Methylquinolines

2-Methylquinoline (Quinaldine) [91-63-4]
3-Methylquinoline [612-58-8]
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7-Methylquinoline [612-60-2]
8-Methylquinoline [611-32-5]
Methylquinoline (Not Further Specified) [27601-00-9]

Summary Report of Toxicological Literature

March 2002

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Summary Report of Toxicological Literature

Prepared for

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March 2002

Executive Summary

4-methylquinoline was nominated in 2001 for carcinogenicity and comparative metabolism (with quinoline) studies by the Carcinogen Identification Committee for the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment. The nomination is based on concern for potential human exposure resulting from the ubiquitous occurrence of 4-methylquinoline as a contaminant in the environment and evidence for carcinogenicity in experimental animal studies.

Several methylquinolines have been previously nominated to the NTP for toxicity and/or carcinogenicity studies. 2- and 4-Methylquinoline were nominated for carcinogenicity studies in 1984 and were not selected for testing at that time based on low commercial production and limited information regarding the potential for human exposure. 6-, 7-, and 8-Methylquinoline were nominated and selected for genotoxicity testing in 1985.

There are common sources for environmental release and human exposure for many of the methyquinolines, and toxicity information is available from recent studies for several compounds in this class. This report briefly summarizes available information on the seven methylquinolines in which the methyl groups are attached to ring carbon atoms to aid in the evaluation of the need for additional toxicology studies for 4-methylquinoline.

Uses and Sources of Exposure

2-, 6-, and 8-methylquinoline are used in pharmaceuticals manufacturing. 7- and 8-Methylquinoline are used to inhibit steel corrosion. 2-Methylquinoline is also used in the production of dyes, food coloring, and of organic chemicals and acid-base indicators. Humans may be exposed to these compounds during the manufacturing process. Methylquinolines have been identified in coal tar and among byproducts of wood processing. Occupational exposure may occur in the production of dyes, food coloring, pharmaceuticals, organic chemicals, acid-base indicators and steel. Also, 2-methylquinoline was found in workplace air at aluminum plants. Human inhalation exposure occurs from smoking tobacco and from exposure to second-hand smoke. Dermal exposure is possible through treatment of skin disorders with coal tar. 2-Methylquinoline may be ingested by eating contaminated fish or by drinking decaffeinated coffee. 3-Methylquinoline may be ingested, or inhaled, from autolyzed yeast extract used as a food flavorant. 4-methylquinoline may be inhaled from urban particulate matter. 6-Methylquinoline exposure may also result from consuming whiskey and tea.

Toxicological Data

<u>For all compounds</u>

Genotoxicity: When methylquinolines were compared to quinoline for mutagenicity in *Salmonella typhimurium* strain TA100, only 4-methylquinoline and 6-methylquinoline were more mutagenic than quinoline. The mutagenicity of 7-methylquinoline was comparable to quinoline; 2-, 3-, 5, and 8-Methylquinoline were less mutagenic than quinoline.

Immunotoxicity: Coal tar, which contains 2-, 6-, 7-, and 8-methylquinoline, caused guinea-pig epidermis to thicken.

<u>2-Methylquinoline</u>

General toxicology: The oral LD_{50} in rats has been reported as 1,230 mg/kg (8.590 mmol/kg) and the dermal LD_{50} in rabbits has been reported as 1,870 μL/kg (1,980 mg/kg). It caused severe eye irritation in rabbits at a dose of 750 μg (5.24 μmol).

Genotoxicity: 2-Methylquinoline had the weakest mutagenicity among the methylquinolines. It was not mutagenic when tested at concentrations of 50 to 500 μg (0.35 to 3.5 μmol) per plate in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 with and without metabolic activation. It was not mutagenic at 7 mM (1002.33 μg/mL) in *S. typhimurium* strain TM677 with metabolic activation. However, 2-methylquinoline was mutagenic at concentrations of 100 to 600 μg (0.708 to 4.19 μmol) per plate in *S. typhimurium* strain TA100 with metabolic activation. In another study, 2-methylquinoline was mutagenic in *S. typhimurium* [strain not provided] at 2 μmol (300 μg) per plate in the absence of metabolic activation.

Immunotoxicity: 2-Methylquinoline inhibited interferon induction in mouse embryo fibroblast cultures, but it had no effect on interferon induction in mice *in vivo* when given intraperitoneally. When tested on rabbit skin at 10 mg (0.70 mmol) or 500 mg (3.49 mmol) for 24 hours, 2-methylquinoline had a mild irritant effect. In human patch testing, 2-methylquinoline induced dermal sensitization, but the authors attributed this effect to 'group allergies' induced in combination with other substances.

3-Methylquinoline

Genotoxicity: 3-Methylquinoline was not mutagenic in the "mutational enhancement" test at concentrations of 25 to 100 μg/mL (0.17 to 4.19 μmol/mL) in the *Escherichia coli* HCR+ strain. It was mutagenic at concentrations of 100 to 600 μg (0.708 to 4.19 μmol) per plate in *S. typhimurium* strain TA100 with metabolic activation. 3-Methylquinoline was mutagenic at concentrations of 1 μmol (100μg) per plate in the absence of metabolic activation.

4-Methylquinoline

Carcinogenicity: The development of liver tumors in male mice exposed as newborns and the initiation of skin tumors in two studies in female mice serve as evidence for the carcinogenicity of 4-methylquinoline. Further evidence include short-term tests demonstrating clear evidence of mutagenicity, induction of unscheduled DNA synthesis in rat hepatocytes *in vitro*, and because of its strong chemical structural analogy with a known carcinogen. 4-Methylquinoline was found to be a skin tumor initiator in Sencar mice.

5-Methylquinoline

5-Methylquinoline was mutagenic at concentrations of 100 to 600 μg (0.708 to 4.19 μmol) per plate in *S. typhimurium* strain TA100 with metabolic activation.

6-Methylquinoline

General toxicology: The oral LD_{50}s in rats has been reported as 800 mg/kg (5.59 mmol/kg) and 1,260 mg/kg (8.799 mmol/kg). The intraperitoneal LD_{50} in mice has been reported as 386 mg/kg (2.70 mmol/kg). The dermal LD_{50} in rabbits has been reported was 5g/kg (0.03 mol/kg).

Genotoxicity: 6-Methylquinoline was mutagenic at concentrations of 25 μg (0.17 μmol) per plate in *S. typhimurium* [strain not provided] without metabolic activation. 6-Methylquinoline was mutagenic in *S. typhimurium* strain TA98 without metabolic activation [concentration not provided]. 6-Methylquinoline was mutagenic at concentrations of 25 μg (0.17 μmol) per plate in *S. typhimurium* [strain not provided] in the microsomal mutagenicity assay. 6-Methylquinoline was not mutagenic in the Basc test on *Drosophila melanogaster* at 10 mM (1,400 μg/mL). It induced chromosomal aberrations and sister chromatid exchanges (SCE) *in vitro* [additional details not provided].

Immunotoxicity: 6-Methylquinoline administered topically to rabbits at 500 mg (3.49 mmol) for 24 hours was a moderate irritant.

7-Methylquinoline

Carcinogenicity: 7-Methylquinoline was not significantly tumorigenic when applied topically to Sencar mice [dose and exposure details not provided].

Genotoxicity: 7-Methylquinoline was mutagenic at concentrations of 100 to 600 μg per plate in *S. typhimurium* strain TA100 with metabolic activation. 7-Methylquinoline was found to be mutagenic at concentrations of 25 μg (0.17 μmol) per plate in *S. typhimurium* [strain not provided] without metabolic activation. 7-Methylquinoline induced chromosome aberrations and SCE *in vitro* [additional details not provided].

8-Methylquinoline

Carcinogenicity: No significant increase in liver tumors (all adenomas) was observed in male CD-1 mice injected intraperitoneally three times with 8-methylquinoline. No carcinogenic effect was observed in female mice administered the same treatment or in a subcutaneous injection study in Sprague-Dawley rats. However, 8-methylquinoline demonstrated skin tumor-initiating activity in a dermal exposure study. 8-Methylquinoline has not been listed as 'causing cancer' nor have any authoritative reviewed it.

Genotoxicity: 8-Methylquinoline was mutagenic in each of the four *S. typhimurium* studies located. It was mutagenic at concentrations of 100 to 600 μg (0.708 to 4.19 μmol) per plate in strain TA100 with metabolic activation. 8-Methylquinoline was mutagenic at concentrations of 2 μmol (300 μg) per plate when tested without metabolic activation [strain not provided]. It caused unscheduled DNA synthesis in concentrations of 1 mmol/L (143.19 mg/L) in rat hepatocytes. 8-methylquinoline also caused chromosome aberrations and SCE *in vitro* [additional details not provided].

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1.0 Basis for Nomination

4-methylquinoline was nominated in 2001 for carcinogenicity and comparative metabolism (with quinoline) studies by the Carcinogen Identification Committee for the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment. The nomination is based on concern for potential human exposure resulting from the ubiquitous occurrence of 4-methylquinoline as a contaminant in the environment and evidence for carcinogenicity in experimental animal studies.

Several methylquinolines have been previously nominated to the National Toxicology Program (NTP) for toxicity and/or carcinogenicity studies. 2- and 4-Methylquinoline were nominated for carcinogenicity studies in 1984 and were not selected for testing at that time based on low commercial production and limited information regarding the potential for human exposure. 6-, 7-, and 8-Methylquinoline were nominated and selected for genotoxicity testing in 1985.

2.0 Introduction

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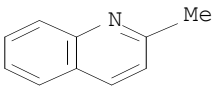
[91-63-4]



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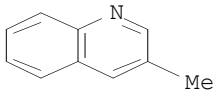

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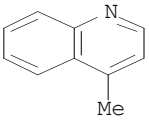

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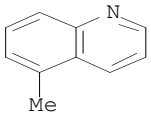

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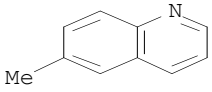

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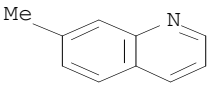
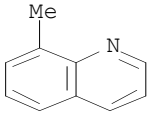
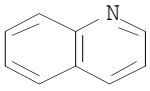


8-Methylquinoline
[611-32-5]



Methylquinoline
[27601-00-9]



D1— Me

There are common sources for environmental release and human exposure for many of the methyquinolines and toxicity information is available from recent studies for several compounds in this class. The following report serves as a supplement to the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) report on 4-methylquinoline (OEHHA, 2000). This report is not intended to be comprehensive, but rather, to provide additional information not summarized in that authoritative review. This report focuses on the seven methylquinolines in which the

methyl groups were attached to ring carbon atoms. A tabular summary of available literature including the studies described in this report is provided in Appendix B.

All seven methylquinolines have been identified in cigarette smoke (Adams et al., 1983). Levels of methylquinolines were somewhat less in smoke from filtered cigarettes, as compared to non-filtered cigarettes. Mainstream smoke of an 85-mm U.S.-blended tobacco unfiltered cigarette contained a total of 0.7 μg methylquinoline isomers (Dong et al., 1978a). 2-, 4-, and 6-Methylquinoline were identified as nicotine pyrolysis products (Schmeltz et al., 1979). 2-, 6-, 7-, and 8-Methylquinoline were identified in coal tar (Coal Tar Research Association, 1965; cited by Sarkany and Gaylarde, 1976).

When methylquinolines were compared to quinoline for mutagenicity in *Salmonella typhimurium* strain TA100, only 4-methylquinoline and 6-methylquinoline were more mutagenic than quinoline. The mutagenicity of 7-methylquinoline was comparable to quinoline (Dong et al., 1978b).

3.0 2-Methylquinoline; Quinaldine (CAS RN 91-63-4)

3.1 Uses

2-Methylquinoline is used as an intermediate in the production of dyes and in food coloring. It constitutes 0.5% or less of the food coloring Quinoline Yellow WS (Kamath, undated) or Food Yellow 13 (European Union, 1999), which is banned in the United States, Australia, and Norway (lactose.co.uk, undated). It is also used in the manufacture of pharmaceuticals, organic chemicals, and acid-base indicators (NTP, 2001-001424). 2-Methylquinoline is used as a fish anesthetic in pisciculture to relieve stress from handling (Sills, 1973a; Sills, 1973b; Syndel Laboratories Ltd., 2002). It was also listed by the Skincare Institute (undated) as a "harmful cosmetic chemical in today's cosmetics."

2-Methylquinoline is supplied by Alfa Aesar/Johnson Matthey, 98% purity, in 25-g, 100-g, and 500-g amounts (Alpha Aesar, undated) and by TCI America, 95+% purity, in 25-g and 200-g amounts (TCI America, 1999). Chemcyclopedia (Block, 2002) also listed SST Corp. of Clifton, N.J., as a vendor.

3.2 Production

2-Methylquinoline may be produced by first producing quinoline via the Scraup synthesis. Aniline is heated with glycerol, concentrated sulfuric acid, and an oxidizing agent, e.g., the nitro compound corresponding to aniline, arsenic acid or ferric chloride. Subsequently, glycerol is dehydrated to acrolein, which is added to aniline to form B-anilinopropinaldehyde, then undergoes cyclization to form 1,2-dihydroquinoline and oxidation to quinoline. 2-methylquinoline is formed by alkylating quinoline via irradiation in a solution of benzene-containing acetic acid (Holter, 1985).

3.3 Environmental Fate and Occurrence

In Puget Sound, marine sediment was found to have low levels of 2-methylquinoline, with concentrations becoming higher based on proximity to urban areas (Furlong and Carpenter, 1982). It was also identified in raw U.S. sewage and primary and secondary effluents, concentrated in the solid phase of wastes at a publicly owned U.S. treatment

plant (Melcer et al., 1995). Additionally, 2-methylquinoline has been identified in creosote-contaminated soil (Meyer et al., 1999; Brumley et al., 1991), in groundwater from hazardous waste sites in Florida and Minnesota (Ondrus and Steinheimer, 1990), in an aquifer contaminated by wood-treatment chemicals (Pereira et al., 1987b), and in an industrial park (Gas Works Park) in Seattle, WA (Turney and Goerlitz, 1990). 2-Methylquinoline was among numerous compounds determined in oil shale retort water (Dobson et al., 1985). It has also been identified in the air in Liverpool, England; fossil fuel combustion in the winter was the main source (Chen and Preston, 1998).

In the environment, 2-methylquinoline is transformed by *Alcaigenes* and *Arthrobacter* species to 3,4-dihydroxy-2-oxo-1,2-dihydroquinoline, followed by decomposition to quinisatin. Quinisatin then decomposes to anthranilic acid (CAS RN 118-92-3) and isatin (CAS RN 91-56-5) (Dembek et al., 1989). Johansen et al. (1997) reported that 2-methylquinoline was resistant to degradation by *Desulfobacterium indolicum*, and Pereira et al. (1987a; cited by Bollag and Kaiser, 1991) noted that it does not degrade in mixed culture fermentation.

3.4 Exposure Potential

Occupational exposure may occur from inhalation at aluminum reduction plants, where 2-methylquinoline was found in workplace air (Thrane and Stray, 1986), and during the manufacturing of dyes, pharmaceuticals, organic chemicals, and acid-base indicators (NTP, 2001-001424). Data from NIOSH Occupational Surveys indicated that the total number of workers potentially exposed to 2-methylquinoline dropped from 28,314 in 1974 to 4,782 in 1983 (National Occupational Hazard Survey, 1972-1974; National Occupational Exposure Survey, 1981-1983, both cited by RTECS, 2001).

Inhalation exposure occurs from smoking cigarettes or from exposure to second-hand smoke (Adams et al., 1983). Dermal exposure to 2-methylquinoline might be through treatment of skin disorders with coal tar (Sarkany and Gaylarde, 1976). Another source of human exposure may be from eating fish, which were found to contain residues of 2-methylquinoline. Analytical methods have been developed for determining 2-methylqinoline levels in fish muscle tissue for consumer safety testing (Allen and Hunn, 1986; Allen and Sills, 1970a; Allen and Sills, 1970b). Ingesting decaffeinated coffee or inhaling its vapors could also be a source of 2-methylquinoline exposure; the compound was found in vapor from decaffeinated coffee that was heated to 350 degrees (Sasaki et al., 1987).

3.5 Absorption, Distribution, Metabolism, and Excretion

When tested *in vitro*, 2-methylquinoline was metabolized to 2-methylquinoline-5,6-dihydro-5,6-diol (Saeki et al., 1996; cited by OEHHA, 2000).

Rabbits injected subcutaneously with 2-methylquinoline excreted 3-hydroxyquinaldine, 6-hydroxyquinaldine, quinaldic acid, and several unknown compounds in the urine. When given orally, 2-methylquinoline was excreted unchanged (Komiya, 1965).

2-Methylquinoline was not detected in the urine of 200 normal human subjects or of 25 patients with transitional cell carcinoma of the bladder (Williams, 1988).

3.6 Toxicity Studies

General Toxicity: When 2-methylquinoline was administered orally to rats, the LD_{50} was 1,230 mg/kg (8.590 mmol/kg). When applied to the skin of rabbits, the LD_{50} was 1,870 μL/kg (1,980 mg/kg) (Archives of Industrial Hygiene and Occupational Medicine, 1951; cited by RTECS, 2001). 2-Methylquinoline caused severe eye irritation in rabbits at a dose of 750 μg (5.24 μmol) and was found to be moderately toxic via oral and dermal routes (doses not provided) (NTP, 2001-001424).

Genotoxicity: 2-Methylquinoline had the weakest mutagenicity among the methylquinolines (Sengoku et al., 1989 abstr.). 2-Methylquinoline was not mutagenic when tested at concentrations of 50 to 500 μg (0.35 to 3.5 μmol) per plate in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 with and without metabolic activation (Bowden et al., 1976). It was not mutagenic at 7mM (1002.33 μg/mL) in *S. typhimurium* strain TM677 with metabolic activation (Phillips Petroleum, 1992). However, 2-methylquinoline was mutagenic at concentrations of 100 to 600 μg (0.708 to 4.19 μmol) per plate in *S. typhimurium* strain TA100 with metabolic activation (Dong et al., 1978b). In a study reported in RTECS (2001), 2-methylquinoline was mutagenic in *S. typhimurium* (strain n.p.) at 2 μmol (300 μg) per plate in the absence of metabolic activation (Takahashi et al., 1988, cited by RTECS, 2001).

Immunotoxicity: 2-Methylquinoline inhibited interferon induction in mouse embryo fibroblast cultures (Sonnenfeld, 1983), but it had no effect on interferon induction in mice *in vivo* when given intraperitoneally (Sonnenfeld and Hudgens, 1983). When tested on rabbit skin at 500 mg (3.49 mmol) for 24 hours, 2-methylquinoline had a mild effect (Marhold, 1986, cited by RTECS, 2001), and it caused mild skin irritation in rabbits when 10 mg (0.70 mmol) was applied for 24 hours (NTP, 2001-001424). Coal tar, which contains 0.6% to 4.2% 2-methylquinoline, caused guinea-pig epidermis to thicken (Coal Tar Research Association, 1965; cited by Sarkany and Gaylarde, 1976; Sarkany and Gaylarde, 1976). In human patch testing, 2-methylquinoline induced dermal sensitization. Reactions to 2-methylquinoline and certain other compounds were "considered to be group allergies since contact is hardly possible with these substances [in isolation] in everyday life" (Pevny and Hutzler, 1988).

4.0 3-Methylquinoline (CAS RN 612-58-8)

4.1 Uses

3-methylquinoline is available in bulk quantities from TCI America (2000). No information on its uses was located.

4.2 Production

No production information on 3-methylquinoline was located.

4.3 Environmental Fate and Occurrence

In activated sewage sludge, *Comamonas testosteroni* 63 metabolized 3-methylquinoline to 3-methyl-2-oxo-1,2-dihydroquinoline; 6-hydroxy-3-methyl-2-oxo-1,2-dihydroquinoline; 5,6 dihydrodiol-3-methyl-2-oxo-1,2-dihydroquinoline; 5,6-dihydroxy-3-methyl-2-oxo-1,2-dihydroquinoline; 3-methyl-5-hydroxy-6-(3-carboxyl-3-oxopropenyl)-1*H*-2-pyridon; and 2,5,6-trihydroxy-3-methylpyridine. The latter is further degraded into unidentified products (Schach et al., 1993; cited by Etienne, 2001). In tests run on a nitrogen-containing shale oil fraction, *Pseudomonas* species hydroxylated the 2-position of 3-methylquinoline (Aislabie et al., 1990). Microbial degradation of 3-methylquinoline by *D. indolicum* gave a 2-quinolinone (also called 2-hydroxy) derivative (Johansen et al., 1997). Also, *Pseudomonas putida* and *Rhodococcus* sp. B1 biodegrade 3-methylquinoline (NC-IUBMB, 1999).

4.4 Exposure Potential

Occupational exposure may occur from inhalation at aluminum reduction plants, where 3-methylquinoline was found in workplace air (Thrane and Stray, 1986).

Inhalation exposure occurs from smoking cigarettes or from exposure to second-hand smoke (Adams et al., 1983). Exposure may also occur from foods; 3-methylquinoline was found among numerous other volatile compounds from autolyzed yeast extract used as food flavorant (Pino et al., 1999).

4.5 Absorption, Distribution, Metabolism, and Excretion

When tested *in vitro*, 3-methylquinoline was metabolized to 3-methylquinoline-5,6-dihydro-5,6-diol (Saeki et al., 1996; cited by OEHHA, 2000).

4.6 Toxicity Studies

Genotoxicity: 3-Methylquinoline was not mutagenic in the "mutational enhancement" test at concentrations of 25 to 100 μg/mL (0.17 to 4.19 μmol/mL) in the *Escherichia coli* HCR+ strain (Sideropoulos and Specht, 1984). It was mutagenic at concentrations of 100 to 600 μg (0.708 to 4.19 μmol) per plate in *S. typhimurium* strain TA100 with metabolic activation (Dong et al., 1978b). 3-Methylquinoline was mutagenic at concentrations of 1 μmol (100μg) per plate in the absence of metabolic activation (Takahashi et al., 1988; cited by RTECS, 2001).

5.0 4-Methylquinoline; Lepidine (CAS RN 491-35-0)

5.1 Uses

4-Methylquinoline is available from TCI America of Portland, OR., which sells it in quantities of 25 mL and 500 mL, 98+% purity, and from Penta Manufacturing Co. of Livingston, NJ., which lists the chemical in its catalog under kosher products (Block, 2002; TCI America, 1999; Penta Manufacturing Company, undated). No information on its uses was located.

5.2 Production

No production information on 4-methylquinoline was located.

5.3 Environmental Fate and Occurrence

4-Methylquinoline is an environmental contaminant primarily associated with the recovery of hydrocarbons from shale oil and coal gasification and wood treatment processes (OEHHA, 2000). 4-Methylquinoline has been identified in soil (Meyer et al., 1999; Brumley et al., 1991), freshwater streams, and groundwater (Middaugh et al., 1991) contaminated by creosote. 4-Methylquinoline was found in the aqueous phase, but not the oily-tar phase of contaminated groundwater (Pereira et al., 1983). It was found in sediment contaminated with road runoff in England (Boxall and Maltby, 1995). 4-Methylquinoline and its derivative, 2-hydroxy-4-methylquinoline (CAS RN 607-99-9), were identified in groundwater from hazardous waste sites in Florida and Minnesota (Ondrus and Steinheimer, 1990), and in an aquifer contaminated by wood-treatment chemicals (Pereira et al., 1987b). It was also identified in contaminated groundwater at a gas works park in Seattle, WA (Turney and Goerlitz, 1990) and in raw sewage, primary and secondary effluents, and in the solid phase of wastes at a publicly owned treatment plant in the U.S. (Melcer et al., 1995).

Microbes collected from soil at an abandoned coal gasification site degraded 4-methylquinonline to the 2-hydroxy derivative, which eventually disappeared, and to hydroxy-4-methylcoumarin. The authors claimed that this is the first report of methylquinolines undergoing aerobic biodegradation (Sutton et al., 1996). 4-Methylquinoline is degraded to 4-methyl-2-oxo-1,2-dihydroquinoline; 8-hydroxy-4-methyl-2-oxo-1,2-dihydroquinoline; 7,8-dihydroxy-4-methyl-2-oxo-1,2-dihydroquinoline; and possibly 6-hydroxy-5-(2-carboxyethenyl)-4-methyl-1*H*-2-pyridone (a benzo ring-opened product) by *Pseudomonas putida* (Ruger et al., 1993). Degradation of 4-methylquinoline by *D. indolicum* gave only the 2-quinolinone (also called 2-hydroxy) derivatives (Johansen et al., 1997). *Rhodococcus* sp. B1, *C. testosteroni* 63, and *Serratia marcescens* also degrade 4-methylquinoline (NC-IUBMB, 1999). 4-Methylquinoline in mixed culture fermentation was converted to 1,4-dimethyl-2(1H)-quinolinone (Pereira et al., 1987a; cited by Bollag and Kaiser, 1991). With cell extract fermentation, it was converted to 4-methyl-2(1H) quinolinone (Pereira et al., 1987b). These reactions produce the intermediate 2-hydroxy-4-methylquinoline and also produce 2-methoxy-4-methylquinoline (Bollag and Kaiser, 1991).

5.4 Exposure Potential

Occupationally, workers may be exposed to 4-methylquinoline in creosote and tar plants, and in other industrial sites. The total number of workers potentially exposed to 4-methylquinoline was 1,557 in 1983 based on a NIOSH Occupational Survey (NOES, 1981-1983; cited by RTECS, 2001).

Exposure to 4-methylquinoline occurs from smoking cigarettes or from exposure to second-hand smoke (Adams et al., 1983). Exposure may also occur based on its presence in food flavorings (Hayatsu, 1991) and in urban particulate matter (OEHHA, 2000).

5.5 Absorption, Distribution, Metabolism, and Excretion

When tested *in vitro*, 4-methylquinoline was metabolized to 4-hydroxymethylquinoline; 3-hydroxy-4-hydroxy-methylquinoline; 4-methylquinoline *N*-oxide; and 3-hydroxy-4-

methylquinoline (Saeki et al., 1996; cited by OEHHA, 2000). 2(1*H*)-Quinolinone,4-methyl-; and 4-quinolinemethanol are also metabolites of 4-methylquinoline (Johansen et al., 1997; Ondrus and Steinheimer, 1990; Ruger et al., 1993; Sutton et al., 1996; [Pereira et al., 1987a; cited by Bollag and Kaiser, 1991]).

5.6 Toxicity Studies

OEHHA (2000) reported on several carcinogenicity studies of 4-methylquinoline in mice (via intraperitoneal administration) and in rats (via subcutaneous administration). Two initiation/promotion studies were also summarized, where 4-methylquinoline was administered as the initiator to female mice. Genotoxicity studies reported include multiple *Salmonella* reverse mutation assays and a single *in vitro* test in mammalian cells. Based on the results of those studies, OEHHA (2000) concluded that:

> *There is evidence for the carcinogenicity of 4-methylquinoline, with the development of liver tumors in male mice exposed as newborns via three intraperitoneal injections and the initiation of skin tumors in two studies in female mice. Further evidence of carcinogenic potential is provided by clear evidence of mutagenicity in short-term tests, induction of unscheduled DNA synthesis in rat hepatocytes in vitro, and by strong chemical structural analogy with a known carcinogen.*

Other information not reported in OEHHA (2000): 4-Methylquinoline was found to be a skin tumor initiator when bioassayed in Sencar mice (dose and exposure n.p.) (Lavoie et al., 1983; cited by HSDB, 2002).

Among the methylquinolines, 4-methylquinoline was found to have the strongest mutagenicity in *S. typhimurium* strain TA100 (Sengoku et al., 1989 abstr.). 4-Methylquinoline was mutagenic at 90 μM (13 μg/mL) in *S. typhimurium* strain TM677 with metabolic activation (Phillips Petroleum, 1992).

4-Methylquinoline inhibits rat-platelet aggregation induced by thrombin in a dose-dependent manner (Chaudhury et al., 1988).

6.0 5-Methylquinoline (CAS RN 7661-55-4)

6.1 Uses

No information on the use of 5-methylquinoline was located.

6.2 Production

No information on the production of 5-methylquinoline was located.

6.3 Environmental Fate and Occurrence

No environmental fate and occurrence information on 5-methylquinoline was located.

6.4 Exposure Potential

Exposure to 5-methylquinoline may occur from smoking cigarettes or from exposure to second-hand smoke (Adams et al., 1983).

6.5 Absorption, Distribution, Metabolism and Excretion

No information on the absorption, distribution, metabolism and excretion of 5-methylquinoline was located.

6.6 Toxicity Studies

Genotoxicity: 5-Methylquinoline was mutagenic at concentrations of 100 to 600 μg (0.708 to 4.19 μmol) per plate in *S. typhimurium* strain TA100 with metabolic activation (Dong et al., 1978b).

7.0 6-Methylquinoline (CAS RN 91-62-3)

7.1 Uses

6-Methylquinoline is used in fragrances for soaps, perfumes, and creams (NTP, 2001a). It is also used as an intermediate in pharmaceutical manufacturing by Sumikin Chemical Co., Ltd. (undated).

6-Methyquinoline is available from TCI America in 25-g and bulk quantities (TCI America, 1999; 2000). It is also available from Wilshire Chemical Company, Inc. (undated). Penta Manufacturing Co. (undated) of Livingston, NJ., also supplies the chemical as a "kosher product" (Block, 2002).

7.2 Production

No information on the production of 6-methylquinoline was located.

7.3 Environmental Fate and Occurrence

6-Methylquinoline has been identified in creosote-contaminated soil in the United States (Brumley et al., 1991) and in the air in Liverpool, England (Chen and Preston, 1998). The source of the air pollutant was attributed to fossil fuel combustion in winter.

Based on tests run on a nitrogen-containing shale oil fraction, *Pseudomonas* species hydroxylated the 2-position of 6-methylquinoline (Aislabie et al., 1990). *Pseudomonads* degraded 6-methylquinoline to hydroxy-derivatives after acclimation in aqueous and nonaqueous immobilized-cell bioreactors (Rothenburger and Atlas, 1993). Degradation of 6-methylquinoline by *D. indolicum* gave 2-quinolinones, which were further degraded to the 3,4-dihydro-2-quinolinones (Johansen et al., 1997). The fungus *Cunninghamella elegans* transformed 6-methylquinoline to 6-hydroxymethylquinoline (6-quinoline-methanol) (major derivative), quinoline-6-carboxylic acid, and 6-methylquinoline *N*-oxide (Mountfield and Hopper, 1998).

7.4 Exposure Potential

Occupationally, workers may be exposed to 6-methylquinoline in creosote and tar plants, and in other industrial sites.

Inhalation exposure to 6-methylquinoline occurs from smoking cigarettes or from exposure to second-hand cigarette smoke (Adams et al., 1983). Exposure may occur from ingestion of whiskey, tea, pharmaceuticals, and artificial food flavorings (NTP,

2001a; Sumikin Chemical Co., Ltd., undated). Dermal exposure to 6-methylquinoline may come from coal tar used to treat skin disorders (Sarkany and Gaylarde, 1976).

7.5 Absorption, Distribution, Metabolism, and Excretion

When tested *in vitro*, 6-methylquinoline was metabolized to 5-hydroxy-6-methylquinoline (116529-84-1); 6-methylquinoline 5,6-epoxide (149635-36-9); 6-methylquinoline 7,8-epoxide (149635-37-0); 6-methylquinolinylphenol (149939-03-7); and 6-(hydroxymethyl) quinoline (100516-88-9) (Scharping et al., 1993).

7.6 Toxicity Studies

General Toxicology: The oral LD_{50} in rats has been reported as 800 mg/kg (5.59 mmol/kg) (RTECS, 2001) and 1,260 mg/kg (8.799 mmol/kg) (NTP, 2001-001858). With intraperitoneal administration to mice, the LD_{50} was 386 mg/kg (2.70 mmol/kg) (Food and Cosmetics Toxicology, 1979, cited by RTECS, 2001; NTP, 2001-001858). With dermal administration to rabbits, the LD_{50} was 5g/kg (0.03 mol/kg) (Food and Cosmetics Toxicology, 1979, cited by RTECS, 2001).

Genotoxicity: 6-Methylquinoline was not mutagenic in the Basc test on *Drosophila melanogaster* at 10 mM (1,400 μg/mL) (Wild et al., 1983). 6-Methylquinoline was mutagenic at concentrations of 25 μg (0.17 μmol) per plate in *S. typhimurium* (strain n.p.) without metabolic activation (Society of Toxicology, 1980; RTECS, 2001; NTP, 2001-001858). In another study, 6-methylquinoline was mutagenic at concentrations of 1-4 μmol (100 to 600 μg) per plate in *S. typhimurium* strain TA100 when tested with metabolic activation (Dong et al., 1978b) but not when tested without metabolic activation at the same dose level (Wild et al., 1983). 6-Methylquinoline was mutagenic in *S. typhimurium* strain TA98 without metabolic activation (concentration n.p.) (Nagao et al., 1977; cited by Kier et al., 1986). It induced chromosomal aberrations and sister chromatid exchanges (SCE) *in vitro* (additional details n.p.) (NTP, 2001a).

Immunotoxicity: 6-Methylquinoline administered topically to rabbits at 500 mg (3.49 mmol) for 24 hours was a moderate irritant (RTECS, 2001). Coal tar, which contains up to 1% 6-methylquinoline, caused guinea-pig epidermis to thicken (Coal Tar Research Association, 1965; cited by Sarkany and Gaylarde, 1976; Sarkany and Gaylarde, 1976).

8.0 7-Methylquinoline (CAS RN 612-60-2)

8.1 Uses

7-Methylquinoline is used to inhibit corrosion in steel (NTP, 2001b), and it is available from TCI America in 5-g and bulk quantities (TCI America, 1999; 2000).

8.2 Production

No information on the production of 7-methylquinoline was located.

8.3 Environmental Fate and Occurrence

7-Methylquinoline has been identified in raw sewage and primary and secondary sewage treatment effluents in the United States, concentrated in the solid phase of wastes at a publicly owned treatment plant (Melcer et al., 1995).

In tests run on a nitrogen-containing shale oil fraction, *Pseudomonads* species hydroxylated the 2-position of 7-methylquinoline (Aislabie et al., 1990). The 2-hydroxylation products did not undergo further microbial degradation in anoxic freshwater sediments (Liu et al., 1994).

8.4 Exposure Potential

Inhalation exposure to 7-methylquinoline occurs from smoking cigarettes or from exposure to second-hand smoke (Adams et al., 1983). Dermal exposure may occur from coal tar used to treat skin disorders (Sarkany and Gaylarde, 1976).

8.5 Absorption, Distribution, Metabolism, and Excretion

No information was located on absorption, distribution, metabolism, and excretion for 7-methylquinoline.

8.6 Toxicity Studies

Carcinogenicity: 7-methylquinoline was not significantly tumorigenic when applied topically to Sencar mice (dose and exposure n.p.) (Lavoie et al., 1983; cited by HSDB, 2002).

Genotoxicity: 7-Methylquinoline was mutagenic at concentrations of 100 to 600 μg per plate in *S. typhimurium* strain TA100 with metabolic activation (Dong et al., 1978b). A study by Epler et al. (1978) reported mutagenicity in the same strain when tested with metabolic activation, although information on concentrations tested was not provided. Another study by Beauchamp and Shelby (date n.p.; cited by Epler et al., 1979), also reported 7-methylquinoline as mutagenic in *S. typhimurium* strain TA100, although neither the testing concentration nor metabolic status was provided in the source paper. 7-Methylquinoline was found to be mutagenic at concentrations of 25 μg (0.17 μmol) per plate in *S. typhimurium* (strain n.p.) without metabolic activation (Society of Toxicology, 1980, cited by RTECS, 2001; NTP, 2001-001859). 7-Methylquinoline induced chromosome aberrations and SCE *in vitro* (additional details n.p.) (NTP, 2001b).

Immunotoxicity: Coal tar, which contains up to 2.1% 7-methylquinoline, caused guinea-pig epidermis to thicken (Coal Tar Research Association, 1965; cited by Sarkany and Gaylarde, 1976; Sarkany and Gaylarde, 1976).

9.0 8-Methylquinoline (CAS RN 611-32-5)

9.1 Uses

8-Methylquinoline is used to inhibit corrosion in steel (NTP, 2001c). Coal tar preparations that contain 8-methylquinoline have been used to treat human and animal skin disorders (Sarkany and Gaylarde, 1976). 8-Methylquinoline is used as an intermediate for pharmaceutical manufacturing by Sumikin Chemical Co., Ltd. (undated) of Japan. Both TCI America and Wilshire Chemical Company, Inc. supply 8-methylquinoline; TCI America supplies it in 25-g and bulk quantities (TCI America, 1999; 2000; Wilshire Chemical Company, Inc., undated).

9.2 Production

First Chemical Corporation is identified as a producer of 10,000 to 500,000 pounds of 8-methylquinoline in 1998 (U.S. EPA Office of Pollution Prevention and Toxics, 2001).

9.3 Environmental Fate and Occurrence

In the United States, 8-methylquinoline has been identified in creosote-contaminated soil (Brumley et al., 1991), in a particle fraction of diesel particulates (Hanson et al., 1979), in raw sewage and primary and secondary effluents, and in the solid phase of wastes at a publicly owned treatment plant (Melcer et al., 1995).

In tests run on a nitrogen-containing shale oil fraction, *Pseudomonads* species hydroxylated the 2-position of 8-methylquinoline (Aislabie et al., 1990). Microbial degradation of 8-methylquinoline by *D. indolicum* gave the corresponding 2-quinolinones, which were further degraded to the corresponding 3,4-dihydro-2-quinolinones (Johansen et al., 1997). The 2-hydroxylation products did not undergo further microbial degradation in anoxic freshwater sediments (Liu et al., 1994). *Rhodococcus* sp. B1 and *C. testosteroni* 63 also degrade 8-methylquinoline (NC-IUBMB, 1999).

9.4 Exposure Potential

Occupationally, workers may be exposed to 8-methylquinoline in wood treatment plants using creosote and in other industrial settings.

The public may be exposed via diesel fuel exhaust. Inhalation exposure to 8-methylquinoline may occur from smoking cigarettes or from exposure to second-hand smoke (Adams et al., 1983). Dermal exposure may come from coal tar used to treat skin disorders (Sarkany and Gaylarde, 1976).

9.5 Absorption, Distribution, Metabolism, and Excretion

When tested *in vitro*, 8-methylquinoline was metabolized to 8-methylquinoline *N*-oxide (4053-38-7); 5-hydroxy-8-methylquinoline (16026-71-4); *trans*-3,4-dihydro-8-methyl-3,4-quinolinediol (149635-38-1); *trans*-5,6-dihydro-8-methyl-5,6-quinolinediol (149665-55-4); and 8-methylquinolinylphenol (149939-02-6) (Scharping et al., 1993). Also, 8-quinolinemethanol (16032-35-2) is a potential fungal metabolite of 8-methylquinoline (Mountfield and Hopper, 1998).

9.6 Toxicity Studies

Carcinogenicity: OEHHA (2000) reported that 8-methylquinoline has also been tested in the same bioassay series as 4-methylquinoline. Results were reported as follows:

> *Among male CD-1 mice injected intraperitoneally three times with 8-methylquinoline as neonates, an increase in liver tumors (all adenomas) was observed at one year, although this increase was not statistically significant (8/28, treated vs. 4/21, controls) [LaVoie et al., 1988]. No carcinogenic effect was observed in female mice or in a subcutaneous injection study in Sprague-Dawley rats (LaVoie et al., 1988). 8-Methylquinoline demonstrated skin tumor-*

initiating activity in the dermal exposure study reported by LaVoie et al. (1984). 8-Methylquinoline has not been listed as 'causing cancer' nor have any authoritative bodies under Proposition 65 reviewed it.

Genotoxicity: 8-Methylquinoline was mutagenic in each of the four *S. typhimurium* studies located. It was mutagenic at concentrations of 100 to 600 μg (0.708 to 4.19 μmol) per plate in strain TA100 with metabolic activation (Dong et al., 1978b). A study by Epler et al. (1978) reported mutagenicity in the same strain when tested with metabolic activation, although information on concentrations tested was not provided. Another study by Beauchamp and Shelby (date n.p.; cited by Epler et al., 1979), also reported 8-methylquinoline as mutagenic in *S. typhimurium* strain TA100, although neither the testing concentration nor metabolic status was provided in the source paper. RTECS (2001) reported 8-methylquinoline as mutagenic at concentrations of 2 μmol (300 μg) per plate when tested without metabolic activation; information on strain was not available in the database record (Nagao et al., 1977; cited by RTECS, 2001). It caused unscheduled DNA synthesis in concentrations of 1 mmol/L (143.19 mg/L) in rat liver (LaVoie et al.,1991; cited by RTECS, 2001). 8-methylquinoline caused chromosome aberrations and SCE *in vitro* (additional details n.p.) (NTP, 2001c).

Immunotoxicity: Coal tar, which contains 0.6% to 4.2% 8-methylquinoline, caused guinea-pig epidermis to thicken (Coal Tar Research Association, 1965; cited by Sarkany and Gaylarde, 1976; Sarkany and Gaylarde, 1976).

10.0 Methylquinoline (not further specified) (CAS RN 27601-00-9)

Searches were conducted for methylquinoline (not otherwise specified). However, no relevant information not otherwise mentioned in previous sections was identified in the literature.

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14.0 Acknowledgements

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15.0 Units and Abbreviations

μg/L = microgram(s) per liter
μg/mL = microgram(s) per milliliter
μg = microgram
μg per plate = microgram(s) per plate
μmol = micromole(s)
μM = micromolar
μmol per plate = micromoles per plate
μL/kg = microliters per kilogram
ACGIH = American Conference of Governmental Industrial Hygienists
bw = body weight
CNS = central nervous system
EPA = Environmental Protection Agency
F = female(s)
g = gram(s)
g/mL = gram(s) per milliliter
h = hour(s)
HD = high dose
HSDB = Hazardous Substances Data Bank

i.p. = intraperitoneal(ly)
kg = kilogram(s)
L = liter(s)
lb = pound(s)
LC = liquid chromatography
LC_{50} = lethal concentration for 50% of test animals
LD_{50} = lethal dose for 50% of test animals
LD = low dose
M = male(s)
mg/kg = milligram(s) per kilogram
mg/m^3 = milligram(s) per cubic meter
mg/mL = milligram(s) per milliliter
mL/kg = milliliter(s) per kilogram
mM = millimolar
mmol = millimole(s)
mmol/kg = millimoles per kilogram
mol = mole(s)
mol. wt. = molecular weight
NIEHS = National Institute of Environmental Health Sciences
NIOSH = National Institute for Occupational Safety and Health
n.p. = not provided
OSHA = Occupational Safety and Health Administration
PEL = permissible exposure limit
ppb = parts per billion
ppm = parts per million
p.o. = peroral(ly), *per os*
REL = relative exposure limit
s = second(s)
s.c. = subcutaneous(ly)
TSCA = Toxic Substances Control Act
TWA = time-weighted average
USEPA = U.S. Environmental Protection Agency
wk = week(s)
yr = year(s)

APPENDIX A: DESCRIPTION OF THE METHYLQUINOLINES LITERATURE SEARCH STRATEGY, DATABASES USED, AND BIOMEDICAL DATABASE RESULTS (TALLIES AND TOTALS)

Search Strategy

Internet searches on methylquinolines using the Google.com search engine retrieved the OEHHA (California EPA) draft (a pdf file), material safety data sheets, and miscellaneous other materials included in the search package and/or the reference set. TOXNET searches were done in EMIC and GENETOX. The CAS RNs of all the methylquinolines were searched at the TSCA Inventory Update Rule site.

Registry File and CAPLUS (same content as HCAPLUS)

Initial searches were done in the Registry file and CAPLUS to identify synonyms of the methylquinolines and synonyms and CAS RNs of possible or actual metabolites. Keywords used in CAPLUS included the CAS RNs combined with the terms "metab? OR excret? OR urin? OR blood OR plasma OR serum OR lymph? OR pharmacokinetic? OR toxicokinetic?". Eleven of the 97 records were printed. Additional CAPLUS records were obtained from the 10 most recent publications included in the ALL format of the Registry records. A few of these records were included in the package.

A list of hydroxylated and otherwise oxidized compounds and their CAS RNs was compiled from the indexing of the CAPLUS records. Additional Registry records were printed for about 30 of these compounds.

Searches in the Biomedical Databases MEDLINE, CANCERLIT, TOXLINE, NIOSHTIC, AGRICOLA, ESBIOBASE, BIOTECHNO, CABA, EMBASE, BIOSIS, LIFESCI

The Registry numbers of those compounds that had entries in the biomedical databases (as listed on the Registry records) were used in the search strategy for those databases. In addition, various name fragments were used in the biomedical databases strategy, which is shown below.

RTECS and Biomedical Databases Search Session

```
     (FILE 'HOME' ENTERED AT 15:59:22 ON 24 OCT 2001)

     FILE 'RTECS' ENTERED AT 15:59:32 ON 24 OCT 2001
L1             1 S 93-10-7
L2             1 S 4053-40-1
L3             1 S 7661-55-4
L4             1 S 91-63-4
L5             1 S 612-58-8
L6             1 S 491-35-0
L7             1 S 91-62-3
L8             1 S 612-60-2
L9             1 S 611-32-5

     FILE 'MEDLINE, CANCERLIT, TOXLINE, NIOSHTIC, AGRICOLA, ESBIOBASE,
     BIOTECHNO, CABA, EMBASE, BIOSIS, LIFESCI' ENTERED AT 16:02:26 ON 24 OCT
     2001
L10          686 S METHYLQUINOLINE?
L11          403 S QUINALDINE
L12           95 S LEPIDINE
L13            0 S TOLUQUINOLINE
L14          350 S 7661-55-4 OR 27601-00-9 OR 91-63-4 OR 612-58-8 OR 491-35-0 OR
                   91-62-3 OR 612-60-2 OR 611-32-5
L15         1116 S L10 OR L11 OR L12
L16         1205 S L15 OR L14 [Methylquinolines]
L17            0 S QUINOLINYLMETHANOL?
L18            0 S QUINALDINOL
L19           36 S HYDROXYMETHYLQUINOLINE?
L20          251 S QUINOLINEMETHANOL?
L21            0 S QUINOLIN(2A)CARBINOL
L22            7 S HYDROXYMETHYL(W)QUINOLINE?
L23          291 S L19 OR L20 OR L22
L24          175 S 93-10-7 OR 56026-00-7 OR 4363-93-3 OR 1780-17-2 OR 16032-35-2
                   100516-88-9 or 607-66-9
L25           27 S METHYL(2A)QUINOLINOL
L26          317 S L23 OR L25
L27         2380 S FORMYLQUINOLINE? OR QUINOLINECARBOXALDEHYDE? OR HYDROXYQUINAL... [Did not
                   use this set because it was so large.  Used terms singly and left out L33.]
L28          358 S HYDROXYLEPIDINE OR LEPIDINOL OR LEPIDINONE OR METHYLCARBOSTYRIL OR
METHYLQUINOLIN(2A)ONE? OR METHYL(2A)QUINOLONE?
L29          817 S L23 OR L24 OR L25 OR L25 OR L28
L30           15 S FORMYLQUINOLINE?
L31           61 S QUINOLINECARBOXALDEHYDE?
L32           34 S HYDROXYQUINALDINE
L33         1917 S QUINOLINECARBOXYLIC(W)ACID [Did not use this large set.]
L34           26 S CARBOXYQUINOLINE?
L35          197 S QUINALDIC(W)ACID
L36            0 S QUINOLINYLCARBOXYLIC(W)ACID
L37          332 S L30 OR L31 OR L32 OR L34 OR L35
L38         1041 S L29 OR L37 [Presumed methylquinoline metabolites/biodegradation products]
L39          982 S L38 NOT L16 [Presumed metabolites set reduced after removal of overlap with
                               methylquinolines set.]
                 SET DUPORDER FILE
L40          709 DUP REM L16 (496 DUPLICATES REMOVED)
L41          709 SORT L40 1-709 TI                                    [Methylquinolines set after
                                                                duplicate
                                                                       removal; sorted by title]
                 SAVE L41 L650SBASEBIO/A
L42          609 DUP REM L39 (373 DUPLICATES REMOVED)
L43          609 SORT L42 1-609 TI
                 SAVE L43 L650SOTHRBIO/A [Presumed metabolites set after duplicate
removal; in alphabetical order by title]
```

Results

Results Tallies for Biomedical Databases

Biomedical Databases		Number of Records	Adjusted[a]	Number Printed (Plus L42)
Methylquinolines set				
L40	709 DUP REM L16 (496 DUPLICATES REMOVED)			
	ANSWERS '1-137' FROM FILE MEDLINE	137	147	28 (55)
	ANSWERS '138-141' FROM FILE CANCERLIT	4	4	1 (6)
	ANSWERS '142-294' FROM FILE TOXLINE	153	157	61 (69)
	ANSWERS '295-302' FROM FILE NIOSHTIC	8	8	3 (5)
	ANSWERS '303-322' FROM FILE AGRICOLA	20	20	3 (5)
	ANSWERS '323-332' FROM FILE ESBIOBASE	10	10	1 (1)
	ANSWERS '333-350' FROM FILE BIOTECHNO	18	18	3 (3)
	ANSWERS '351-390' FROM FILE CABA	40	41	1 (1)
	ANSWERS '391-582' FROM FILE EMBASE	192	192	14 (26)
	ANSWERS '583-703' FROM FILE BIOSIS	121	121	4 (11)
	ANSWERS '704-709' FROM FILE LIFESCI	6	6	0 (0)
	Total	709	724	113 (182)

[a] Fifteen metabolism records from MEDLINE, TOXLINE, and CABA in this answer set had already been printed from CAPLUS because of its more extensive indexing.

Metabolites (actual and conjectural) set

L42	609 DUP REM L39 (373 DUPLICATES REMOVED)	
	ANSWERS '1-152' FROM FILE MEDLINE	152
	ANSWERS '153-160' FROM FILE CANCERLIT	8
	ANSWERS '161-192' FROM FILE TOXLINE	32
	ANSWERS '193-196' FROM FILE NIOSHTIC	4
	ANSWERS '197-206' FROM FILE AGRICOLA	10
	ANSWERS '207-215' FROM FILE ESBIOBASE	9
	ANSWERS '216-227' FROM FILE BIOTECHNO	12
	ANSWERS '228-260' FROM FILE CABA	33
	ANSWERS '261-473' FROM FILE EMBASE	213
	ANSWERS '474-606' FROM FILE BIOSIS	133
	ANSWERS '607-609' FROM FILE LIFESCI	3

METHYLQUINOLINES SEARCH PACKAGE DESCRIPTION
(File L650_Package_Description.doc)

SUBJECT	MEDLINE	CANCERLIT	TOXLINE	NIOSHTIC	AGRICOLA	ESBIOBASE	BIOTECHNO	CABA	EMBASE	BIOSIS	LIFESCI	RTECS	EMIC	GENETOX	CAPLUS	NTP	INTERNET MISC.	REGISTRY	Total
01 Use & Prodn.			1		1				1						1	3	10		17
02 Exposure	2	1	9		2					1		2			2				19
03 Acute Toxicity									2			3							5
04 Microb. Biodegrdn	6		8				1			1					1		1		18
04 Environ.			17	2		1									2				22
05 Authori-tative Rev.																	1		1
06 Subchronic			1																1
07 Carcinog.	3		2																5
08 Immuno-toxicity	2		1						1										4
09 Genetic Toxicity	2		11				1			2		7	6	8					37
10 Repro. Toxicity			1																1
11 Review			1																1
12 ADME	6						1	1	2						3				13
12 Quinaldic Acid	4			1					1	1									7
12 Enzymes																	1		1
12 Registry Metabolites																		27	27
13a Chem. i.d.																		9	9
13b Proper-ties	1			1					1						1	4	2		10
20 Endocrine Modulation									1						1				2

SUBJECT	MEDLINE	CANCERLIT	TOXLINE	NIOSHTIC	AGRICOLA	ESBIOBASE	BIOTECHNO	CABA	EMBASE	BIOSIS	LIFESCI	RTECS	EMIC	GENETOX	CAPLUS	NTP	INTERNET MISC.	REGISTRY	Total
24 Regulations																	4		4
25 SAR			6						1			2	1	1		10			21
25 Quinaldic Acid Biol. Activity	8	2	1	1					3										15
28 Effects on Enzymes	2																		2
Other Data									2										2
Totals	36	3	59	5	3	1	3	1	15	5	0	14	7	9	11	17	19	36	244

APPENDIX B: SUMMARY OF AVAILABLE LITERATURE ON METHYLQUINOLINES (ILS Codes L650, L652-L658) TO SUPPLEMENT A RECENT REVIEW (MeQ = Methylquinoline)

Main Subject Code (Description at First Entry) Publication	Report Value	Cited by OEHHA, Calif. EPA (2000 draft)	L650 (MeQ n.o.s.)	L652 (2-MeQ)	L653 (3-MeQ)	L654 (4-MeQ)	L655 (5-MeQ)	L656 (6-MeQ)	L657 (7-MeQ)	L658 (8-MeQ)	Other Subject Codes and Description If Not Cited by OEHAA (2000)
01-Use, Production, Producers, Processes, Supplier 01 Acheson (1960)	B			x		x					Synthetic pathways from different starting materials depending on position of methyl group.
01 Allen and Sills (1973)	C			x							13b Preparation and properties of quinaldine sulfate, a fish anesthetic
01 Boyadzhieva (1981) (Bulgarian)	C					x					No abstract. Study of the influence of lepidine on the course of the mild chronic form of alloxanic diabetes. Oral drug. Rat experiment.
01 Chemcyclopedia Online 2001	B (3)			x		x		x			Vendors
01 Dong et al. (1978c)	A			x		x				x	Purification of commercially available methylquinolines for carcinogenesis testing. Some alkylquinolines were contaminated with isomers.
01 Kamath (undated)	B			x							Intermediate in the production of dyes and the food color Quinoline Yellow WS.
01 Mcateer et al. (1997)	B-/C						X		x	x	Example of a patented production method for methylquinolines (Reilly Industries, Inc., USA)
01 NTP (2001-01 to -03) (Lower case letter will be appended to publication year, if cited.)	B (3)							x	x	x	09a Testing status pages state uses and results of genetic toxicity studies.
01 ScienceNet (2001)	B-/C			x							13b
01 Skincare Institute (undated)	B-/C			x							Quinaldine is merely listed as a "harmful cosmetic chemical in today's cosmetics."
01 Sumikin (undated)	B-/C							x		x	Compounds are listed as intermediates for pharmaceuticals (Pharma Outsourcing Associates web page). Only laboratory methods.
01 TCI America (2000)	B				x				x	x	Supplier listing for bulk organic chemicals.
01 U.S. EPA (TSCA Inventory Update Rule database) (2000)	B+									x	Only methylquinoline in the database: >10,000 lb/yr production.
01 Wilshire Chem. Co. (undated)	B-/C							x		x	Compounds are merely listed by this supplier.
02 Exposure (See also 04 Environment...) Adams et al. (1983)	B/U			x	x	x	X	x	x	x	13c All 7 methylquinolines were determined in smoke from commercial U.S. cigarettes (somewhat less was found in smoke from filtered cigarettes).

Main Subject Code (Description at First Entry) Publication	Report Value	Cited by OEHHA, Calif. EPA (2000 draft)	L650 (MeQ n.o.s.)	L652 (2-MeQ)	L653 (3-MeQ)	L654 (4-MeQ)	L655 (5-MeQ)	L656 (6-MeQ)	L657 (7-MeQ)	L658 (8-MeQ)	Other Subject Codes and Description If Not Cited by OEHAA (2000)
02 Allen and Hunn (1986)	B/U			x							12 Rapid fish uptake and elimination (depuration after exposure) of the lipophilic anesthetic.
02 Allen and Sills (1970a)	B-/U			x							13c Consumer safety requires quinaldine residue analysis. Analytical method described detected concentrations of 0.01 to 10.0 ppm. (May have used only spiked samples.)
02 Allen and Sills (1970b)	B-/C			x							13c Anal. method's sensitivity was 0.01 ppm quinaldine in fish muscle.
02 Bull (1982)	C					x					18 pp. on numerous compounds. Title: Experimental methods for evaluating the health risks associated with organic chemicals in drinking water.
02 Dong et al. (1978a)	B/U		x								04, 13c Mainstream smoke of an 85-mm U.S.-blended tobacco unfiltered cigarette contained a total of 0.7 microgram methylquinoline isomers. Quinoline concentrations were 11 times higher in sidestream smoke than in mainstream smoke.
02 Dong et al. (1978b)	B/U		x			x		x			04, 09a, 13c Similar content to above. Origin of quinolines and benzoquinolines in cigarette smoke is pyrolysis. 4-MeQ and 6-MeQ were more mutagenic in Salmonella than quinoline.
02 Hayatsu (1991)	B					x					11, 13c Numerous compounds in this book, *Mutagens in Food: Detection and Prevention*. Lepidine is used as a food flavoring.
02 Kaden et al. (1979)	[A]	x		x		x					09a Numerous compounds found in soot were tested in the Ames assay.
02 Luhning and Harman (1971)	C			x							13c Sampling for fish residues of quinaldine.
02 Pino et al. (1999) (Spanish)	U				x						13c 3-Methylquinoline was found among numerous other volatile compounds of autolyzed "yeast ext[ract] used as food flavorant..."
02 RTECS (2001)	U (2)			x		x					Data from NIOSH Occupational Surveys. The total number of workers potentially exposed to 2-MeQ dropped from 28314 in 1974 (NOHS) to 4782 in 1983 (NOES). The total number of workers potentially exposed to 4-MeQ was 1557 in the 1983 survey.
02 Sasaki et al. (1987)	B-/U			x		x					2-MeQ was found in vapor from overheated decaffeinated coffee. 4-Methyl-2(1*H*)-quinolinone was also identified.
02 Schmeltz et al. (1979)	B-					x		x		x	04, 13c 2-, 4-, and 6-MeQ were identified as nicotine pyrolysis products.
02 Schnick and Meyer (1978)	C			x							Re: Registration of fishery chemicals.
02 Sills (1973a)	B+			x							Quinaldine residues in 10 fish species after anesthesia with the sulfate. (No abstract)

Main Subject Code (Description at First Entry) Publication	Report Value	Cited by OEHHA, Calif. EPA (2000 draft)	L650 (MeQ n.o.s.)	L652 (2-MeQ)	L653 (3-MeQ)	L654 (4-MeQ)	L655 (5-MeQ)	L656 (6-MeQ)	L657 (7-MeQ)	L658 (8-MeQ)	Other Subject Codes and Description If Not Cited by OEHAA (2000)
02 Sills (1973b)	B			x							Quinaldine residues in fish after anesthesia by a mixture of quinaldine sulfate and MS-222. (No abstract)
02 Thrane and Stray (1986)	B-/C				x	x					2- and 3-MeQ were found in workplace air at an aluminum reduction plant. (No abstract)
03 Acute Toxicity Piskarev et al. (1978) (Russian)	B-/C			x							Quinaldic acid showed high activity in protecting mice against acute hypoxia. 2-MeQ was also tested.
03 RTECS (2001)	A			x				x			
03 Sarkany and Gaylarde (1976)	B-/C			x						x	02 Effect of coal tar fractions on guinea pig and human skin. Coal tar preparations have been used to treat human and animal skin disorders. Coal tars are prepared by the destructive distillation of coal.
04 Environmental Occurrence, Fate, and Persistence (Folder 1: Biodegradation) Aislabie et al. (1990)	U				x			x	x	x	*Pseudomonas* species hydroxylated the 2 position of all but 2-MeQ, which resisted biodegradation. One strain could degrade 2-MeQ. Tests were run on a nitrogen-containing shale oil fraction.
04 Bollag and Kaiser (1991)	B-					x					11 Microbial transformation of heteroaromatic compounds and their derivatives under aerobic conditions was reviewed. (No abstract) [Quinoline derivatives are classified as azaarenes.]
04 Dembek et al. (1989)	U			x							*Alcaigenes* and *Arthrobacter* species transformed 2-MeQ to 3,4-dihydroxy-2-oxo-1,2-dihydroquinoline followed by decomposition to quinisatin and its decomposition to anthranilic acid (118-92-3) and isatin (91-56-5).
04 Etienne (2001)	U				x						Microbial degradation described by Schacht et al. (1993) is depicted in molecular structure diagrams with identification of enzymes involved.
04 Johansen et al. (1997a)	B			x	x	x		x		x	Microbial degradation of the methylquinolines by *Desulfobacterium indolicum* was compared to that of methylindoles (which have one fewer C in the heterocyclic ring). 6- and 8-MeQ gave the corresponding 2-quinolinones, which were further degraded to the corresponding 3,4-dihydro-2-quinolinones. 2-MeQ was resistant. 3- and 4-MeQ gave only the 2-quinolinone (also called 2-hydroxy) derivatives (4-MeQ gave 607-66-9).
04 Johansen et al. (1997b)	B			x	x	x		x		x	13c Similar to above. The article described the degradation pathway in a biofilm system under denitrifying conditions. The analytical method for determining the metabolites was described.
04 Liu et al. (1994)	U			x		x		x	x	x	The 2-hydroxylation products did not undergo further microbial degradation in anoxic freshwater sediments.

Main Subject Code (Description at First Entry) Publication	Report Value	Cited by OEHHA, Calif. EPA (2000 draft)	L650 (MeQ n.o.s.)	L652 (2-MeQ)	L653 (3-MeQ)	L654 (4-MeQ)	L655 (5-MeQ)	L656 (6-MeQ)	L657 (7-MeQ)	L658 (8-MeQ)	Other Subject Codes and Description If Not Cited by OEHAA (2000)
04 Meyer et al. (1999)	B-/U			x		x					The article reported analytical method development for determining 2- and 4-MeQ microbial metabolites in creosote-contaminated soil. The metabolites are not identified in the abstract.
04 Mountfield and Hopper (1998)	U							x			The fungus *Cunninghamella elegans* transformed 6-MeQ to 6-hydroxymethylquinoline (6-quinolinemethanol) (major), quinoline-6-carboxylic acid, and 6-methylquinoline *N*-oxide.
04 Ondrus et al. (1990)	U			x		x					13c Sampling and analysis procedures were reported. Groundwater [leachate?] from hazardous waste sites in Florida and Minnesota contained 2-MeQ and 2-hydroxy-4-methylquinoline (607-66-9).
04 Pereira et al. (1987)	B-/C			x		x					Fate and movement of azaarenes and their anaerobic biotransformation products in an aquifer contaminated by wood-treatment chemicals. 2-Hydroxy-4-methylquinoline (607-66-9) is the only MeQ metabolite indexed.
04 Rothenburger and Atlas (1992 abstr.)	C							x			See full article.
04 Rothenburger and Atlas (1993)	U							x			*Pseudomonads* degraded 6-MeQ to hydroxy derivatives after acclimation in aqueous and nonaqueous immobilized-cell bioreactors.
04 Ruger et al. (1993)	U					x					A *Pseudomonas putida* strain degraded 4-MeQ to 4-methyl-2-oxo-1,2-dihydroquinoline, 8-hydroxy-4-methyl-2-oxo-1,2-dihydroquinoline, 7,8-dihydroxy-4-methyl-2-oxo-1,2-dihydroquinoline, and possibly 6-hydroxy-5-(2-carboxyethenyl)-4-methyl-1*H*-2-pyridone (a benzo ring-opened product).
04 Schach et al. (1993)	U				x						*Comamonas testosteroni 63* in activated sewage sludge metabolized 3-MeQ to 3-methyl-2-oxo-1,2-dihydroquinoline, 6-hydroxy-3-methyl-2-oxo-1,2-dihydroquinoline, 5,6-dihydroxy-3-methyl-2-oxo-1,2-dihydroquinoline, and 2,5,6-trihydroxy-3-methylpyridine. See Etienne (2001) for a graphic depiction of this metabolic pathway.
04 Shukla and Kaul (1981 abstr.)	C			x		x					Microbial metabolism of quinoline derivatives. (No abstract)
04 Sutton et al. (1996)	U					x					Microbes collected from soil at an abandoned coal gasification site degraded 4-MeQ to the 2-hydroxy derivative (607-66-9), which eventually disappeared, and a hydroxy-4-methylcoumarin. The authors claimed that this is the first report of methylquinolines' undergoing aerobic biodegradation.

Main Subject Code (Description at First Entry) Publication	Report Value	Cited by OEHHA, Calif. EPA (2000 draft)	L650 (MeQ n.o.s.)	L652 (2-MeQ)	L653 (3-MeQ)	L654 (4-MeQ)	L655 (5-MeQ)	L656 (6-MeQ)	L657 (7-MeQ)	L658 (8-MeQ)	Other Subject Codes and Description If Not Cited by OEHAA (2000)
04 Zhang et al. (1998)	B-/C		x								Chinese wastewater treatment technology and Chinese coal. Nothing organic-compound-specific was in the abstract.
04 Environmental Occurrence (Second Folder 04) Benfanati et al. (1996)	B-/C	x									13c Identification of organic contaminants in leachates from industrial waste landfills.
04 Boxall and Maltby (1995)	U					x					4-MeQ was found in sediment contaminated with road runoff in England.
04 Brumley et al. (1991)	U			x		x		x		x	13c Methylquinolines were determined in U.S. creosote-contaminated soil.
04 Chaudhury et al. (1988)	B			x							22, 30 4-MeQ and/or other compounds present in crude oils inhibited rat platelet aggregation role of calcium. (No abstract)
04 Chen and Preston (1998)	B			x				x			13c 2- and 6-MeQ were determined in the air of Liverpool, England. Fossil fuel combustion in winter was the main source of azaarenes.
04 Chuang et al. (1992)	B-/C		x								Methylquinolines were determined in the air of Chinese homes cooking with smoky coal under unvented conditions. Such use has been associated with lung cancer in Chinese women.
04 Dmitrikov et al. (1984)	B-/C		x								13c Methylquinolines and dimethylquinolines were found in coal tar (isomers were not specified in the abstract).
04 Dobson et al. (1985)	B-/C			x							13c 2-MeQ was among numerous compounds determined in oil shale retort water.
04 Enzminger and Ahlert (1987)	C			x							Title: Environmental fate of polynuclear aromatic hydrocarbons in coal tar. (No abstract)
04 Falkovich and Rudich (2001)	B		x								02, 13c Methylquinoline isomers and numerous other compounds were determined in urban aerosols in Israel. (No indexing of specific compounds)
04 Frei et al. (1974)	C			x							02, 13c Method for determining nitrogen heterocyclic compounds in polluted air.
04 Furlong and Carpenter (1982)	B-/C			x							13c Marine sediment (Puget Sound) core analysis indicated low-level natural sources of azaarenes with higher concentrations associated with proximity to urban areas. "Gross differences in azaarene composition exist between European and American air particulates and sediments, suggesting differences in azaarene sources."
04 Hanson (1979)	B-/C		x								02, 13c A methylquinoline was identified in a particle fraction of diesel particulates in the United States.

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04 Junk and Ford (1980)	C			x							11 Title: A review of organic emissions from selected combustion processes. (No abstract; > 100 compounds are indexed)
04 Lipscomb et al. (1997)	B-/C		x								Unspecified methylquinolines were determined in the vapor and/or particulate phase from combustion of advanced composite materials.
04 Loring et al. (1998)	C				x				x	x	Marine sediments near New Brunswick were analyzed for metals, PAHs, quinolines, and other pollutants.
04 Melcher et al. (1995)	B			x		x			x	x	PAHs and methylquinolines were determined in U.S. raw sewage and primary and secondary effluents.
04 Middaugh et al. (1991)	B-/C					x					4-MeQ and other pollutants from an abandoned U.S. creosote works were determined in a freshwater stream and groundwater.
04 Onuska and Terry (1989)	C			x	x	x		x	x	x	13c Azaarenes were determined in sediments.
04 Pereira et al. (1983)	B-/C			x							13c Aqueous and oily-tar phases of groundwater contaminated by coal-tar wastes contained numerous organic bases. Quinolines were found in the aqueous phase.
04 Phillips Petroleum (1992?)	A			x		x					02, 09a A TSCA test submission. Mutagenicity of kerosene soot and associated polycyclic aromatic hydrocarbons to *Salmonella typhimurium*. (No abstract)
04 Turney and Goerlitz (1990)	B-/C			x		x					"Organic contamination of ground water at Gas Works Park Seattle Washington." (No abstract; numerous compounds indexed)
05 Authoritative Reviews OEHHA/Calif. EPA (2000 draft)	A			x	x	x	X	x	x	x	This review gives little information on topics usually included in Sections 1 through 8 of the ILS Toxicological Summaries.
06 Subchronic Toxicity DuPont (1994)	A			x							03, 08 This TSCA test submission included acute toxicity, dermal irritation, dermal sensitization, and subchronic toxicity studies in rats, guinea pigs, and/or rabbits.
07a Carcinogenesis and 07b Initiation/Promotion Studies 07a Fukushima et al. (1981)	[A]	x						x		x	Rats were fed diets containing the compounds for 2 years.
07a LaVoie et al. (1983)	[A]	x				x			x		Skin tumor initiation studies in mice. 4-MeQ was significantly carcinogenic.
07b LaVoie et al. (1984)	[A]	x		x	x		X			x	4-MeQ- and 8-MeQ-initiated skin cancer in mice when promoted by TPA.

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07a LaVoie et al. (1987 abstr.)	C					x				x	This abstract described experiments in mice and rats.
07a LaVoie et al. (1988)	[A]	x				x				x	4-MeQ given i.p. or s.c. was carcinogenic in male neonatal mice but not in newborn rats.
08 Immunotoxicity 08 Pevny and Hutzler (1988) (German)	U?			x							18 Human patch testing with a series of quinoline derivatives indicated that quinaldine induced dermal sensitization. Reaction to quinaldine and certain other compounds was "considered to be group allergies since contact is hardly possible with these substances in everyday life." **Would need article for allergy incidence in the 316 patients suspected of allergy to quinoline derivatives.**
08 Sonnenfeld (1983 abstr.)	C			x							Title: Effect of tobacco smoke components and carcinogens on interferon induction. Mechanistic studies.
08 Sonnenfeld (1983)	B			x							Quinaldine inhibited interferon induction in mouse embryo fibroblast cultures.
08 Sonnenfeld and Hudgens (1983)	B			x							Quinaldine given i.p. had no effect on interferon induction in mice *in vivo*.
09a Genetic Toxicity Benson and Kubrick	B							x	x		28 Studies included Ames tests and effects on rat lung and aryl hydrocarbon hydroxylase activity.
09a Bowden et al. (1976)	B			x							Tryptophan metabolites, including quinaldine, were tested in the Ames assay.
09a Debnath et al. (1992)	[A]			x	x	x		x	x	x	25 Assays with Salmonella tester strains TA98 and TA100. "A QSAR study based on hydrophobicity and molecular orbital determinants."
09a Dong et al. (1978)	[A]			x	x	x	X	x	x	x	Ames test with TA100.
09a Epler et al. (1978)	A								x	x	Mutagenicity tests were performed with Salmonella strains TA98, TA100, and TA1537; *Escherichia coli*; *Saccharomyces cerevisiae*; *Drosophila melanogaster*; Chinese hamster cell cultures; human cell cultures; and mice (dominant lethal test).
09a Epler et al. (1979)	A								x	x	Ames tests with Salmonella strains TA98, TA100, TA1535, TA1537, and TA1538.
09a GENETOX (1995)	B- (8)			x	x	x	X	x	x	x	Data are from Kier et al. (1986) and ____ (1978).
09a Hashimoto et al. (1979)	[A]	x				x					4-MeQ *N*-oxide was also tested.
09a Kaden et al. (1979)	[A]	x		x		x					An abstract for this study is in Folder 02.

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09a Kier et al. (1986)	B-/C										11 See GENETOX entry.
09a LaVoie et al. (1991)	[A]	x		x		x		x		x	25 4- and 8-MeQ induced UDS in rat hepatocytes. Genotoxicity was correlated with carcinogenicity in this SAR study.
09a Morita and Mifuchi (1972) (Japanese)	C										17 Only closely related structural analog in this study was 2-MeQ *N*-oxide. Title: Carcinogenicity of the compounds related to 4-nitroquinoline 1-oxide and induction of respiration deficient mutants and abnormal cell division in yeast. (No abstract)
09a Nagao et al. (1977)	[A]	x				x		x	x	x	Ames tests with Salmonella TA98 and TA100 included quinaldic acid and 2-methyl-8-hydroxyquinoline.
09a Ogawa et al. (1987)	[A]	x		x	x	x		x	x	x	Ames tests with Salmonella TA98, TA100, TA1537, and TA2637.
09a RTECS (2001)	B (5)					x	X	x	x	x	Need to see if any of the studies cited were not identified by OEHHA (2000) or the October 2001 literature search.
09a Saeki et al. (1996)	[A]	x		x	x	x		x	x		25 SAR. Metabolites tested included 4-MeQ *N*-oxide (4053-40-1) and 4-hydroxymethylquinoline (4-quinolinemethanol, 6281-32-9).
09a Sengoku et al. (1989 abstr.)	B-/C			x		x					12, 25 (No abstract)
09a Shibamoto (1989)	B			x			X				02 2-MeQ and 5-MeQ were identified as a Maillard (browning) reaction product. (No abstract)
09a Sideropoulos and Specht (1984)	A-				x						Salmonella TA98 and TA100, *E. coli* HCR+
09a Sugimura et al. (1976)	[A]	x				x		x	x	x	25 Title: Overlapping of carcinogens and mutagens. (No abstract)
09a Takahashi et al. (1988)	[A]	x	x								25 SAR was studied. Fluorine substitution may deprive the quinolines of mutagenic activity.
09a Walsh and Claxton (1987)	C					x			x		25 Title: Computer-assisted structure-activity relationships of nitrogenous cyclic compounds tested in Salmonella assays for mutagenicity. (No abstract)
09a Wild et al. (1983)	A							x			01, 02 Compounds tested were artificial flavoring substances. 6-MeQ was mutagenic in the Ames test. Other tests included the Basc test on *D. melanogaster* and the micronucleus test on mouse bone marrow.
09a Willems et al. (1992)	[A]	x									Compounds tested in the Ames assay included 1-methylquinoline 5,6-oxide. (The methyl group is on the ring nitrogen.)

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10 Reproductive Toxicity Billard (1981)	B-			x							Title: Effect of some fish anesthetics on gamete survival during artificial insemination of rainbow trout. (No abstract)
11 Reviews (see also Folder 05)	B					x					Title: Fragrance raw materials monographs: *p*-Methylquinoline. 2 pp. (No abstract)
12 ADME (see also Folder 02 Biodegradation for microbial metabolism) Auletta et al. (1974)	A			x							Title: Influence of route of administration on distribution of quinaldine (NBC 143057) in mice. (No abstract)
12 Brown et al. (1972)	B-/C			x							Title: Contributions to the pharmacology of quinaldine (uptake and distribution in the shark and comparative metabolism). (No abstract)
12 Jorgenson et al. (1978)	B-/C			x							Quinaldine is a scent constituent of male red fox (*Vulpes vulpes*) urine.
12 Kato et al. (2000)	[A]	x				x					4-MeQ metabolism was studied in 3-methylcholanthrene-induced rat liver microsomes *in vitro*. Major product 4-hydroxymethylquinoline (4-quinolinemethanol, 6281-32-9); minor product 3-hydroxy-4-methylquinoline. Substitution of a fluorine atom at position 2 prevented formation of the 3-hydroxy derivative, possibly by inhibiting the formation of the enamine epoxide in the pyridine ring.
12 Komiya (1965) (Japanese)	A/U			x							Rabbits injected s.c. with quinaldine excreted 3-hydroxyquinaldine, 6-hydroxyquinaldine, quinaldic acid (93-10-7), and several unknown compounds in their urine. When given orally, quinaldine was excreted unchanged.
12 Niwa et al. (1987)	B-/C										18, 19 2-Methyl-1,2,3,4-tetrahydroquinoline was determined in human brains (normal subjects and subjects that suffered Parkinsonism).
12 Oliver et al. (1977)	U			x							Quinaldine and 2-hydroxymethylquinoline (2-quinolinemethanol) form in greyhound urine if it is not preserved. 2-Hydroxymethylquinoline forms in 3-4 days at room temperature and quinaldine after about two weeks.
12 Oliver et al. (1978)	U			x							13c The quinoline artifacts in greyhound urine interfere with determination of basic drugs.

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12 Scharping et al. (1993)	A-							x		x	Metabolites in rat microsomal preparations *in vitro*: 6-Methylquinoline: 5-Hydroxy-6-MeQ (116529-84-1), 6-MeQ 5,6-epoxide (149635-36-9), 6-MeQ 7,8-epoxide (149635-37-0), 6-methylquinolinylphenol (149939-03-7). 8-Methylquinoline: 8-MeQ N-oxide (4053-38-7), 5-hydroxy-8-MeQ (16026-71-4), *trans*-3,4-dihydro-8-methyl-3,4-quinolinediol (149635-38-1), *trans*-5,6-dihydro-8-methyl-5,6-quinolinediol (149665-55-4), 8-methylquinolinylphenol (149939-02-6).
12 Trams and Brown (1970)	B-/C			x							Title: Metabolism of quinaldine (2-methylquinoline). Uptake and excretion by nurse sharks. (No abstract)
12 Williams (1986)	U			x							The quinolines found in decayed greyhound urine were shown to be derived from tryptophan by radiolabeling. 2-Aminomethylquinoline is excreted in fresh urine.
12 Williams (1988)	U			x							The quinolines found in greyhound urine were not detected in the urine of 200 normal human subjects or of 25 patients with transitional cell carcinoma of the bladder.
12 Wood (1993)	U			x							2-MeQ is a minor volatile constituent of skunk defensive spray.
12 Enzymes in Metabolism of Methylquinolines and Quinaldic Acid NC-IUBMB (1999)	U?				x	x				x	Oxidoreductases section of Enzyme Supplement 5 (1999) of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology.
12 Metabolism of Quinaldic Acid and Its Recognition as a Tryptophan Metabolite	U? (7)										This folder contains seven database records. Quinaldic acid (2-quinolinecarboxylic acid) is a common human and canine metabolite of tryptophan. Metabolites include 4-hydroxyquinaldic acid and 4,8-dihydroxyquinaldic acid. As an endogenous tryptophan metabolite, it has been found in rat brain. Tamada et al. (1967) studied "the formation of carcinogenic substances: formation of carcinogen 8-hydroxyquinaldic acid..." from tryptophan metabolite xanthurenic acid in rats (no abstract; title is poorly worded and may be interpreted differently). Quinaldylglycyltaurine and quinaldylglycylglycine are cat urinary metabolites of quinaldic acid. Quinaldic acid metabolism has also been studied in rabbits.
12 Metabolites (Reported and Conjectural) Registry records in CASRN order.				x				x		x	The folder contains 27 Registry records and a handwritten summary of metabolites identified in different mammalian and microbial metabolism studies. Many of the records are annotated with the identities of articles that reported the compounds. Most of these compounds were the subject of searches in the biomedical databases.

Main Subject Code (Description at First Entry) Publication	Report Value	Cited by OEHHA, Calif. EPA (2000 draft)	L650 (MeQ n.o.s.)	L652 (2-MeQ)	L653 (3-MeQ)	L654 (4-MeQ)	L655 (5-MeQ)	L656 (6-MeQ)	L657 (7-MeQ)	L658 (8-MeQ)	Other Subject Codes and Description If Not Cited by OEHAA (2000)
13a Chemical Identification	U		x	x	x	x	X	x	x	x	13b Some Registry records include calculated properties, including molecular weight, log P, and water solubility at different pH values. Registry and *Merck Index* (Budavari, 1996) records are in order of methyl substitution. Besides the methylquinolines assigned, the folder contains records for methylquinoline *N*-oxide and 2-methylquinoline ethiodide. Compounds not listed by TSCA: 3-MeQ and 5-MeQ.
13b Chemical-Physical Properties and Chemical Reactivities Acheson (1960)	Have B-			x		x					Classical preparative methods for methylquinolines. Methyl groups of quinaldine and lepidine, like those of 2- and 4-methylpyridine, are very reactive whereas the methyl group of 3-MeQ is "comparatively unreactive."
13b J.T. Baker (undated)	B-/C			x							MSDS
13b Buryan et al. (1989) (Russian)	C			x	x	x	X	x	x	x	Capillary GC retention indexes were correlated with boiling points and other parameters.
13b Kato et al. (1964) (Japanese)	C			x		x					Title: Reaction of quinaldine, lepidine, and their *N*-oxides with amyl nitrite.
13b KDB (Korean Thermophys. Properties Data Bank) (undated)	B-/C			x		x		x	x	x	Boiling points and vapor pressures plus other thermophysical properties seldom included in the ILS reviews.
13b Mirrless et al. (1976)	B-/C					x					Log P measurements using HPLC
13b Radian (NTP Chemical Repository database)	B (4)			x				x	x	x	No record was found for 4-MeQ.
13b Van de Rostyne and Prausnite (1980)	U			x							Quinaldine's vapor pressure at different temperatures (not specified in abstract) varied between 0.0107 and 0.135 mm Hg.
20 Endocrine Modulation Przeslawski et al. (1996)	B-/C						X	x		x	Title: Synthesis and .alpha.-2-adrenergic activity of quinoline and quinoxaline analogs of medetomidine, an antihypertensive with sedative properties. [Medetomidine is a 4-benzylimidazole derivative (see *Merck Index* monograph 5830)].
20 Thomas and Smith (1993)	B			x							Quinaldine estrogen-receptor binding in a screening assay using cytosolic extracts from spotted sea trout.

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24 Regulations FDA (2001a)	A			x							01 Condensation of quinaldine with phthalic anhydride followed by sulfonation with oleum (sulfuric acid containing sulfur trioxide) gives the color additive for drugs D&C Yellow No. 10. 21 CFR 74.1710: The dye should contain no more than 0.2% "sulfonated quinaldines, sodium salts."
24 FDA (2001b)	A			x							02 21 CFR 74.1711 The dye D&C Yellow No. 11, which is principally 2-(2-quinolyl)-1,3-indanedione, should contain no more than 0.2% quinaldine. The dye is used to color externally applied drugs.
24 FDA (2001c)	A					x					01, 02 21 CFR 172.515 Lepidine is listed as a permitted flavoring agent for addition to food for human consumption.
24 U.S. EPA (2001)	A			x							01 40 CFR 414.111 Appendix A. Several industrial waste streams are listed in this section as sources of copper and subject to toxic pollutant standards for indirect discharge point sources. Among these is the stream from quinaldine production by the Skraup reaction of aniline and crotonaldehyde.
25 Structure-Activity Relationships Birkholz et al. (1990)	C		x								Aquatic toxicity of three methylquinoline isomers, 14 dimethylquinolines, and related compounds.
25 GENETOX (1991)	U										Inconclusive results in Ames test with 8-hydroxy-2-methylquinoline (826-81-3).
25 Klopman et al. (1990)	C			x				x			CASE SAR methodology applied to 808 chemicals from Gene-Tox database Salmonella studies.
25 Mifuchi et al. (1963) (EMIC record)	C										Title: Induction of respiration-deficient mutant of *Saccharomyces cerevisiae* by carcinogenic agent 4-nitroquinoline *N*-oxide and the existence of toxohormone-like factor in the mutant. (No abstract). Indexing includes 2-methylquinoline *N*-oxide (1076-28-4).
25 Mohammad (1986a)	C					x					Title: Carcinogenic mechanism for polycyclic hydrocarbons: Extended electrophilicity theory.
25 Mohammad (1986b)	C					x					Title: Extended correlation of a bond reactivity index with carcinogenicity and metabolism of polycyclic hydrocarbons: A molecular orbital theory.
25 NTP TR-276 (1985)	U										No evidence for carcinogenicity of 8-hydroxyquinoline (148-24-3) in rats and mice (feed studies).
25 NTP TR-456 (1997)	U										Some evidence for carcinogenicity of 1,2-dihydro-2,2,4-trimethylquinoline (147-47-7) was reported in male rats (dermal studies) with no evidence for female rats and no evidence for both sexes of mice. The compound was negative in one-year dermal initiation/promotion studies in female Sencar mice.

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25 NTP TR-463 (1997)	U										Some evidence for carcinogenicity of D&C Yellow No. 11 (8003-22-3), an analog of 2-methylquinoline, was observed in male and female rats in feed studies (mice were not tested).
25 NTP (1998)											The NTP 1998 annual plan stated that 14-day and 90-day dosed-feed toxicity studies in rats and mice have been completed (contact Dr. P. Chan, ETP, NIEHS). Ethoxyquin is a 1,2-dihydro-2,2,4-trimethylquinoline derivative. A technical report was not prepared according to the 10/11/01 Management Status Report.
25 NTP (2001-04)											Transgenic model evaluation for 8-hydroxyquinoline (148-24-3). 24-week studies in Tg.AC mice (topical) and p53 heterozygous mice (dosed feed). Toxicity technical reports were not prepared according to the 10/11/01 Management Status Report. No results here.
25 NTP (2001-05)	U										Target organs and levels of evidence from NTP TR-456 (1,2-dihydro-2,2,4-trimethylquinoline monomer).
25 NTP (2001-06)	U										Summary of several quinoline (91-22-5) genetic toxicology studies.
25 NTP (2001-07)	U										Quinoline sulfate (530-66-5) was inconclusive in one and positive in another sex-linked recessive lethal (SLRL)/reciprocal translocation study in *Drosophila*. [Could this be an error and the positive result have been in Salmonella? See next entry.]
25 NTP (2001-08a & -08b)	U										Testing status for 8-hydroxyquinoline summarizes genetic toxicity and carcinogenesis bioassays. 8-Hydroxyquinoline sulfate (134-31-6) was inconclusive in the SLRL assay in *Drosophila* and positive in the Salmonella assay.
25 NTP (2001-09)	U										4-Nitroquinoline *N*-oxide (56-57-5) was positive in numerous genetic toxicology studies.
25 NTP (2001-10)											The testing status page for 1,2-dihydro-2,2,4-trimethylquinoline lists several short-term toxicity studies, but does not give the results. Results found in NTP TR-456 are summarized.
25 RTECS (2001)	U										Record for quinaldic acid stated that results were inconclusive in the histidine reversion Ames test.
25 RTECS (2001)	U										Record for 4-MeQ *N*-oxide lists a 1979 report of an Ames test.
25 Schultz et al. (1980)	C			x							10 SAR between physical-chemical properties and reproductive impairment in *Tetrahymena pyriformis*.
25 Schultz et al. (1982)	C			x							SAR using molecular connectivity. (No abstract)

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25 Biological Activity of Quinaldic Acid	U (15)										The biomedical databases contained more than 1900 records (without duplicate removal) on quinolinecarboxylic acids. This answer set was not included in the search results. However, numerous studies were noted for quinaldic acid (2-quinolinecarboxylic acid). This folder contains 15 database records. Bryan (1969, 1971) reported that quinaldic acid and certain other tryptophan metabolites were carcinogenic when implanted as pellets in the bladders of mice. Gold (1974) reported that quinaldic acid exhibited an anticarcinogenic effect in cancer cells and perfused rat liver, possibly by inhibition of gluconeogenesis. Other studies report a hypoglycemic action of quinaldic acid in rats. Matsushima et al. (1983) (Japanese) reported early induction of mouse urinary bladder ornithine decarboyxlase activity by bladder carcinogens (no abstract). Wolf (1984) reported on the relationship between tryptophan metabolites and bladder cancer.
28 Effects on Enzymes Naoi and Nagatsu (1987)	U			x							Quinaldine inhibited type A monoamine oxidase in human placental mitochondria.
28 Naoi and Nagatsu (1988)	U			x		x		x	x	x	Methylquinolines markedly inhibited type A monoamine oxidase in human brain synaptosomal mitochondria but were weak inhibitors of type B MAO.
Other Data Boyadzhieva (1982) (Bulgarian)						x					4-MeQ (lepidine) presumably has an hypoglycemic action in alloxan-induced diabetic rats. (No abstract).
Paskov and Boyadzhieva (1981) (Bulgarian)						x					See above.

NOTES:

2-Methylquinoline is also called quinaldine.
4-Methylquinoline is also called lepidine.

Compound Tallies (ILS Code and CASRN):

MeQ (L650; 27601-00-9)	11 (3.5%)
2-MeQ (L652; 91-63-4)	87 (28.3%)

Database Tallies:

MEDLINE	36	BIOSIS	5
CANCERLIT	3	LIFESCI	0

3-MeQ (L653; 612-58-8)	22 (7.4)	TOXLINE	59	RTECS	14
4-MeQ (L654; 491-35-0)	63 (20.3%)	NIOSHTIC	5	EMIC	7
5-MeQ (L655; 7661-55-4)	11 (3.5%)	AGRICOLA	3	GENETOX	9
6-MeQ (L656; 91-62-3)	40 (12.9%)	ESBIOBASE	1	CAPLUS	11
7-MeQ (L657; 612-60-2)	35 (11.3%)	BIOTECHNO	3	NTP (4 Radian)	17
8-MeQ (L658; 611-32-5)	40 (12.9%)	CABA	1	Internet Miscellaneous	19
		EMBASE	15	Registry	36
Total	311			Total Database	244

Report Values:

Definite inclusion if a full report is assigned:

[A] (17 entries) [References cited by OEHHA (2000 draft). Acquisition of original articles may be unnecessary.]
A (16 entries)
A- (2 entries) [Acquire A, A-, and B+ references if in English. Otherwise, use abstract of database record.]
B+ (2 entries)

Consider for inclusion, but other identified sources may provide the same information:

B (40 entries) [Many of these may be needed to develop a full report.]
U (65 entries) [If time permits, writer may wish to use several of the database records to provide supplemental information.]

Low likelihood of inclusion, but may need to consider if information on a report topic is scarce:

B- or B-/C (46 entries)
No rating (5 entries) [Insufficient information to judge value]

Do not consider for inclusion:

C (25 entries)