Quinolines: Human health tier II assessment

03 July 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Quinoline	91-22-5
Quinoline, 2-methyl-	91-63-4
Quinoline, 4-methyl-	491-35-0

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

NICNAS has made every effort to assure the quality of information available in this report. However, before relying on it for a specific purpose, users should obtain advice relevant to their particular circumstances. This report has been prepared by NICNAS using a range of sources, including information from databases

ACRONYMS & ABBREVIATIONS

Grouping Rationale

Quinoline and two other structurally related chemicals, 2- and 4-methylquinoline, are assessed together in this report as they are all reported to be used as fragrance compounds.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the International Fragrance Association (IFRA) Survey Transparency List.

The chemicals have reported cosmetic/domestic use as fragrance compounds (IFRA survey, 2011; CosIng).

Quinoline has reported commercial uses, including:

- as a corrosion inhibitor; and
- in construction materials.

The chemicals have reported site-limited uses, including:

- in manufacturing other chemicals; and
- as solvents for resins and terpenes.

The following non-industrial uses have been identified:

- quinoline is an antimalarial drug;
- quinoline is used in preserving anatomical specimens; and
- all the chemicals are food additives.

Restrictions

Australian

No known restrictions have been identified.

International

Quinoline is listed on the following (CosIng):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products.

No known international restrictions have been identified for 2- or 4-methylquinoline.

Existing Worker Health and Safety Controls

Hazard Classification

Quinoline is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xn; R21/22 (acute toxicity)
- Xi; R36/38 (irritation)
- R45 Carc. Cat 2 (carcinogenicity)
- R68 Mut. Cat 3 (mutagenicity)

Neither 2- nor 4-methylquinoline is listed on the HSIS (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

Quinoline has an exposure limit of 0.1 mg/m^3 (0.001 ppm) time weighted average (TWA) and 0.5 mg/m^3 short-term exposure limit (STEL) in different countries such as the USA, Latvia and Russia.

No specific international exposure standards are available for 2- or 4-methylquinoline.

Health Hazard Information

Since the chemicals are structurally similar, when data for the chemicals being assessed are not available, health hazard data for any of the three chemicals are used to read-across, where appropriate, to derive the systemic hazards of the other two chemicals. The 2- and 4-methylquinoline isomers are expected to be the most similar of the seven methylquinoline isomers, and so results for 2-methylquinoline are considered to apply to 4-methylquinoline.

Toxicokinetics

In a dog study, intravenous (i.v.) administration of quinoline at 20 or 25 mg/kg bw resulted in rapid and almost complete metabolism of the chemical within 24 hours. There were decreasing concentrations of quinoline in the plasma over four hours and <0.5 % of the administered quinoline was excreted in the urine unchanged over 24 hours. The major urinary metabolite was 3-hydroxyquinoline, as a glucuronide conjugate, which accounted for approximately 30 % of the administered dose of quinoline in dogs. Other glucuronide conjugates, as well as sulfate conjugates, were formed during metabolism, but accounted for a smaller proportion of the metabolites excreted in the urine (US EPA IRIS, 2001). Information on the extent of absorption and excretion via other routes (e.g. the faeces) was not available.

In rabbits injected subcutaneously with 2-methylquinoline (also known as quinaldine; dose not available), 2-hydroxyquinaldine, 6-hydroxyquinaldine, quinaldic acid and several undetermined chemicals were excreted in the urine. When rabbits were orally administered 2-methylquinoline (dose not available), the chemical was excreted unchanged (NTP, 2002). No further details were available.

Acute Toxicity

Oral

Quinoline is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available data support this classification for all three chemicals.

The following oral median lethal dose (LD50) values were available for quinoline (Clayton & Clayton, 1994; HSDB; REACH; RTECSa):

- 262 mg/kg bw in Wistar rats,
- 331 mg/kg bw in rats (strain not specified); and
- 460 mg/kg bw in Sherman rats.

Reported signs of toxicity for quinoline included lethargy, respiratory distress and coma (Clayton & Clayton, 1994; HSDB).

The oral LD50 for 2-methylquinoline was 1230 mg/kg bw in rats (RTECSb).

Dermal

Quinoline is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in the HSIS (Safe Work Australia). The available data support this classification for all three chemicals.

The following dermal LD50 values were available for quinoline (REACH; RTECSa):

- 1377 mg/kg bw in Sprague Dawley (SD) rats; and
- 590 mg/kg bw in rabbits.

The dermal LD50 for 2-methylquinoline was 1978 mg/kg bw in rabbits (RTECSb).

Inhalation

The limited data available on quinoline are insufficient to derive a conclusion on the acute inhalation toxicity of the chemicals.

In albino rats (n = 6), inhalation (whole body) of saturated quinoline vapour, calculated to be approximately 17 ppm, for six or eight hours did not result in any deaths. However, rats exposed to super-saturated quinoline vapour (produced by heating the chemical at 100 °C), calculated to be approximately 4000 ppm, resulted in all animals dying within 5.5 hours (Clayton & Clayton, 1994; REACH). This information indicates that the median lethal concentration (LC50) of quinoline vapour in rats is between 17 ppm and 4000 ppm.

In SD rats (n = five/sex), inhalation (whole body) of saturated quinoline vapour (concentration not measured) for seven hours resulted in 9/10 rats dying within four days (REACH).

Observation in humans

Systemic absorption of quinoline can cause nausea, abdominal pain, vomiting, high temperature, dizziness, tachycardia (rapid heart beat) and fainting (Clayton & Clayton, 1994).

Corrosion / Irritation

Skin Irritation

Quinoline is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia). The available data for quinoline (moderate skin irritation following 24 hour exposure) do not support this classification but are not sufficient to recommend an amendment to the classification.

The limited information available for 2-methylquinoline indicates it is a mild skin irritant (irritation scores not available) following a 24-hour exposure and therefore, hazard classification for 2- and 4-methylquinoline is not recommended.

In a skin irritation test (according to the US Code of Federal Regulations (CFR) Title 16, section 1500.41) in rabbits (n = 6), 0.5 mL of quinoline was applied (occlusively) on intact and abraded skin for 24 hours and the animals were observed for 72 hours. The erythema and oedema scores were 0.9/3 and 1.5/3, respectively, for intact and abraded skin after 24 hours. The effects were not reversible after 72 hours. It was concluded that the chemical was a skin irritant (REACH).

In a Draize test, when 100 mg of quinoline was applied to the skin of rabbits for 24 hours, moderate skin irritation was observed (irritation scores not available) (RTECSa).

In a Draize test, when 500 mg of 2-methylquinoline was applied to the skin of rabbits for 24 hours, mild irritation was observed (irritation scores not available) (RTECSb).

Eye Irritation

Quinoline is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in the HSIS (Safe Work Australia). The available animal data support this classification for quinoline. Although human data indicate severe eye effects (see **Observation in humans** below), details on those observations were not available to consider a higher hazard classification. No data are available for 2- or 4-methylquinoline, but due to structural similarity, hazard classification is recommended for these two chemicals (see **Recommendation** section).

In an eye irritation study (according to the US CFR Title 16, section 1500.42) in rabbits (n = 6), 0.1 mL of quinoline was applied to one eye of each animal for 24 hours and the animals were observed for seven days. The irritation scores at 24–72 hours after application were 0.8/1 for corneal irritation, 0.5/1 for iris irritation, 2/3 for conjunctival redness and 2.2/3 for conjunctival chemosis. Effects were not reversible within the seven-day observation period. The chemical was reported to be severely irritating to the eyes (REACH). The reversibility of eye effects was not investigated for up to 21 days after exposure as per the Organisation for Economic Cooperation and Development (OECD) test guidelines (TG) for eye irritation studies.

Observation in humans

Quinoline has been reported to be irritating to skin and severely irritating to eyes, with the potential to cause permanent corneal damage and retinitis (HSDB).

Sensitisation

Skin Sensitisation

Based on the available data for quinoline, the chemicals are not considered to be skin sensitisers.

In a mouse local lymph node assay (LLNA), quinoline was applied (25 µL) at 0, 0.5, 1.0, 2.5, 5.0 or 10.0 % concentrations (in acetone:olive oil at 4:1), to the dorsal surface of each ear in female CBA/CaOlaHsd mice (n = 4/dose), once daily for three days (OECD TG 429). The stimulation indices (SI) were all below the threshold of 3 and were determined to be 1.07, 1.16, 1.26, 1.70 and 1.11 at 0.5, 1.0, 2.5, 5.0 and 10.0 %, respectively. The chemical was not determined to be a skin sensitiser (REACH).

Repeated Dose Toxicity

Oral

Based on the available data for quinoline, the chemicals are not considered to cause serious health effects from repeated oral exposure (however, see **Genotoxicity** and **Carcinogenicity** sections).

In a repeated dose oral toxicity study (similar to OECD TG 407), male Fischer 344/DuCrj (F344/DuCrj) rats (n = five/dose) were administered quinoline at 0, 25, 50, 100 or 200 mg/kg bw/day for 28 days. One death was reported in the highest dose group on day 12, and body weight gain was significantly decreased by approximately 24 % and 53 % in the 100 and 200 mg/kg bw/day groups, respectively, compared with controls. Clinical signs of toxicity included diarrhoea, reduced activity, and staining around the eyes and nose in the 200 mg/kg bw/day group (Asakura et al., 1997; REACH).

In a repeated dose oral toxicity study (similar to OECD TG 453), male SD rats (n = 6 for control and n = 20/dose) were exposed to quinoline at 0, 0.05, 0.10 or 0.25 % (estimated to be equivalent to 0, 25, 50 and 125 mg/kg bw/day) in the diet for 40 weeks. Final body weights were reduced by 17.9, 33.4 and 51.2 % in rats exposed to quinoline at 0.05, 0.10 and 0.25 %, respectively, compared with controls. Absolute liver weights were increased in all treated rats. The non-neoplastic changes observed in rats at all doses included infiltration of liver progenitor (oval) cells, bile duct proliferation and fatty liver (Hirao et al., 1976; US EPA IRIS, 2001; REACH).

In a repeated dose oral toxicity study, male Wistar rats (n = 5–18/dose) were exposed to 0 or 0.25 % quinoline in the diet for 4, 8, 12, 16 or 20 weeks, with or without a recovery period of 4, 8, 12 or 16 weeks. Body weight gain was reduced and liver weights were increased in all treated rats, but both changes were reversible within four weeks of cessation of quinoline exposure. Enlarged liver cells and increased serum aspartate aminotransferase enzyme activity (an enzyme normally contained in the liver, but released into circulation with liver damage) were also reported in all treated rats. Endothelial dysplasia and increased alkaline phosphatase activity, as well as hyperplastic nodules were reported, from week 16 and during week 20 of the study, respectively. Deaths were reported due to the treatment (details not available) (US EPA IRIS, 2001; REACH).

In a repeated dose oral toxicity study, male hypertensive SHR rats and Wistar Kyoto (WKY) rats (n = 10 for control and n = 20 for treatment) were exposed to quinoline at 0 or 0.2 % in the diet for 32 weeks. Based on food intake, the dose was calculated to be 29 mg of quinoline/rat/day. In all treated rats, body weight gain was reduced for the duration of the study, food intake was reduced in the first week of the study and liver weights were increased (US EPA IRIS, 2001; REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Quinoline is classified as hazardous—Category 3 mutagenic substance—with the risk phrase ‘Possible risk of irreversible effects’ (Xn; R68) in the HSIS (Safe Work Australia). Based on the positive results observed for quinoline in several in vitro and in vivo genotoxicity assays, this classification is supported. In vivo germ cell assays in *Drosophila melanogaster* were negative, confirming the existing classification for quinoline.

Only limited in vitro genotoxicity data are available for the two methylquinoline isomers, with some positive results. Quantitative Structure–Activity Relationship (QSAR) modelling using OASIS–TIMES (Optimized Approach based on Structural Indices Set–Tissue MEtabolism Simulator) predicted that both methylquinoline isomers would be negative for mutagenicity in various assays (Ames test, chromosomal aberrations, in vivo liver clastogenicity and in vivo micronucleus). Overall, there are insufficient data to propose a mutagenicity classification for the methylquinoline isomers.

Several in vitro genotoxicity assays with quinoline gave positive results (US EPA IRIS, 2001; NTP, 10441-R; REACH):

- positive results in several bacterial reverse mutation assays (Ames tests) using *Salmonella typhimurium* strain TA100 with metabolic activation, but negative without metabolic activation;

- weakly positive or negative results in several Ames tests using *S. typhimurium* strains TA98, TA1537 and TA1538;
- positive results in two bacterial forward mutation assays using *S. typhimurium* strain TM677, with metabolic activation only;
- mixed results in several in vitro mammalian chromosome aberration tests in Chinese hamster ovary (CHO) cells and positive results in Chinese hamster lung (CHL) fibroblasts with metabolic activation;
- positive results in several sister chromatid exchange (SCE) assays and gene mutation assays in CHO cells, with metabolic activation only;
- induction of gene mutations in a mouse lymphoma cell forward mutation assay, at 62.5–1100 µg/mL, without metabolic activation;
- induction of transformations in BALB/c-3T3 cells at 0.276–6.32 mM;
- induction of unscheduled DNA synthesis (UDS) in hepatocytes of male F344 rats, at concentrations of 1.10–3.00 M, and in human hepatocytes at 0.3 mM (but not at 0.03 mM);
- positive results in an alkaline elution assay for DNA single strand breaks in rat hepatocytes, at 3 mM (but not at 0.3 or 0.03 mM); and
- formation of adducts with nucleic acids in rat microsomes (dose not specified).

Several in vivo genotoxicity assays with quinoline also gave positive results (Asakura et al., 1997; US EPA IRIS, 2001; REACH):

- in a UDS assay, male Alpk:AP rats administered a single oral gavage dose at 0, 100, 150, 175, 225, 250, 350 or 500 mg/kg bw gave ambiguous results;
- induction of chromosome aberrations, SCE and replicative DNA synthesis in hepatocytes of F344/DuCrj rats that received the chemical at 25, 50, 100 or 200 mg/kg bw by either a single oral dose or daily oral doses for 28 days;
- in two transgenic mouse mutagenicity assays, male lacZ mice that received the chemical by intraperitoneal (i.p.) injection at 50 mg/kg bw/day for four days, showed gene mutations in the liver, but not in the lungs, kidneys, spleen, bone marrow orand testes;
- positive results in a semi-conservative DNA synthesis (S-phase mitogenesis) assay in hepatocytes of mice (administered quinoline at 40, 100 or 225 mg/kg bw, once by oral gavage) and rats (administered quinoline at 40 or 100 mg/kg bw once by oral gavage), but not in guinea pigs (administered quinoline at 40, 60, 80 or 100 mg/kg bw once by oral gavage); and
- positive results in a bone marrow micronucleus assay in male CD-1 mice administered quinoline by a single i.p. injection at 25, 50 or 100 mg/kg bw.

However, there were a few in vivo assays that produced negative results with quinoline: a liver micronucleus assay in male ICR mice and male F344 rats (at 0.5 mmol/kg bw/day for three days); a reticulocyte (peripheral blood cells) micronucleus assay in male lacZ mice (at 50 mg/kg bw/day for two days); a bone marrow micronucleus assay in F344/DuCrj rats (at oral doses of 25, 50, 100 or 200 mg/kg bw/day for one or 28 days); a chromosome aberration assay and SCE assay in bone marrow cells of B6C3F$_1$ mice (at 25, 50 or 100 mg/kg bw) (Asakura et al., 1997; NTP, 10441-R; REACH). Negative results were also reported in several reciprocal translocation assays and several sex-linked recessive lethal mutation assays in *D. melanoganster* where the larvae were exposed to quinoline at 75 or 130 ppm by contact with treated food, or males were exposed at 100 or 200 ppm in the diet, or at 600 ppm by injection (NTP, 10441-R; REACH).

The following in vitro genotoxicity data are available for the two methylquinolines.

For 2-methylquinoline (NTP, 2002):

- positive results in an Ames test at 100–600 µg/plate (0.71–4.19 µmol), using *S. typhimurium* strain TA100, with metabolic activation;
- negative results in Ames tests at 50–500 µg/plate (0.35–3.5 µmol), using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, with or without metabolic activation; and
- negative results in a bacterial forward mutation assay at 7 mM (1002 µg/mL), using *S. typhimurium* strain TM677, with metabolic activation.

For 4-methylquinoline (OEHHA, 2000):

- positive results in several Ames tests at 500 µg/plate or 0–2.5 µmol/plate, using *S. typhimurium* strains TA98 and TA100 with metabolic activation, but negative results without metabolic activation;
- positive results in a bacterial forward mutation assay in *S. typhimurium* strain TM677 at 70–700 µM, with metabolic activation;
- positive results in a UDS assay at 0.1 and 1.0 mM, using hepatocytes of male SD rats; and
- negative results in an Ames test using *S. typhimurium* strains TA1537 or TA2637, without metabolic activation.

No in vivo genotoxicity data are available for 2- or 4-methylquinoline.

Carcinogenicity

Quinoline is classified as hazardous—Category 2 carcinogenic substance—with the risk phrase ‘May cause cancer’ (T; R45) in the HSIS (Safe Work Australia). The available data for quinoline support this classification. The available mechanistic data for 4-methylquinoline and the limited mutagenicity data for both methylquinoline isomers (see **Genotoxicity** section) are insufficient to support a carcinogenicity classification for the methylquinoline isomers.

Male SD rats (n = six for control and n = 20/dose) were exposed to quinoline at 0, 0.05, 0.10 or 0.25 % (estimated to be equivalent to 0, 25, 50 and 125 mg/kg bw/day) in the diet for 40 weeks. There was decreased survival with increasing doses and the mortalities were associated with increased incidence of malignant

liver tumours (hepatocellular carcinomas and haemangiosarcomas) in treated rats, and subsequent rupture of the vascular-type tumours (haemangiosarcomas). Lung metastases (secondary tumours) were observed in two rats at 0.10 % (Hirao et al., 1976; US EPA IRIS, 2001; REACH).

Various rodents (n = 80 mice/sex, n = 25 rats/sex, n = 25 hamsters/sex, n = 22 guinea pigs/sex) were exposed to 0.2 % quinoline in the diet for 30 weeks. Mice were affected by pneumonia in the first six weeks of study, with deaths reducing the group to n = 10/sex. Unexplained mortalities were also reported in rats (10 males and three females), hamsters (four females) and guinea pigs (one male and five females). Only rats and mice developed tumours in this study, with increased incidence of hepatocellular carcinomas (increased by 10 % in male mice, 13 % in male rats and 9 % in female rats) and haemangioendotheliomas (increased by 80 % in male and female mice, 73 % in male rats and 32 % in female rats). Lung metastases were reported in four male rats and one female rat (US EPA IRIS, 2001; REACH).

In a carcinogenicity study (similar to EU guideline B32), male Wistar rats (n = 5–18/dose) were exposed to 0 or 0.25 % quinoline in the diet for 4, 8, 12, 16 or 20 weeks, with or without a recovery period of 4, 8, 12 or 16 weeks. Deaths were reported, either due to the treatment (details not available) or rupture of tumours. Rats exposed to quinoline for ≥12 weeks showed an increased incidence of liver tumours (haemangioendotheliomas) compared with controls (US EPA IRIS, 2001; REACH).

Male hypertensive SHR rats and Wistar Kyoto (WKY) rats (n = 10 for control and n = 20 for treatment) were exposed to quinoline at 0 or 0.2 % in the diet for 32 weeks. Based on food intake, the dose was calculated to be 29 mg quinoline/rat/day. Malignant liver tumours (haemangioendothelial sarcomas—a vascular neoplasm) were reported in treated rats, but SHR rats were less susceptible than WKY rats since the tumour incidence was 7 % compared with 93 %. It was concluded that vascular injury (as exists in the hypertensive SHR rats) was not related to the development of vascular tumours following quinoline administration, but that strain differences in metabolic activation could be a factor (US EPA IRIS, 2001; REACH).

Limited mechanistic data are available on 4-methylquinoline. Neonatal CD-1 mice were exposed to 4-methylquinoline by i.p. injection (0.25 µmol/mouse on postnatal day (PND) 1, 0.50 µmol/mouse on PND 8 and 1.00 µmol/mouse on PND 15). No tumours were seen in females, but males had significantly increased incidence of liver tumours (adenomas and hepatomas), compared with the control mice. Lung tumours were observed in 2/28 treated males and 2/29 treated females. Neonatal SD rats exposed to 4-methylquinoline by subcutaneous injection (200 µmol/kg bw on PND 1, 100 µmol/kg bw once weekly during weeks 2–7 and 200 µmol/kg bw once during week eight) had no significant increases in tumour incidence, compared with controls (OEHHA, 2000).

In two tumour initiation–promotion studies, female Hfd:SENCAR mice were dermally treated with 100 µL of 0.5 % 4-methylquinoline in acetone (study one) or 0.75 % 4-methylquinoline in acetone (study two) with 10 doses on alternate days. Significantly increased incidence of skin tumours were observed in the mice that received 4-methylquinoline (or benzo[a]pyrene—the positive control) compared with the negative controls (OEHHA, 2000).

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects such as carcinogenicity and mutagenicity. The chemicals may also cause harmful systemic effects from acute oral and dermal exposure, and harmful local effects including eye irritation. While there are limited data for the methylquinoline isomers, the potential for carcinogenicity cannot be ruled out for these chemicals.

Public Risk Characterisation

Although use in cosmetic or domestic products in Australia is not known, the chemicals are reported to be used in cosmetics/domestic products as fragrance compounds (IFRA use survey, 2011; CosIng). However, the maximum use concentrations in consumer products as fragrance ingredients are not available.

The EU has banned the use of quinoline in cosmetics. Currently, there are no restrictions on using this chemical in Australia. In the absence of any regulatory controls, the characterised critical health effects have the potential to pose an unreasonable risk under the identified uses.

Occupational Risk Characterisation

Given the critical systemic long-term health effects of carcinogenicity and mutagenicity, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) is considered appropriate for quinoline. The available data also support classifying the two methylquinoline isomers under the HSIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of quinoline in cosmetic/domestic products be managed through changes to the Poisons Standard (SUSMP), and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemicals is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Given the risk characterisation, it is recommended that quinoline should be included in the Poisons Standard (SUSMP), to prohibit its use in cosmetic/domestic products.

Consideration should be given to the following:

- quinoline is a Category 2 carcinogen and Category 3 mutagen;
- quinoline has acute oral and dermal toxicity;
- quinoline is an irritant to the eyes and the skin;
- there are no data on reproductive and developmental toxicity; and
- there are overseas restrictions for the use of quinoline in cosmetics.

Work Health and Safety

The chemicals are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Quinoline should continue to have all existing risk phrases as indicated in the table below. The two methylquinoline isomers should also have all risk phrases indicated in the table below, apart from the risk phrases 'Irritating to skin' (Xi; R38), 'Possible risk of irreversible effects' (Xn; R68) and 'May cause cancer' (T; R45).

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Harmful in contact with skin (Xn; R21)	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
Irritation / Corrosivity	Irritating to eyes (Xi; R36) Irritating to skin (Xi; R38)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal and ocular exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;

- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

References

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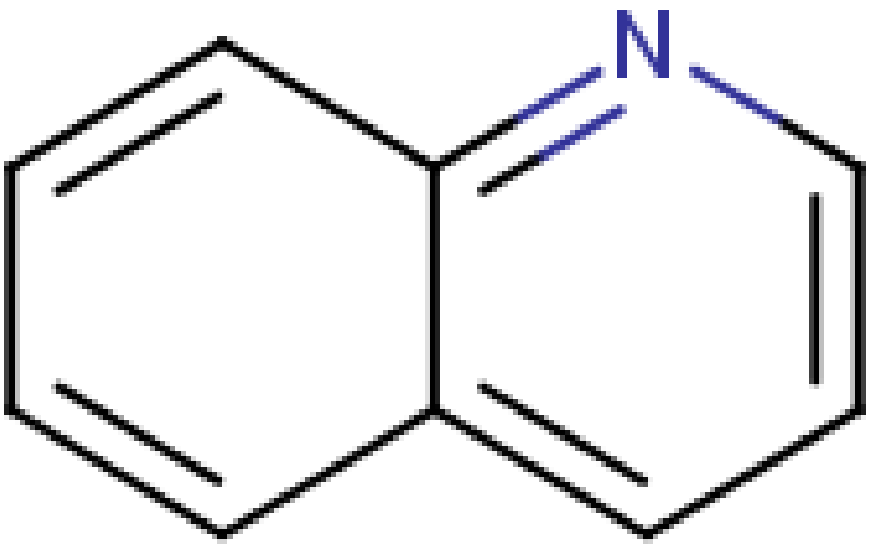
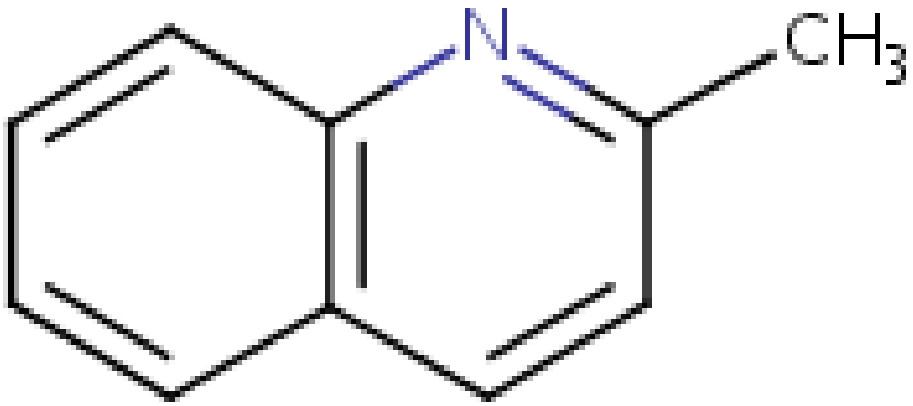
Last Update 03 July 2015

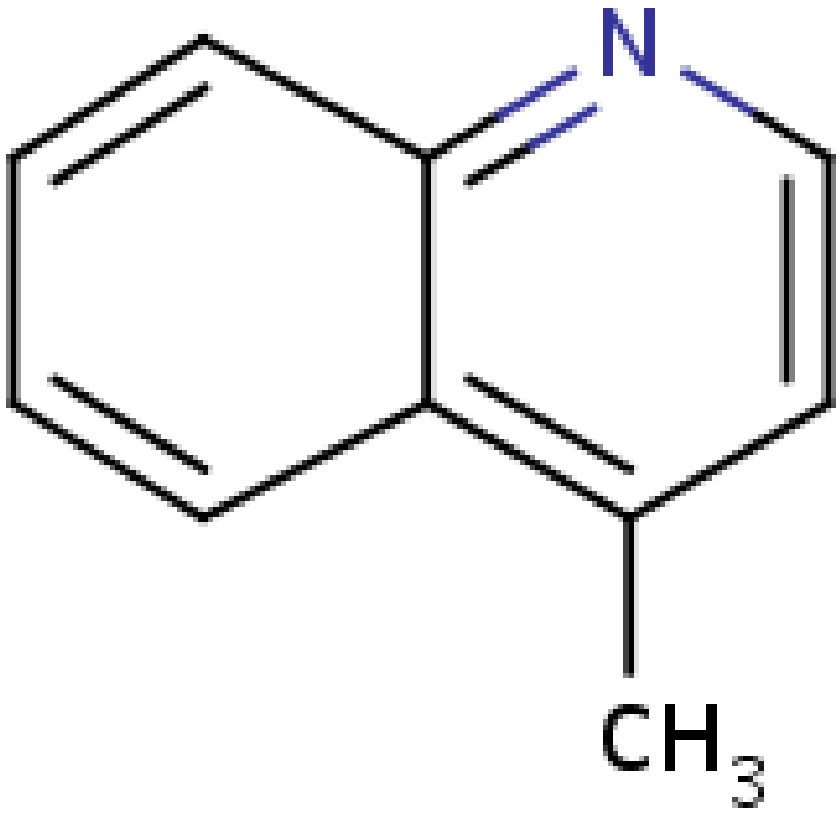
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Quinoline** chinoline 1-azanaphthalene 1-benzazine 2,3-benzopyridine leucoline
CAS Number	91-22-5
Structural Formula	
Molecular Formula	C9H7N

Molecular Weight	129.16

Chemical Name in the Inventory and Synonyms	**Quinoline, 2-methyl-** quinaldine 2-methylquinoline 2-methylchinoline o-methylquinoline
CAS Number	91-63-4
Structural Formula	
Molecular Formula	C10H9N
Molecular Weight	143.19

Chemical Name in the Inventory and Synonyms	**Quinoline, 4-methyl-** lepidene 4-methylquinoline cincholepidine gamma-methylquinoline p-methylquinoline
CAS Number	491-35-0
Structural Formula	

	
Molecular Formula	C10H9N
Molecular Weight	143.19

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