Hydroxylamine and its salts: Human health tier II assessment

27 November 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Hydroxylamine, hydrochloride	5470-11-1
Hydroxylamine	7803-49-8
Hydroxylamine, sulfate (2:1) (salt)	10039-54-0
Hydroxylamine, sulfate (1:1) (salt)	10046-00-1

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

This group consists of hydroxylamine and soluble hydroxylamine salts. Depending on the pH, hydroxylamine, sulfate (2:1) and hydroxylamine, sulfate (1:1) are dissociated into SO_4^{2-} and $[NH_3\text{-}OH]^+$. Similarly, hydroxylamine, hydrochloride dissociates into Cl^- and $[NH_3\text{-}OH]^+$. Hydroxylamine is considered to be the moiety responsible for systemic toxicity. Local toxicity will depend on the dissociation constant (pKa) of the chemical and therefore read across is less applicable.

Most of the available toxicity data are for hydroxylamine, sulfate (2:1) and no data were found for hydroxylamine, sulfate (1:1). Data for the chemicals in this group have been used to infer effects for hydroxylamine, sulfate (1:1) in the absence of any specific data and, for the chemicals where there are data gaps, according to the principles of ‘read across’ (OECD, 2014).

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

Hydroxylamine, sulfate (2:1) was reported during the 2006 High Volume Industrial Chemicals List (HVICL) call for information with a total volume of 100–1000 tonnes. The chemical has reported commercial use as a process regulator.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening information data set International Assessment Profile (OECD SIAP); Galleria Chemica; the Substances and Preparations in the Nordic countries (SPIN) database; the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the European Union Risk Assessment Report (EU RAR).

Hydroxylamine, hydrochloride and hydroxylamine, sulfate (2:1) have reported cosmetic use as antioxidants. However, none of the chemicals in this group are in the *Compilation of ingredients used in cosmetics in the United States* (ed. Bailey, 2011). They are all listed in the Cosmetic Ingredients and Substances Database (CosIng) as chemicals that are carcinogenic, mutagenic or have reproductive toxicity (CMR, Category 2) that can only be used in a cosmetic product if approved by the European Union Scientific Committee on Consumer Safety (SCCS). The approval has not been given to date.

Hydroxylamine has reported domestic uses including in paints, lacquers and varnishes.

Hydroxylamine, sulfate (2:1) has reported domestic uses including as cleaning or washing agents.

No products were found containing these chemicals in the US Household Products Database. The EU RAR (2008) concluded that consumer exposure to hydroxylamine, sulfate (2:1) in photographic developers could occur but would be negligible apart from accidental exposures. Changes in photographic technology indicate that public exposures would be very limited.

The salts have reported commercial uses including as:

- photographic developers;
- electroplating agents;
- process regulators;
- corrosion inhibitors;
- reprographic agents;
- impregnation materials; and
- antioxidants for fatty acids and soaps.

The salts have site-limited uses including as:

- reducing agents; and
- intermediates in perfume and rubber synthesis.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- Council of Europe Resolution AP (92) 2 on control of aids to polymerisation for plastic materials and articles—Limits for finished articles: 0.05 mg/kg hydroxylamine derivatives.

Existing Worker Health and Safety Controls

Hazard Classification

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

- Xn; R21/22;
- Xn; R48/22 (repeat dose toxicity);
- Xi; R36/38 (irritation);
- Xi; R43 (sensitisation); and
- Xn; R40 (carcinogenicity).

Hydroxylamine is classified as:

- Xn; R21/22;
- Xn; R48/22 (repeated dose toxicity);
- Xi; R37/38/41 (irritation);
- Xi; R43 (sensitisation); and
- Xn; R40 (carcinogenicity).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

There are limited toxicokinetic data available for this group of chemicals.

Toxicokinetic studies on absorption, distribution or excretion of hydroxylamine, sulfate (2:1) in vivo are not available and only a few in vitro studies exist.

Hydroxylamine is formed as an intermediate during cellular metabolism. Hydroxylamine reductase is found in the mitochondria of mice, rat and pig hepatocytes (liver cells). An in vivo rat study described partial metabolic oxidation of hydroxylamine to nitrate. Absorption via oral and inhalation uptake is expected to be high, based on experimental data. Physical-chemical data of hydroxylamine, sulfate (2:1), animal data on systemic effects and occupational dermal exposure scenarios under non-occlusive conditions, suggest that dermal uptake is likely to be low (SIAP, 2008).

Haematotoxic effects, which have been observed after repeated oral and dermal application of hydroxylamine, sulfate (2:1) to rats, rabbits and cats indicate that absorption occurs (EU RAR, 2008).

Four Sprague Dawley (SD) rats were given a single dose of 20 µmol ^{15}N-hydroxylamine hydrochloride (equivalent to about 7 mg/kg bw) by stomach tube. The total elimination of ^{15}N-nitrate in the urine was 4.7 % of the administered radioactivity. The largest proportion was found on the fourth day after exposure. The nitrate excretion was not increased after induction with 500 mg of Arochlor 1254/kg bw (REACH).

Acute Toxicity

Oral

The chemicals are classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The available data (median lethal dose (LD50) 545–652 mg/kg bw for rats) for hydroxylamine, sulfate (2:1), hydroxylamine and hydroxylamine, hydrochloride support this classification (SIAP, 2008; REACH). Reported signs of toxicity in rats include dyspnoea, trembling convulsions, tremors and lateral position. At necropsy, blue-violet discolouration and distended spleens were observed (EU RAR, 2008).

Methaemoglobin formation was observed in rats, cats and rabbits following acute oral or dermal exposures to hydroxylamine, sulfate (2:1) in toxicity tests (EU RAR, 2008). This altered form of haemoglobin cannot carry oxygen. High levels might be formed following exposure to certain toxic substances.

Dermal

The chemicals are classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in HSIS (Safe Work Australia). The available data for hydroxylamine, sulfate (2:1) (LD50—1500–2000 mg/kg bw for rabbits) support this classification. Reported signs of toxicity in rats and rabbits include anaemia with methaemoglobin formation, and enlarged and darkened spleens regardless of the dose level (EU RAR, 2008).

In a test conducted according to OECD Test Guideline (TG) 402, male and female New Zealand White rabbits were treated with single applications of hydroxylamine, sulfate (2:1) at doses of 500 mg/kg (five/sex), 1000 mg/kg (five males), 1500 mg/kg (five/sex), 2000 mg/kg (six males and four females) and observed for 14 days. Control rabbits were treated with water (five/sex). Seven of the rabbits (7/10) receiving the highest dose (2000 mg/kg) died or were euthanised after three days. Acute haemorrhagic dermatitis was present in each of the rabbits that died. Necropsy examination of the tissues revealed severe haemorrhagic necrosis of the skin characterised by massive subepithelial and dermal lesions, which often extended from just beneath the epithelium to the cutaneous muscle layer; the blood appeared brown. The skin lesions of the surviving animals were characterised by haemorrhage, oedema, bulla (blister) formation, vascular congestion, and massive heterophil infiltrates. Changes in other tissues could not definitively be attributed to compound-induced toxicity. However, it appeared that the deaths might have been related to circulatory collapse (shock) brought on by neurogenic pain reflexes associated with the skin lesions. Lesions in the liver and kidneys supported this contention. Few treatment-related changes were present in survivors. The skin contained residual, but healing changes. The spleens of 3/3 in the high and 4/10 in the mid dose groups of euthanised rabbits contained increased amounts of haemosiderin pigment. Red cell damage was detected. Other tissue alterations were judged to have been unrelated to the treatment (EU RAR, REACH).

A test in rats resulted in a dermal LD50 >500 mg/kg bw for hydroxylamine, sulfate (2:1). Female rats were exposed for 24 hours to a single application of the chemical moistened with water under occlusion. Ten animals per group were exposed to doses of 10, 100, and 500 mg/kg bw. One group of animals received 10 mg/kg of the test material via a subcutaneous injection (as a 1 % aqueous solution) as a rough indicator of complete dermal absorption of the test material. No mortality occurred within this test. Moderate skin irritation and, to a lesser extent, necrosis and sloughing were evident (EU RAR, 2008).

A dermal LD50 of 100–500 mg/kg bw was established for rabbits in a study that compared occlusive and semi-occlusive dermal exposure of hydroxylamine, sulfate (2:1). Ten animals per group were exposed to doses of 1, 10, 100 and 500 mg/kg bw under a plastic cover (occlusive exposure) and doses of 100, 500 and 1,000 mg/kg bw used gauze (semi-occlusive exposure). The plastic covering was not used at the 1000 mg/kg level since earlier findings indicated such an exposure would be 100 % lethal to

the rabbits. Subcutaneous injection of 10 mg/kg of the substance was used as a rough indicator of complete dermal absorption of the test material. Exposure to 100 mg/kg bw of the chemical resulted in some deaths, depending upon the nature of the covering (0/10 for semi-occlusive exposure and 2/10 for occlusive exposures). Similarly, dosing at 500 mg/kg bw produced very different outcomes depending on whether a semi-occlusive (1/10 deaths) or occlusive covering was used (9/10 deaths). There were no deaths (0/10) following semi-occlusive exposures to the chemical at 1000 mg/kg (EU RAR, 2008).

The toxicity of this salt is significantly higher under occlusive than semi-occlusive conditions, probably due to aggravated corrosivity and enhanced dermal uptake of the substance after skin damage (EU RAR, 2008). A dose of 1 mg/kg bw can be considered as the no observed adverse effect level (NOAEL) for occlusive application of the substance in the rabbits exposed to hydroxylamine, sulfate (2:1) for 24 hours. A dermal NOAEL of 500 mg/kg bw can be derived for semi-occlusive acute exposure (SIAP, 2008).

Inhalation

No toxic effects were observed in rats exposed to saturated vapours of hydroxylamine, sulfate (2:1) (SIAP, 2008). However, due to the physico-chemical properties of the substance (solid at room temperature and a salt character) the vapour pressure of the chemical is assumed to be very low. The vapour pressure of the chemical after saturation in air must also be very low. Hence, it is questionable whether the method used in the two reported inhalation studies resulted in any significant, toxicologically relevant concentrations (EU RAR, 2008).

Corrosion / Irritation

Respiratory Irritation

Hydroxylamine is classified as hazardous with the risk phrase ‘Irritating to respiratory system’ (Xi; R37) in HSIS (Safe Work Australia).

No studies are available concerning the potential of respiratory tract irritation from these chemicals. Although there is a corresponding lack of data, further testing is not considered to be a priority. It is assumed that risk reduction measures necessary to reduce other health risks (repeated dose toxicity, carcinogenicity) will efficiently reduce the possible risks of respiratory tract irritation (EU RAR, 2008).

Skin Irritation

The chemicals are classified as hazardous with the risk phrase ‘Irritating to skin’ (Xi; R38) in HSIS (Safe Work Australia). Limited data are available for two of the salts in this group. Based on the weight of available evidence, this classification is supported.

In all data sources, skin irritation data for the free base was read across from the data available for the salts. However, because of the difference in pKa between these chemicals, this is not considered to be valid; therefore, no data were available to support or amend the classification for hydroxylamine.

Information from non-standard animal data demonstrates moderate to severe irritating, and even corrosive, properties of hydroxylamine, sulfate (2:1), depending on the time of exposure. The skin of an unknown number of rabbits was exposed to an unknown amount of an 80 % aqueous preparation for 1, 5 and 15 minutes and for 20 hours (no information or further details). Skin irritation was assessed 24 hours after exposure. No skin irritation was observed after the one or five minute exposures; minimal to no erythema was observed after a 15-minute exposure; severe skin irritation was observed after the 20-hour skin exposure (this irritation reversed within eight days) (EU RAR 2008, REACH).

In a Draize skin test with one rabbit, a four-hour occlusive skin exposure to 50 mg (moistened with water) resulted in erythema grade 1 at the 24-hour post exposure observation. No other lesions were observed (EU RAR, 2008).

The skin of an unknown number of rabbits was exposed to an unknown amount of an 80 % aqueous preparation of hydroxylamine, hydrochloride for 1, 5 and 15 minutes and for 20 hours (no information on further details). Skin irritation was

assessed 24–48 hours following the exposures. Mild erythema was observed that was fully reversible within five days (REACH). The quality of the data is insufficient to support amending the classification for this chemical.

Eye Irritation

The chemicals are classified as hazardous in HSIS with the risk phrase 'Irritating to eyes' (Xi; R36), apart from hydroxylamine which has the risk phrase 'Risk of serious eye damage' (R41) (Safe Work Australia).

There are some data supporting strong eye irritation and possibly irreversible eye damage following exposure to the salts of hydroxylamine. However, the quality of the data and/or the consistency of results are not sufficient to warrant amending the classification for these chemicals. In all data sources, as for skin irritation, eye irritation data for the free base was read across from the data available for the salts. However, because of the difference in pKa between these chemicals, this is not considered to be valid; therefore, no data were available to support or amend the classification for hydroxylamine.

Data on eye irritation following exposure to hydroxylamine, sulfate (2:1) are conflicting and the irreversibility of effects was not documented. Severe conjunctival irritation and severe corneal opacity resulted 24 hours after an instillation of 50 mm^3 of the pure chemical into the eye of one rabbit. The following effects are reported (no scores given):

- mild conjunctival redness and mild conjunctival oedema one hour after instillation;
- mild conjunctival redness, severe oedema and severe corneal opacity after 24 hours; and
- mild corneal opacity after eight days.

Information on reversibility of the observed corneal opacity was not reported.

In a second eye irritation test with one rabbit, moderate eye irritation was observed following exposure to 0.1 mL of hydroxylamine, sulfate (2:1) (no data on purity). The following mean scores or observations were made:

- 3 for conjunctival redness (at 24 hours, 48 hours and 72 hours post application);
- 1.3 for conjunctival oedema;
- grade 1 iritis (detected only on day one);
- no corneal opacity; and
- conjunctival irritation that reversed by eight days after exposure (EU RAR 2008).

In a study conducted similarly to OECD TG 405, approximately 50 mg hydroxylamine, hydrochloride was applied to the conjunctival sac of one eye of four rabbits. Talcum powder was used on the other eye for each rabbit as a control. The animals were observed several times on the treatment day and up to eight days afterwards. The eyes were not washed out after 24 hours as specified in the OECD TG. A mean score of 2 was observed for corneal opacity (scored at 24 and 48 hours for two of the rabbits and 24, 48 and 72 hours for the other two animals); 0.42 for iris lesions; 0.38 for conjunctival redness; and 0.9 for chemosis. Many of these effects were not reversible within the eight-day observation period.

Observation in humans

Limited information in humans indicates that concentrations of 1 % hydroxylamine, sulfate (2:1) and above caused skin irritation (SIAP, 2008). Human experience with local irritation/corrosion caused by this salt is mentioned in the literature, but relevant details are not available (EU RAR, 2008).

Sensitisation

Respiratory Sensitisation

In a test with guinea pigs that were first treated under the conditions of a Magnusson Kligman Test (positive results) and subsequently subjected to an inhalation aerosol challenge or an intratracheal challenge, no indication for pulmonary sensitisation was detected. However, this test procedure is rarely used, and no data are available on its validity. Therefore, the negative result obtained cannot be used for hazard assessment (EU RAR, 2008).

Skin Sensitisation

The skin sensitising properties of hydroxylamine, sulfate (2:1) and hydroxylamine were demonstrated in the laboratory and in humans (EU RAR, 2008).

The majority of studies (4/5) conducted on guinea pigs using the guinea pig maximisation test (GPMT) found sensitising effects associated with treatment of hydroxylamine, sulfate (2:1) (REACH).

One study used the available literature to rank hydroxylamine, sulfate (2:1) and 52 additional compounds. This chemical ranks in the middle for the mouse ear swelling test (MEST), in category III (moderate) for GPMT, negative with the Buehler test and the epicutaneous maximisation test, and positive with respect to human data (EU RAR, 2008).

Prior to the first induction treatment in an MEST, mice received two intradermal injections totalling 0.05 mL FCA (foetal calf albumin) into the stomach region. The animals were then topically dosed at the stomach site with 100 µL of hydroxylamine, sulfate (2:1) in solvent or the solvent at three consecutive days. Following a rest period of seven days, 20 µL of the test compound in solution was applied to the right ear. After 24 and 48 h the thickness of both ears was measured. Test and control groups consisted of 10–15 and 5–10 mice, respectively. A total of 72 compounds were tested. The concentration of the chemical was 10 % in 25 % ethanol for all treatments, and 33 % of the mice showed a positive reaction (Gad et al. 1986). The identical test procedure as described by Gad et al. (1986) was used by two laboratories. Both laboratories reported negative results with the chemical. It is concluded that this method is a useful model for identifying strong contact sensitisers (examples: DNCB, glutaraldehyde) but is not reliable for detecting weak or moderate allergens (Dunn et al. 1990) (EU RAR, 2008).

Observation in humans

Several reports of contact dermatitis caused by either hydroxylamine, sulfate (2:1) or hydroxylamine, hydrochloride are available.

Seven of the 20 employees involved in producing hydroxylamine, hydrochloride were sensitised after a remarkably short period of time (2–60 days). Five of the 13 workers engaged in producing cycloserine developed contact dermatitis on the upper limbs, face and neck. Hydroxylamine, hydrochloride is a component in cycloserine production and patch tests (test concentration: 1 % in water) confirmed the clinical diagnosis of topical eczema caused by this salt (EU RAR, 2008).

Nine of 11 workers exposed to hydroxylamine (hydrochloride, sulfate) developed contact dermatitis on the face, neck and upper limbs and, in addition, showed fissures and onycholysis (detachment of finger or toenails from the nail bed). Thirty-four control subjects were also tested and 14 subjects demonstrated a positive response after being challenged with 1 % or 2 % of the test substance in water (EU RAR, 2008).

Hydroxylamine, sulfate (2:1) gave positive results in 3/76 human subjects after repeated insult patch testing at 0.05 % in a detergent solution (EU RAR, 2008).

Repeated Dose Toxicity

Oral

The chemicals are classified as hazardous with the risk phrase ‘Harmful: Danger of serious damage to health by prolonged exposure if swallowed’ (Xn; R48/22) in HSIS (Safe Work Australia).

Considering the lowest observed adverse effect levels (LOAELs) available from a 24-month rat study (1.0 and 1.6 mg/kg bw/d for males and females respectively) conducted in accordance with OECD TG 453, and based on the treatment-related effects reported in various repeated dose toxicity studies, this classification should be amended to 'Toxic: Danger of serious damage to health by prolonged exposure if swallowed' (T; R48/25). See **Recommendation** Section.

In a combined chronic toxicity/carcinogenicity study conducted according to OECD TG 453, hydroxylamine, sulphate (2:1) (commercial grade purity) was administered to groups of 50 male and 50 female rats in drinking water at concentrations of 0, 5, 20 and 80 ppm for 24 months (main groups). In order to define the test substance's haematotoxic potential, groups of 10 animals per sex and dose were treated for 12 months (satellite groups). In these satellite animals, assays of blood parameters were performed every three months. The doses administered corresponded to a mean daily intake in the main groups of about 0, 0.2, 1.0, and 3.7 mg/kg bw/d hydroxylamine, sulphate (2:1) in males and 0, 0.4, 1.6, and 6.2 mg/kg bw/d in females; and in the satellite groups of about 0, 0.3, 1.1, and 4.5 mg/kg bw/d in males and 0, 0.4, 1.6, and 6.2 mg/kg bw/d in females. The main observations were significant reductions in erythrocyte counts, haemoglobin concentrations and haematocrit values; increases in mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH); and an increased number of Heinz bodies, Howell-Jolly bodies, and reticulocytes in the peripheral blood. These adverse effects were associated with increased spleen weights, increased red blood cell regeneration by the bone marrow and increased extramedullary haematopoiesis in the spleen and the liver. At 20 ppm (equivalent to about 1.0 mg/kg bw/d in males and 1.6 mg/kg bw/d in females), haemosiderin storage in the spleen (a sign of haemolysis) was significantly increased when compared with controls in male rats after 12 months of treatment, and in female rats after 24 months of treatment, respectively. No haematotoxic effects were detected in animals given 5 ppm. Therefore, the NOAEL for systemic effects was 5 ppm, corresponding to a mean daily hydroxylamine, sulphate (2:1) intake of about 0.2/0.3 mg/kg bw/d in males and 0.4 mg/kg bw/d in females (EU RAR, 2008).

In a subchronic oral toxicity study conducted similarly to OECD TG 408, groups of 10 male and 10 female rats received hydroxylamine, sulphate (2:1) in drinking water at concentrations of 0, 10, 50, or 250 ppm for 90 consecutive days. The doses administered corresponded to a mean daily intake of about 0, 0.9, 4 or 21 mg/kg bw/d. Repeated administration of 50 and 250 ppm (equivalent to about 4 and 21 mg/kg bw/d respectively) to rats through the drinking water for three months led to toxicity in male and female rats at both dose levels. The chemical led to haemolytic anaemia (dose-related) in both males and females in the 50 and 250 ppm groups, with methaemoglobinaemia and increases in the weight of the spleen and liver together with the specific histopathological findings in the liver and spleen of increased haemosiderin deposits. The NOAEL for all adverse effects of this rat study was 10 ppm (equivalent to about 0.9 mg/kg bw/d) hydroxylamine, sulphate (2:1) for both sexes (EU RAR, 2008).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

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

There are no in vitro genotoxicity data for hydroxylamine, sulfate (2:1) or hydroxylamine (REACH).

Hydroxylamine, hydrochloride produced mainly negative results in the following in vitro assays (REACH; EU RAR, 2008):

- reverse mutations in bacterial systems (strains of *Salmonella typhimurium and Escherichia coli*);
- mutations in mouse lymphoma cells (both studies reported weakly positive results);
- chromosomal aberrations in various mammalian cells (all four studies found positive results, but suffered from severe methodological insufficiencies, such as not using metabolic activation and/or positive controls);

- sister chromatid exchange in Chinese Hamster cell line V79 and lymphocytes from the Indian muntjac (both studies found weakly positive results, but suffered from severe limitations as described for the chromosomal aberrations studies); and
- unscheduled DNA synthesis (UDS) in rat hepatocytes.

Data from in vivo genotoxicity studies are available for hydroxylamine, sulfate (2:1) and hydroxylamine, hydrochloride.

The sulfate salt produced negative results in the following studies in mice:

- two bone marrow micronucleus tests (OECD TG 474); and
- a rodent dominant lethal test.

Carcinogenicity

The chemicals are classified as hazardous—Category 3 carcinogenic substance—with the risk phrase 'Limited evidence of carcinogenic effect' (Xn; R40) in HSIS (Safe Work Australia). The available data support this classification.

There are no human data on carcinogenicity.

In a standard combined chronic toxicity/carcinogenicity toxicity study conducted according to OECD TG 453 (24-month drinking water study, see description under **Repeat dose toxicity** for more information), hydroxylamine, sulfate (2:1) treatment was associated with an increased incidence of splenic haemangiosarcomas in males treated at ≥5 ppm, equivalent to about ≥0.2 mg/kg/bw/d. Splenic haemangioma development was observed in females treated at 80 ppm, equivalent to about 6.2 mg/kg bw/d. Angiomatous hyperplasia in the spleen, considered as a precursor lesion of angiomatous tumours (haemangioma, haemangiosarcoma), was observed in animals of both sexes at 80 ppm. The LOAEL was 5 ppm. Although the database for mice is insufficient, the data available indicated that the chemical might induce spleen tumours in the rat. It was considered that the chemical has no genotoxic potential and the carcinogenicity observed in laboratory animals is mediated by a non-genotoxic mechanism most likely involving erythrotoxicity (SIAP, 2008).

Reproductive and Developmental Toxicity

There are limited available data regarding reproductive or developmental effects for these chemicals. Observed effects occur at higher doses than those observed for maternal haematological effects in other repeated dose studies (see **Repeat dose toxicity**).

A three month oral repeated dose toxicity study of hydroxylamine, sulfate (2:1) conducted in accordance with OECD TG 414 and good laboratory practice (GLP) in rats showed no indications of impairment in male and female reproductive organs up to and including the highest tested dose level of about 21 mg/kg bw/d (NOAEL). The NOAEL for systemic adverse effects of this study was 0.9 mg/kg bw/d for both sexes based on findings of haemolytic anaemia with methaemoglobinaemia and changes in organ weights as well as histopathological changes in the spleen and liver at higher dosages (REACH).

In a prenatal toxicity study conducted in accordance with OECD TG 414 and GLP in rats, groups of 22–24 pregnant rats were treated with hydroxylamine, sulfate (2:1) at dosages of 1, 3, 10, and 20 mg/kg bw/d from gestation day six to day 15. A NOAEL (oral) for embryo-foetotoxicity of 20 mg/kg bw/d (highest dose) was derived due to the absence of any relevant treatment-related effects. The maternal LOAEL was 10 mg/kg bw/d based on haematological effects (REACH).

Data from studies investigating the potential for hydroxylamine, sulfate (2:1) to prevent tumours in mice and rats showed that the chemical induced impaired ovarian function and morphology as well as impaired development and morphology of mammary gland tissues following prolonged treatment with high doses in drinking water. A LOAEL of about 67 mg/kg bw/d was determined for rats based on retarded mammary gland development (EU RAR, 2008).

No human data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation of these chemicals include systemic long-term effects (carcinogenicity) and local effects such as irritation and skin sensitisation. The chemicals can also cause harmful effects following repeated exposure (haematological effects).

Public Risk Characterisation

Given the uses identified for these chemicals, it is unlikely that the public will be exposed. Limited international use information has indicated that public exposure to some of these chemicals in photographic developers could be possible. However, given that the vast majority of uses of these chemicals are commercial or site-limited and the identified public use is diminishing, exposure to consumers is expected to be minimal (see the **Use Section**). Hence, the public risk from these chemicals is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation 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 long-term systemic health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular, and inhalation 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 for these chemicals support an amendment to the classification. See **Recommendation Section** below.

NICNAS Recommendation

Assessment of these chemical 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.

Regulatory Control

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.

The following table reflects the classifications for the three salts of this group.

Hydroxylamine has different risk phrases R37 (the remaining chemicals are not classified for this effect) and R41 (the remaining chemicals in the group have R36) for respiratory and eye hazards respectively. The GHS classifications for this chemical are:

- 'Causes serious eye irritation - Cat 1 (H318)'; and
- 'May cause respiratory irritation - STOT SE (H335)'.

Apart from these differences, hydroxylamine has the same hazard classifications as listed for the rest of the chemicals in this group (see the table below).

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful: Danger of serious damage to health by prolonged exposure if swallowed (Xn; R48/22)* 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)
Sensitisation	* May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: Danger of serious damage to health by prolonged exposure if swallowed (T; R48/25)	Causes damage to organs through prolonged or repeated exposure - Cat. 1 (H372)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

[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 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 which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- 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.

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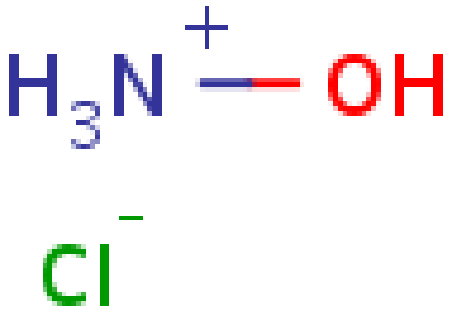
Last Update 27 November 2014

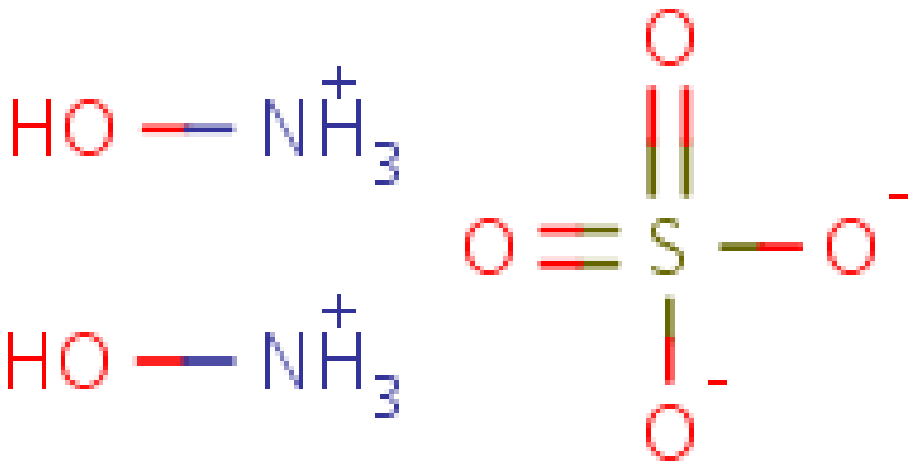
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Hydroxylamine, hydrochloride** hydroxylammonium chloride
CAS Number	5470-11-1
Structural Formula	
Molecular Formula	ClH.H3NO
Molecular Weight	69.49

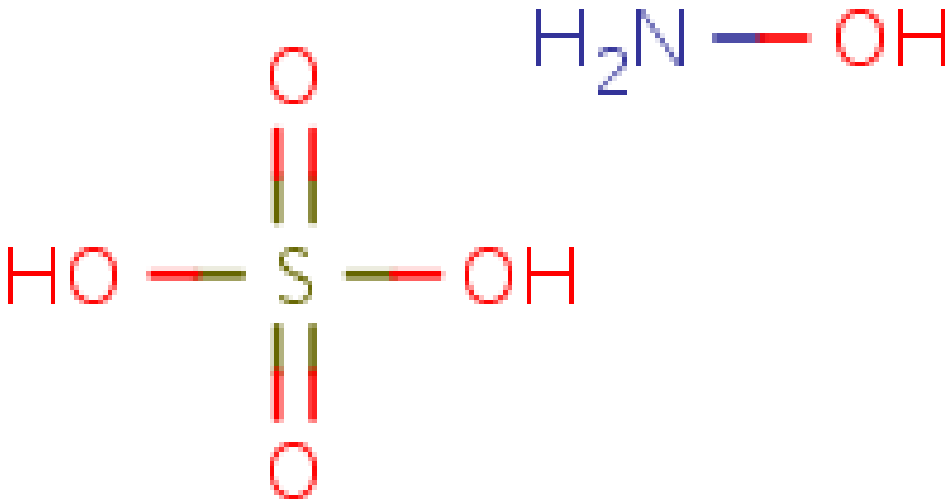
Chemical Name in the Inventory and Synonyms	**Hydroxylamine** oxammonium

CAS Number	7803-49-8
Structural Formula	
Molecular Formula	H3NO
Molecular Weight	33.03

Chemical Name in the Inventory and Synonyms	**Hydroxylamine, sulfate (2:1) (salt)** hydroxylamine, sulfate bis(hydroxylammonium)sulphate
CAS Number	10039-54-0
Structural Formula	

	
Molecular Formula	H3NO.1/2H2O4S
Molecular Weight	164.14

Chemical Name in the Inventory and Synonyms	**Hydroxylamine, sulfate (1:1) (salt)** hydroxylammonium acid, sulfate hydroxylammonium hydrogen sulphate
CAS Number	10046-00-1
Structural Formula	

	
Molecular Formula	H3NO.H2O4S
Molecular Weight	131.75

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