Nitric acid, zinc salt: Human health tier II assessment

27 November 2014

CAS Number: 7779-88-6

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.

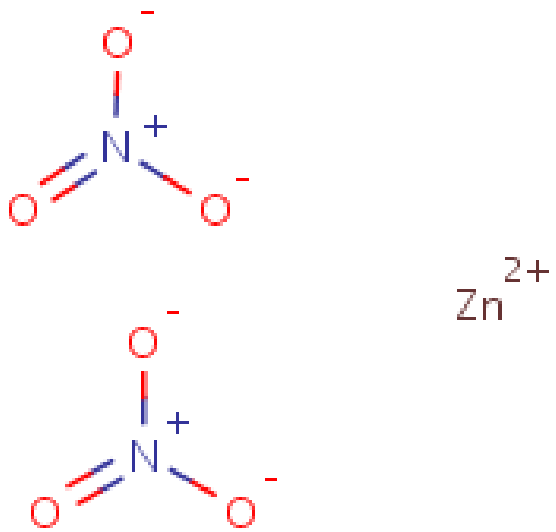
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Zinc nitrate Zinc dinitrate
Structural Formula	
Molecular Formula	HNO3.1/2Zn
Molecular Weight (g/mol)	189.4
Appearance and Odour (where available)	Moist white or translucent crystals with mild nitric acid odour.
SMILES	N(=O)(=O)O{-}.[Zn]{2+}.O{-}N(=O)=O

Import, Manufacture and Use

Australian

The following Australian industrial uses for this chemical have been identified from safety data sheets (SDS):

The chemical has reported commercial uses including as:

- a latex coagulant;
- an acidic catalyst; and
- a mordant in dyeing.

The chemical has reported site-limited uses including in manfacturing other chemicals.

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database and United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary.

The chemical has reported cosmetic uses including as a skin conditioning agent.

The chemical has reported domestic use including in:

- surface treatments; and
- paints and fillers.

The chemical has reported commercial uses including as:

- an acidic catalyst;
- a corrosion inhibitor;
- a mordant in dyeing; and
- a latex coagulant.

The chemical has reported site-limited uses including:

- in manufacturing other chemicals; and
- as an electroplating agent.

Restrictions

Australian

The use of the chemical for human internal use is listed in the *Poisons Standard* (*Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP) in Schedule 4 (Prescription Only Medicine).

International

The chemical is listed on the following (Cosing):

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down. Maximum concentration in ready-for-use preparations is 1 % (as zinc).
- Health Canada list of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

The following international exposure standards are identified (Galleria Chemica):

- for zinc and its inorganic compounds (respirable fraction) a time weighted average (TWA) exposure limit of 0.1 mg/m^3 and a short-term exposure limit (STEL) of 4 ppm have been set in Germany.

No other international standards have been identified.

Health Hazard Information

Zinc is an essential trace element for all organisms and has a range of functions in normal metabolic and physiological processes in humans. Zinc nitrate is a highly soluble inorganic salt and readily dissociates into zinc cations and nitrate anions; the former are likely to be the driver of the biological activity associated with the chemical. Due to the paucity of information regarding the toxicology of zinc nitrate specifically, data on similar zinc compounds (including zinc chloride and zinc sulfate) will be used to inform several aspects of this risk assessment. This approach is appropriate given the similar solubilities of these chemical compounds.

Toxicokinetics

No data exist for the toxicokinetics of zinc nitrate; however, numerous studies have assessed the absorption, distribution, metabolism and excretion of other zinc compounds with similar solubilities.

Absorption

Oral absorption of zinc has been observed to vary between 8–80 %. People with zinc deficiencies tend to absorb a higher proportion of the element when it is administered orally. In contrast, gastrointestinal uptake can be reduced in persons with high zinc intake (EU RAR, 2004).

Dietary factors are likely to influence the gastrointestinal absorption of zinc cations, including consuming certain animal and plant proteins (such as casein and soy), as well as alcohol intake. Zinc absorption might also be influenced by the endogenous secretion of zinc into the intestinal lumen via the gastrointestinal epithelium, as well as bile and pancreatic secretion (EU RAR, 2004; EPA IRIS, 2005).

Animal studies have shown that inhaled zinc can be absorbed in any region of the respiratory system. However, the rate at which it occurs appears to be a function of the clearance mechanisms associated with each of these regions (nasopharynx, tracheobronchial and alveolar regions). One study reported absorption values of 4.8–17.6 % in the nasopharynx, 12.5–48 % in the tracheobronchial region and up to 100 % in the alveolar regions for the more soluble forms of zinc compounds (including zinc nitrate) (EU RAR, 2004).

Although no quantitative data on the inhalational absorption of zinc nitrate in humans exist, elevated concentrations in the blood and urine of persons occupationally exposed to zinc oxide fumes suggest that some extent of pulmonary absorption of zinc occurs.

Dermal absorption of zinc is thought to be minimal. In one study, acidic solutions of zinc chloride, applied to the shaven, intact dorsal skin of Sprague Dawley (SD) rats resulted in 3.6–6.1 % absorption. Less acidic solutions containing $ZnCl_2$ resulted in <2 % absorption (Hallmans & Liden, 1978).

There are no quantitative data to demonstrate the absorption of zinc cations through intact skin in humans. However, absorption has been reported through damaged or burned skin.

Distribution

Zinc is distributed throughout all tissues in humans and is a cofactor in over 300 enzyme systems. The highest concentrations of zinc in human tissues have been found in bone and muscle (60 % and 30 %, respectively), followed by the prostate, liver and kidneys (Plum et al., 2010).

A study was performed on the distribution of zinc in male Wistar rats. After being intubated with 0.1 µCi (3.7 kBq) ^{65}Zn as zinc chloride, animals were euthanised at different time-points (ranging from six hours to 14 days) and the distribution of zinc was assessed. Zinc was found in the highest amount within the small intestine, liver, kidneys and large intestine, and in smaller amounts in lungs and spleen. Bone and muscle were not assessed (REACH).

Metabolism

Zinc is not metabolised and is typically found in the body as a divalent cation complexed with albumin or other serum proteins (EPA IRIS, 2005).

Excretion

In humans, approximately 70–80 % of total ingested zinc is excreted via the faeces (5–10 mg/day depending on the concentration of dietary zinc). Zinc is also excreted via the urine (10 %), sweat, saliva, breast milk and may also be excreted via hair (EU RAR, 2004).

Acute Toxicity

Oral

The chemical was shown to have moderate acute toxicity following oral exposure.

In a study conducted in accordance with the Organisation for Economic Co-operation and Development Test Guideline (OECD TG) 423 (Acute Oral Toxicity—Acute Toxic Class Method) the median lethal dose (LD50) in male Wistar rats is 300–2000 mg/kg bw zinc nitrate. The same LD50 range has been reported in a study assessing oral exposure of zinc nitrate in SD rats (REACH).

Dermal

Zinc nitrate and other zinc-containing compounds possess similar dermal bioavailabilities. One such compound is zinc sulfate heptahydrate and its capacity to induce acute dermal toxicity is likely to reflect that of zinc nitrate. Based on the OECD TG study below, acute dermal toxicity of zinc nitrate is expected to be low.

Zinc sulfate heptahydrate (CAS No. 7446-20-0) had low acute toxicity in animals following dermal exposure. The LD50 in Wistar rats is greater than 2000 mg/kg bw. Clinical signs of toxicity consisted of erythema, scales and/or scabs in the treated skin area between observation days two and eight (EU RAR, 2004; REACH).

Inhalation

No data are available on the inhalation toxicity of zinc nitrate. However, based on data on zinc sulfate (CAS No. 7733-02-0) low acute toxicity is expected for zinc nitrate from inhalation exposure.

Zinc sulfate had low acute toxicity in animal tests following inhalation exposure, with no mortalities or toxic effects observed (median lethal concentration—LC50—2,000 mg Zn/m^3).

In this study, female SD rats were exposed to zinc sulfate at concentrations of 600, 940, 1220 or 1950 mg Zn/m^3 for 10 minutes. Animals exhibited respiratory distress and pathological examination revealed pulmonary lesions including discolouration (consistent with acute inflammatory changes in the pulmonary vasculature), congestion, oedema, interstitial emphysema, atelectasis, hyperaemia and haemorrhage (REACH).

Observation in humans

There are a lack of data on the acute toxicity of zinc nitrate in humans and very little reliable data on the acute toxicity of other zinc-containing compounds in humans.

There is one published report of a woman who died following accidental ingestion of 28 g zinc sulfate. The female experienced nausea, vomiting, and developed tachycardia and hyperglycaemia. The woman died five days later of haemorrhagic pancreatitis and renal failure (REACH).

In another report of the accidental ingestion of zinc compounds, a 24-year-old man consumed 90 mL of zinc chloride in solution (unknown concentration), which resulted in local caustic effects including erosive pharyngitis and esophagitis with severe pain. The subject also presented with lethargy and confusion. Consistent with acute pancreatitis, the subject also experienced nausea, vomiting, abdominal pain, hypocalcaemia and hyperamylasaemia (REACH).

Corrosion / Irritation

Skin Irritation

The limited available data suggest that zinc nitrate is not corrosive. While dermal exposure can result in irritation, the interpretation of the in vitro data is difficult for hazard classification purposes, as the study has not been conducted according to OECD TGs.

A study was carried out to assess the potential of zinc nitrate hexahydrate to irritate and/or corrode skin using the in vitro EpiDerm Skin Irritation Test. The test evaluates the response of a 3-dimensional (3D) in vitro reconstructed human epidermal model ‘EpiDerm’ to the test material. The test is performed over the course of four days, consisting of pre-incubation, a 60-minute exposure, a 42-hour post-incubation and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) viability assay. The chemical is classified as an irritant if the tissue viability relative to the negative control is reduced to 50 % or less after the test material is administered. Following a single administration, tissue viability was reduced to 32.5 %, and following a repeated test, was reduced to 38.9 %. Therefore, the results of this study indicate that zinc nitrate hexahydrate is a skin irritant (REACH).

A study was performed in accordance with OECD TG 431 to assess the corrosive potential of zinc nitrate. This study also employed a 3D in vitro reconstructed human epidermal model to make predictions on the effects of dermal exposure to this chemical. The results of this investigation suggest that the chemical is not corrosive under these conditions.

Eye Irritation

In an in vitro assay that has not yet been validated, the chemical was found to fall within the range of 'non-irritating' to 'slightly irritating'. However, based on read-across data from zinc sulfate, it is expected that zinc nitrate is likely to be a severe irritant to eyes.

In vitro

A study was performed to assess zinc nitrate as an ocular irritant using the HET-CAM test (hen’s egg test on the chorioallantoic membrane). The study involves assessing the response of the chorioallantoic membrane of a fertilised and incubated hen’s egg to a test chemical. The response of this membrane to the chemical can be used to make assumptions on the expected effects of exposing the chemical to the eyes. Haemorrhage, coagulation and vessel lysis are assessed. The findings of this particular study indicated that the test material falls into the range of non-irritating to slightly irritating (REACH).

In vivo

There are no data available on zinc nitrate. Data on zinc sulfate are reported below.

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 respectively) and conjunctival chemosis (mean scores 2, 2.7 and 3.7 respectively) were reported. Corneal injury and epithelial damage were observed in 2/3 animals, but resolved within 72 hours. White necrotic spots protruding from the tissue of the lower eyelid, nictitating membrane and/or sclera were evident 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

Zinc nitrate does not induce dermal sensitisation in animals.

A 2010 study assessed the potential of zinc nitrate to act as a sensitising agent. Following pilot studies to gauge the appropriate dose for testing, guinea pigs were treated topically, three times, at one week intervals with the test material (500 mg/animal) together with an adjuvant. Animals were observed for signs of hypersensitivity following the final exposure; however, no such reaction occurred following secondary challenges, indicating that zinc nitrate did not act as a skin sensitiser under these test conditions (REACH).

Repeated Dose Toxicity

Oral

No data are available on the repeated dose toxicity of zinc nitrate. However, given the similar bioavailability of zinc nitrate and other soluble zinc compounds, the following studies of zinc sulfate will be used to predict the oral repeated dose toxicity of zinc nitrate.

In a 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 (equivalent to 42.7/46.4, 458/479 and 4,927/4,878 mg/kg bw for males/females, respectively) 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 (Maita et al., 1981).

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 (equivalent to 23.2/24.5, 234/243, and 2,514/2,486 mg/kg bw for males/females, respectively) zinc sulfate heptahydrate (CAS No. 7446-20-0) in the diet. A 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 $\leq$3000 ppm (Maita et al., 1981).

Dermal

No reliable data are available on the repeated dose toxicity of zinc nitrate (or other zinc compounds) via the dermal route.

Inhalation

No reliable data are available on the repeated dose toxicity of zinc nitrate via inhalation. However, given the similar bioavailability of zinc nitrate and other soluble zinc compounds, data from zinc sulfate are read-across to zinc nitrate.

In a well-documented 16-week repeated dose inhalation study, which meets basic scientific principles, 12 male Wistar Kyoto rats per dose were exposed to aerosolised zinc sulfate (CAS No. 7733-02-0) to evaluate cardiac changes and toxicity. Rats were exposed via the nose only, at doses of 10, 30 or 100 mg zinc/m^3 (environmentally relevant levels) for five hours a day, three days a week and then euthanised 48 hours after the last exposure. The mass median aerodynamic diameter (MMAD) was 31, 35 and 44 mm for low medium and high doses respectively, and a geometric standard deviation (GSD) of 1.8, 1.6 and 1.8 mm 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 macrophage, neutrophil, eosinophil and lymphocyte numbers in 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 analyses, subchronic exposure to 100 mg 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 effects on gene expression. The significance of these effects were not clear (REACH).

Observation in humans

Although no studies have investigated the repeated dose toxicity of zinc nitrate in humans, the effect of ingesting other zinc compounds (typically associated with dietary zinc supplementation) have been reported. Collectively, they suggest that increased consumption of zinc through zinc supplementation may result in copper deficiency as well as several other haematological effects including anaemia, neutropenia, hypocholesterolaemia, immunotoxic and gastrointestinal effects (EPA IRIS, 2005).

Genotoxicity

The genotoxicity of zinc nitrate and other soluble zinc-containing compounds have been assessed in numerous in vitro and in vivo experiments, yielding conflicting results.

Given the essential role of zinc in human physiology, the element is unlikely to induce genotoxicity. In the majority of studies, soluble zinc-containing compounds failed to induce genetic alterations in in vitro (Ames and mitotic gene conversion assays) and in vivo studies (chromosomal aberration, dominant lethal and comet assays). In some experiments, soluble zinc-containing

compounds were found to be capable of inducing genotoxicity (host-mediated, cytogenic assays and unscheduled DNA synthesis (UDS) tests).

Zinc nitrate

An in vitro study was carried out in compliance with OECD TG 471 (bacterial reverse mutation test) to assess the mutagenic potential of zinc nitrate. In this Ames study, zinc nitrate (50–5000 µg) was non-mutagenic at all doses for the bacterial strains used in this study (four indicator *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA 1537 and one indicator *Escherichia coli* WP2 uvrA strain) (REACH).

No in vivo studies have assessed zinc nitrate for genotoxicity.

Other soluble zinc chemicals

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. The weight of evidence indicates that the chemicals are not mutagenic to germ cells (NICNAS).

Carcinogenicity

No carcinogenicity data are available on zinc nitrate. However, limited human and animal data are available on other soluble zinc-containing compounds.

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

Considering genotoxicity assays of zinc are recognised 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 chemical.

Other soluble zinc compounds

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 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).

Epidemiological studies

Several epidemiological studies have attempted to assess the relationship between exposure to zinc and the incidence of cancer. A cohort study of 4,802 refinery workers in electrolytic zinc and copper plants employed between 1946 and 1975, demonstrated slightly reduced mortality rates amongst workers exposed to zinc alone.

Rates of cancer were only analysed for the entire cohort (all 4,802 workers). An association between cancer mortality and employment in zinc and or copper refineries was not found. However, because the study did not assess the link between zinc exposure and cancer mortality separately, no definitive conclusions can be drawn on zinc compounds as carcinogens (Logue et al., 1982).

Another study has reported that age- and sex-adjusted mortality rates were elevated in a former lead and zinc mining and smelting region in the US. Interestingly, the analysis revealed elevated rates of lung cancer in the region. Due to a number of other unaccounted for variables, it is impossible to draw a definitive association between zinc exposure and cancer rates in this study.

A large prospective cohort study published in 2003 examined the association between the consumption of supplemental zinc and prostate cancer among 46,974 American men. Supplemental zinc intake, at doses up to 100 mg/day, was found not to be associated with elevated prostate cancer risk. The authors concede that it is not possible to draw a direct correlation between

zinc supplementation and prostate cancer due to unaccounted variables. They suggest the need for further mechanistic studies to explore the link between zinc and prostate carcinogenesis (Leitzmann et al., 2003).

Zinc deficiency or supplementation might influence carcinogenesis; however, there is no clear experimental or epidemiological evidence to support a direct role for zinc nitrate or similar compounds in carcinogenesis.

Reproductive and Developmental Toxicity

No data are available on the reproductive and developmental toxicity of zinc nitrate. However, a well-characterised two-generation reproductive toxicity study on zinc chloride demonstrated that any reproductive and developmental effects were only observed secondary to maternal toxicity (NICNAS). Based on read-across data from zinc chloride, it is unlikely that zinc nitrate will exhibit specific reproductive or developmental toxicity.

Zinc chloride

A reproductive toxicity study was carried out on zinc chloride in accordance with OECD TG 416 (a two-generation reproduction toxicity study). Male and female SD rats were administered the chemical at doses of 0, 7.5, 15 or 30 mg/kg bw/d over two successive generations. In the F0 generation, males experienced 0, 8, 20 and 12 % mortality, and the mortality in the female (F0) animals was stated as 12–24 %. In the F1 generation, the males experienced 0, 12, 8 and 4 % mortality, and the females experienced 0, 8, 12 and 20 % mortality. Exposure of F0 and F1 parental rats also resulted in a significant reduction in fertility, viability and the body weight of F1 and F2 pups from the high-dose group. There were no significant changes in litter size, weaning ratio and sex ratio. Reductions in organ weights (brain, liver, kidney and spleen in males, and uterus and spleen in females) (F0 and F1) were observed (REACH).

Administration of the chemical to adult male and female rats throughout the study resulted in significant effects on adults and their offspring at 15 and 30 mg/kg bw/d including lesions in the gastrointestinal tract (male and female rats F0 and F1). With significant effects seen in the parental animals at the two highest doses, it appears that the reproductive effects seen were secondary to parental toxicity. The no observed adverse effect level (NOAEL) is the lowest concentration (7.5 mg/kg bw/d).

Other soluble zinc compounds

Reproductive and developmental toxicity has been investigated in several studies using zinc sulfate. 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/d zinc sulfate heptahydrate), required to produce these adverse effects do not satisfy the criteria for classification.

Epidemiological studies

Relatively few studies have assessed reproductive and developmental toxicity associated with other soluble zinc compounds in humans.

A study published in 1976 evaluated the effect of zinc supplementation during the third trimester of pregnancy. The authors reported an increase in the incidence of stillbirths and one premature birth in these women. However, there are significant limitations on the validity of this study (ADSTR, 2005). A more recent set of experiments assessed the effect of zinc supplementation during pregnancy (20 mg daily). In this double blind randomised control study, there were no differences whatsoever in maternal and foetal health as a result of zinc supplementation (Mahomed et al., 1989).

Two other human studies have been performed that support the findings of Mahomed and colleagues. Both found that there were no effects on the newborns of mothers consuming 0.3 mg Zn^{2+}(as zinc citrate)/kg bw/d (Simmer et al., 1991) or 0.06 mg Zn^{2+}(as zinc aspartate)/kg bw/d (Kynast & Saling, 1986) during the last two trimesters of pregnancy.

Other Health Effects

Neurotoxicity

No quantitative data are available on the neurotoxicity of zinc nitrate in humans. Some information has been garnered from reports detailing the intentional inhalation of metallic paint aerosols. Exposure to these aerosols resulted in staggered gait, visual hallucinations and other non-specific neurological effects. However, the data are confounded as the exposure to zinc compounds detailed in this study occurred in combination with exposure to copper compounds and hydrocarbons (Wilde, 1975).

Non-specific manifestations of neurotoxicity have been reported in humans following acute oral exposure to zinc compounds. These include light-headedness, dizziness, headache and lethargy). There are also limited data suggesting that high doses of zinc can result in neuronal degradation and alter normal hypothalamic processes in rats (ADSTR, 2005).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral exposure) and local effects (eye, and possibly skin irritation).

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used in skin conditioning cosmetic products overseas. In such cosmetic formulations, the chemical is expected to be used at low concentrations. At low concentrations, irritant 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, oral, dermal and ocular exposure of workers to the chemical can occur, particularly where manual or open processes are used. These might include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemical at lower concentrations can also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical local and systemic acute health effects, the chemical can pose an unreasonable risk to workers unless adequate control measures to minimise dermal and ocular exposure to the chemical are implemented. 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 HSIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of the 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 chemical is 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)
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, dermal and ocular exposure to the chemical 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 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 chemical.

Guidance on managing risks from hazardous chemicals is 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 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

Chemsupply Australia. MSDS for Zinc Nitrate. Accessed November 2014 at http://chemsupply.customer-self-service.com/images/ZL0081CH7H.pdf

CosIng. Cosmetic Ingredients and Substances. Accessed November 2014 at http://ec.europa.eu/consumers/cosmetics/cosing/.

European Union Risk Assessment Report (EU RAR), 2004. Zinc Chloride CAS No. 7646-85-7 EINECS No. 231-592-0. Accessed October 2014 at http://echa.europa.eu/documents/10162/abd0dc4f-ef23-48f6-b27c-b671b5cf703a

Hallmans, G.,& Liden, S. (1978). Penetration of 65Zn through the skin of rats. Acta dermato-venereologica, 59(2), 105-112.

Kynast, G.,& Saling, E. (1986). Effect of oral zinc application during pregnancy. Gynecologic and obstetric investigation, 21(3), 117-123.

Leonard, A., Gerber, G. B.,& Leonard, F. (1986). Mutagenicity, carcinogenicity and teratogenicity of zinc. Mutation Research/Reviews in Genetic Toxicology, 168(3), 343-353.

Mahomed, K., James, D. K., Golding, J.,& McCabe, R. (1989). Zinc supplementation during pregnancy: a double blind randomised controlled trial. BMJ: British Medical Journal, 826-830.

Maita, K., Hirano, M., Mitsumori, K., Takahashi, K.,& Shirasu, Y. (1981). Subacute toxicity studies with zinc sulfate in mice and rats. Journal of Pesticide Science (Japan).

National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Inventory Multi-Tiered and Prioritisation (IMAP) Human Health Tier II Assessment for Soluble zinc salts. Available at http://www.nicnas.gov.au

National Pollutant Inventory (NPI). Accessed October 2014 at http://www.npi.gov.au/index.html

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.

REACH Dossier. Zinc Nitrate (CAS No. 7779-88-6) Accessed October 2014 at http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea5a29e-51b1-3639-e044-00144f67d031/AGGR-d72f7620-2472-4ad1-8ef0-d8b0f25ba9f4_DISS-9ea5a29e-51b1-3639-e044-00144f67d031.html#AGGR-d72f7620-2472-4ad1-8ef0-d8b0f25ba9f4

Substances in Preparations in Nordic Countries (SPIN). Accessed November 2014 at http://195.215.202.233/DotNetNuke/default.aspx

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 October 2014 at http://www.epa.gov/iris/subst/0426.htm

United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary. Accessed November 2014 at http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp

Walters, M.,& Roe, F. J. C. (1965). A study of the effects of zinc and tin administered orally to mice over a prolonged period. Food and cosmetics toxicology, 3, 271-276.

Wilde, C. (1975). Aerosol metallic paints: Deliberate inhalation. A study of inhalation and/or ingestion of copper and zinc particles. Substance Use& Misuse, 10(1), 127-134.

Last update 27 November 2014

Share this page