Zinc chloride (ZnCl2): Human health tier II assessment

27 November 2014

CAS Number: 7646-85-7

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.

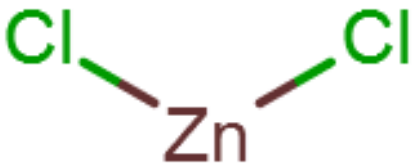
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Zinc dichloride
Structural Formula	
Molecular Formula	Cl2Zn
Molecular Weight (g/mol)	136.3

Appearance and Odour (where available)	Odourless, white crystaline solid
SMILES	Cl[Zn]Cl

Import, Manufacture and Use

Australian

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was between 100 and 1000 tonnes.

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

The chemical has reported commercial uses including:

- in fluxes (soldering and welding);
- as a mordant in printing and dyeing textiles;
- in mercerising cotton;
- in sizing and weighting fabrics; and
- in carbonising woollen goods.

The chemical has reported site-limited uses including:

- in manufacturing other chemicals;
- as an agent in vulcanising rubber;
- as a tissue fixative in preserving anatomical specimens; and
- in manufacturing parchment paper, artificial silk, activated carbon, cold water glues, magnesia cements and cement for metals.

The chemical also has a reported non-industrial use as an astringent (pharmaceutical).

International

The following international uses have been identified through the 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; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic uses including:

- in oral care and soothing products;
- in hair products; and
- in cosmetic biocides.

The chemical has reported domestic uses including:

- in paints, lacquers and varnishes;
- as a surface treatment; and
- in odour agents.

The chemical has reported commercial uses including in:

- fluxes (soldering and welding);
- corrosion inhibitors;
- absorbents and adsorbents; and
- conductive agents.

The chemical has reported site-limited use including in electroplating agents.

The chemical also has a reported non-industrial use as an astringent (pharmaceutical).

Restrictions

Australian

This chemical is listed in the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP) in Schedules 2 and 6.

Schedule 6: 'except when included in Schedule 2, or in preparations containing 5 per cent or less of zinc chloride' (SUSMP, 2014).

Schedule 2 chemicals are pharmacy medicine. 'These are substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person' (SUSMP, 2014).

Schedule 6 chemicals are labelled with 'Poison'. 'These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label' (SUSMP, 2014).

International

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 preparation is 1 % (as zinc).'

Existing Work Health and Safety Controls

Hazard Classification

The chemical is 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)
- C; R34 (Corrosivity)

Exposure Standards

Australian

The chemical has an exposure standard of 1 mg/m^3 time weighted average (TWA) and 2 mg/m^3 short-term exposure limit (STEL).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (TWA) of 0.5–1 mg/m^3 and 2 mg/m^3 short-term exposure limit (STEL) in different countries such as Canada (Alberta, British Columbia, Quebec), the USA (California, Minnesota, Hawaii, Alaska, Washington), Denmark, Iceland, the United Kingdom and Switzerland.

Health Hazard Information

The human body typically contains 2–3 g of zinc, an essential element for human health (Plum et al., 2010). It is a component of numerous proteins and has a wide array of functions in mammalian metabolic processes. Zinc is also vital for healthy endocrine and exocrine functions. Intoxication through excessive intake of zinc is uncommon, due to tightly controlled zinc homeostasis in humans. Zinc deficiency, caused by malnutrition, ageing and disease represents a far more significant risk to health (Plum et al., 2010).

It is expected that, after ingestion, all zinc compounds (including zinc chloride), once in the stomach, dissociate into the ionic species and it is the zinc cation that is the main determinant of the biological activities of zinc compounds. As a result, studies assessing zinc compounds (other than zinc chloride) will be used in this assessment where appropriate. Given the essential role of chloride anions in normal physiological functions (Hartzell et al., 2005), they are not considered toxicologically relevant.

Toxicokinetics

Absorption

Absorption of zinc from oral exposure 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 excessive zinc intake (EU RAR, 2004).

Numerous dietary factors are likely to influence the gastrointestinal absorption of zinc cations, including the consumption of plant proteins, such as soy and phytate, animal proteins, including casein, as well as the intake of alcohol. Zinc absorption may also be influenced by the endogenous secretion of zinc into the intestinal lumen via the gastrointestinal epithelium, as well as that contained in bile and pancreatic secretions (EPA IRIS, 2005; EU RAR, 2004)

Animal studies have shown that inhalational absorption of zinc may occur 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 (citrate and nitrate) (EU RAR, 2004).

Although no quantitative data on the inhalational absorption of zinc chloride ($ZnCl_2$) exist in humans, elevated concentrations of zinc in the blood and urine of persons occupationally exposed to zinc oxide fumes suggest that, to some extent, pulmonary absorption 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 a dermal absorption of less than 2 % (Hallmans & Liden, 1978).

There are no quantitative data to support 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 are found in bone and muscle (60 % and 30 %, respectively), followed by the prostate, liver and kidney (Wastney et al., 2014). A similar pattern of distribution has been demonstrated in animals.

Metabolism

Zinc does not undergo metabolism 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 is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The available data (median lethal dose—LD50—1,100 mg/kg bw in rats and 1,260 mg/kg bw in mice) support this classification (EU RAR, 2004; REACH).

In studies performed in accordance with the Organisation for Economic and Co-operation and Development (OECD) Test Guideline (TG) 401, zinc chloride had an LD50 of 1,100 mg/kg bw in rats and 1,260 mg/kg bw in mice. Reported signs of toxicity in rats included weakness, pupil constriction, conjunctivitis, erythema, decreased food and water consumption, weight loss and tail haemorrhage. Reported signs of toxicity in mice included conjunctivitis, piloerection, tail haemorrhage, weakness, decreased food/water consumption and weight loss (REACH).

Dermal

No data are available. However, given the similar dermal bioavailability of zinc chloride and zinc sulfate, the following study, carried out in accordance with OECD TG 402 that assessed zinc sulfate heptahydrate, is likely to reflect the nature of dermal acute toxicity of zinc chloride. Based on the study below, acute dermal toxicity of zinc chloride is expected to be low.

The chemical zinc sulfate heptahydrate (CAS No. 7446-20-0) induced low acute toxicity in animals following dermal exposure. The LD50 in Wistar rats was >2000 mg/kg bw. Clinical signs of toxicity consisted of erythema, scales and/or scabs in the treated skin area between observation days 2–8 (EU RAR, 2004; REACH).

Inhalation

The chemical has moderate acute toxicity through inhalation exposure with a median lethal concentration (LC50) of <4095 mg/m^3 zinc chloride for a 10 minute exposure.

A study was conducted in female SD rats to assess the effect of inhalational exposure to zinc chloride on the respiratory system. Animals were exposed to the test material at a concentration of 600, 940, 1,220 and 1950 mg Zn/m^3 (molar ratio of Zn: $ZnCl_2$ is 1:2.1) for 10 minutes. All three animals died at the highest dose tested. The animals exhibited respiratory distress. Pathological examination of the lungs revealed dark red discolouration (consistent with vasodilation and vascular congestion), patchy discolouration, oedema, interstitial emphysema, atelectasis, hyperaemia and haemorrhage. Based on the these results, the acute inhalation LC50 was <1950 mg Zn/m^3 in rats (Karlsson et al., 1986).

Observation in humans

Limited data exist for the acute gastrointestinal toxicity of zinc chloride in humans.

One study detailed a case wherein a 24-year-old male accidentally ingested approximately 90 mL of zinc chloride in solution (unknown concentration), which resulted in local caustic effects including erosive pharyngitis and oesophagitis together with associated 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).

There is also one published report of a woman who died after accidently ingesting 28 g of zinc sulphate. The female developed tachycardia, hyperglycaemia and experienced acute emesis. The woman died five days later of haemorrhagic pancreatitis and renal failure (REACH).

A well-recognised, self-limiting acute illness called ‘metal fume fever’ has also been described following inhalation of metal oxide fumes. Although not specific to zinc alone, instances of zinc oxide-associated ‘metal fume fever’ have been recorded (Gordon and Fine, 1992).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrase 'Causes burns' (C; R34) in HSIS (Safe Work Australia). The available data support this classification.

In skin irritation studies, 0.5 ml of a 1 % $ZnCl_2$ solution was applied to the dorsal skin of mice, rabbits and guinea pigs (in open patch tests) and rabbits (in occlusive patch tests). In the open patch test, 4/4 rabbits and 6/6 mice exhibited severe irritation, 3/8 guinea pigs exhibited moderate irritation and in the occlusive patch, test 4/4 rabbits developed severe irritation. The severe skin effects in the open patch tests were characterised by parakeratosis, hyperkeratosis, inflammatory changes in the epidermis and superficial dermis, as well as acanthosis of the follicular epithelia. In the occlusive patch test, animals developed similar, but more severe effects as well as erythema and ulceration (Lansdown, 1991).

Observation in humans

Limited data exist on the irritation potential of zinc chloride in humans.

One study described instances where concentrated zinc chloride was unintentionally splashed into the eyes of two patients. Corneal oedema developed and some permanent corneal fibrosis resulted. Recovery required 6–28 weeks. Despite medical intervention, one of the patients permanently lost all olfactory function as a result of the chemical entering the nasal passages (Houle & Grant, 1973).

Accidental respiratory exposure to zinc chloride has resulted in human toxicity (EU RAR, 2004). One study reported that inhalational exposure to zinc chloride at a concentration of 4,075 mg/m^3 (duration of exposure not indicated) resulted in dyspnoea, throat pain, bronchial inflammation, cyanosis, secondary bronchopneumonia, pleuritic chest pain, a productive cough, chest pain, nausea, emesis, headache, pulmonary oedema and fibrosis (Johnson & Stonehill, 1961).

Sensitisation

Skin Sensitisation

No data are available on the sensitising potential of zinc chloride in animals. However, data from zinc sulfate heptahydrate (CAS No. 7446-20-0) suggest that zinc chloride is unlikely to be a skin sensitiser.

In a guinea pig maximisation test carried out according to OECD TG 406, 10 female Dunkin Hartley guinea pigs were intradermally injected with a solution containing 0.1 % zinc sulfate heptahydrate (CAS No. 7446-20-0) and then epidermally exposed to a 50 % zinc sulfate solution. Animals were challenged twice: at 21 and 28 days after the epidermal exposure. Non-specific signs of irritation were observed, but zinc sulfate did not induce hypersensitivity under these test conditions (EU RAR, 2004; REACH).

In a modified mouse local lymph node assay (LLNA), three female Balb/c mice were administered 25 µL of a solution containing 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 exposure. The incorporation of labelled tritiated thymidine was determined by comparing the proliferation of cells harvested from test versus control animals. A stimulation index was determined as 1.41 and, under the criteria of this study, the chemical is not considered to be a skin sensitiser (EU RAR, 2004; REACH).

Repeated Dose Toxicity

Oral

Limited data are available on the repeated dose toxicity of zinc chloride. Due to the expected similar bioavailability of soluble zinc compounds in the stomach, data on zinc sulfate will be used to determine the repeated dose toxicity of zinc chloride.

Considering that the no observed effect levels (NOEL) available from 90-day mouse and rat studies were >100 mg/kg bw/d zinc sulfate heptahydrate (CAS No. 7446-20-0), and based on the treatment-related effects reported in various repeated dose toxicity studies, zinc chloride is not considered to cause serious damage to health from repeated oral exposure.

Zinc chloride

In a study not conducted according to OECD test guidelines, Wistar rats were treated orally with zinc chloride at a concentration of 0.12 mg Zn/cm^3 (equivalent to 25 mg $ZnCl_2$/kg bw) in drinking water, daily for 28 days. A significant increase in the percentage of reticulocytes and polychromatophilic erythrocytes, as well as a decrease in haemoglobin levels were noted in peripheral blood (REACH). A dose-dependent effect was not demonstrated in this study as only one dose was tested.

Zinc sulfate heptahydrate

In a study conducted in compliance with OECD TG 408 (repeated dose 90-day oral toxicity study in rodents), imprinting control region (ICR) mice were divided into four groups, each including 12 animals/sex and fed a diet containing zinc sulfate heptahydrate at 0, 300, 3,000 or 30,000 ppm (equivalent to 43/47, 458/479 and 4,927/4,878 mg/kg bw for males/females, respectively) for 13 weeks. Animals in the 30,000 ppm group exhibited retarded growth with low food and water intake, as well as abnormalities in several haematological and biochemical parameters. Histopathological lesions included catarrhal inflammation in the upper intestine, ulceration of the stomach, pancreatic lesions and proliferation of immature erythropoietic cells in the spleen. Under the test conditions, the NOEL was determined to be 3,000 ppm (458 mg/kg/d in male mice; 479 mg/kg/d in female mice) (REACH).

In a study similar to OECD TG 408, 12 Wistar rats per sex were fed a diet containing zinc sulfate heptahydrate at 0, 300, 3,000 or 30,000 ppm for 13 weeks (equivalent to 23/25, 234/243, and 2,514/2,486 mg/kg bw for males/females, respectively). Animals in the 30,000 ppm group exhibited retarded growth along with low food intake, and abnormalities in several haematological parameters and regressive changes of the pancreas. There were no noteworthy clinical signs in either sex in groups treated with the chemical $\leq$3,000 ppm. Under the test conditions, the NOEL of zinc sulfate in rats was determined to be 3000 ppm (roughly equivalent to 234 mg/kg/day in male rats; 243 mg/kg/day in female rats).

Dermal

No data are available on repeated dose toxicity from dermal exposure for zinc chloride or similar compounds.

Inhalation

No data are available on repeated dose toxicity from inhalation exposure for zinc chloride. However, the effects observed in a non guideline repeated dose inhalation study using zinc sulfate (CAS No. 7733-02-0) did not meet the criteria for hazard classification.

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 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 euthanised 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 a geometric standard deviation of 1.8, 1.6 and 1.8 µm for low, medium and high doses respectively. No exposure-related pulmonary or cardiac pathology was noted, nor were there any significant changes in plasma or serum biomarkers. No statistically significant changes in macrophage, neutrophil, eosinophil or lymphocyte numbers were observed 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

The genotoxicity of zinc chloride has been evaluated in numerous in vitro and in vivo experiments. There are also many studies that have assessed other soluble zinc compounds. Given the essential role of zinc in human physiology, it is unlikely to be genotoxic. However, conflicting results have been generated across experimental studies. In the majority of studies, zinc-containing compounds failed to induce genetic alterations (in vitro: Ames and mitotic gene conversion assays) and (in vivo: chromosomal aberration, comet and dominant lethal assays). In some experiments, zinc-containing compounds were found to be capable of inducing genotoxicity (host-mediated, cytogenic assays and unscheduled DNA synthesis (UDS) tests). Two studies on the genotoxicity of zinc chloride are described below.

In vitro

A non-guideline study was performed to investigate the genotoxic potential of zinc chloride on human dental pulp cells (D824 cells). Chromosome aberrations in the cells were assessed when treated with three different doses of zinc chloride (for three or 30 hours). Zinc chloride failed to induce chromosomal alterations (in the presence and absence of an exogenous metabolic activator). The percentages of cells with polyploid or endoreduplication were not enhanced by zinc chloride. Under the test conditions this chemical was shown not to promote genotoxicity in human dental pulp cells in vitro (REACH).

In vivo

An in vivo experiment was conducted to assess whether zinc chloride could induce chromosomal aberrations using mouse bone marrow cells. This study did not comply with OECD test guidelines.

Male C57 black mice were exposed to zinc chloride daily through a standard low-calcium diet for one month. Metaphase bone marrow cells (500 cells) were collected and stained from each animal using lacto-orcein and assessed for chromosomal aberrations. The test material caused severe chromosomal anomalies, particularly in animals kept on a low-calcium diet under the conditions of the test (REACH).

Based on the available data, there is insufficient evidence to classify zinc chloride as genotoxic (ATSDR, 2005). It is noteworthy that further testing may be required to assess the potential of zinc chloride to induce genetic mutations in vivo (EU RAR, 2004).

Other soluble zinc compounds

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, comet and dominant lethal assays) tests for gene mutation and clastogenicity. The weight of evidence indicates that the chemicals are not mutagenic to germ cells (NICNAS).

Carcinogenicity

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

According to the U.S. Environmental Protection Authority (EPA) Guidelines for Carcinogen Risk Assessment (U.S. 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.

Zinc chloride

In a 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 the exposure period. At the lower doses of 1, 1.3 and 12.8 mg zinc/m^3, there was no increase in the incidence of neoplasias (ATSDR, 2005).

Similar dose levels were administered to guinea pigs and rats in separate experients 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 (see NICNAS assessment for hexachloroethane (CAS No. 67-72-1)) limit the usefulness of these studies (ATSDR, 2005).

A study reported that testicular teratomas arose in poultry, birds and rats following repeated intratesticular injection of zinc chloride (Leonard et al., 1986). This study is quite limited in that very few experimental details were provided and the route of exposure is not relevant for risk characterisation.

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 also 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, no pancreatic, pituitary or adrenal tumours were observed (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. 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 conclusion can be drawn about the carcinogenicity of zinc compounds (Logue et al., 1982).

Another study has reported that age and sex-adjusted mortality rates were elevated in a former lead/zinc mining and smelting region in the United States. 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 direct correlations between zinc supplementation and prostate cancer due to unaccounted variables. They suggested the need for further mechanistic studies to explore the link between zinc and prostate carcinogenesis (Leitzmann et al., 2003).

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

Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

Reproductive toxicity

A reproductive toxicity study was carried out with zinc chloride in accordance with OECD TG 416 (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, kidneys and spleen in males; uterus and spleen in females) (F0 and F1) were observed (REACH).

Lesions in the gastrointestinal tract were seen in both male and female rats (F0 and F1) at concentrations of 15 and 30 mg/kg bw/d. 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. 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) for both parental toxicity and reproductive effects is the lowest concentration (7.5 mg/kg bw/d).

Developmental toxicity

The developmental toxicity of zinc chloride in animals has been examined in one non-guideline study. Mice received a single intraperitoneal (IP) injection of 12.5, 20.5 or 25 mg $ZnCl_2$/kg bw on gestation day (GD) 8, 9, 10 or 11. Exposure resulted in a significant dose-related increase in the incidence of skeletal anomalies. Toxic effects on mothers and foetuses were the greatest when $ZnCl_2$ was administered at 20.5 mg/kg bw on GD day 10. Because of a lack of additional information provided in this study, and considering the route of administration is not a relevant exposure route for humans, the results cannot be used in assessing the chemical's risk potential (REACH).

Other soluble zinc compounds

Reproductive and developmental toxicity have 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 developmental toxicity associated with zinc chloride and other 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 in relation to 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 attributable to 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 exist on the neurotoxic effects of zinc chloride in humans. Some information has been garnered from reports detailing the intentional inhalation of metallic paint aerosols. Exposure to zinc compounds resulted in staggered gait and visual hallucinations. These 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 alteration of normal hypothalamic processes in rats (ADSTR, 2005).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (corrosivity). While effects on fertility have been observed at very high doses of soluble zinc chemicals, the levels at which this occurs are unlikely to result from industrial use of the chemicals.

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used in cosmetic products in both 'soothing' and oral care products as well as in cosmetic biocides overseas. However, the use of the chemical in cosmetics is restricted as it is currently listed in Schedule 6 of the SUSMP for preparations with concentrations >5 %. At concentrations greater than 5 %, a number of warning statements, first aid instructions and safety directions apply. The current controls are considered adequate to minimise the risk to public health posed by domestic and cosmetic products containing the chemical, therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, 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 maintaining 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 could 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 HSIS (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 by inhalation (Xn; R20)	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Causes burns (C; R34)*	Causes severe skin burns and eye damage - Cat. 1 (H314)

[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 in accordance with the product label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, occular and inhalation 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 may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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.

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