Quinine and its salts: Human health tier II assessment

25 November 2016

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Cinchonan-9-ol, 6'-methoxy-, dihydrochloride, (8.alpha.,9R)-	60-93-5
Cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate (2:1) (salt)	804-63-7
Cinchonan-9-ol, 6'-methoxy-, monohydrochloride, (8.alpha.,9R)-	130-89-2
Cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-	130-95-0
Cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate (1:1) (salt)	549-56-4
Cinchonan-9-ol, 6'-methoxy-, monohydrochloride, dihydrate, (8.alpha.,9R)-	6119-47-7
Cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate(2:1) (salt), dihydrate	6119-70-6
Cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate (1:1) (salt), heptahydrate	6183-68-2
Cinchonan-9-ol, 6'-methoxy-, hydrochloride, (8.alpha.,9R)-	7549-43-1

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

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The parent chemical, quinine, and eight water soluble chloride or sulfate salts of quinine are assessed together in this report as they share common uses and are expected to have similar systemic toxicity profiles due to the same parent base.

Import, Manufacture and Use

Australian

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

The following non-industrial uses have been identified in Australia:

- quinine sulfate is an active ingredient in a euthanasia solution for horses, dogs and cats registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA);
- quinine dihydrochloride (CAS No. 60-93-5), quinine sulfate dihydrate (CAS No. 6119-70-6) and quinine bisulphate (CAS No. 549-56-4, anhydrous; CAS No. 6183-68-2, heptahydrate) are active ingredients in separate medicinal products registered by the Therapeutic Goods Administration (TGA); and
- quinine is a food additive and natural toxicant according to Food Standards Australia New Zealand (FSANZ).

International

The following international uses have been identified through the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011); European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the European Commission Cosmetic Ingredients and Substances (CosIng) database; and the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary.

The chemical quinine (CAS No. 130-95-0) and its salts have reported cosmetic use as denaturants, hair conditioning agents, masking agents and fragrance ingredients.

The chemicals quinine, quinine dihydrochloride and quinine bisulfate have reported site-limited use as intermediates in the manufacture of other chemicals.

The following non-industrial uses have been identified internationally through Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US National Library of Medicine's Household Products Database; REACH; and various international references (WHO Joint Expert Committee on Food Additives (JECFA), (1990); JECFA, 1993; European Food Safety Authority (EFSA), (2015)):

- all chemicals (*except* quinine hydrochloride (unspecified), CAS No. 7549-43-1) have reported use in medicines;
- all chemicals have reported use as bittering or flavouring agents in food and beverages;

- quinine hydrochloride dihydrate (CAS No. 6119-47-7) has reported animal health use in a fish pond treatment product at concentrations of 2.5–10 %; and
- quinine has reported use as a biocide in pest control products and disinfectants.

Restrictions

Australian

Quinine is listed in the *Poisons standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedules 4, 5 and 7 (SUSMP, 2016).

Schedule 4:

'QUININE for human therapeutic use **except** when the maximum recommended daily dose is 50 mg or less of quinine'

Schedule 5:

'QUININE in preparations for veterinary use containing 1 per cent or less of quinine'

Schedule 7:

'QUININE for veterinary use **except** when included in Schedule 5'

Schedule 4 chemicals are described as 'Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.' Schedule 4 chemicals are labelled with 'Prescription Only Medicine or Prescription Animal Remedy' (SUSMP, 2016).

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2016).

Schedule 7 chemicals are described as 'Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.' Schedule 7 chemicals are labelled with 'Dangerous Poison' (SUSMP, 2016).

Quinine is listed in the *Australia New Zealand Food Standards Code* in Schedules 15 and 19.

Quinine has a maximum permitted level as a food additive (Schedule 15) and a maximum level as a natural toxicant (Schedule 19) of:

- 100 mg/kg in water based flavoured drinks (only in tonic, bitter and quinine drinks);
- 300 mg/kg in wine based drinks and reduced alcohol wines; and
- 300 mg/kg in other mixed alcoholic beverages not classified elsewhere (FSANZ, 2016).

International

All chemicals (*except* quinine hydrochloride) are listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down;
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down; and
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down.

For all of the above, the maximum concentration allowed in ready for use hair preparations is 0.5% (as quinine base) in rinse-off products and 0.2% (as quinine base) in leave-on products.

The chemicals quinine dihydrochloride, quinine monohydrochloride (CAS No. 130-89-2) and quinine hydrochloride dihydrate are listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist') (Galleria Chemica).

The chemicals quinine sulfate anhydrous (CAS No. 804-63-7), quinine monohydrochloride and quinine sulfate dihydrate are listed on the EU Regulation 872/2012—List of flavouring substances which can be used in food. The chemicals, individually or in combination, are restricted as follows (Galleria Chemica):

- not more than 100 mg/kg (as quinine base) in non-alcoholic beverages and alcoholic beverages (including alcohol-free and low-alcoholic counterparts); and
- not more than 250 mg/kg (as quinine base) in spirit drinks.

No known international restrictions have been identified for quinine hydrochloride (unspecified).

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific international exposure standards are available.

Health Hazard Information

Since the salts of quinine are water soluble, all of these chemicals are expected to have a similar systemic toxicity as the parent base. Therefore, health hazard information available for any of the chemicals is considered appropriate to derive the systemic hazards of the other chemicals.

Toxicokinetics

Quinine is an aryl amino alcohol alkaloid and is the main alkaloid compound from the bark of the cinchona tree. Sulfate and chloride salts of the chemical are currently used as anti-malarial medications and have been used for this purpose since the early 19th century. Following oral administration in healthy individuals, >80 % of quinine is absorbed, mainly from the upper gastrointestinal tract; approximately 10 % of quinine undergoes first pass metabolism. The time to maximum plasma concentration is 3–8 hours. Quinine circulates mostly protein-bound in blood (69–92 % in healthy individuals) and is widely distributed to organs/tissues (liver > plasma > muscle [skeletal and cardiac] > brain). The plasma elimination half-life of quinine in healthy individuals is reported to be 9.7–12.5 hours (Paintaud et al., 1993; Brunton, 2011; EFSA, 2015; HSDB).

Quinine undergoes hepatic biotransformation primarily by the oxidative cytochrome P450 enzyme, CYP3A4, and to a lesser extent by the enzymes CYP2C19 > CYP2C9 > CYP2D6. The metabolic reactions are hydroxylation (on the quinoline and quinuclidine rings), demethylation and ketone formation. Four primary metabolites are generated (3-hydroxyquinine, 2´-quinone, O-desmethylquinine, and 10,11-dihydroxydihydroquinine), followed by six secondary metabolites (3-hydroxy-2'-quinone, O-desmethyl-2'-quinone, O-desmethyl-3-hydroxyquinine, O-desmethyl-3-hydroxy-2'-quinone, 10,11-dihydroxydihydro-2'-quinone and 10,11-dihydroxydihydro-O-desmethylquinine). The major metabolite is 3-hydroxyquinine, and all metabolites are detected in plasma and urine (Bannon et al., 1998; Brunton, 2011; Marcsisin et al., 2013; EFSA, 2015; HSDB).

Approximately 20 % of the administered compound is excreted unchanged in the urine, and the remainder is excreted as metabolites. Quinine is re-absorbed when the urine is alkaline, and therefore, acidification of the urine promotes renal excretion. Quinine itself does not accumulate in the body. The major metabolite, 3-hydroxyquinine, can bioaccumulate. Although it is less potent than the parent compound, it can be toxic for patients with kidney failure (Bannon et al., 1998; Brunton, 2011; Marcsisin et al., 2013; EFSA, 2015; REACHa).

Acute Toxicity

Oral

Based on the available data, the chemicals are considered to have moderate acute oral toxicity, warranting hazard classification (see **Recommendation** section).

The reported oral median lethal dose (LD50) values were (HSDB; REACHa; REACHb; REACHc):

- 1800 mg/kg bw in guinea pigs exposed to quinine;
- 641, 660 and 1392 mg/kg bw in rabbits, mice and rats, respectively, exposed to quinine dihydrochloride; and
- 456 mg/kg bw in rats exposed to quinine bisulfate, which is reported to equate to 351 mg/kg bw quinine base.

Dermal

No data are available for the chemicals.

Inhalation

No data are available for the chemicals.

Observation in humans

In humans, ingestion of 2–8 g of quinine has been reported to be fatal in adults. With acute overdose, toxic effects can include irreversible deafness, pulmonary oedema and cardiac arrhythmias (Brunton, 2011; EFSA, 2015). This equates to a dose of approximately 29–114 mg/kg bw in a 70 kg person.

Corrosion / Irritation

Skin Irritation

Based on the limited available data in guinea pigs, the chemicals are not considered to be irritating to skin up to 25 % concentration. Occupational exposure to the chemicals has been reported to cause irritant dermatitis in workers suggesting irritation as the cause, instead of allergy (Hardie et al., 1978) (see **Sensitisation: Observation in humans** section).

No skin irritation was reported in guinea pigs following exposure to quinine hydrochloride via intradermal or epicutaneous routes at 0.25 % and 25 %, respectively, when used in the induction phase of a guinea pig maximisation test (Wahlberg & Boman, 1981).

Eye Irritation

The available data indicate that the chemicals are not corrosive or severe eye irritants, up to a 20 % concentration. However, the available data are insufficient to derive a conclusion on the eye irritation potential of the chemicals.

In an in vitro test (the bovine corneal opacity and permeability test method (BCOP) for identifying ocular corrosives and severe irritants), conducted according to the Organisation for Economic Cooperation and Development (OECD) test guideline (TG) 437, corneas from fresh bovine eyes were exposed to quinine as a 20 % suspension in physiological saline for four hours. The mean in vitro irritancy score (IVIS) for quinine was reported to be 18.15, which falls in the mid-range of scores (IVIS 3–55), where no prediction on irritancy can be made (REACHa). According to the OECD TG 437, 'A substance that induces an IVIS superior or equal to 55.1 is defined as a corrosive or severe irritant'; and 'However, a chemical that is not predicted as causing serious eye damage or as not classified for eye irritation/serious eye damage with the BCOP test method would require additional testing (in vitro and/or in vivo) to establish a definitive classification'.

Sensitisation

Skin Sensitisation

Based on the available data in guinea pigs and humans (see **Observation in humans** below), the chemicals are considered to cause skin sensitisation, warranting hazard classification (see **Recommendation** section).

In a guinea pig maximisation test conducted similar to OECD TG 406, animals (n = 20/group) were exposed to quinine hydrochloride at 0.25 % in distilled water for intradermal induction; pre-treated with sodium lauryl sulfate before being exposed to quinine hydrochloride at 20 % in petrolatum for epicutaneous induction; and challenged 21 days later with 1, 5 or 10 % quinine hydrochloride in petrolatum by topical application for 24 and 48 hours. Quinine was reported to be a grade V allergen or potent contact allergen, since sensitisation was observed in 80–95 % of animals exposed to the chemical at 5 or 10 % at both 24 and 48 hour time-points (Wahlberg & Boman, 1981; REACHa).

Observation in humans

Most of the human case reports indicate the chemicals to have potential for skin sensitisation.

In five case studies in males (aged 25–40 years), exposure to quinine (indirectly from a contraceptive pessary used by their wives, which contained quinine, or directly through use of a hair lotion that contained quinine or via consumption of bitter flavoured beverages) caused present or past contact dermatitis (skin rash and inflammation). Patch testing using 1 % quinine sulfate (n = 1) or 2 % quinine sulfate (n = 4) resulted in positive reactions in all patients, confirming that quinine is a contact allergen (Calnan & Caron, 1961).

Recurrent contact dermatitis was reported in a 15-month old child exposed on the upper chest for three months to a topical respiratory decongestion balm. Patch testing confirmed an allergy to quinine, one of the components of the topical balm (Dias et al., 1994).

In a 26-year old Japanese man, examination of asymptomatic swelling and redness led to a fixed eruption diagnosis (adverse skin reaction), secondary to quinine consumption of tonic beverages. An oral challenge test using tonic water, and a patch test using 1 % quinine hydrochloride were both positive. Severe redness and swelling of the lips was observed four days after the man drank tonic water; a large blister and redness was observed at the patch test site two days after exposure to quinine hydrochloride. Eleven other cases (n = 6 males, n = 5 females, 23–57 years old) of fixed eruption attributed to quinine in tonic beverages have also been reported and confirmed by oral challenges or patch testing (Ohira at al., 2013).

Other hypersensitivity reactions have also been reported in humans, including anaphylactic shock, anaphylactoid reactions, urticaria (hives, upper dermis swelling), angio-oedema (swelling below the dermis layer), serious skin rashes, facial swelling, bronchospasm and pruritus (severe skin itching) (HSDB).

Irritant dermatitis was reported in process workers in a factory manufacturing quinine bisulfate, but with potential exposure to up to 13 different quinine or quinidine (the stereoisomer of quinine) products. Employees with a current or past history of skin disorders were examined (n = 23, from a total of 73 employees), and skin disorders from 15 of the 23 employees were deemed to be work-related. Exposure to quinine was deemed the cause of skin disorders in 13 of the 15 work-related cases, with development of symptoms typically occurring four to eight weeks post-exposure (range two weeks to eight months). However, negative

results were observed during patch testing and medical opinion based on clinical examination suggested that the effects were caused by irritation, rather than allergy. For the majority of workers, the effects were reversed following cessation of exposure, or spontaneously cleared even with continued exposure (Hardie et al., 1978).

Repeated Dose Toxicity

Oral

Based on the available data in rats and humans (see **Observation in humans** below), the chemicals are not considered to cause serious systemic health effects from repeated oral exposure.

In a repeated dose oral toxicity study, Sprague Dawley (SD) rats (n = 20/sex/dose) were exposed to quinine hydrochloride in the diet at 0, 1, 10, 40, 100 or 200 mg/kg bw/day for 13 weeks. Ophthalmoscopic (eye), haematological and biochemical examinations were performed at weeks 4 and 12. A subset of rats (n = 5/sex/group) were not euthanised at the end of the 13 weeks, but instead maintained for a further six weeks, without any treatment. The no observed adverse effect level (NOAEL) was reported to be 40 mg/kg bw/day, based on reduced body weight gain at ≥100 mg/kg bw/day and reduced food intake at 200 mg/kg bw/day. These effects were reversed in animals during the six week recovery period. Male rats exposed at ≥100 mg/kg bw/day and female rats exposed at 200 mg/kg bw/day showed increased plasma urea; females exposed at ≥100 mg/kg bw/day showed reduced total serum protein and globulin at week 12; and female rats exposed at ≥100 mg/kg bw/day showed moderate or marked periportal (liver) glycogen depletion. No effects were observed in the eye by indirect ophthalmoscopy (all doses) or histopathological assessment of the optic nerve (200 mg/kg bw/day group only); and no effects were observed on hearing function by pinna reflex tests (JECFA, 1990; REACHa).

To more accurately evaluate the NOAEL, another repeated dose oral toxicity study was performed in SD rats (n = 20/sex/dose) by administering quinine hydrochloride in the diet at 0, 60, 85 or 120 mg/kg bw/day for 13 weeks. Similar to the previous study, a subset of rats (n = 5/sex/group) were maintained without further treatment for a recovery period of six weeks. The NOAEL was reported to be 60 mg/kg bw/day, based on reduced body weight gain and food intake at ≥85 mg/kg bw/day. The effects on body weight gain were reversed, and the effects on food intake were partially reversed, during the recovery period. In males exposed at ≥85 mg/kg bw/day, kidney weights were also affected (variably reported as decreased or increased), but there were no morphological changes. Circulating phosphorous levels were elevated in females exposed at 120 mg/kg bw/day, even through the recovery phase. Fur loss was noted in rats exposed at 120 mg/kg bw/day and this was reported to be associated with treatment (JECFA, 1990; REACHa).

In another repeated dose oral toxicity study, SD rats (n = 5/sex/dose) were exposed to quinine hydrochloride in the diet at 0, 85 or 200 mg/kg bw/day for 13 weeks, primarily for the assessment of ototoxicity (inner ear damage). Hearing sensitivity was not affected in the audible sound frequency range of 2.5–30 kHz and there were no histopathological changes in the ear (REACHa).

Dermal

No data are available for the chemicals.

Inhalation

No data are available for the chemicals.

Observation in humans

In safety testing in human volunteers (20 males and 12 females; aged 18–50 years), quinine hydrochloride administered orally in gelatin capsules at up to 160 mg/day for 21 days did not cause changes in urinary, blood, cardiovascular or auditory parameters compared with the lactose placebo control. The NOAEL was determined to be 72 mg of quinine base/person/day based on transient involuntary eye movements (by electronystagmography (ENG) recording) observed at higher doses (JECFA, 1993; EFSA, 2015).

In another study, human volunteers (6 males and 14 females) consumed 1.25 L of tonic water containing a total of 100 mg quinine hydrochloride per day for 14 days. Blurred vision (n = 7), poor focussing (n = 5) and headaches (n = 14) were reported. Significant changes in the field of vision were also reported (by Goldmann visual field testing), but these effects were reversed when assessed four months after exposure ended. There were no alterations to visual acuity, audiometry or clinical chemistry parameters (JECFA, 1990).

Recordings by ENG were abnormal in some subjects (3 out of 4) exposed orally to 105 mg of quinine per day in tonic water for 14 days, but not in subjects exposed to 52.5 mg quinine (n = 9) or the control group (n = 4). No treatment-related effects were reported in subjects (n = 5/group) exposed orally to 0 or 120 mg quinine hydrochloride per day for 14 days (JECFA, 1990).

Genotoxicity

Based on the negative results observed in the well-conducted in vitro genotoxicity assays and weight of evidence from the available in vivo genotoxicity studies, the chemicals are not considered to be genotoxic.

The following in vitro tests showed negative results (EFSA, 2015):

- two bacterial reverse mutation assays using *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 102 with quinine monohydrochloride at up to 5000 µg/plate, with or without metabolic activation; and

- a micronucleus test in human lymphocytes with quinine monohydrochloride at up to 400 µg/mL for up to 24 hours.

These studies were performed according to the OECD test guidelines (EFSA, 2015).

Several in vivo tests for genotoxicity were negative (JECFA, 1990; EFSA, 2015; REACHa):

- negative results in a chromosomal aberration assay in C3H mice, NMRI mice and hamsters exposed to quinine hydrochloride once by oral gavage at 110 mg/kg bw;
- negative results in a micronucleus test in NMRI mice and hamsters, but positive results in C3H mice, exposed to quinine hydrochloride once by oral gavage at 110 mg/kg bw; and
- negative results in a micronucleus test in bone marrow from NMRI mice exposed to quinine dihydrochloride twice by intraperitoneal injection or oral gavage at 0.5 mM/kg bw.

These studies were reported to be 'limited' or 'insufficient' as they were not performed according to the OECD test guidelines (EFSA, 2015).

Carcinogenicity

Only one study, with limited relevance, is available for quinine sulphate at 0.3 %. The available data are insufficient to derive a conclusion on carcinogenicity of the chemicals.

In a carcinogenicity study examining individual spermicide ingredients, female BALB/c (Bagg albino) mice were treated with 0.3 % quinine sulphate (in gum tragacanth; 0.1 mL) by intravaginal injection, twice weekly for 40 weeks. The positive control was 7, 12-dimethylbenz(a)anthracene (DMBA) at 0.3 % concentration. The uterus, cervix, vagina and perineal skin were examined for neoplasms and hyperplastic lesions at the latter of the time of death or at 18–20 months of age. Treatment specific tumours were not observed in the mice exposed to quinine (or the untreated or vehicle control mice), compared with vaginal and perineal malignant tumours in 75 % of mice exposed to DMBA. Inflammatory changes (leucocyte infiltration and epithelial hyperplasia) were observed in the cervix and vaginal wall of all treated animals. Although it was reported that the study was not designed to examine effects other than genital lesions, one mouse treated with quinine sulfate had a mammary tumour that was not present in the control groups (Boyland et al., 1966). The significance of the mammary tumour is unknown.

There are no structural alerts for carcinogenicity for any of the chemicals (QSAR Toolbox v3.4.0.17).

Reproductive and Developmental Toxicity

Based on the available data, the chemicals are not expected to cause developmental toxicity. The limited available data in female rats and pregnant women indicate the chemicals have no reproductive toxicity in females, but no test data are available on males.

In a teratology study, female SD rats (n = 25/group) were exposed to quinine hydrochloride at 0, 50, 100 or 200 mg/kg bw/day by oral gavage, once daily on gestation day (GD) 6–15. Animals were euthanised on GD 20. Body weight gain was reduced, water intake was increased, and salivation and fur loss were observed in the dams exposed at ≥100 mg/kg bw/day; food intake was reduced in the dams exposed at 200 mg/kg bw/day. Pregnancy parameters, resorptions, litter size, sex ratio and major malformations were not affected by treatment. In offspring exposed at 200 mg/kg bw/day, litter weights were significantly reduced and there was a significantly increased incidence of variant sternebrae (JECFA, 1990; REACHa). Since these effects coincided with maternal toxicity, the chemical is not considered to cause developmental toxicity.

In epidemiological studies of pregnant women treated with quinine as an anti-malarial medication, ‘there is no evidence of an increased risk' of 'abortion in pregnant women ... [or] eye defects and hearing loss in newborns' (EFSA, 2015).

Risk Characterisation

Critical Health Effects

For industrial uses including cosmetic use, the critical health effects for risk characterisation are skin sensitisation and harmful effects following acute oral exposure.

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemicals are reported to be used in cosmetic products (e.g. hair preparations) overseas. The use of these chemicals in ready for use hair preparations is restricted to 0.5% (as quinine base) in rinse-off products and 0.2% (as quinine base) in leave-on products.

Quinine is listed in the SUSMP in Schedules 4 for therapeutic use, and Schedules 5 and 7 for veterinary uses. In the absence of regulatory controls for cosmetic use of these chemicals, the characterised critical health effects (skin sensitisation and harmful effects from oral exposure) have the potential to pose an unreasonable risk under the identified uses.

Occupational Risk Characterisation

During product formulation, dermal exposure may 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 dermal 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 hazard classification of the chemicals in 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 the chemicals in cosmetics be managed through changes to poisons scheduling, 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

Products, including cosmetics, containing the chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2016).

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.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

[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 dermal and oral 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 hazardous chemicals 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:

- 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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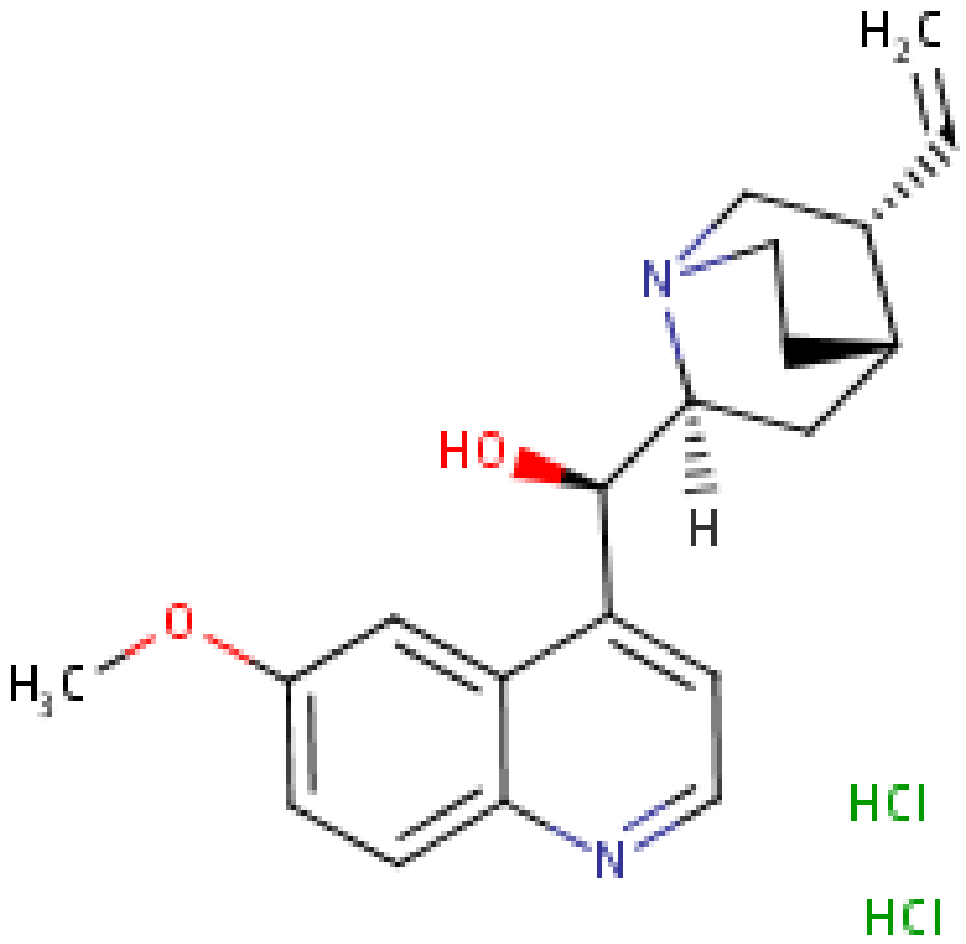
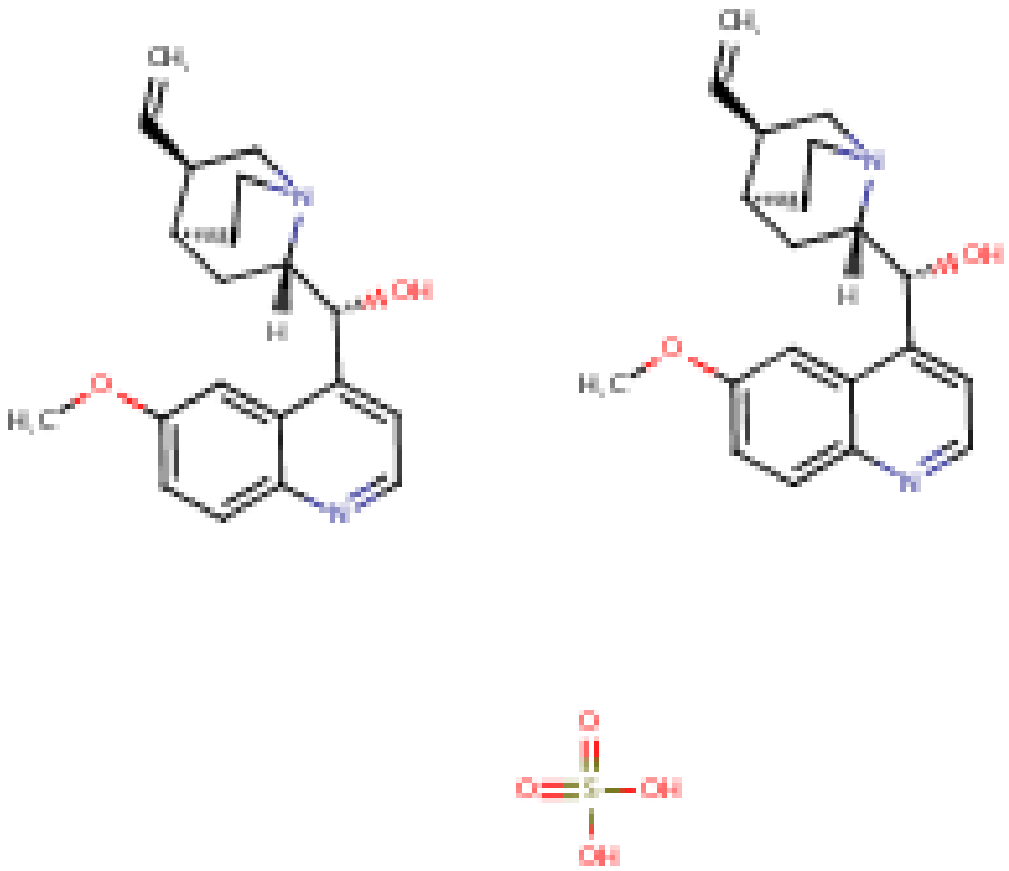
Last Update 25 November 2016

Chemical Identities

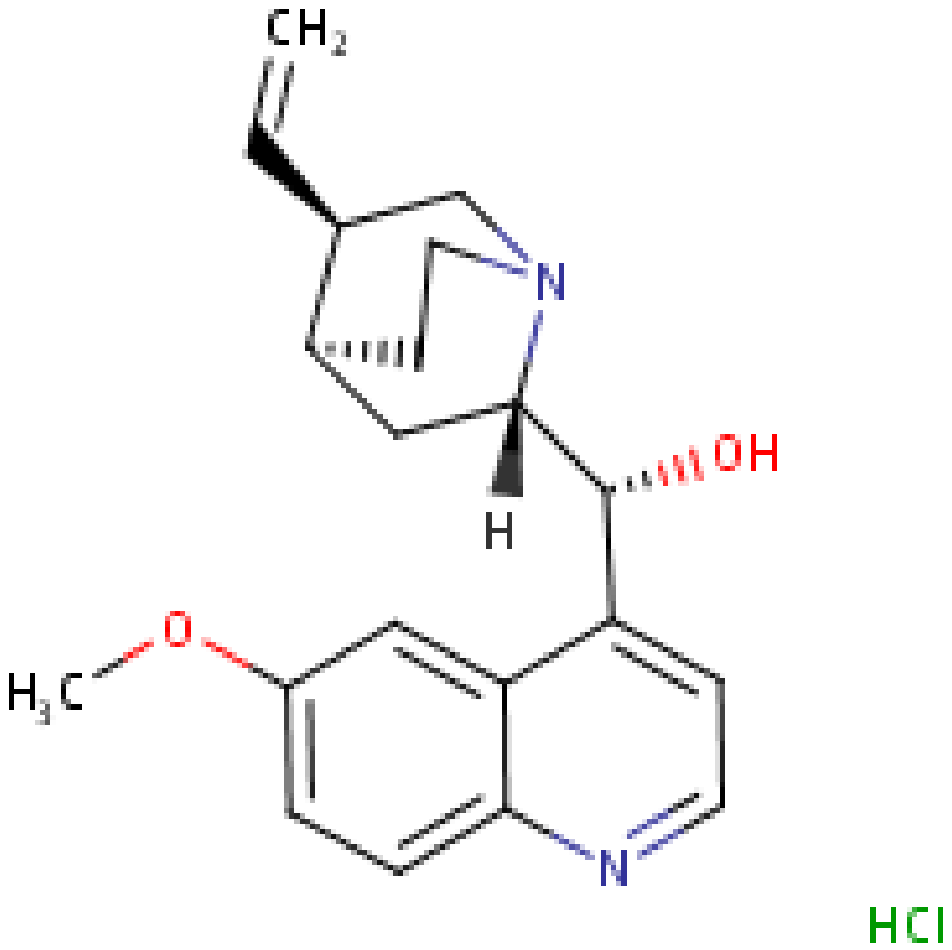
Chemical Name in the Inventory and Synonyms	**Cinchonan-9-ol, 6'-methoxy-, dihydrochloride, (8.alpha.,9R)-** quinine dihydrochloride acid quinine hydrochloride quinine bimuriate
CAS Number	60-93-5
Structural Formula	

	
Molecular Formula	C20H24N2O2.2ClH
Molecular Weight	397.34

Chemical Name in the Inventory and Synonyms	**Cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate (2:1) (salt)** quinine sulfate anhydrous quinine sulfate (2:1) quinine hydrogen sulfate coco-quinine
CAS Number	804-63-7
Structural Formula	

	
Molecular Formula	C20H24N2O2.1/2H2O4S
Molecular Weight	746.92

Chemical Name in the Inventory and Synonyms	**Cinchonan-9-ol, 6'-methoxy-, monohydrochloride, (8.alpha.,9R)-** quinine monohydrochloride quinine hydrochloride quinine chloride quinine muriate
CAS Number	130-89-2
Structural Formula	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Molecular Weight	360.88

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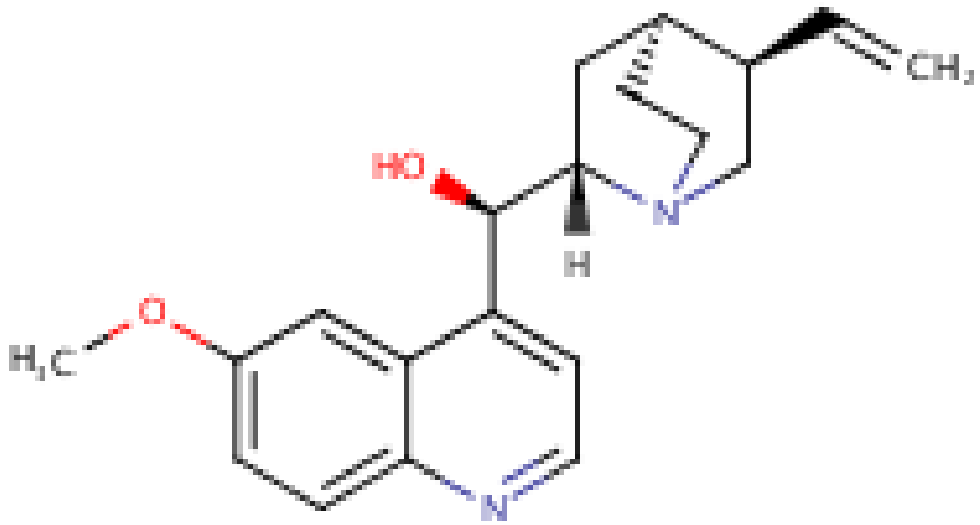
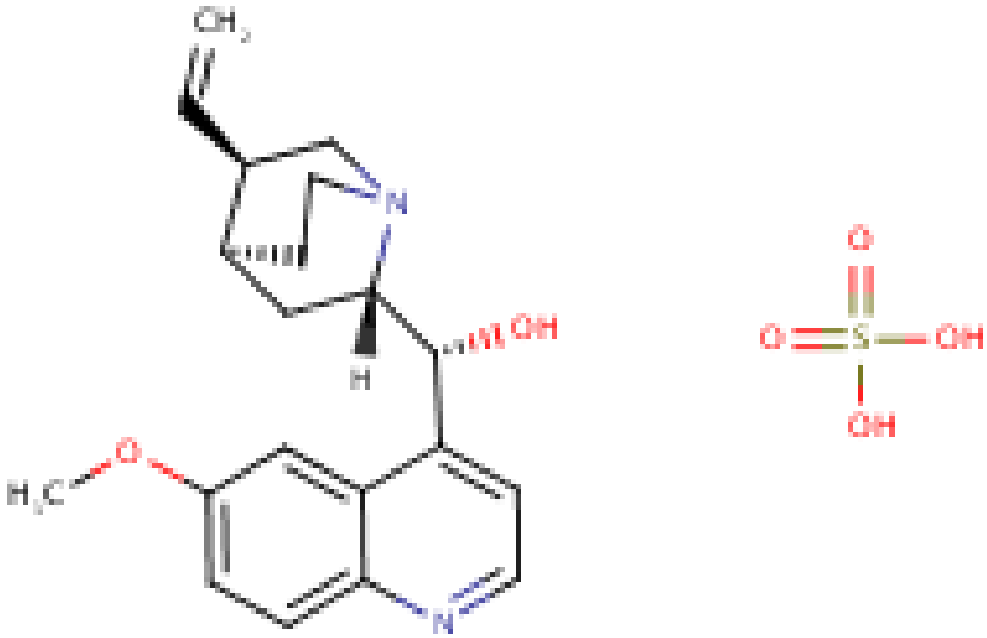
CAS Number	130-95-0
Structural Formula	

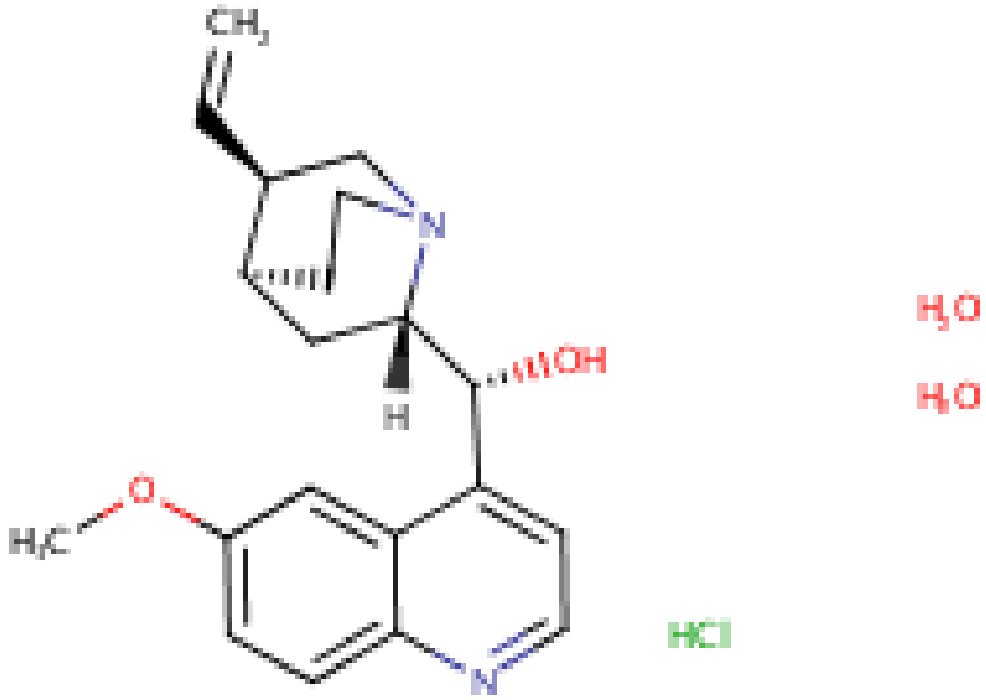
	
Molecular Formula	C20H24N2O2
Molecular Weight	324.42

Chemical Name in the Inventory and Synonyms	**Cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate (1:1) (salt)** quinine bisulfate quinine sulfate (1:1) quinine hydrogen sulfate
CAS Number	549-56-4
Structural Formula	

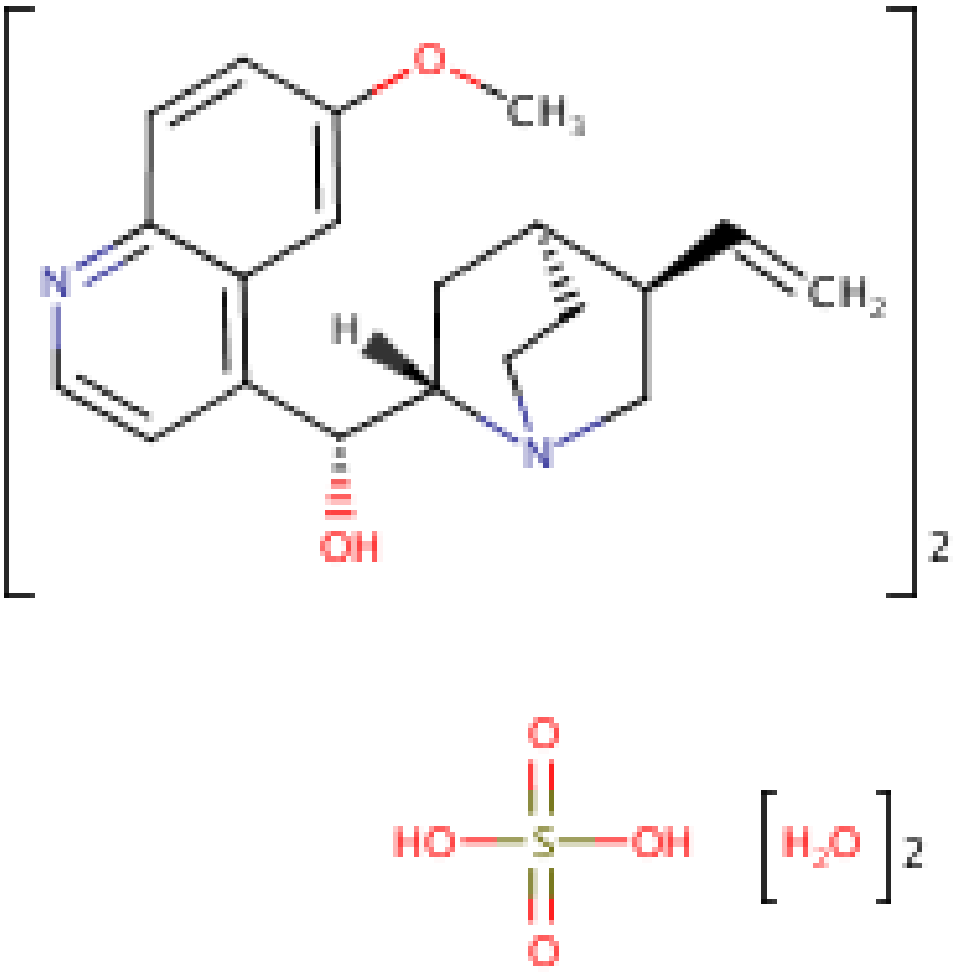


Molecular Formula	C20H24N2O2.H2O4S
Molecular Weight	422.50

Chemical Name in the Inventory and Synonyms	**Cinchonan-9-ol, 6'-methoxy-, monohydrochloride, dihydrate, (8.alpha.,9R)-** quinine hydrochloride dihydrate
CAS Number	6119-47-7
Structural Formula	

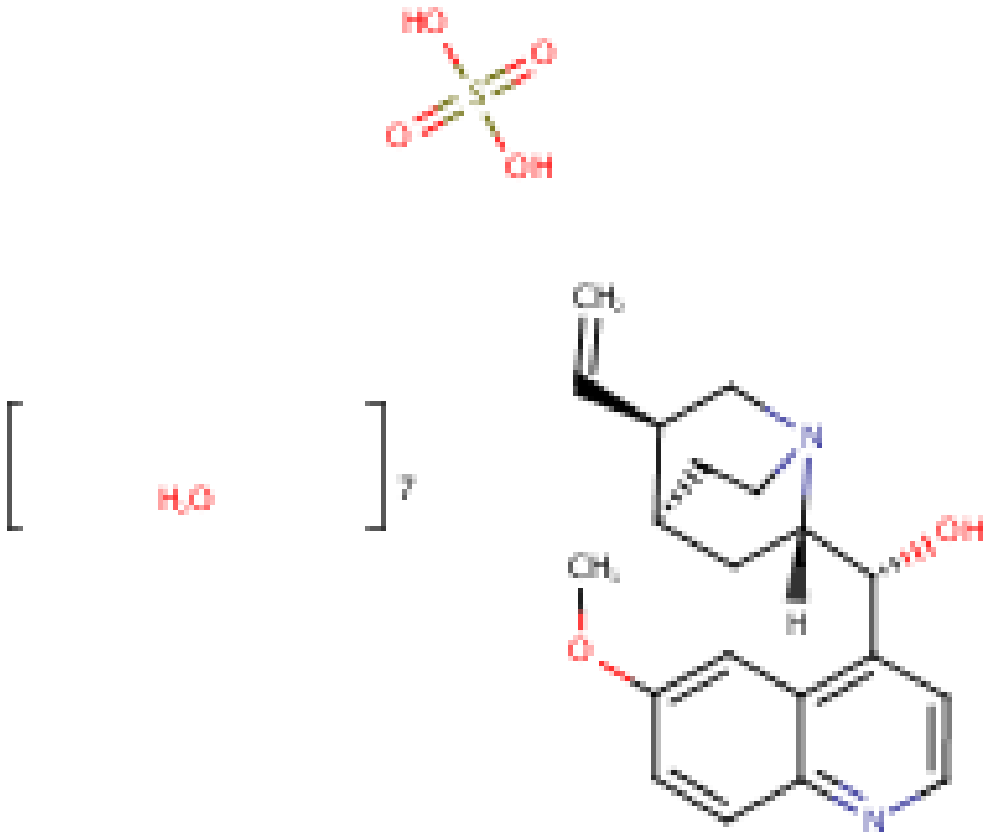
	
Molecular Formula	C20H24N2O2.ClH.2H2O
Molecular Weight	396.91

Chemical Name in the Inventory and Synonyms	**Cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate(2:1) (salt), dihydrate** quinine sulfate dihydrate quinine sulfate (2:1) dihydrate qualaquin chininum sulphuricum
CAS Number	6119-70-6
Structural Formula	

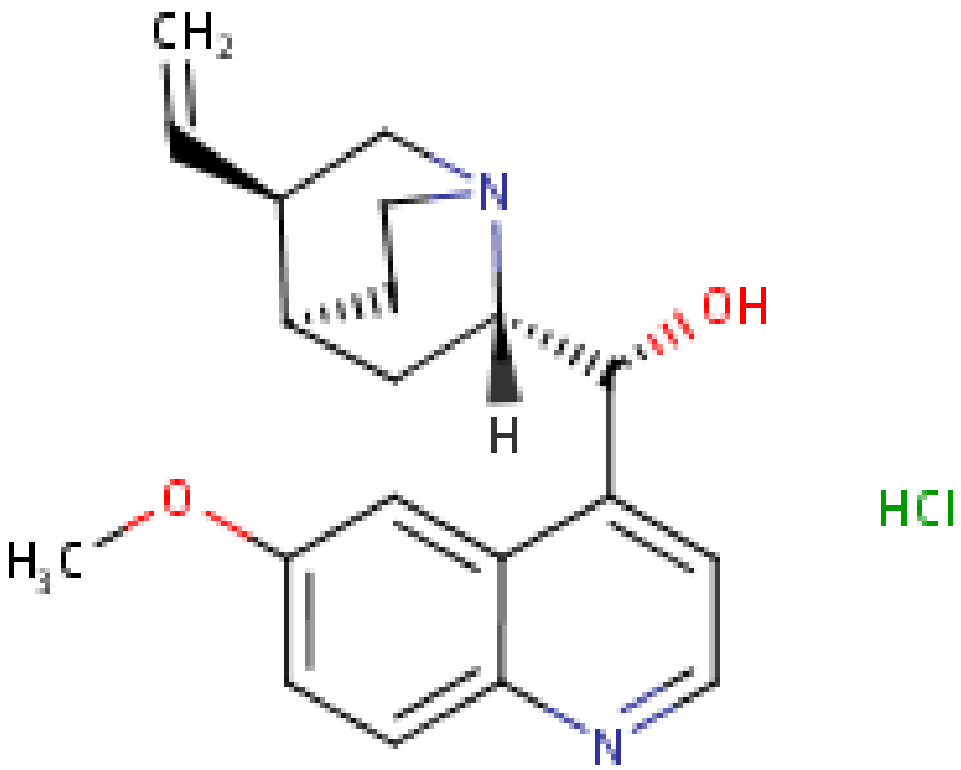


Molecular Formula	C20H24N2O2.1/2H2O4S.H2O
Molecular Weight	782.95

Chemical Name in the Inventory and Synonyms	**Cinchonan-9-ol, 6'-methoxy-, (8.alpha.,9R)-, sulfate (1:1) (salt), heptahydrate** quinine bisulfate heptahydrate
CAS Number	6183-68-2
Structural Formula	

	
Molecular Formula	C20H24N2O2.H2O4S.7H2O
Molecular Weight	548.60

Chemical Name in the Inventory and Synonyms	**Cinchonan-9-ol, 6'-methoxy-, hydrochloride, (8.alpha.,9R)-** quinine hydrochloride (unspecified) chinimetten
CAS Number	7549-43-1
Structural Formula	

	
Molecular Formula	C20H24N2O2.xClH
Molecular Weight	Unspecified

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