Lithium chloride: Human health tier II assessment

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Lithium chloride (LiCl)	7447-41-8
Lithium chloride, monohydrate	16712-20-2

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 consist of two inorganic lithium salts—lithium chloride (CAS No. 7447-41-8) and lithium chloride, monohydrate (CAS No. 16712-20-2), which is lithium chloride hydrated with one molecule of water.

Lithium chloride is extremely hygroscopic and readily absorbs water vapour. Anhydrous lithium chloride can be formed by heating the hydrated forms.

Hydrates are taken as being covered by listing of the anhydrous form on the Australian Inventory of Chemical Substances (the Inventory). Other potential hydrated forms of these chemicals not listed on the inventory are also covered by this assessment.

Import, Manufacture and Use

Australian

The chemical, lithium chloride (CAS No 7447-41-8), has reported non industrial use in food safety products, such as ingredients in microbial broths.

No specific Australian use, import, or manufacturing information has been identified for the chemical, lithium chloride, monohydrate (CAS No 16712-20-2).

International

The following international uses have been identified through the European Chemicals Agency (ECHA) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the Organisation for Economic Co-operation and Development (OECD) Existing Chemicals Database; eChemPortal; Galleria Chemica; Health Canada Cosmetic Ingredient Hotlist; New Zealand Inventory of Chemicals (NZIoC); Substances and Preparations in the Nordic countries (SPIN) database;

the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US National Toxicology Program (US NTP); and the US Department of Health and Human Services Household Products Database (US HPD).

Lithium chloride is listed in the INCI dictionary and European Commission database for information on cosmetic substances (CosIng) with no reported function. It is listed in the Compilation of Ingredients Used in Cosmetics in the United States (Personal Care Products Council, 2011), indicating its use in two cosmetic products. It was identified in four bath products in the Environmental Working Group (EWG) Skin Deep Cosmetics Database.

The following domestic uses have been reported for the chemicals in this group in—detergents; automotive care products (motor oils, hydraulic liquids, etc.); fragrances and air fresheners; paints and coatings; adhesives and sealants; and printing inks and toners. There is no evidence from available North American databases (US HPD) for use of this chemical in consumer products, indicating that it is not likely to be widely available for domestic use.

The following commercial uses have been reported in—diagnostics; water treatment; manufacture of paper, batteries, and mineral waters; construction; welding and soldering; air conditioning and refrigeration; photographic industry; and pyrotechnics.

The following site-limited uses have been reported in—manufacture of lithium, production of electronic devices; manufacture of chemicals and chemical products; research and development; and as laboratory chemicals.

Lithium chloride is on the OECD high production volume list, with an estimated manufacture and/or import value of 1000-10,000 tonnes per year in the EU.

Restrictions

Australian

No known restrictions have been identified.

International

No known international restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified for lithium and its soluble inorganic salts (Galleria Chemica):

- an exposure limit of 0.02 mg/m^3 time weighted average (TWA) in different countries such as Russia and Lithuania; and
- a reported MAK value (maximum permissible concentration in the workplace air) of 0.2 mg/m^3 (measured as the inhalable fraction of the aerosol), pregnancy risk group C (International Programme on Chemical Safety (IPCS), 1997).

Health Hazard Information

Limited data are available for some of the systemic toxicological endpoints for the chemicals in this group. Since the systemic toxicity of these chemicals is expected to be similar and driven predominantly by the lithium ion (Li^+), data obtained from studies with other lithium compounds have been read across for the relevant toxicological endpoints for this human health risk assessment.

Toxicokinetics

The chemicals in this group are highly soluble in water, readily dissociating into lithium (Li^+) and chloride (Cl^-) ions. The lithium ion is the primary focus for the toxicokinetic assessment of these chemicals. Since chloride is one of the most physiologically abundant ionic groups in the human body, the relative amount resulting from lithium chloride absorption is not expected to have a significant impact on the toxicokinetic processes.

These chemicals are readily and almost completely absorbed through the gastro-intestinal tract, with peak plasma levels occurring in humans 30–60 minutes after a single oral dose (Nordic Expert Group, 2002; REACH). While lithium is rapidly distributed to the kidneys following absorption, transfer to other organs such as the liver, bone, muscle and brain is slower (HSDB; REACH). Lithium is excreted primarily in the urine and to a much lesser extent in sweat, faeces and saliva (Hanlon et al., 1949; Young, 2009; HSDB; REACH). Urinary clearance of lithium is fast with greater than 50 % and 90 % excreted within 24 and 48 hours, respectively (HSDB; REACH). Lithium readily crosses the placenta and is secreted in breast milk (Nordic Expert Group, 2002; HSDB). Lithium can accumulate in the bone and endocrine glands (thyroid, pituitary, thymus and adrenals), and to a lesser extent in the brain, muscle, liver, colon and kidney (Birch, 1988; Nordic Expert Group, 2002; Pottegard et al., 2016).

The outermost waterproof layer of the skin (stratum corneum) is an effective barrier against water soluble substances (Marieb, 1998). Dermal absorption of these chemicals, therefore, is expected to be minimal and bioavailability from this route of exposure is considered to be negligible. One study reported that there was no significant elevation in serum lithium levels in healthy volunteers (n=53) exposed to lithium chloride during a spa treatment (20 minutes/day, 4 days/weeks for two consecutive weeks) when compared with unexposed controls (Nordic Expert Group, 2002; REACH).

Uptake of lithium through the respiratory passage has been shown to be high (up to 90 %) in humans using respirators containing a lithium chloride coated heat and moisture exchange unit (Nordic Expert Group, 2002). In a study in rats exposed for 3 hours to lithium chloride in aerosol form (from a solution containing 1 % lithium), inhalation uptake was reported to be 17 % (Nordic Expert Group, 2002).

Acute Toxicity

Oral

The chemicals in this group have moderate acute toxicity on oral exposure with a reported median lethal dose (LD50) of 526 mg/kg bw in rat, warranting hazard classification (see **Recommendation** section).

The following oral LD50 values have been reported for lithium chloride from various studies—rat (526, 757 and 1530 mg/kg bw), mouse (1165 mg/kg) and rabbit (750, 800 and 850 mg/kg bw) (Nordic Expert Group, 2002; REACH; RTECS). Reported signs of acute toxicity included vomiting, loss of appetite, dehydration, fall in body temperature, diarrhoea, breathing difficulties, muscular weakness, hyperirritability, stupor and convulsions (HSDB; RTECS).

Dermal

The chemicals in this group have low acute toxicity on dermal exposure with a dermal LD50 greater than 2000 mg/kg bw. Dermal absorption of these highly water soluble chemicals through the outermost layer of the skin is expected to be minimal (see **Toxicokinetics** section).

A guideline study (Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 402) showed that the dermal LD50 for lithium chloride was greater than 2000 mg/kg bw in rats (REACH). No treatment-related adverse effects were observed in the animals throughout the study.

Inhalation

The chemicals in this group have low acute toxicity on inhalation exposure with a median lethal concentration (LC50) greater than 5 mg/L.

In a guideline study (OECD TG 403), the 4-hour LC50 for lithium chloride (delivered as an aerosol for nose-only exposure) was greater than 5.57 mg/L in rats (REACH). There was one animal death. The following treatment-related adverse effects were observed—increased secretions from mouth, eyes and nose, sometimes bloody or pigmented; decreased mobility; shortness of breath; and squinting eyes. The effects were all reversed within 3–10 days.

Observation in humans

Mortality due to acute overdose of lithium, mainly seen as a result of accidental or deliberate ingestion of lithium medication, is rare if recognised quickly and treated aggressively (Friedberg et al., 1991; Birch, 1999; HSDB; NICNAS). A probable oral lethal dose of 0.5–5 g/70 kg bw has been reported in humans (HSDB).

Lithium overdose can be life-threatening in people predisposed to decreased levels of sodium (Na^+) in their bodies (e.g. dehydration, reduced salt intake, etc.) (McKnight et al., 2012; HSDB). Several cases of acute lithium poisoning leading to respiratory, neuro-muscular and cardiac complications, coma, and death were reported in the 1940s when lithium chloride was marketed as a dietary substitute for sodium chloride (table salt) for cardiac patients, and consequently withdrawn (Hanlon et al., 1949; Radomski et al., 1950). Retrospective studies have shown that variations in sodium regulation in the kidney have a significant impact on the excretion of lithium, with increased resorption of sodium in the kidneys reducing the rate of urinary clearance of lithium (Radomski et al., 1950; Nordic Expert Group, 2002; HSDB).

Acute-chronic lithium toxicity is mainly seen during medical treatment with lithium (see **Repeated dose toxicity: Observation in humans** section).

Corrosion / Irritation

Respiratory Irritation

Respiratory irritation effects were not observed in a study in rabbits repeatedly exposed to aerosols of lithium chloride (see **Repeated Dose Toxicity: Inhalation** section).

Skin Irritation

Based on available data, the chemicals in this group may be slightly irritating to skin but the reported effects do not warrant hazard classification.

In a dermal irritation study conducted similarly to OECD TG 404, lithium chloride anhydrous was not irritating to intact rabbit skin when applied as a neat substance (REACH). All 3 test animals showed mild to moderate redness (erythema) (scores 1.3, 3.3, 0.7), and slight swelling (oedema) (no scores available) immediately after treatment. These effects were reversed within 72 hours in 2 animals, while the third developed a scab on the test site, which persisted to day 14.

In an older standard Draize test, lithium chloride (CAS No. 7447-41-8) was reported to cause severe irritation in rabbits when applied topically as a neat substance (0.5 g) for 24 hours (RTECS). No data was available on whether the skin was intact or abraded.

Eye Irritation

Based on available data, the chemicals in this group are irritating to eyes. The effects observed in the conjunctivae are sufficient to warrant hazard classification (see **Recommendation** section). Due to only two animals being tested with unrinsed eyes and differences in the reversibility of the effects in these animals, data are not sufficient to conclusively sub-categorise for eye irritation. In these circumstances, the general principle is that the most severe of the eye irritation sub-categories should apply.

In an acute eye irritation study conducted similarly to OECD TG 405, lithium chloride anhydrous was irritating to rabbit eyes when applied as a neat substance (REACH). Of the four animals tested, the eyes of two were rinsed with tap water 20-30 seconds after treatment, while the eyes of the other two were left unrinsed. Slight to mild corneal opacity (scores 0.7, 2, 0, 2), moderate to severe conjunctival redness (scores 2, 3, 2, 2), swelling/chemosis (scores 1.3, 1.7, 1, 2.3), and iritis (only at 24 hours post-treatment) were seen in all treated eyes. One of the unrinsed eyes also showed white, brown and haemorrhagic areas on the conjunctivae. All these effects were fully reversed by day 7 in both rinsed eyes and one of the unrinsed eyes, and by day 14 for the other unrinsed eye.

In a standard Draize test, lithium chloride (CAS No. 7447-41-8) was reported to cause moderate irritation in rabbit eyes when applied as a neat substance (100 mg) unrinsed (RTECS). No other study data was available.

Sensitisation

Skin Sensitisation

Based on available data, the chemicals in this group are not expected to induce skin sensitisation.

In a Buehler test conducted similarly to OECD TG 406 (n=10 treatment group + 10 control), a solution of lithium chloride used for both topical induction and challenge did not produce a dermal response in guinea pigs (REACH).

Repeated Dose Toxicity

Oral

Available animal data and clinical observations (see **Observation in humans** section) indicate that the chemicals in this group can cause neurological dysfunction on repeated oral exposure. Whilst effects in animals were observed at higher doses, the positive human data warrants hazard classification (see **Recommendation** section). Prolonged or repeated oral exposure to lithium in humans is also associated with renal toxicity.

In a repeated oral dose toxicity study, the no observed adverse effect level (NOAEL) for lithium was determined to be 13.9 mg/kg bw/day in albino Wistar rats (REACH). In this 2-year study, the animals (both sexes) were given lithium chloride in drinking water at concentrations of 20 mmol/L and 50 mmol/L. Except for slight and transitory initial disturbances, no adverse behavioural or health effects were seen in the 20 mmol/L group. The plasma lithium levels in this group were 1.5 to 2 mmol. In the 50 mmol/L group, the food and water intake was reduced within a few days of dosing. This was followed by progressive drowsiness and asocial behaviour from days 3–5, difficulty in rousing, staggered/hesitant gait when roused, and fine muscular tremor when resting. The weight of the animals dropped steadily and health rapidly deteriorated to stupor and death within 2–3

weeks. The corresponding plasma lithium levels were 3 mmol (behavioural changes) to 8 mmol (death). Based on the results, the worst case NOAEL was determined to be at plasma lithium level of 2 mmol (i.e., approximate lithium dose of 13.9 mg/kg bw/day, based on the animals' daily water intake of 10–12 g/0.1 kg bw). This NOAEL is equivalent to 85 mg/kg bw/day lithium chloride anhydrous and 120 mg/kg bw/day lithium chloride monohydrate.

Dermal

No data are available. However, dermal absorption of these highly water soluble chemicals through the outermost layer of the skin is expected to be minimal (see **Toxicokinetics** section).

Inhalation

In a non-guideline repeated dose inhalation study, rabbits were exposed to aerosols of lithium chloride containing 0.6 and 1.9 mg Li/m^3 (mass median aerodynamic diameter 1 µm), for 4–8 weeks, 5 days/week, 6 hours/day. There were no significant irritation effects observed or significant changes in the oxidative metabolic activity in the macrophages or in the content of phospholipids in lung tissue (Nordic Expert Group, 2002). It is not clear from the study if systemic effects were examined.

Observation in humans

Occupational lithium poisoning is rare despite the widespread use of lithium and its compounds (HSDB).

Acute-chronic lithium toxicity is mainly seen during medical treatment with lithium. Lithium has a narrow therapeutic index, between serum concentrations of 0.6 and 1.2 mmol/L, achieved with the current oral dosage regime of 500–1200 mg/day (approximating to 7–17 mg/kg bw/day, in 70 kg adult) (Timmer and Sands, 1999; Young, 2009; HSDB). In general, lithium toxicity increases with serum lithium concentration: it is mild at 1.5–2.0 mmol/L; moderate at 2.0-2.5 mmol/L; and severe and life-threatening over 2.5 mmol/L (Timmer and Sands, 1999; HSDB). Even within the therapeutic range, mild and sometimes transient signs of toxicity such as fine hand tremor, lethargy, irritability, increased thirst, polyuria, nausea and dry mouth are seen (Birch, 1988; HSDB). Moderate toxicity is associated with confusion, disorientation, drowsiness, restlessness, slurred speech, unsteady gait, tremors, and cardiac irregularities (Timmer and Sands, 1999; HSDB). Severe toxicity is associated with seizures, neurological impairment (sometimes permanent), renal insufficiency, coma, and if not treated, death (Apte and Langston, 1983; Timmer and Sands, 1999; HSDB). Drug-interactions, co-existing illnesses, and altered potassium and sodium levels in the body increase lithium toxicity (Timmer and Sands, 1999).

Long-term or prolonged use of lithium is associated with increased risk of hypothyroidism, hyperparathyroidism, reduced urinary concentrating ability, increased white blood cell count, and weight gain (Birch, 1999; Timmer and Sands, 1999; McKnight et al., 2012).

Genotoxicity

Based on weight of evidence from available data, the chemicals in this group are not expected to be genotoxic.

In vitro data

Lithium chloride (CAS No. 7447-41-8) was not mutagenic in the following (Haworth et al., 1983; Leonard et al., 1995; HSDBa):

- *Salmonella typhimurium* TA1535, TA1537, TA98, and TA100 (Ames test) with or without metabolic activation; and
- *Bacillus subtilis* strains H17 and M45 *(rec-assay)* without metabolic activation.

Positive results were reported in an in vitro mammalian chromosome aberration test in human lymphocytes and a HeLa DNA synthesis inhibition test in vitro (Nordic Expert Group, 2002).

Data on various lithium salts (carbonate, citrate, hydroxide and hypochlorite) showed that lithium was not mutagenic in a variety of test systems (Leonard et al., 1995; Weiner et al., 1990; Young, 2009; NICNAS; REACH), which included:

- bacteria (*Escherichia coli; S. typhimurium*) (various reverse mutation assays);
- mouse lymphoma cells (in vitro mammalian cell mutagenicity assay);
- rat primary hepatocytes (unscheduled DNA synthesis (UDS) assay); and
- the sex-linked recessive lethality test in *Drosophila melanogaster.*

Considering the chemical properties of lithium compounds, the Nordic Expert Group stated that lithium compounds were unlikely to act as direct mutagens (Nordic Expert Group, 2002; REACH). There were some reports of positive genotoxic effects for various lithium compounds, but only at high doses (equivalent to therapeutic doses or higher) (Nordic Expert Group, 2002). A possible explanation for the apparent genotoxicity of lithium may be the secondary effect of increased cell survival resulting from the chemical inhibition of the enzyme, glycogen synthase kinase (GSK) (Nordic Expert Group, 2002) (see **Carcinogenicity** section).

In vivo data

While chromosomal aberrations have been reported in the bone marrow cells of mice dosed with lithium compounds (acetate, carbonate, chloride and citrate), clinical data show that lithium treatment did not induce any chromosomal changes in humans (Leonard et al., 1995; Nordic Expert Group, 2002; HSDBa). Data from several clinical studies in patients undergoing lithium treatment (with lithium carbonate, lithium sulfate or lithium acetate) showed no significant increases in frequency/number of chromosomal aberrations or lesions, or sister chromatid exchanges in the patients' peripheral blood cells (lymphocytes) when compared to the control population (Leonard et al., 1995; Young, 2009; HSDB; NICNAS).

Carcinogenicity

While animal data is limited, extensive clinical experience with long-term use of lithium suggests that the cancer risk from the chemicals in this group is low.

Although lithium has been used for decades in medicine, none of the clinical trials to date reported significant positive correlation between long-term use of lithium and cancer.

A review of clinical trials in 1984 showed no association between lithium treatment and thyroid cancer, despite the thyroid concentrating lithium to a large degree in the body (Young, 2009). A more recent nationwide case-control study in Denmark found that long-term use (5 or more years) of lithium was not associated with an overall increased risk of colorectal adenocarcinoma (Pottegard et al., 2016).

In one study investigating the carcinogenic risk of lithium, mice predisposed to the formation of tumours, were treated with lithium for 60 days (Young, 2009; Pottegard et al., 2016). The treatment did not produce a significant increase in the number of tumours and only modestly increased the size of tumours.

Other factors which may have a bearing on the carcinogenic potential of lithium are:

- lithium stimulates proliferation of stem cells, including bone marrow and neural stem cells in humans (Birch, 1999; Young, 2009);
- lithium has been shown to stimulate the release of tumour necrosis factor (TNF) in macrophages (Birch, 1999); and
- lithium has been shown to inhibit an enzyme called GSK-3 beta (GSK-3b) in humans, which appears to have tumour suppressing effects in some cancers and tumour stimulating effects in some others (Young, 2009; Pottegard et al., 2016).

Reproductive and Developmental Toxicity

Lithium treatment has been associated with effects on foetal development and male fertility. However, based on available animal data and clinical observations, it is not possible to draw a definitive conclusion. Overall, the risk is considered low at therapeutic

doses.

The following clinical data from patients undergoing lithium treatment are available.

Lithium readily crosses the placenta and can potentially effect foetal development. The US Food and Drug Administration (FDA) states that lithium may cause foetal harm when administered to pregnant women and classifies it as pregnancy category D (HSDB; US FDA). There is clinical evidence of increased risk of cardiac and other malformations, in particular Ebstein's anomaly, in children born to mothers who received lithium treatment during early pregnancy (Leonard et al., 1995; Young, 2009; McKnight et al., 2012; HSDB; NICNAS). Cases of neurological, cardiac, and hepatic abnormalities similar to those seen with lithium toxicity in adults have been observed in newborns exposed to lithium in the womb during late pregnancy (US FDAa). However, several other studies have concluded that lithium at therapeutic levels was not teratogenic (Leonard et al., 1995; NICNAS). Data from birth registries and various large-scale, multi-centre studies of pregnancy outcomes in women undergoing lithium treatment during first trimester or entire term of pregnancy, did not show a significant teratogenic risk (Leonard et al., 1995; REACH). There is also conflicting evidence of association between lithium exposure and increased incidences of miscarriages and pre-term deliveries (HSDB). The inconsistencies in clinical observations may be due to individual genetic predispositions, sensitivities and metabolism, or differences in the bioavailability of lithium at critical times during pregnancy (Leonard et al., 1995). Furthermore, given the narrow therapeutic range of lithium, any developmental toxicity seen may also be a direct result of maternal toxicity. Considering these factors, in general, pregnant women receiving lithium treatment are required to be carefully monitored.

A relatively recent in vitro study with human sperm reported that lithium decreased sperm motility at semen concentrations comparable to those seen in patients undergoing lithium treatment (Nordic Expert Group, 2002). However, there is no clinical evidence of lithium treatment significantly affecting male fertility.

The following animal data are available for reproductive toxicity.

In a 2-generation reproduction toxicity study (OECD TG 416), lithium carbonate did not affect reproductive capacity of Wistar rats dosed at 0, 5, 15 or 45 mg/kg bw/day (REACH). Significant signs of systemic toxicity, which included body weight gain, increased water consumption, morphological changes in liver and kidneys, and adrenals and thyroid (in some animals), were seen at 15 mg/kg bw/day in the parental generation (P0) but not in the first or second generations (F1 and F2). None of the reproductive parameters were effected in the P0, F1 or F2. While the NOAEL for systemic toxicity in parental rats (P0) was 15 mg/kg bw/day, the study concluded a reproductive and foetal NOAEL of 45 mg/kg bw/day.

In a poorly described study, mice exposed to lithium chloride (50 mmol/L) in drinking water, 2–5 weeks before mating and during lactation had fewer, more spaced out litters when compared to controls (Nordic Expert Group, 2002). The animals’ plasma lithium level was around 0.7 mmol. Higher mortality rate, and delayed postnatal growth and development were seen in the pups of the test mice. Mice given drinking water containing lithium chloride at 100 mmol/L did not reproduce at all. No data was available on the toxic effects of the chemical at either concentration.

Significant inhibition of spermatogenesis was reported in a study in immature rats following a 15-day treatment with daily subcutaneous injections of 2 mg/kg bw lithium chloride (Nordic Expert Group, 2002). The study concluded that lithium adversely affected testicular function by reducing serum levels of follicle stimulating hormone, luteinising hormone, prolactin and testosterone.

The following animal data are available for developmental toxicity.

In 2-generation reproduction toxicity study (described above), lithium carbonate did not cause developmental effects in either generation. There were no external abnormalities in the pups (REACH).

In a prenatal developmental toxicity study (OECD TG 414), lithium carbonate was not teratogenic in Crl: CD(SD) rats dosed at 0, 10, 30 or 90 mg/kg bw/day from gestation days 5–19 (REACH). Treatment-related effects were observed in the pregnant females dosed at 90 mg/kg bw/day, including piloerection, and slight but significant net weight change and decreased food intake. No signs of developmental toxicity were observed at any dose. The study concluded a maternal NOAEL of 30 mg/kg bw/day and a developmental NOAEL greater than or equal to 90 mg/kg bw/day.

A teratogenicity study examining the effect of prolonged subtoxic lithium ingestion (lithium chloride) on pregnancy was conducted in a group of 52 test and 100 controls rats (albino Wistar). The animals were administered the chemical in a concentration of 20 mmol/L in drinking water, which produced plasma lithium levels of 1.5–2.0 mmol/L. There were no differences in pup size and weight. No malformations or other defects were observed in the lithium exposed litters. The young

that were maintained at the same lithium concentration in the drinking water showed slightly lower growth, but developed into adult rats indistinguishable from normal rats (HSDBa).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation for the chemicals in this group include systemic acute toxicity from oral exposure and eye irritation.

While there may be long-term systemic toxicity and possible developmental (foetal) and reproductive (male) toxicity, they are not likely to be relevant for non-clinical uses of these chemicals.

Public Risk Characterisation

Although Australian cosmetic use information is not available for the chemicals in this group, they are reported to have limited cosmetic use in the US (see **Import, manufacture and use** section). They are reported to be used in two products in the US, most likely bath salts (EWG; US HPD). Considering the minimal dermal absorption of these chemicals and the limited use in cosmetic products, the public risk from these chemicals is not considered to be unreasonable.

While Australian domestic use information is not available for these chemicals, the available North American database does not give evidence for a widespread use in consumer products (US HPD). Considering the limited use of these chemicals in domestic products, the public risk from these chemicals is not considered to be unreasonable.

While lithium occurs naturally in the environment, it is at such low concentrations that exposure through ingesting food and drinking water is not expected to present a risk to public health. The lithium concentrations in serum from non-patient populations are approximately 1000 times lower than the concentrations found in patients taking medicines containing lithium (SCOEL, 2010).

Overall, risk to public health is not considered unreasonable and further risk management is not required.

Occupational Risk Characterisation

During product formulation, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise ocular and inhalation exposure are implemented. Good hygiene practices to minimise oral exposure are expected to be in place. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

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

While there may be long-term systemic toxicity and possible developmental (foetal) and reproductive (male) toxicity, the available data on serum values of workers exposed to lithium indicate very low serum levels of lithium. Therefore, systemic adverse effects due to lithium are unlikely to occur from occupational exposure to lithium and lithium compounds (SCOEL, 2010).

NICNAS Recommendation

Assessment of these 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

Public Health

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319)
Repeat Dose Toxicity	Not Applicable	Causes damage to nervous system through prolonged or repeated exposure - Cat. 1 (H372)

[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

Advice for industry

Control measures

Control measures to minimise the risk from ocular and inhalation exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;

- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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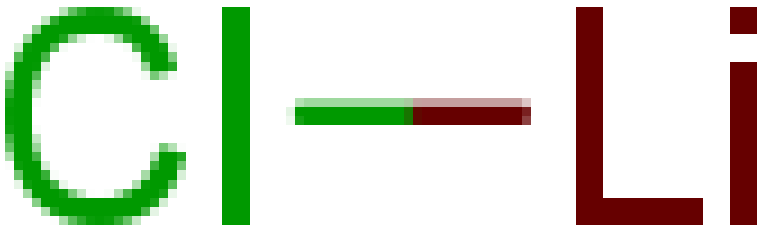
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Lithium chloride (LiCl)** lithium chloride, anhydrous
CAS Number	7447-41-8
Structural Formula	
Molecular Formula	ClLi

Molecular Weight	42.39

Chemical Name in the Inventory and Synonyms	**Lithium chloride, monohydrate** lithium(1+) ion hydrate chloride
CAS Number	16712-20-2
Structural Formula	
Molecular Formula	ClLi.H2O
Molecular Weight	60.41

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