Soluble zinc salts: Human health tier II assessment

18 September 2014

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Acetic acid, zinc(2+) salt	557-34-6
Acetic acid, zinc(2+) salt, dihydrate	5970-45-6
Sulfuric acid, zinc salt (1:1), monohydrate	7446-19-7
Sulfuric acid, zinc salt (1:1), heptahydrate	7446-20-0
Sulfuric acid, zinc salt (1:1)	7733-02-0
Zinc, bis(glycinato-N,O)-, (T-4)-	14281-83-5

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 chemicals in this group are soluble zinc compounds. Upon dissolution, the Zn^{2+} cation is formed and is considered to be the moiety responsible for systemic toxicity (EU RAR, 2004). The counter ion within this group of chemicals does not significantly contribute to the toxicity. The chemicals in this group are considered to have similar bioaccessibility and bioavailability; that is, these zinc chemicals release the Zn^{2+} ion into biological fluids based on their solubility at similar pH's and, therefore, can be assessed collectively.

Considering that sulfuric acid, zinc salt (1:1) (zinc sulfate—CAS No. 7733-02-0) has similar bioaccessibility and bioavailability in biological fluids to the other chemicals in this group, where data are lacking for these other chemicals, data available for zinc sulfate can be 'read across' to this chemical group. Zinc chloride (CAS No. 7646-85-7) was not included as a member of this group due to more severe eye irritation (local toxicity) compared with members of this group. However, considering the very similar bioavailability in biological fluids to zinc sulfate, zinc chloride was used as an analogue chemical to assess the systemic hazards of chemicals in this group where there are data gaps, using read across according to the principles of the OECD (2014).

Import, Manufacture and Use

Australian

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was between 1000 and 9999 tonnes for zinc sulfate (CAS No. 7733-02-0) and zinc sulfate heptahydrate (CAS No. 7446-20-0). Volume data were not available for other chemicals in this group.

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

The chemical zinc sulfate (CAS No. 7733-02-0) has reported domestic and commercial use including:

- as cleaning/washing agents and additives.

The following chemicals have reported site-limited use including:

- as chemical intermediates (zinc sulfate (CAS No. 7733-02-0) and zinc sulfate heptahydrate (CAS No. 7446-20-0));
- as flotation agents (zinc sulfate (CAS No. 7733-02-0));
- as fixing agents (zinc sulfate (CAS No. 7733-02-0)); and
- paper bleaching (zinc sulfate (CAS No. 7733-02-0)).

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; and Consumer Product Information Database (CPID).

This group of zinc chemicals has reported cosmetic use including:

- as components in cosmetic astringents (bath, skin and hair care preparations);
- as components in biocides (deodorants); and
- as components in oral care agents (tooth paste).

The chemical zinc glycinate (CAS No. 14281-83-5) has reported cosmetic use as:

- as a buffering agent; and
- as a pH adjuster.

The chemical zinc sulfate (CAS No. 7733-02-0) has reported domestic use including:

- in washing detergent.

The chemical zinc sulfate (CAS No. 7733-02-0) has reported commercial use including:

- as a component in glass polishing kits; and
- in paints, lacquers and varnishes.

The range of zinc sulfate chemicals has reported site-limited use including:

- as chemical intermediates;
- as floatation agents;

- as fixing agents; and
- in paper bleaching.

The following non-industrial uses have been identified for zinc sulfate (CAS No. 7733-02-0):

- as garden fertilizer; and
- as a mineral supplement.

Restrictions

Australian

The chemical zinc sulfate (CAS No. 7733-02-0) is listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in Schedule 6 with the following entry:

Zinc sulfate **except**:

a) when included in or expressly excluded from Schedule 4; or

b) in other preparations containing 5 per cent or less of zinc sulfate.

International

The compound zinc is listed on the following (Galleria Chemica):

Council of Europe Resolution ResAP(2008)1 on requirements and criteria for the safety of tattoos and permanent make-up (PMU)—Maximum allowed concentrations of impurities in products for tattoos and PMU. Compound zinc (Zn); 50 ppm.

No international restrictions have been identified for the chemicals in this group.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals zinc sulfate (CAS No. 7733-02-0) and zinc sulfate heptahydrate (CAS No. 7446-19-7) are classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xn; R22 (Acute toxicity)

Xn; R41 (Eye irritation)

Exposure Standards

Australian

No specific exposure standards were available for this group of chemicals.

International

The following exposure standards were identified (Galleria Chemica):

An exposure limit for zinc and its inorganic compounds (inhalable fraction) (TWA) of 2 mg/m^3 and (respirable fraction) (TWA) of 0.1 mg/m^3 in Germany.

An exposure limit (TWA) of 0.1 mg/m^3 for zinc acetate (CAS No. 557-34-6) in Russia.

No specific exposure standards were available for other members of this group.

Health Hazard Information

Zinc is an essential trace element for humans and animals and required for metabolism, cell growth and division, as well as essential for endocrine and exocrine function. The human body contains 2-3 g of zinc, and the recommended dietary allowance (RDA) is 11 mg/day for men and 8 mg/day for women (Plum et al., 2010). Intoxication by excessive zinc exposure is rare; zinc deficiency caused by malnutrition, ageing, disease or deregulated homeostasis is a far more common risk to human health (Plum et al., 2010).

Toxicokinetics

The zinc salts within this group are all soluble in water and highly bioavailable (EU RAR, 2004; O'Neil et al, 2013; Prasad et al., 1993).

Oral absorption has been observed to vary from 8-80% in humans. People with zinc deficiencies tend to absorb greater proportions of administered Zn^{2+}, while in those with excessive zinc, gastrointestinal intake is less (EU RAR, 2004). Absorption can be influenced by dietary intake, where a decrease is observed associated with high levels of plant protein, alcohol or bovine serum albumin. Conversely, absorption can be increased due to casein in milk (IRIS, 2005). Gastrointestinal absorption of zinc is biphasic, with rapid absorption occurring in the small intestine, followed by a saturable slow phase. Zinc is absorbed by both saturable carrier-mediated protein (cysteine-rich intestinal protein - CRIP) and by passive diffusion (EPA IRIS 2005). A comparative study demonstrated soluble zinc acetate and zinc sulfate have similar bioavailability after oral ingestion where maximal plasma zinc concentrations were 221 and 225 μg/dL respectively (Prasad et al., 1993).

Absorption following inhalation exposure to zinc depends on the clearance mechanisms present in the different parts of the airway. Studies reported inhalation absorption for soluble zinc citrate and nitrate is up to 40 %. The fractions absorbed in the different airway regions were reported to be 4.8-17.6 % in the nasopharynx, 12.5-48 % in the tracheobronchial region and up to 100 % in the pulmonary region. Remaining zinc salts would be moved into the gastrointestinal tract by mucociliary movement and absorbed at a similar rate to ingested zinc (EU RAR, 2004).

Dermal absorption of zinc has been demonstrated to be relatively low in in vivo animal studies. Absorption of zinc chloride acidified at pH 4, on intact skin of male Sprague Dawley (SD) rats was reported to be less than 2 % (EU RAR, 2004). Human studies have reported dermal absorption through damaged or burned skin but no statistically significant absorption through intact skin (EU RAR, 2004).

Once absorbed, the zinc ion is widely distributed in the body as it is a cofactor in over 300 enzyme systems. Nearly 90 % is found in muscles and bone. In animals studies, the highest level of zinc found was in the small intestine, followed by the kidney, liver and large intestine, six hours after oral ingestion of zinc chloride in Wistar rats. Fourteen days after administration, the highest levels of the chemical could be found in the hair, testicles, liver and large intestine of rats. In humans, the distribution is similar; however, increased levels in the liver, pancreas and prostate and decreased levels in the uterus and aorta have been observed with increased age. Zinc does not undergo metabolism and is normally found in the body as a divalent cation complexed to albumin and metallothionein proteins.

Faecal elimination is the primary route of elimination after oral exposure (70-80%). This is followed by elimination via urine (10 to 25 %), sweat and saliva. Zinc has also been known to be incorporated into hair and secreted in breast milk (EU RAR, 2004).

Acute Toxicity

Oral

Zinc sulfate (CAS No. 7733-02-0) and zinc sulfate heptahydrate (CAS No. 7446-19-7) are classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia). Based on the similar bioavailability of the chemicals in this group to zinc sulfate, the data available support the extension of this classification to other chemicals in this group.

Moderate acute toxicity was reported in mice (median lethal dose—LD50—926 to 1891 mg/kg bw) and rats (LD50—920 to 2949 mg/kg bw) after oral administration of zinc sulfate (CAS No. 7733-02-0) and zinc sulfate heptahydrate (CAS No. 7446-19-7) (EU RAR, 2004; REACH).

In a study carried out using OECD Test Guideline (TG) 423, zinc sulfate heptahydrate had an LD50 between 1000 to 2000 mg/kg bw in rats of both sexes. Reported signs of toxicity include hunched posture, lethargy, ataxia, piloerection, splayed gait, laboured respiration, emaciation, red-brown staining around the eyes and diarrhoea (EU RAR, 2004; REACH).

Dermal

Zinc sulfate (CAS No. 7733-02-0) had low acute toxicity in animal tests following dermal exposure. Based on the similar bioavailability of the chemicals in this group to zinc sulfate, the data available support this conclusion for other chemicals within the group.

The median lethal dose (LD50) in Wistar rats was greater than 2000 mg/kg bw. Clinical signs of toxicity consisted of low grade erythema, scales and/or scabs on skin exposed to zinc sulfate (CAS No. 7733-02-0) (EU RAR, 2004; REACH).

Inhalation

The chemical zinc sulfate (CAS No. 7733-02-0) had low acute toxicity in animal tests following inhalation exposure, with no mortalities or toxic effects observed. Based on the similar bioavailability of the chemicals in this group to zinc sulfate, the data available support this conclusion for other chemicals in this group.

In a well documented inhalation study, male Syrian hamsters were exposed (whole body) to an aerosol of zinc sulfate (CAS No. 7733-02-0) at concentrations of 0.8, 3.1, 6.5 and 20.3 mg/m^3 for four hours. Under the test conditions, pulmonary macrophage clearance was significantly reduced at greater than 3.1 mg/m^3 with an EC50 (concentration of test material to produce a 50% decrease in phagocytosis) value of 4.5 mg/m^3 for sulfate ions (as a surrogate for zinc ions) (EU RAR, 2004; REACH).

In another study, anaesthetised dogs exposed to an aerosol of zinc sulfate (CAS No. 7733-02-0) from 4.1 to 8.8 mg/m^3 for four hours showed no effect on breathing mechanics, haemodynamics and arterial blood gases. At a concentration of 15.8 mg/m^3 for 7.5 minutes, there were no observed alternations in total respiratory resistance, static lung compliance, or functional residual capacity. In addition, there were no significant alterations in mean pulmonary arterial and carotid arterial pressures, cardiac output, heart rate, stroke volume or arterial pH levels (EU RAR, 2004; REACH).

Observation in humans

Gastrointestinal toxicity has been reported in humans. One fatal case was recorded after 28 g of zinc sulfate ingestion. After ingestion, the female started vomiting and developed tachycardia as well as hyperglycaemia. The female died five days later of haemorrhagic pancreatitis and renal failure (Plum et al., 2010). Various other human cases report severe diarrhoea, vomiting and abdominal pain after ingesting 2.5 g to 112 g of zinc sulfate (UK PID, 1998).

Corrosion / Irritation

Skin Irritation

Zinc sulfate (CAS No. 7733-02-0) produced no skin irritation in studies that were performed in accordance with OECD TG 404. Based on the similar bioavailability of the chemicals in this group to zinc sulfate, the data available support this conclusion for other chemicals in this group.

In a skin irritation study carried out according to OECD TG 404, three male New Zealand White rabbits were exposed to 0.5 g of moistened zinc sulfate applied onto clipped skin for four hours, using a semi-occlusive dressing. Observations were made one, 24, 48 and 72 hours after exposure. No symptoms of skin irritation, systemic toxicity or mortality occurred (EU RAR, 2004; REACH).

In a non guideline study, 0.5 mL (1 % w/v in deionised water) zinc sulfate was applied to the clipped skin of New Zealand White rabbits (four per test) using open and occlusive patches for an exposure duration of five days. Low levels of erythema were observed in one out of four animals of each test group after five days' exposure (REACH).

Eye Irritation

Zinc sulfate (CAS No. 7733-02-0) was reported to severely irritate the eyes when tested according to OECD TG 405. Based on the similar bioavailability of the chemicals in this group to zinc sulfate, the data available support the extension of this classification to other chemicals in this group.

In an eye irritation study carried out according to OECD TG 405, three male New Zealand White rabbits were treated with 98.1 mg of zinc sulfate into the conjunctival sac of one eye. Eyes were unrinsed and examined at one, 24, 48 and 72 hours and seven, 14 and 21 days after treatment. The average scores for conjunctival redness (mean scores over 24 to 72 hours of 2, 2.7, 2.7) and conjunctival chemosis (mean scores 2, 2.7 and 3.7) were reported. Corneal injury and epithelial damage was observed in two out of three animals; this resolved within 72 hours. White necrotic spots protruded from the tissue of the lower eyelid, nictitating membrane and/or sclera in all animals from day seven until termination at 21 days. The persistence and severity of the ocular irritation is classifiable as serious damage to the eyes.

Sensitisation

Skin Sensitisation

The negative results observed for the chemical zinc sulfate heptahydrate (CAS No. 7446-20-0) in two skin sensitisation animal studies (guinea pig maximisation test and local lymph node assay) support a conclusion that the chemical is not a skin sensitiser. Based on the similar bioavailability of the chemicals in this group to zinc sulfate, the data available support this conclusion for other chemicals in this group.

In a guinea pig maximisation test carried out according to OECD TG 406, ten female Dunkin Hartley guinea pigs were intradermally injected with a 0.1 % concentration of zinc sulfate heptahydrate (CAS No. 7446-20-0) and then epidermally exposed to a 50 % concentration. Animals were challenged twice, the first two weeks after the epidermal exposure with a 50 % concentration and the second challenge a week after the first. Non-specific signs of irritation were observed but zinc sulfate did not induce hypersensitivity under the conditions of this study (EU RAR, 2004; REACH).

In a modified mouse local lymph node assay (LLNA), three female Balb/c mice were exposed to a 25 μL solution of 10 % zinc sulfate in 20 % ethanol to the dorsum of both abraded ears for three consecutive days. Lymph node cells were harvested four days after application. The incorporation of labelled tritiated thymidine was determined by comparing proliferation of cells from treated to those of non-treated cells. A stimulation index was determined as 1.41 and under the criteria of this study, the chemical is not considered to be a sensitiser (EU RAR, 2004; REACH).

Repeated Dose Toxicity

Oral

Considering the no-observed-effect levels (NOELs) available from 90-day mouse and rat studies are greater than 100 mg/kg bw/day zinc sulfate heptahydrate (CAS No. 7446-20-0), and based on the treatment-related effects reported in various repeat dose toxicity studies, the chemical is not considered to cause serious damage to health from repeated oral exposure. Based on the similar bioavailability of the chemicals in this group to zinc sulfate, the data available support this conclusion for other chemicals in this group.

In an repeated dose 90 day oral toxicity study similar to OECD TG 408, 12 ICR mice per sex per dose were exposed to 0, 300, 3000 and 30000 ppm of zinc sulfate heptahydrate (CAS No. 7446-20-0) in the diet. A no-observed-effect level (NOEL) was determined to be 3000 ppm (equivalent to 458 mg/kg/day in males and 479 mg/kg/day in females). Mortality was observed in animals exposed to the highest concentration of 30000 ppm (33.3% in males and 8.3% female). Other observations at this dose included; retarded growth, reduced food and water intake, and moderate changes in haematology. Gross pathology and histopathology showed changes in kidneys, thyroids, pancreas, gastrointestinal tract and spleen at the 30000 ppm concentration (EU RAR, 2004; REACH).

In another repeated dose 90 day oral toxicity study carried out according to OECD TG 408, 12 Wistar rats per sex per dose were exposed to 0, 300, 3000 and 30000 ppm zinc sulfate heptahydrate (CAS No. 7446-20-0) in the diet. A no-observed-effect level (NOEL) was determined to be 3000 ppm (equivalent to 234 mg/kg bw/day in males and 243 mg/kg bw/day in females). Animals exposed to the highest dose of 30000 ppm displayed dwarfism and depressed weight gain, moderate changes in haematology (reduction in leukocyte count, slight decrease in haematocrit and haemoglobin concentration in males). Histopathology revealed pancreatic lesions, degeneration and necrosis of acinar cells and interstitial fibrosis at 30000 ppm. There were no clinical signs in either sex at less than or equal to 3000 ppm (EU RAR, 2004; REACH).

Dermal

No data are available.

Inhalation

The effects observed in a non guideline repeat dose inhalation study using zinc sulfate (CAS No. 7733-02-0) did not meet the criteria for hazard classification. Based on the similar bioavailability of the chemicals in this group to zinc sulfate, the data available support this conclusion for other chemicals in this group.

In a well-documented 16 week repeat dose inhalation study, which meets basic scientific principles, 12 male per dose Wistar Kyoto rats were exposed to aerosolised zinc sulfate (CAS No. 7733-02-0) to evaluate cardiac changes and toxicity. Rats were exposed via nose only, at doses of 10, 30 and 100 μg zinc/m^3 (environmentally relevant levels) for five hours a day, three days a week and then sacrificed 48 hours after the last exposure. The mass median aerodynamic diameter (MMAD) was 31, 35 and 44 μm for low medium and high doses respectively and geometric standard deviation (GSD) of 1.8, 1.6 and 1.8 μm for low, medium and high doses respectively. No exposure related pulmonary or cardiac pathological changes were noted, nor were there significant changes in plasma or serum markers. No significant changes were observed in macrophages, neutrophils, eosinophils and lymphocytes on analysis of bronchoalveolar lavage fluid. However, cytosolic and mitochondrial analysis showed decreased activity in succinate dehydrogenase and cytosolic glutathione peroxidase activity, while increased mitochondrial ferritin levels were observed. In cardiac gene array analysis, subchronic exposure to 100 μg of the chemical resulted in changed expression levels of cardiac genes involved in cell signalling events, ion channel regulation and coagulation. It was concluded that, under the test conditions described, subchronic inhalation of zinc sulfate at environmentally relevant levels induced cardiac effects. However, these effects are not clear functional disturbances or morphological changes and therefore do not meet the criteria for hazard classification (REACH).

Observation in humans

Multiple studies on increased zinc consumption due to zinc supplements have demonstrated a resulting copper deficiency manifested by decreased copper metalloenzyme activity, as well as haematological effects such as anaemia, neutropaenia, decreased cholesterol levels, immunotoxic and gastrointestinal effects (EPA IRIS, 2005).

Genotoxicity

Zinc sulfate (CAS No. 7733-02-0) and zinc acetate (CAS No. 557-34-6) gave mixed results in several in vitro (Ames, mitotic gene conversion) and in vivo (chromosomal aberration, dominant lethal assay, comet) tests for gene mutation and clastogenicity. Given the essential role of zinc, it is not anticipated to be genotoxic. The weight of evidence indicates that the chemicals are not mutagenic to germ cells.

In vitro studies

Bacterial reverse mutation assays (Ames test) conducted in *Salmonella typhimurium* TA 1535, TA 1537, TA 98 and TA 100 with zinc sulfate (CAS No. 7733-02-0) at doses up to 3600 μg/plate were negative, with and without metabolic activation. Furthermore, in another Ames test in *S. typhimurium* strain TA 102 with zinc sulfate (dose levels of 10, 30, 100, 300, 100 and 3000 nM/plate), cytotoxicity was observed at 3000 nM and no significant increases in the frequency of revertant colonies were recorded at any dose (REACH).

Conflicting results have been reported in gene mutation studies. In one gene mutation study conducted with the diploid strain D4 of *Saccharomyces cerevisiae* with zinc sulfate (CAS No. 7733-02-0), results were negative and zinc did not induce mitotic gene conversion at the loci *ade2* and *trp5*, after exposure for four hours (REACH). However, in another similar gene mutation study using strain D7 of *S. cerevisiae* with zinc sulfate (CAS No. 7733-02-0), a weakly positive response was observed for induction of gene conversion at the *trp5* locus and reverse mutation at the *ilv* locus (REACH).

Similar equivocal results were reported with zinc acetate. No mutagenic activity was observed with or without hepatic homogenates in *S. cerevisiae* assays over a dose range of 50 to 72000 μg/plate, and zinc acetate was negative in the unscheduled DNA synthesis assay in rat hepatocytes over a dose range of 10 to 1000 μg/ml. Zinc acetate did not induce chromosomal aberrations in unstimulated human lymphocyte cultures. However, in a mouse lymphoma assay, a dose-dependent positive response was reported with or without metabolic activation after exposure to zinc acetate. Similarly, in an in vitro cytogenetic assay in Chinese hamster ovary cells, a positive dose-dependent response with and without metabolic activation was reported (EPA IRIS, 2005).

In vivo studies

In a mammalian bone marrow chromosome aberration test, zinc sulfate (CAS No. 7733-02-0) was administered via intraperitoneal injection to NMRI mice at dose concentrations of 28.8, 57.5 and 86.3 mg/kg. Examinations were conducted at 0 and 24 hours after exposure. Under the test conditions reported, the chemical was non-mutagenic (REACH).

In several studies (host mediated point mutation assay in mice, and chromosome aberration assay in rats) conducted by the same research group, zinc sulfate (CAS No. 7733-02-0) was administered daily via oral gavage at doses of 2.75, 27.5 or 275 mg/kg bw for five days. Under the test conditions, zinc sulfate was reported to be weakly positive in the host mediated point mutation assay in mice, although negative in the chromosome aberration study conducted in rats (REACH).

In a comet assay to detect DNA damage, zinc sulfate (CAS No. 7733-02-0) was administered via a single oral gavage dose (concentrations of 5.70, 8.55, 11.40, 14.25, 17.10 and 19.95 mg/kg bw) to six male Swiss mice per dose. Whole blood samples were collected at 24, 48, 72, 96 and one week after exposure. A clear dose dependent response was reported with significant DNA damage at all the tested doses compared to controls, indicating potent genotoxicity (REACH).

In a sex linked recessive lethal test in *Basc Drosophila melanogaster*, zinc sulfate (CAS No. 7733-02-0) was administered at a dose of 5 mM, which was close to the LD50 value, via food for a duration of three successive broods (approx. four days). The experiment was done in triplicate, where in two out of three replicates, there was no significant increase of sex-linked recessive lethal mutations (REACH).

In a rodent dominant lethal assay, zinc sulfate (CAS No. 7733-02-0) was administered daily via oral gavage, at doses of 2.75, 27.5 or 275 mg/kg bw, for five days. Under the test conditions, zinc sulfate was reported to be non-mutagenic in the dominant lethal assay conducted in rats (REACH).

Carcinogenicity

Limited human and animal data are available on soluble zinc compounds.

According to the U.S. EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is *inadequate information to assess carcinogenic potential of zinc* due to inadequate or inconclusive studies from occupational exposure to zinc and carcinogenic animal studies.

Considering genotoxicity assays of zinc are considered to give an overall negative result, and given the high levels of endogenous zinc, the data available do not support a recommendation to classify this group of chemicals.

In a well documented carcinogenicity study, male and female Chester Beatty mice were exposed to zinc sulfate (CAS No. 7733-02-0) in drinking water (4.4 g/L (1000 ppm zinc) and 22 g/L (5000 ppm zinc)) for a duration of 45 weeks. Histopathology reported no difference between treated and control groups regarding the incidence of forestomach epithelial hyperplasia. There were no differences in the incidences of hepatoma, malignant lymphoma and lung adenoma observed between treatment and control groups under the test conditions (REACH). In a similar study where C3H mice were exposed to zinc sulfate in daily drinking water for up to 14 months, there were no observed pancreatic, pituitary or adrenal tumours (EPA IRIS, 2005).

In another limited carcinogenicity study, female Porton mice (98-100 per group) were exposed to concentrations as high as 121.7 mg zinc/m^3 of a zinc oxide/hexachloroethane smoke mixture (which produces zinc chloride), for one hour per day, five days per week for 20 weeks. Statistically significant increases in the incidence of alveologenic carcinoma were reported 13 months after the end of exposure period. At lower exposure doses of 1, 1.3 and 12.8 mg zinc/m^3, there was no increase in observed incidence of tumours (ATSDR, 2005). Similar dose levels were administered to guinea pigs and rats, and no significant carcinogenic responses were observed. Several confounding factors, including the short duration of the exposure (20 weeks), the use of only females and the presence of several other compounds in the smoke with carcinogenic potential, limit the usefulness of these studies (ATSDR, 2005).

Epidemiological studies

Conclusions are difficult to draw from epidemiological studies evaluating the possible carcinogenic effects of zinc, as they have been limited by other confounding factors including smoking habits, occupational exposure (e.g. in mining and associated activities) and residence.

A United States study evaluated a cohort of 46974 men between 1986 to 2000, for the occurrence of prostate cancer. From the 2901 cases of prostate cancer identified, there were 434 cases that were classified as advanced cancer. Although zinc supplementation did not appear to increase the frequency of developing prostate cancer, men who had taken zinc supplements of >100 mg zinc per day had a greater probability of developing advanced cancer, if a tumour occurred (ATSDR, 2005).

Reproductive and Developmental Toxicity

Reproductive and developmental toxicity has been investigated in several studies. Studies in rats provide evidence that high doses of zinc adversely affect spermatogenesis in males and impair fertility in females. The very high concentrations of zinc compounds (equivalent to ≥ 1000 mg/kg bw zinc sulfate heptahydrate), required to produce these adverse effects do not satisfy the criteria for classification.

In a non guideline study, male Charles Foster rats were administered 4000 ppm zinc as zinc sulfate (CAS No. 7733-02-0) in the diet for 30 days, before mating with unexposed females. Mating with treated males significantly lowered the incidence of conception, and resulted in lower number of live births per mated female, although there were no stillbirths or malformed young reported. There was a significant increase of zinc content in the testes and sperm of treated rats. While motility of sperm was significantly reduced, viability was unaffected (EU RAR, 2004; REACH).

In two separate studies, male SD rats were administered up to 500 ppm of supplemental zinc (form not specified) in the diet for six or eight weeks. In one study, there were no significant alterations in reproductive tissue weights (testes, caput epididymis, seminal vesicles and prostate), although zinc affected enzyme activities in reproductive tissues (increased arylsulfatase activity in the epididymis (caudal and caput) regions and increased leucyl amino peptidase activity in the testes, caudal epididymis and prostate gland). Histological examination in the first study revealed meiotic arrest at the primary spermatocyte stage, degenerating secondary spermatocytes and arrested spermatogenesis. The second study also reported no effect on relative testicular weight; however, flow cytometry data indicated that excess zinc could cause abnormalities in the chromosome structure of sperm (EPA IRIS, 2005).

In another reproductive study, 15 female Charles Foster rats were administered via their daily diet, 4000 ppm of zinc as zinc sulfate (supplemental zinc intake was estimated in the report to be 450 mg/kg day as determined using reference values for food intake and body weight (EPA, 1988)), for 18 days beginning immediately after coitus. The incidence of conception was significantly reduced in treated animals compared to the controls (5/12 compared to 12/12). However, treated animals that did conceive showed no alteration in the number of implantation sites, no effect on the number of resorption sites, and there were no stillbirths. Malformations were not seen in the offspring of treated rats (EPA IRIS, 2005, REACH). A second test was performed with the same doses for 21 days prior to mating, 5 days during mating and 18 days post coitum. In test 2, no significant difference in incidence of conception or implantation sites was observed between the control and treatment groups. These results suggest that zinc altered normal conception when administered after coitus but showed no effect when initiated with sufficient time before coitus (REACH).

In another study, 13 female rats (strain not specified) were administered 150 ppm supplemental zinc (as zinc sulfate, approx. 20 mg/kg bw/day total zinc) in diet. The dams were sacrificed at day 18 of gestation and although there were no alterations in the number of implantation sites, there was a statistically significant increase in the number of resorptions (to 9.5%) observed in treated animals (EPA IRIS, 2005).

In a single generation reproduction toxicity study, male and female SD rats were exposed to zinc chloride (3.6, 7.2, 14.4 or 28.8 mg of zinc/kg bw/day as zinc chloride) by gavage for seven days per week for 77 days prior to cohabitation and during the 21 day cohabitation period. Females were further exposed during the 21 day gestation and lactation periods. The fertility indices in all dose groups were significantly lower than in the control groups. In the two highest dose groups, the number of live pups per litter were significantly decreased (EPA IRIS, 2005).

In a reliable developmental toxicity study, 14 to 19 female Dutch rabbits were administered daily doses of zinc sulfate (0.6, 2.8, 13 and 60 mg/kg bw/day) by gavage during days six to 18 of gestation. No discernible effects were reported on maternal survival, body weight gains, number of corpora lutea, implantations or resorptions. There were no observed effects on the number of live litters, foetus weights or observed abnormalities between exposed or control groups (REACH). A similar negative finding was observed in female CD-1 mice and Wistar rats that were administered daily doses of zinc sulfate (0.3, 1.4, 6.5 and 30 mg/kg bw and 0.4, 2.0, 9.1 and 42.5 mg/kg bw respectively) by gavage during days six to 15 of gestation (REACH). Pregnant hamsters were administered up to 88 mg/kg bw/day of zinc sulfate during days six to ten of gestation; no adverse effects on females or foetuses were observed (REACH).

In a well documented reproductive toxicity study, six Cheviot sheep per dose (zero to six weeks pregnant) were administered via the daily diet, zinc sulfate (doses of 30, 150 and 750 mg/kg bw/day of zinc) until parturition. At the highest dose, feed consumption and weight gain were reduced in pregnant sheep. After day 61, two ewes died, one of which was not pregnant, and four ewes aborted early. The cause of death was not determined; however, very high tissue zinc concentrations and very low tissue copper concentrations were observed in nonviable lambs. Reproductive and developmental toxicity were observed secondary to maternal toxicity (REACH).

In a limited inhalation study, female mice, rats and guinea pigs were exposed to concentrations as high as 121.7 mg zinc/m^3 of a zinc oxide/hexachloroethane smoke mixture (which produces zinc chloride), for one hour per day, five days per week for 20 weeks. Histopathology reported no adverse effects on the mammary glands, ovaries, fallopian tubes, or uteri at 18 months (ATSDR, 2005).

Pregnant women receiving zinc supplements (0.3 mg zinc/kg/day as zinc sulfate) during the last two trimesters did not display any changes to maternal body weight gain, blood pressure, postpartum haemorrhage or infection (ATSDR, 2005).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity by the oral route of exposure) and local effects (eye damage) for this chemical group. While fertility toxicity has been observed at very high doses, the levels at which this occurs are unlikely to result from industrial use of the chemicals.

Public Risk Characterisation

Although the public may be exposed to the chemical through cosmetic and domestic uses, given the low hazard of the chemicals, the chemicals are not considered to pose an unreasonable risk to public health.

The chemicals in this group are used as buffering agents, astringents and biocides in cosmetics (CosIng) and, therefore, public exposure to high concentrations of the chemicals is not expected through cosmetic uses. If the concentrations in cosmetics are low, irritation effects are not expected; therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During product formulation, ocular 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 lower concentrations may 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 systemic and local health effects, the chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemicals 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 appropriate controls.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation section**).

NICNAS Recommendation

Assessment of the chemicals is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

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 hazards 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)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)

[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 chemical should be used according to the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral 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 chemical is used. Examples of control measures which may 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 chemical 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 chemical.

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 assist with meeting 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 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 chemical has not been undertaken as part of this assessment.

References

Agency for Toxic Substances and Disease Registry (ATSDR) 2005. Toxicological profile for Zinc. Accessed September 2014 at **http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=302&tid=54**

European Union Risk Assessment Report (EU RAR), 2004. Zinc Sulfate CAS No. 7733-02-0 EINECS No. 231-793-3. Accessed September 2014 at **http://echa.europa.eu/documents/10162/c235a91f-5d2b-4660-a30f-9e67941ec71e**

Galleria Chemica. Accessed September 2014 at **https://jr.chemwatch.net/galleria/**

OECD (2014). Guidance on Grouping of Chemicals, Second Edition. Environment Directorate. Joint meeting of the Chemicals Committee and the Working party on Chemicals, Pesticides and Biotechnology. Series on Testing& Assessment No. 194. Accessed September 2014 at **http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en**

O'Neil MJ, Heckelman PE, Dobbelaar PH, Roman KJ, Kenny CM& Karaffa LS 2013. The Merck Index, Fifteenth Edition. The Royal Society of Chemistry

Plum LM, Rink L& Haase H 2010. The Essential Toxin: Impact of Zinc on Human Health. International Journal Environmental Research and Public Health 7 (4) pp. 1342-1365.

Prasad AS, Beck FWJ& Nowak J 1993. Comparison of absorption of five zinc preparations in humans using oral zinc tolerance test. The Journal of Trace Elements in Experimental Medicine 6 pp. 109-115.

REACH Dossier. Zinc sulfate (CAS No. 7733-02-0). Accessed September 2014 at **http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea6e4f0-6833-6c9a-e044-00144f67d031/AGGR-b3d3c5e4-7e5a-44f2-92a0-fe6e04ecbb06_DISS-9ea6e4f0-6833-6c9a-e044-00144f67d031.html#AGGR-b3d3c5e4-7e5a-44f2-92a0-fe6e04ecbb06**

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed September 2014 at **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2013. Accessed September 2014 at **http://www.comlaw.gov.au/Details/F2013L01607/Download**

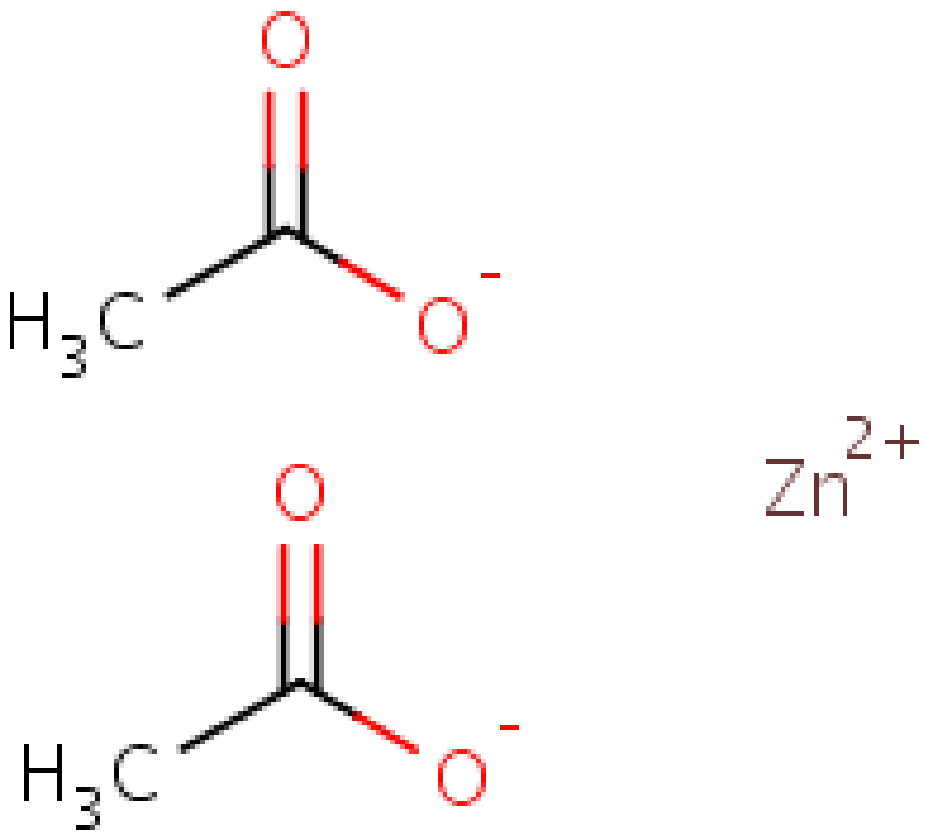
U.S. Environmental Protection Agency (EPA) 1988. Recommendations for and documentation of biological values for use in risk assessment. Accessed September 2014 at **http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855#Download**

U.S. Environmental Protection Agency (EPA), 2005. In Support of Summary Information on the Integrated Risk Information System (IRIS). Toxicological Review of Zinc and Compounds (CAS No. 7440-66-6). Accessed September 2014 at **http://www.epa.gov/iris/subst/0426.htm**

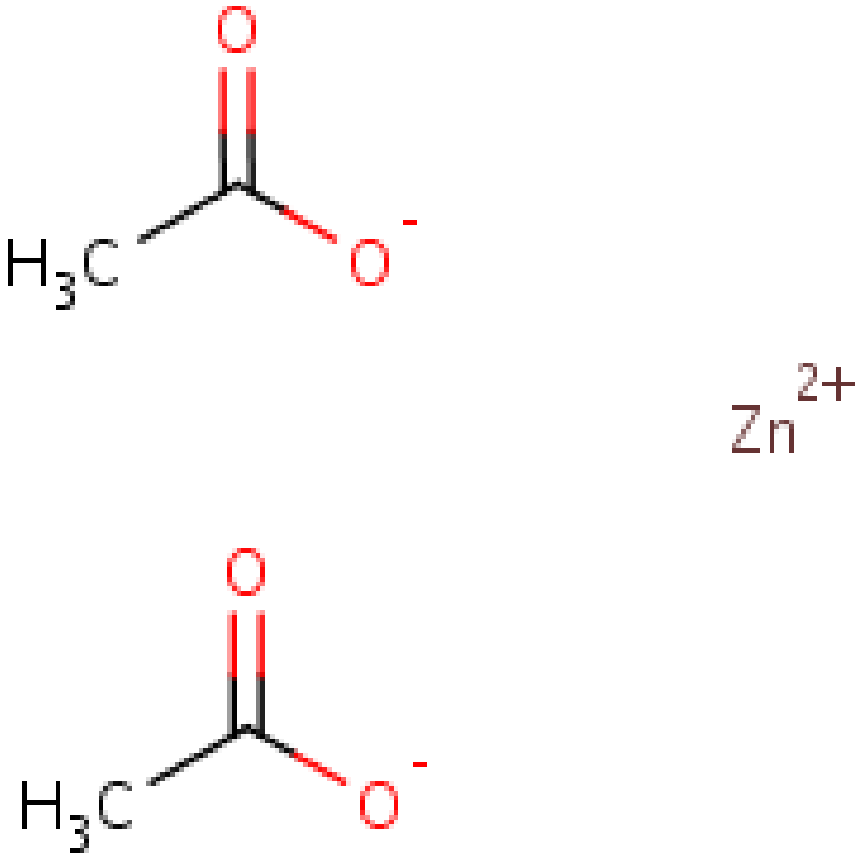
Last Update 18 September 2014

Chemical Identities

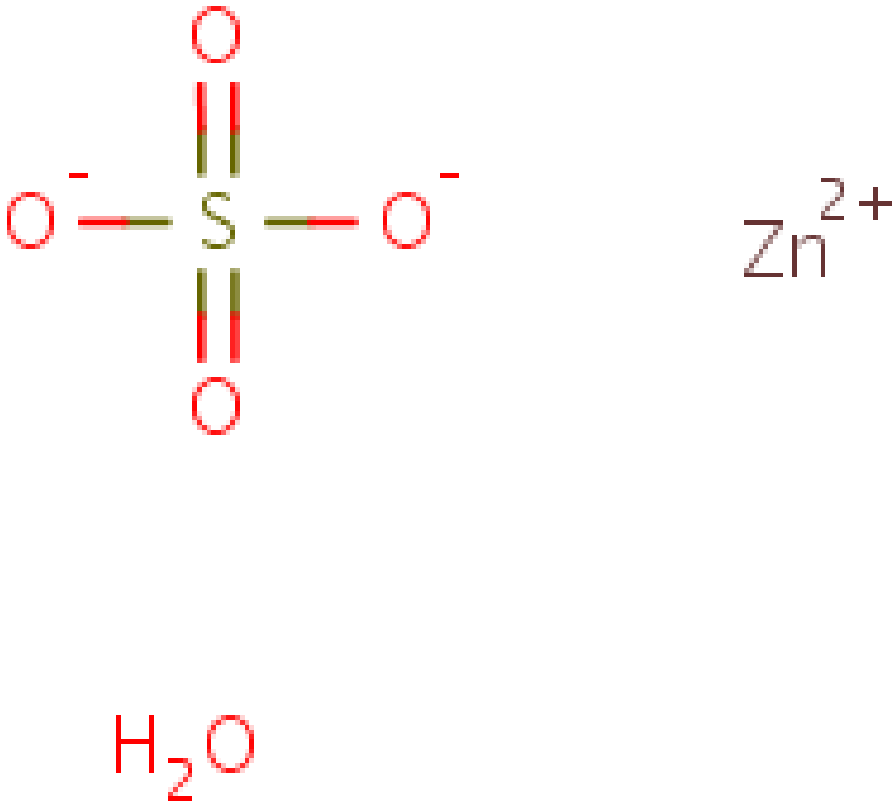
Chemical Name in the Inventory and Synonyms	**Acetic acid, zinc(2+) salt** Zinc acetate Zinc acetate anhydrous

	Zinc diacetate Dicarbomethoxyzinc
CAS Number	557-34-6
Structural Formula	
Molecular Formula	C2H4O2.1/2Zn
Molecular Weight	183.477

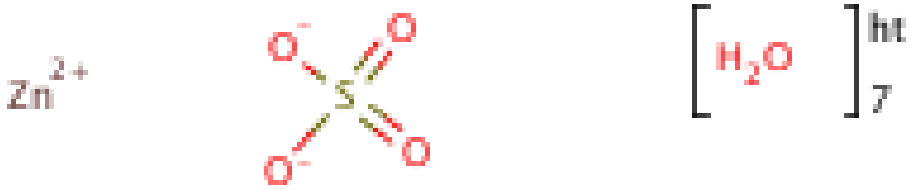
Chemical Name in the Inventory and Synonyms	**Acetic acid, zinc(2+) salt, dihydrate** Zinc diacetate, dihydrate Zinc(II) acetate dihydrate Zinc acetate
CAS Number	5970-45-6
Structural Formula	

	
Molecular Formula	C2H4O2.H2O.1/2Zn
Molecular Weight	183.477

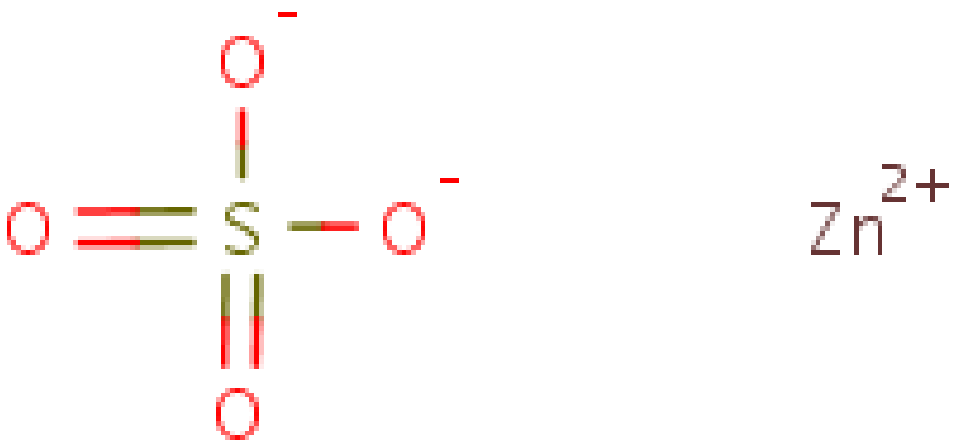
Chemical Name in the Inventory and Synonyms	**Sulfuric acid, zinc salt (1:1), monohydrate** Zinc sulfate monohydrate
CAS Number	7446-19-7
Structural Formula	

	
Molecular Formula	H2O4S.H2O.Zn
Molecular Weight	179.467

Chemical Name in the Inventory and Synonyms	**Sulfuric acid, zinc salt (1:1), heptahydrate** Zinc sulfate (ZnSO4) heptahydrate Zinc vitriol (heptahydrate) Verazinc
CAS Number	7446-20-0
Structural Formula	

	
Molecular Formula	H2O4S.7H2O.Zn
Molecular Weight	287.556

Chemical Name in the Inventory and Synonyms	**Sulfuric acid, zinc salt (1:1)** Zinc sulfate Zinc vitriol Bonazen Solvezinc Optised
CAS Number	7733-02-0
Structural Formula	

	
Molecular Formula	H2O4S.Zn
Molecular Weight	161.452

Chemical Name in the Inventory and Synonyms	**Zinc, bis(glycinato-N,O)-, (T-4)-** Bis(glycinato)zinc Glycine, zinc salt Zinc, bis(glycinato)- Zinc bisglycinate Zinc Chelazome
CAS Number	14281-83-5
Structural Formula	

	
Molecular Formula	C4H8N2O4Zn
Molecular Weight	213.507

Share this page