



Figure 1: Structure of Quinoline

Introduction

Under the *Canadian Environmental Protection Act, 1999* (CEPA 1999) the Minister of Health may gather information, conduct investigations and evaluations, including screening assessments, relevant for the purpose of assessing whether a substance is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Screening health assessments focus initially on conservative assessment of hazard or effect levels for critical endpoints and upper-bounding estimates of exposure, after consideration of all relevant identified information. Decisions based on the nature of the critical effects and margins between conservative effect levels and estimates of exposure take into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. Additional background information on screening health assessments conducted under this program is available at http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/index_e.html.

A State of the Science Report for a screening assessment has been prepared on quinoline (see Figure 1) on the basis that this compound was included in the Domestic Substances List pilot phase for screening as a substance likely to be prioritized on the basis for greatest potential for human exposure.

This draft State of the Science Report for a screening assessment and associated unpublished supporting working documentation were prepared by evaluators within the Existing

Substances Division of Health Canada; the content of these documents was reviewed at several meetings of senior Divisional staff. The draft Report was subsequently externally reviewed for adequacy of data coverage and defensibility of the conclusions. The supporting working documentation is available upon request by e-mail from ExSD@hc-sc.gc.ca

Information identified as of July 2003 was considered for inclusion in this Report. The critical information and considerations upon which this Report is based are summarized below. Additional data identified between this date and the end of the external peer review period (April, 2004) were also scoped and determined not to impact upon the conclusions presented here.

Identity, Use and Sources of Exposure

Quinoline is an N-heterocyclic compound with the chemical structure presented in Figure 1. Based on a survey made under CEPA 1999, Section 71, one or more companies reported manufacture or import of this substance in excess of 10 000 kg during the calendar year 2000 (Environment Canada, 2001). Quinoline is used as a solvent, chemical intermediate and corrosion inhibitor and in the manufacture of pharmaceuticals (Finley, 1996). It is formed during the incomplete combustion of nitrogen-containing substances (e.g., petroleum, coal) and is therefore dispersed in the environment as a component of suspended particulate matter emitted from sources such as automobile exhaust and petroleum or coal refining facilities (Dong and Locke, 1977). Quinoline was identified as being used as a component in fragrance mixtures (RIFM, 2003), and as such, there is potential for the population to be exposed to quinoline through the use of consumer product formulations that include this ingredient.

Exposure Assessment, Hazard Characterization and Risk Evaluation

Based on the limited available information on concentrations of quinoline in ambient air and indoor air (Chuang et al., 1991¹), surface water (as a surrogate for data on drinking water concentrations) (Merriman, 1988) and soil (Webber, 1994), the upper-bounding estimate of daily intake for the general Canadian population ranges from 4.6 µg/kg-bw per day (for those 60+ in age) to 14.1 µg/kg-bw per day (for those 6 months to 4 years of age), with indoor air potentially representing the most important source of exposure (see Table 1). Including exposure to quinoline from smoking tobacco would increase the estimated daily intake of exposure 21-fold. Based on confidential information provided through Section 71 (Environment Canada, 2001), the estimated daily intake of quinoline from consumer products was calculated to be 1.08×10^{-2}

¹ The units given in the Chuang et al. (1991) study are inconsistent and possibly erroneous, as values were reported in µg/m³ in the tables and ng/m³ in the text. As a worst-case scenario, µg/m³ was used for this assessment but this may lead to an overestimation of quinoline in indoor and ambient air.

µg/kg-bw per day for adults (20–59 years of age), which does not contribute significantly to the estimate of daily intake from environmental media.

Confidence in the exposure database is considered to be low. Data were available on levels of quinoline for the environmental media that are most relevant to general population exposure (i.e., water and indoor/ambient air). However, estimates of exposure from drinking water were based on a detection limit (0.001 µg/L) reported for surface water, and the study of indoor air used for the estimate was from Columbus, Ohio (Chuang *et al.*, 1991). The U.S. study was selected because it was considered to be more comprehensive than the Canadian study as there was a larger sample size, more information on sampling conditions (e.g., smoking versus non-smoking households) and concurrent measurements in ambient air to allow comparison. The U.S. value was similar to that reported in the Canadian study (i.e., 26 µg/m³ versus 22 µg/m³), however there is uncertainty that the units in the study by Chuang *et al.*, (1991) were reported correctly and the values chosen may significantly overestimate human exposure to quinoline in ambient and indoor air. Comparison of the concentrations of quinoline in ambient and indoor air measured in Ohio show that the concentrations measured indoors are significantly higher than ambient concentrations. This indicates that there are additional sources of quinoline located within the home. Consumer products represent a potential source of exposure, but calculated intake estimates from this route are not sufficient to lead to the elevated concentrations measured in indoor air. The sources of the elevated quinoline levels are unidentified, but exposure likely results from combustion sources within the home. Although the study conducted by Chuang *et al.* (1991) attempted to evaluate the impact of combustion sources within the home on quinoline concentrations, the sample size was not large enough to be statistically significant. Although no data were available on quinoline levels in food, this is not expected to be a significant source of intake, as quinoline is unlikely to bioaccumulate due to a low octanol/water partition coefficient.

Table 2 contains a summary of the available health effects information for quinoline. The U.S. Environmental Protection Agency has published an assessment of quinoline (U.S. EPA, 2001). In the studies reviewed in the U.S. EPA (2001) assessment, there were increased incidences of an unusual tumour (i.e., hemangioendotheliomas) in multiple strains of rats and mice exposed orally, hepatic tumours (i.e., adenomas and hepatomas) in mice following single intraperitoneal injections at an early age and skin tumours in mice exposed dermally in an initiation–promotion study. Many of these studies are dated and are limited by the use of only one sex of animals, small dose groups, short durations of exposure and, in some cases, a lack of statistical analyses. The critical study, which was originally selected by the U.S. EPA (2001), for which the exposure–response relationship was best characterized, was a bioassay by Hirao *et al.* (1976) in which increased incidences of hepatocellular carcinomas and hemangioendotheliomas and/or hemangiosarcomas were observed in the livers of male rats exposed to concentrations of 0, 0.05, 0.10 or 0.25% quinoline in the diet (equivalent to 0, 25, 50 and 125 mg/kg-bw per day,

respectively; U.S. EPA, 2001) for up to 40 weeks. Based upon a relatively extensive *in vivo* and *in vitro* genotoxicity database, quinoline is considered to be genotoxic (U.S. EPA, 2001).

Non-neoplastic effects, including increased absolute and relative liver weights, fatty changes, bile duct proliferation and oval cell infiltration of the liver, were also observed at all doses (i.e., ≥ 25 mg/kg-bw per day) in the study by Hirao et al. (1976). Similar non-neoplastic effects on the liver have been observed in other limited investigations of shorter duration or by less relevant routes of exposure in rats, mice, guinea pigs and hamsters. The US EPA (2001) noted that the observed non-neoplastic hepatic changes, body weight loss and early mortalities were considered by the authors of these studies (and by the US EPA in a previous assessment) to be related to the hepatocarcinogenicity of quinoline. The US EPA further indicated that while the relationship of some non-neoplastic effects (e.g., body and liver weight changes, and oval cell infiltration, proliferation of bile ducts, and fatty degeneration of parenchymal cells) to tumour formation was not as clear, it is likely that these effects were at least confounded by tumour formation in the liver and were not reported in a manner that would allow a meaningful quantitative characterization of the dose-response relationship.

On the basis of sufficient evidence of carcinogenicity in experimental animals and supporting evidence of genotoxicity, the U.S. EPA (2001) concluded that quinoline is “likely to be carcinogenic in humans.” Recent data do not materially impact upon the selection of the critical study or the conclusions reached by the U.S. EPA (2001).

Confidence in the toxicological database for quinoline is considered to be moderate. Although there is an extensive database of genotoxicity assays, the available carcinogenicity studies are somewhat limited and dated.

While weight of evidence for potential modes of induction of tumours or relevance to humans has not been considered in detail in this evaluation, the U.S. EPA (2001) noted that it is possible that both mitogenic and genotoxic mechanisms are involved in quinoline-induced hepatocarcinogenicity; however, further research is needed before any conclusion can be reached. Consideration of data on a selected number of quinoline analogues and the outputs of quantitative structure–activity relationship modelling for both quinoline and its analogues did not add or detract from the weight of evidence for carcinogenicity or genotoxicity from the empirical data for quinoline. Comparison of the critical effect level for non-neoplastic effects (i.e., 25 mg/kg-bw per day) with the upper-bounding estimate of exposure (i.e., 14.1 μ g/kg-bw per day) results in a margin of exposure of approximately 1770. While this margin for non-neoplastic effects is relatively large in view of the conservative nature of the comparison, the potential of quinoline to induce tumours through direct interaction with genetic material cannot be precluded. Therefore, the outcome of this evaluation on quinoline is that it is suspected that this margin may not be adequate to account for the uncertainties in the database, particularly regarding the mode of tumour induction.

Data addressing uncertainties in intraspecies and interspecies variations in sensitivity and mode of induction of effects would permit a more definitive conclusion.

Table 1: Upper-bounding estimates of daily intake of quinoline by the general population in Canada

Route of exposure	Estimated intake ($\mu\text{g}/\text{kg}\text{-bw}$ per day) of quinoline by various age groups						
	0–6 months ^{1,2,3}		0.5 – 4 years ⁴	5 – 11 years ⁵	12 – 19 years ⁶	20 – 59 years ⁷	60+ years ⁸
	formula fed	not formula fed					
Ambient air ⁹	0.19		0.41	0.32	0.18	0.16	0.14
Indoor air ¹⁰	6.4		13.6	10.6	6.0	5.2	4.5
Drinking water ¹¹	1.1×10^{-4}	4.0×10^{-5}	4.5×10^{-5}	3.5×10^{-5}	2.0×10^{-5}	2.1×10^{-5}	2.2×10^{-5}
Food ¹²		NA ¹³	NA	NA	NA	NA	NA
Soil ¹⁴	2×10^{-4}		4×10^{-4}	1×10^{-4}	3×10^{-5}	2.5×10^{-5}	2.5×10^{-5}
Total intake	6.6	6.6	14.1	11.0	6.2	5.4	4.6

¹ No data on levels of quinoline in breast milk were identified.

² Assumed to weigh 7.5 kg, to breathe 2.1 m³ per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed), and to ingest 30 mg of soil per day (EHD, 1998).

³ For formula-fed infants, intake from water is synonymous with intake from food. No data on concentrations of quinoline in formula were identified for Canada. For non-formula fed infants, approximately 50% are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW, 1990 in EHD, 1998).

⁴ Assumed to weigh 15.5 kg, to breathe 9.3 m³ per day, to drink 0.7 L of water per day, and to ingest 100 mg of soil per day (EHD, 1998).

⁵ Assumed to weigh 31.0 kg, to breathe 14.5 m³ per day, to drink 1.1 L of water per day, and to ingest 65 mg of soil per day (EHD, 1998).

⁶ Assumed to weigh 59.4 kg, to breathe 15.8 m³ per day, to drink 1.2 L of water per day, and to ingest 30 mg of soil per day (EHD, 1998).

⁷ Assumed to weigh 70.9 kg, to breathe 16.2 m³ per day, to drink 1.5 L of water per day, and to ingest 30 mg of soil per day (EHD, 1998).

⁸ Assumed to weigh 72.0 kg, to breathe 14.3 m³ per day, to drink 1.6 L of water per day, and to ingest 30 mg of soil per day (EHD, 1998).

⁹ The highest concentration of quinoline (5.5 $\mu\text{g}/\text{m}^3$) measured in 10 samples of ambient air in a residential area in Columbus, Ohio, was used to calculate the upper-bounding limit of exposure estimate (Chuang et al., 1991). The units given in the Chuang et al. (1991) study are inconsistent and possibly erroneous, as values were reported in both $\mu\text{g}/\text{m}^3$ and ng/m^3 . As a worst-case scenario, $\mu\text{g}/\text{m}^3$ was used for this exposure assessment but this may lead to an overestimation of quinoline in ambient air. Canadians are assumed to spend 3 hours outdoors each day (EHD, 1998). Available data from which the critical data were selected included a study of non-point source and point source of quinoline in ambient air in the United States (Hawthorne and Seivers, 1984).

¹⁰ The maximum average concentration of quinoline in indoor air (26 $\mu\text{g}/\text{m}^3$), based on six samples collected from three non-smoking homes in Columbus, Ohio, was used to calculate the Upper Bounding Estimate of Exposure (Chuang et al., 1991). The units given in the Chuang et al. (1991) study are inconsistent and possibly erroneous, as values were reported in both $\mu\text{g}/\text{m}^3$ and ng/m^3 . As a worst-case scenario, $\mu\text{g}/\text{m}^3$ was used for this exposure assessment but this may lead to an overestimation of quinoline in indoor air. Canadians are assumed to spend 21 hours indoors each day (EHD, 1998). The concentration used was similar to a composite of sample extracts taken from 757 Canadian homes (i.e., 22 $\mu\text{g}/\text{m}^3$) (Otson et al., 1994).

- ¹¹ No data on levels of quinoline in drinking water were identified. As a surrogate, the detection limit (0.001 µg/L) for measuring quinoline in samples of surface water from Rainy River, Ontario, was used to calculate the upper-bounding limit of exposure estimate (Merriman, 1988). For formula-fed infants, the concentration of quinoline in the water used to reconstitute formula accounts for the intake of quinoline from food. Available data from which the critical data were selected included two point source studies of quinoline in surface water from Ontario (Marsalek and Schroeter, 1988; Merriman, 1988) and one from Japan (Yasuhara et al., 1999), and two point source studies of quinoline in groundwater from the United States (Pereira et al., 1987; Godsy et al., 1992) and one from Denmark (Johansen et al., 1997).
- ¹² No data on levels of quinoline in food were identified.
- ¹³ NA = not available
- ¹⁴ The highest concentration (60 µg/kg dry weight) of quinoline detected among soil samples collected from southern Ontario was used to estimate an upper-bounding limit of exposure (Webber, 1994). Available data from which the critical data were selected include a study of soil levels in two locations in Ontario (Golder Associates Ltd., 1987).

Table 2: Summary of health effects information for quinoline

Endpoint	Lowest effect levels ¹ /Results
Acute toxicity	<p>Lowest oral LD₅₀ (rat) = 331 mg/kg-bw (Marhold, 1986) [Additional study: Smyth et al., 1951]</p> <p>Lowest dermal LD₅₀ (rabbit) = 540 µL/kg-bw (Smyth et al., 1951) [Additional study: Marhold, 1986]</p>
Short-term repeated-dose toxicity	no data
Subchronic toxicity	no data
Chronic toxicity/ carcinogenicity	<p>Lowest oral (diet) non-neoplastic LOEL (rat) = 25 mg/kg-bw per day: increased absolute and relative liver weights, fatty change, bile duct proliferation and oval cell infiltration; 40-week study with 0, 0.05, 0.10 or 0.25% in diet (0, 25, 50 or 125 mg/kg-bw per day; conversion by U.S. EPA, 2001) (Hirao et al., 1976)</p> <p>Dietary carcinogenicity bioassay (male rats): 0, 0.05, 0.10 or 0.25% in diet (0, 25, 50 or 125 mg/kg-bw per day; conversion by U.S. EPA, 2001) for 16–40 weeks; increased incidence (compared with controls) of hepatocellular carcinomas (0/6, 3/11, 3/16 and 0/19 at 0, 25, 50 and 125 mg/kg bw/day, respectively) and hemangioendotheliomas and/or hemangiosarcomas (0/6, 6/11, 12/16 and 18/19 at 0, 25, 50 and 125 mg/kg bw/day, respectively) starting at 25 mg/kg-bw per day (Hirao et al., 1976). The U.S. EPA (2001) indicated that the low incidence of hepatocellular carcinomas in the high dose group may have been due to early mortality from rupture of hemangioendotheliomas and/or hemangiosarcomas.</p> <p>Similar tumours were observed in additional dietary studies in mice and rats at doses ≥25 mg/kg bw/day, but not in hamsters or guinea pigs (Shinohara et al., 1977; Hasegawa et al., 1989; Futakuchi et al., 1996). Liver tumours were also observed in intraperitoneal administration studies in newborn mice (LaVoie et al., 1987, 1988; Weyand et al., 1993). Skin tumour incidence was increased in a dermal initiation–promotion study in mice (LaVoie et al., 1984), and quinoline was reported to act as a tumour promoter in a dietary study in rats (Saeki et al., 1997). No increase in tumour incidence over controls was observed in a subcutaneous administration study in newborn rats (LaVoie et al., 1988).</p>
Developmental toxicity	Other than the carcinogenicity studies in newborn mice reported above, no studies of the effects of quinoline on developing organisms have been identified.
Reproductive toxicity	no data
Genotoxicity and related endpoints: <i>in vivo</i>	<p>Clastogenicity, micronucleus test</p> <p>Positive: liver, mouse (Lefevre and Ashby, 1992) [oral; 40-225 mg/kg]; liver, rat (Ashby et al., 1989) [oral; 225-500 mg/kg]; bone marrow, mouse (Hamoud et al., 1989) [i.p.; 25-100 mg/kg]</p> <p>Negative: bone marrow, rat (Asakura et al., 1997) [Oral; 25-200 mg/kg bw/day]</p> <p>Chromosomal aberrations</p> <p>Positive: liver, rat (Asakura et al., 1997) [Oral; 25-200 mg/kg bw/day]</p> <p>Mutagenicity</p> <p>Positive: lac Z transgenic mouse (Suzuki et al., 1998) [i.p.; 50 mg/kg]</p> <p>Sister chromatid exchange</p>

Endpoint	Lowest effect levels ¹ /Results
	Positive: liver, rat (Asakura et al., 1997) [oral; 25-200 mg/kg bw/day] Unscheduled DNA synthesis Equivocal: liver, rat (Ashby et al., 1989) [oral; 100-500 mg/kg]
Genotoxicity and related endpoints: <i>in vitro</i>	Mutagenicity Positive: <i>S. typhimurium</i> TA100, with activation (Nagao et al., 1977; U.S. EPA, 1985; LaVoie et al., 1991; Debnath et al., 1992); <i>S. typhimurium</i> TA98, with activation (Epler et al., 1977; Nagao et al., 1977; Sideropoulos and Specht, 1984; Takahashi and Ono, 1993; Willems <i>et al.</i> , 1992; JETOC, undated); TA1537, with activation (Epler et al., 1977). Negative: <i>S. typhimurium</i> TA1535, TA1537, TA1538, TA100 and TA98, with activation (Epler et al., 1977; U.S. EPA, 1985; LaVoie et al., 1991; Debnath et al., 1992); <i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, without activation (Epler et al., 1977; Sideropoulos and Specht, 1984; Takahashi and Ono, 1993; Willems <i>et al.</i> , 1992; JETOC, undated) DNA adduct formation Positive: liver, rat (Tada et al., 1980) Unscheduled DNA synthesis Positive: liver, rat, with activation (LaVoie et al., 1991)
Neurotoxicity	Intraatriatal microdialysis study (male rats): 10mM tetrahydroquinoline infused for 10 hours; no evidence of dopaminergic neurotoxicity (Booth et al., 1989)

¹ LD₅₀ = median lethal dose; LOEL = lowest-observed-effect level.

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