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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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U.S. Environmental Protection Agency
Washington, DC

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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 IRIS Hotline at 301-345-2870.

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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, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry effects) and systems 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 judgment 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 identification and dose-response assessments for quinoline has followed the general guidelines for risk assessment as set forth by the National Research Council (NAS, 1983). EPA guidance documents that were used in the development of this assessment include the following: the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a); *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986b); *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c); *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991); *Proposed Guidelines for Carcinogen Risk Assessment* (1996a); *Reproductive Toxicity Risk Assessment Guidelines* (U.S. EPA, 1996b); *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a); *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988); (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a); *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); *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995a); *Science Policy Council Handbook: Peer Review*

(U.S. EPA, 1998b, 2000a); Memorandum from EPA Administrator, Carol Browner, dated March 21, 1995, Policy for Risk Characterization (U.S. EPA, 1995b); *Science Policy Council Handbook: Risk Characterization* (U.S. EPA, 2000b).

Literature search strategies employed for this compound were based on the CASRN and at least one common name. At a minimum, the following databases were searched: RTECS, 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

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.

The following is a brief summary of what is known regarding the environmental fate and transport of quinoline. A more in-depth discussion of this and other exposure issues can be found in the EPA Health and Environmental Effects Profile for Quinoline (U.S. EPA, 1985).

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 also likely to be photolyzed at rates that depend 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. Given 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.

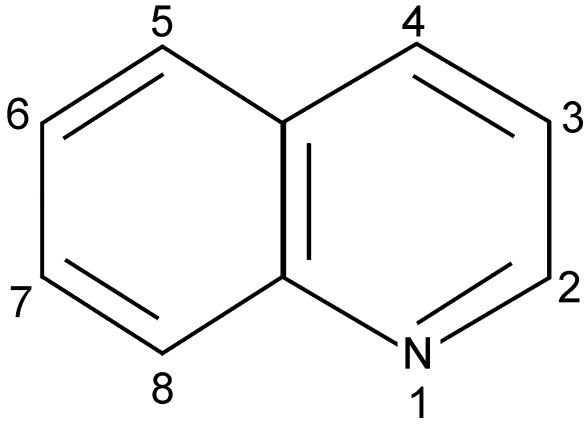

Figure 1. Chemical structure of quinoline.

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	

Sources of quinoline include petroleum, coal processing, wood preservation, 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 quinoline is likely to partition into water, given its moderate water solubility and low log K_{ow} of 2.03. Once quinoline partitions to water, it is not likely to volatilize to air because of its low Henry's Law constant (2.49×10^{-7} atm-m^{3}mol^{-2}). There was no relation between adsorption and soil carbon content. Biodegradation is likely to take place but, on the basis of information available for quinoline in water, hydrolysis, oxidation, and volatilization should not be significant.

Quinoline released to the atmosphere is likely to react with hydroxyl radicals, with an estimated reaction half-life of 2.51 days (HSDB, 1999). Because of its 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.

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

Novack 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. These results suggest that quinoline is rapidly metabolized. Novack and Brodie (1950) also examined the urinary excretion of quinoline and its metabolites. Dogs were administered either 20 or 25 mg/kg quinoline by i.v. and urine was collected for 24 hours following treatment. Less than 0.5% of the administered quinoline was excreted unchanged, indicating that quinoline was almost completely metabolized in the body. The amount of the metabolite 3-hydroxyquinoline recovered from the urine accounted for approximately 30% of the administered dose. An average of 4% of the recovered 3-hydroxyquinoline metabolite was in the free hydroxyquinoline form; the remainder was as a conjugated form (possibly the glucuronate or sulfate or both). When 3-hydroxyquinoline was administered (0.6 mg/kg i.v. to two dogs), 34% and 35% of the administered dose was recovered in the urine in a conjugated form. Free 3-hydroxyquinoline was found only in negligible amounts. The fact that administration of both quinoline and 3-hydroxyquinoline resulted in recovery of the same fraction of administered dose of the latter in urine suggests that quinoline was almost completely metabolized to 3-hydroxyquinoline in an initial oxidation step. The data also suggests that roughly one-third of this initial 3-hydroxyquinoline is then conjugated and excreted in the urine, with the remainder being metabolized further to other derivatives of quinoline not accounted for in this study.

In a metabolism study of quinoline in rabbits, Smith and Williams (1955) examined the urine of rabbits for glucuronide and sulfate conjugates. Each of 16 rabbits received 250 mg/kg of quinoline orally, and their 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 (Q-5,6-diol) was isolated. About 3%–4% of quinoline was excreted as Q-5,6-diol. 3-Hydroxyquinoline and 2,6-hydroxyquinoline were also 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.

Tada et al. (1980) found that 3-hydroxyquinoline (Figure 2) was released from isolated quinoline-bound adducts, suggesting that quinoline had been metabolically activated in its pyridine moiety. Saeki et al. (1993) provided further confirmation of this by showing that fluorine (F) substitution at position 3 deprives quinoline of its mutagenicity and, when mixed with microsomal enzymes, results in the formation of benzene epoxides of a similar metabolic pattern as that obtained from unfluorinated quinoline. This latter finding suggests that epoxidation of the benzene moieties of quinoline is most likely a detoxification process. Saeki et al. (1993) proposed the detoxification and activation pathways for quinoline illustrated in Figure 2.

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 (quinoline-N-oxide) was clearly detected in human microsomal preparations, but was

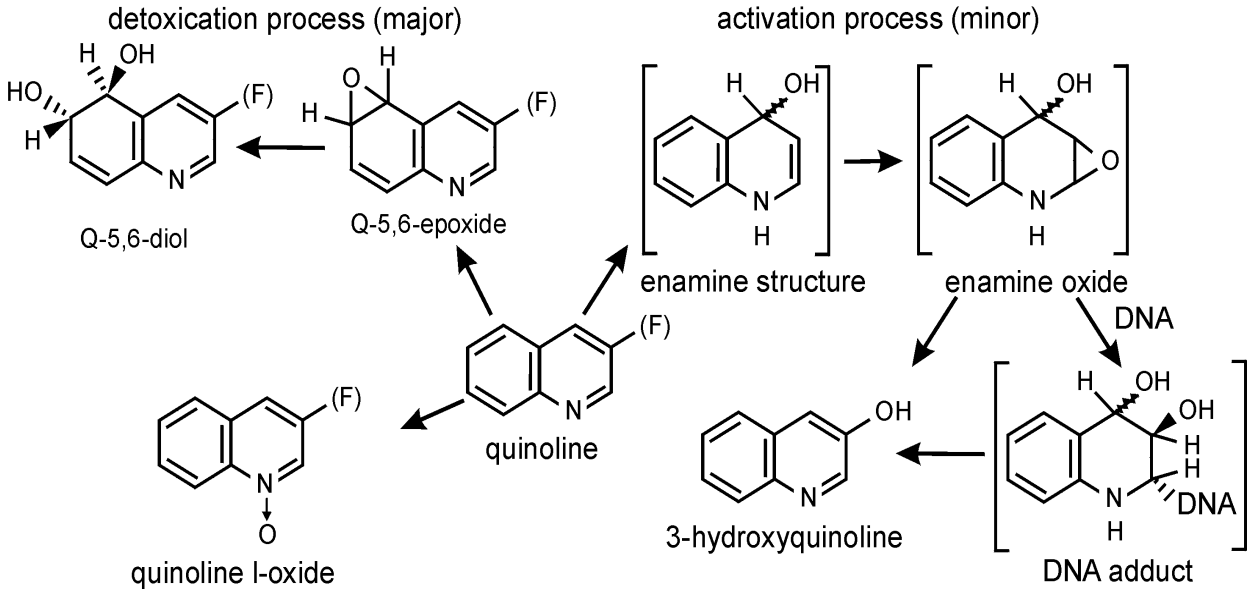

Figure 2. Postulated metabolic pathway for detoxification and activation of quinoline (Saeki et al., 1993).

barely detectable in rat microsomes. This latter finding is not in agreement with Cowan et al. (1978), discussed above, who reported detecting quinoline-N-oxide following incubation of quinoline with liver microsomes of rats and other species. This difference could be due to the use of liver microsomes from two different rat strains. Cowan et al. (1978) used male Wistar rats and Reigh et al. (1996) used male Sprague-Dawley rats. Although the difference noted between these two studies could suggest a strain-specific metabolic path, it could also be due to experimental error on the part of one or the other study groups. CYP2A6 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. 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 i.v. 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 administration of an oral dose of 250 mg/kg (Smith and Williams, 1955). 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 investigate the carcinogenic effects of quinoline following oral exposure, but none exposed animals for more than 40 weeks, because of early onset of tumors and early mortality.

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 megalocytosis 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 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 (3-FQ), or 5-fluoroquinone (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, 200 mg/kg i.p. injection of the liver carcinogen diethylnitrosamine (DEN). 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. 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 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.

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. Other In Vivo Studies

LaVoie et al. (1984) tested quinoline and other compounds for tumor-initiation potential on the skin of Hfd: SENCAR BR female mice with promotion by tetradecanoyl phorbol acetate (TPA) (LaVoie et al., 1984). Each compound was applied at 0.75% concentration in acetone to the shaved backs of 50-55 day old mice. The quinoline exposed, positive control (benzo[a]pyrene) and negative control (acetone) groups each consisted of 40 mice. Ten initiating subdoses of quinoline were applied every other day until a full initiation dose of 7.5 mg/mouse was reached. A lower initiating dose of 0.03 mg/mouse was used for benzo[a]pyrene. Ten days after the last application of the initiator, promotion was begun by applying 2.0 μg of TPA in 0.1 mL acetone twice weekly for 18 weeks. Quinoline induced skin tumors in 53% of the mice, relative to 7.5% in the negative control and 63% in the positive controls.

Liver tumors (adenomas and hepatomas) were observed in newborn CD-1 mice exposed to quinoline via i.p. injection (LaVoie et al., 1987, 1988; Weyland et al., 1993). Virtually the same experimental design was used for all three of these i.p. studies. In each case quinoline exposure was compared to a negative control (exposure to DMSO only) and exposure to other (usually structurally related) compounds. Pups in the exposure groups (37-101 pups/group) received 5, 10 and 20 μL of a 0.05-M solution of quinoline or related compound in DMSO on days 1, 8, and 15 of life, respectively, resulting in a total dose of 1.75 μmol/mouse. Pups in the control groups (35-97 pups/group) received 5, 10, and 20 μL of DMSO only on days 1, 8, and 15

of life, respectively. In all cases, pups were sacrificed and examined histologically at 52 weeks of age, except in one case where five animals exposed to quinoline were sacrificed and examined at 35 weeks of age (LaVoie et al., 1987). No lesions were reported in any of the tissues examined (macroscopically and microscopically) from the quinoline-exposed animals sacrificed at 35 weeks of age, nor in any hepatic tissues from quinoline-exposed female mice at 52 weeks of age, though a slight increase in lymphomas was observed in female mice at 52 weeks (LaVoie et al., 1987, 1988). Each study, however, reported significant liver tumor (adenoma and hepatoma) incidences, 71%, 61%, and 79% relative to controls, 5.9%, 0%, and 19%, respectively, in male mice exposed to quinoline and sacrificed at 52 weeks (included in these percentages are mice that died no less than 6 months after treatment).

Quinoline was also administered subcutaneous to the suprascapular area of newborn Sprague-Dawley rats (LaVoie et al., 1988), which received injections of 200 μmol/kg body weight in DMSO on the first day of life, 100 μmol/kg weekly at weeks 2-7, and 200 μmol/kg at week 8. Surviving rats were sacrificed at 78 weeks of age. No significant difference in tumor incidence was observed between rat pups that had been treated with quinoline and controls.

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* (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 moiety 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 of quinoline shown in Figure 2, Section 3.

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 in the metabolism of quinoline between rats and humans 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 the 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. 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 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.

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 to 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 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 demonstrate that the liver is 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. (1989) point out that increases 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, including oval cell infiltration, proliferation of bile ducts, and fatty degeneration of parenchymal cells (Hirao et al., 1976; Shinohara et al., 1977), to tumor formation are not as clear. However, none of these effects can be associated with a subsequent, adverse noncancer endpoint, and all occurred at doses that also caused tumor formation, an endpoint that is probably a confounding factor for the liver weight and possibly other effects.

Effects from oral exposure either could not be disassociated with carcinogenic effects or were not reported in a manner that would allow for a meaningful quantitative dose-response assessment. No human or animal inhalation toxicity data were available for consideration of an RfC. For these reasons, and in accordance with minimum database requirements outlined in EPA methods (U.S. EPA, 1994b), 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. 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), 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 hepatocarcinogenicity 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, 1996a) on the basis of observations of exposure-related increased incidence of an unusual malignant tumor in multiple strains of rats and mice, in multiple experiments using oral, dermal, i.p., and s.c. dosing, and 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, 1986a). 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.[1]

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 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. No tumors, but basophilic altered foci, were observed in female newborn mice.

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[1]In accordance with EPA cancer guidelines (U.S. EPA, 1986a), "agents for which there is 'sufficient' evidence from animal studies and for which there is 'inadequate evidence' or 'no data' from epidemiologic studies would usually be categorized under Group B2."

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 (U.S. 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; Hamoud 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 et al., 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 that inform with respect to the susceptibility of children to the toxic effects of quinoline. There are studies in CD-1 mice that indicate that acute i.p. (LaVoie et al., 1987, 1988; Weyland et al., 1993) exposures to quinoline at an early age (1, 8, and 15 days after birth) may result in a tumorigenic response later in life. Quinoline administered by the i.p. route of exposure to newborn CD-1 mice (total dose of 1.75 μmol/mouse) and by *sc* exposure to Sprague-Dawley rats (approximately 200 μmol/kg body weight) caused liver tumors (carcinomas, adenomas and basophilic altered foci) in 60%-80% of male newborn mice after 35 weeks but not in male mice examined prior to 35 weeks, nor in female mice and newborn male and female rats that survived at least 35 weeks (LaVoie et al., 1987, 1988; Weyland et al., 1993). Because there are no studies that have examined the impact of i.p. injections of quinoline at a later age, it is not possible to determine whether these studies are indications of a susceptibility that is unique to childhood. However, a fact worth noting is that although these studies seem to

indicate that newborn male mice are particularly sensitive relative to newborn females and rats to quinoline exposure, older male mice exposed to quinoline in their diet at a later age (weeks 9 to 39) show no such relative sensitivity (Shinohara et al., 1977). There are no studies that have examined the potential hepatocarcinogenicity of quinoline in newborn mice or rats exposed by the oral or inhalation route (routes that would be more relevant than the intraperitoneal route to human exposures). Although these studies of newborn mice and rats may suggest a need for further study into the childhood susceptibility of quinoline, their significance with respect to humans cannot be determined at this time.

4.7.2. Possible Gender Differences

There are no human studies that inform with respect to possible gender difference in toxic effects from quinoline exposure. Male newborn mice (exposed by intraperitoneal or subcutaneous routes) and male adult rats (administered quinoline by the oral route) are considerably 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). The reason for this apparent gender difference is not known, and there are no data at this time to indicate that sex-related differences are due to gender differences in either microsomal metabolism or toxicokinetics of quinoline in rodents. Quinoline initiated skin tumors in female SENCAR mice following dermal application (LaVoie et al., 1984); however, male mice were not examined. The relevance of these animal data to the potential for gender differences in human response to quinoline exposure is not known.

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, 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 owing 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, respectively. This study's limitations include small sample size, only males were 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 bet 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 (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. Noncancer oral exposure data 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, 1994b), 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 database requirements outlined in EPA methods (U.S. EPA, 1994b), 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 have 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 authors of this assessment determined that, despite the recognized limitations of the critical study (e.g., small sample size, the fact that only males were examined, the limited toxicity parameters examined, early deaths, and the lack of statistical analyses), "data sets (rats and mice) were cogent enough to warrant a cancer potency determination under the assumption that quinoline is a human carcinogen." Considering the apparent high potency of this compound, EPA continues to maintain the need for a potency determination for quinoline. However, some changes to the quantitative assessment approach are recommended. The previous cancer assessment and 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) study because this study provided dose-response data for the induction of hepatic 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[a]	Incidence
	No. responding/No. tested or examined
0	0/6 [2/83][b]
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

[a]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.
[b]Historical controls as reported by Anver et al. (1982).

5.3.3. Dose Adjustments

In the previous assessment, 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 addition, animal doses were adjusted to human doses using 2/3 power scaling.

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 B, 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 short experiment duration than the earlier procedure used by EPA (1985). Animal doses were adjusted to human doses using 3/4 power scaling. In accordance with Agency policy (U.S. EPA, 1996a), a worst-case human exposure scenario of daily exposure, beginning at age 0 and ending at age 70, was assumed for both assessments.

5.3.4. Dose-Response Modeling and Extrapolation Methods

EPA (1985) used a linearized multistage model in existence at that time (Federal Register, 1980) to calculate a cancer slope factor (q_1*) for humans, which represents an upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime

exposure. As discussed above, a correction for the short experiment length was made prior to computation of the q_1* derived from the animal studies.

The present risk estimate is derived using the two-step default extrapolation procedure recommended in EPA's proposed cancer guidelines (U.S. EPA, 1996a). Under this procedure, the first step is to conduct dose-response modeling in the observable range to obtain a "point of departure" at the low end of the observable range (in this case, the LED_{10} is used, i.e., the 95% lower confidence limit on the dose corresponding to a 10% extra risk). The second step is to "extrapolate" to lower doses using either a linear extrapolation from the point of departure to 0 dose, 0 extra risk, or a "margin of exposure analysis" for carcinogens with nonlinear modes of action (in this case, linear extrapolation is warranted by the positive evidence of genotoxicity for quinoline; thus, the slope factor is $0.1/LED_{10}$).

The LED_{10} 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 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 exposure group were therefore employed for quantifying 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, the historical control data were used. Details of the reassessment are presented in Appendix B.

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 3.1 $(mg/kg/day)^{-1}$ $0.1/LED_{10}$ value[2] derived here is recommended over the somewhat greater EPA (1985) estimate of 12.5 $(mg/kg/day)^{-1}$ for several reasons. It is based on the linear extrapolation method described in more recent EPA proposed cancer guidelines (U.S. EPA, 1996a). Uncertainty is reduced 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 decreased uncertainty further. In the study by Hirao et al. (1976), only six 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 $0.1/LED_{10}$ of 3.1 $(mg/kg/day)^{-1}$ is in good agreement with the q_1* of 3.2 $(mg/kg/day)^{-1}$ derived using methods described in the EPA (1986a) guidelines (see Appendix B).

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[2]The LED_{10} represents the 95% lower confidence limit on a dose associated with 10% extra risk adjusted for background.

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 (U.S. 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.

Although oral (dietary) studies in rats and mice have been performed, noncancer effects could not be disassociated with carcinogenic effects or were not reported in a manner that would allow for development of an RfD. However, oral studies in rats and mice (Hirao et al., 1976; Hasegawa et al., 1989; Shinohara et al., 1977; Futakuchi et al., 1996) and dermal (LaVoie et al., 1984) and i.p. injection studies in mice (LaVoie et al., 1987, 1988; Weyland et al., 1993) revealed no noncancer effects at exposure levels that did not also result in early-onset hepatocarcinogenic effects.

No human or animal inhalation toxicity data were available for derivation of an inhalation noncancer RfC or 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 tumor promoter tetradecanoyl phorbol acetate (LaVoie et al., 1984) suggests that quinoline can initiate skin tumors (no other tumor types were reported) without first-pass metabolism in the liver, but the question of whether inhaled quinoline would have such effects without promotion remains.

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, hemangioendotheliomas 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. In accordance with EPA cancer guidelines (U.S. EPA, 1986a), quinoline is classified as a Group B2 "*probable human carcinogen*," with sufficient evidence of carcinogenicity in animals as evidenced by observations of increased incidence of an unusual malignant tumor in multiple strains of rats and mice, multiple experiments using oral, dermal, i.p., and s.c. dosing, and at an early age. This evidence for quinoline's carcinogenicity in rats and mice, along with evidence demonstrating its genotoxicity, supports a determination that quinoline is *likely to be carcinogenic in humans* in accordance with more recent, 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 recognizes that quinoline is a potent carcinogen with a short latency period and estimates human cancer risk from an oral carcinogenicity bioassay in male rats (Hirao et al., 1976). An oral slope factor of 3 $(mg/kg/day)^{-1}$ for humans, which represents the slope of a straight line between the LED_{10} (lower bound 95% confidence limit on the dose that causes a 10% increase in the extra risk of an effect) and the estimated background rate, was derived from the animal data (in accordance with EPA policy, only one significant figure is retained).

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APPENDIX A. EXTERNAL PEER REVIEW— SUMMARY OF EXTERNAL PEER REVIEW COMMENTS AND DISPOSITION

The Toxicological Review that supports the IRIS file for quinoline has undergone both internal peer review performed by scientists within EPA or other Federal agencies and a more formal external peer review performed by scientists chosen by EPA's contractor in accordance with existing guidance (U.S. EPA, 1994b). Comments made by the internal reviewers were addressed prior to submitting the documents for external peer review and are not part of this appendix. Public comments also were read and carefully considered. The external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific questions in areas of scientific controversy or uncertainty. A summary of comments made by the external reviewers (organized by the original charges posed) and EPA's response to these comments follows.

Comments Submitted in Response to General Charges

1. *Are you aware of any other data/studies that are relevant for the assessment of the adverse health effects of this chemical?*

Comment: In general, the reviewers felt that the quinoline toxicological review is a "well written" and "accurate representation" of the available, relevant data/studies. One reviewer mentioned that the American Industrial Hygiene Association (AIHA) has developed a 0.1 ppm (0.5 mg/m^3) Workplace Environmental Exposure Level (WEEL) Guide for quinoline, and suggested that a review of the basis for this benchmark might turn up a useful reference. This reviewer also offered a 1999 reference from Mutagenicity Research titled "Antimutagenic effects and possible mechanisms of actions of vitamins and related compounds against genotoxic heterocyclic amines from cooked foods."

Response to comment: No new studies were obtained from an investigation into the basis for the AIHA WEEL for quinoline. The quinoline WEEL was based largely on the carcinogenic potential of quinoline as determined by the studies addressed in the EPA Toxicological Review. The Mutagenicity Research reference offered was considered, but did not provide a significant enough contribution to be cited.

2. *For the RfD and RfC, has the most appropriate critical effect been chosen?*

Comment: One reviewer commented that an AIHA WEEL had been derived for quinoline, apparently to suggest that EPA should examine the basis for the WEEL and determine whether such basis warranted the derivation of an RfC/RfD. No critical effect for a noncancer benchmark was suggested, however. The other two reviewers clearly stated their determination that the decision not to derive RfD and RfC values was fully justified.

Response to comment: As stated above, the WEEL for quinoline was based primarily on the carcinogenicity of quinoline. It provides no basis for the derivation of an RfC/RfD.

3. *Have the noncancer and cancer assessments been based on the most appropriate studies?*

Comment: None of the reviewers offered any studies that would support the derivation of an RfD/RfC, and at least two of the three reviewers clearly stated that the decision not to derive a noncancer benchmark was warranted by the lack of appropriate studies. All three reviewers felt that the Hirao et al. (1976) study was the most appropriate study available for the quantitative cancer assessment, and that the additional studies identified were appropriate as qualitative support.

Response to comment: None required.

4. *Should other studies be included under the "Supporting/Additional" category in support of the RfD/RfC?*

Comment: No other studies were identified.

Response to comment: None required.

5. *For the noncancer assessments, are there other data that should be considered in developing the uncertainty factors or the modifying factor?*

Comment: No other studies were identified.

Response to comment: None required.

6. *Do the confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the studies chosen, the relevancy of the effects to humans, and the comprehensiveness of the database?*

Comment: Two reviewers questioned the assignment of medium confidence to the quinoline oral carcinogenicity database (Section II.B.4 of the IRIS summary). One suggested that the database should be assigned low confidence. The other suggested that a distinction should be made regarding confidence for a qualitative assessment (which the reviewer deemed to be medium) versus confidence for a quantitative assessment (which the reviewer deemed to be low).

Response to comment: With respect to the quinoline database, the Agency agrees that it would be helpful to distinguish between the strength of the available information for making qualitative versus quantitative determinations. Section II.B.4 of the IRIS summary has been revised to reflect this distinction.

Comments Submitted in Response to Quinoline-Specific Charges

1. ***Regarding the RfD and RfC****, is the determination that "none of the oral exposure data were reported in a manner that would allow for a meaningful quantitative dose-response assessment" and that "no human or animal inhalation toxicity data were available for consideration of an RfC" appropriate? Was adequate justification provided for the Agency's position?*

Comment: All reviewers, with respect to the RfD, and two of three reviewers, with respect to the RfC, indicated that these determinations were appropriate and adequately justified. With respect to the RfC, one reviewer suggested that the data used to establish the AIHA WEEL might be suitable for setting an RfC, but did not provide or hazard a guess at what that data might have been.

Response to comment: As stated above, the quinoline WEEL does not provide a basis for the establishment of an RfD or RfC.

2. ***Regarding the cancer assessment****, did the assessment make appropriate use of liver effects that may have been precursors to tumor formation in its qualitative and quantitative considerations? Was the time-to-tumor approach and the use of the multistage Weibull model in the TOX_RISK version 3.5 software an appropriate approach, and was enough detail presented to adequately inform the reader regarding model results and how to duplicate the quantitative assessment?*

Comment: All three reviewers indicated that precursor liver effects were appropriately used and considered in the IRIS assessment. However, one reviewer felt that the text needed to "acknowledge more forcefully and in greater detail that, despite strong suspicions, the mode of action is not known definitely." One reviewer made no comment regarding the time-to-tumor approach because of "no access to TOX-RISK." Another reviewer felt that the use of the TOX-RISK Weibull model was appropriate and that the "rationale for developing the quantitative risk value is adequately described in the text." The third reviewer felt that the available data were "insufficient to justify quantifying [quinoline's] cancer potency," but that the time-to-tumor approach was described in sufficient detail and was the "best mathematical selection in light of the very short latency in tumor formation and of the suggestive evidence of increased incidence of tumors with increasing duration of exposure" for quantification. This reviewer further stated that, if an attempt is made to quantify quinoline's potency in this manner, it should be qualified as "a default procedure that is consistent with an important toxicological observation (short latency), but that a great deal more data would be needed to determine if this particular model is suitably representative of the actual dose-response relationship(s)."

Response to comment: The Agency recognizes the very limited nature of the cancer data available for quinoline, but feels that, given the clear high potency of this compound, the data for quinoline are sufficient to justify an attempt to quantify its cancer potency. This same reasoning was used by the authors of the original cancer potency estimate. The following text was added to

the discussion in the Toxicological Review of the old cancer potency estimate and the need for a new cancer potency estimate:

> The authors of this [previous] assessment determined that, despite the recognized limitations of the critical study (e.g., small sample size, the fact that only males were examined, the limited toxicity parameters examined, early deaths, and the lack of statistical analyses), "data sets (rats and mice) were cogent enough to warrant a cancer potency determination under the assumption that quinoline is a human carcinogen." Considering the apparent high potency of this compound, EPA continues to maintain the need for a potency determination for quinoline. However, some changes to the quantitative assessment approach are recommended. . . .

Other General Comments Submitted

Comment: One reviewer requested more detail (page 3) concerning the potential for human exposure.

Response to comment: The reviewer may not be completely aware that the focus of the IRIS Toxicological Review is almost completely on the health hazards of the compound. The IRIS Toxicological Review was supplemented with the following additional information.

> The following is a brief summary of what is known regarding the environmental fate and transport of quinoline. A more in-depth discussion of this and other exposure issues can be found in the EPA Health and Environmental Effects Profile for Quinoline (U.S. EPA, 1985).

APPENDIX B
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 B-1 below.

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).

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

Dose level[a]	Mean length of experiment (weeks)	Incidence
		No. responding/ No. examined
0	104[b]	2/83[b]
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

[a]Because 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.

[b]Historical controls as reported by Anver et al. (1982). Incidence data were from the "CD" and "HAP" Sprague-Dawley rats at 18-23 or 24-29 months of age with either liver hemangioma or hemangiosarcoma. This was taken as the incidence at 104 weeks. 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 the short experiment duration 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. A rat weight of 350 g was used.

3. Model Fit

The one-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 (one-stage Weibull model)

Parameter estimates: Q_0 = 2.335E-4; Q_1 = 1.026E-3; T_0 = 0; Z = 1.

Unit potency is computed for risk (extra risk) of 1.0E-6: MLE (i.e., maximum likelihood estimate, or "best estimate") = 1.57 per mg/kg/day; 95% upper bound (q1*) = 3.24 per mg/kg/day.

LED_{10} = 32.55 µg/kg/day. Using the linear extrapolation method of the 1996 proposed cancer guidelines (i.e. $0.1/LED_{10}$) yields a potency of 3.07 per mg/kg/day.