EPA

TOXICOLOGICAL REVIEW

OF

QUINOLINE

(CAS No. 91-22-5)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

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EXTERNAL REVIEW DRAFT

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CONTENTS—TOXICOLOGICAL REVIEW FOR QUINOLINE

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FOREWORD . . . . . .

AUTHORS, CONTRIBUTORS, AND REVIEWERS . . . . . .

1. INTRODUCTION . . . . . .

2. CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS . . . . . .

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS . . . . . .
   - 3.1. ABSORPTION . . . . . .
   - METABOLISM . . . . . .
   - EXCRETION . . . . . .

4. HAZARD IDENTIFICATION . . . . . .
   - 4.1 STUDIES IN HUMANS . . . . . .
   - 4.2 PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION . . . . . .
   - 4.3 REPRODUCTIVE/DEVELOPMENTAL STUDIES IN ANIMALS—ORAL AND INHALATION . . . . . .
   - 4.4 OTHER STUDIES . . . . . .
     - 4.4.1. Neurotoxicity . . . . . .
     - 4.4.2. Genotoxicity . . . . . .
   - 4.5 SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS . . . .
   - 4.6 WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION . . . . . .

4.6.1. Human . . . . . .
4.6.2. Animal . . . . . .
4.6.3. Mode of Action . . . . . .
4.7 SUSCEPTIBLE POPULATIONS . . . . . .
4.7.1. Possible Childhood Susceptibility . . . . . .
4.7.2. Possible Gender Differences . . . . . .

5. DOSE-RESPONSE ASSESSMENTS . . . . . .
5.1. ORAL REFERENCE DOSE (RfD) . . . . . .
5.2. INHALATION REFERENCE CONCENTRATION (RfC) . . . . . .
5.3 CANCER ASSESSMENT . . . . . .
5.3.1 Choice of Study/Data with Rationale and Justification . . . . . .
5.3.2 Dose-response Data . . . . . .
5.3.3 Dose Adjustments . . . . . .
5.3.5 Oral Slope Factor . . . . . .

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE . . . . . .
6.1 HUMAN HAZARD POTENTIAL . . . . . .
6.2 DOSE RESPONSE . . . . . .

7. REFERENCES . . . . . .

Appendix A
Oral Cancer Risk Estimate . . . . . .

Appendix B
External Peer Review—Summary of Comments and Disposition . . . . . .

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard identification and dose-response assessment in IRIS pertaining to chronic exposure to quinoline. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of quinoline.

In Section 6, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose-response. Matters considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's Risk Information Hotline at 513-569-7254.

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Summaries of the external peer reviewers' comments and the disposition of their recommendations are in Appendix A.

1. INTRODUCTION

This document presents background and justification for the hazard and dose-response assessment summaries in EPA's Integrated Risk Information System (IRIS). IRIS Summaries may include an oral reference dose (RfD), inhalation reference concentration (RfC), and a carcinogenicity assessment.

The RfD and RfC provide quantitative information for noncancer dose-response assessments. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as some carcinogenic responses. 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. The inhalation RfC is analogous to the oral RfD. The inhalation RfC considers toxic effects for both respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). It is generally expressed in units of mg/m^3.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral exposure and inhalation exposure. The information includes a weight-of-evidence judgement of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates are presented in three ways. The *slope factor* is the result of the 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. Another form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000; 1 in 100,000; or 1 in 1,000,000.

Development of these hazard identifications and dose-response assessments for quinoline

followed the general guidelines for risk assessment set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: the *Guidelines for Carcinogen Risk Assessment (*U.S. EPA, 1986a); *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c); *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1988); *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991a); *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b); *Peer Review and Peer Involvement at the U.S. Environmental Protection Agency* (U.S. EPA, 1994c); *Proposed Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1995a), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995b); *Proposed Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1996a); *Science Policy Council Handbook*: *Peer Review* (U.S. EPA, 1998b); and the memorandum from EPA Administrator Carol Browner, dated March 21, 1995, Subject: Guidance on Risk Characterization.

Literature search strategies employed for this compound were based on the CAS registry number (RN) and at least one common name. At a minimum, the following databases were searched: HSDB, TSCATS, CCRIS, GENETOX, EMIC, EMICBACK, DART, ETICBACK, TOXLINE, CANCERLINE, MEDLINE, and MEDLINE backfiles. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document.

2. CHEMICAL AND PHYSICAL INFORMATION RELEVANT TO ASSESSMENTS

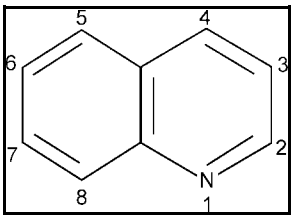


FIGURE 1.

Chemical Structure of Quinoline

Quinoline (Figure 1) is a hygroscopic liquid that is colorless, has a pungent odor, and darkens with age. It is soluble in alcohol, ether, benzene, and carbon disulfide, and is sparingly soluble in water. Quinoline is a weak tertiary base. It forms salts in acids and exhibits reactions similar to benzene and pyridine, and can engage in both electrophilic and nucleophilic substitution (HSDB 1999). Physical properties are listed in Table 1.

Sources of quinoline include petroleum, coal processing, production and use facilities, and shale oil (HSDB 1999). It is used as an intermediate in the production of various compounds including 8-hydroxyquinoline, hydroxyquinoline sulfate, and copper-8-hydroxyquinolate. Quinoline is also a solvent for resins and terpenes, and is used in the production of paints.

When released to soil, quinoline is likely to leach quickly into groundwater (HSDB 1999). Experiments to determine K_{oc} (79–205) predicted that less than 0.5% of quinoline released would sorb to sediments and particulates, and it is likely to partition into water (log K_{ow} = 2.03). There was no relation between adsorption and soil carbon content. Quinoline is not likely to volatilize from soil due to a low Henry's Law Constant (2.49×10^{-7} atm-m^{3}mol^{-2}). Biodegradation is likely

to take place, but hydrolysis, oxidation, and volatilization should not be significant.

When released to aquatic systems, quinoline will biodegrade (HSDB 1999). The rate depends upon temperature and microbial conditions with complete degradation occurring within 5 days. Quinoline is likely to be photolyzed at rates which depends on pH, depth of water, season, and presence of humic acids. Photolytic half-lives range from 21 days during the summer to 160 days during the winter. A low henry's law constant predicts little volatilization. Based on a bioconcentration Factor (BCF) of 21 and a K_{oc} of 79–205, sorption to suspended sediments and bioaccumulation are likely to be responsible for a moderate-to-low level of removal from aquatic systems.

Quinoline released to the atmosphere is likely to react with hydroxyl radicals with an estimated reaction half-life of 2.51 days (HSDB 1999). Due to strong absorption of light wavelengths >290 nm, quinoline has the potential for direct photolysis in the atmosphere. Removal from the atmosphere can occur via wet and dry deposition.

TABLE 1.

Chemical and Physical Properties of Quinoline

Property	Information	Reference
Molecular weight	129.16	HSDB 1999
Molecular Formula	C_9H_7N	
Density at 25°C	1.0900	
Melting point	-15°C	
Boiling point (760 mmHg)	237.63°C	
Density at 30°C	1.08579 g/cm^3	
Vapor pressure at 25°C	9.10 x 10^{-3} mm Hg	
Henry's law constant	2.49 x 10^{-7} atm-m^{3}mol^{-2}	
Water solubility at 25°C	6,110 mg/L	
pK_a	9.5	
K_{oc}	79–205	
Bioconcentration factor	21	
Log K_{ow}	2.03	

3. TOXICOKINETICS RELEVANT TO ASSESSMENTS

3.1. ABSORPTION

Limited animal excretion data demonstrate that quinoline is absorbed from the gastrointestinal tract. Rabbits were orally administered 250 mg/kg bodyweight (bw) quinoline, and a 24-hour urine sample was collected (Smith and Williams 1955). Based on an estimation of free and total quinoline excreted in urine, approximately 6.7–11.0% of the quinoline was excreted as a labile compound that yielded quinoline on heating with acid.

3.2. METABOLISM

Novak and Brodie (1950) provided evidence that quinoline is almost completely metabolized in the dog. In this study, a dog was given an intravenous (i.v.) injection of quinoline (25 mg/kg) and plasma concentrations of quinoline were determined during a 4-hour period. The plasma concentrations of quinoline at 0.25, 0.75, 2, and 4 hours were 16.9, 5.1, 2.6 and 0.7 mg/L, respectively. The authors believe these results indicate that quinoline is rapidly metabolized. Novak and Brodie (1950) also examined the urinary excretion of quinoline and its metabolites. Dogs were administered either 20 or 25 mg/kg quinoline and urine was collected for 24 hours following treatment. Less than 0.5% of the administered quinoline was excreted unchanged, indicating to the authors that quinoline was almost completely metabolized in the body. The metabolite 3-hydroxyquinoline was recovered from the urine. An average of 4% was in the free hydroxyquinoline form while the remainder was as a conjugated form (possibly the glucuronate or sulfate or both). When the fate of 3-hydroxyquinoline was studied (0.6 mg/kg i.v. to 2 dogs), 34 and 35% of the administered dose were recovered in the urine in a conjugated form. Free 3-hydroxyquinoline was found in only negligible amounts. The authors concluded that the main route of metabolism appears to be an initial oxidation of quinoline to 3-

hydroxyquinoline, found primarily in urine in a conjugated form.

In a metabolism study of quinoline in rabbits, Smith and Williams (1955) examined the urine of rabbits for glucuronide and sulfate conjugates. Sixteen rabbits received a total of 8 g of quinoline orally, and the urine was collected for 24 hours. Glucuronide and sulfate conjugate fractions were separated. The sulfate conjugate fraction contained 6-hydroxyquinolyl-5-sulfuric acid, from which 5,6-dihydroxyquinoline was isolated. About 3–4% of quinoline was excreted as 5,6-dihydroxyquinoline. 3-Hydroxyquinoline and 2,6-hydroxyquinoline were isolated from the glucuronide conjugate fractions.

Cowan et al. (1978) investigated the N-oxidation of quinoline by hepatic microsomal preparations from various species including rabbit, hamster, guinea pig, rat, and mouse. Pulmonary microsomal metabolism was examined only in the guinea pig and rabbit. Quinoline-N-oxide was detected in liver microsomal preparations obtained from all species. Lung microsomes metabolized quinoline to quinoline-N-oxide in rabbits but not guinea pigs.

The cytochrome P450-dependent metabolism of quinoline has been studied. Utilizing *in vitro* liver microsomal preparations, Reigh et al. (1996) determined the cytochrome P450 enzyme species that mediates quinoline metabolite formation in both humans and rats. Some differences in the microsomal metabolism of quinoline were observed between humans and rats. Quinoline-1-oxide, a metabolite of quinoline, was clearly detected in human microsomal preparations, but was barely detectable in rat microsomes. The study authors depicted quinoline-1-oxide to be structurally the same as quinoline-N-oxide. Therefore, the results of this study do not support the findings of Cowan et al. (1978), which were discussed above. CYT2A6 was shown to be the primary cytochrome P450 species involved in the formation of quinoline-1-oxide in human liver microsomes. The results revealed that CYP2A6 was also involved in the formation of quinoline-5,6-epoxide but not quinoline-5,6-diol. A cDNA-expressed human microsomal epoxide hydrolase was shown to efficiently convert the epoxide to the diol. Epoxide hydrolase activity

was also demonstrated in rat liver microsomes. CYP2E1 was determined to be the principal cytochrome P450 involved in the formation of 3-hydroxyquinoline, another metabolite of quinoline, in human and rat microsomes. Rat microsomal CYP2E1 was also involved in the formation of quinoline-5,6-epoxide in this species.

Reigh et al. (1996) also conducted a preliminary kinetic analysis of quinoline metabolism in human liver microsomes. Formation of quinoline-5,6-diol was found to be monophasic, while formation of quinoline-1-oxide and 3-hydroxyquinoline was biphasic.

3.3. DISTRIBUTION

Information on the distribution of quinoline was not located in the available data.

3.4. EXCRETION

In rabbits and dogs, quinoline and its metabolites are excreted in the urine. Urinary excretion of quinoline and its metabolites was nearly complete 24 hours after oral dosing of dogs with 20 or 25 mg/kg (Novack and Brodie 1950). Less than 0.5% of the administered quinoline was excreted unchanged. Approximately 29–32% of the administered quinoline was recovered from the urine as 3-hydroxyquinoline (free and conjugated forms). Approximately 0.4–0.8% of free quinoline was detected in rabbit urine collected 24 hours after an administration of an oral dose of 250 mg/kg. Approximately 6.7–11.0 % of the quinoline was determined to be excreted as a labile compound that yields quinoline on heating with acid. About 3–4% of quinoline was excreted as the metabolite 5,6-dihydroxyquinoline.

4. HAZARD IDENTIFICATION

4.1 STUDIES IN HUMANS

No subchronic or chronic studies of humans exposed to quinoline have been identified.

4.2 PRECHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

No chronic studies and no inhalation studies of animals exposed to quinoline have been identified. The studies described below were designed to study the carcinogenic effects of quinoline following subchronic oral 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.

4.3 REPRODUCTIVE/DEVELOPMENTAL STUDIES IN ANIMALS—ORAL AND INHALATION

No animal reproductive/developmental studies of oral or inhalation exposure to quinoline have been identified.

4.4 OTHER STUDIES

4.4.1. Neurotoxicity

The potential dopaminergic neurotoxicity of quinoline was evaluated in rats utilizing an intrastriatal microdialysis method that measures dopamine release from neurons (Booth et al. 1989). The interest of the study was to assess the possibility that nitrogen heterocyclic compounds present in the environment or produced *in vivo* contribute to the neuronal degenerative processes involved in idiopathic Parkinson's disease. This interest arose from the observation that cyclic tertiary amine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can produce neurochemical and neuropathological changes that are similar to idiopathic Parkinson's disease. The results of the study showed that quinoline is not a dopaminergic neurotoxin.

4.4.2. Genotoxicity

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).

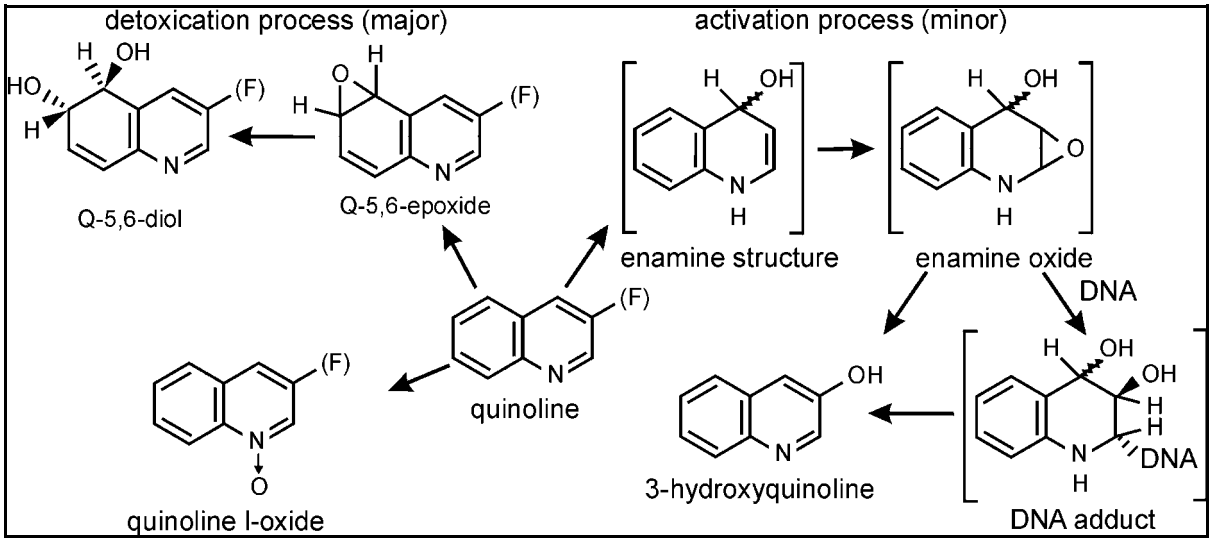
The fact that quinoline mutagenicity requires S-9 activation indicates that it must be metabolized to its active moeity by liver enzymes, presumably cytochrome P450 (or P448)

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 of quinoline shown in Figure 2.

FIGURE 2.

Postulated Metabolic Pathway for Detoxicifcation and Activation of Quinoline

Adapted from: Saeki et al., 1993



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. The authors speculated that the hepatocarcinogenicity of quinoline to the rat and mouse could be related to a nongenotoxic (mitogenic) mechanism of action. They also suggested that the mitogenicity of quinoline correlates better with its hepatocarcinogenicity than does its genotoxicity *in vivo.*

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.

4.5 SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS

No human studies pertaining to subchronic or chronic toxicity or carcinogenicity of quinoline were identified. Limited information regarding the oral toxicity of quinoline in animals following subchronic exposures was available from carcinogenicity bioassays. The Hirao et al. (1976) study included a control and three dose groups of Sprague-Dawley rats fed quinoline in their diets for up to 40 weeks. 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 4-20 weeks in the Hasegawa et.al. (1989) study to 30 weeks in the Shinohara et al. (1977) study.

In addition to carcinogenic effects, these 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.

4.6 WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION

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. 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) 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 data from human epidemiological 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 1996a).

4.6.1. Human

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.

4.6.2. Animal

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, which primarily impact the dose-response assessment for quinoline (Section 5.3), were addressed in section 4.2 and 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.

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.

Quinoline is a mutagen in *Salmonella typhimurium* in the presence of metabolic activation

(EPA, 1985; LaVoie et al. 1991). Quinoline has also been shown to induce chromosome aberrations and sister chromatid exchanges in the rat liver and micronucleus formation in the bone marrow of CD1 male mice (Asakura et al. 1997; Hamund et al. 1989). Although a predominance of data suggest that quinoline is genotoxic, the results of at least one study indicate that a nongenotoxic (i.e., mitogenic) mechanism of action may play a role in its hepatocarcinogenicity (Lefevre and Ashby 1992).

4.6.3. Mode of Action

As was discussed in section 4.4.2, the genotoxicity of quinoline is supported by a large database of mutagenicity assays, particularly from *in vitro* studies. To express mutagenicity, quinoline must be converted by CYP450 enzymes to an active metabolite, thought to be an epoxide of its pyridine moeity (Takahashi et al., 1988; Saeki et al., 1993). Recent *in vivo* work has shown quinoline to cause chromosome aberrations and sister chromatid exchanges in the liver cells of rats following oral (gavage) doses (Asakura eta l., 1997). However, others have observed a correlation between *in vivo* mitogenic (nongenotoxic) activity of quinoline and its hepatocarcinogenicity (Ashby et al. 1989; Lefevre and Ashby 1992). Quinoline has been demonstrated to induce a mitogenic response in the livers of rats and mice, but not guinea pigs. Hepatocarcinogenicity has been observed in the rat and the mouse, but not the hamster or guinea pig. It is possible that the hepatocarcinogenicity of quinoline is promoted to some extent by a nongenotoxic mechanism that impacts the mitotic activity of rat and mouse liver cells, but more work needs to be done in this area before anything definitive can be concluded.

4.7 SUSCEPTIBLE POPULATIONS

4.7.1. Possible Childhood Susceptibility

There are no human studies suggesting that children are more susceptible to the toxic

effects of quinoline. Limited animal bioassays that examined the potential tumorigenicity of quinoline (administered by the intraperitoneal route of exposure) in newborn CD-1 mice and Sprague-Dawley rats revealed liver tumors (carcinomas, adenomas and basophilic altered foci) in 60% of male newborn mice but not newborn male or female rats (LaVoie et al. 1987; LaVoie et al. 1988; Weyland et al. 1993). Five percent of newborn female mice exhibited only basophilic altered foci in the liver. There are no studies that have examined the potential hepatocarcinogenicity of quinoline in newborn mice or rats exposed by the oral or inhalation route (more relevant than the intraperitoneal route to human exposures). The significance of the findings in newborn male mice to humans is not known.

4.7.2. Possible Gender Differences

There are no human data which suggest that gender differences in toxicity or tumorigenicity might occur as a result of exposure to quinoline. Male newborn mice (exposed by intraperitoneal or subcutaneous routes) and male adult rats (administered quinoline by oral route) may be more sensitive to quinoline-induced hepatocarcinogenicity than are the females of these species(LaVoie et al. 1988; Shinohara et al. 1977;Weyland et al. 1993). There are no data to indicate that sex-related differences are due to gender differences in either microsomal metabolism or toxicokinetics of quinoline. The relevancy of the animal data to human health is not known. Quinoline initiated skin tumors in female SENCAR mice following dermal application (LaVoie et al. 1984); however, male mice were not examined. The significance of the studies in newborn rodents and the tumor-initiating properties of quinoline in the skin of female mice to humans is not clear.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

Chronic oral toxicity data on quinoline were limited to the results of several studies designed to assess the carcinogenic potential of this compound. All of the studies had limitations. 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 due to 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 were examined, a lack of statistical analyses, 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 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 (e.g., 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, and 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 data were reported in a manner that would allow for a meaningful quantitative dose-response assessment. In accordance with minimum data base requirements outlined in EPA methods (EPA, 1994), an RfD was not derived.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

No human or animal 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.

5.3 CANCER ASSESSMENT

There are no human studies addressing the potential carcinogenicity of quinoline. Despite the limitations of available animal carcinogenicity studies, these studies provide 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). This cancer assessment as well as a recent reassessment of the Hirao et al. (1976) study by EPA are discussed below. No human or animal toxicity data were available for consideration of an inhalation cancer assessment.

5.3.1 Choice of Study/Data with Rationale and Justification

EPA (1985) chose the Hirao et al. (1976) because this study 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, EPA (1985) assumed that a significant percentage of the hemangioendotheliomas were malignant. There was a dose-dependent increase in the incidence of hemangioendotheliomas that was associated with increased mortalities and body weight loss.

5.3.2 Dose-response Data

Dose-response data from the Hirao et al. (1976) study are summarized below in Table 2.

Table 2
Incidence of hepatic hemangioendotheliomas or hemangiosarcomas in male Sprague-Dawley rats treated with quinoline for 40 weeks.

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).

5.3.3 Dose Adjustments

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 as described below and in Appendix A, 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 the procedure 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.

5.3.4 Extrapolation Method(s)

EPA (1985) used the linearized multistage model developed by Kenneth Crump to calculate a cancer slope factor (q_1*) for humans. A correction of time-to-tumor development was made prior to computation of the q_1* derived from the animal studies. Animal doses were adjusted to human doses using 2/3 power scaling.

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). Details of the reassessment are presented in Appendix A.

5.3.5 Oral Slope Factor

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* 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 (1996a) proposed guidelines (see Appendix A). 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 (see section 4.4.2.).

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1 HUMAN HAZARD POTENTIAL

Quinoline can be derived from petroleum, coal processing, production and use facilities, and shale oil. It is used as an intermediate in the production of various compounds and paints, and as a solvent for resins and terpenes. Quinoline may enter the environment through atmospheric emissions and waste waters of petroleum, shale oil, coal processing, and wood preservation, production, and use facilities (HSDB 1999). Quinoline has been detected in suspended particulate matter in urban atmospheres (EPA 1985). Underground coal gasification at experimental sites has been a source of quinoline contamination of groundwater (HSDB 1999). Quinoline is also a component of tobacco smoke (HSDB 1999). Therefore, there is potential exposure of the general population to quinoline in the environment. Occupational exposure to higher levels of quinoline may be expected among workers involved in its production and use.

Acute exposures to quinoline vapors can result in irritation to eyes, nose, and throat , and may cause headaches, dizziness, and nausea in humans (EPA 1985). No human epidemiological studies or case reports addressing the potential chronic toxicity or carcinogenicity of quinoline were identified, though enzymes that mediate the metabolic activity of quinoline have been identified in both rats and humans (Reigh et al., 1996). Limited oral carcinogenicity bioassays in various laboratory animals have demonstrated that quinoline exposure can lead to tumor formation relatively quickly (within 12 weeks) in rats and mice. One of the tumors observed, hepatocarcinogenesis (hepatic vascular tumors), is rare in these species and similar to the tumors resulting from exposure to vinyl chloride, a known human carcinogen. Further, *in vitro* and *in vivo* studies have shown quinoline to be both genotoxic and mitogenic. U.S. EPA (1985) classified quinoline as Group C carcinogen (i.e., possible human carcinogen) and concluded that the “data sets (rats and mice) were cogent enough to warrant a cancer potency determination

under the assumption that quinoline is a human carcinogen." In addition, because quinoline has been shown to increase the incidence of rarely observed vascular tumors of the liver in both sexes of two rodent species, it is considered "likely to be carcinogenic in humans" in accordance with the proposed EPA carcinogen risk assessment guidelines (U.S. EPA 1996a).

6.2 DOSE RESPONSE

No noncancer dose-response assessment was performed for either oral or inhalation exposure to quinoline because the database lacked suitable human or animal data. The present cancer risk assessment estimates human cancer risk from an oral carcinogenicity bioassay in male rats (Hirao et al. (1976). An oral slope factor of 4.5 $(mg/kg/day)^{-1}$ for humans was calculated from the animal data.

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Appendix A
Oral Cancer Risk Estimate

1. Data

The incidence of hepatic hemangioendotheliomas or hemangiosarcomas in male rats from the Hirao et al. (1976) study was modeled. The incidence of this tumor is summarized in Section 5.3 and in Table A-1 below.

Table A-1
Incidence of hepatic hemangioendotheliomas or hemangiosarcomas in male Sprague-Dawley rats treated with quinoline for 40 weeks.

Dose Level*	Mean Length of Experiment (weeks)	Incidence
		No. Responding/ No. Examined
0	40	2/83**
0.05% (25 mg/kg/day)	36.5	6/11
0.10% (50 mg/kg/day)	27.3	12/16
0.25% (125 mg/kg/day)	20	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). The historical controls were used for dose-response modeling because there were only 6 animals in the concurrent control group, and these were only allowed to live for 40 weeks (0/6 responding).

2. Computational Models

As indicated in Section 5.3.3 of the toxicological review for quinoline, a time-to-tumor model is employed because it should more accurately compensate for survival time differences between dose groups than the procedure used previously by EPA (1985). The general model used for the time-to-tumor analyses was the multistage Weibull model, which has the form:

$$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k)*(t - t_0)^z]$$

where P(d,t) represents the probability of a tumor (or other response) by age t (in bioassay weeks) for dose d, and parameters $z \geq 1$, $t_0 \geq 0$, and $q_i \geq 0$ for i=0, 1, ..., k, where k = the number of dose groups - 1. The parameter t_0 represents the time between when a potentially fatal tumor becomes observable and when it causes death. In these analyses, all tumors were assumed to be incidental, partly because individual animal data were not available and the study authors did not make a clear distinction between benign and malignant tumors, but also because an assessment of the risk of developing the tumor, rather than the risk of dying from the tumor, was desired.

The analyses were conducted using the computer software TOX_RISK version 3.5 (Crump et al., ICF Kaiser International, Ruston, LA), which is based on Weibull models taken from Krewski et al. (1983). Parameters are estimated using the method of maximum likelihood.

3. Model Fit

The 1-stage Weibull model was selected based on the values of the log likelihoods according to the strategy used by NIOSH (1991). If twice the difference in log likelihoods was less than a chi-square with degrees of freedom equal to the difference in the number of stages included in the models being compared, then the models were considered comparable and the

most parsimonious model (i.e., the lowest-stage model) was selected.

4. Results (1-stage Weibull model)

Parameter estimates: Q_0 = 2.335E-4; Q_1 = 1.026E-3

Unit Potency is computed for risk (extra risk) of 1.0E-6: MLE = 1.962E+0; Upper Bound (q1*) = 4.509E+0 per mg/kg/day.

LED_{10} (μg/kg/day) = 2.337E+1. Using the linear extrapolation method of the 1996 proposed cancer guidelines (i.e. 0.1/LED_{10}) yields a potency of 4.3 per mg/kg/day.

Appendix B

External Peer Review—Summary of Comments and Disposition