Cysteine and its salts: Human health tier II assessment

12 December 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
L-Cysteine, hydrochloride	52-89-1
L-Cysteine	52-90-4
L-Cysteine, hydrochloride, monohydrate	7048-04-6

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 compound α-L-amino acids (including L-cysteine) are normal constituents of protein, whereas D-amino acids are not although small amounts may be found in foodstuffs during food processing (due to racemisation) and in living organisms (due to isomerisation of L-amino acids) (EFSA AFC, 2008).

L-cysteine is a naturally occurring non-essential amino acid. Cysteine hydrochloride is a soluble salt of cysteine and hydrochloric acid, either in anhydrous (cysteine HCl) or monohydrate (cysteine HCl.H2O) forms. The chemicals have the same general structure, where a central carbon atom (the α-carbon) to which an amino group, a carboxylate group, a hydrogen atom and an R (side chain) group are attached (McKee & McKee, 2017). The chemicals also have similar uses, toxicokinetics and hazard profiles and; therefore, they are grouped together for the purpose of this human health assessment. The speciation of these chemicals in biological fluids is pH dependent, but independent of the original form.

Import, Manufacture and Use

Australian

The chemicals have reported site-limited uses in the manufacture of bioreagents for cell culture, scientific research and development (Sigma-Aldrich SDS).

The chemicals have reported non-industrial uses as in food, pharmaceuticals, and as active constituents (cysteine only) for agricultural and pesticide products (Galleria Chemica).

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature Cosmetic Ingredient (INCI) Dictionary; US National Library of Medicine Household Products Database (cysteine HCl only); PubChem; Hazardous Substances Data Bank (HSDB); and other assessments (CIR, 2013; EFSA, 2019).

By acting as antioxidants, antistatic, reducing agents or pH adjusters, cysteine and cysteine HCl have reported:

- cosmetic uses in perfumes, fragrances (masking), hair conditioning, hair waving or straightening products (aerosol), nail creams, face and neck personal care products (excluding shaving preparations). According CIR (2013), use concentrations for cosmetics are: ≤0.05 % in leave on; ≤5% (cysteine) or ≤6 % (cysteine HCl) in rinse off; and ≤0.05 % in aerosolised or spray products. Cysteine and its derivatives have no reported uses in baby products, bathing products or products applied in the eye area or mucous membrane.
- domestic uses in air fresheners, adhesives, sealants, polishes, wax blends, washing and cleaning products, leather impregnation and care products, anti-freeze and de-icing products.
- commercial (widespread) uses by professional workers in coatings, thinners, paint removers, photochemicals, lubricants, greases, in fillers, putties, plasters, modelling clay, washing and cleaning, in leather tanning, textile dyes, finishing and impregnation products. There is also wide dispersive indoor use as processing aids in open systems.
- site-limited uses as chemical intermediates, in the manufacture of fine chemicals (i.e. complex, pure chemicals with multistep production), fermentation, water softeners, pulp and paper products, ink and toners, coatings and paint removers, leather tanning, textile dyes, finishing and impregnating products, and processing aids (such as pH regulators, flocculants, precipitants, neutralisation agents).

Cysteine HCl.H20 has reported site-limited uses in the manufacture of fine chemicals only.

Scented articles (e.g. clothes, compact discs, papers) containing cysteine or its salts also have household use and mostly serve as indoor exposure sources.

The chemicals have reported non-industrial uses in food (flavouring, leavening or flour treatment agent at up to 90 ppm), fodder, biocidal products (disinfectants, ant control at maximum 8 %), veterinary medicines and pharmaceuticals.

Restrictions

Australian

No known restrictions have been identified.

Impurities identified for the chemicals in this group are commonly heavy metals, particularly arsenic (As; max. 1.5 mg/kg), lead (Pb; max. 5 mg/kg), cadmium, iron and mercury (CIR, 2013; Rubino, 2015; EFSA, 2019; Sigma-Aldrich SDS). These impurities are controlled through the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons; SUSMP 2019).

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

Cysteine has the following workplace exposure standard (Galleria Chemica):

8-hour TWA (time weighted average) = 2 mg/m^3 (Latvia, Russia).

Health Hazard Information

Cysteine is unique amongst the twenty natural human amino acids as it contains a reactive sulfhydryl (–SH) or thiol group. Cysteine is crucial for detoxification (redox homeostasis), protein synthesis (e.g. disulfide bonds strengthening tertiary and quaternary structures), and diverse metabolic functions (e.g. synthesis of antioxidant glutathione, amino sulfonic acid taurine, inorganic sulfate (SO_4^{2-}), hydrogen sulfide (H_2S), or acetyl-coenzyme A (acetyl-CoA) involved in the citric acid cycle following degradation to pyruvate (an energy intermediate)) (Stipanuk & Caudill, 2019; PubChem). The thiol group also has a high affinity for heavy metals such as mercury, lead, cadmium and arsenic (Rubino, 2015).

Cysteine is a component of β-keratin, where the disulfide bonds cause keratin to be hard (in nails and teeth), flexible (in hair) or soft (in skin) (Burns et al., 2016; PubChem). However, there is not sufficient evidence to substantiate the claim that there are effects on the maintenance of normal nails, hair, skin, collagen or glutathione formation in relation to the consumption or cosmetic uses of cysteine (EFSA NDA, 2010).

Toxicokinetics

Although the absorption and metabolism of L-amino acids from dietary protein have been extensively studied, there is minimal information on toxicokinetics of single amino acids or mixtures of amino acids after ingestion of large amounts. L-amino acids (including L-cysteine) are readily absorbed through the intestinal mucosa and enter the circulation via the hepatic portal system. They have higher affinity for transport across the intestinal membranes than the D-amino acids. Absorbed amino acids are widely distributed into tissues as biologically active protein with ~0.5 % as free amino acids. Humans have no storage mechanisms for amino acids. Excess amino acids are deaminated to yield a-ketoacids, which are either completely oxidised to carbon dioxide and water, or provide 3–4 carbon units in glucose via gluconeogenesis, or to yield ketone bodies via ketogenesis. Excretion of amino acid nitrogen (N) as urea in the urine (following the removal of amino group and conversion of ammonia (NH_4^+)) amounts to an average of 10–15 g N/day in humans (WHO, 2006; EFSA AFC, 2008; Stipanuk & Caudill, 2019).

As a non- or semi-essential amino acid in adults, cysteine can be absorbed from dietary protein or derived endogenously from the transfer of sulfur atom of methionine (by transmethylation and transsulfuration) and of carbon chain and nitrogen of serine. Cysteine may be regarded as an essential amino acid in infants, the elderly, and individuals with certain metabolic disease or suffering from malabsorption syndromes (Shibui et al., 2017; PubChem).

Cysteine can be incorporated into new protein synthesis (including as the precursor of glutathione), non-protein synthesis (e.g. acetyl-CoA), or undergo catabolism, primarily in the liver. The major degradation pathway of excess cysteine involves the initial oxidation of cysteine to cysteinesulfinate (regulated by cysteine dioxygenase in response to sulfur amino acid intake), which may be then decarboxylated to form taurine, or may undergo transamination via the putative intermediate β-sulfinylpyruvate to yield pyruvate and sulfite (SO_3^{2-}). Sulfite is further oxidised to sulfate (SO_4^{2-}). The carbon chain of cysteine is converted to pyruvate or remains with the sulfur and nitrogen of cysteine in taurine. Cysteine catabolism also occurs by desulfuration of cysteine to release alanine or pyruvate and hydrogen sulfide (H_2S or HS^-), which is oxidised to thiosulfate (SSO_3^{2-} or $H_2S_2O_3$), sulfite, and then sulfate. Both sulfate and taurine are excreted in the urine, with sulfate normally accounting for >80 % of the total sulfur excretion (EFSA AFC, 2008; Courtney-Martin & Pencharz, 2016; Shibui et al., 2017; Stipanuk & Caudill, 2019; HSDB).

Acute Toxicity

Oral

The chemicals are considered to have moderate acute oral toxicity (oral median lethal dose (LD50) <2000 mg/kg bw), and hazard classification for this group is warranted on the weight of evidence basis (see **Recommendation** section). This takes into account:

- the mortality rate and severity of sublethal effects reported in available studies
- the decreased LD50 values with increasing bioavailability through parental routes
- no storage mechanisms for amino acids in humans
- serious toxicity potential from excessive intake of cysteine or its salts
- the recommended daily intake of 4.1 mg/kg for cysteine or total 15 mg/kg for sulfur amino acids in adults (WHO, 2007).

For cysteine (CAS No. 52-90-4), the following LD50 values were reported (WHO, 2006; Chemica Galleria; HSDB; REACHa):

- In rats: LD50 = 1890 mg/kg bw (oral), 1620 mg/kg bw (intraperitoneal), 1550 mg/kg bw (subcutaneous), 1140 mg/kg bw (intravenous). Sublethal effects were somnolence (general depressed activity), dyspnea and changes in urine composition.
- In mice: LD50 = 660–1502 mg/kg bw (oral), 1400 mg/kg bw (intraperitoneal), 1360 mg/kg bw (subcutaneous), 1250 mg/kg bw (intravenous). Sublethal effects were ataxia, somnolence, and respiratory depression.
- In a non-standard test, LD50 values between 6350–5580 mg/kg bw (male-female) were calculated for cysteine from the number of deaths after 72 hours. However, it was reported that the majority of rats died within 4 hours, and there was no difference in LD50 between sexes. Animals exhibited from mild convulsion, respiratory distress to central nervous paralytic symptoms, including decreased spontaneous exercise, weakening or disappearing of reflexes, becoming stationary in the abdominal position, then entering anaesthetic condition before death. Autopsy revealed internal organ (abdominal and chest regions) and intracranial haemorrhage, cerebral congestion, heart stoppage in contracted position in decedents (WHO, 2006; REACHa).

For cysteine HCl (CAS No. 52-89-1) (Sigma-Aldrich SDS):

- In mice: LD50 = 1250 mg/kg bw (intraperitoneal), 771 mg/kg bw (intravenous).

For cysteine HCl.H20 (CAS No. 7048-04-6) (REACHb—a dossier for cysteine HCl):

- In rats: LD50 >2000 mg/kg bw in an acute oral toxicity test (OECD Test Guideline (TG) 423—Acute toxic class method).

Dermal

The chemicals are expected to have low acute dermal toxicity.

In standard tests (OECD TG 402 – Acute dermal toxicity), LD50 values >2000 mg/kg bw in rats were reported for cysteine (semi-occlusive) and cysteine HCl.H20 (occlusive) after 24-hour application (HSBD; REACHa; REACHb).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemicals are not expected to cause skin irritation.

Cysteine (500 mg) was not irritating to the skin of rabbits after 4-hour semi-occlusive application (OECD TG 404 – Acute Dermal Irritation/Corrosion) (REACHa).

Cysteine HCl was considered non-corrosive to skin, given requirements for cell viability ≥50 % and ≥15 % after 3 and 60 minutes, respectively, were met in a guideline test (OECD TG 431—In vitro skin corrosion: reconstructed human epidermis (RhE) method) (REACHb).

Cysteine HCl.H20 was considered non-irritant to skin, given requirements for cell viability >50 % and standard deviation (SD) ≤18 % were met in a guideline test (OECD TG 439 – In vitro skin irritation: reconstructed human epidermis method) (REACHb).

Eye Irritation

Based on the available data, the chemicals are expected to cause slight eye irritation, not warranting hazard classification for this group.

Cysteine (100 mg) was slightly irritating to the eyes of rabbits in an acute eye irritation/corrosion test (OECD TG 405). Conjunctival redness (score 2) was observed up to 48 hours in 3/3 animals and discharge in 1/3 animal. The reactions fully reversed within 72 hours. Corneal opacity, iris and conjunctival oedema (chemosis) had reported scores of 0 (REACHa).

For cysteine HCl, an in vitro irritancy score (IVIS) of 80.28 (average) was determined in a guideline test (OECD TG 437 – Bovine corneal opacity and permeability (BCOP) method). The IVIS is a calculation based on both opacity and permeability values. If the IVIS >55, the test chemical is predicted to be classified as 'irreversible effects on the eye' (Category 1). However, the scorings for opacity and permeability were claimed contradictory and the results were not considered for classification (REACHb). The original study report was not available for verification.

For cysteine HCl.H20, IVIS values of 9.8 and 47.5 (average) in two separate OECD TG 437 BCOP tests were reported (REACHb). The guideline indicates that for IVIS between >3 and ≤55, no prediction can be made, and this BCOP method is not recommended for the identification of test chemicals that should be classified as 'irritating to eyes' (Category 2 or 2A) or as 'mildly irritating to eyes' (Category 2B).

Observation in humans

Cysteine (3 % neutral solution) was not irritating to the human eyes (HSDB; REACHa).

Sensitisation

Skin Sensitisation

Limited data are available. Sensitising potential of pure cysteine and its salts is not likely based on the results below.

In a skin sensitisation study (OECD TG 429—Local Lymph Node Assay (LLNA)), cysteine produced a stimulation index (SI) of ~1 for three tested concentrations of 3.125 %, 6.25 % and 12.5 % (REACHa).

In an LLNA test (OECD TG 429), cysteine HCl.H20 produced SI of 2, 2.3, and 2.3 for tested concentrations of 10 %, 25 % and 50 %, respectively (REACHb).

Repeated Dose Toxicity

Oral

Based on the available data, the chemicals are not expected to have the potential to be harmful to human health following repeated exposure at the normal dietary intake. The daily intake of 4.1 mg/kg/day for cysteine or total 15 mg/kg/day (adults) and 31 mg/kg/day (6-month infants) for sulfur amino acids are recommended by WHO (2007). Excessive intake of cysteine or cystine (a dimer of cysteine) may result in a disruption of the cellular metabolic homeostasis, cell vacuolation or fatty change, degeneration of parenchyma, and consequent liver and kidney necrosis (Klavins, 1963; Sawamoto et al., 2003a; REACHa).

In a 93-day oral repeated dose study, cysteine was given to Wistar rats (10/sex/dose) via gavage at 0, 100, 300, 600, 3000 mg/kg bw/day. At 3000 mg/kg bw/day, decreased spontaneous activity from day 5, reduced food intake and body weight gain, as well as deaths (6 animals, 3/sex) starting from day 32 were observed. Congestion and haemosiderin (iron-storage pigment) deposition in the spleen, congestion of cortex and medulla of the kidneys, vacuolation and focal eosinophilic necrosis were found in nearly all decedents. Adverse effects in surviving animals included decreased glucose and haemoglobin, increased liver enzymes, liver weight, and total cholesterol. Histological findings included bleeding and congestion of intestine, liver (6/7 males and 2/7 females) and kidneys (2/7 males and 4/7 females), and fibrosis of Glisson’s sheath periphery in the liver (more than half of the animals). In male rats, absolute and relative weights of the spleen increased at ≥600 mg/kg bw/day. In female rats, liver congestion (2/10 animals) and urea nitrogen decreased at ≥600 mg/kg bw/day, and relative weight of the lungs and sodium increased at ≥300 mg/kg bw/day (REACHa). The no observed effect level (NOEL) is considered to be 100 mg/kg bw/day .

Following 180- and 30-day gavage exposure, the NOELs for cysteine were reported to be <100 (male rats) and <200 (rats and mice) mg/kg bw/day, respectively. Adverse effects included congestion and haemorrhage of the brain, heart, liver, kidneys and other internal organs, possibly due to dilation of the capillaries and hyperpermeability of the blood (REACHa; WHO, 2006).

In a 28-day oral repeated dose study, cysteine was administered by gavage to Sprague Dawley rats (6 males/dose) at 0, 500, 1000, 2000 mg/kg bw/day (nominal). One rat at high dose died on day 6 due to a technical error. At 500 mg/kg bw/day, signs of kidney injuries such as increases in water intake, urinary volume, chlorine excretion, number of basophilic tubules, and basophilic tubule with eosinophilic materials in the lumen were observed. At 1000 mg/kg bw/day, salivation, increased kidney weight, and dark red areas in the glandular stomach were reported. At 2000 mg/kg bw/day, increased reticulocyte counts indicative of potential anaemia, focal erosions in the glandular stomach and hyaline casts in the kidney were reported. A no observed adverse effect level (NOAEL) was not determined, given the effects were observed at the lowest dose tested. For comparison, the toxicological profiles of L-cysteine and D-cysteine were similar although there were slight differences in the dose responses (Shibui et al., 2017; REACHa).

In a 28-day intravenous repeated dose study (10 male pubertal rats/dose), cysteine treatment resulted in reduced body weight gain, decreased spontaneous activity, increased salivation, ptosis, tremor, mild anaemia (including increased reticulocyte counts) at 1000 mg/kg bw/day. Histopathological findings were seen in the cerebellum (necrosis of Purkinje cells and granular layer), epididymis (sperm granulomas), and kidney (tubular basophilia and hyaline casts in the lumen at ≥300 mg/kg bw/day) (Sawamoto et al., 2003b).

Cysteine (100 mg/kg/day oral for 10 days) increased oxidation rate of ethanol in dogs. No further information is available (HSDB).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available data, the chemicals are not expected to cause germ cell mutagenicity.

In vitro

Cysteine was:

- positive (*Salmonella typhimurium* TA92, TA97, TA100, TA104 with metabolic activation; and TA102 with and without metabolic activation) and negative (TA98, TA1535, TA1537, TA1538 with and without metabolic activation) in Ames tests (Glatt, 1989; Stark et al., 1989; REACHa)
- negative (Chinese hamster lung fibroblasts) in a *Hprt* gene mutation test (OECD TG 476) (REACHa)
- negative (Chinese hamster lung fibroblasts and ovary cells) in chromosomal aberration tests (WHO, 2006; REACHa)
- positive (human lymphocytes) and negative (Chinese hamster V79 cells) in sister chromatid exchange (SCE) tests (Speit et al., 1980; WHO, 2006).

Cysteine HCl was:

- positive in Ames tests (TA100 with metabolic activation; and TA2637 with and without metabolic activation) (Ishidate et al., 1984; REACHb)
- positive (Chinese hamster fibroblasts) and negative (human blood cells) in chromosomal aberration tests (Ishidate et al., 1984; REACHb)

In vivo

Cysteine HCl was negative in a bone marrow micronucleus test in mice (Hayashi et al., 1988; REACHa).

Carcinogenicity

Limited data are available. The chemicals are not expected to have carcinogenic potential for humans.

In a 108-week drinking water carcinogenicity study, Fischer 344 rats (50/sex/dose) were given cysteine HCl at 0, 0.25 or 0.5 % (~ 0, 133–148, and 235–280 mg/kg bw/day for males-females). There were no statistically significant differences between treated and control rats in the neoplasm incidences. Non-neoplastic effects such as necrosis of renal papillae (2/43 and 6/38 female rats at 0.25 % and 0.5 %, respectively), calcification of the renal papillae (2/38 female rats at 0.5 %), and focal necrosis of the proximal tubules (2/41 males and 1/38 female at 0.5%) were reported. A single female of each treated group showed hyperplasia of the kidney pelvis (Kitahori et al., 1997; REACHa).

Reproductive and Developmental Toxicity

Limited data are available. The chemicals are not expected to cause adverse reproductive or developmental effects following repeated exposure at the normal dietary intake. Excessive systemic exposure to cysteine and its salts may have the potential to affect fertility and/or cause delayed sexual maturation in the pubertal reproductive tract.

Cysteine was included in the diet of pregnant rats (4/dose) at 0 or 3500 ppm (equivalent to 0 and 175 mg/kg bw/day) from gestation through to weaning of the pups (F1 generation). At weaning, 2 male and 3 female offspring per dose were retained for F2–F3 breeding, and 12 male and 24 female offspring for F4–F6 breeding. The F6 generation rats were given cysteine at approximately 0, 1.75, 17.5, or 175 mg/kg bw/day. The study was terminated at the F7 generation. Examination of the F5 rats revealed no evidence of pathology. No reproductive or developmental effects were reported, except increased absolute (but not relative) weights of the liver and kidney of the F5–F6 rats at the highest dose. The authors concluded that consumption of bread baked with cysteine (up to 175 mg/kg bw/day) did not cause reproductive or developmental toxicity in rats over six generations (Frape et al., 1971; WHO, 2006).

Cysteine (1000 mg/kg bw/day intravenous for more than 1 week before mating) was reported to affect the ovary and decrease litter size in rats. This was considered related to the degeneration and/or death of ovulated unfertilised oocytes and embryos with changes in the zona pellucida of follicles (HSDB; PubChem).

Cysteine (1000 mg/kg bw/day intraperitoneal) caused sperm granulomas, possibly forming around leaked spermatozoa in the epididymides of pubertal rats. The observed incidences were 0/6, 3/6, 5/6, and 6/6 rats after 0, 2, 3, and 4 weeks of daily exposure, respectively. The sperm granulomas were unilateral or bilateral, and frequently involving the proximal cauda region of the epididymides (Sawamoto et al., 2003a).

Other Health Effects

Neurotoxicity

Based on the available animal data, cysteine and its salts may have the potential to cause neurotoxicity at high doses in newborn infants.

Cysteine (1200–1300 mg/kg bw subcutaneous injection in infant rats on postnatal day 4) caused atrophy of the brain and associated behavioural deficits (e.g. spontaneous alternation, pattern discrimination, hyperactivity in the open field). It was reported that 80 % of animals had 30–40 % reduction and 20 % of animals had 60–80 % reduction in brain wet weights, with cerebral cortex, hippocampus and thalamus most affected. The behaviour changes in surviving cysteine-treated animals were considered similar to those reported in adult rats with extensive hippocampal damage (Shapre et al., 1975; Karlsen et al., 1981).

Systemic administration of cysteine to immature rodents was shown to overstimulate neuron receptors (excitotoxic) and may be mediated through N-methyl-D-aspartate (NMDA) subtype of glutamate receptor, and hence cysteine and glutamate could have a synergistic effect. The excitotoxic potency of cysteine was significantly sensitive to physiological concentrations of bicarbonate ion (Olney et al., 1990; Puka-Sundvall et al., 1995).

Cysteine (1200 mg/kg bw subcutaneous injection on the last day of pregnancy in rats and mice) induced brain degeneration one day later in the foetus (HSDB).

Risk Characterisation

Critical Health Effects

The critical human health effect for risk characterisation is acute oral toxicity. The chemicals can cause harmful effects to human health following excessive systemic exposure. The daily intake of 4.1 mg/kg/day for cysteine or total 15 mg/kg/day (adults) and 31 mg/kg/day (6-month infants) for sulfur amino acids are recommended by WHO (2007).

No data are available regarding the health effects following inhalation exposure.

Public Risk Characterisation

The chemicals have reported cosmetic, domestic and commercial uses overseas. According the Cosmetic Ingredient Review Expert Panel (CIR, 2013), cosmetic use concentrations currently are: ≤0.05 % in leave on; ≤5% (cysteine) or ≤6 % (cysteine HCl) in rinse off; and ≤0.05 % in aerosolised or spray products. The same use concentrations, use patterns, and hence widespread public exposure are expected in Australia, mainly through the skin and eyes. Incidental inhalation (from aerosolised or powder products) and ingestion can also occur.

The CIR Expert Panel (CIR, 2013) indicated that up to 95–99 % of the droplets and/or particles (aerodynamic diameters >10 µm) released from cosmetic sprays containing amino acids (including cysteine) are not expected to be respirable into the gas exchange region of the lungs, but likely to deposit in the nasopharyngeal and bronchial regions and subsequently undergo elimination. Propellant sprays may yield a greater fraction of droplets and/or particles <10 µm, compared with pump sprays. Cysteine and its salts are not used in any baby products, bathing products or products applied in the eye area or mucous membrane (CIR, 2013).

Cysteine and its salts must be ≥98 % pure (CIR, 2013) and the presence of heavy metals as impurities are controlled through the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2019).

Taking into consideration the uses and existing restrictions described above, the chemicals are not expected to pose an unreasonable risk to public health at current specified use concentrations and types of products.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure of workers to the chemicals may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemicals at higher concentrations is expected. The level and route of exposure will vary depending on the method of application and work practices employed.

For cysteine HCl.H20, there were 1–25 % of particles were <50 µm and the products had a dusting potential ranging from <0.1–35.3 g/m^3, according to EFSA FEEDAP (2014).

Given the critical systemic acute health effects and uncertainty following inhalation exposure, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise relevant exposure are implemented. Good hygiene practices to minimise oral exposure are expected to be in place.

The chemical 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 appropriate controls.

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

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemical 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

Work Health and Safety

The chemicals in this group 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]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)

[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, ocular and inhalation 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:

- 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 chemical[s] 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 the chemicals has not been undertaken as part of this assessment.

References

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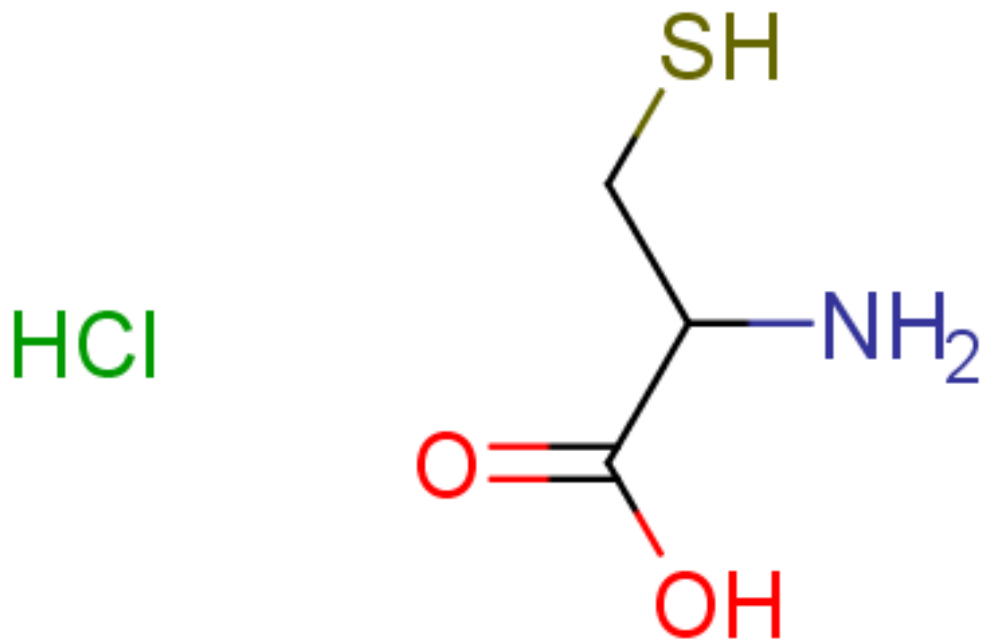
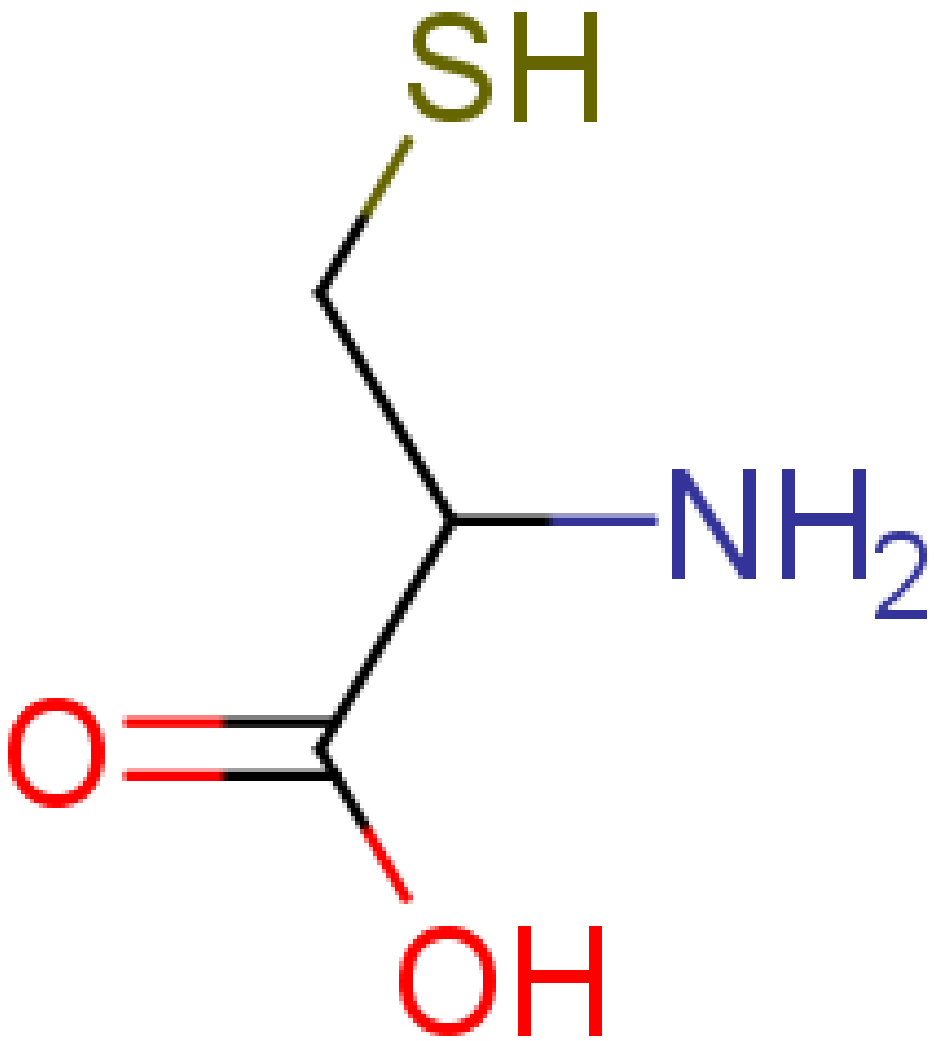
Last Update 12 December 2019

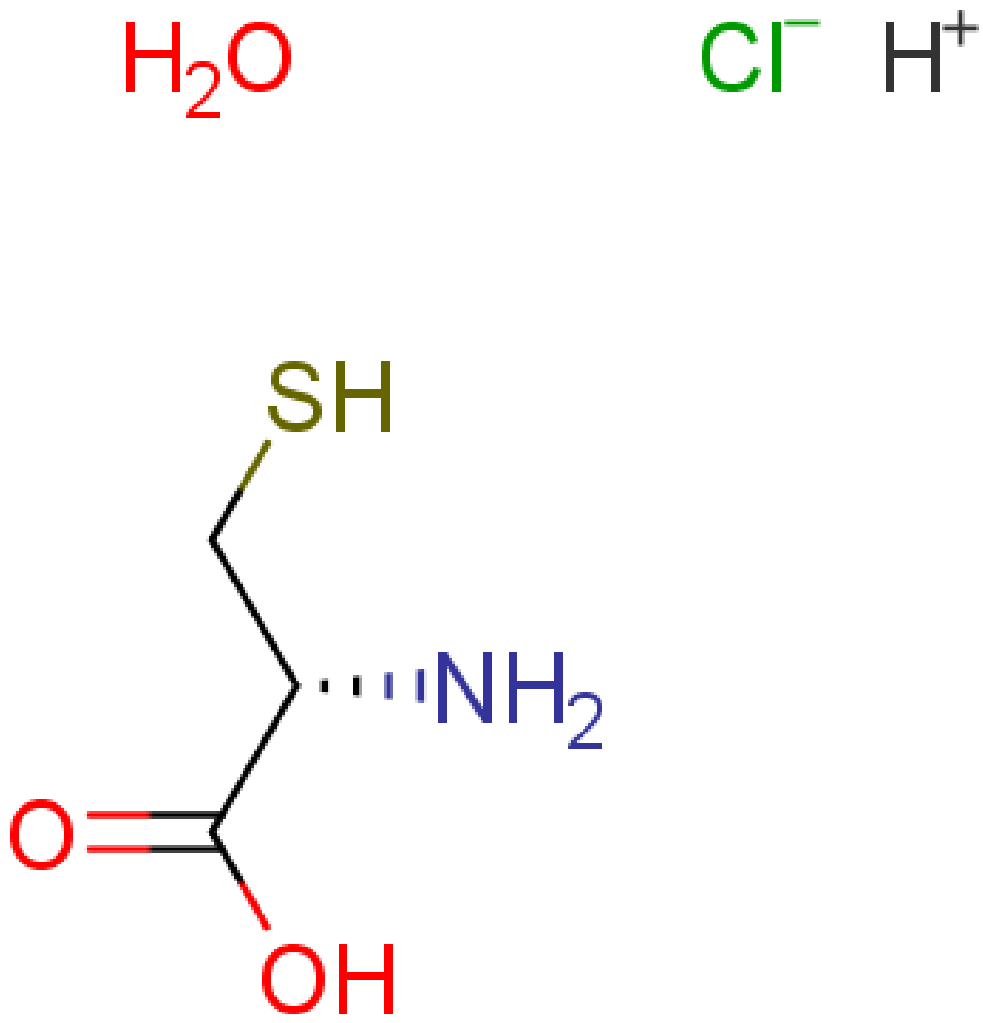
Chemical Identities

Chemical Name in the Inventory and Synonyms	**L-Cysteine, hydrochloride** cysteine HCl (INCI) (2R)-2-amino-3-sulfanylpropanoic acid hydrochloride cysteine, chlorhydrate cysteine chlorohydrate
CAS Number	52-89-1
Structural Formula	
Molecular Formula	C3H7NO2S.ClH

Molecular Weight	157.61

Chemical Name in the Inventory and Synonyms	**L-Cysteine** cysteine (INCI) 2-amino-3-mercaptopropanoic acid a-amino-ß-thiolpropionic acid ß-mercaptoalanine thioserine
CAS Number	52-90-4
Structural Formula	
Molecular Formula	C3H7NO2S
Molecular Weight	121.16

Chemical Name in the Inventory and Synonyms	**L-Cysteine, hydrochloride, monohydrate** cysteine hydrochloride monohydrate (cysteine HCl.H2O) (2R)-2-amino-3-sulfanylpropanoic acid hydrate hydrochloride
CAS Number	7048-04-6

Structural Formula	
Molecular Formula	C3H7NO2S.ClH.H2O
Molecular Weight	175.63

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