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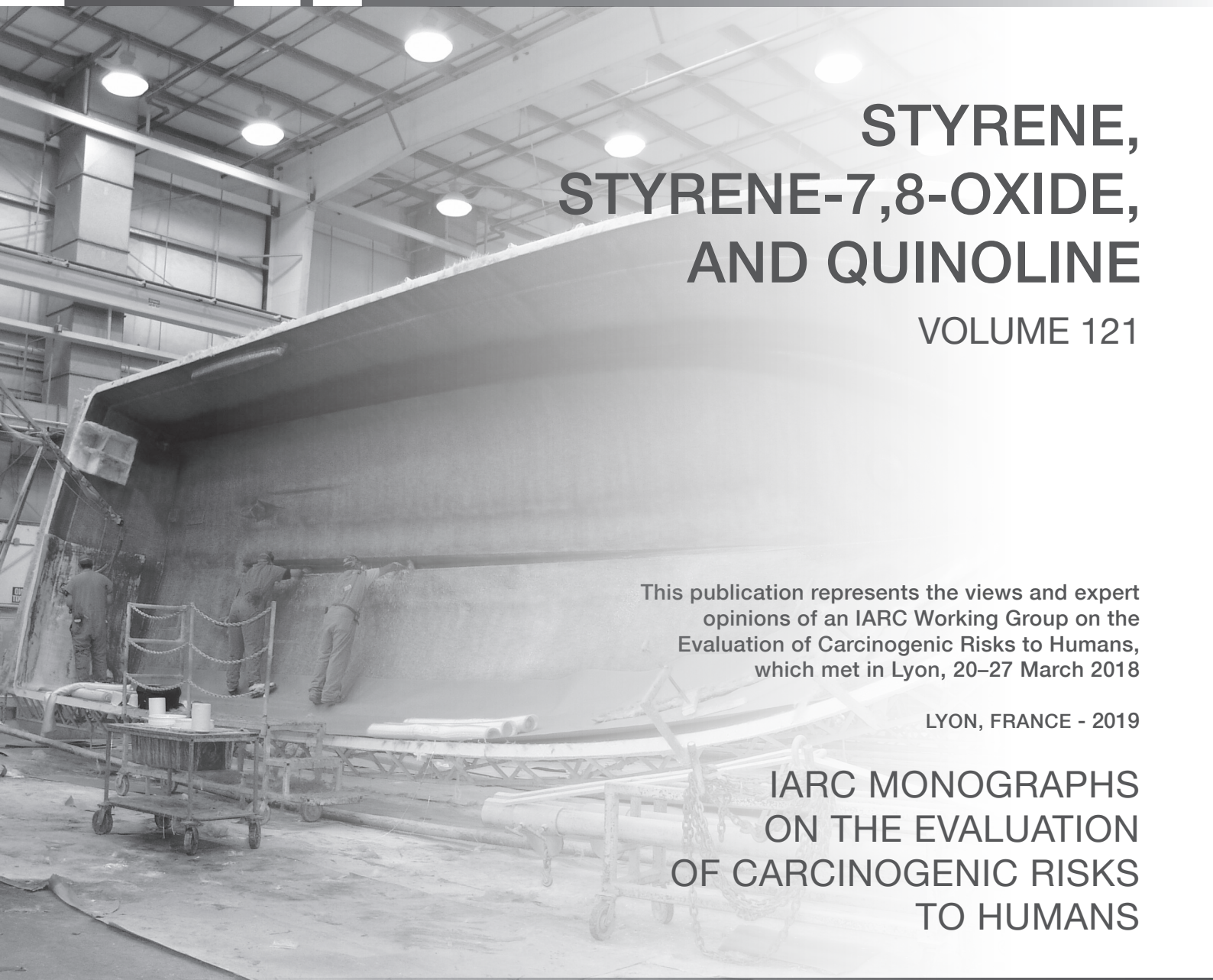

STYRENE, STYRENE-7,8-OXIDE, AND QUINOLINE

VOLUME 121

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International Agency for Research on Cancer

World Health Organization

QUINOLINE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. (CAS) Reg. No.: 91-22-5

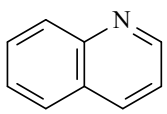
CAS name: 1-Azanaphthalene

IUPAC systematic name: Quinoline

Synonyms: 1-Benzazine, chinoline, quinolin, 2,3-benzopyridine, leucol

1.1.2 Structural and molecular formulae, and relative molecular mass

Structural formula:



Quinoline

Molecular formula: C_9H_7N

Relative molecular mass: 129.16 (Merck, 2017)

1.1.3 Chemical and physical properties of the pure substance

Description: Quinoline is a colourless, hygroscopic, weakly basic liquid with a characteristic unpleasant odour. It turns brown on exposure to light. It absorbs as much as 22% water (O'Neil, 2006).

Melting/freezing point: –15 °C (Merck, 2017)

Boiling point: 237–238 °C at 101 kPa (Merck, 2017)

Density: 1.09 g/cm^3 at 25 °C (Merck, 2017)

Relative density: $d_{20/4}$, 1.0900 (water, 1) (Merck, 2017)

Solubility in organic solvents: Soluble in carbon tetrachloride and miscible with ethanol, ether, acetone, benzene, and carbon disulfide (Lide, 2003); dissolves sulfur, phosphorous, and arsenic trioxide (O'Neil, 2006)

Solubility in water: 6 g/L at 20 °C (Merck, 2017)

Dissociation constant: pK_a, 4.90 at 20 °C (Lide, 2003)

Vapour pressure: 11 Pa at 25 °C (Merck, 2017)

Relative vapour density: 4.5 (air, 1) (Weiss, 1986)

Odour threshold: 71 ppm = 375 mg/m^3 (HSDB, 2017)

Reactivity: May attack some forms of plastic (Weiss, 1986); forms explosive mixtures with air on intense heating. Development of hazardous combustion gases (nitrogen oxides) or vapours possible in the event of fire (Merck, 2017). Protect from light and moisture (O'Neil, 2006).

Octanol/water partition coefficient (P): log K_{ow}, 2.03 (HSDB, 2017)

Conversion factor: 1 ppm = 5.28 mg/m^3 at 25 °C and 101.3 kPa

Table 1.1 Examples of some quinolinium salts

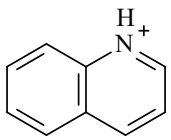
Salt	CAS No.	Formula	Relative molecular mass	Reference
Quinolinium hydrogen sulfate	530-66-5	$C_9H_9NO_4S$	227.23	O'Neil (2006)
Quinolinium chloride	530-64-3	C_9H_8ClN	165.62	O'Neil (2006)
Quinolinium bromide	ChemSpider ID: 378462	C_9H_8BrN	210.07	ChemSpider (2017)
Quinolinium dichromate	56549-24-7	$C_{18}H_{16}Cr_2N_2O_7$	476.32	PubChem (2017)
Quinolinium chlorochromate	108703-35-1	$C_9H_7ClCrNO_3$	264.61	PubChem (2017)

CAS, Chemical Abstracts Service.

1.1.4 Chemical and physical properties of some quinolinium salts

As a base, quinoline forms quinolinium salts upon contact with acids.

Basic structural formula of quinolinium salts:



Quinolinium ion

Some quinolinium salts are listed in Table 1.1.

Quinolinium chlorochromate is an efficient reagent for oxidative cleavage of oximes via the use of microwave irradiation, and pestle and mortar (Singh et al., 2003).

1.1.5 Technical products and impurities

Commercial quinoline has a purity of at least 90%. The chromatographic composition of this product is typically 92% quinoline and 5% isoquinoline by weight. Impurities include methylquinolines, 2,8-dimethylquinoline, and some homologues of isoquinoline (Finley, 1999).

1.2 Production and use

1.2.1 Production process

Many different methods currently exist for the synthesis of quinoline and its derivatives (Organic Chemistry Portal, 2017). Quinoline may be prepared by the classical Skraup synthesis from 1880 of heating aniline with glycerol in the presence of sulfuric acid and an oxidising agent such as nitrobenzene (O'Neil, 2006).

The Skraup synthesis is very energy intensive, and many modifications have been introduced (Batista et al., 2016). For example, quinoline can be continuously produced (42% yield) from aniline and glycerol in a reactor by microwaves under pressure (12 bar) and reduced temperature (200 °C) (Saggadi et al., 2015).

1.2.2 Production volume

About 35 years ago, the world production of quinoline was more than 2000 United States tons [2032 metric tonnes] annually. Annual production in the USA was at least 45.4 tons [> 40.8 tonnes] in 1978, and in 1982 the USA produced 2.27 tons [1.82 tonnes] and imported 39.6 tons [35.4 tonnes] (HSDB, 2017).

According to the United States Environmental Protection Agency (EPA) Chemical Data Access Tool, the aggregate production volume of quinoline in the USA was in the range of 100 000–500 000 pounds/year [~45–227 metric tonnes] for 2011. National production volume data for subsequent years are not publicly available. Data were provided for four companies, of which one produced 145 909 pounds [~66 metric tonnes] of quinoline per year. Quinoline is currently imported in confidential amounts into the USA (EPA, 2017).

This substance is manufactured and/or imported into the European Economic Area in

quantities of 100–1000 tonnes per year (ECHA, 2018). Data on exact quantities are not publicly available.

One or more companies in Canada reported the manufacture or import of quinoline in excess of 20 000 kg during the calendar year 2000 as part of chemical compounds comprising less than 1% quinoline; however, more recent data are not available (Government of Canada, 2011a).

Quinoline is included in the 2007 Organisation for Economic Co-operation and Development list of high production volume chemicals, which are those chemicals produced or imported at quantities greater than 1000 tonnes per year in at least one member country and/or region (OECD, 2009). In 2018, Chemical Sources International reported the following registered quinoline manufacturers: USA (19), Japan (2), United Kingdom (2), and 1 each in Canada, China, Hong Kong Special Administrative Region (China), France, Germany, and Switzerland (Chemical Sources International, 2018).

1.2.3 Uses

The main application of quinoline is the production of 8-quinolinol, which is obtained by alkaline fusion of quinoline-8-sulfonic acid.

Quinoline is used as a solvent in the production of dyes, paints, and other chemicals. A recently developed application is in the preparation of ionic liquid crystal solvents, such as *N*-alkylquinolinium bromide (Lava et al., 2012). It is also used as a reagent, a corrosion inhibitor, in metallurgical processes, and as an intermediate in the manufacture of pharmaceuticals and veterinary drugs (Gerhartz, 1993; O'Neil, 2006; Government of Canada, 2011b). Quinoline can be used to prepare and/or produce: nicotinic acid and its derivative niacin or vitamin B_3; antimalarial medicines (chloroquine, quinine, and mefloquine); 8-hydroxyquinoline sulfate (CAS No. 148-24-3), a metal chelating agent which is used in cosmetics; and dyes and pigments used in textiles, for example, Quinoline Yellow (CAS No. 8003-22-3). Quinoline Yellow is also used as a greenish-yellow food additive in certain countries. In the European Union (E-number E104) and Australia, Quinoline Yellow is permitted in beverages and is used in foods such as sauces, decorations, and coatings. Quinoline Yellow is not listed as a permitted food additive in Canada or the USA, but it is used in medicines and cosmetics and is known as D&C Yellow 10. The Codex Alimentarius does not list it (Abbey et al., 2013).

1.3 Measurement and analysis

1.3.1 Detection, separation, and quantification

Quinoline is an azaarene. Azaarenes are *N*-heterocyclic analogues of PAHs. Because azaarenes are more hydrophilic and have some basic (alkaline) properties as a result of nitrogen in the aromatic ring, the chromatography is considerably more difficult than analogous PAH separations (Steinheimer & Ondrus, 1986).

(a) Tars and fuels

Quinoline (and pyridine) has been pre-concentrated and determined in gasoline and diesel fuel by differential pulse voltammetry (Okumura & Ramos, 2007). The method had good agreement with an ultraviolet (UV) spectrometric technique based on the *F*-distribution and Student *t*-distribution. The limit of detection (LOD) for quinoline was 5 µg/L, and the spike recovery was 94%.

(b) Ambient air

Özel et al. (2011) developed a method to determine various nitrogen-containing compounds including quinoline in airborne particulate matter of diameter less than 2.5 µm ($PM_{2.5}$) from urban air. Two types of chemical analysis were performed on the collected samples, the

first using direct thermal desorption of analytes to comprehensive two-dimensional gas chromatography (GC×GC) and time-of-flight mass spectrometry (MS), and the second using water extraction of filters and solid-phase extraction (SPE) clean-up before GC×GC with nitrogen chemiluminescence detection. The LOD and limit of quantitation (LOQ) in standards for analysing quinoline by the first method were 4.36 µg/L and 18.9 µg/L, and by the second (more sensitive) method 2.24 µg/L and 9.71 µg/L, respectively. Quinoline was detected in the $PM_{2.5}$ air samples collected.

In the large Chinese city of Xian, azaarenes, including quinoline, bound to $PM_{2.5}$ were sampled on a filter. After being spiked with internal standards, the azaarene fraction of the sample was isolated by pressurized liquid extraction. The fraction was then extracted twice using dichloromethane. The analytes were measured by GC mass spectrometry (MS) in selected ion monitoring (SIM) mode. The average recovery of quinoline was 75 ± 5%. The relative standard deviation (RSD) for the replicate measurements (n = 3) of quinoline was 7–10%. The LOD of the analytical method was calculated as the mass of the target compound that produces a signal that is 3 times the baseline noise in the chromatogram (Bandowe et al., 2016).

(c) Water

A method to analyse several azaarenes, including quinoline, in various water sources was developed by Steinheimer & Ondrus (1986). The azaarene fraction was separated from its carbon analogues on n-octadecyl packing material by elution with acidified water and/or acetonitrile. The authors used bonded-phase extraction followed by high-performance liquid chromatography (HPLC) on flexible-walled, wide-bore columns with fluorescence and UV detection. The recovery of azaarenes at concentrations of parts per billion was close to the LOQ, and the detection of less than 1 ng quinoline (50 µg/L using a 20-µL injection) was possible. The method could be used to detect concentrations of parts per trillion in relatively pure water samples, and to assess azaarenes in complex, highly contaminated waters containing PAHs and other organics that might be expected to provide significant interference.

A high-sensitivity analytical method for assessing heteroaromatic compounds, including quinoline, in creosote-contaminated groundwater was developed with acceptable reproducibility (mean RSD, 19%), providing an LOQ of 50 ng/L (Johansen et al., 1996). The best technique (in terms of highest recovery and reproducibility) for sample preparation and analysis was determined to be the classic liquid-liquid extraction with dichloromethane from weakly basic solutions and GC-MS in SIM mode analysis of concentrated extracts. The recovery for spiked quinoline by extraction by dichloromethane was 98%; the recovery of quinoline analysed in groundwater was 71–74% and RSD varied over the range 2.6–20%.

Liquid chromatography tandem MS analysis of tar oil compounds in groundwater contaminated with tar oils in Germany revealed the occurrence of quinoline as well as its hydroxylated and hydrogenated metabolites (Reineke et al., 2007).

(d) Soil

Meyer et al. (1999) developed a simple and reproducible method which provided the simultaneous determination of PAHs and heteroaromatic compounds (N, S, O) and their degradation products in soils polluted with creosote. A sample of contaminated soil was acidified, extracted with dichloromethane and heptane, and transferred in concentrated extract on an SPE column. The fraction with quinoline was eluted with dichloromethane and/or methanol and transferred to an SPE cartridge. The basic fraction was then eluted with ammonia dissolved in methanol. The identification and quantification was performed

using either GC-MS or HPLC with diode array detection (DAD).

A method to determine azaarenes in soils using HPLC with UV-DAD or fluorescence detector (FD) was developed by Švábenský et al. (2007). Soil samples were extracted with acetonitrile and methanol (80:20, volume/volume), concentrated, filtered using a syringe filter, further concentrated under a stream of nitrogen, and analysed by HPLC. The LOD for quinoline was 2.14 ng per injection for UV-DAD and 12.7 ng per injection for FD. The LOD values obtained with FD were comparable with those published for GC flame ionization detector and GC-MS techniques.

(e) Textiles

Textiles may contain dyes based on quinoline. Luongo et al. (2016a) developed a method for the determination of aniline and quinoline compounds in textiles. Textile samples of cotton, polyamide, or polyester were extracted by dichloromethane, concentrated, and passed through graphitized carbon black SPE cartridges that selectively retain dyes and other interfering compounds present in the matrix, producing an extract suitable for GC-MS analysis. Recovered samples were assessed by spiking with a known amount of all the analytes before extraction. The recovery for quinoline was 79–83%, the LOD was 2.0 pg injected, and the LOQ was 5 ng/g.

1.3.2 Exposure assessment and biomarkers

No information was available to the Working Group on biomarkers of exposure to quinoline in humans.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

Quinoline occurs in small amounts (average, 0.3%) in coal tar and may be isolated by distillation (O'Neil, 2006; Seidel, 2006). Quinoline may enter the environment through atmospheric emissions and wastewaters of petroleum, shale oil, coal processing, and the application of coal tar creosote in wood preservation, and tobacco smoke. Quinoline is a major contaminant of soil and groundwater at sites where coal tar creosote has been used in wood preservation (Bennett et al., 1985; Pereira et al., 1987; Blum et al., 2011). The uses of quinoline in manufacturing, and as a corrosion inhibitor and as a solvent, (see Section 1.2.3) also provide avenues for its release to the environment through effluents and various waste streams (EPA, 1985, 2001). Environmental quinoline is often a component of complex mixtures, which include quinoline derivatives, volatile organic compounds, PAHs, and heteroaromatic compounds (N, S, O) (see Table 1.2).

Quinoline is soluble in water, mobile in groundwater, and subject to aerobic and anaerobic biodegradation processes; however, it has also been described as resistant to biodegradation (Thomsen et al., 1999; Deng et al., 2011; Bai et al., 2015; Xu et al., 2017). Some studies have investigated factors that control its persistence and mobility in the environment; for instance, soil characteristics and pH are known to affect quinoline mobility (Pereira et al., 1987; Fowler et al., 1994; Thomsen et al., 1999; Deng et al., 2011; Bai et al., 2015; Xu et al., 2017).

Quinoline is not known to bioaccumulate in mammals or fish (Novack & Brodie, 1950; Bean et al., 1985).

Table 1.2 Detection of quinoline and derivatives and other compounds in polluted groundwater

Pollutants	Origin of groundwater pollution	References
72 neutral, 41 basic, and 22 acidic compounds; quinoline, isoquinoline, methylquinolines, dimethylquinolines, (methyl)tetrahydroquinolines	Coal gasification site	Stuermer et al. (1982)
Quinoline, quinolinone, isoquinoline, isoquinolinone, 2- and 4-methylquinoline, (di)methylquinolinones, 2-methylisoquinolinone, benzoquinolines	Former wood-treatment plant site, Pensacola, Florida, USA	Pereira et al. (1987), Ondrus & Steinheimer (1990), Godsy et al. (1992)
111 polycyclic aromatic compounds, including N-/S-/O-heteroaromatic compounds, quinoline, 2-methylquinoline, (di)methylquinolines, isoquinoline, (iso)quinolinones, benzoquinolines, 1,2,3,4-tetrahydro(methyl)quinolines	Former coal tar distillation and wood-treatment plant at a Superfund site, St Louis Park, Minnesota, USA	Pereira et al. (1983), Rostad et al. (1985), Ondrus & Steinheimer (1990)
Polycyclic aromatic compounds and 17 N-heteroaromatic compounds; isoquinoline, quinolinones, methylquinolines, isoquinoline, quinolinones (quinoline not reported)	Coal and oil gasification site with non-aqueous phase liquids	Turney & Goerlitz (1990)
Isoquinolinone, methyl and dimethyl derivatives of quinolinone (quinoline not reported)	Former gas plant	Edler et al. (1997)
Several N-/S-/O-heteroaromatic compounds; quinoline, 2-methylquinoline, 2-hydroxyquinoline, 1-hydroxyisoquinoline, alkylquinolines	Three different creosote sites	Johansen et al. (1997)
16 polycyclic aromatic compounds and 23 N-heteroaromatic compounds; quinoline, isoquinoline, methylquinolines, dimethylquinolines, benzoquinolines	Subsurface non-aqueous-phase liquids at coke ovens site (steel production)	Baechler & MacFarlane (1992)

Compiled by the Working Group

(a) Water

Quinoline is often included in studies reporting the multitude of groundwater contaminants resulting from coal gasification or from the contamination of sites with creosote (Stuermer et al., 1982; Pereira et al., 1983; Rostad et al., 1985; Blum et al., 2011). For instance, 22 acidic, 72 neutral, and 41 basic compounds were isolated and identified in three groundwater samples collected near two underground coal gasification sites in north-east Wyoming, USA, 15 months after the end of gasification (Stuermer et al., 1982). Among the basic compounds, quinoline and other alkylated derivatives were identified; concentrations of 0.45, 7.1, and 14.0 µg/L were reported for quinoline and isoquinoline combined (Stuermer et al., 1982).

The need for rot-resistant wood products for railroad ties, pilings, poles, and other uses resulted in the establishment of about 400 creosote-treating facilities in the USA (EPA, 1981). Coal tar creosote, coal tar, and coal tar pitch have been found in at least 46 of the 1613 current or former sites identified in the EPA National Priorities List (ATSDR, 2002). In Germany, more than 1400 sites contaminated with coal tar have been identified (Blum et al., 2011). The United States Geological Survey extensively studied the fate of quinoline in two such creosote-contaminated sites in the USA: one in Pensacola, Florida (Bennett et al., 1985) and the other in St Louis Park, Minnesota (Rostad et al., 1985). In both cases the plants were operating for more than five decades, contaminating the groundwater and local aquifers.

In a wood-preserving facility occupying 18 acres within the city limits of Pensacola, Florida from 1902 to 1981, creosote and pentachlorophenol were solubilized with diesel and used to treat utility poles and lumber (Pereira et al., 1987). Wastes were discharged into two unlined surface impoundments in hydraulic connection with the sand and gravel aquifer (Pereira et al., 1987). A groundwater sample collected within the site, drawn from a depth of 6 m, indicated a concentration of 288 µg/L for quinoline and 5818 µg/L for the oxygenated derivative 2(1*H*)-quinolinone (Pereira et al., 1987). Ondrus & Steinheimer (1990) reported a quinoline concentration of 11.2 mg/L and a corresponding 2-hydroxyquinoline concentration of 42 mg/L in a single groundwater sample from the Pensacola site. The concentrations of isoquinoline and 1-hydroxyisoquinoline were 1.8 mg/L and 6.9 mg/L, respectively, suggesting microbial degradation.

The operation of a coal tar distillation and wood-preserving facility in St Louis Park, Minnesota from 1918 to 1972 resulted in extensive groundwater contamination and led to the closure of eight municipal wells in the vicinity; quinoline was qualitatively identified with 49 other compounds in the aqueous phase of a groundwater sample (Pereira et al., 1983). Azaarenes of high molecular weight were identified among 22 compounds in the oily tar phase of the groundwater sample (Pereira et al., 1983). Rostad et al. (1985) performed additional analysis on the St Louis Park groundwater, identifying 111 PAHs and determining octanol/water partition coefficients for a set of PAHs and N-/S-/O-heteroaromatic compounds including quinoline.

A groundwater sample from an active municipal well nearly 1 mile from the former site of the St Louis Park creosote plant yielded quinoline and 1-hydroxyisoquinoline concentrations of less than 15 ng/L; concentrations of isoquinoline and 2-hydroxyquinoline were measured at less than 70 ng/L and less than 10 ng/L, respectively (Ondrus & Steinheimer, 1990).

Adams & Giam (1984) identified 31 azaarenes in the wastewater collected from an onsite storage pond where creosote–pentachlorophenol was applied as a wood preservative in central Texas, USA. The quinoline concentration of 260 mg/L represented a sizeable fraction of the total azaarene concentration of 1300 mg/L (Adams & Giam, 1984).

Quinoline is associated with urban pollution and has been detected in urban rainwater. Concentrations of 1–4 µg/L were reported for quinoline, isoquinoline, and their substituted compounds combined for three rainwater samples collected in Los Angeles, USA during 1981–1982 (Kawamura & Kaplan, 1983).

Quinoline, methylquinolines, benzoquinoline, and methylbenzoquinolines were qualitatively identified in a sample taken from the River Waal at Brakel, Germany (Meijers & Van der Leer, 1976).

An EPA analysis of the FracFocus Chemical Disclosure Registry 1.0 indicated that quinoline was reported in 0.02% of chemical disclosures in 20 states in which hydraulic fracturing was conducted between 1 January 2011 and 28 February 2013 (Yost et al., 2017).

(b) Sediment and soil

Less than 5% of the sediment samples collected from 443 sites in 19 major United States river basins during 1992–1995 tested positive for quinoline (Lopes et al., 1997).

Analysis of the water-soluble fraction of creosote-contaminated sediment obtained from a Superfund site located on the Elizabeth River in Virginia, USA revealed the presence of naphthalene and other PAHs, but an absence of quinoline and isoquinoline (Padma et al., 1998). The authors attributed the absence of quinoline to its water solubility or microbial degradation.

Furlong & Carpenter (1982) confirmed the presence of quinoline in marine sediments of Puget Sound, north-west Washington, USA. Of the 39 sediment samples collected at six different

Puget Sound sites, quinoline was detected in 75% at a range of 160–6600 ng/g organic carbon. Quinoline was detected in all three samples from nearby Lake Washington at a concentration of 120–1300 ng/g organic carbon. Furlong & Carpenter (1982) attributed quinoline and other two- and three-ring azaarenes in the surface sediments of Puget Sound to air particulate matter arising from petroleum combustion (Furlong & Carpenter, 1982).

(c) Air

Chuang et al. (1991) measured the indoor air levels of PAHs in eight homes in Columbus, Ohio, USA during the winter of 1986/1987. Average 8-hour indoor concentrations of quinoline within the range 10–26 μg/m^3 were measured in homes occupied by non-smokers and 93–560 μg/m^3 in the homes of smokers (Chuang et al., 1991). The average outdoor concentration of these residences, in areas characterized as devoid of apparent contamination sources and low in traffic, was 3.3 μg/m^3 (range, 0.78–5.5 μg/m^3) (Chuang et al., 1991).

Quinoline was measured in two particulate matter samples collected in the urban air above New York City with high-volume samplers (Dong et al., 1977). Quinoline was found at concentrations of 69 and 22 ng per 1000 m^3, isoquinoline at 180 and 140 ng per 1000 m^3, and several alkyl derivatives of quinoline.

A low Henry Law constant is an indication of insignificant volatilization of quinoline from surface waters (EPA, 2001). Air samples collected from a pilot-scale shale oil wastewater treatment facility at the Logan Wash site, Colorado, USA in 1982 contained quinoline at 6 μg/m^3 in indoor air and 1 μg/m^3 in outdoor air (Hawthorne & Sievers, 1984). Concentrations below the LOD (0.05 μg/m^3) were measured in the rural air of an undeveloped region of the shale oil region and in the urban air of Boulder, Colorado, USA.

Quinoline emissions in the USA reported to the EPA decreased from 9.9 tonnes in 2000 (18 industry submissions) to 0.27 tonnes in 2015 (10 industry submissions) (EPA, 2015).

(d) Tobacco

Indoor concentrations of quinoline and isoquinoline were found to correlate closely with nicotine, and may serve as markers of indoor levels of environmental tobacco smoke (Chuang et al., 1991). The estimated correlation coefficients between quinoline and nicotine and between isoquinoline and nicotine were 0.96 ($P = 0.0001$) and 0.97 ($P = 0.0001$), respectively (Chuang et al., 1991).

1.4.2 Exposure of the general population

The general population may be exposed to quinoline by the inhalation of cigarette smoke or environmental tobacco smoke, or from particulate matter in urban air. Quinoline and isoquinoline are found in tobacco smoke, but not tobacco leaf (Stedman, 1968). Quinoline has been quantified in cigarette mainstream smoke at 0.17–1.30 μg per cigarette by Adams et al. (1983), at 0.19 μg per cigarette by White et al. (1990), and at 0.23–0.30 μg per cigarette by Chen & Moldoveanu (2003). Relative to non-filtered cigarettes, filters were found to reduce quinoline in smoke by 36–50% with a similar reduction in tar of 28–63% (Adams et al., 1983).

The potential for skin exposure exists from clothing containing dyes based on quinoline and for oral exposure through food colorants based on quinoline. Quinoline is used in the dyeing process of textiles (Lam et al., 2012), and the presence of quinoline and quinoline derivatives has been confirmed in clothing items (Luongo et al., 2014, 2016a,b; Antal et al., 2016). Luongo et al. (2014) detected quinoline and 10 quinoline derivatives in 31 textile samples purchased between 2011 and 2012 from different shops in Stockholm, Sweden. Quinoline was detected in all garments made of polyester at concentrations in the range 26–16 700 ng/g with a mean

concentration of 4700 ng/g, 600 times quinoline concentrations in cotton garments. In a subsequent study, the average washout of quinoline from clothing textiles was determined to be about 20% after the items had been washed 10 times (Luongo et al., 2016b). [This suggests a potential for skin exposure from clothing containing dyes based on quinoline. Furthermore, because dyes based on quinoline may have mutual food and textile usage (i.e. Quinoline Yellow), the potential for oral exposure through food colorants based on quinoline cannot be ruled out.]

Groundwater contamination may pose an additional risk of exposure to quinoline for populations accessing aquifers proximate to creosote wood preservation sites (Bennett et al., 1985; Pereira et al., 1987; Thomsen et al., 1999; Zhang et al., 2010).

1.4.3 Occupational exposure

The most probable route of occupational exposure to quinoline is by inhalation of particulates or vapours from the processing of petroleum, the processing and production of shale oil, or the use of coal-derived products (Gammage, 1983). There is also potential for exposure to quinoline in industries where quinoline is used as a solvent or chemical intermediate; however, no relevant occupational data were available to the Working Group. A Finnish study of workers involved in railway repair and construction found that the handling of wood impregnated with creosote resulted in the exposure of workers to quinoline at concentrations of less than 0.1 mg/m^3 (18 workers), and that the assembly of switch elements resulted in exposure to concentrations of less than 0.2 mg/m^3 (8 workers) (Heikkilä et al., 1987).

1.5 Regulations and guidelines

The American Industrial Hygiene Association set a 2011 Workplace Environmental Exposure Level for quinoline of 0.001 ppm (8-hour time-weighted average) with a "skin" notation, indicating that quinoline may be absorbed in toxicologically significant amounts through the skin (American Industrial Hygiene Association, 2013). The GESTIS database of International Limit Values for 30 countries, including various European Union Member States, specified a quinoline 8-hour time-weighted average of occupational limit for only one country (Latvia, 0.1 mg/m^3) (IFA 2017).

2. Cancer in Humans

No data on the carcinogenicity of quinoline in humans were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1.

3.1 Mouse

3.1.1 Oral administration

(a) Feeding

Two groups of 40 male and 40 female ddY mice (age, 8 weeks) were given 0.2% quinoline [purity not reported] in commercial basal diet for 30 weeks (Shinohara et al., 1977). There were no untreated controls. One half of the number of males and females died of pneumonia within the first 6 weeks of the experiment. Only 10 males and 10 females survived after 30 weeks, and data were presented from these animals. The body weights of both male and female mice decreased during the experiment, but it was not reported

Table 3.1 Studies of carcinogenicity in experimental animals exposed to quinoline

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, Crj: BDF_1 (M) 6 wk 55–65 wk Matsumoto et al. (2018)	Drinking-water Quinoline, > 99.6% Deionized water 0, 150, 300, 600 ppm ad libitum 50, 50, 50, 50 46 (at 65 wk), 15 (at 65 wk), 0 (at 65 wk), 0 (at 55 wk)	*Liver* Hepatocellular carcinoma 0/50*, 4/50, 0/50, 1/50 Histiocytic sarcoma 0/50*, 0/50, 3/50, 1/50 Haemangiosarcoma 0/50*, 2/50, 1/50, 12/50** *Subcutis* Haemangioma 0/50, 0/50, 1/50, 0/50 Haemangiosarcoma 0/50*, 2/50, 2/50, 3/50 *Retroperitoneum* Haemangioma 0/50*, 0/50, 0/50, 3/50 Haemangiosarcoma 0/50*, 35/50**, 38/50**, 35/50** *Mesenterium* Haemangioma 0/50, 1/50, 1/50, 2/50 Haemangiosarcoma 0/50*, 19/50**, 22/50**, 16/50**	 *$P < 0.01$ (Peto trend test) *$P < 0.01$ (Peto trend test) *$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test) NS *$P < 0.01$ (Peto trend test) *$P < 0.01$ (Peto trend test) *$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test) NS *$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	Principal strengths: studies in both males and females; data obtained from all treated animals; extensive histopathology; GLP study

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Matsumoto et al. (2018) (cont.)		*Mediastinum*: haemangiosarcoma 0/50, 2/50, 0/50, 1/50 *Peritoneum*: haemangiosarcoma 0/50, 0/50, 0/50, 1/50 *All organs* Haemangioma 1/50*, 2/50, 3/50, 7/50** Haemangiosarcoma 0/50*, 43/50**, 47/50**, 43/50** Haemangioma or haemangiosarcoma (combined) 1/50*, 44/50**, 47/50**, 46/50**	NS NS *$P < 0.01$ (Peto trend test), **$P < 0.05$ (Fisher exact test) *$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test) *$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	
Full carcinogenicity Mouse, Crj: BDF_1 (F) 6 wk 44–50 wk Matsumoto et al. (2018)	Drinking-water Quinoline, > 99.6% Deionized water 0, 150, 300, 600 ppm ad libitum 50, 50, 50, 50 49 (at 50 wk), 20 (at 50 wk), 6 (at 50 wk), 0 (at 44 wk)	*Liver* Hepatocellular adenoma 0/50, 0/50, 2/50, 1/50 Histiocytic sarcoma 0/50*, 2/50, 6/50**, 4/50 Haemangioma 0/50*, 1/50, 2/50, 5/50** Haemangiosarcoma 0/50, 0/50, 0/50, 2/50 *Subcutis* Haemangioma 0/50*, 0/50, 7/50**, 15/50** Haemangiosarcoma 0/50*, 4/50, 15/50**, 33/50**	NS *$P < 0.01$ (Peto trend test), **$P < 0.05$ (Fisher exact test) *$P < 0.01$ (Peto trend test), **$P < 0.05$ (Fisher exact test) NS *$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test) *$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	Principal strengths: studies in both males and females; data obtained from all treated animals; extensive histopathology; GLP study

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Matsumoto et al. (2018) (cont.)		*Ovary*: haemangiosarcoma 0/50*, 1/50, 4/50, 1/50 *Retroperitoneum* Haemangioma 0/50*, 5/50**, 1/50, 1/50 Haemangiosarcoma 0/50*, 27/50**, 36/50**, 32/50** *Mesenterium* Haemangioma 0/50, 2/50, 2/50, 2/50 Haemangiosarcoma 0/50*, 18/50**, 18/50**, 11/50** *Mediastinum* Haemangioma 0/50, 0/50, 0/50, 1/50 Haemangiosarcoma 0/50*, 2/50, 3/50, 1/50 *Peritoneum* Haemangioma 0/50*, 2/50, 6/50**, 2/50 Haemangiosarcoma 0/50*, 3/50, 6/50**, 15/50*** *All organs* Haemangioma 1/50*, 9/50**, 16/50**, 24/50**	*P < 0.01 (Peto trend test) *P < 0.05 (Peto trend test), **P < 0.05 (Fisher exact test) *P < 0.01 (Peto trend test), **P < 0.01 (Fisher exact test) NS *P < 0.01 (Peto trend test), **P < 0.01 (Fisher exact test) NS *P < 0.01 (Peto trend test) *P < 0.01 (Peto trend test), **P < 0.05 (Fisher exact test) *P < 0.01 (Peto trend test), **P < 0.05 (Fisher exact test), ***P < 0.01 (Fisher exact test) *P < 0.01 (Peto trend test), **P < 0.01 (Fisher exact test)	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Matsumoto et al. (2018) (cont.)		Haemangiosarcoma 0/50*, 43/50**, 48/50**, 49/50**	*$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	
		Haemangioma or haemangiosarcoma (combined) 1/50*, 45/50**, 48/50**, 50/50**	*$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	
Full carcinogenicity Mouse, CD-1 (M) Newborn 52 wk LaVoie et al. (1987)	Intraperitoneal injection Quinoline, > 99% pure DMSO 0 (control), 1.75 µmol total dose 5, 10, and 20 µL of either DMSO (control) or a 0.05 mol/L solution of quinoline in DMSO on days 1, 8, and 15 of life, respectively 35, 41 17 (at 35 wk), 17 (at 35 wk)	*Liver* [Hepatocellular] adenoma 0/17, 4/17	NS	Principal strengths: studies in both males and females Principal limitations: use of single dose; no body-weight data; no discussion of clinical signs; statistical test not specified Number of animals at start = M+F combined
		Total tumours: 0, 15		
		Hepatoma [hepatocellular carcinoma] 1/17, 8/17*	*$P < 0.01$	
		Total tumours: 1, 37		
		Hepatic tumours [hepatocellular tumours] 1/17, 12/17*	*$P < 0.005$	
		Haematopoietic and lymphoid tissues: lymphoma or leukaemia (combined) 1/17, 1/17	NS	
Full carcinogenicity Mouse, CD-1 (F) Newborn 52 wk LaVoie et al. (1987)	Intraperitoneal injection Quinoline, > 99% pure DMSO 0 (control), 1.75 µmol total dose 5, 10, and 20 µL of either DMSO (control) or a 0.05 mol/L solution of quinoline in DMSO on days 1, 8, and 15 of life, respectively 35, 41 18 (at 35 wk), 10 (at 35 wk)	*Liver* [Hepatocellular] adenoma 0/18, 1/10	NS	Principal strengths: studies in both males and females Principal limitations: use of single dose; no body-weight data; no discussion of clinical signs; statistical test not specified Number of animals at start = M+F combined
		Total tumours: 0, 1		
		Hepatoma [hepatocellular carcinoma] 0/18, 0/10	NS	
		Haematopoietic and lymphoid tissues: lymphoma or leukaemia (combined) 0/18, 4/10*	*$P < 0.05$	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, CD-1 (M) Newborn 52 wk LaVoie et al. (1988)	Intraperitoneal injection Quinoline, > 99% pure DMSO 0 (control), 1.75 µmol total dose 5, 10, and 20 µL of either DMSO (control) or a 0.05 mol/L solution of quinoline in DMSO on days 1, 8, and 15 of life, respectively 46, 56 21 (at 6 mo), 19 (at 6 mo)	*Liver* [Hepatocellular] adenoma 0/21, 13/19* Hepatoma [hepatocellular carcinoma] 0/21, 2/19	*[$P < 0.0001$] NS; when hepatocellular adenomas and carcinomas are combined, the overall incidence of hepatocellular tumours (15/19) is significantly increased ($P < 0.05$, χ^2 test)	Principal strengths: studies in both males and females Principal limitations: use of single dose; no body-weight data; no discussion of clinical signs Repeat of the earlier study of LaVoie et al. (1987). Quinoline treatment produced a significant increase in the incidence of hepatocellular tumours in male mice only. In contrast to the 1987 study, there was a higher proportion of quinoline-induced hepatocellular adenomas than carcinomas in these mice. Number of animals at start = M+F combined
Full carcinogenicity Mouse, CD-1 (F) Newborn 52 wk LaVoie et al. (1988)	Intraperitoneal injection Quinoline, > 99% pure DMSO 0 (control), 1.75 µmol total dose 5, 10, and 20 µL of either DMSO (control) or a 0.05 mol/L solution of quinoline in DMSO on days 1, 8, and 15 of life, respectively 46, 56 21 (at 6 mo), 27 (at 6 mo)	*Liver* [Hepatocellular] adenoma 0/21, 0/27 Hepatoma [hepatocellular carcinoma] 0/21, 0/27	NS NS	Principal strengths: studies in both males and females Principal limitations: use of single dose; no body-weight data; no discussion of clinical signs Repeat of the earlier study of LaVoie et al. (1987). No liver tumours were detected in quinoline-treated female mice; 3 mice with lung tumours and 5 mice with lymphomas or leukaemias in the 27 surviving treated female mice, but these results were not significant. Number of animals at start = M+F combined

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Full carcinogenicity Mouse, CD-1 (M) Newborn 52 wk Weyand et al. (1993)	Intraperitoneal injection Quinoline, > 98% pure DMSO 0 (control), 1.75 µmol total dose 5, 10, and 20 µL of either DMSO (control) or a 50 mmol/L solution of quinoline in DMSO on days 1, 8, and 15 of life, respectively 97, 85 38 (at 2 mo), 33 (at 2 mo)	*Liver* [Hepatocellular] adenoma 0/38, 15/33 (45%)* [Hepatocellular] carcinoma 0/38, 1/33 (3%)	*[$P < 0.0001$, Fisher exact test] NS	Principal strengths: both sexes used Principal limitations: no body-weight data Number of animals at start = M+F combined
Full carcinogenicity Mouse, CD-1(F) Newborn 52 wk Weyand et al. (1993)	Intraperitoneal injection Quinoline, > 98% pure DMSO 0 (control), 1.75 µmol total dose 5, 10, and 20 µL of either DMSO (control) or a 50 mmol/L solution of quinoline in DMSO on days 1, 8, and 15 of life, respectively 97, 85 46 (at 2 mo), 37 (at 2 mo)	*Liver* [Hepatocellular] adenoma 0/46, 0/37 [Hepatocellular] carcinoma 0/46, 0/37	NS NS	Principal strengths: both sexes used Principal limitations: no body-weight data Number of animals at start = M+F combined

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Initiation–promotion (tested as initiator) Mouse, SENCAR (F) 50–55 d 22 wk (initiation + TPA treatment) LaVoie et al. (1984)	Skin application Quinoline, > 99.8% pure Acetone 0 (control), 7.5 mg total dose 0 (control) or 0.75% in 0.1 mL acetone applied to skin in 10 doses (every other day) 40, 40 NR, NR	*Skin*: tumours (macroscopic examination) 3/39 (7.5%), 21/40 (53%)* Tumour multiplicity: 0.08, 0.73 Total tumours: 3, 29	*$P < 0.01$, χ^2 test NR NR	Principal limitations: only one dose group; no histopathological examination Initiation–promotion study with quinoline being tested as an initiator (for 20 days) followed (after 10 days) by promotion with 2.0 µg TPA (2×/wk for 18 wk); for comparison, quinoline at 7.5 mg total dose produced 0.73 skin tumours per mouse and benzo[*a*] pyrene at 0.03 mg total dose produced 2.1 skin tumours per mouse
Full carcinogenicity Rat, Sprague-Dawley (M) NR 40 wk Hirao et al. (1976)	Oral administration Quinoline, > 99.8% pure Diet 0, 0.05, 0.1, 0.25% of diet 6, 20, 20, 20 6, 11 (at 16 wk), 16 (at 16 wk), 19 (at 16 wk)	*Liver* Haemangioendothelioma [haemangiosarcoma] 0/6, 6/11 (54%)*, 12/16 (75%)**, 18/19 (95%)*** Nodular hyperplasia 0/6, 6/11 (54%)*, 4/16 (25%), 0/19 (0%) Hepatocellular carcinoma 0/6, 3/11 (27%), 3/16 (19%), 0/19	*[$P < 0.05$, Fisher exact test], **[$P < 0.005$], ***[$P < 0.0001$] *[$P < 0.05$, Fisher exact test] [NS]	Principal strengths: multiple dose study Principal limitations: no statistics reported in the article; dose selection criteria not given; data not taken from all animals; poor survival in high- and medium-dose animals
Carcinogenicity with other modifying factor Rat, Sprague-Dawley (M) 8 wk 30 wk Shinohara et al. (1977)	Oral administration Quinoline, NR Diet 0, 0.075% of diet NR 10 (at 26 wk), 20 (at 26 wk)	*Liver* Hepatocellular carcinoma 0/10, 0/20 Haemangioendothelioma [haemangiosarcoma] 0/10, 6/20 (30%)	NS [NS]	Principal limitations: only one dose group; short duration of exposure; limited experimental details; only one sex used; number of animals at start unspecified

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Full carcinogenicity Rat, Wistar (M) 7 wk up to 20 wk Hasegawa et al. (1989)	Oral administration Quinoline, NR Diet 0 (20 wk, control), 0.25 (12 wk exposure), 0.25 (12 wk exposure + 4 wk), 0.25 (12 wk exposure + 8 wk), 0.25 (16 wk exposure), 0.25 (16 wk exposure + 4 wk), 0.25 (20 wk exposure) % of diet NR 12, 11, 12, 12, 14, 18, 16	Liver: haemangioendothelioma [haemangiosarcoma] 0/12, 1/11 [9%], 2/12 (17%), 5/12 (42%)*, 4/14 (29%)*, 4/18 (22%), 5/16 (31%)*	*$P < 0.05$ (Fisher exact test)	Principal limitations: only one sex was used; only one time-matched control group; number of animals at start unspecified
Full carcinogenicity Rat, SHR (M) 5 wk 32 wk Futakuchi et al. (1996)	Oral administration Quinoline, NR Powdered diet 0, 0.2% of diet 10, 16 9, 15	*Liver* Haemangioendothelial sarcoma [haemangiosarcoma] 0/9, 1/15 (7%) Hyperplastic nodules 0/9, 3/15 (20%)	NS NS	Principal strengths: chemical intake measured Principal limitations: only one dose group; only one sex used; short duration
Full carcinogenicity Rat, WKY (M) 5 wk 32 wk Futakuchi et al. (1996)	Oral administration Quinoline, NR Powdered diet 0, 0.2% of diet 10, 16 10, 8	*Liver* Haemangioendothelial sarcoma [haemangiosarcoma] 0/10, 14/15 (93%)* Hyperplastic nodules 0/10, 3/15 (20%)	*$P < 0.001$, Fisher exact test NS	Principal strengths: chemical intake measured Principal limitations: only one dose group; only one sex used; short duration
Full carcinogenicity Rat, F344/DuCrj (M) 6 wk 76–96 wk Matsumoto et al. (2018)	Drinking-water Quinoline, > 99.6% Deionized water 0, 200, 400, 800 ppm ad libitum 50, 50, 50, 50 49 (at 96 wk), 19 (at 96 wk), 0 (at 95 wk), 0 (at 76 wk)	*Liver* Hepatocellular adenoma 1/50*, 10/50**, 10/50**, 9/50** Hepatocellular carcinoma 0/50*, 22/50**, 24/50**, 18/50**	*$P < 0.05$ (Peto trend test), **$P < 0.01$ (Fisher exact test) *$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	Principal strengths: studies in both males and females; data obtained from all treated animals; extensive histopathology; GLP study

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Matsumoto et al. (2018) (cont.)		Hepatocellular adenoma or carcinoma (combined) 1/50*, 31/50**, 29/50**, 23/50**	*$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	
		Haemangiosarcoma 0/50*, 25/50**, 34/50**, 43/50**	*$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	
		Nasal cavity Haemangioma 0/50, 0/50, 1/50, 0/50	NS	
		Sarcoma (NOS) 0/50*, 1/50, 5/50**, 1/50	*$P < 0.01$ (Peto trend test), **$P < 0.05$ (Fisher exact test)	
		Esthesioneuroepithelioma 0/50*, 0/50, 1/50, 6/50**	*$P < 0.01$ (Peto trend test), **$P < 0.05$ (Fisher exact test)	
		Lung Haemangiosarcoma 0/50, 0/50, 2/50, 1/50	NS	
		Adenosquamous carcinoma 0/50, 0/50, 1/50, 0/50	NS	
		Mediastinum: sarcoma (NOS) 0/50*, 1/50, 2/50, 3/50	*$P < 0.01$ (Peto trend test)	
		Mesenterium: haemangiosarcoma 0/50*, 0/50, 2/50, 2/50	*$P < 0.05$ (Peto trend test)	
		Peritoneum: haemangiosarcoma 0/50*, 0/50, 0/50, 1/50	NS	
		Adipose tissue: haemangiosarcoma 0/50*, 2/50, 0/50, 3/50	*$P < 0.01$ (Peto trend test)	
		All organs: haemangiosarcoma 0/50*, 26/50**, 36/50**, 45/50**	*$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Full carcinogenicity Rat, F344/DuCrj (F) 6 wk 88–104 wk Matsumoto et al. (2018)	Drinking-water Quinoline, > 99.6% Deionized water 0, 150, 300, 600 ppm ad libitum 50, 50, 50, 50 41 (at 104 wk), 17 (at 104 wk), 2 (at 104 wk), 0 (at 88 wk)	*Liver* Hepatocellular adenoma 1/50*, 30/50**, 31/50**, 33/50**	*$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	Principal strengths: studies in both males and females; data obtained from all treated animals; extensive histopathology; GLP study
		Hepatocellular carcinoma 0/50*, 5/50**, 16/50***, 21/50***	*$P < 0.01$ (Peto trend test), **$P < 0.05$ (Fisher exact test), ***$P < 0.01$ (Fisher exact test)	
		Hepatocellular adenoma or carcinoma (combined) 1/50*, 32/50**, 38/50**, 42/50**	*$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	
		Haemangiosarcoma 0/50*, 15/50**, 27/50**, 41/50**	*$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	
		Nasal cavity: sarcoma (NOS) 0/50, 0/50, 1/50, 1/50	NS	
		Lung: haemangiosarcoma 0/50, 2/50, 0/50, 0/50	NS	
		Ovary: haemangioma 0/50, 1/50, 0/50, 0/50	NS	
		Retroperitoneum: haemangiosarcoma 0/50, 0/50, 0/50, 1/50	NS	
		Peritoneum: haemangiosarcoma 0/50, 0/50, 1/50, 0/50	NS	
		Adipose tissue: haemangiosarcoma 0/50, 0/50, 2/50, 0/50	NS	
		All organs: haemangiosarcoma 0/50*, 17/50**, 28/50**, 42/50**	*$P < 0.01$ (Peto trend test), **$P < 0.01$ (Fisher exact test)	

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence and/or multiplicity of tumours	Significance	Comments
Full carcinogenicity Rat, Sprague-Dawley (M) Newborn 78 wk LaVoie et al. (1988)	Subcutaneous injection Quinoline, > 99% pure DMSO DMSO at 500 µL/kg bw 1×/wk for 8 wk (control), or quinoline at 200 µmol/kg bw at wk 1, at 100 µmol/kg bw at wk 2–7, and 200 µmol/kg bw at wk 8 50, 101 27, 25	*Liver* [Hepatocellular] adenoma 3/27, 1/25 Hepatoma [hepatocellular carcinoma] 2/27, 0/25	NS NS	Principal strengths: studies in both males and females Principal limitations: high mortality after the initial dose; no body-weight data; only one variable dose group This study could have been compromised significantly by the high mortality rate following the initial injection of 200 µmol/kg bw of quinoline. Only 41 of the 101 pups survived, resulting in 59% mortality. In the surviving rats, carcinogenicity could have been reduced by the significant toxicity; no weight data were given to provide an assessment of toxicity in treated versus control animals during the study. Number of animals at start = M+F combined
Full carcinogenicity Rat, Sprague-Dawley (F) Newborn 78 wk LaVoie et al. (1988)	Subcutaneous injection Quinoline, > 99% pure DMSO DMSO at 500 µL/kg bw 1×/wk for 8 wk (control), or quinoline at 200 µmol/kg bw at wk 1, at 100 µmol/kg bw at wk 2–7, and 200 µmol/kg bw at wk 8 50, 101 22, 15	*Liver* [Hepatocellular] adenoma 1/22, 0/15 Hepatoma [hepatocellular carcinoma] 0/22, 0/15	NS NS	Principal strengths: studies in both males and females Principal limitations: high mortality after the initial dose; no body-weight data; only one variable dose group This study could have been compromised significantly by the high mortality rate following the initial injection of 200 µmol/kg bw of quinoline. Only 41 of the 101 pups survived, resulting in 59% mortality. In the surviving rats, carcinogenicity could have been reduced by the significant toxicity; no weight data were given to provide an assessment of toxicity in treated versus control animals during the study. Number of animals at start = M+F combined

bw, body weight; d, day(s); DMSO, dimethyl sulfoxide; F, female; GLP, good laboratory practice; M, male; mo, month(s); NOS, not otherwise specified; NR, not reported; NS, not significant; ppm, parts per million; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; wk, week(s)

whether these weight losses were significant. The liver weight as a percentage of the body weight increased in mice of both sexes due to tumour development and/or swelling of the liver. Grossly, the livers of mice had multiple small and large nodules measuring up to 1.0 cm in diameter. Some tumorous nodules showed focal haemorrhagic change, but metastasis to other organs from liver tumours was not observed. The 10 surviving mice per sex were examined for changes to their livers; there were 8 male mice with haemangioendotheliomas [haemangiosarcomas] (80%) and 1 with hepatocellular carcinoma (10%), and there were 8 female mice with haemangioendotheliomas [haemangiosarcomas] (80%). [The Working Group noted that the principal limitations of the study included the use of a single dose, the short duration of exposure, the poor survival due to pneumonia, and the lack of controls. Although the occurrence of haemangiosarcomas in both male and female mice was 80%, the significance of this finding could not be determined due to the lack of controls. The Working Group concluded that this study was inadequate for the evaluation of the carcinogenicity of quinoline in experimental animals.]

(b) Drinking-water

In a good laboratory practice (GLP) study, four groups of 50 male and 50 female Crj:BDF_1 mice (SPF) (age, 6 weeks) were given quinoline (purity, > 99.6%) at 0, 150, 300, or 600 ppm in deionized water for varying periods of time (Matsumoto et al., 2018). Body weight and the consumption of food and water were measured once per week for the first 14 weeks of the administration period, and every 2 weeks thereafter.

The initial design was to expose mice to quinoline in their drinking-water for up to 104 weeks; however, dose-related decreases in survival occurred, necessitating the early termination of the experiment. All mice were observed daily for clinical signs and mortality, and animals found moribund were killed and their organs removed, weighed, and examined for macroscopic lesions at necropsy. All organs and tissues, including the entire respiratory tract, were examined for histopathology.

All male mice exposed to quinoline at 300 and 600 ppm were dead by the end of weeks 65 and 55, respectively, and there were only 15 surviving mice (30%) in the group exposed at 150 ppm; this group was terminated at week 65. The survival rate of the control males at week 65 was 92% (46/50). All female mice exposed to quinoline at 600 ppm were dead by the end of week 44, and there were only 6 surviving mice (12%) in the group exposed at 300 ppm; this group was terminated at week 50. The survival rates of the female controls and group exposed at 150 ppm at week 50 were 98% (49/50) and 40% (20/50), respectively. The decreased survival in treated males and females was attributed to deaths due to haemangiomas or haemangiosarcomas of the retroperitoneum, mesenterium, or subcutis. The earliest malignant tumour deaths were observed at weeks 36, 40, and 32 in the males and at weeks 33, 28, and 27 in the females exposed at 150, 300, and 600 ppm, respectively. The growth rates of all exposed males and the females exposed at 600 ppm were generally less than those of the controls throughout the study period.

The incidences of haemangiosarcoma and haemangioma were increased in exposed male mice, whereas no haemangiosarcomas and only one haemangioma (of the liver) were observed in 50 male controls. Quinoline significantly increased the incidence of haemangiosarcoma, in the liver of mice exposed at 600 ppm as well as in the retroperitoneum and in the mesenterium of mice exposed at all dose levels. In addition, in all organs combined, quinoline significantly increased the incidence of haemangioma in mice exposed at 600 ppm. Further, significant increases in the incidence of haemangiosarcoma and of haemangioma or haemangiosarcoma (combined) were seen in all organs combined at all dose levels. There was also a significant positive

trend in the incidences of hepatocellular carcinoma, liver histiocytic sarcoma, retroperitoneum haemangioma, and subcutis haemangiosarcoma.

In female mice, no haemangiosarcomas and only one haemangioma (of the ovary) were observed in 50 female controls. Quinoline significantly increased the incidence of histiocytic sarcoma in the liver (at 300 ppm), and of haemangioma in the liver of (at 600 ppm). The compound significantly increased the incidence of subcutis haemangioma and of subcutis haemangiosarcoma in mice exposed at 300 and 600 ppm. Quinoline also significantly increased the incidence of haemangioma in the retroperitoneum of mice exposed at 150 ppm, and of haemangiosarcoma in the retroperitoneum and of haemangiosarcoma in the mesenterium at all dose levels. In the peritoneum, quinoline significantly increased the incidence of haemangioma in mice exposed at 300 ppm, and of haemangiosarcoma in mice exposed at 300 and 600 ppm. For all organs combined, quinoline significantly increased the incidence of haemangioma, of haemangiosarcoma, and of haemangioma or haemangiosarcoma (combined) at all dose levels. There was also a significant positive trend in the incidences of ovary haemangiosarcoma and mediastinum haemangiosarcoma.

[The Working Group noted the early onset of rare tumours of various embryological origins at the lowest dose tested and the very poor survival due to tumour induction. The Working Group also noted that the principal strengths of this GLP study included: the use of both males and females, the use of multiple dose levels, the accurate determination of compound exposure, the reporting of body weight and survival data, the fact that results were obtained from all treated animals, and the extensive histopathological examination of all organs.]

3.1.2 Intraperitoneal injection

Groups of 41 male and 41 female CD-1 mouse pups were given intraperitoneal injections of quinoline (purity, > 99%) in dimethyl sulfoxide (DMSO) (LaVoie et al., 1987). Each pup was given 5, 10, and 20 µL of either DMSO (control) or of a 0.05 mol/L solution of quinoline on days 1, 8, and 15 of life, respectively. Each mouse received a total amount of 1.75 µmol of quinoline. Five of the mice given quinoline were killed at age 35 weeks, and there was no evidence of any lesions in these mice. The remaining mice exposed to quinoline and the DMSO controls were killed at age 52 weeks. A total of 27 (17 males and 10 females) of the 41 mice exposed to quinoline and all 35 (17 males and 18 females) of the mice given DMSO survived at 52 weeks. In the 17 male mice given quinoline, there were 4 mice with hepatic [hepatocellular] adenomas and 8 ($P < 0.01$) mice with hepatomas [considered by the Working Group to be hepatocellular carcinomas]. The incidence of hepatic tumours [hepatocellular tumours] (12/17, 71%) was significantly increased ($P < 0.005$) in male mice compared with controls. The tumour response in the 10 female mice given quinoline included 4 ($P < 0.05$) mice with lymphoma. There was 1 hepatoma [hepatocellular carcinoma] in the 17 male mice and no tumours in the 18 female mice treated with DMSO. [The Working Group noted the principal strength of the study was that both male and female mice were used. The principal limitations included the use of a single dose, the absence of body-weight data, the lack of a discussion of clinical signs, and the unspecified statistical test.]

In a second study in newborn CD-1 mice (LaVoie et al., 1988), 56 male and 56 female pups were given intraperitoneal injections of quinoline (purity, > 99%) in DMSO. Each pup was given 5, 10, and 20 µL of either DMSO (control) or of a 0.05 mol/L solution of quinoline on days 1, 8, and 15 of life, respectively. Each mouse was

given a total amount of 1.75 µmol of quinoline. The highest mortality was observed among the pups given quinoline, of which 18% had died by the third week of life. A total of 46 (19 males and 27 females) of the 56 mice given quinoline and 42 (21 males and 21 females) of the 46 mice given DMSO survived at 52 weeks, at which point they were killed. In the 19 male mice given quinoline, there were 13 mice with hepatic [hepatocellular] adenomas [$P < 0.0001$], 2 mice with hepatomas [hepatocellular carcinomas], and 1 with a lymphoma or leukaemia. The incidence of hepatic [hepatocellular] tumours in male mice (15/19, 79%) was significantly increased ($P < 0.05$) compared with controls. The tumour incidence in the 27 female mice given quinoline included 3 mice with lung tumours and 5 with lymphomas or leukaemias. In the 21 mice of each sex treated with DMSO, there was 1 lymphoma or leukaemia in females and 4 males with liver tumours (the types of liver tumours were not indicated, but they were not identified as liver adenomas or hepatomas). [The Working Group noted the principal strength of the study was that both male and female mice were used. However, the study was limited by the use of a single dose, the absence of body-weight data, and the lack of a discussion of clinical signs.]

In a third study (Weyand et al., 1993), 85 male and 85 female CD-1 mouse pups were given intraperitoneal injections of quinoline (purity, > 98%) in DMSO. Each pup received 5, 10, and 20 µL of a 50 mmol/L solution of quinoline in DMSO on days 1, 8, and 15, respectively. Each mouse was given a total of 1.75 µmol of quinoline. Negative control groups (97 males, 97 females) were given DMSO alone on days 1, 8, and 15 of life. A total of 70 (33 males and 37 females) of the 85 mice given quinoline and 84 (38 males and 46 females) of the 97 mice given DMSO survived at 52 weeks, at which point they were killed. After histopathological examination, the neoplastic response in the male mice given quinoline included 15 mice with liver adenomas [hepatocellular adenomas] (45%) [$P < 0.0001$] and 1 with a liver carcinoma [hepatocellular carcinoma] (3%). The neoplastic response in the female mice given quinoline included two mice with liver tumours (5%) (not diagnosed as hepatocellular adenomas or carcinomas), and one with a lung tumour (3%). No liver tumours were observed in female mice exposed to quinoline or in male and female controls. [The Working Group noted the principal strength of the study was that both males and females were used; however, the study was limited by the absence of body-weight data.]

3.1.3 Initiation–promotion

The tumour-initiating activity of quinoline (purity, ≥ 99.8%) was examined on the skin of 40 female HfD: SENCAR BR mice (age, 50–55 days) (LaVoie et al., 1984). Control mice (40 per group) were treated with either benzo[*a*]pyrene or acetone. Quinoline was applied at a 0.75% concentration in 0.1 mL of acetone in 10 separate doses every other day (total initiating dose, 7.5 mg). Negative control mice were treated with acetone only. Positive control mice were treated topically with benzo[*a*]pyrene at a total initiating dose of 0.03 mg. At 10 days after the last application of the initiator, promotion was started by applying 2.0 µg of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in 0.1 mL acetone twice per week for 18 weeks. Skin tumours were counted each week. At experimental week 22, 53% ($P < 0.01$) of mice treated with quinoline plus TPA had gross skin tumours with an average of 0.73 tumours per mouse. In mice treated with acetone plus TPA, 7.5% had gross skin tumours with an average of 0.08 tumours per mouse. In mice treated with benzo[*a*]pyrene plus TPA, 63% ($P < 0.01$) had gross skin tumours with an average of 2.1 tumours per mouse. [The Working Group noted the principal limitations of the study were the use of a single dose and the lack of histopathological examination.]

3.2 Rat

3.2.1 Oral administration

(a) Feeding

Sixty male Sprague-Dawley rats [age not reported] weighing 160–185 g were given quinoline (purity, > 99.8%) in a semi-synthetic diet for 40 weeks (Hirao et al., 1976). The rats were divided into three groups of 20, and each group was treated with 0.05, 0.1, or 0.25% quinoline, respectively. Rats that died before week 16 of the study were excluded from the effective numbers of animals. Most rats treated with the medium or high dose of quinoline died before the end of the study due to toxicity of quinoline or to rupture of vascular tumours in the liver. The tumour response in the 11 surviving rats treated with 0.05% quinoline included 3 rats with hepatocellular carcinoma (27%) and 6 with liver haemangioendothelioma [haemangiosarcoma] (54%) [$P < 0.05$]. In the 16 surviving rats treated with 0.1% quinoline, 3 had hepatocellular carcinoma (19%) and 12 had liver haemangioendothelioma [haemangiosarcoma] (75%) [$P < 0.005$]. In the 19 surviving rats treated with 0.25% quinoline, there were no hepatocellular carcinomas and 18 rats had liver haemangioendothelioma [haemangiosarcoma] (95%) [$P < 0.0001$]. There were no tumours in the livers of the 6 control rats. [The Working Group noted that the study benefited from the multiple doses used. However, the study was limited by not providing the dose selection criteria, the poor survival in medium- and high-dose groups, and the lack of statistical analysis.]

Shinohara et al. (1977) evaluated the effects of dietary quinoline in Wistar rats and Sprague-Dawley rats. In a first experiment, 50 Wistar rats (age, 8 weeks; equal numbers of males and females) were given a basal diet containing 0.2% quinoline (Nakarai Pure Chemical Co., Japan) [purity unspecified] for up to 30 weeks. There were no rats on a control diet. A total of 15 of the 25 male rats and 22 of the 25 female rats survived after 26 weeks (effective number of animals). Gross examination showed that the livers of rats exposed to quinoline had numerous small and large nodules which measured up to 2.5 cm in diameter. Histologically, of the 15 surviving male rats given quinoline, there were 2 rats with hepatocellular carcinomas (13.3%) and 11 with haemangioendotheliomas [haemangiosarcomas] (73.3%) of the liver. Of the 22 surviving female rats, there were 2 with hepatocellular carcinoma (9.1%) and 7 with haemangioendothelioma [haemangiosarcoma] (31.8%) of the liver. Male rats had a higher incidence of haemangioendotheliomas [haemangiosarcomas] than female rats ($P < 0.02$).

In a second experiment, one group of male Sprague-Dawley rats (age, 8 weeks) received 0.075% quinoline in basal diet for 30 weeks; another group of male rats was given a control diet only [number of animals at start, unspecified]. The effective number of animals (those alive at 26 weeks) was 20 exposed and 10 control rats. Gross examination showed that the livers of rats exposed to quinoline had solitary or multiple spotted lesions in the liver measuring 1–2 mm in diameter; these lesions were not quantified. Histologically, 6 of the 20 rats (30.0%) exposed to quinoline [not significantly increased compared with controls] had haemangioendothelioma [haemangiosarcoma] of the liver; there were no treated rats with hepatocellular carcinoma. There were no liver tumours in the controls (0/10). [The Working Group noted that the principal strength of the study was that both males and females were used in the first experiment. The principal limitations included the lack of a control group in the first experiment, the use of only a single dose in both experiments, the short duration of exposure, the use of male rats only in the second experiment, and the limited reporting of experimental details in both experiments. The Working Group concluded that the first experiment was inadequate for the evaluation of the

carcinogenicity of quinoline in experimental animals.]

Five groups comprising a total of 170 male Wistar rats (age, 7 weeks) [number of animals at start unspecified] were given quinoline (Katayama Chemical Co., Japan) [purity not stated] in a powdered diet for 4, 8, 12, 16, or 20 weeks (Groups I–V, respectively). Subgroups (totalling 15 in number) of 5–18 rats from each of Groups I–V were killed at experimental weeks 4, 8, 12, 16, and 20 (Hasegawa et al., 1989). Group VI (Subgroup 16) comprised 12 rats that were not exposed to quinoline and killed at 20 weeks [tumour data for 7 of the 16 subgroups are reported in Table 3.1]. Several rats died before they were scheduled to be killed, as a result of either the toxic effects of the quinoline or the rupture of vascular tumours of the liver. Rats exposed to quinoline gained weight more slowly than controls, but normal body weights were restored within 4 weeks after cessation of treatment. In the 11 rats of Group III (exposed for 12 weeks) killed after 12 weeks, 1 (9%) had haemangioendothelioma [haemangiosarcoma] of the liver. In the 12 rats of Group III killed after 16 weeks, 2 (17%) had haemangioendotheliomas [haemangiosarcomas] of the liver. In the 12 rats of Group III killed after 20 weeks, 5 (42%, $P < 0.05$) had haemangioendotheliomas [haemangiosarcomas] of the liver. In the 14 rats of Group IV (exposed for 16 weeks) killed after 16 weeks, 4 (29%, $P < 0.05$) had haemangioendotheliomas [haemangiosarcomas] of the liver. In the 18 rats of Group IV killed after 20 weeks, 4 (22%) had haemangioendotheliomas [haemangiosarcomas] of the liver. In the 16 rats of Group V (exposed for 20 weeks), 5 (31%, $P < 0.05$) had haemangioendotheliomas [haemangiosarcomas] of the liver. None of the 12 control rats in Group VI on basal diet for 20 weeks developed any lesions in the liver. It was concluded that the critical period for the induction of tumours in animals treated with 0.25% dietary quinoline is 12 weeks. [The Working Group noted that the study was limited by the use of only male rats and only one time-matched control group.]

In a study of the effects of hypertension on vascular carcinogenesis induced by exposure to quinoline, two strains of male rats (age, 5 weeks), SHR (high hypertension) and its parent strain Wistar Kyoto (WKY) that differ in their tendency towards spontaneous hypertension, were given 0.2% quinoline (Wako Pure Chemical Industry, Ltd, Japan) [purity not stated] in their diet for 32 weeks (Futakuchi et al., 1996). There were 16 exposed and 10 control rats per strain at the beginning of the study. Body-weight gain was retarded by exposure to quinoline for both strains from the first week until the end of the experiment. After week 25, of the groups exposed to quinoline 8 WKY rats died of haemangiosarcoma and 1 SHR rat died of an unknown cause. Histological findings in the 15 SHR rats exposed to quinoline for at least 25 weeks included 1 (7%) with haemangiosarcoma of the liver and 3 (20%) with liver hyperplastic nodules. In contrast, in the 15 WKY rats exposed to quinolone for at least 25 weeks, 14 (93%, $P < 0.001$) had liver haemangiosarcomas and 3 (20%) had liver hyperplastic nodules. No liver lesions were observed in the 9 SHR and 10 WKY controls. [The Working Group noted that the measurement of quinoline intake was the principal strength of this study; however, the study was limited by the use of only one sex, the single dose, and its short duration.]

(b) Drinking-water

In a GLP study, four groups of 50 male F344/DuCrj rats (SPF) (age, 6 weeks) were given quinoline (purity, > 99.6%) either at 0 (control), 200, 400, or 800 ppm in drinking-water for various periods of time (Matsumoto et al., 2018). Similarly, four groups of 50 female rats of the same strain and age were given quinoline at 0, 150, 300, or 600 ppm in drinking-water for various periods of time. The initial design was to expose rats to quinoline for up to 104 weeks; however, dose-related decreases in survival necessitated the early

termination of the experiment. All rats were observed daily for clinical signs and mortality, and animals found moribund were killed and their organs removed, weighed, and examined for macroscopic lesions at necropsy. All organs and tissues, including the entire respiratory tract, were examined for histopathology.

All male rats given quinoline at 400 and 800 ppm were dead by the end of weeks 95 and 76, respectively. Further, there were only 19 surviving rats (38%) in the group exposed at 200 ppm at week 96; the study was therefore terminated at that point. The survival rate of the control males at week 96 was 98% (49/50). All females exposed to quinoline at 600 ppm were dead by the end of week 88. However, the other groups had a fairly high number of surviving animals at that point, so the study was continued to week 104. The survival rates of the control, low-dose (150 ppm), and medium-dose (300 ppm) females at the end of the 104 weeks were 82% (41/50), 34% (17/50), and 4% (2/50), respectively. The decreased survival in males and females was attributed to death due to tumours of the liver. The earliest deaths due to malignant tumours were observed at weeks 75, 37, and 22 in the male groups exposed at 200, 400, and 800 ppm, respectively, and at weeks 68, 33, and 40 in the female groups exposed at 150, 300, and 600 ppm, respectively. The growth rates of all exposed males and of the females exposed at 300 and 600 ppm were generally less than the controls throughout the study period.

In male rats, exposure to quinoline significantly increased the incidence of hepatocellular adenoma, of hepatocellular carcinoma, of hepatocellular adenoma or carcinoma (combined), of haemangiosarcoma in the liver, and of haemangiosarcomas in all organs at all dose levels. No haemangiosarcoma or hepatocellular carcinoma and only one hepatocellular adenoma were observed in 50 male controls. In addition to vascular and hepatic tumours, quinoline significantly increased the incidences of nasal cavity sarcoma (not otherwise specified) in rats exposed at 400 ppm, and of nasal esthesioneuroepithelioma in rats exposed at 800 ppm; no such tumours were observed in controls. There was also a significant positive trend in the incidences of mediastinum sarcoma (not otherwise specified), mesenterium haemangiosarcoma, and adipose tissue haemangiosarcoma.

In female rats, exposure to quinoline significantly increased the incidence of hepatocellular adenoma, of hepatocellular carcinoma, of hepatocellular adenoma or carcinoma (combined), of haemangiosarcoma in the liver, and of haemangiosarcoma in all organs combined at all dose levels. No haemangiosarcoma or hepatocellular carcinoma was observed, and only one hepatocellular adenoma was observed in 50 female controls.

[The Working Group noted the early onset of rare tumours of various embryological origins at the lowest dose tested and the very poor survival due to tumour induction. The Working Group also noted that the principal strengths of this GLP study included the use of both males and females, the multiple dose levels, the accurate determination of compound exposure, the reporting of body-weight and survival data, the results obtained from all treated animals, and the extensive histopathological examination of all organs.]

3.2.2 Subcutaneous injection

In a study of carcinogenicity in newborn Sprague-Dawley rats, 101 males and 101 females were given a subcutaneous injection of quinoline (purity, > 99%) in DMSO at a dose of 200 µmol/kg body weight (bw) within the first 24 hours of life (LaVoie et al., 1988). Control groups of 50 males and 50 females were given a subcutaneous injection of DMSO at 500 µL/kg bw. A mortality rate of 59% was observed among the rats exposed to quinoline following the first injection; only 41 out of the 101 survived. The subsequent injections given once per week during weeks 2–7

were therefore reduced to 100 µmol/kg bw. The final injection given at week 8 was at the high dose of 200 µmol/kg bw. All control rats were given DMSO at 500 µL/kg bw for weeks 2–8. All rats were killed at 78 weeks. One liver adenoma [hepatocellular adenoma] was observed in the 25 surviving males exposed to quinoline. There were no liver tumours in any of the 15 surviving females exposed to quinoline. Of the 50 rats given DMSO, 27 males and 22 females survived. One (4.5%) of the control females had a liver adenoma [hepatocellular adenoma], and five (18.5%) of the control males had liver tumours: three adenomas [hepatocellular adenomas] and two hepatomas [hepatocellular carcinomas]. [The Working Group noted the higher incidence of liver tumours in the DMSO control rats compared with treated rats. The Working Group also noted that the principal strengths of the study were the use of both males and females, and the fact that treatment was given over most of the lifespan. However, the study was limited by the use of only a single variable dose, the high mortality after the initial dose, the absence of body-weight data, and the lack of discussion of clinical signs.]

3.3 Syrian golden hamster

Fifty Syrian golden hamsters (age, 8 weeks) were given 0.2% quinoline [purity not stated] in the diet for 30 weeks (Shinohara et al., 1977). There were equal numbers of males and females in the study. There were no liver tumours in the 25 surviving males or the 19 surviving females (effective number of animals) after 26 weeks of exposure to quinoline. [The Working Group noted that the principal limitations of the study included: a lack of controls given the basal diet for 30 weeks, the use of only one dose group, the short duration of exposure, and the limited reporting of experimental details. The Working Group concluded that the study was inadequate for the evaluation of the carcinogenicity of quinoline in experimental animals.]

3.4 Guinea-pig

Forty-four Hartley guinea-pigs (age, 8 weeks) were given 0.2% quinoline [purity not stated] in their diet for 30 weeks (Shinohara et al., 1977). There were equal numbers of males and females in the study. There were no liver tumours in the 21 surviving males or the 17 surviving females (effective number of animals) after 26 weeks of exposure to quinoline. [The Working Group noted that the principal limitations of the study included: a lack of controls given the basal diet for 30 weeks, the use of only one dose group, the short duration of exposure, and the limited reporting of experimental details. The Working Group concluded that the study was inadequate for the evaluation of the carcinogenicity of quinoline in experimental animals.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

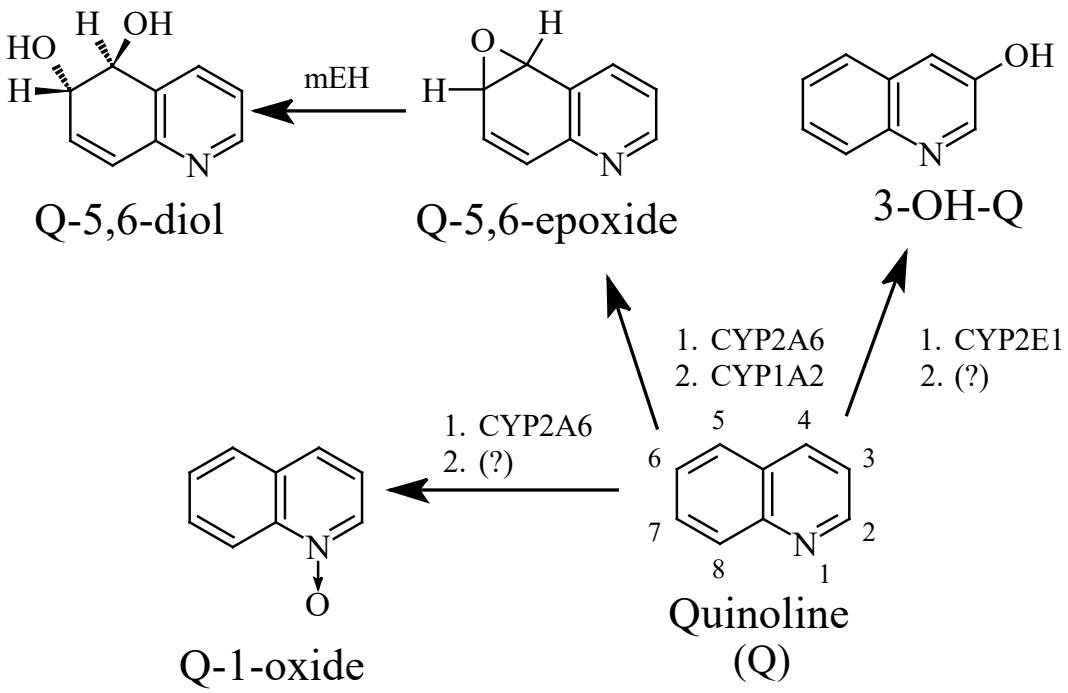
Relevant studies on the absorption, distribution, metabolism, and excretion of quinoline include in vitro studies in human and experimental systems, and in vivo studies in experimental animals. No data on humans exposed to quinoline, or on dermal absorption, were available to the Working Group. A specific focus in the published literature has been the biotransformation pathway underlying the mutagenicity of quinoline.

4.1.1 Humans

No data in exposed humans were available to the Working Group.

An in vitro metabolism study on quinoline was performed using individual cDNA-expressed cytochrome P450 (CYP) enzymes from human (and rat, see Section 4.1.2) hepatic microsomes

Fig. 4.1 Metabolic pathways of quinoline in human liver microsomes



CYP, cytochrome P450; mEH, microsomal epoxide hydrolase
Adapted from Reigh et al. (1996). Cytochrome P450 species involved in the metabolism of quinoline. *Carcinogenesis*, 1996, volume 17, issue 9, pages 1989–1996, by permission of Oxford University Press.

(Reigh et al., 1996). CYP2A6 was found to be the primary isozyme involved in the formation of quinoline-1-oxide, and CYP2E1 is the principal isozyme involved in the formation of 3-hydroxyquinoline. CYP2A6 and CYP1A2 are responsible for the formation of 5,6-dihydroquinoline-5,6-epoxide (also reported as quinoline-5,6-epoxide or 5,6-dihydro-5,6-epoxyquinoline), a precursor of 5,6-dihydroxy-5,6-dihydroquinoline (also reported as quinoline-5,6-diol, 5,6-dihydroquinoline-5,6-diol, 5,6-dihydroxyquinoline, 5,6-dihydro-5,6-dihydroxyquinoline) (see Fig. 4.1). Conversion of quinoline-5,6-epoxide to quinoline-5,6-diol was effectively mediated by cDNA-expressed human microsomal epoxide hydrolase. Kinetic analysis has shown that the formation of quinoline-5,6-diol is monophasic, and that of quinoline-1-oxide and 3-hydroxyquinoline is biphasic.

4.1.2 Experimental systems

(a) Absorption, distribution, and excretion

In a study by Novack & Brodie (1950), dogs were given quinoline intravenously at 25 mg/kg body weight (bw). After dosing, quinoline plasma concentrations of 16.9, 5.1, 2.6, and 0.7 mg/L were measured at 0.25, 0.75, 2, and 4 hours, respectively, and less than 0.5% of quinoline was excreted with urine in a free form within 24 hours of dosing. These data indicate that quinoline

was distributed rapidly and metabolized almost completely.

Absorption and excretion were also demonstrated in rabbits given quinoline orally (Smith & Williams, 1955; see the following section).

(b) Metabolism

(i) In vivo studies

In the study in dogs mentioned in the previous section (Novack & Brodie, 1950), 3-hydroxyquinoline was identified as a major metabolite of quinoline, accounting for 29–32% of the given dose (25 mg/kg bw). Of this amount, 4% was excreted in a free form while the remainder was excreted as an acid-hydrolysable conjugate, perhaps glucuronide and/or sulfate. When 3-hydroxyquinoline was given intravenously to two dogs at a dose of 0.6 mg/kg bw, 34% and 35% was recovered in urine in a conjugated form, although the amount of excreted free 3-hydroxyquinoline was negligible.

Smith & Williams (1955) investigated the metabolism of quinoline in rabbits dosed orally at 250 mg/kg bw or at 0.5 g per animal. In 24-hour urine samples, glucuronide and sulfate fractions were separated and hydrolysed to obtain products identified as 3-hydroxyquinoline, 2,6-dihydroxy-2,6-dihydroquinoline, and 5,6-dihydroxy-5,6-dihydroquinoline. Formation of 2,6-dihydroxy-2,6-dihydroquinoline may be initiated by the oxidation at C-2 or C-6, since both possible intermediates, 2-quinolone (2-hydroxyquinoline) or 6-hydroxyquinoline, had been described previously (Scheunemann, 1923; Knox, 1946). 5,6-Dihydroxy-5,6-dihydroquinoline, accounting for 3–4% of the administered dose of quinoline, occurred in the urine as a monosulfate (6-hydroxy-5,6-dihydroquinolyl-5-sulfuric acid). In contrast, 3-hydroxyquinoline and 2,6-dihydroxy-2,6-dihydroquinoline were excreted as glucuronides. About 10% of quinoline was excreted as an unknown labile compound that yielded the parent compound on heating with acid. Compounds 3-, 5-, and 6-hydroxyquinoline were mainly metabolized by direct conjugation. Further, 3-hydroxyquinoline was converted in a small extent to 2,3-dihydroxy-2,3-dihydroquinoline, and 6-hydroxyquinoline to 2,6-dihydroxy-2,6-dihydroquinoline and 5,6-dihydroxy-5,6-dihydroquinoline, although no oxidative product of 5-hydroxyquinoline has been detected (Smith & Williams, 1955).

(ii) In vitro studies

In vitro N-oxidation of quinoline by the hepatic and pulmonary microsomal preparations was studied by Cowan et al. (1978). Quinoline-1-oxide was detected in hepatic microsomal preparations from four rodent species and rabbits. Pulmonary microsomes isolated from rabbits, but not from guinea-pigs, exhibited oxidative activity. Later studies with hepatic microsomal fractions from rats treated with specific enzymatic inducers or inhibitors indicated that N-oxidation is catalysed by (phenobarbital-inducible) CYP monooxygenases, whereas oxidation at the 5,6-position is catalysed by CYP1A1 (Tada et al., 1982). Metabolism of quinoline and isoquinoline in rat liver microsomes was compared by LaVoie et al. (1983). The major metabolite of quinoline was identified as 5,6-dihydroxy-5,6-dihydroquinoline, while 3-hydroxyquinoline and quinoline-1-oxide were among the minor metabolites.

As noted in Section 4.1.1, an in vitro study compared metabolism of quinoline in rat hepatic microsomes (Reigh et al., 1996) with that in human hepatic microsomes. The types of CYP isoenzymes involved in the corresponding metabolic pathways differed notably between the species. The formation of quinoline-1-oxide in rat hepatic microsomes was negligible but it was enhanced by pre-treatment with phenobarbital, acting as CYP3A2 inducer. The enzymes responsible for the formation of quinoline-5,6-epoxide were CYP1A2 and CYP1A1, and the formation of 3-hydroxyquinoline was mediated by CYP2E1.

Similarly, in vitro formation of quinoline metabolites as catalysed by five purified mammalian (species unspecified) CYP450 enzymes was described by Dowers et al. (2004). Quinoline-1-oxide was a major metabolite upon incubation with CYP3A4 and 2A6, a relevant but not major metabolite with CYP2B4, but was not detected with CYP1A2 and only traces were found in incubations with CYP2E1. 3-Hydroxyquinoline was a major metabolite upon incubation with CYP2E1, 1A2, and 2B4. With all isozymes tested, 5- and 8-hydroxyquinoline were produced. Small amounts of 6-hydroxyquinoline were produced with all isoenzymes except CYP1A2.

Quinoline metabolism was also studied in incubations with rat olfactory mucosa and NADPH in vitro. Quinoline-1-oxide and quinoline-5,6-epoxide appeared to be the main metabolites; other products were unspecified diols. The rate of quinoline-1-oxide formation in microsomes from olfactory mucosa was about 3-fold that in hepatic microsomes. Inhibition studies confirmed the dominant role of CYP isoenzymes in the biotransformation of quinoline (Thiebaud et al., 2013).

4.2 Mechanisms of carcinogenesis

Quinoline has been studied for genotoxic potential primarily using non-human mammalian in vivo and in vitro models, as well as bacterial mutagenicity assays. These studies are summarized in Table 4.1, Table 4.2, and Table 4.3.

4.2.1 Genetic and related effects

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

(i) Non-human mammals in vivo

No effect was seen on unscheduled DNA synthesis in hepatocytes isolated from rats following single oral gavage doses of quinoline at up to 500 mg/kg bw (Ashby et al. 1989).

Quinoline given to transgenic mice (MutaMouse) by intraperitoneal injection at 50 mg/kg bw per day for 4 days consistently elevated the mutation frequency of the *lacZ* and *cII* transgenes in liver tissue 14 days after treatment (Miyata et al., 1998; Suzuki et al., 1998; Suzuki et al., 2000), but did not change the mutation frequency of the *lacZ* gene in kidney, lung, spleen (Suzuki et al., 1998), bone marrow, or testis (Miyata et al., 1998). When the *cII* gene was sequenced from liver DNA, the majority of quinoline-induced mutations were G:C to C:G transversions (Suzuki et al., 2000).

Micronuclei were significantly increased in the livers of rats given quinoline by oral gavage at 15 mg/kg bw per day for 14 days or 30 mg/kg bw per day 28 days (Uno et al., 2015). However, micronuclei were not increased in the rat bone marrow (immature erythrocytes), colon, or stomach after a higher daily gavage dose (up to 120 mg/kg bw for 14 days or 28 days) (Uno et al., 2015), or in the rat bone marrow (immature erythrocytes) after a single dose by gavage at 200 mg/kg bw or after treatment every day for 28 days (Asakura et al., 1997). Chromosomal aberrations were significantly increased in hepatocytes isolated from rats following a single dose (100 mg/kg bw) or a dose (25 mg/kg bw) once per day for 28 days by gavage (Asakura et al., 1997). In the same study, sister-chromatid exchanges were significantly increased in rat hepatocytes after a single dose (50 mg/kg bw) or a dose (25 mg/kg bw) once per day for 28 days by gavage. Quinoline given intravenously at 500 µmol/kg bw significantly increased micronuclei in the livers of mice that underwent partial hepatectomy when sampled 5 or 10 days after exposure (Saeki et al., 2000),

Table 4.1 Genetic and related effects of quinoline in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Unscheduled DNA synthesis	Rat, Alpk:AP (M)	Liver	–	500 mg/kg	Oral gavage ×1, sampled at 16 h		Ashby et al. (1989)
Mutation	MutaMouse, CD2 (M)	Liver	+	50 mg/kg	Intraperitoneal injection 1×/d for 4 d, sampled at 14 d		Miyata et al. (1998)
Mutation	MutaMouse, CD2 (M)	Bone marrow, testis	–	50 mg/kg	Intraperitoneal injection, 1×/d for 4 d, sampled at 14 d		Miyata et al. (1998)
Micronuclei	MutaMouse, CD2 (M)	Peripheral blood	–	50 mg/kg	Intraperitoneal injection, 1×/d for 2 d, sampled at 24 h		Miyata et al. (1998)
Mutation	MutaMouse, CD2 (F)	Liver and after partial hepatectomy	+	50 mg/kg	Intraperitoneal injection, 1×/d for 4 d, sampled at 14 d		Suzuki et al. (1998)
Mutation	MutaMouse, CD2 (M)	Liver	+	50 mg/kg	Intraperitoneal injection, 1×/d for 4 d, sampled at 14 d	The majority of quinoline-induced mutations were G:C to C:G transversions	Suzuki et al. (2000)
Mutation	MutaMouse, CD2 (F)	Kidney, lung, spleen	–	50 mg/kg	Intraperitoneal injection, 1×/d for 4 d, sampled at 14 d		Suzuki et al. (1998)
Micronuclei	Rat, Crl:CD(SD) (M)	Liver	+	15 mg/kg	Oral gavage ×1/d for 14 d (or at 30 mg/kg/d for 28 d)		Uno et al. (2015)
Micronuclei	Rat, Crl:CD(SD) (M)	Bone marrow, colon, stomach	–	60 mg/kg	Oral gavage ×1/d, 28 d (or 120 for 14 d)		Uno et al. (2015)
Micronuclei	Rat, F344/Du Crj (M)	Bone marrow	–	200 mg/kg bw	Oral gavage ×1, or ×1/d for 28 d, sampled at 24 hours		Asakura et al. (1997)
Chromosomal aberrations	Rat, F344/Du Crj (M)	Liver	+	25 mg/kg bw	Oral gavage ×1/d for 28 d, sampled at 24 h	Dose-dependent increases in chromosomal aberrations (0, 25, 50, 100, and 200 mg/kg bw)	Asakura et al. (1997)
Sister-chromatid exchange	Rat, F344/Du Crj (M)	Liver	+	50 mg/kg bw	Oral gavage ×1 or 25 mg/kg bw for 28 d, dose–response analysis; sampled at 24 h		Asakura et al. (1997)
Micronuclei	Mouse, ICR (M)	Liver	+	0.5 mmol/kg bw	Intraperitoneal injection, ×1, sampled at 5 or 10 d	Mice underwent partial hepatectomy	Saeki et al. (2000)
Micronuclei	Mouse, ICR (M)	Liver	–	0.5 mmol/kg bw	Intraperitoneal injection, ×3, sampled at 6 or 11 d	Mice did not undergo partial hepatectomy	Saeki et al. (2000)
Micronuclei	Rat, F344 (M)	Liver	±	0.5 mmol/kg	Intraperitoneal injection, ×3, sampled at 6 or 11 d	Rats did not undergo partial hepatectomy	Hakura et al. (2007)

Table 4.1 (continued)

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Micronuclei	Mouse, CD-1 (M)	Bone marrow	+	25 mg/kg	Intraperitoneal injection, ×1, sampled at 48 h		Hamoud et al. (1989)
Sister-chromatid exchange	Mouse, $B6C3F_1$ (M)	Bone marrow	–	100 mg/kg	Intraperitoneal injection, ×1, sampled at 23 and 42 h	MTD, 100 mg/kg; ≥ 200 mg/kg lethal	McFee (1989)
Chromosomal aberrations	Mouse, $B6C3F_1$ (M)	Bone marrow	–	100 mg/kg	Intraperitoneal injection ×1; sampled at 17 and 36 h	MTD, 100 mg/kg; ≥ 200 mg/kg lethal	McFee (1989)

bw, body weight; d, day(s); F, female; h, hour(s); HID, highest ineffective dose; LED, lowest effective dose (units as reported); M, male; MTD, maximum tolerated dose; SD, standard deviation

[a] +, positive; –, negative; ±, equivocal (variable response in several experiments within an adequate study)

Table 4.2 Genetic and related effects of quinoline in non-human mammalian cells in vitro

Endpoint	Species, strain	Tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Chromosomal aberrations	Chinese hamster	Lung, Don cells	–	NT	1 mM		Abe & Sasaki (1977)
Chromosomal aberrations	Chinese hamster	Lung fibroblasts	±	+	0.3 mg/mL	3-h incubation followed by 24-h expression period; chromosomal aberrations analysis included gaps	Matsuoka et al. (1979)
Chromosomal aberrations	Chinese hamster	Ovary, CHO-W-B1	–	+	500 µg/mL	2-h incubation followed by 8–12-h expression period; results obtained at one of two laboratories	Galloway et al. (1985)
Chromosomal aberrations	Chinese hamster	Ovary, CHO-W-B1	–	–	550 µg/mL	2-h incubation followed by 8–12-h expression period; results obtained at one of two laboratories	Galloway et al. (1985)
Chromosomal aberrations	Chinese hamster	Lung fibroblasts	NT	+	0.03 mg/mL	6-h incubation followed by 18-h expression period	Suzuki et al. (2007)
Micronuclei	Chinese hamster	Lung fibroblasts	NT	+	0.05 mg/mL	6-h incubation followed by 72-h expression period	Suzuki et al. (2007)
Sister-chromatid exchange	Chinese hamster	Lung, Don cells	–	NT	1 mM	26-h exposure	Abe & Sasaki (1977)
Sister-chromatid exchange	Chinese hamster	Ovary, CHO-W-B1	–	+	4.4 µg/mL	2-h exposure followed by 24-h expression period; study compared concurrently produced results between two laboratories	Galloway et al. (1985)
DNA strand breaks	Rat, NR	Isolated hepatocytes	+	NT	1 mM	Primary hepatocytes exposed for 3 h	Sina et al. (1983)
Unscheduled DNA synthesis	Rat, Sprague-Dawley	Isolated hepatocytes	+	NT	1 mM	Exact duration of exposure was not reported (18–20 h)	LaVoie et al. (1991)

h, hour(s); HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested

[a] +, positive; –, negative; ±, equivocal (variable response in several experiments within an adequate study)

Table 4.3 Genetic and related effects of quinoline in non-mammalian species

Test system (species, strain)	End-point	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Drosophila melanogaster, Canton-S males mated to Basc females	Sex-linked recessive lethal mutations	–	NT	600 ppm, 1 injection	Adult male flies were treated for the study	Zimmering et al. (1985)
Drosophila melanogaster, Canton-S males mated to Basc females	Sex-linked recessive lethal mutations	–	NT	130 ppm in feed	Flies were exposed throughout the larval stage of development	Valencia et al. (1989)
Salmonella typhimurium, TA100	Mutation	–	+	40 µg/plate		Talcott et al. (1976)
Salmonella typhimurium, TA98, TA1535, TA1537	Mutation	–	–	100 µg/plate		Talcott et al. (1976)
Salmonella typhimurium, TA100	Mutation	–	+	50 µg/plate		Epler et al. (1977)
Salmonella typhimurium, TA98	Mutation	–	±	100 µg/plate		Epler et al. (1977)
Salmonella typhimurium, TA1535, TA1537	Mutation	–	–	200 µg/plate		Epler et al. (1977)
Salmonella typhimurium, TA100, TA98	Mutation	–	+	1 µM/plate		Nagao et al. (1977)
Salmonella typhimurium, TA100	Mutation	–	+	100 µg/plate		Hollstein et al. (1978)
Salmonella typhimurium, TA98, TA1535, TA1537	Mutation	–	–	100 µg/plate		Hollstein et al. (1978)
Salmonella typhimurium, TA100, TA98	Mutation	NT	+	50 µg/plate		Haworth et al. (1983)
Salmonella typhimurium, TA100	Mutation	NT	+	30 µg/plate		LaVoie et al. (1991)
Salmonella typhimurium, TA100	Mutation	NT	+	25 µg/plate		Debnath et al. (1992)
Salmonella typhimurium, TA100	Mutation	NT	+	0.4 µmol/plate		Willems et al. (1992)
Salmonella typhimurium, TA198	Mutation	NT	+	NR	LED not reported	Willems et al. (1992)
Salmonella typhimurium, TA1535, TA1537	Mutation	NT	–	200 µg/plate		Willems et al. (1992)
Salmonella typhimurium, TA100	Mutation	NT	+	0.2 µmol/plate		Kato et al. (1999)
Salmonella typhimurium, TA100	Mutation	–	+	79 mg/L		Neuwoehner et al. (2009)
Salmonella typhimurium, TA98	Mutation	–	–	158.1 mg/L		Neuwoehner et al. (2009)

HIC, highest ineffective concentration; LEC, lowest effective concentration; LED, lowest effective dose; NR, not reported; NT, not tested; ppm, parts per million

[a] +, positive; –, negative; ±, equivocal (variable response in several experiments within an adequate study)

but not when non-hepatectomized mice were intravenously exposed to quinoline at 0.5 mmol/kg bw, once a day for three consecutive days, and sampled 6 days after exposure (Hakura et al., 2007). Results for non-hepatectomized rats that underwent the same experimental exposure were equivocal (Hakura et al., 2007).

Micronuclei were significantly increased in immature erythrocytes taken from the bone marrow of mice 48 hours after intraperitoneal injection with quinoline at 25 mg/kg bw; however, the increase was less than 2-fold that in controls (Hamoud et al., 1989). Micronuclei were not increased in peripheral blood of the MutaMouse 24 hours after treatment with quinoline by intraperitoneal injection at 50 mg/kg bw once per day for 2 days (Miyata et al., 1998). Chromosomal aberrations and sister-chromatid exchanges were not increased in the bone marrow of mice given quinoline by intraperitoneal injection at 100 mg/kg bw (McFee, 1989).

(ii) Non-human mammalian cells in vitro

Quinoline at 1 mM significantly increased unscheduled DNA synthesis in isolated rat hepatocytes (LaVoie et al., 1991). DNA single-strand breaks were detected in the alkaline elution assay when isolated rat hepatocytes were exposed to quinoline (1 mM) (Sina et al., 1983). In a study comparing results between two laboratories, both reported significantly increased sister-chromatid exchanges, but only one laboratory reported significantly increased chromosomal aberrations in the presence of exogenous metabolic activation in Chinese hamster ovary cells (Galloway et al., 1985). Sister-chromatid exchanges and chromosomal aberrations were not increased in Chinese hamster lung Don cells by quinoline (1 mM) in the absence of exogenous metabolic activation (Abe & Sasaki, 1977). Chromosomal aberrations (Matsuoka et al., 1979; Suzuki et al., 2007) and micronuclei (Suzuki et al., 2007) were significantly increased in Chinese hamster lung fibroblasts in the presence of exogenous metabolic activation.

(iii) Non-mammalian systems in vivo

Quinoline was negative in the *Drosophila melanogaster* sex-linked recessive lethal test in adult flies (Zimmering et al., 1985), or when larvae were exposed throughout development (Valencia et al., 1989).

(iv) Non-mammalian systems in vitro

In *Salmonella typhimurium*, quinoline was positive in TA100 in the assay for reverse mutation in the presence of metabolic activation in studies conducted by various research groups (Talcott et al., 1976; Epler et al., 1977; Nagao et al., 1977; Hollstein et al., 1978; Haworth et al., 1983; LaVoie et al., 1991; Debnath et al., 1992; Willems et al., 1992; Kato et al., 1999; Neuwoehner et al., 2009). Willems et al. (1992) demonstrated that the mutagenic activity of quinoline in TA100 increased with increasing concentrations of induced rat liver S9 mix (Willems et al., 1992). Results were variable for TA98 (Epler et al., 1977; Nagao et al., 1977; Hollstein et al., 1978; Haworth et al., 1983; Willems et al., 1992; Neuwoehner et al., 2009) and TA1537 (Talcott et al., 1976; Epler et al., 1977; Hollstein et al., 1978; Willems et al., 1992) in the presence of exogenous metabolic activation. Negative results were obtained for quinoline in TA1535 with exogenous metabolic activation (Talcott et al., 1976; Epler et al., 1977; Hollstein et al., 1978; Willems et al., 1992). Quinoline was negative in TA100, TA98, TA1535, and TA1537 in the absence of exogenous metabolic activation (Talcott et al., 1976; Epler et al., 1977; Nagao et al., 1977; Hollstein et al., 1978; Haworth et al., 1983; Neuwoehner et al., 2009).

4.2.2 Other mechanistic data

To identify the structural requirements for the mutagenicity of quinoline, the activities of quinoline and 23 quinoline derivatives were compared in the Ames assay in the presence

of exogenous metabolic activation (Hollstein et al., 1978). It was suggested that C-2 and C-3 of quinoline are critical sites for the production of the proposed mutagenic intermediate, quinoline-2,3-epoxide. Alternate routes of activation, possibly independent of C-2 and C-3, may also play a minor role in quinoline mutagenicity.

The structure of the reactive intermediate that forms quinoline–nucleic-acid adducts was investigated by Tada et al. (1980). Adducts were produced by in vitro incubation of quinoline with yeast RNA, RNA polynucleotides, or calf thymus DNA in the presence of NADPH and rat liver microsomes, and were split by acid or alkali hydrolysis. Most of the quinoline residues, whether reacted with RNA or DNA, were released as 3-hydroxyquinoline. This suggests that a 2,3- or 3,4-epoxy derivative of quinoline is the reactive intermediate for nucleic acid modification. However, similar mutagenic potency of 4-methylquinoline and its tumorigenic activity on mouse skin suggests that formation of an electrophilic oxide at C-3 and C-4 is unlikely to be involved in the ultimate activation of quinoline (LaVoie et al., 1983, 1984).

Additional support for C-3 of quinoline being critical for mutagenicity was provided by Takahashi et al. (1988). Substituting C-3 with fluorine abolished the mutagenicity of quinoline, whereas mutagenicity was maintained but reduced when C-6 and C-8 were substituted with fluorine. Conversely, substitution of C-5 enhanced the mutagenicity of quinoline. In the same study, quinoline substituted with chlorine at C-2 or C-3 was not mutagenic but 4-chloroquinoline was slightly mutagenic. The 2,3-epoxide of the 1,4-hydrate form of quinoline was proposed as the intermediate responsible for mutagenicity.

Saeki et al. (1993) confirmed that the non-mutagenic 3-fluoroquinoline yielded metabolites at its benzene ring similar in type and quantity to the metabolites of mutagenic quinoline (5,6-dihydroxy-5,6-dihydro derivatives). This strongly suggests that the mutagenic activity of quinoline is prevented by fluorination at C-3, which then cannot undergo oxidation to the proposed mutagen, quinoline-2,3-epoxide. Oxidation at the benzene ring is considered to be a detoxification pathway of quinoline biotransformation. A similar conclusion was made in another study with 12 various di-, tri-, and tetra-fluoroquinolines (Kato et al., 1999). None of the quinoline derivatives with fluorine substituting for C-3 were mutagenic. In contrast, the mutagenicity of quinoline was enhanced when fluorine was substituted at C-5 or C-7, possibly because of inhibition of the major detoxification pathway affecting the benzene ring of quinoline.

The observation that C-3 fluorination abolishes the mutagenicity of quinoline in the Ames assay was investigated further using additional in vitro assays for genotoxicity. In Chinese hamster lung fibroblasts, fluorine substitution at C-3 clearly reduced the potency of quinoline in the micronucleus and chromosomal aberration assays, whereas substitution at C-5, C-6, or C-8 had comparatively modest effects (Suzuki et al., 2007); this pattern of responses was similar to those observed using the Ames assay. Furthermore, unscheduled DNA synthesis was induced in isolated rat hepatocytes when quinoline was fluorinated at C-5, C-6, C-7, or C-8 or methylated at C-4 or C-8, but not when fluorinated at C-2, C-3, or C-4, or methylated at C-2 or C-6 (methylations at other carbons were not tested) (LaVoie et al., 1991).

The apparent requirement of C-3 for the genotoxic activity of quinoline was tested in vivo. Quinoline and 5-fluoroquinoline, but not 3-fluoroquinoline, given by intraperitoneal injection at 50 mg/kg bw, once per day for 4 days, significantly increased the *lacZ* transgene mutation frequency in the liver tissue of the MutaMouse by 4–5-fold (Miyata et al., 1998). However, 3-fluoroquinoline given by a single intraperitoneal injection at 500 µmol/kg bw significantly increased micronuclei in the livers of mice that underwent

partial hepatectomy when sampled 5 or 10 days after exposure, although the increase was not as high as that obtained with quinoline (Saeki et al., 2000).

One study used quantitative real-time polymerase chain reaction to evaluate gene expression in the liver tissue of male B6C3F$_1$ mice 4 or 48 hours after treatment with quinoline by intraperitoneal injection at 100 mg/kg bw; quinoline was one of eight chemicals considered to be genotoxic hepatocarcinogens and one of four chemicals considered to be non-genotoxic hepatocarcinogens evaluated in the study (Watanabe et al., 2012). The set of genes evaluated by Watanabe et al. (2012) was previously shown to be associated with exposure to a different set of well-characterized genotoxicants and non-genotoxicants using the same mouse model and tissue (Watanabe et al., 2009). A principal component analysis of the gene expression data classified quinoline within the category of "genotoxic hepatocarcinogen" (Watanabe et al., 2012).

4.3 Other adverse effects

In a cancer bioassay conducted using male and female Crj:BDF1 mice and F344/DuCrj rats (Matsumoto et al., 2018), quinoline given orally via drinking-water induced non-neoplastic lesions in the nasal cavities of mice and angiectasis in the liver, a lesion that was associated with liver haemangiocarcinogenicity induced by quinoline. In rats, quinoline induced acidophilic foci, basophilic foci, and clear cell foci in the liver, central necrosis and focal necrosis in the liver, and basal cell hyperplasia and atrophy of the olfactory epithelium.

5. Summary of Data Reported

5.1 Exposure data

Quinoline is a colourless liquid with an unpleasant odour. It is a heterocyclic aromatic compound belonging to the group of azaarenes, and is classed as a high production volume chemical. It is used as a solvent or intermediate in the production of vitamin B_3, pharmaceuticals and veterinary drugs, anticorrosive agents, and dyes used for textiles, cosmetics, foods, and drinks.

Quinoline is a major pollutant of soil and groundwater at sites contaminated by coal tar and creosote. The most probable route of worker exposure to quinoline is by inhalation of particulates or vapours. Occupational exposure to quinoline may occur during petroleum and shale oil processing, the production or use of products derived from coal tar, and in industries where quinoline is used as a solvent or chemical intermediate. Very few data on occupational exposure were available to the Working Group.

Tobacco smoke is an important source of quinoline exposure. Environmental monitoring data indicate that the general population may be exposed to quinoline in particulate matter in urban air. Groundwater contamination may pose an additional risk of quinoline exposure for populations accessing aquifers near sites of creosote wood preservation. The potential for skin exposure exists from clothing containing quinoline-based dyes.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

There were five studies of the carcinogenicity of quinoline in mice: one good laboratory practice (GLP) study by drinking-water in males and

females, three studies by intraperitoneal injection in males and females, and one initiation–promotion study by skin application in females.

In the study by drinking-water, quinoline significantly increased the incidences (with a significant positive trend) of haemangioma of the liver, subcutis, peritoneum, and retroperitoneum, and haemangioma in all organs combined in females, of haemangioma in all organs combined in males, of haemangiosarcoma of the liver in males, of haemangiosarcoma of the peritoneum and subcutis in females, of haemangiosarcoma of the retroperitoneum and mesenterium, and haemangiosarcoma in all organs combined in males and females, of haemangioma or haemangiosarcoma (combined) in all organs combined in males and females, and of histiocytic sarcoma of the liver in females. There was also a significant positive trend in the incidences of hepatocellular carcinoma, histiocytic sarcoma of the liver, haemangioma of the retroperitoneum, and haemangiosarcoma of the subcutis in males, and in the incidences of haemangiosarcoma of the ovary and mediastinum in females. For many of these rare tumour types of various embryological origins, tumours in both males and females occurred at an early onset, at the lowest dose tested, and caused the early death of the mice.

In the studies by intraperitoneal injection, quinoline significantly increased the incidence of lymphoma in females in one study, of hepatocellular adenoma in males in two studies, of hepatocellular carcinoma in males in one study, and of hepatocellular adenoma or carcinoma (combined) in males in two studies. Quinoline initiated skin tumours in the initiation–promotion study.

There were seven studies of the carcinogenicity of quinoline in rats: five studies of exposure by feed in males, one GLP study by drinking-water in males and females, and one study by subcutaneous injection in males and females.

Quinoline significantly increased the incidence of haemangiosarcoma of the liver in males in three studies of exposure to quinoline via feed. Two studies of exposure to quinoline via feed and the study by subcutaneous injection yielded negative results.

In the study with drinking-water, quinoline significantly increased the incidences (with a significant positive trend) of haemangiosarcoma of the liver and in all organs combined in males and females, of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) in males and females, and of sarcoma (not otherwise specified) of the nasal cavity and of nasal esthesioneuroepithelioma in males. There was also a significant positive trend in the incidences of sarcoma (not otherwise specified) of the mediastinum as well as haemangiosarcoma of the mesenterium and of the adipose tissue in males. For many of these rare tumour types of various embryological origins, tumours in both males and females occurred at an early onset, at the lowest dose tested, and caused the early death of the rats.

5.4 Mechanistic and other relevant data

No data on absorption, distribution, metabolism, or excretion in exposed humans were available. No data on dermal absorption were available. Absorption and excretion of quinoline was demonstrated in orally dosed rabbits. Quinoline was distributed rapidly and metabolized almost completely following intravenous exposure in dogs.

Regarding the key characteristics of carcinogens, there is *moderate* evidence that quinoline is metabolized to an electrophile based on the indirect observation that the genotoxic effects of quinoline (see paragraph below) appear to require metabolic activation. No studies were available in humans or in human cells. In two studies conducted in vivo, one in dogs and one in rabbits, and in studies conducted in vitro in

different species, rapid oxidation dependent on cytochrome P450 (CYP) produced 3-hydroxyquinoline, quinoline-5,6-diol, and quinoline-1-oxide as major metabolites in mammals. These metabolites were also produced in vitro in a study in which human CYPs were expressed. Mutagenicity studies in vivo and in vitro using quinoline derivatives suggested an azaarene oxide on the pyridine ring as a mutagenic intermediate; however, DNA adducts formed by quinoline have not been characterized.

There is *strong* evidence that quinoline is genotoxic. No data are available in exposed humans or in human systems. Quinoline induced chromosomal damage, including micronuclei, chromosomal aberrations, and sister-chromatid exchanges, in the liver of rats, but chromosomal damage (micronuclei) was not induced in other rat tissues including bone marrow, colon, and stomach. Quinoline induced mutations in the liver of transgenic mice, but not in the bone marrow, kidney, lung, spleen, or testes. Following metabolic activation, quinoline induced chromosomal damage (micronuclei, chromosomal aberrations, and sister-chromatid exchanges) in mammalian cells in vitro, and mutagenicity in the Ames assay.

No additional information in humans or in experimental systems, including on the eight remaining key characteristics of carcinogens, was available.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of quinoline.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of quinoline.

6.3 Overall evaluation

Quinoline is *possibly carcinogenic to humans (Group 2B).*

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