or guinea pigs; however, the duration of the experiment was only 30 weeks.

In the second series of experiments, male Sprague-Dawley rats were treated with 0.075% quinoline in the diet for 30 weeks. A control group was included. The same liver lesions reported for rats in the first series of experiments (trace severity) were also noted in the second phase of the experiment. The incidences of hemangioendotheliomas, hepatocellular carcinomas, and nodular hyperplasia in the treated male rats were 6/20, 0/20, and 9/20, respectively. These tumors were not observed in the control rats.

The results of the Shinohara et al. (1977) study indicate species differences in regard to liver tumorigenesis by quinoline, with mice and rats being most susceptible and hamsters and guinea pigs being resistant. Limitations of this study include that only one dose level was examined; there were no controls for the first series of experiments; only one sex was examined in the second series of experiments; there was no statistical analysis; and only limited parameters were examined.

Hasegawa et al. (1989) reported hepatic effects in an oral carcinogenicity bioassay designed to assess the effect of exposure duration on liver tumor induction. In this study, groups of male Wistar rats were administered 0.25% quinoline in the diet for 0 (control), 4, 8, 12, 16 or 20 weeks. Quinoline intake was reported to be 0.56, 1.21, 1.88, 2.59, or 3.33 grams/rat at weeks 4, 8, 12, 16, and 20, respectively. Rats were either sacrificed immediately after these time intervals, or were sacrificed at 4, 8, 12, 16, or 20 weeks after cessation of treatment. The study authors stated that main organs and any gross pathological lesions were subjected to histologic examination. Hepatic alterations observed in the treated rats consisted of gross findings (black nodules or cysts at >12 weeks), increased SGOT activity (≥4 weeks), increased alkaline phosphatase activity (16 weeks), increased relative liver weights (≥4 weeks), megalocytosis (≥4 weeks), endothelial dysplasia (≥16 weeks), and hyperplastic nodules (at 20 weeks). Body weights were decreased in the treated animals at all exposure durations. The authors reported that several rats died during the period between the scheduled sacrifice times due to rupture of the vascular tumors of the liver.

An increased incidence of hepatic hemangioendotheliomas was observed in rats treated with quinoline for ≥12 weeks. The incidences of hepatic hemangioendotheliomas in rats treated with quinoline for 12 weeks, and then sacrificed at the intervals described above, were 1/11 (12 weeks), 2/12 (16 weeks), and 5/12 (20 weeks). After 16 weeks of treatment prior to sacrifice, the incidences were 4/14 (16 weeks) and 4/18 (20 weeks). Following 20 weeks of treatment, the incidence was 5/16 ($p=0.044$).

An increase in the incidence of endothelial dysplasia (stated by the study authors as a preneoplastic precursor) was also observed in rats treated with quinoline. Hasegawa et al. (1989) concluded that the critical period for induction of tumors with 0.25% quinoline is 12 weeks, and that it is likely that quinoline possesses strong initiating potential rather than promoting activity for hepatic hemangiocellular carcinogenesis assuming an analogy to the two-stage carcinogenesis hypothesis in skin and hepatocytes. This study is limited in that only one dose level and only one sex were examined, and not all relevant endpoints (such as food consumption, urinalysis, and hematology) were studied.

Quinoline can apparently act as a promoter of liver carcinogenicity as well (Saeki et al., 1997). Quinoline, 3-FQ, or 5-FQ were fed to F344 male rats in their diet (0.1%, and 0.05%) for a period of 6 weeks following a single i.p. injection of the liver carcinogen diethylnitrosamine (DEN, 200 mg/kg). Control groups were administered DEN alone. All rats were subjected to a partial (two-thirds) hepatectomy at the end of week 3 and sacrificed at the end of week 8. The number and areas of GST-P (placental glutathione S-transferase)-positive foci induced in the liver increased significantly as a result of treatment with 0.1% quinoline.

Futakuchi et al. (1996) conducted a study to determine the susceptibility of the spontaneously hypertensive rat (SHR) to quinoline-induced hepatic hemangioendothelial sarcomas, considered a vascular neoplasm originating from hepatic endothelial cells. Male SHR and Wistar Kyoto rats (WKY), the parent strain of SHR, were administered 0.2% quinoline in the diet for 32 weeks. The number of rats with hepatic hemangioendothelial sarcomas was 7% for SHR and 93% for WKY. The results of this study show that the SHR is less susceptible to hepatic carcinogenicity than is the WKY. Based on the lack of findings of vascular lesions, the authors concluded that the observed vascular tumorigenesis was not directly related to vascular physiological injury. The study authors speculated that the observed strain differences in carcinogenic response very likely involve differences in metabolic activation between the two strains of rats.

Quinoline has also been reported to be a hepatocarcinogen in newborn mice or rats following intraperitoneal or subcutaneous exposure (LaVoie et al. 1987; LaVoie et al. 1988; Weyland et al. 1993). Hepatic tumors (carcinomas, adenomas, and basophilic altered foci) were observed in male newborn mice, but not male or female newborn rats. Only basophilic altered foci were observed in female newborn mice.

Quinoline initiated skin tumors in female SENCAR mice following dermal application (LaVoie et al. 1984). Male mice were not examined.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Numerous reports are available regarding the *in vitro* mutagenicity of quinoline activated with S-9, a supernatant fraction from arochlor, 3-methylcholanthrene and β-naphthoflavone-

treated rats, in both reverse and forward mutation assays with several strains of *Salmonella typhimurium* (EPA, 1985; LaVoie et al., 1991). Quinoline was found to have significant activity in the *Salmonella typhimurium* strain TA100 but generally not in strains TA1537 and TA1538 (EPA, 1985), nor TA98 (Debnath et al. 1992), suggesting that it may be acting via base-pair substitution (EPA, 1985).

The fact that quinoline mutagenicity requires S-9 activation indicates that it must be metabolized to its active moeity by liver enzymes, presumably cytochrome P450 (or P448) enzymes (Hollstein et al., 1978; EPA, 1985). In rat microsomal preparations, quinoline has been shown to bind to various nucleic acids including RNA and DNA to form adducts (Tada et al. 1980). The results suggest that the cytochrome P-450-linked monooxygenase system is involved in the binding process. Chemical hydrolysis of the quinoline-nucleic acid adducts resulted in the liberation of 3-hydroxyquinoline, a metabolite of quinoline. The authors interpreted these results to suggest that a 2,3- or 3,4-epoxy derivative of quinoline is the reactive intermediate for nucleic acid modification. Support for this hypothesis comes from more recent studies involving fluorine and chlorine substitution at various locations on the quinoline rings. 3-Fluoro-, 2- and 3-chloro-quinolines were less mutagenic than all other fluoro and chloro substituted derivatives of quinoline (Takahashi et al., 1988; Saeki et al., 1993). The 3-Fluoro derivative of quinoline completely blocks the mutagenic activity of quinoline. Substitution at other locations do not reduce quinolines mutagenicity, and in some cases enhance it (presumably by inhibiting detoxification pathways). Takahashi et al. (1988) suggest that it is the 2,3-epoxide that is the active metabolite based on the fact that the 4-chloro isomer is weakly mutagenic (presumably no mutagenicity would be observed if a 3,4-epoxide were necessary), the 4-methyl isomer is strongly mutagenic (suggested to be due to suppression of detoxification of the 2,3 epoxide) and the 2-methyl isomer is weakly mutagenic (the authors report that methyl substitution at the site of epoxide formation is known to partially reduce mutagenicity). Lavoie et al. (1983) proposed that the 5,6 epoxide of quinoline is the carcinogenic moeity. However, quinoline is still mutagenic when halogenated at the 5 or 6 position, and the 5,6 epoxide of quinoline is much less mutagenic than quinoline itself (Saeki et al. 1993). Using this and information on the metabolism of 3-fluoroquinone, Saeki et.al. (1993) proposed human and rat metabolic pathways for detoxification and activation, with a 2,3-epoxide of quinoline forming the ultimate DNA adduct.

Reigh et al. (1996) claim to have identified the cytochrome P450 enzymes responsible quinoline metabolite formation in human and rat liver microsomes. In particular, CYP2E1 was shown to be involved in the formation of 3-hydroxyquinoline (3-OHQ) in both rat and human liver microsomes, which may be an important intermediate in the pathway to the formation of the mutagenic epoxide discussed above. Reigh et al. (1996) also pointed out some possible species differences in the metabolism of quinoline between rats and humans that suggest the need for further investigations in this area.

The *in vitro* results discussed so far and *in vitro* studies showing that microsomally activated quinoline can induce unscheduled DNA synthesis (UDS) in rat hepatocytes (LaVoie et al. 1991) seem to suggest that the genotoxicity of quinoline plays an important role in its

hepatocarcinogenicity. However, equivocal results were reported in a study designed to evaluate the ability of quinoline to initiate UDS in rat liver *in vivo* (Ashby et al. 1989). Ashby et al. (1989) reported marginal positive responses for some individual animals but there were no clear group-positive responses and no dose relationship. The authors concluded that quinoline is unclassifiable in the *in vivo* UDS test. They also determined that structurally related chemical, 8-hydroxyquinoline, which was mutagenic to *Salmonella* (Nagao et al., 1977) but non-carcinogenic in an NTP (1985) chronic bioassay, was inactive in the UDS assay. However, during the course of studies performed to determine whether quinoline was active in the UDS assay, Ashby et al. (1989) observed an increased incidence of semi-conservative DNA synthesis (S-phase) in the rat liver cells, which led them to perform S-phase and micronucleus assays for quinoline and 8-hydroxyquinoline. Quinoline was found to be a powerful S-phase inducer, with an optimum response between 16 and 36 hours after oral dosing of 225-500 mg/kg, while the same doses of 8-hydroxyquinoline did not induce S-phase. The mitogenicity of quinoline was also indicated by a subsequently elevated incidence of mitotic figures and by its ability to act as a chemical mitogen in the liver micronucleus assay. In a similar S-phase assay, quinoline was also shown to be a mitogen to the mouse liver, but not the guinea pig liver (Lefevre and Ashby 1992), corresponding to the relative sensitivity of these two species to quinoline induced tumor formation.

Recent studies by Asakura et al. (1997) and Suzuki et al. (1998), however, lend further support to the proposed genotoxicity mechanism. Asakura et al. (1997) examined the potential of quinoline to induce chromosome aberrations and sister chromatid exchanges in the rat liver utilizing an *in vivo* cytogenetic assay. Hepatocytes were isolated 4–48 hours following a single dose of 200 mg/kg bodyweight or 24 hours after 28 repeated doses (once daily) of 25–200 mg/kg/day by gastric intubation. Both treatment regimens resulted in the induction of chromosome aberrations and sister chromatid exchanges in the liver. Cytogenetic effects induced in the liver by repeated doses of quinoline were shown to be greater than those induced by a single dose. In addition, quinoline induced replicative DNA synthesis in the rat liver but, contrary to findings in CD1 mice (Hamoud et al. 1989), it did not induce micronucleus formation in the bone marrow of rats. The results of the Asakura et al. (1997) study suggest that quinoline is a genotoxic carcinogen to the rat liver, having both tumor-initiating and tumor-promoting activity.

Suzuki et al. (1998) conducted a study to evaluate the mutagenicity of quinoline in an in vivo mutation assay system using the lac Z transgenic mouse (Muta Mouse). Mutation was only induced in the liver, the target organ of carcinogenesis by quinoline, but not in the other organs examined, i.e. lung, kidney and spleen. Mutant frequency in the liver was 4-fold higher than in the untreated control animals. Dimethylnitrosamine, used as a positive control, induced mutation at a frequency 5-fold higher in the liver and 3-fold higher in the spleen than in their respective control organs. Given the studies that show quinoline to be genotoxic, and those discussed above concerning the *in vivo* mitogenicicity of quinoline, it is possible that there are both genotoxic and mitogenic components to the pathogenesis of the hepatocarcinogenicity of quinoline.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Limitations in the available studies which impact the dose-response assessment for quinoline include small sample sizes, examination of only one sex in some cases, early mortality, the lack of statistical analyses, the lack of clear distinction between hemangioendotheliomas and hemangiosarcomas and/or short durations of exposure. Nevertheless, they provide strong evidence of hepatocarcinogenesis (including vascular tumors of the liver) in the rat and the mouse by the oral route of exposure. One of the tumor types, hemangioendotheliomas, is uncommon in the rat and the mouse. In addition, quinoline has been shown to be a tumor initiator in the skin of female SENCAR mice. Also, the mutagenicity and mitogenicity of quinoline has been demonstrated in the rat and mouse liver.

EPA performed a cancer dose-response assessment based on the oral carcinogenicity bioassay of Hirao et al. (1976) (EPA 1985). The current reassessment of the Hirao et al. (1976) study by EPA is summarized below. Both the previous and current assessments are discussed in more detail in the toxicological review (U.S. EPA, 2000) associated with this summary profile.

____II.B.1.1. Oral Slope Factor -- 5 per (mg/kg)/day
(Hirao, 1976; hepatic hemangioendotheliomas or hemangiosarcomas)

____II.B.1.2. Drinking Water Unit Risk -- 1 E−4 per (μg/L)

____II.B.1.3. Extrapolation Method - The EPA (1985) study made an adjustment to reflect the fact that the different treatment groups were terminated before the end of the normal lifespan of the rats, which is typically 104 weeks in experimental studies. The doses were adjusted by a factor $[L_e/L]^3$, where L_e is the length of the experiment and L is the normal lifespan. This factor is used because tumor rate generally increases by at least the 3rd power of age, and adjusting the doses by a factor of $[L_e/L]^3$ is analogous to adjusting the slope factor (unit risk) by $[L/L_e]^3$. The mean length of experiment for the control, low-, mid-, and high-dose animals was 40, 36.5, 27.3, and 20 weeks, respectively. Thus the adjusted doses for these dose groups were 0, 1.08, 0.90, and 0.89 mg/kg/day, respectively.

In the present reassessment, the mean survival time for each dose group was employed directly in a time-to-tumor dose-response model, using administered dose levels of 25, 50 and 125 mg/kg/day, rather than dose levels adjusted for fractions of a lifespan. This procedure should more accurately compensate for survival time differences between dose groups than that used by EPA (1985). Animal doses were adjusted to human doses using 3/4 power scaling. Humans were assumed to be exposed 24 hours/day, 7 days/week, 52 weeks/year beginning at age

0 and ending at age 70.

The present risk estimate was calculated using the computer software TOX_RISK version 3.5 (Crump et al., ICF Kaiser International, Ruston, LA) which was based on multistage Weibull models taken from (Krewski et al, 1983). The 1-stage Weibull model was selected based on the values of the log likelihoods. While individual time-to-tumor data are preferred, they were unavailable in the Hirao et al. (1976) study. Mean time-to-tumor for each exposure group was therefore employed for quantitating cancer risk. It was assumed that all the animals in each dose group died at the end of the mean experimental period for that dose group (i.e., 40, 36.5, 27.3, and 20 weeks for the 0, 25, 50, and 125 mg/kg/day dose groups, respectively). Further details are presented below and in the toxicological review associated with this assessment (U.S. EPA, 2000).

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E−4 (1 in 10,000)	8 E−1 μg/L
E−5 (1 in 100,000)	8 E−2 μg/L
E−6 (1 in 1,000,000)	8 E−3 μg/L

___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor type -- hepatic hemangioendotheliomas (or hemangiosarcomas)
Test animals -- male Sprague-Dawley rats
Route -- oral, dietary
Source -- Hirao et al., 1976

Dose Level*	Incidence
	No. Responding/No. Tested or Examined
0	0/6 [2/83]**
0.05% (500 ppm; 25 mg/kg/day)	6/11
0.10% (1000 ppm; 50 mg/kg/day)	12/16
0.25% (2500 ppm; 125 mg/kg/day)	18/19

*Since food consumption data were not provided, U.S. EPA (1985) converted the dose levels (% in feed) to mg/kg/day values by assuming that a rat consumes a daily amount of food equal to 5% of its body weight.
** Historical controls as reported by Anvers et al. (1982).

___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The Hirao et al. (1976) study was chosen for this dose-response assessment because it provided dose-response data for the induction of hemangioendotheliomas (or hemangiosarcomas) in rats. The tumors could not be classified as to their exact degree of malignancy. However, it is assumed that a significant percentage of the hemangioendotheliomas were malignant (U.S. EPA, 1985). There was a dose-dependent increase in the incidence of hemangioendotheliomas that was associated with increased mortalities and body weight loss.

The current reassessment of the cancer oral slope factor for quinoline is still based on a limited study (Hirao et al., 1976) that was of less than lifetime duration, involved just 20 animals per dose group, and did not report individual animal data. However, the q_1* of 4.5 $(mg/kg/day)^{-1}$ derived here is recommended over the somewhat greater EPA (1985) estimate of 12.5 $(mg/kg/day)^{-1}$ for several reasons. Uncertainty is reduced by use of mean time-to-tumor for each dose group, eliminating the need to adjust dose by the cube of experiment duration/lifespan. The inclusion of 83 historical controls from a study reported by Anver et al. (1982) using the same strain of rats decreased uncertainty further. In the study by Hirao et al. (1976), only 6 controls were reported, and these were examined after only 40 weeks. Finally, animal to human dose conversion used scaling to the 3/4 power, the factor currently used by EPA, rather than 2/3 power as was done in the earlier assessment.

The recommended q_1* of 4.5 $(mg/kg/day)^{-1}$ is also in good agreement with an $0.1/LED_{10}$ (the 95% lower confidence limit on a dose associated with 10% extra risk adjusted for background) of 4.3 per mg/kg/day derived using the linear extrapolation method according to the EPA (1996) proposed cancer guidelines. The linear extrapolation method, which under the proposed guidelines involves taking the slope of the straight line from the LED10 to the origin (i.e., 0 extra risk at 0 dose), is warranted by the positive evidence of genotoxicity.

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

Only one study (Hirao et al. 1976) was identified that provided dose-response data for the induction of hemangioendotheliomas (or hemangiosarcomas) . Confidence in this database is medium. The findings are supported by Shinohara et al. (1977), Hasegawa et al. (1989) and Futakuchi et al. (1996). Uncertainty in the development of the q_1* was reduced by use of mean time-to-tumor for each dose group and inclusion of 83 historical controls. The q_1* is in agreement with that derived using the current proposed EPA (1996) linear extrapolation method.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM

INHALATION EXPOSURE

No human or animal inhalation toxicity data were available for consideration of carcinogen risk from inhalation exposure. See sections I.A. and II.A. and II.B. for a discussion of the available toxicity data from other routes of exposure, including information on EPA support documents, reviews and contacts associated with this assessment.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

__II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 2000

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to the Toxicological Review for Quinoline.

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- 00/00/00

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (fax), or RIH.IRIS@EPAMAIL.EPA.GOV (Internet address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Substance Name -- Quinoline
CASRN -- 91-22-5
Last Revised -- 00/00/00

__VI.A. ORAL RfD REFERENCES

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_VII. REVISION HISTORY

Substance Name -- Quinoline
CASRN -- 91-22-5

Date	Section	Description

_VIII. SYNONYMS

Substance Name -- Quinoline
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91-22-5