Frontier article

Toxicity of lithium to humans and the environment—A literature review

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A B S T R A C T

Lithium concentrations in the surface and underground waters may be higher than general environment in places where lithium-rich brines and minerals occur, and in places where lithium batteries are disposed of. This review has indicated that lithium is not expected to bioaccumulate and its human and environmental toxicity are low. Lithium is not a dietary mineral for plants but it does stimulate plant growth. Large doses of lithium (up to 10 mg/L in serum) are given to patients with bipolar disorder. At 10 mg/L of blood, a person is mildly lithium poisoned. At 15 mg/L they experience confusion and speech impairment, and at 20 mg/L Li there is a risk of death. A provisional recommended daily intake of 14.3 μg/kg body weight lithium for an adult has been suggested.

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1. Introduction

Lithium is present in the earth’s crust to the extent of about 0.006 wt% (Habashi, 1997). It is the 27th most abundant element in nature. The major lithium minerals with commercial value are classified into three major groups:

(a) silicates (spodumene—LiAlSi₂O₆, petalite—LiAlSi₄O₁₀)
(b) micas [lepidolite—K[Li,Al][Al,Si]₄O₁₀][F,OH]₂, zinnwaldite—K[Li,Al₃][Al, Si]₄O₁₀][F,OH]₂
(203) and (c) phosphates (mainly amblygonite—[Li, Na][Al]F, OH]PO₄).

Lithium minerals are mined around the world in various places such as Manona—Zaire, Bikita—Zimbabwe, Greenbushes—Western Australia, La Corne and Bernic Lake—Canada, Kola Peninsula—Russia and Altai Mountains—China to make various lithium mineral products (Moore, 2007). The processing of lithium-containing minerals in general comprises crushing, wet grinding in a ball mill, sizing, flotation using fatty acid containing minerals in general comprises crushing, wet grinding in a ball mill, sizing, gravity concentration and flotation using fatty acid (oleic acid) as the collector. Tailings are discharged to storage areas, and the decanted water is usually recovered for reuse.

The major lithium mineral in the ore is spodumene, which is considered insoluble in water and dilute acids. However, a recent unpublished work (Aral, 2007) has indicated that small amount of dissolution may be occurring during processing of the ore especially in the grinding stage with some additional dissolution in the dilute (0.01 M) sulphuric acid treatment of the concentrate. The dissolved lithium found in the tailing dams of such lithium mineral beneficiation plants could be as high as 13 mg/L.

Lithium is also found in natural brines (Salar de Atacama—Chile, Salar de Hombre Muerto and Salar de Rincon—Argentina, and Searle’s Lake and Clayton Valley in the USA) and lakes (Great Salt Lake, USA; Zabuye Lake, Tibet; Dachaidan, Qinghai—China and Dead Sea, Israel) (Habashi, 1997). The lithium content of these brines varies from 20 mg/L in the Dead Sea to 1500 mg/L in Salar de Atacama (Habashi, 1997; Moore, 2007). Geochemically, lithium is a highly mobile element, therefore, the environmental and occupational health and safety risks related to lithium in brines are higher.

A source of lithium posing impact to the environment is spent lithium batteries. Consumers routinely dispose of batteries along with other garbage in the municipal solid waste (NEMA, 2001).

There is growing community concern about the health and safety of workers and the impact on the environment coupled with increasing company reporting and accountability. In the area of lithium toxicity to humans and the environment, the information is scattered across various scientific disciplines. The objective of this study is to prepare a compilation and critically review the leading international health, safety and environmental journals, toxicological databases and websites to ascertain the impacts of lithium on flora, fauna and humans. This literature search covered the relevant sites of the ISI Web of Science (that indexed more than 5700 major journals across 164 scientific disciplines) and key databases including Agency for Toxic Substances and Disease Registry (ASTDR), Australian Safety and Compensation Council (ASCC), Centers for Disease Control and Prevention (CDC), ECOTOX, MEDLINE and TOXLINE.

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2. Environmental and toxicological impacts of lithium

2.1. Toxicology

The Australia Inventory of Chemical Substances (AICS, 2007) has classified metallic lithium as a health, physiochemical and/or ecotoxicological hazard according to the National Occupational Health and Safety Commission (NOHSC) approved criteria for classifying hazardous substances. Lithium, lithium aluminium hydride, and lithium methanolate are found on the Danish list of dangerous substances (Kjelholt et al., 2003), therefore, lithium is used therapeutically on physical tolerance differs between individuals. The primary target poisoned, at 15 mg/L they experience confusion and speech intake level. At 10 mg/L of blood, a person is mildly lithium weight. In humans, 5 g of LiCl can result in fatal poisoning. Lithium dose of LiCl in rats has been measured at 526–840 mg/kg body Chemically, lithium resembles sodium but is more toxic. A lethal appears to be an essential element for life (Le´onard et al., 1995; contains up to 8.0 wt% Li2O, and this lithium is tightly bound to the crystal structure and, therefore, it alone does not pose a toxicological problem. However, when spodumene is crushed, it generates silica-rich dust which is a health and safety hazard. Finely ground lithium minerals, especially lithium-containing phosphate ores, are more susceptible to water and dilute acid leaching than unground ores due to increased surface area (Aral, 2007).

Upon oral intake, metallic lithium is mildly toxic, however, physical tolerance differs between individuals. The primary target organ for lithium toxicity is the central nervous system (Kjelholt et al., 2003); therefore, lithium is used therapeutically on membrane transport proteins when treating manic depression. Chemo- logically, lithium resembles sodium but is more toxic. A lethal dose of LiCl in rats has been measured at 526–840 mg/kg body weight. In humans, 5 g of LiCl can result in fatal poisoning. Lithium carbonate is applied in psychiatry in doses close to the maximum intake level. At 10 mg/L of blood, a person is mildly lithium poisoned, at 15 mg/L they experience confusion and speech impairment, and at 20 mg/L Li there is a risk of death. In therapeutic doses, damages on the central nervous system and the kidneys have been reported.

Lithium does not have a known biological use and does not appear to be an essential element for life (Léonard et al., 1995; Lenntech, 2007). The amount of lithium in the human body is approximately 7 mg. Lithium is absorbed from the gastrointestinal tract (Casaret and Doull, 1987; Ellenhorn and Barceloux, 1988; Linakis, 2007; Schrauzer, 2002) and excreted primarily through the kidneys after approximately 24 h (Freeman and Freeman, 2006). Serum concentrations of lithium reach a peak about 30 min after oral ingestion, followed by a plateau at 12–24 h. Lithium ions cross the cell membrane slowly; this may account not only for the prolonged excretion of lithium but also for the 6–10 days delay needed to achieve the full therapeutic response in humans. Although lithium is not an essential element, it may influence metabolism.

According to Schrauzer (2002), the average daily lithium intake of a 70 kg adult (American) is between 0.65 and 3.1 mg/day. Major dietary sources of lithium are grains and vegetables (0.5–3.4 mg Li/kg food), dairy products (0.50 mg Li/kg food) and meat (0.012 mg Li/kg food) (Weiner, 1991). In places like Chile where lithium-rich salinas could contain up to 1500 mg/L Li, the total lithium ions cross the cell membrane slowly; this may account not only for the prolonged excretion of lithium but also for the 6–10 days delay needed to achieve the full therapeutic response in humans. Although lithium is not an essential element, it may influence metabolism.

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maintenance lithium therapy for bipolar disorder become toxic at some point during their course of therapy (Amidsen, 1988). In 1996, 5,102 lithium exposures were reported to the American Association of Poison Control Centers with nearly 75% of those suffering exposure seeking medical attention (Litovitz et al., 1997).

The mechanisms by which lithium could bring about changes in mood are still poorly understood. Among others, it has been suggested (Manji and Lenox, 1994) that it may affect transcriptional and post-transcriptional factors via protein kinase. It has been suggested (Schrauzer and Shrestha, 1990) that countries where the drinking water contains little or no lithium have a higher rate of crimes, suicides and police arrests for drug addiction than countries where lithium levels in drinking water are 0.07–0.17 mg/L. Several suicide attempts using lithium carbonate have also been reported (Czeizel, 1994).

Gastrointestinal disturbances, oedema and tremor are common side effects of lithium treatment (Tandon et al., 1998). The preliminary study of Kato et al. (1996) showed that the hand tremor may be a potential indicator of overdose for the therapeutic bipolar disorder treatment.

Lithium salts induce renal toxicological symptoms (sclerotic glomeruli and tubular damage) (Chmielnicka and Nasiadek, 2003). The inability of the nephron to concentrate urine during lithium treatment is correlated to the occurrence of histological change. Lithium also produces many metabolic changes. In terms of mineral metabolism, lithium competes with sodium, potassium, magnesium, and calcium, in that order, and displaces them from intracellular and bone sites in this progression. Interaction of toxic metals and essential elements in the kidneys has been demonstrated in biological and toxic aspects. Sadosty et al. (1999) reported that following ingestion, serum concentrations of lithium peaked at 1–12 h. Lithium is not protein bound, and after ingestion it slowly equilibrates between the extracellular and intracellular spaces. The delay in equilibration between serum lithium concentrations and intracellular lithium concentrations approximated 6–10 days. In the study by Chmielnicka and Nasiadek (2003), the authors determined the dose-dependent lithium concentrations in serum and urine and also an estimation of some biochemical indicators of nephrotoxicity detectable at an earlier stage. Rats were orally given lithium carbonate, 10 mg Li/kg (group I) and 20 mg Li/kg (group II), five times a week during 5 weeks. Control rats were treated with 0.9% NaCl (group III) during the same period. During the experiment the lithium concentration in serum and urine of rats was dependent on the daily administration doses in comparison with the control group. After the first week of intragastric exposure to lithium carbonate in daily doses of 10 mg Li/kg body weight rats, a notable increase of copper concentration in urine was observed. At the same time higher activity of N-acetyl-β-glucosaminidase (NAG) in the urine of rats was also observed in comparison with the control group. Increased urinary concentration of proteins was noted also after the first week but after daily administered 20 mg Li/kg.

The results of Chmielnicka and Nasiadek’s investigations showed that oral administration of lithium carbonate-induced renal toxicity in the rat as well as the injurious symptoms which were found to be directly related to the dose effect and to the concentration of this metal in serum and urine. Excretion of lithium is predominantly by the kidney and approximately 80% of lithium is reabsorbed by the proximal renal tubule and 20% is excreted in the urine. Concentrations of lithium in the brain are similar to those found in the plasma. The authors observed disturbances in the kidney function in rats after lithium intoxication and also as a diuresis and proteinuric effect. The renal elimination of lithium influences several factors, including sodium and water balance. It is known that lithium competes with sodium and potassium at the renal tubular level, therefore, sodium and water balance causes not only the serum level of lithium but also its toxicity. The most important in lithium toxicity is dehydration which will produce sodium and water imbalance.

In a study by Tandon et al. (1998) lithium carbonate was administered at a dose level of 1.1 g/kg food to rats fed normal protein (18%), low-protein (8%) and high-protein (30%) diets for a period of 1 month. A highly significant (53%) increase in the level of lipid peroxidation was observed in protein-deficient rats but this increase was marginal in rats fed a high-protein diet. Terao et al. (2006) showed that a potentially beneficial effect of lithium is that it may block the accumulation of amyloid-β (Aβ) peptides that cause dementia in mice.

2.1.1. Genetic toxicity

Léonard et al. (1995) reviewed the information available in the literature on the genetic toxicity of lithium. Lithium causes disturbances in the development of invertebrates. Development is also inhibited in whole rat embryos cultured from day 9.5 (Klug et al., 1992). In intact animals, results vary: several types of abnormalities (e.g. reduced number and weight of the litter, more resorptions, ‘wavy’ ribs, incomplete ossification) were observed (see for example the review by Domingo, 1994). These discrepancies may be due to a different sensitivity of the species and strains used the stress of daily injection and/or differences in lithium concentrations present in serum during critical periods of development. Pregnant mice given lithium carbonate over several days yielding serum levels comparable to those in humans treated for manic-depressive disorders did not show any effect, but six times higher doses caused malformations in the offspring (Smithberg and Dixit, 1982).

2.1.2. Teratogenicity

Teratogenicity is the ability to cause defects in a developing foetus. It is a potential side effect of many drugs such as thalidomide. In a study of the effect of lithium carbonate on pregnant mice (Smithberg and Dixit, 1982), chronic exposure to lithium doses that produced serum levels of the same order as seen in patients was toxic but did not affect the entire litter nor was it teratogenic to individual mice embryos. Many authors have reported that lithium causes congenital defects, especially of the cardiovascular system such as Ebstein’s anomaly (a rare cardiac defect) when given to women during the first trimester of pregnancy (reviewed in Briggs et al., 1983; Birch, 1988; Ferner and Smith, 1991, 1992). This claim gave rise to the foundation of a ‘Register of Lithium Babies’ in Risskov (Denmark) and, later, of an ‘American Registry of Lithium Babies’ in San Francisco. A first analysis of the records of 60 children borne by mothers who received lithium treatment during the first trimester or the entire pregnancy published in 1971 (Schou and Amidsen, 1971) did not reveal any association of lithium treatment with a higher teratogenic risk. A multi-center study of pregnancy outcome after therapeutic lithium exposure during the first trimester also did not show any significant teratogenic risk (Jacobson et al., 1992). Others (Kallen and Tandberg, 1983; Kallen, 1988; Zalstein et al., 1990) also conclude that lithium given in therapeutic doses is not teratogenic.

Giles and Bannigan (1997) evaluated the maternal toxicity and teratogenicity of lithium following intrauterine injection with 300 mg/kg body weight lithium carbonate (Li2CO3) in pregnant CD-1 mice at the developmental stage of neurulation. Controls were untreated or given equimolar amounts of NaCl or Na2CO3. Their pharmacokinetic study showed that lithium was rapidly absorbed from the peritoneal cavity after the above-stated dose,
achieved peak serum levels of ~68 mg/L within 1 h, had a half-life in the blood of 5 h and was completely cleared by 16–24 h after injection. Doses of Li$_2$CO$_3$ >300 mg/kg body weight were toxic to adult CD-1 mice. At 3 h after treatment, cell death became evident in the neuroepithelium. These experiments suggest that the developing vascular system may be a target for lithium. In addition, the possibility is discussed that lithium-induced cell death in the neuroepithelium may lead to neural tube defects.

2.1.3. Mutagenicity

Mutagenicity is the ability to cause genetic mutations in sperms, eggs other cells. Despite the extensive therapeutic use of lithium carbonate, few investigations on the mutagenic potential of lithium compounds have been carried out. Lithium could have several ways of acting on DNA: Li binds selectively to DNA of lithium compounds have been carried out. Lithium could have lithium carbonate, few investigations on the mutagenic potential by King et al. (1979) with trilithium citrate (C$_6$H$_5$Li$_3$O$_7$) in the Ames test on Salmonella typhimurium (34 µmol per test plate), in the Escherichia coli test (10 µmol per test plate), in the host-mediated assay with E. coli and in mice (~28 mg/kg intraperitoneal), and in the sex-linked recessive lethality test in Drosophila melanogaster (3 days feeding with ~140 mg/L). High concentrations of LiCO$_3$ (3 mg/mL) slightly inhibited DNA synthesis in V79 Chinese hamster cells and human EUE fibroblasts, and this effect was lessened by the addition of S9 fraction (a post-mitochondrial), and in the sex-linked recessive lethality test in Drosophila melanogaster (3 days feeding with ~140 mg/L). High concentrations of LiCO$_3$ (3 mg/mL) slightly inhibited DNA synthesis in V79 Chinese hamster cells and human EUE fibroblasts, and this effect was lessened by the addition of S9 fraction (a post-mitochondrial) unscheduled DNA synthesis induced in V79 Chinese hamster cells and human EUE fibroblasts, and this effect was lessened by the addition of S9 fraction (a post-mitochondrial). In the neuroepithelium, the latter results remain doubtful, particularly since the number of patients was too small and no details on methods or number of cells analysed are given in the paper. The increase in satellite association reported by de la Torre and Krompotic (1975) also cannot be considered proof of a mutagenic action of lithium in vitro, inasmuch as the authors did not observe any significant increase in chromosome aberrations in patients compared with control subjects.

2.1.4. Carcinogenicity

Léonard et al. (1995) indicated that no information on possible carcinogenic effects of lithium compounds was available. However, this seems unlikely in view of the known biological mechanisms of action of lithium.

2.2. Environmental toxicology

Lithium is generally found naturally in the aquatic and terrestrial environment but in small concentrations (see Table 1) (Bowen, 1979; Wedepohl, 1995; Sposito, 1986; Birck, 1988; Ribas, 1991).

2.2.1. Aquatic environments

Lithium is found primarily in ionic form in water. Lithium metal reacts with water to form lithium hydroxide and hydrogen. The lithium concentration in fresh water and sea water is on the µg/L-level (Kjølholt et al., 2003). According to the literature (Schrauzer, 2002; Lenntech, 2007) surface water contains lithium at levels between 1 and 10 µg/L, seawater contains approximately 0.17 mg/L lithium (Mason, 1974) and the lithium concentrations in ground water may reach 0.5 mg/L. Rivers generally contain around 3 µg/L Li whereas in the lithium-rich regions of northern Chile, the lithium content of the surface waters could be as high as 5.2 mg/L. Worldwide mineral water contains 0.05–1 mg/L lithium, however, higher levels up to 100 mg/L can be found in some natural mineral waters (Schrauzer, 2002).

A review of lithium in the aquatic environment in the US (Kszos and Stewart, 2003) found that lithium was detected at low concentrations (~0.002 mg/L) in the major rivers of the US. Further studies (Kszos et al., 2003) identified lithium concentrations in surface waters were typically <0.04 mg/L but could be elevated in contaminated streams.

Huh et al. (1998) studied lithium and its isotopes in the lower reaches of 13 major rivers of the world and a number of major lakes (Table 2). The lithium concentration (expressed as nanomoles (nM)) varied from 96.5 for the Amazon River, 125 for the Congo, 579 for the Ganges, to 813 for the Mississippi River. The lithium isotopic composition appeared to be more a function of

| Table 1 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Typical background concentrations of lithium in the environment |
| Fresh water (µg/L) | Seawater (µg/L) | Sediment (mg/kg) | Soil (mg/kg) | Earth’s crust (mg/kg) | Atmosphere (ng/m³) |
| 0.07–40 | 170–190 | 56 | 3–350 | 20–60 | 2 |

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the fractionation processes during partial weathering of aluminosilicate rocks to form neoformed clays, and in the case of evaporites (rock composed of minerals derived from the evaporation of mineralised water), the concentration in the solution from which the secondary lithium minerals precipitated, rather than bedrock type or age. Comparison with the major element and strontium isotope dataset suggested that the important processes affecting river-dissolved lithium isotopic compositions are isotopic fractionation between solution and secondary minerals and the degree of weathering. In addition is the effect of the bedrock type makes the lithium isotopic system complicated.

Hamilton (1995) investigated the acute toxicity of boron, lithium, selenite, selenium, uranium, vanadium and zinc to early stages of development of Colorado squawfish (*Ptychocheilus lucius*), razorback sucker (*Xyrauchen texanus*), and bonytail (*Gila elegans*) in a water quality simulating the middle Green River. His study showed that the overall rank order of toxicity to all species was vanadium = zinc > selenite > lithium = uranium > selenite > boron.

Kszos et al. (2003) evaluated the toxicity of lithium to *Pimephales promelas* (fathead minnow), *Ceriodaphnia dubia*, and a freshwater snail (*Ellmia clavaeformis*). They found that for most natural waters, the presence of sodium is sufficient to prevent lithium toxicity. However, in areas of historical disposal or heavy processing or use, an evaluation of lithium from a water quality perspective would be warranted.

Studies (Lenntech, 2007; US EPA, 2008) have identified toxicity levels in certain organisms (see Table 3). Effective concentration (EC50) is the concentration of a material in water, a single dose which is expected to cause a biological effect on 50% of a group of test animals. Lethal concentration (LC50) is the amount of a substance in air that, when given by inhalation over a specified period of time, is expected to cause the death in 50% of a defined animal population. The acute environmental effect concentration (measured as EC50) on *Daphnia magna* was determined to be 33–197 mg/L, which is at least 100 times higher than the level in fresh water. Both lithium chloride and lithium sulphate have high water solubility, and the compounds will dissociate in aqueous environment. No lithium compounds are classified for adverse environmental effects. No data regarding bioaccumulation of lithium was found but based on its low affinity to particles, it is not expected to bioaccumulate.

### Table 2

<table>
<thead>
<tr>
<th>Name</th>
<th>Li (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lake Tanganyika</td>
<td>0.014</td>
</tr>
<tr>
<td>Caspian Sea</td>
<td>0.280</td>
</tr>
<tr>
<td>Lake Baikal</td>
<td>2.0</td>
</tr>
<tr>
<td>Dead Sea</td>
<td>14.0</td>
</tr>
</tbody>
</table>


### Table 3

<table>
<thead>
<tr>
<th>Species</th>
<th>Latin name (common name)</th>
<th>Compound</th>
<th>Exposure duration</th>
<th>EC50 (mg/L)</th>
<th>LC50 (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mollusc</td>
<td><em>Dreissena polymorpha</em> (Zebra mussel)</td>
<td>LiCl</td>
<td>24 h</td>
<td>185–232</td>
<td></td>
</tr>
<tr>
<td>Crustacean</td>
<td><em>Daphnia magna</em> (water flea)</td>
<td>Li2SO4</td>
<td>24 h</td>
<td>33–197</td>
<td></td>
</tr>
<tr>
<td>Worm</td>
<td><em>Tubifex tubifex</em> (Tubicid worm)</td>
<td>Li2SO4</td>
<td>24–96 h</td>
<td>9.3–44.8</td>
<td>1–8.4</td>
</tr>
<tr>
<td>Fish</td>
<td><em>Pimephales promelas</em> (fathead minnow)</td>
<td>LiCl</td>
<td>26 days</td>
<td>12–8.7</td>
<td>9.2–62</td>
</tr>
<tr>
<td>Fish</td>
<td><em>Tanichthys albonubes</em> (white cloud mountain minnow)</td>
<td>LiCl</td>
<td>48 h</td>
<td>12–8.7</td>
<td>9.2–62</td>
</tr>
</tbody>
</table>


### 2.2.2. Terrestrial environments

On land, lithium can be found as lithium carbonate (Li2CO3), lithium chloride (LiCl) or lithium oxide (Li2O). Lithium is found in trace amounts in all soils primarily in the clay fraction, and to a lesser extent in the organic soil fraction, in amounts ranging from 7 to 200 μg/g (Schrauzer, 2002). The source of lithium is usually from sedimentary rocks (Chan et al., 1997). For example, carbonates precipitated from evaporated lake water can have high lithium concentrations, as demonstrated by a Dead Sea aragonite with 19 ppm lithium. Some lithium in carbonate-rich rivers, especially those that are not highly evaporitic, come from associated shales, e.g., calcareous shales from the Ellis Group of Yellowstone National Park contained 18 ppm lithium.

Authigenic clays (i.e., those occurring in the place where they were originally formed) are enriched in lithium (200–500 ppm in smectites) relative to other rock types (igneous rocks 30 ppm, detrital clays 70–80 ppm) (Chan et al., 1997). Li+ has the weakest sorption chemistry of all the alkalis, and its affinity with clays is considered to be due to the isomorphic substitution of Mg2+ for Al3+ in the octahedral layer leaving a vacant position to accommodate Li+. Examination of lithium exchange in complex soil solutions and pure clay mineral systems has shown that lithium is selectively absorbed over other cations and apparently fixed in a non-exchangeable form (Anderson, 1989). Adsorption onto suspended sediments in rivers may also play a role but preliminary experiments (Chan et al., 1997) suggested that only about 1 ppm lithium is adsorbed onto clays and river sediments (i.e., 1%). Lithium concentrations are in general proportional to magnesium (due to ionic radius similarities) but only poorly correlated with other major ions and even silicon and potassium though these are almost exclusively from the weathering of aluminosilicates. This is consistent with the tendency of lithium to be retained in secondary clays, substituting for Mg2+ or occupying the vacancy generated by Mg2+ substitution of Al3+.

Lithium is taken up by all plants and although it appears not to be required for their growth and development, stimulation of plant growth has been observed (Schrauzer, 2002; Lenntech, 2007). The amount of lithium in plants usually lies between 0.2 and 30 ppm due to preferential uptake or rejection across species. Plants such as *Cirsium arvense* and *Solanium dulcamara* accumulate lithium in concentrations of three- to six-fold over other plants. Nightshade species may reach concentrations of up to 1 mg/g. Salt-tolerant plants such as *Carduus arvense* and *Holoschoenus vulgaris* may reach lithium contents of 99.6–226.4 μg/g. Lithium concentrations in plant foodstuffs vary widely from 0.01 ppm (dry basis) in bananas to 55 ppm in oats (Shacklette et al., 1978). Lithium is relatively toxic to citrus plants.

There appears to be a greater uptake of lithium by plants in acidic soils. Soil acidity increases the solubility of the heavier metallic elements such as iron, nickel, cobalt, manganese and copper, and to some extent also aluminium, lead and cadmium. Plant lithium levels are directly and significantly correlated with the concentrations of these elements. Calcium can be added to...
soils to prevent toxicity and the uptake of lighter minerals (Schrauwer, 2002; Lenntech, 2007).

Lithium in plants and animals interacts with sodium and potassium as well as with enzymes requiring magnesium. Its complexing properties are stronger than those of Na⁺ and K⁺ but weaker than those of Mg²⁺. At concentrations attained during therapy, Li⁺ and Mg²⁺ are present in comparable concentrations; thus, Li⁺ binds to sites not occupied by Mg²⁺. Once all Mg²⁺ sites are saturated, Li⁺ substitutes for Na⁺ and K⁺. All alkali metal ions are exchanged more than 1000 times more rapidly than Mg²⁺; this may explain why lithium preferentially affects the activity of Mg²⁺-containing enzymes (Birch, 1976, 1988). Chlorophyll mutants were produced in the progeny of Pisum abиссинicum plants (von Rosen, 1957) treated with lithium nitrate in addition to other nitrates (Cu, Zn, Cr, Mn, Fe, Co, Ni, Al). This was most likely due to the presence of the other confirmed mutagenic metal nitrates.

In an early study (Morris, 1958), yeast (Saccharomyces cerevisiae) was shown to take up limited amounts of lithium, and growth inhibition occurred at high levels (115–400 ppm). Tsuruta (2005) examined the accumulation of lithium by microorganisms. Among the 70 strains of 63 species tested (20 bacteria, 18 actinomycetes, 18 fungi and 14 yeasts), a high lithium accumulations ability was exhibited by strains of the bacteria Arthrobacter nicotianae (~1.0 mg/g dry weight cells) and Brevibacterium helvovolum (~0.7 mg/g dry weight cells). Further work was pending to devise a practical approach for removing and recovering lithium from aquatic systems using various microorganisms.

Lithium in the environment is mostly sourced from lithium-based grease (lithium hydroxide monohydrate) in vehicles and leaching from alkali granitic rocks. A 7-week exposure of earthworms (Eisenia fetida) identified a mortality rate at lithium chloride concentrations of approximately ~70 mg/kg soil (US EPA, 2008). A limited investigation of the levels of lithium and other elements in major emissions and waste streams was conducted in Denmark in 2001 (Kjølholt et al., 2003). In the Danish study, lithium was found in all environmental samples especially compost, waste water, sewage sludge and sediment from road runoff retention basins (Table 4). The concentration in effluent from waste water treatment plants was low and was not considered as being acutely toxic to aquatic organisms.

A source of lithium posing impact to the environment is spent lithium batteries. Consumers routinely dispose of batteries along with other garbage in the municipal solid waste (NEMA, 2001). Spent consumer lithium batteries disposed in this manner are generally considered not to pose environmental or safety hazards. This is based on the assumption that lithium metal (that reacts violently with water to produce explosive hydrogen gas) is no longer reactive as the metallic lithium and is converted into a non-reactive lithium oxide once the battery is discharged. Lithium batteries can often be associated with heavy metals such as cobalt and manganese, and could contain an organic solvent (propylene carbonate and 1,2 dimethoxyethane) solution of lithium perchlorate, acetoniirile solution with lithium bromide (US EPA, 1984). Lithium thionyl chloride batteries have a non-aqueous thionyl chloride solution containing lithium aluminium chloride. Liquid thionyl chloride vapoourises upon exposure to air and the fumes are highly toxic (DPPEA, 2000). Lithium sulphur dioxide batteries typically contain strips of lithium metal as the anode as well as a non-aqueous electrolyte consisting primarily of sulphur dioxide (SO₂) and smaller concentrations of acetoniirile (CH₃CN) and a lithium salt, typically lithium bromide (LiBr). Acetoniirile (CH₃CN) will decompose to form toxic cyanide fumes when heated (US EPA, 1984). The US Environmental Protection Agency (US EPA, 1984) made a statement on the regulatory status of spent and/or discarded lithium sulphur dioxide-type batteries and considered these batteries to be hazardous waste.

### Table 4

<table>
<thead>
<tr>
<th>Emission/waste type</th>
<th>Li concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compost</td>
<td>4.64 mg/kg</td>
</tr>
<tr>
<td>Compost from household waste</td>
<td>4.69 mg/kg</td>
</tr>
<tr>
<td>Compost from garden waste</td>
<td></td>
</tr>
<tr>
<td>Landfill leachate</td>
<td></td>
</tr>
<tr>
<td>Landfill 1</td>
<td>0.2 µg/L</td>
</tr>
<tr>
<td>Landfill 2</td>
<td>0.049 µg/L</td>
</tr>
<tr>
<td>Stack gas from municipal solid waste incineration</td>
<td></td>
</tr>
<tr>
<td>Incinerator 1, semi-dry gas cleaning</td>
<td>&lt;9.1 µg/m³</td>
</tr>
<tr>
<td>Incinerator 2, wet gas cleaning</td>
<td>1.0 µg/m³</td>
</tr>
<tr>
<td>Municipal solid waste gas cleaning residuals</td>
<td></td>
</tr>
<tr>
<td>Landfill leachate, semi-dry gas cleaning</td>
<td>0.285 mg/L</td>
</tr>
<tr>
<td>Landfill leachate, wet gas cleaning</td>
<td>0.367 mg/L</td>
</tr>
<tr>
<td>Waste water and sludge from municipal water treatment plant</td>
<td></td>
</tr>
<tr>
<td>Plant 1, effluent</td>
<td>11.4 µg/L</td>
</tr>
<tr>
<td>Plant 2, effluent</td>
<td>21.2 µg/L</td>
</tr>
<tr>
<td>Plant 1, sludge</td>
<td>6.06 mg/kg</td>
</tr>
<tr>
<td>Plant 2, sludge</td>
<td>5.02 mg/kg</td>
</tr>
<tr>
<td>Road runoff retention basins, sediment</td>
<td></td>
</tr>
<tr>
<td>Motorway 1</td>
<td>16.3 mg/kg</td>
</tr>
<tr>
<td>Motorway 2</td>
<td>15.5 mg/kg</td>
</tr>
</tbody>
</table>

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2.3. Exposure limits and regulations

According to the material safety data sheet (Chemwatch, 2004), lithium does not have an occupational exposure limit, however, data are normally available for lithium compounds. For example, the American Conference of Governmental Industrial Hygienists (ACGIH, 1992) has recommended an exposure limit data of 25 µg/m³ of lithium hydride for respirable dust or fumes for TLV-TWA (time-weighted average concentrations for a normal 8 h working day and a 40 h working week to which all workers may be repeatedly exposed without adverse effects). The same exposure limit has been quoted by others (CDC, 2007; Deutsche Forschungsgemeinschaft, 1992).

According to the Australian Capital Territory Environment Protection Regulation (EPA, 2005), lithium is listed as a pollutant that causes environmental harm in irrigation water supplies. The concentration of lithium entering waterways should be less than or equal to 2.5 mg/L.

### 3. Conclusions

The primary findings of this review were:

- Lithium is found in all organs and tissues. It is uniformly distributed in body water, absorbed from the intestinal tract and excreted primarily through the kidneys.
- Based on lithium intake data in different countries, a provisional recommended daily intake of 1.0 mg/lithium/day for a 70 kg adult American has been proposed. Major dietary sources are grain and vegetables and animal-derived foods. In some areas, the drinking water is a source of lithium.
- Human lithium deficiency diseases have not been observed. However, some observations have suggested that low lithium intakes cause behavioural defects.
● Persons at risk of developing lithium deficiency are those with kidney disease and dialysis patients.

● The reproductive effects of lithium are highly unlikely in an occupational setting but may pose a risk to those being treated for manic-depressive disorders. Lithium compounds are not significantly clastogenic (capable of causing breakage of chromosomes) and, based on studies on microorganisms, only a doubtful mutagenic activity. Information on teratogenic effect is contradictory.

● Lithium is taken up by plants. It does not appear to be required for growth and development but it has been observed to stimulate plant growth.

● At high levels in the soil, lithium is toxic to all plants but uptake and sensitivity to lithium are species dependent. In general, more lithium is taken up by plants from acidic soils than alkaline soils.

● Lithium batteries are generally considered not an environmental hazard except when containing toxic (heavy) metals and disposed of in large quantities.

The literature survey has indicated that lithium is not expected to bioaccumulate, and that its human and environmental toxicity is low. Neither lithium intake from food and water nor from occupational exposure presents a toxicological hazard. It does not appear to pose a large threat to flora and fauna neither on land nor in water. A release of lithium-containing waste can result in wide dispersal due to low biological uptake and sorption to particulate in water. A release of lithium-containing waste can result in wide dispersal due to low biological uptake and sorption to particulate material. Only in one Australian jurisdiction, the concentration of lithium entering waterways has been limited to less than or equal to 2.5 mg/L. Based on the information gathered in this report, the lithium brine and mineral processing industries should be in a position to set self-regulatory guidelines on occupational exposure from handling lithium, and discharge limits for waste waters.

This review has identified a number of areas where further research is required. For example, on the human side, determining the amount of lithium that is beneficial to health would assist in establishing recommended daily intake levels. It could also be useful to obtain a better understanding of the mechanisms by which lithium could bring about change in the mood. Understanding the molecular target of lithium could shed light on the cause and origins of bipolar disorder and may make it possible to identify additional therapies for this disorder. On the animal side, further research is required to determine the lithium requirements for different animal species and measuring the lithium levels at which behavioural defects are observed. On the environmental side, further testing of chronic sub-lethal toxicity and modelling biotic ligand toxicity is recommended.

Acknowledgments

This literature review study was funded by Talison Minerals (formerly Sons of Gwalia) the world's largest lithium mineral producer in Australia. The authors wish to thank Talison Minerals' Pat Scallan and Ray Hoes for their permission to publish this paper. We also thank for the reviewers for helpful comments on the manuscript.

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