Quinoline; CASRN 91-22-5

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Quinoline

File First On-Line 09/27/2001

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	qualitative discussion	09/27/2001*
Inhalation RfC (I.B.)	qualitative discussion	09/27/2001*
Carcinogenicity Assessment (II.)	yes	09/27/2001*

*A comprehensive review of toxicological studies was completed (July 20, 2006) — please see sections I.A.6., I.B., and II.D.2. for more information.

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 — 09/27/2001

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.

I.A.1. Oral RfD Summary

An oral RfD for quinoline is not available at this time.

I.A.2. Principal and Supporting Studies (Oral RfD)

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. All of these oral studies had limitations, some major.

The oral carcinogenicity study by Hirao et al. (1976) reported minimal hepatic changes in rats fed diets containing 0.05% (low-dose), 0.10% (mid-dose), or 0.25% (high-dose) quinoline for 16-40 weeks. These changes included increased absolute and relative liver weights, fatty change, slight-to-moderate bile duct proliferation, and slight-to-moderate oval cell infiltration. None of these data were reported in a manner that would allow for an appropriate and meaningful quantitative dose-response assessment (e.g., variance information was not provided for body weight change, liver weight change was not reported, and lesions were reported categorically). Nodular hyperplasia, a preneoplastic lesion, was observed in the mid- and high-dose animals. The dose-response for fatty change and nodular hyperplasia paralleled that for hepatocellular carcinoma. SGOT and alkaline phosphatase activities were slightly increased in the low-dose animals; liver enzyme activity was not measured in mid- or high-dose animals. There was a dose-dependent decrease in terminal body weights. Early mortality was high in the mid- and high-dose animals because of rupture of vascular tumors of the liver. The average survival periods for the control, low-, mid,- and high-dose animals were 40, 36.5, 27.3, and 20 weeks. This study's limitations include small sample size, only males being examined, a lack of statistical analyses, early death and the examination of a limited number of toxicity parameters.

Minimal hepatic lesions were also reported in the carcinogenicity bioassay by Shinohara et al. (1977). In one experiment of the study, rats, mice, hamsters, and guinea pigs were administered 0.2% quinoline in the diet for 30 weeks. Mice and rats exhibited oval cell formation, bile duct proliferation, megalocytosis, and nodular hyperplasia. Fatty change was

also seen in the rat. Hamsters, but not guinea pigs, displayed megalocytosis and oval cell formation. No controls were used in the first experiment; therefore, it is difficult to fully interpret the significance of the findings. In the second series of experiments, increased absolute and relative liver weights, trace oval cell formation, trace bile duct proliferation, moderate fatty change, moderate megalocytosis, and nodular hyperplasia were observed in rats fed 0.075% quinoline in the diet for 30 weeks. The increase in liver weight was attributed to the development of tumors. 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, no statistical analysis was conducted, and only limited parameters were examined.

Similar hepatic effects to those described above were noted in the carcinogenicity bioassay by Hasegawa et al. (1989). The Hasegawa et al. (1989) study was designed to assess the effect of duration on tumor induction. Changes consisted of increased liver weight, increased SGOT and alkaline phosphatase activities, megalocytosis, gross findings (black nodules or cysts), endothelial dysplasia, and hyperplastic nodules. The study authors considered the increase in alkaline phosphatase at weeks 16 and 20 an endothelial marker enzyme reflecting the increased size of tumors. Body weights were decreased in the treated animals at all exposure durations. Deaths due to rupture of tumors were also reported. This study also had limitations, including examination of only one dose level and only one sex, and lack of measurement of all relevant endpoints including food consumption, urinalysis, and hematology.

Although the above-mentioned studies were limited, hepatic changes, decreased body weight, and mortality due to rupture of tumors were consistent findings. Hepatic changes included tumor formation (as discussed in detail in Section 4.2.2). The hepatic changes (increased liver weight, fatty change, increased liver enzyme activity, oval cell infiltration, preneoplastic lesions), early mortalities, and body weight loss were considered by the various study authors to be related to the process of hepatocarcinogenesis. 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), and effects such as megalocytosis, endothelial dysplasia, and nodular hyperplasia appeared to be strongly correlated with increased tumor size and incidence. It is also likely that the weight changes, and possibly the histopathological changes, were at least confounded by the formation of tumors. Thus, noncancer effects from oral exposure were confounded by and could not be disassociated from the carcinogenic effects of quinoline, and were not reported in a manner that would allow for a meaningful quantitative dose-response assessment. For these reasons, and in accordance with minimum database requirements outlined in EPA methods (U.S. EPA, 1994), an RfD was not derived.

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, 2001

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. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Agency Consensus Date — 09/21/2001

A comprehensive review of toxicological studies published through July 2006 indicated that there is insufficient health effects data to derive an RfD for Quinoline at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Quinoline
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The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88-066F, August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F, October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are 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.

No human or animal inhalation toxicity data were available for consideration of an RfC. In accordance with minimum database requirements outlined in EPA methods (U.S. 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.

A comprehensive review of toxicological studies published through July 2006 indicated that there is insufficient health effects data to derive an RfC for Quinoline at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II. Carcinogenicity Assessment for Lifetime Exposure

Quinoline
CASRN — 91-22-5
Last Revised — 09/27/2001

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 µg/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. However, laboratory studies have shown that quinoline is mitogenic and mutagenic in vitro and in vivo (U.S. EPA, 1985; Hamoud et al., 1989; LaVoie et al., 1991; Lefevre and Ashby, 1992; Asakura et al., 1997; Suzuki et al., 1998), and that humans and rats share a common quinoline-metabolizing P450 enzyme (Reigh et al., 1996).

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 newborn male mice following intraperitoneal exposure (LaVoie et al., 1987, 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.

Quinoline is considered *likely to be carcinogenic in humans* in accordance with proposed EPA carcinogen risk assessment guidelines (U.S. EPA, 1996) on the basis of observations of exposure-related increased incidence of an unusual malignant tumor in multiple strains of rats and mice, multiple experiments using oral, i.p. and s.c. dosing at an early age. This determination is supported by studies that demonstrate that quinoline is genotoxic. EPA (1985) previously classified quinoline as a Group C *possible human carcinogen* under the existing EPA cancer guidelines (U.S. EPA, 1986). However, recent evidence from mitogenicity and mutagenicity studies and two dietary studies in rats (Futakuchi et al., 1996; Hasegawa et al., 1989) indicate that "sufficient" animal evidence exists, and that quinoline would now be classified as a Group B2 *probable human carcinogen* under the 1986 guidelines.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

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, although Reigh et al. (1996) identified cytochrome P450 enzymes common to both rats and humans that mediate quinoline metabolic activity. In particular, CYP2E1 was shown to be involved in the formation of 3-hydroxyquinoline (3-OHQ) in both rat and human liver microsomes. This is important because 3-OHQ is a possible intermediate in the pathway to the formation of the 2,3-epoxide of quinoline, which has been suggested to be the active mutagenic metabolite of quinoline (Takahashi et al., 1988). Although no human studies are available to assess the potential for sensitive subpopulations, animal studies have shown that exposure to quinoline at an early age (1, 8, and 15 days after birth) can result in a tumorigenic response later in life of newborn mice and rats, particularly males, suggesting a need for further study into the childhood susceptibility of quinoline (LaVoie et al., 1987, 1988; Weyland et al., 1993; Shinohara et al., 1977).

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 oxaloacetic 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 all dose groups; the mean survival period was 36.5 ± 5.0 weeks, 27.3 ± 6.0 weeks, and 20.0 ± 3.8 weeks in the low-, mid-, and high-dose groups, respectively. 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 incidences 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 authors' report that these foci "showed the same histological pattern as hemangiosarcomas with large irregular nuclei and many mitotic figures" is sufficient evidence to suggest that they were related to the liver tumors and did not originate in the lungs. 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 (i.e., rats died of ruptured hemangiosarcomas before they had time to contract other liver carcinomas). 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, whereas only male Sprague-Dawley rats were examined in the second series of experiments. In the first series of experiments, animals were given a 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. The authors stated that "some of the rats [four males and one female] had hemorrhagic metastatic foci in the lungs," without indicating the basis for the determination that these tumors did not originate in the lungs. However, given that these lung tumors occurred only in the mid- and high-dose groups and that Hirao et al. (1976) reported metastatic foci in the lungs that had the same histological pattern as hemangiosarcomas of the liver, it is reasonable to assume, for the purposes of this assessment, that these authors are correct in this regard. 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 from 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; p 0.05). After 16 weeks of treatment prior to sacrifice, the incidences were 4/14 (16 weeks; p 0.05) and 4/18 (20 weeks). Following 20 weeks of treatment and immediate sacrifice, the incidence was 5/16 (p 0.05). Incidence in control animals sacrificed at 20 weeks following no treatment was 0/12. In addition, no tumors were observed in animals exposed to quinoline for 4 and 8 weeks and sacrificed after a latency period of from 0 to 16 weeks (not exceeding 20 weeks treatment + latency period).

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-fluoroquinone, or 5-fluoroquinone was 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%, but not 0.05%, 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. On the basis of the lack of findings of vascular lesions, the authors concluded that the observed vascular tumorigenesis was not directly related to vascular physiological injury. The strain differences in carcinogenic response reported in this study are most likely the result of differences in metabolic activation between the two strains of rats.

Quinoline has also been reported to be a hepatocarcinogen in newborn male mice following intraperitoneal exposure (LaVoie et al., 1987, 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 Beta-naphthoflavone-treated rats, in both reverse and forward mutation assays with several strains of *Salmonella typhimurium* (U.S. 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 (U.S. EPA, 1985), nor TA98 (Debnath et al., 1992), suggesting that it may be acting via base-pair substitution (U.S. 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; U.S. 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 P450-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. These results 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- and 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. Substitutions at other locations do not reduce quinoline's 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 because of 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 for 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 between rats and humans in the metabolism of quinoline that suggest the need for further investigations in this area.

In vitro studies show that microsomally activated quinoline can induce unscheduled DNA synthesis (UDS) in rat hepatocytes (LaVoie et al., 1991). These in vitro UDS results together with the in vitro results discussed above suggest that the genotoxicity of quinoline may play 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 a structurally related chemical, 8-hydroxyquinoline, which was mutagenic to *Salmonella* (Nagao et al., 1977) but noncarcinogenic 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 semiconservative 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, whereas 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 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 fourfold higher than in the untreated control animals. Dimethylnitrosamine, used as a positive control, induced mutation at a frequency fivefold higher in the liver and threefold 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 mitogenicity of quinoline, it is possible that there are both genotoxic and mitogenic components to the pathogenesis of the hepatocarcinogenicity of quinoline. It is also apparent that conjugation of quinoline can play an important detoxification role, depending upon the site at which quinoline is conjugated (Takahashi et al., 1988; Saeki et al., 1993). However, specific detoxification pathways have not been identified.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

Limitations in the available studies that 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 ample evidence of hepatocarcinogenesis (including vascular tumors of the liver) in the rat and the mouse by the oral route of exposure, particularly because of the relatively short latency. 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 previously performed a cancer dose-response assessment based on the oral carcinogenicity bioassay of Hirao et al. (1976) (U.S. 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, 2001) associated with this summary profile.

II.B.1.1. Oral Slope Factor

3 per (mg/kg)/day (see text discussion below) (Hirao et al., 1976; hepatic hemangioendotheliomas or hemangiosarcomas)

II.B.1.2. Drinking Water Unit Risk

9E-5 per (µg/L) (represents the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to 1 µg quinoline/L in water)

II.B.1.3. Extrapolation Method

EPA (1985) 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 third power of age, and adjusting the doses by a factor of $[L_e/L]^3$ is consistent with 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 the shorter experiment duration than that used earlier by EPA (1985). Animal doses were adjusted to human doses using 3/4 power scaling. Humans were assumed to have daily exposure, beginning at age 0 and ending at age 70.

The present risk estimate was calculated with the computer software TOX_RISK version 3.5 (Crump et al., ICF Kaiser International, Ruston, LA), which uses multistage Weibull models taken from Krewski et al. (1983). The one-stage Weibull model was selected based on the values of the log likelihoods. Although individual time-to-tumor data are preferred, they were unavailable in the Hirao et al. (1976) study. Mean data for each dose group were 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., 36.5, 27.3, and 20 weeks for the 25, 50, and 125 mg/kg/day dose groups, respectively). For the controls, historical control data from Anver et al. (1982) were used. This approach resulted in the calculation of an LED_{10} (i.e., lower bound 95% confidence limit on the dose that causes a 10% increase in the extra risk of an effect) of 32.6 µg/kg/day and an oral slope factor ($0.1/LED_{10}$) of 3 $(mg/kg/day)^{-1}$ for humans (in accordance with EPA policy, only one significant figure is retained). The linear extrapolation method described in EPA's proposed cancer guidelines (U.S. EPA, 1996) was used to obtain this estimate. Linear extrapolation is warranted by the positive evidence of mutagenicity for quinoline. Further details of this calculation are presented in the toxicological review associated with this assessment (U.S. EPA, 2001).

The estimated oral cancer slope factor of 3 $(mg/kg/day)^{-1}$ was used to obtain the following risk levels, which can be thought of as 95% lower bound risk estimates.

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E 4 (1 in 10,000)	1 µg/L
E 5 (1 in 100,000)	0.1 µg/L
E 6 (1 in 1,000,000)	0.01 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
Reference — 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% (1,000 ppm; 50 mg/kg/day)	12/16
0.25% (2,500 ppm; 125 mg/kg/day)	18/19

*Because food consumption data were not provided, 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 Anver et al. (1982).

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The cancer oral slope factor for quinoline is 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 study does provide dose-response data that clearly indicate 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.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

No reliable human epidemiological studies are available that address the potential carcinogenicity of quinoline. However, laboratory studies have shown that quinoline is mitogenic and mutagenic in vitro and in vivo, and that humans and rats share a common quinoline-metabolizing P450 enzyme (Reigh et al., 1996). The evidence that quinoline is carcinogenic in rats and mice is strengthened by observations of a short latency period for the formation of tumors and the formation of tumors (hemangioendotheliomas) that are rarely observed in these rodent species. Taken together, these facts strengthen the potential relevance to humans of studies that show quinoline to be hepatocarcinogenic in rats and mice following oral and i.p. exposures.

The oral cancer slope factor of 3 $(mg/kg/day)^{-1}$ is based on the linear extrapolation method described in EPA proposed cancer guidelines (U.S. EPA, 1996). Uncertainty is reduced from the 1985 assessment by using time-to-tumor modeling, 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 decreases uncertainty further. However, only one study was identified that provided dose-response data for the induction of hemangioendotheliomas (or hemangiosarcomas), and the limitations in the Hirao et al. (1976) study (e.g., few animals, study terminated after only 40 weeks, no individual animal data) are too significant to warrant any more than low confidence in the slope factor estimate.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

No human or animal inhalation toxicity data were available for derivation of an inhalation cancer slope factor. There are no pharmacokinetic data available that would allow for the use of oral data to postulate the effects of inhalation exposures. Further, there is evidence to suggest that first-pass liver metabolism that can occur subsequent to oral and i.p., but not

inhalation and s.c. exposures, may play an important role in the formation of liver tumors. Liver tumors have been observed in rats and mice exposed to quinoline via oral and i.p. routes of exposure, but not in rats exposed subcutaneously, despite the fact that the s.c. injections resulted in maximally tolerated doses more than 40 times higher than i.p. doses given to mice (LaVoie et al., 1988). The observation of skin tumors on mice dermally exposed to quinoline and a tumor promoter, tetradecanoyl phorbol acetate (LaVoie et al., 1984), suggest that quinoline can initiate skin tumors (no other tumor types were reported) without first-pass metabolism in the liver. See Sections I.A, 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, 2001

Other EPA Documentation — U.S. EPA, 1985

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. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 09/21/2001

A comprehensive review of toxicological studies published through July 2006 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for Quinoline and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Quinoline
CASRN — 91-22-5

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

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VII. Revision History

Quinoline
CASRN — 91-22-5

Date	Section	Description
09/27/2001	I.,II.,VI	Assessment first on-line
12/03/2002	I.A.6., I.B., II.D.2.	Screening-Level Literature Review Findings message has been added.
09/28/2006	I.A.6., I.B., II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Quinoline
CASRN — 91-22-5
Last Revised — 09/27/2001

- 91-22-5
- 1-Azanaphthalene
- 1-Benzazine
- Benzopyridine
- Leucoline
- Benzo[b]pyridine
- 1-Benzine
- Chinoleine
- Chinoline
- Leucol
- Leukol
- B-500