Quinolinols: Human health tier II assessment

08 March 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
8-Quinolinol, sulfate (2:1) (salt)	134-31-6
8-Quinolinol	148-24-3
8-Quinolinol, sulfate (salt)	3819-18-9

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 maintained by third parties, which include data supplied by industry. NICNAS has not verified and cannot guarantee the correctness of all information obtained from those databases. Reproduction or further distribution of this information may be subject to copyright protection. Use of this information without obtaining the permission from the owner(s) of the respective information might violate the rights of the owner. NICNAS does not take any responsibility whatsoever for any copyright or other infringements that may be caused by using this information.

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemical oxyquinoline and two of its sulfate salts are assessed together as they are expected to have similar systemic toxicity profiles due to the same parent base. The chemicals are being re-assessed at the Tier II level under the IMAP framework following the availability of new data. Conclusions based on the new data supersede the decisions made in the previous Tier II IMAP assessment (published July 2015).

Import, Manufacture and Use

Australian

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

The chemical oxyquinoline sulfate has reported non-industrial use in pesticides. The Australian Pesticides and Veterinary Medicine Authority (APVMA) has 8-hydroxyquinoline sulfate (synonym for oxyquinoline sulfate) listed as an active constituent exempt from the requirements of APVMA approval for use in agricultural or veterinary chemical products (APVMA, 2018).

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) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemicals oxyquinoline and oxyquinoline sulfate (2:1) have reported cosmetic uses as:

- preservatives (cosmetic antimicrobials, cosmetic biocides);
- chelating agents; and
- stabilising agents.

Information provided to the US Food and Drug Administration (FDA) and Cosmetic Toiletry and Fragrance Association (CTFA) in 2002 indicates use in a limited number of fragrance preparations, colouring and non-colouring hair preparations and skin preparations at concentrations up to 0.1 % (CIR, 2006). The chemicals are listed in the Compilation of Ingredients Used in Cosmetics in the United States (Personal Care Products Council, 2011), indicating use in 4 and 27 cosmetic products for oxyquinoline and oxyquinoline sulfate (2:1), respectively. The chemicals were identified in a single deodorant product and a moisturiser used for hands, face and lips in the Environmental Working Group (EWG) Skin Deep Cosmetics Database.

The chemicals oxyquinoline and oxyquinoline sulfate (2:1) have reported domestic use as disinfectants. There is no evidence from available North American databases (US Households Product database) for use of these chemicals in consumer products, indicating that they are not likely to be widely available for domestic use.

The chemical oxyquinoline has reported commercial uses including as a:

- corrosion inhibitor; and
- stabiliser.

The chemicals oxyquinoline and oxyquinoline sulfate (2:1) have reported site-limited uses, including in:

- manufacturing other chemicals; and
- precipitating and separating metals.

The chemicals oxyquinoline and oxyquinoline sulfate (2:1) have reported non-industrial use as antiseptic compounds (with bacteriostatic, fungistatic, anti-helminthic or amoebicidal action).

No specific international use, importation, or manufacturing information has been identified for oxyquinoline sulfate.

Restrictions

Australian

'OXYQUINOLINE and its non-halogenated derivatives for human therapeutic use, **except** in preparations for external use containing 1 per cent or less of such substances' is listed in Schedule 2 of the *Poisons Standard*—the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP). This entry covers all chemicals in this assessment (SUSMP, 2019).

Schedule 2 chemicals are described as 'Substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person' (SUSMP, 2019).

International

All chemicals are listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’). They are 'Permitted at concentrations equal to or less than 0.3% as stabilizers for hydrogen peroxide in rinse-off hair-care preparations, and 0.03% in leave-on preparations' (Galleria Chemica).

The chemicals oxyquinoline and oxyquinoline sulfate (2:1) are listed on the following (Galleria Chemica):

- the EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products except for the uses provided for in No 51 in Annex III (maximum concentration of 0.3 % (as base) as a stabiliser for hydrogen peroxide in rinse-off hair products and maximum concentration of 0.03 % (as base) as a stabiliser for hydrogen peroxide in leave-on hair products);
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down

  '- stabilizer for hydrogen peroxide in rinse-off hair-care preparations, maximum authorised concentration in the finished product of 0.3 % calculated as base; and

  - stabilizer for hydrogen peroxide in non-rinse-off hair-care preparations, maximum authorised concentration in the finished product of 0.03 % calculated as base.'

The US Cosmetic Ingredient Review (CIR) Expert Panel concluded that oxyquinoline and oxyquinoline sulfate are safe as stabilisers for hydrogen peroxide in rinse-off hair care cosmetic products 'in the present practices of use'. For leave-on cosmetic products; however, the absence of impurity information and ultraviolet (UV) absorption data resulted in a finding that the available data are insufficient to support the safety of these chemicals (CIR, 2006).

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia):

- Acute toxicity – Category 4; H302 (Harmful if swallowed)
- Acute toxicity – Category 4; H332 (Harmful if inhaled)

This classification is based on the recommended amendment to the hazard classification in the Hazardous Substances Information System (HSIS) (the Safe Work Australia online classification database at the time) from the IMAP assessment published in Tranche 14 (July 2015).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific international exposure standards are available.

Health Hazard Information

As oxyquinoline and two of its sulfate salts are expected to have similar systemic toxicity due to the same parent base, health hazard information available for any of the chemicals is considered appropriate to derive the systemic hazards of the other chemicals.

Toxicokinetics

In male and female rats administered single oral doses of oxyquinoline at 10 mg/kg bw, the chemical was readily absorbed from the gastrointestinal tract, based on high levels of urinary excretion. The relative systemic bioavailability was 63 %. There was minimal tissue distribution, with small amounts (<1 %) measured in spleen, kidney and liver at 72 hours only. Approximately 80 % of the chemical was eliminated via urine and 4 % via faeces at 8 hours, and elimination was 'almost complete' at 120 hours. The half-life of excretion was 28 minutes (RAC, 2015).

In male albino Donryu rats intravenously administered oxyquinoline at 15 mg/kg bw, the chemical was metabolised to glucuronide and sulfate conjugates within 8 hours. Glucuronide metabolites were excreted in both the urine (60 % of the total dose) and bile (9 % of the total dose), whereas sulfate metabolites were excreted in the urine only (23 % of the total dose). There was some intestinal re-absorption of the glucuronide metabolites (NTP, 1985; EMEA, 1998; CIR, 2006; RAC, 2015).

Acute Toxicity

Oral

The chemicals are classified as hazardous with hazard category 'Acute Toxicity Category 4' and hazard statement 'Harmful if swallowed' (H302) in the HCIS (Safe Work Australia). The available data for rats support this classification, although the chemical appears to be more toxic in mice.

The following oral median lethal dose (LD50) values were available for oxyquinoline (NTP, 1985; EMEA, 1988; CIR, 2006; RAC, 2015; HSDB; REACHa; RTECSa):

- 177 mg/kg bw in male and female CFI mice;
- 220–280 mg/kg bw in mice (strain not specified);
- 790–800 mg/kg bw in male and female Wistar rats;
- 1200–2300 mg/kg bw in rats (strain not specified); and
- 1205 mg/kg bw in guinea pigs (strain not specified).

The following oral LD50 values were available for oxyquinoline sulfate (2:1) (EMEA,1988; CIR, 2006; RTECSb):

- 800 mg/kg bw in rats (strain not specified);
- 1200 mg/kg bw in rats (strain not specified); and
- 1200–2520 mg/kg bw and 2520–3180 mg/kg bw in female and male beagle dogs, respectively.

In an in vitro assay (neutral red uptake cytotoxicity assay on Balb/3T3 cells), the estimated oral LD50 was 84 mg/kg bw (REACHb).

Observed sub-lethal effects in the in vivo studies included lethargy, ataxia and signs of abdominal pain.

Dermal

Based on the available data, the chemicals are considered to have low acute dermal toxicity.

The following dermal LD50 values were available:

- >10000 mg/kg bw in male and female Wistar rats exposed to oxyquinoline (RAC, 2015); and

- >4000 mg/kg bw in rats (strain not specified) exposed to oxyquinoline sulfate (2:1) (RTECSb).

Inhalation

The chemicals are classified as hazardous with hazard category 'Acute Toxicity Category 4' and hazard statement 'Harmful if inhaled' (H332). The data used to classify the chemicals previously were not comprehensive, and the more detailed information now available is sufficient to warrant that the chemicals not be classified for this endpoint.

Five male and five female CD rats were exposed to an aerosol of oxyquinoline at a concentration of 1.21 mg/L, continuously for six hours. No deaths or signs of toxicity or irritancy were observed (CIR, 2006).

Corrosion / Irritation

Skin Irritation

Based on the available data from a study performed in accordance with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 404, oxyquinoline is not considered to cause skin irritation. No data are available for the sulfate salts.

In an acute dermal irritation study (OECD TG 404), female New Zealand White (NZW) rabbits (n = 3) were exposed (semi-occlusive) to 0.5 g oxyquinoline on shaved skin for 4 hours and monitored for 72 hours. No erythema or oedema were observed over the 72-hour observation period (REACHa).

In two separate Draize tests in NZW rabbits (n = 6 or 8), 500 mg of oxyquinoline was applied (occlusive) to intact or abraded skin for 24 hours and mild irritation was reported at that time-point. At 7 days, there was no erythema or oedema (CIR, 2006; RAC, 2015; RTECSa).

Eye Irritation

Based on the available data from guideline studies, the chemicals are considered to cause eye irritation. The observation that a corneal lesion in one animal persisted until at least day 20 and results from an in vitro eye irritation study, warrant hazard classification for both the parent base and sulfate salts (see **Recommendation** section).

In an acute eye irritation study (OECD TG 405), 0.1 g of oxyquinoline was applied to one eye in female NZW rabbits (n = 3). Eyes were not rinsed and animals were observed for up to 20 days. There were no effects on the iris reported throughout the study. Conjunctival redness (average 72 hr score = 1.2) and chemosis (average 72 hr score = 0.4) was observed in all animals, but effects were reversed within 7 days. Corneal opacity was observed in one rabbit only (average 72 hr score = 0.3), but this effect did not reverse by 20 days (REACHa).

In a non-guideline study, 100 mg of oxyquinoline was applied to six rabbit eyes. Five of the animals had ocular irritation, with corneal opacity reported in four of the animals (CIR, 2006).

In a Draize test in rabbits, 100 mg of oxyquinoline was applied to rabbit eyes for 24 hours and mild irritation was reported, that was reversible in 4 days. The primary irritation index was 15.3 (out of a possible 110) (CIR, 2006; RTECSa).

In NZW rabbits (n = 8) exposed to 0.1 mL of a 10 % solution of oxyquinoline, there were no eye irritation effects over a 72 hr observation period (RAC, 2015).

In an in vitro eye irritation study (the bovine corneal opacity and permeability (BCOP) test, OECD TG 437), bovine corneas were exposed to oxyquinoline sulfate (2:1) at 20 % w/v in 0.9 % sodium chloride for 4 hours. The corneas were then rinsed and opacity and permeability measured by spectrophotometric analysis. The in vitro irritancy score (IVIS) was determined to be 134, and interpreted to reflect irreversible eye damage (REACHb).

Sensitisation

Skin Sensitisation

No animal study data are available. Based on the available data in humans (see **Observation in humans** below), and an in chemico assay, the chemicals are considered to be skin sensitisers, warranting hazard classification (see **Recommendation** section). Sub-classification was not possible based on the available data.

In an in chemico skin sensitisation study (the Direct Peptide Reactivity Assay (DPRA), OECD TG 442C) using oxyquinoline sulfate (2:1), approximately 41 % cysteine peptide depletion was observed, indicative of moderate reactivity. Precipitation precluded use of the lysine depletion values. The DPRA is proposed to measure protein reactivity, which is the molecular initiating event of the skin sensitisation adverse-outcome pathway (AOP) (REACHb).

Observation in humans

In three human patch tests (n = 100–127), topical application of oxyquinoline resulted in positive sensitisation responses in 4.7–8 % of subjects (RAC, 2015; REACHa). The concentration of the applied test substance, duration of the studies and specific details about the mode of application are unknown.

In an epidermal test for contact eczema caused by drug treatments over 6 years, 3/450 patients showed hypersensitivity to oxyquinoline and it was concluded that the chemical is a weak allergen (RAC, 2015).

In a dermatitis patient treated with oxyquinoline sulfate as an aqueous solution (0.1 %) and as an ointment (0.02 %), eczema was exacerbated. After switching treatment, there was a delayed improvement in the eczema. A subsequent epidermal patch test using solutions of oxyquinoline sulfate showed positive sensitisation responses at concentrations >0.01 %. It was concluded that the chemical could be a ‘powerful skin sensitiser’ (RAC, 2015).

There was no evidence of sensitisation in a human repeated insult patch test with oxyquinoline at 1 % in petrolatum. A group of 193 subjects with normal skin completed the study, which involved nine consecutive applications of 0.2 g under occlusive patches followed by a challenge patch applied after 10–15 days (CIR, 2006).

The use of oxyquinoline sulfate (2:1) as an agent to treat amoebiasis has resulted in frequent allergic reactions (HSDB).

Repeated Dose Toxicity

Oral

Based on the available data for oxyquinoline, the chemicals are not considered to cause severe health effects from repeated oral exposure.

Two 13-week National Toxicology Program (NTP) studies were available in rats and mice using oxyquinoline. One study exposed Fischer 344/N (F344/N) rats (n = 10/sex/dose) to oxyquinoline at 0, 800, 1500, 3000, 6000 or 12000 ppm in the diet for 13 weeks. Based on food intake, the doses were calculated to be 0, 48, 87, 168, 342 and 660 mg/kg bw/day for male rats and 0, 66, 128, 180, 324 and 660 mg/kg bw/day for female rats. At 12000 ppm, final body weights in male rats were reduced by 18 % compared with controls. Food intake was reduced by 24–32 % in female rats of the 3000, 6000 or 12000 ppm dose groups, compared with controls. No treatment-related histopathological changes were reported. The other study exposed B6C3F$_1$ mice (n = 10/sex/dose) to oxyquinoline at 0, 400, 800, 1500, 3000 or 6000 ppm in the diet for 13 weeks. Based on food intake, the doses were calculated to be 0, 60, 113, 195, 405 and 774 mg/kg bw/day for males and 0, 77, 166, 275, 1176 and 888 mg/kg bw/day for females. (The anomalous dosing in female mice is aligned directly to their food intake). At 6000 ppm, final body weights were reduced by 11 % and 10 % in males and females, respectively, compared with controls. Food intake was also reduced in mice in the 6000 ppm dose group by 18 % and 26 % in males and females, respectively, compared with controls. No

treatment-related histopathological changes were reported in mice in the highest dose group (mice in the other dose groups were not examined) (NTP, 1985).

More recent 13-week studies also confirm the lack of severe health effects. Wistar rats (n = 10/sex/dose) were exposed to oxyquinoline at 0, 1000, 3000 or 6000 ppm in the diet (equivalent to approximately 0, 106, 324 and 586 mg/kg bw/day (OECD TG 408). There was reduced food intake (males and females) and body weight (males only) at the highest dose, as well as haematological changes (females: reduced red blood cell count and haematocrit; males: increased mean corpuscular volume) at doses ≥3000 ppm (≥324 mg/kg bw/day). In beagle dogs (n = 4/sex/dose) exposed to oxyquinoline at 0, 10, 50 or 100 mg/kg bw/day (OECD TG 409), food intake was reduced in females at ≥50 mg/kg bw/day. No other treatment related adverse effects were reported (RAC, 2015).

In another repeated dose oral toxicity study, male F344/DuCrj rats (n = 5/dose) were administered oxyquinoline at 0 or 500 mg/kg bw/day for 28 days. Body weight gain was significantly decreased (by approximately 10 %) in treated animals compared with controls (Asakura et al., 1997).

In other studies using oxyquinoline, the following observations were reported (NTP, 1985):

- no histopathological changes in male or female F344 rats administered the chemical by oral gavage doses at 0, 0.1, 3.0, 10 or 30 mg/day, 5 days per week for 52 weeks;
- decreased terminal body weights, hepatic toxicity and renal toxicity in rats exposed to the chemical at 100–250 mg/kg bw in diet for 30–40 days;
- iron accumulation (haemosiderosis) in the liver and spleen, and reduced body weight gain (by 22 %) in male F344 rats exposed to the chemical at 8000 ppm in the diet for 16 or 52 weeks, respectively, compared with controls; and
- decreased food intake from week 52 onwards in male and female F344 rats that received the chemical at 1000 ppm in the diet for up to 104 weeks.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available data, the chemicals are not considered to be genotoxic. This conclusion is supported by studies performed in accordance with OECD guidelines, where some in vitro genotoxicity was observed, but there was no in vivo genotoxicity.

Both positive and negative results were reported in several in vitro genotoxicity assays for oxyquinoline (IARC, 1977; NTP, 1985; EMEA, 1998; CIR, 2006; RAC, 2015; NTP, 10598-N; REACHa):

- negative results in Ames tests (OECD TG 471) with *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 using the chemical at up to 1000 µg/plate, with and without metabolic activation;
- weakly positive or negative results in several Ames tests with *S. typhimurium* strain TA98 using the chemical at 20–40 µg/plate, with and without metabolic activation;
- positive results in several Ames tests with *S. typhimurium* strain TA100 using the chemical at 20–40 µg/plate, with metabolic activation, and negative results without metabolic activation;
- equivocal induction of aneuploidy in the fungus *Neurospora crassa*;

- induction of chromosomal aberration in the root tips of *Vicia faba* (broad bean);
- some DNA damage (not significant) in Chinese hamster V79 cells;
- positive results in a chromosome aberration assay (OECD TG 473) in Chinese hamster V79 cells exposed at up to 125 µg/mL without metabolic activation, and at up to 8 µg/mL with metabolic activation;
- positive results in two sister chromatid exchange (SCE) assays and weakly positive results in two chromosome aberrations assays in Chinese hamster ovary (CHO) cells;
- positive results in a mouse lymphoma cell (L5178Y tk+/tk-) forward mutation assay;
- no transformation of BALB/c-3T3 cells at concentrations of 0.031, 0.063, 0.125, 0.250 or 0.500 µg/mL for 72 hours;
- no induction of unscheduled DNA synthesis (UDS) in rat hepatocytes incubated at concentrations of 2.5, 5.0, 10.0 or 25.0 µg/mL for 18 hours; and
- increased chromatid aberrations (not significant) in human leukocytes.

In vivo genotoxicity assays gave mostly negative results for oxyquinoline (Asakura et al., 1997; IARC, 1977; NTP, 1985; EMEA, 1998; US EPA IRIS, 2001; CIR, 2006; RAC, 2015; NTP, 10598-N; REACHa):

- no significant induction of chromosome aberrations or replicative DNA synthesis in hepatocytes, and negative results in a bone marrow micronucleus assay in F344/DuCrj rats that received the chemical at 500 mg/kg bw by either a single oral dose or daily oral doses for 28 days;
- induction of SCE in hepatocytes of F344/DuCrj rats administered the chemical at 500 mg/kg bw by either a single oral dose or daily oral doses for 28 days;
- ambiguous results overall (no dose–response effect, marginally positive effects in individual animals only) in a UDS assay in hepatocytes from male Alpk:AP rats that received the chemical by a single oral gavage dose of 100, 150, 175, 225, 250, 350 or 500 mg/kg bw;
- negative results in a semi-conservative DNA synthesis (S-phase mitogenesis) assay in hepatocytes of rats that received the chemical once by oral gavage at 225–500 mg/kg bw;
- negative results in an erythrocyte micronucleus assay (OECD TG 474) in male and female NMRI mice exposed to the chemical by intraperitoneal (i.p.) injection at 7, 17.5 or 35 mg/kg bw;
- positive results in an erythrocyte micronucleus assay in male CD-1 mice exposed to the chemical by i.p. injection at 25, 50 or 100 mg/kg bw (dose dependent increases in micronucleated monochromatic erythrocytes; and small but significant increases in micronucleated polychromatic erythrocytes after 24 hours at 100 mg/kg bw, after 72 hours at 50 mg/kg bw and after 48 hours at 25 mg/kg bw);
- negative results in a chromosome aberration assay and SCE assay in bone marrow cells of B6C3F1 mice exposed to the chemical by i.p. injection at up to 100 mg/kg bw;
- positive results in a chromosome aberration assay in bone marrow cells of mice administered the chemical by an i.p. injection at 40 mg/kg bw, although control mice were not used in this study;
- negative results in a chromosome aberration assay (OECD TG 483) in spermatogonial cells from NMRI mice exposed once by oral gavage at up to 300mg/kg bw;
- negative results in reciprocal translocation assays in *Drosophila melanogaster* exposed to 8-hydroxyquinoline by feeding and injection (doses not available); and
- inconclusive or negative results in two sex-linked recessive lethal mutation assays in *D. melanogaster* (chemical doses and route of administration not available).

The following data were available for oxyquinoline sulfate (2:1) (EMEA, 1998; CIR, 2006; RAC, 2015; NTP, M20337; REACHb):

- positive results in Ames tests with *S. typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 (chemical doses not available), with and without metabolic activation;

- positive results in a mouse lymphoma cell (L5178Y tk+/tk-) forward mutation assay at 0.4–3.2 µg/plate;
- 'clastogenic effects' in human lymphocytes exposed at 2.6–5.3 µg/mL; and
- equivocal results in a reciprocal translocation assay and a sex-linked recessive lethal mutation assay in *D. melanogaster* (chemical doses and route of administration not available).

The European Chemicals Agency (ECHA) committee for Risk Assessment (RAC) considered the data for oxyquinoline sulfate (2:1) as 'flawed', since experimental details (e.g. study design and chemical purity) were not available (RAC, 2015).

Carcinogenicity

Based on the available data for oxyquinoline, the chemicals are not considered to be carcinogenic.

The International Agency for Research on Cancer (IARC) has classified oxyquinoline as 'not classifiable as to its carcinogenicity to humans' (Group 3), based on no adequate data in humans and inadequate evidence for carcinogenicity in animal testing (IARC, 1987). Although there were some studies in rats and mice with various routes of exposure showing positive results, these were reported as lacking concurrent controls, using a small number of animals or having a short duration of exposure (IARC, 1977). In addition, there is uncertainty whether findings observed in these studies were treatment related, mainly based on low incidence rates, weak dose–response relationships, and the lack of statistical significance (RAC, 2015).

In a two-year carcinogenicity study, F344/N rats (n = 50/sex/dose) were exposed to oxyquinoline at 0, 1500 or 3000 ppm in the diet. Based on food intake, the doses were calculated to be 0, 73 and 143 mg/kg bw/day for male rats and 0, 89 and 166 mg/kg bw/day for female rats. Food intake was reduced by 12 % and 22 % in male and female rats, respectively at 3000 ppm, compared with controls. There were no significant treatment related differences in survival rates or neoplastic lesions between the groups (NTP, 1985).

In a two-year carcinogenicity study, B6C3F$_1$ mice (n = 50/sex/dose) were exposed to 8-hydroxyquinoline at 0, 1500 or 3000 ppm in the diet. Based on food intake, the doses were calculated to be 0, 217 and 396 mg/kg bw/day for males and 0, 349 and 619 mg/kg bw/day for females. Food intake was reduced by 19 % and 28 % in males, and 14 % and 29 % in females, on low and high dose diets, respectively, compared with controls. There were no significant treatment related differences in survival rates or neoplastic lesions between the groups (NTP, 1985).

In another carcinogenicity study, rats were administered oxyquinoline at 8000 mg/kg diet (approximately 400 mg/kg bw/day) for 78 weeks. Liver weights were marginally increased. There was iron accumulation in spleen, liver, heart and kidneys from 4 weeks onwards. There were no significant changes in tumour incidence (EMEA, 1998).

In 24 week studies using various transgenic mouse models (Tg.AC, $p53^{def}$ and c-Ha-*ras*) that are considered to be more cancer-prone or models for rapid carcinogenicity testing, there was no increase in tumours following both dietary and topical administration of oxyquinoline (CIR, 2006).

Reproductive and Developmental Toxicity

Based on the available data for oxyquinoline, the chemicals are considered to cause developmental toxicity, warranting hazard classification (see **Recommendation** section). Effects on reproduction were only seen at doses that caused systemic toxicity.

In a prenatal developmental toxicity study (OECD TG 414), female Wistar rats (n = 25/dose) were administered oxyquinoline at 0, 100, 300 or 600 mg/kg bw/day by oral gavage on gestation day (GD) 6–19. There were no deaths. Maternal food intake on GD 6–20 was reduced by 12 % and 22 % at 300 and 600 mg/kg bw/day, respectively. Maternal body weights on GD20 were reduced by 5 % and 10 % at 300 and 600 mg/kg bw/day, respectively. There were no effects on reproductive parameters, including live and dead foetuses, resorptions, implantation losses, corpora lutea and litter numbers. Foetal body weight was decreased (6–15%) at 300 mg/kg bw/day. Mean placental weight was decreased (6–18 %) at ≥100 mg/kg bw/day. On GD20, there were significantly decreased numbers of foetal ossification centres in anterior phalanges, metacarpals and caudal vertebrae at all doses. Increased incidences of skeletal retardations (not ossified and rudimentary sternebrae) were noted in

foetuses at all doses. There were also increased incidences of skeletal (full and short supernumerary ribs) and visceral (enlarged nasal cavity and unilateral hydronephrosis or kidney swelling) variations at ≥300 mg/kg bw/day (RAC, 2015).

In another prenatal developmental toxicity study (OECD TG 414), female NZW rabbits (n = 25/dose) were administered oxyquinoline at 0, 5, 15 or 60 mg/kg bw/day by oral gavage on gestation day (GD) 6–28. There were no deaths, and no effects on food intake and body weight in the dams. There was one abortion on GD29 in a dam from the 15 mg/kg bw/day group, and one each on GD20 and GD28 in dams from the 60 mg/kg bw/day group. At 60 mg/kg bw/day, there was a decreased number of live born female pups and increased pre-implantation losses. The latter effect was reported not to be treatment related, since dosing commenced on GD6—the point from which implantation is expected to have already occurred. Increased incidence of skeletal retardations (not ossified and rudimentary sternebrae) were noted in foetuses at all doses. On GD20, there were significantly decreased numbers of foetal ossification centres in sternebrae and caudal vertebrae at ≥15 mg/kg bw/day. At ≥15 mg/kg bw/day, there were also increased incidence of head (soft tissue) variations (periorbital eye haemorrhage and retinal folds) and increased incidence of the rare omphalocele (abdominal organs outside the body) malformation. While maternal toxicity was observed in some rabbits in the 15 mg/kg bw/day group, when individual data for offspring is correlated with their parents, the teratogenic effects were observed in all cases without maternal toxicity (RAC, 2015).

In a two-generation reproduction toxicity study (OECD TG 416), Wistar rats (n = 26/sex/dose) were exposed to oxyquinoline at 0, 1000, 3000 or 8000 ppm in the diet (equivalent to approximately 0, 110, 315 and 809 mg/kg bw/day during pre-mating; 0, 123, 344 and 880 mg/kg bw/day during gestation; and 0, 250, 692 and 1914 mg/kg bw/day during lactation). In F0 and F1 parents, body weight was reduced at ≥3000 ppm during pre-mating, gestation and lactation. Food intake in F0 and F1 parents was reduced during pre-mating, gestation and lactation at 8000 ppm; and during pre-mating and lactation (F0 females only) and pre-mating and gestation (F1 females only) at 3000 ppm. Terminal body weight was lower in parental animals exposed at 8000 ppm, by approximately 12 % (both sexes) in the F0 generation, and 30 % (males) and 19 % (females) in the F1 generation. In F0 animals, ovary, kidney and adrenal weights were reduced in females at 8000 ppm; and prostate weight was reduced and spleen weight was increased in males at ≥3000 ppm. In F1 animals exposed at 8000 ppm, kidney, brain and adrenal weights were reduced in both sexes; seminal vesicles, epididymides, testes and liver weights were reduced in males; and ovary weights were reduced in females. In F1 animals exposed at 3000 ppm, seminal vesicle and adrenal weights were reduced in males, and brain weight was reduced in females. There were no histopathological changes associated with the weight changes in the organs. In F0 animals, mating, fertility, gestation, and oestrous cycle were similar with controls at all doses; but at 8000 ppm there was a statistically significant decrease in live born pup numbers compared with controls. In F1 animals, mating, fertility and gestation were similar with controls at all doses; but at 8000 ppm numbers of complete oestrous cycles were reduced, the length of oestrous cycles was increased, and there was a statistically significant decrease in live born pup numbers compared with controls. In F1 and F2 pups exposed at 8000 ppm, body weight was reduced by 13–35 % during postnatal day (PND) 7–21, and by 26–32 % upon termination. Developmental delays were noted in pups from the 8000 ppm groups, including delayed sexual maturation in F1 pups (delayed preputial separation in males and delayed vaginal opening in females); and delayed incisor eruption and eye opening in F2 pups. In F1 and F2 pups at 8000 ppm, brain, spleen and thymus weights were reduced. In pups from the 3000 ppm groups, organ weights were reduced (thymus in F1 males; spleen in F1 and F2 females; brain in both sexes of F2 pups) and there was delayed eye opening in F2 pups (RAC, 2015).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (developmental toxicity) and local effects (skin sensitisation, serious eye damage). The chemicals may also cause systemic acute effects following oral exposure.

Public Risk Characterisation

Based on international uses, the chemicals may be used as preservatives (antimicrobial and biocidal agents) in cosmetics and domestic products in Australia.

Canada and the EU have banned the use of quinolinols in cosmetics, except for their restricted use in hair dyes. The chemicals oxyquinoline and its derivatives are listed on Schedule 2 of the SUSMP for human therapeutic use, except for external use containing ≤1 % of such substances (SUSMP, 2019). This entry does not restrict the use of these chemicals in cosmetics or domestic products in Australia.

While the characterised critical health effects have the potential to pose an unreasonable risk under the identified uses, overseas information indicates that the chemicals have both low frequency of use and use at low concentrations (CIR, 2006). In addition, the chemicals do not seem to be a prevalent cause of contact dermatitis from cosmetic use—there was only 1 reaction reported for oxyquinoline as the causative ingredient for cosmetic allergy in 578 patients (Groot, 1988). Concentrations in therapeutic medicines are also expected to be higher than in cosmetics, and may account for any induction in susceptible individuals.

Considering the limited use of these chemicals in consumer products, the public risk from these chemicals is not considered to be unreasonable. Should data that better characterises exposure become available, further assessment regarding the safety of this group of chemicals may be required.

Occupational Risk Characterisation

During product formulation, oral, dermal and ocular exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal and ocular 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.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of these chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required unless new information regarding the uses of the chemicals in cosmetic or domestic products/scenarios in Australia becomes available.

Regulatory Control

Public Health

Products containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2019).

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)*
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging the unborn child - Cat. 2 (H361d)

[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

Asakura S, Sawada S, Sugihara T, Daimon H and Sagami F 1997. Quinoline-induced chromosome aberrations and sister chromatid exchanges in rat liver. Environmental and Molecular Mutagenesis 30(4) pp. 459–467.

Australian Pesticides and Veterinary Medicines Authority (APVMA) 2018. Active constituents exempt from the requirements of APVMA approval for use in agricultural or veterinary chemical products. Accessed February 2019 at **http://apvma.gov.au/node/4176**

Bailey, JE (ed.) 2011. Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 1st Edition, Personal Care Products Council, Washington, D.C.

Cosmetic Ingredient Review (CIR) 1992. Final report on the safety assessment of oxyquinoline and oxyquinoline sulfate. Journal of the American College of Toxicology 11(4) pp. 497–507

Cosmetic Ingredient Review (CIR) 2006. Final amended report on the safety assessment of oxyquinoline and oxyquinoline sulfate as used in cosmetics. International Journal of Toxicology 25(Suppl 1) pp. 1–9

Environmental Working Group (EWG). Skin Deep Cosmetics Database. Accessed February 2019 at **http://www.ewg.org/skindeep/**

European Chemicals Agency (ECHA) Committee for Risk Assessment (RAC) 2015. Annex 1 Background document to the Opinion proposing harmonised classification and labelling at community level of Quinolin-8-ol; 8-hydroxyquinoline (CAS No. 148-24-3). Accessed February 2019 at **https://echa.europa.eu/sv/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e18079af24**

European Commission Cosmetic Ingredients and Substances (CosIng) Database. Accessed February 2019 at **http://ec.europa.eu/consumers/cosmetics/cosing/**

Galleria Chemica. Accessed February 2019 at **http://jr.chemwatch.net/galleria/**

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at **http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html**

Groot ACD 1988. Adverse Reactions to Cosmetics. Available at **https://www.rug.nl/research/portal/files/49572527/A.C.de_Groot.pdf**

International Agency for Research on Cancer (IARC) 1977. Some Miscellaneous Pharmaceutical Substances, Volume 13. Available at **http://monographs.iarc.fr/ENG/Monographs/vol1-42/index.php**

International Agency for Research on Cancer (IARC) 1987. Overall evaluations of carcinogenicity: An updating of IARC Monographs Volumes 1 to 42, Supplement 7 (Results and Conclusions). Available at **http://monographs.iarc.fr/ENG/Monographs/suppl7/Suppl7-5C.pdf**

National Toxicology Program (NTP) 1985. Technical Report Series No. 276 - Toxicology and Carcinogenesis Studies of 8-hydroxyquinoline in F344/N rats and B6C3F1 mice (Feed Studies). US Department of Health and Human Services Secretary. Available at **http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr200299/abstracts/tr276/index.html**

National Toxicology Program (NTP). 8-hydroxyquinoline 10598-N. US Department of Health and Human Services. Accessed February 2019 at **http://ntp.niehs.nih.gov/testing/status/agents/ts-10598-n.html**

National Toxicology Program (NTP). 8-hydroxyquinoline sulfate M20337. US Department of Health and Human Services. Accessed February 2019 at **http://ntp.niehs.nih.gov/testing/status/agents/ts-m20337.html**

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACHa) Dossier. 148-24-3. Accessed February 2019 at **http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances**

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACHb) Dossier. 134-31-6. Accessed February 2019 at **http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances**

Registry of Toxic Effects of Chemical Substances (RTECSa). 8-quinolinol (CAS No. 148-24-3), RTECS number: VC4200000. Accessed at **http://www.drugfuture.com/toxic/q123-q717.html**

Registry of Toxic Effects of Chemical Substances (RTECSb). 8-quinolinol, sulfate (2:1) (salt) (CAS No. 134-31-6), RTECS number: VC8260000. Accessed at **http://www.drugfuture.com/toxic/q123-q826.html**

Safe Work Australia (SWA). Hazardous Chemical Information System (HCIS). Accessed February 2019 at **http://hcis.safeworkaustralia.gov.au/**

Substances in Preparations in Nordic countries (SPIN) database. Accessed February 2019 at **http://www.spin2000.net/spinmyphp/**

The Poisons Standard February 2019. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 23. Accessed February 2019 at **https://www.tga.gov.au/publication/poisons-standard-susmp**

United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary. Accessed February 2019 at **http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp**

US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR). Accessed February 2019 at **https://actor.epa.gov/actor/home.xhtml**

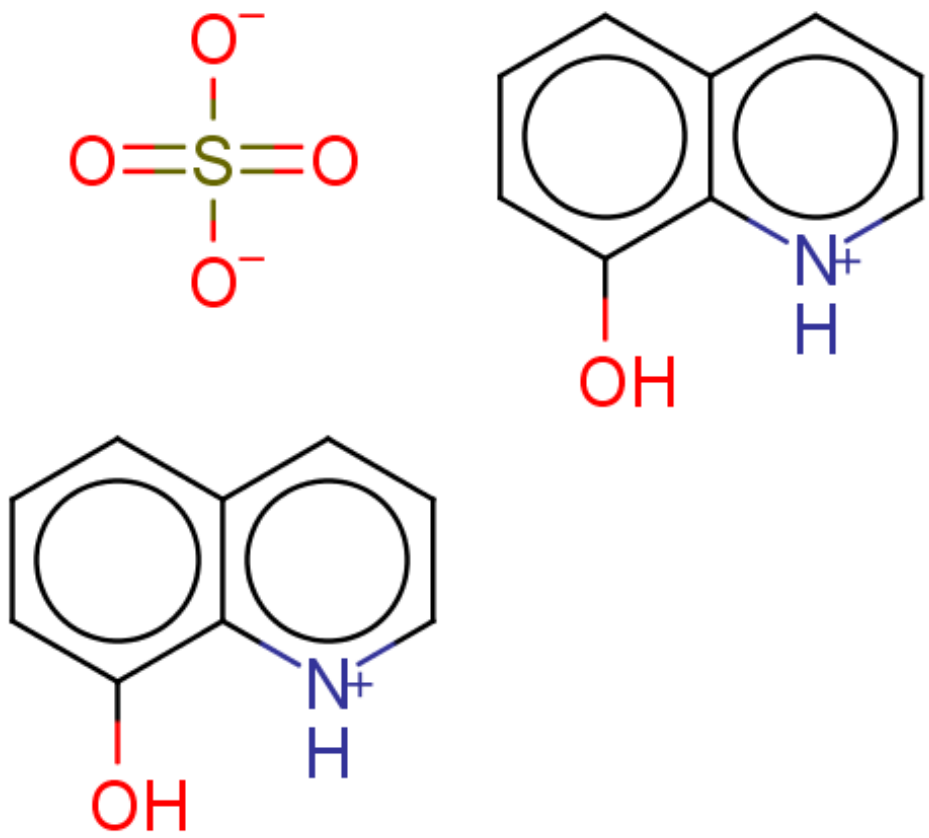
US EPA Integrated Risk Information System (IRIS) 2001. Quinoline (CAS No. 91-22-5). Accessed at **http://www.epa.gov/iris**

US National Library of Medicine's Hazardous Substances Data Bank (HSDB). Accessed February 2019 at **http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB**

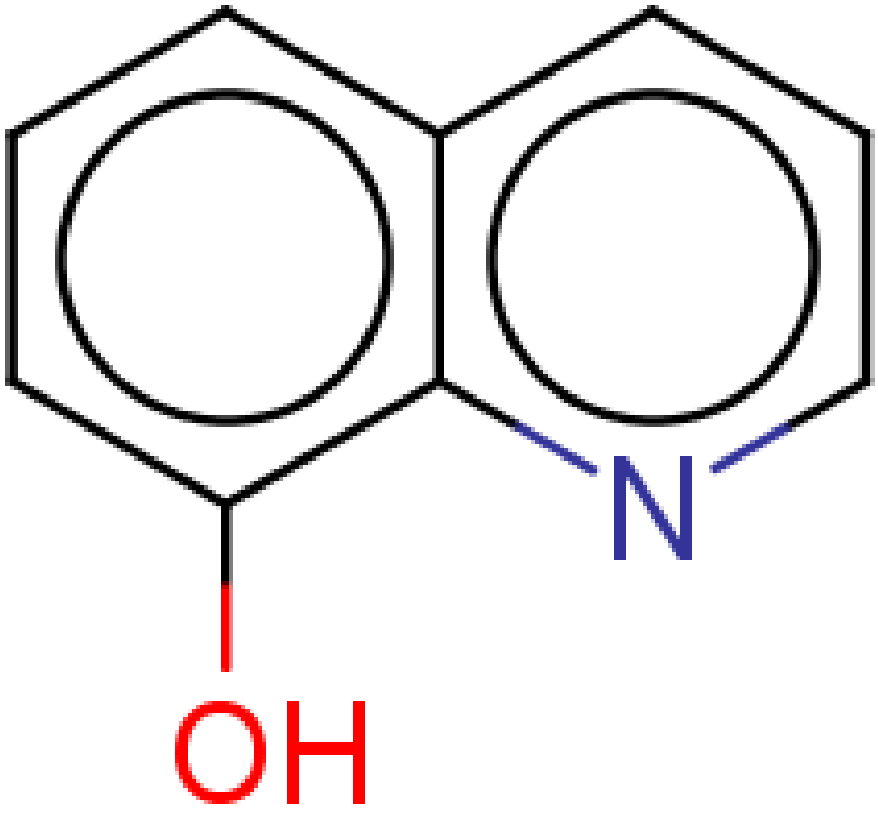
Last Update 08 March 2019

Chemical Identities

Chemical Name in the Inventory and Synonyms	**8-Quinolinol, sulfate (2:1) (salt)** oxyquinoline sulfate (2:1) 8-hydroxyquinoline sulfate (2:1) chinosol bis (8-hydroxyquinolinium) sulfate

CAS Number	134-31-6
Structural Formula	
Molecular Formula	C9H7NO.1/2H2O4S
Molecular Weight	388.40

Chemical Name in the Inventory and Synonyms	**8-Quinolinol** oxyquinoline 8-hydroxyquinoline 1-azanaphthalene-8-ol hydroxybenzopyridine 8-chinolinol
CAS Number	148-24-3
Structural Formula	

	
Molecular Formula	C9H7NO
Molecular Weight	145.16

Chemical Name in the Inventory and Synonyms	**8-Quinolinol, sulfate (salt)** oxyquinoline sulfate 8-hydroxyquinoline sulfate quinosol
CAS Number	3819-18-9
Structural Formula	**No Structural Diagram Available**
Molecular Formula	C9H7NO.xH2O4S

Molecular Weight	Unspecified

Share this page