NR 2002:16

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

131. Lithium and lithium compounds

Birgitta Json Lagerkvist and Birgitta Lindell

Nordic Council of Ministers

ARBETE OCH HÄLSA | VETENSKAPLIG SKRIFTSERIE

ISBN 91-7045-659-3 ISSN 0346-7821 http://www.niwl.se/

Arbetslivsinstitutet
National Institute for Working Life

Arbete och Hälsa

Arbete och Hälsa (Work and Health) is a scientific report series published by the National Institute for Working Life. The series presents research by the Institute's own researchers as well as by others, both within and outside of Sweden. The series publishes scientific original works, dissertations, criteria documents and literature surveys.

Arbete och Hälsa has a broad target-group and welcomes articles in different areas. The language is most often English, but also Swedish manuscripts are welcome.

Summaries in Swedish and English as well as the complete original text are available at www.niwl.se/ as from 1997.

National Institute for Working Life
S-112 79 Stockholm
Sweden

ISBN 91–7045–659–3
ISSN 0346–7821
http://www.niwl.se/
Printed at Elanders Gotab, Stockholm

Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following members:

Gunnar Johanson (chairman)	Karolinska Institutet and National Institute for Working Life, Sweden
Vidir Kristjansson	Administration of Occupational Safety and Health, Iceland
Kai Savolainen	Finnish Institute of Occupational Health, Finland
Vidar Skaug	National Institute of Occupational Health, Norway
Karin Sørig Hougaard	National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as HSELINE, Medline and NIOSHTIC. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee on Occupational Standards is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access is used.

The document aims at establishing dose-response/dose-effect relationships and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on lithium and lithium compounds was made by Dr Birgitta Json Lagerkvist, Umeå University and M Ph Birgitta Lindell, the National Institute for Working Life, Sweden. The draft document was discussed within the Expert Group and the final version was accepted by the Nordic Expert Group November 18, 2002, as its document. Editorial work and technical editing was performed by the Group's Scientific Secretary, Jill Järnberg at the National Institute for Working Life in Sweden.

We acknowledge the Nordic Council for its financial support of this project. More information is found at *www.nordicexpertgroup.org*.

Jill Järnberg — Scientific Secretary

Gunnar Johanson — Chairman

Abbreviations

AAS	atomic absorption spectrophotometry
ACE	angiotensin converting enzyme
ADH	antidiuretic hormone
AES	atomic emission spectroscopy
ATPase	adenosine triphosphatase
CA	chromosome aberrations
cAMP	cyclic adenosine monophosphate
CEGL	continuous exposure guidance level
EEGL	emergency exposure guidance level
CHO	Chinese hamster ovary
GFR	glomerular filtration rate
GSK3	glycogen synthase kinase-3
ICP	inductively-coupled plasma
LC_{50}	lethal concentration for 50% of the exposed animals at single exposure
LD_{50}	lethal dose for 50% of the exposed animals at single administration
Li	lithium
LOAEL	lowest observed adverse effect level
MS	mass spectrometry
NDI	nephrogenic diabetes insipidus
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory drugs
SCE	sister chromatide exchanges
TSH	thyroid-stimulating hormone

Contents

Abbreviations

1. Introduction 1

2. Substance identification 1

3. Physical and chemical properties 1

4. Occurrence, production and use 3
   4.1 Occurrence 3
   4.2 Production 4
   4.3 Use 4

5. Measurements and analysis of workplace exposure 7

6. Occupational exposure data 8

7. Toxicokinetics 10
   7.1 Uptake 10
      7.1.1 Experimental animals 10
      7.1.2 Humans 10
   7.2 Distribution 11
      7.2.1 Experimental animals 11
      7.2.2 Humans 12
   7.3 Biotransformation 12
   7.4 Excretion 12
      7.4.1 Experimental animals 12
      7.4.2 Humans 13
   7.5 Toxicokinetic interactions 13

8. Biological monitoring 14

9. Mechanisms of toxicity 14
   9.1 Local toxicity 14
   9.2 Systemic toxicity 15
      9.2.1 General 15
      9.2.2 Central nervous system 15
      9.2.3 Other organs 16
   9.3 Summary 16

10. Effects in animals and in vitro studies 16
   10.1 Irritation and sensitisation 17
   10.2 Effects of single exposure 18
   10.3 Effects of short-term exposure 18
   10.4 Mutagenicity and genotoxicity 19
   10.5 Effects of long-tem exposure and carcinogenicity 22
   10.6 Reproductive and developmental studies 22

11. Observations in man 24
   11.1 Irritation and sensitisation 24
   11.2 Effects of single exposure 26

11.3 Effects of short-term and long-term exposure 26
11.3.1 Occupational exposure 26
11.3.2 Lithium therapy 26
11.4 Genotoxic effects 30
11.5 Carcinogenic effects 30
11.6 Reproductive and developmental effects 30
12. Dose-effect and dose-response relationships 31
13. Previous evaluations by national and international bodies 33
14. Evaluation of human health risks 34
14.1 Assessment of health risks 34
14.2 Groups at extra risk 35
14.3 Scientific basis for an occupational exposure limit 35
15. Research needs 35
16. Summary 36
17. Summary in Swedish 37
18. References 38
19. Data bases used in search of literture 47
Appendix 1 48
References 48

1. Introduction

Lithium (Li) was discovered in 1817 in petalite rock by Arfwedson. By 1848 it was found that lithium carbonate solutions could solubilise urate crystals *in vitro*. Much interest was then focused on the possible health effects of naturally occurring lithium; review in Triffleman *et al*. (169). During the second half of the 19th century spring water, which was claimed to contain lithium and also lithium salt tablets, were widely used as a remedy to cure gout and other diseases. In 1949, Cade from Australia reported his findings on the use of lithium salts in the treatment of mania (31). At the same time some case studies on the use of lithium chloride as a salt substitute in patients on a low sodium diet suffering from cardiac disease or renal failure were published in the United States and 7 cases of intoxication including 2 deaths were reported (36). This delayed the use of lithium in psychiatry in the United States until 1970 (91). In Australia and Europe lithium salts emerged in the therapy of mania and as a prophylactic drug in manic-depressive states during the 1950s (20). Today especially the carbonate and acetate are used world-wide in the treatment of affective disorders (97). In Sweden lithium sulphate (52) and in Finland lithium sulphate, lithium citrate or lithium carbonate are used for that purpose (121).

Apart from being used in medicine lithium compounds had few other applications until thermonuclear weapons (where lithium-6 is used to produce tritium) were developed after the World War II (8). During the last few decades lithium compounds have been increasingly used in a variety of commercial applications, e.g. in lubricating greases, ceramics and glazes, batteries, welding and brazing fluxes, alloys, and air-conditioning systems (97, 152). Although occupational intoxications from these industrial applications seem conceivable, none has been reported (97). Only a few reports of irritation of the respiratory tract, eyes and skin have been published. However, the literature on lithium therapy and the beneficial, as well as toxic, effects of lithium in patients is abundant.

2. Substance identification

Chemical formulas, molecular weights and CAS numbers of lithium and some lithium compounds are listed in Table 1.

3. Physical and chemical properties

Lithium has atomic number 3 and is the lightest solid element in the periodic system. It is a soft silvery white metal, which quickly becomes covered with a gray oxidation layer when exposed to air. The density is 0.53 g/cm^3. Melting

Table 1. Substance identification of lithium and some of its compounds that may occur in the occupational environment.

Chemical name (Synonym)	Chemical formula	Molecular weight	CAS-No.
Lithium	Li	6.94	7439-93-2
Lithium hydride	LiH	7.95	7580-67-8
Lithium aluminium hydride (Li-tetrahydro-aluminate)	$LiAlH_4$	37.95	16853-85-3
Lithium borohydride (Li-tetrahydroborate)	$LiBH_4$	21.78	16949-15-8
Lithium tetraborate	$Li_2B_4O_7$	169.12	12007-60-2
Lithium metaborate	$LiBO_2$	49.75	13453-69-5
Lithium nitride	Li_3N	34.83	26134-62-3
Lithium boron nitride	Li_3BN_2	59.65	99491-67-5
Lithium amide	$LiNH_2$	22.95	7782-89-0
Lithium nitrate	$LiNO_3$	68.94	7790-69-4
Lithium sulphite	Li_2SO_3	93.94	13453-87-7
Lithium hydroxide	LiOH	23.95	1310-65-2
Lithium hydroxide monohydrate	$LiOH \cdot H_2O$	41.96	1310-66-3
Lithium oxide	Li_2O	29.88	12057-24-8
Lithium chromate	Li_2CrO_4	129.87	14307-35-8
Lithium silicate	Li_2SiO_3	89.96	10102-24-6
Lithium silicate	unspecified	-	12627-14-4
Lithium bromide	LiBr	86.84	7550-35-8
Lithium chloride	LiCl	42.39	7447-41-8
Lithium fluoride	LiF	25.94	7789-24-4
Lithium stearate	$LiC_{17}H_{35}COO$	290.42	4485-12-5
Lithium 12-hydroxy-stearate	$LiC_{17}H_{34}(OH)COO$	306.41	7620-77-1
Lithium ricinoleate	$LiC_{17}H_{32}(OH)COO$	304.40	15467-06-8
Lithium neodecanoate	$LiC_9H_{19}COO$	178.24	27253-30-1
Lithium acetate, dihydrate	$LiCH_3COO \cdot 2\ H_2O$	102.01	6108-17-4
Lithium acetate[a]	$LiCH_3COO$	65.99	546-89-4
Lithium carbonate[a]	Li_2CO_3	73.89	554-13-2
Lithium sulphate[a]	Li_2SO_4	109.94	10377-48-7
Lithium citrate[a]	$Li_3C_3H_4(OH)(COO)_3$	209.92	919-16-4

[a] occurs in pharmaceutical preparations of lithium

points of 178-186 °C and boiling points of 1340-1347 °C (1 atm) have been reported (8, 16, 104, 130). There are two naturally occurring stable isotopes of lithium; lithium-6 (7.4% abundance) and lithium-7 (92.6% abundance), and three radioactive ones with extremely short half-lives (0.8, 0.2, and 10^{-21} seconds respectively) (122). The only oxidation states are 0 and +I (71). The water solubility of some lithium compounds is given in Table 2. Elemental lithium reacts with water to form lithium hydroxide, but less vigorously than sodium (8, 16). Lithium and some of its compounds e.g. lithium hydride, lithium nitride, lithium hydroxide, lithium oxide, lithium amide and lithium carbonate are known to be alkaline (8, 16, 71, 102, 128, 134). However, data on alkalinity have not been found for all compounds.

Metallic lithium reacts with nitrogen gas at room temperature to form a black nitride. Lithium nitride in turn reacts with water to form ammonia and lithium hydroxide, and can ignite spontaneously in damp air. Lithium reacts with

Table 2. Water solubility of some lithium compounds (8, 16).

Substance	Solubility in water
Lithium	Decomposes to LiOH and H_2
Lithium hydride	Decomposes to LiOH and H_2
Lithium oxide	66.7 g/l (0 °C), reacts with H_2O to form LiOH
Lithium hydroxide monohydrate	223 g/l (10 °C), 268 g/l (80 °C)
Lithium carbonate	13.3 g/l (20 °C), 7.2 g/l (100 °C)
Lithium bromide	1450 g/l (4 °C)
Lithium chloride	454 g/l (20 °C)
Lithium stearate	0.1 g/l (18 °C)

ammonia to form the amide, which on heating yields ammonia and lithium imide (Li_2NH) (102, 152).

At 500-700 °C lithium reacts with hydrogen to form lithium hydride. Lithium hydride is an odourless, off-white to grey crystalline solid or a white powder. The compound can be melted without decomposition, and used to produce metal hydrides, e.g. lithium borohydride and lithium aluminium hydride (1, 30, 152). Airborne dust clouds of lithium hydride may explode on contact with heat (1).

The lithium salts used as the electrolyte in the lithium battery technology (see chapter 4.3) are generally white to off-white hygroscopic powders (7). In the presence of moisture, lithium hexafluoroarsenate has the potential to form hydrogen fluoride, a highly corrosive gas (7).

4. Occurrence, production and use

4.1 Occurrence

Lithium compounds are widely distributed in nature, although unevenly and in low concentrations. The lithium content in the Earth's crust is reported to be 50-65 mg/kg (30, 97, 175). Lithium levels in soils are reported to range from 10 to 100 mg/kg in the United States and from 10 to 50 mg/kg in Russia (5).

Reported levels of lithium in water span a wide range world-wide. Chile has the highest reported levels with some rivers showing levels as high as 6 mg Li/l (175). High concentrations of lithium also occur in water from hotsprings and in certain mineral waters. Average values in sea water are 0.18 mg Li/l. The ambient air level of lithium is very low, 2-4 ng Li/m^3 (97, 110); for reviews see (24, 130, 157). Lithium is also found in plants and animals. The concentrations in plants show a wide variation, depending on the geographical location. High lithium levels in soil may be phytotoxic, and e.g. reduce biomass in crops; review in (5).

Thus, there is a natural background exposure to lithium from food and drinking water varying with geographical location and consumption pattern. A number of studies from different countries have reported intake levels from food ranging from 0.02 to 0.54 mg Li/day; reviews in (14, 95, 175). The intake from drinking water has been reported to be from less than 0.001 to approximately 0.3 mg Li/day (175). However, very high intakes via drinking water, more than 5 mg

Li/day, have been reported from certain areas with mineral rich soils, e.g. from Northern Chile (15, 182) (Differences in analytical methods may have influenced the results). In an American assessment of daily intake of lithium from food the values ranged from 0.58-2.8 mg Li/day, with the range based on variation in lithium levels in vegetables and grains. It was also stated that consumption of mineral supplements could result in an additional internal dose of 5-6 mg Li/day. Intake from municipal drinking water was calculated to be up to 1.4 mg Li/day. Furthermore, bottled mineral water may represent a potential source of lithium exposure. It contains 0.002-5.2 mg Li/l. It was reported in the study that the average body burden of lithium in an adult is 2.2 mg (110).

Reported Li levels in serum of healthy subjects generally range from 0.16 to 8.6 μM (95), but levels up to 12 μM have been reported with the highest levels found in Chile (146, 174). The typical plasma Li concentration is 2-3 μM (14-21 μg Li/l) (87). After oral administration of immediate-release lithium tablets the maximal plasma concentrations are 1000-fold greater than typical trace concentrations (87).

4.2 Production

Lithium oxide is mined from the aluminium silicates, spodumene, lepidolite and petalite, and from the phosphate minerals amblygonite and triphylite (30, 97, 152). The total world mine production in 1994 was 9 155 tonnes. The United States was the largest producer (34% of total) followed by Chile (21%), Australia (19%), Russia (9%), Canada (7%), and Zimbabwe (4%) (40).

A variety of lithium compounds are produced from mined ore at lithium processing plants (110). Lithium salts are also extracted from natural salt lakes in the United States, Chile and Brazil (30, 117, 152).

Ores containing lithium minerals with large crystals are sorted mechanically and fine ores are upgraded to 4-7% lithium oxide by a flotation process. The silicate ores, which are those processed most widely, are then chemically cleaved by acid or alkaline processes yielding lithium sulphate, carbonate, chloride and hydroxide (76, 134, 152, 159).

Lithium metal is manufactured by the electrolysis of molten mixtures of lithium chloride and potassium chloride at 400-460 °C (30, 134).

4.3 Use

Figures on end use patterns from 1994 gave the following percentages of the world use of lithium compounds in different industries; ceramics and glass: 45%, primary aluminium: 19%, lubricants: 19%, chemicals: 6%, and synthetic rubber and pharmaceuticals: 2% (40).

Elemental lithium is utilised in metallurgy in special alloys, for the manufacture of lithium hydride, amide and nitride, and for the synthesis of organolithium compounds (30). Metallic lithium is also used in batteries. The lithium-6 isotope is important in nuclear weapons technology and as a breeding material for nuclear-fusion reactors (8, 30).

Lithium carbonate is the industrially most important lithium compound and the starting material for the production of lithium salts (30). Furthermore, it is used in the manufacture of aluminium and as a flux in the glass, enamel and ceramic industries (30, 40). Also lithium borate is used in the ceramic industry as a glaze constituent (16). Another well-known use of lithium carbonate is in the prophylaxis and treatment of affective disorders (129). Other lithium compounds used for that purpose are lithium citrate, lithium sulphate and lithium acetate (52, 97, 121, 123).

Lithium hydroxide (monohydrate) is also an important lithium compound. It is used in alkaline storage batteries and for manufacturing of lithium soaps, e.g. lithium stearate (30, 152, 159). Lithium stearate is used as a thickener or gelling agent for lubricating greases. It is also used as flatting agent in varnishes and lacquers, as corrosion inhibitor in petroleum and in cosmetics (16, 30).

Lithium chloride and lithium bromide are used to absorb moisture in air conditioning systems and in batteries (120, 152). Lithium chloride and lithium fluoride are used in welding and brazing fluxes in the production of lightweight alloys (16, 152). Lithium hypochlorite occurs as a sanitiser in spas and hot tubs (106).

Lithium and lithium compounds have many applications as reagents or catalysts in organic chemistry, e.g. in the synthesis of vitamin A, and in the polymerisation of isoprene to cis-polyisoprene, a synthetic rubber (152). Lithium amide is used to introduce amino groups, as a dehalogenating agent, and as a catalyst (152).

Lithium hydride has industrial importance as a hydrogen source, a drying agent, and a reducing agent in organic synthesis, particularly in the form of its derivates, lithium aluminium hydride and lithium borohydride (30).

Lithium and lithium compounds have been increasingly used in lithium batteries (99). Various lithium compounds may be used as the electrolyte (Table 3).

There is no primary production of lithium in the Nordic countries. In Sweden,

Table 3. Some lithium compounds used as electrolytes in Li battery technology.

Chemical	Reference
Lithium trifluoromethanesulfonate	(7)
Lithium tetrafluoroborate	(7)
Lithium hexafluoroarsenate	(7)
Lithium perchlorate	(7)
Lithium hexafluorophosphate	(7)
Lithium imide	(7)
Lithium bis(trifluoromethane sulfonimide)	(7)
Lithium nitride	(102)
Lithium aluminium	(85)
Lithium silicon	(85)
Lithium chloride	(85)
Lithium fluoride	(85)
Lithium oxide	(85)

Table 4. Some lithium compounds registered in Sweden 2000[a] (Product Register at the Swedish National Chemical Inspectorate, personal communication).

Lithium compound	No. of products	Amount of the compound (tons)
Lithium 12-hydroxystearate	298	498
Lithium carbonate	52	177
Lithium sulphate	22	11
Lithium stearate	33	9
Lithium chloride	32	6
Lithium hydroxide	26	2
Neodecanoic acid, lithium salt	5	2
Lithium oxide	5	1
Lithium acetate, dihydrate	18	0

[a] Compounds used in more than 3 products

513 products containing lithium compounds were listed in the Swedish Product Register in 2000 and the total amount of lithium compounds was approximately 726 tons. Nine compounds were used in more than 3 products (Table 4). Lithium carbonate is used in the glass and ceramics industry and also as a component in floating patty. Lithium hydroxide is used as an additive to potassium hydroxide in big industrial batteries. Lithium hydroxide is also used in the production of lithium stearate. Lithium fats (e.g. lithium 12-hydroxystearate) are used in the automobile industry and also in softeners and cosmetics. Lithium bromide is retailed for use as a moisture absorbent in heat-exchangers. A minor part of the lithium sulphate imported is used in the production of Lithionit tablets. Major industrial uses of lithium compounds in Sweden are listed in Table 5.

Table 5. Major uses of lithium compounds in Sweden in 2000 (Product Register at the Swedish National Chemical Inspectorate, personal communication).

Industry	Amount of lithium compounds (tons)
Industry for glass and glass products	167
Industry for machinery and equipment	149
Maintenance and repair garages for motor vehicles, transport companies, motor vehicles industry	86
Industry for pulp, paper and pulp products	80
Construction industry	11
Industry for basic metals	8
Industry for fabricated metal products	5
Industry for electrical machinery and apparatus	5
Industry for wood and products	2
Companies for forestry	2
Paint industry	2
Food product and beverage industry	0.8
Photographic laboratories	0.4
Industries for cement, lime and plaster	0.4

Table 6. Some lithium compounds registered in Norway 1999[a] (Norwegian Product Register, personal communication).

Lithium compound	No. of products	Amount of the compound (tons)
Lithium carbonate	29	12
Lithium hydroxide monohydrate	9	0.9
Lithium chloride	6	0.7
Neodecanoic acid, lithium salt	29	0.2
Lithium hydroxide	23	<0.01
Lithium acetate	27	<0.01
Benzisothialzolin-3(2H)-one 1,2-, lithium salt	28	<0.01

[a] Compounds used in more than 3 products

In the Norwegian Product Register, products are listed which are hazardous and imported/used in amounts of 100 kg or more per year (Table 6). Compounds like lithium palmitate or lithium stearate, used in lubricating oils, are not registered. Forty-four different lithium compounds were registered in 1999. Only 7 of these were found in more than 3 products. Lithium sulphate was registered in less than 4 products. Lithium carbonate is used in the glass-, building- and construction industries. Lithium acetate is used in small amounts, mainly in the building- and construction industry. Lithium chloride is used in the photographic industry and in the production of electronic devices.

5. Measurements and analysis of workplace exposure

Atomic absorption spectrophotometry (AAS) and flame emission spectroscopy are used in the routine analysis of lithium in mining and metallurgy, and in aqueous solutions and biological fluids (122, 130, 165). According to Amdisen AAS has a higher accuracy at low lithium concentrations than flame emission spectroscopy (4). Concentrations as low as 0.01-0.03 μM Li can be determined with graphite furnace AAS (48, 109). In both AAS and flame emission spectroscopy other cations in plasma or serum cause interference effects, which must be avoided by e.g. using calibration solutions (27, 48, 161). Other methods, which can be used for analysis of lithium are inductively-coupled plasma atomic emission spectrometry (ICP-AES) and mass spectrometry (ICP-MS). A detection limit for Li of 0.04 μM for ICP-AES is reported in one study (125). Sector field inductively-coupled plasma mass spectrometry (ICP-SFMS) has been reported to have a method detection limit of 0.007 μM Li (0.05 μg Li/l) (131).

Workplace air may be sampled after filter collection. In a NIOSH report personal air samples were collected and analysed in accordance with NIOSH method 7300 modified for microwave digestion. The samples were collected on 37 mm mixed cellulose ester filters and analysed by ICP-AES. Serum lithium was measured by ICP-MS (85). In a Canadian study (66) on potters' exposure to a

number of metals, lithium was analysed by ICP-AES in accordance with WCB method 1051.

Ion-selective electrodes, measuring the ionic activity of lithium in blood are now commercially available for use in clinical practice (27). However, a risk of inaccuracies in serum lithium results due to ageing of the electrode has been reported (101).

In biological monitoring care must be taken that samples are collected in lithium-free tubes (especially lithium heparin) (27). Plasma and serum samples may be stored at –15 °C (24).

6. Occupational exposure data

Industrial exposures to lithium may occur e.g. during extraction of lithium from its ores, preparation of various lithium compounds, welding, brazing and enamelling. Lithium fumes are the potential exposure in welding and brazing, particularly from accidents or leaks in the use of the lithium hydrides (16). However, data describing actual exposure levels at workplaces are limited. Occupational exposure in the pharmaceutical industry is considered to be negligible (97).

One NIOSH survey monitored lithium carbonate at a facility involved in the extraction and processing of mineral products from a natural lake brine solution. Airborne dust was measured with personal samplers. Lithium carbonate was detected in 3 of 5 samples at levels corresponding to 0.08, 0.17, and 0.83 mg Li/m^3. No lithium was detected in blood samples of exposed workers, using a method with a detection limit of 0.05 mM Li (117). In another NIOSH report lithium air levels were determined during repair of an air conditioning system. General room air samples ranged from 0.008 to 0.01 mg Li/m^3 (61).

In 1980 NIOSH made a health hazard evaluation at a plant producing lithium compounds (134). Personal and stationary dust samples were collected for measurement of total and respirable dust with specific analysis for lithium content. Exposure data are summarised in Table 7. Blood samples were obtained from 18 exposed workers and from 6 “less exposed” workers. Seventeen gave blood pre and post shift, whereas 7 gave blood only post shift. Blood lithium levels were below the detection limit (0.1 mM) in all but 2 of the specimens. The 2 specimens with detectable levels were pre-shift specimens obtained from a production helper (hydroxide bagging) and a pelletiser operator and were 0.3 and 0.14 mM Li, respectively. No increase was measurable over the shift.

In 1996 NIOSH made a health hazard evaluation at a plant producing battery systems (85). Different lithium compounds were used as electrolytes in the batteries. Air sampling conducted by the company in 1992 showed concentrations of total lithium from 0.07 to 0.475 mg Li/m^3 as 8-10 hours time-weighted averages. In the personal air sampling (full-shift) made in 1996 the concentrations ranged between non-detectable and 0.122 mg Li/m^3. The geometric mean concentration was 0.0018 mg Li/m^3. Serum samples were collected at the end of the

Table 7. Personal breathing zone dust concentrations and area dust concentrations of lithium (adapted from (134)).

Job category/work area	Personal air sampling (mg Li/m^3)				Stationary sampling (mg Li/m^3)	
	Total dust	n	Respirable dust	n		n
LiOH bagging[a]	0.02-0.05	4	0.001-0.01	2	0.02-0.07	2
Li_2CO_3 bagging[a]	0.54-1.84	4	0.01-0.02	2	0.46-0.51	2
Li_2CO_3 grinding[a]	1.08-3.53	2	0.05	1	1.31	1
Special products[a]	nd-0.17	2	0.002	1	0.01	1
Purified carbonate repacking	0.11-0.13	2	0.01	1	0.06	1
Pelletiser area (carbonate)	0.05-0.17	4	0.01	1	0.1	1
Amide packing	nd-0.04	2	0.004	1	0.09-0.16	2
LiCl bagging	0.002-0.03	3	0.002	1	-	
Na_2SO_4 bagging	0.04-0-08	3	0.01	1	-	
Fork lift operator	0.04	1	-		-	
Outside maintenance[b]	0.01-0.07	3	0.01	2	-	
Welder[b]	nd		-		-	
Maintenance man[b]	0.002	1	-		-	
Waste recovery[b]	nd	1	-		-	

nd=not detected
n = number of samples
[a]most workers carried out more than one task during the shift
[b] considered as less exposed workers

work-week and the Li concentrations ranged between non-detectable and 1.6 μM (11.2 μg Li/l) (Table 8). The geometric mean concentration was 0.25 μM (1.75 μg Li/l). Results of the measurements on the 36 workers who participated in both the personal air sampling and biological monitoring showed a correlation between personal air sampling results and serum lithium (Pearson coefficient 0.51, $p<0.01$).

In the ceramic industry kiln emissions and potters' exposure has been studied (66). Different gases and metals were measured in 50 small potteries in the work area and in personal metal samplers. Only 2% of the area samples of lithium were above the detection limit, range <0.005-0.015 μg Li/m^3. Also, only 2% of the personal samples were above the detection limit, range <0.008-<0.125 μg Li/m^3.

In a study on 6 workers exposed to dust of lithium/aluminium alloys serum Li

Table 8. Personal breathing zone dust concentrations and serum concentrations of lithium (adapted from (85)).

Work area	Full-shift personal air samples		Serum samples	
	mg Li/m^3	n	μM Li	n
Process room	0.0198-0.034	2	0.4-1.5	2
Pill room	0.0023-0.1218	13	0.2-1.6	12
Dry room	nd-0.0113	24	nd-0.9	27

nd = not detected
n = number of workers sampled

levels ranged from 0.09 to 0.66 μM (0.6-4.6 μg Li/l). The air levels of the dust were reported to be less than 50% of the German MAK value for aluminium of 6 mg/m^3 (18, 85).

In Norway, occupational exposure to lithium is considered possible in the extraction of crude oil and natural gas, in the iron- and steel industry, in the production of pumps and compressors, in the ship-building and reparation industries, in the distribution of electricity and in welding. Lithium in detectable amounts was found in 58 of 2 360 measurements from welding work 1995-1999 in the EXPO database. The highest value, 0.058 mg Li/m^3, was found in the extraction of crude oil and natural gas (stationary measurement).

7. Toxicokinetics

Lithium has been used as a psychiatric drug for almost half a century and there are a number of reviews and books on lithium pharmacokinetics (10, 25, 35, 38, 162). Because of its low therapeutic index lithium is given according to the serum or plasma level, measured in the morning 12 hours after the latest dose (4) and is given in daily doses defined to keep a therapeutic concentration. The defined daily dose in Sweden in lithium treatment of affective disorders is 167 mg Li (The Swedish Pharmacy Agency, personal communication). In Sweden, the recommended 12-hours serum lithium concentrations are 0.5-0.8 mM in general and 0.9-1.2 mM in some cases (52).

7.1 Uptake

7.1.1 Experimental animals

A great number of studies on the uptake of lithium after oral, intraperitoneal, and intravenous administration have been made; reviews in e.g. (6, 122). After oral administration lithium salts are readily absorbed, e.g. in a study on rats given single doses of lithium chloride or carbonate there was an increase in plasma levels during the first 15 or 30 minutes followed by a plateau that extended for 12 or 24 hours depending on the dose given (113). *In vitro* studies on lithium absorption through intestinal mucosal preparations suggest that the lithium transport is a passive diffusion process via the leaky epithelium of the small intestine (41, 122).

Only a few studies are made on the uptake of inhaled compounds. In rats, the uptake of lithium from an aerosol made from a solution (containing 1% lithium) of the readily soluble salt lithium chloride was approximately 17% in normal breathing rats exposed for 3 hours (72).

7.1.2 Humans

Like sodium and potassium lithium is readily and almost completely absorbed from the gastrointestinal tract. The times to peak and plateau concentrations following a single oral dose of a lithium salt depend on the solubility of the salt and on the rate of dissolution of the tablet or capsule preparations. After an oral

dose of a dilute lithium chloride solution serum lithium concentrations peaked at 30-60 minutes and plateau levels were reached at 12-24 hours (4). There is considerably more variation when the kinetics of conventional tablet preparations are analysed (38). After an oral dose of lithium carbonate tablets complete absorption occurs in approximately 8 hours, with a peak in plasma concentration occurring 1–4 hours after the administration (4, 165). A direct relationship between lithium content in the water supply and blood and plasma levels of lithium has been demonstrated in several studies; review in Barr and Clarke, 1994 (14).

Lithium may also be absorbed via the lungs. A systemic resorption of lithium was shown in a study on 27 intensive care unit patients, who were mechanically ventilated with lithium-chloride-coated heat and moisture exchangers for at least 5 days (133). Serum lithium was non-detectable at the first measurement, whereas 0.01-0.05 mM appeared in the blood from the 1st to the 4th day. In the following days, it remained at this level or increased to 0.1 mM. After cessation of the mechanical ventilation, serum lithium levels went back to undetectable levels within a few days. In a 7 year-old girl, the serum Li concentration rose to about 1 mM after a week, came back to 0.1 mM, rose to 3.9 mM on the 16th day and then returned to the usual low range (0.05-0.1 mM) (133). The authors calculated that for adults, the daily amount of lithium chloride inhaled from a new heat and moisture exchanger (80% of the lithium content) can be considered equivalent to an oral dose of 100 mg/day of lithium chloride or 16 mg Li/day. That is approximately 1/10 of the recommended dose of lithium carbonate in patients. As was shown with the child, clinically relevant or even toxic concentrations might occur in patients with small distribution volumes (133). In another paper it was shown that after 20 minutes of ventilation more than 90% of the lithium chloride content of lithium-chloride-coated heat and moisture exchangers was deposited into the test lung of the breathing model (127).

The absorption of lithium through the skin is considered to be very poor (117, 174). In one study no significant elevation of serum lithium levels was reported in healthy volunteers spending 20 minutes/day, 4 days/week during 2 weeks in a spa with a concentration of approximately 40 mg Li/l, as compared with unexposed controls (106). Similar findings were reported from a study in adult patients suffering from seborrheic dermatitis and treated for 4 weeks with an ointment containing 8% lithium succinate (47).

To conclude, lithium is readily and almost completely absorbed from the gastrointestinal tract, but the absorption rate depends on the solubility of the compound. Lithium may also be extensively absorbed via the lungs, whereas absorption through skin is considered to be poor.

7.2 Distribution

7.2.1 Experimental animals

Early animal studies (in rats, dogs, and monkeys) showed that lithium is widely distributed in tissues after oral, intraperitoneal or intravenous administration;

reviews in e.g. (28, 38). Later studies reported that bone and endocrine glands (thyroid, pituitary, and adrenal) accumulated lithium to a greater extent than other tissues (26, 28). Several studies on lithium concentration in different brain areas have been performed (28). Studies with neutron activation of histological sections cut from the brain of lithium treated mice have shown that the concentration of lithium is greatest in the thalamus ($t_{1/2}$ = 21 hours), slightly less in striatum and neocortex ($t_{1/2}$ approximately 18 hours), and lowest in the hippocampus ($t_{1/2}$ = 14.7 hours) (180). In rats, the levels of lithium in brain 24 hours after treatment with single doses of lithium chloride decreased in the following order: caudate > cerebral cortex >thalamus >hippocampus >cerebellum. After 7 or 14 daily doses of lithium chloride the concentrations of lithium were still highest in the cerebral cortex and caudate, and lowest in the cerebellum (69, 136).

7.2.2 Humans

From the systemic circulation lithium is initially distributed in the extracellular fluid and then accumulates to various degrees in different organs. The ion probably does not bind to plasma or tissue proteins to a great extent, and the final volume of distribution is similar to that of the total body water (33, 87). Lithium can substitute for sodium or potassium in several transport proteins thus providing a pathway for lithium entry into cells (166). Lithium is distributed unevenly in the tissues. At steady-state the concentration is lower in the liver, erythrocytes and cerebrospinal fluid than in serum. In contrast, it is higher in e.g. kidneys, thyroid and bone (10, 38, 123, 142). Brain lithium concentrations are typically less than those in serum after both acute doses and at steady state. In most studies brain lithium concentrations exhibit later peaks and slower rates of elimination than serum concentrations (87). Lithium crosses the placenta and is excreted in breast milk, breast milk levels being approximately 50% of that of maternal serum (165, 171). The serum lithium concentrations in nursing infants have been reported to be 10-50% of the mothers' lithium levels (100, 144).

7.3 Biotransformation

Lithium is not metabolised to any appreciable extent in the human body (87, 104, 129).

7.4 Excretion

7.4.1 Experimental animals

The renal elimination of lithium has been investigated in a number of studies. It has been shown that lithium is mainly excreted via the kidneys through glomerular filtration and that a considerable fraction of the filtered lithium is subsequently reabsorbed in the tubules (140). Like in humans, lithium clearance in animals is closely related to the sodium balance, and the risk of lithium intoxication is inversely correlated with sodium intake (38, 124, 140). In a review by Attias *et al.* 2- and 3-compartment models of distribution and elimination are discussed (9).

The first study proposing a 2-compartment model of lithium for the rat appeared in 1975 (94). The distribution half-time after a single intraperitoneal injection of 2 mmol Li/kg body weight (Li-adipinat) was 5 hours (94). In a later study it was shown that the distribution- and elimination half-times in rats decreased with age (86). The elimination half-time in serum after single or few doses of lithium has been reported to be 11-12 hours in adult rats, and 23 hours in 5-day-old rats (86, 94). The higher half-time in rat pups was correlated to a lower renal clearance and to a higher rate of tubular reabsorption of lithium; review in (9). In a cross-over study, Rosenthal *et al*. found a mean plasma lithium half-time of 21.6 hours in adult dogs given 1 mmol/kg body weight of a 4% aqueous solution of lithium chloride as a single intravenous dose (132).

7.4.2 Humans

Over 95% of a single oral dose of lithium ion is excreted unchanged through the kidneys; reviews in e.g. (10, 38). One- to two thirds of the dose administered is excreted during a 6-12 hours initial phase, followed by slow excretion over the next 10-14 days. Less than 1% of a single dose of lithium leaves the human body in faeces and 4-5% is excreted in the sweat. Lithium is freely filtered through the glomeruli, and approximately 80% is reabsorbed together with sodium and water mainly in the proximal tubules. With repeated administration lithium excretion increases during the first 5-6 days until a steady state is reached between ingestion and excretion (10, 166). Two- and three-compartment models have been used to describe lithium kinetics in man. The reported distribution half-times in serum and plasma are approximately 2-6 hours. Lithium has an elimination half-time of 12–27 hours after a single dose, but its elimination half-time can increase to as long as 58 hours in elderly individuals or patients taking lithium chronically (9, 166). However, the volume of distribution and clearance are relatively stable in an individual patient, although there is a considerable variation in lithium pharmacokinetics among subjects (9, 10). Excretion of lithium is directly related to the glomerular filtration rate (GFR), so factors that decrease GFR (e.g. kidney disease or normal ageing) will decrease lithium clearance (10, 123, 173). In addition, factors that increase proximal tubular reabsorption of sodium (e.g. extrarenal salt loss, decreased salt intake, or the use of diuretic drugs) decrease the clearance of lithium (123).

In summary, the excretion of lithium is chiefly through the kidneys. Factors that decrease GFR or increase proximal tubular reabsorption of sodium will decrease the clearance of lithium. After chronic administration of lithium the elimination half-time is increased.

7.5 Toxicokinetic interactions

About 80% of the filtered load of lithium is reabsorbed in the proximal renal tubuli in tandem with sodium. This close association with sodium homeostasis explains that the effects and toxicity of lithium in lithium therapy are largely related to alterations in sodium balance (affecting the tubular reabsorption of

sodium and hence lithium), and to renal states affecting the GFR (87). Thiazide diuretics which inhibit distal tubular sodium reabsorption may increase the proximal tubular reabsorption of sodium and hence lithium, and lead to toxic lithium concentrations (59, 129). The use of certain non-steroidal antiinflammatory drugs (NSAIDs) may increase the serum lithium and decrease the clearance of lithium probably through inhibition of prostaglandin synthesis, which in turn affects the electrolyte transport in tubuli (59, 118). Disturbances in fluid and electrolyte regulatory mechanisms may also occur with angiotensin converting enzyme (ACE) inhibitors (11). Increased serum concentrations of lithium have been reported in patients taking ACE-inhibitors against hypertonia. The mechanism is unclear but it has been suggested that supression of the renin-angiotensin-aldosterone system by ACE-inhibitors may be responsible (129).

8. Biological monitoring

Monitoring studies on biological levels in workers are virtually missing, whereas biological monitoring of urinary, plasma and serum levels in general populations and psychiatric patients is common. Urine is not a suitable medium for lithium monitoring, because the excretion rate of lithium varies over the day, even if the amount of lithium excreted per 24 hours during steady state is essentially equal to the daily dose (35). The possibility of using salivary lithium for monitoring dosing has been extensively investigated. However, saliva lithium levels are limited by wide interindividual variability of the saliva to plasma ratio, and there is controversy over the intraindividual stability of this ratio (35, 165).

Monitoring of serum lithium levels may not reflect the body burden. Red blood cell lithium levels may be a more accurate reflection of tissue concentrations (149). The lithium erythrocyte/plasma ratio has been recommended as a marker for compliance in lithium treated patients, as it does not change much in steady state conditions (35). In a study on lithium exposed workers a correlation between lithium in personal air samples and serum was shown (85).

9. Mechanisms of toxicity

9.1 Local toxicity

Lithium and some lithium compounds are irritating or even corrosive to the mucosa of the respiratory tract and eyes and to the skin, due to alkalinity. These compounds are either alkaline *per se*, or form alkaline compounds on contact with water. For example, pure lithium and lithium hydride form highly alkaline lithium hydroxide (16). However, strong reducing properties, as with lithium hydride, may also contribute to the irritant action of a compound (1). The toxicity of lithium hydride differs markedly from that of the soluble salts because of its great

chemical reactivity, particularly with moisture, producing marked irritancy and corrosiveness to tissues (16).

9.2 Systemic toxicity

9.2.1 General

The pharmacological activity of lithium is dominated by changes in neurotransmission, neuroendocrine function and renal mechanisms (46). The mechanism(s) of its cerebral and actions in other organs remain unclear. However, the atomic and ionic radii of lithium and magnesium are similar, the electronegativity is the same as that of calcium, and the hydrated radius and polarising power of lithium lie between those of magnesium and calcium. Due to these similarities lithium may interact with magnesium- and calcium dependent processes in physiology e.g. at binding sites on proteins (27, 38, 97). In fact, interaction with group IIA (Mg, Ca) cations, e.g. in the inositol lipid cycle, has been proposed as a basis for the pharmacological mode of action of lithium (27, 28). In biological systems, e.g. in transport across membranes, lithium may also interact with sodium and potassium (38). Both membrane transport systems and ion channels play roles in the regulation of intracellular lithium (96). Some important mechanisms operating in the central nervous system are described below. These mechanisms are to various extents operative also in other organs.

9.2.2 Central nervous system

Universal cerebral inositol depletion has been put forward as one plausible mechanism by which lithium causes mood stabilisation. Allison and Stewart (2) demonstrated that lithium irreversible inhibits inositol-1-monophosphatase and Berridge and others (17, 22, 69, 81, 90, 96, 136, 181) have shown that the reduction of cerebral inositol levels was associated with this action of lithium.

Evidence has also been demonstrated that lithium inhibits the activity of adenylate cyclase, and thus the formation of cyclic adenosine monophosphate (cAMP) in a variety of signalling pathways. Inhibition of both noradrenaline and forskolin stimulated accumulation of cAMP by lithium has been reported (112, 148).

It has also been suggested that the target of lithium action could be glycogen synthase kinase-3 (GSK3). As GSK3 is a pro-apoptotic signalling enzyme, inhibition of the enzyme by lithium may have a protective effect in neuronal cells (82, 111).

Hashimoto *et al*. have shown that lithium has neuroprotective actions. They showed that lithium inhibited glutamatergic excitotoxicity by inhibiting the N-methyl D-aspartate receptor mediated calcium influx (63). The authors suggest that interaction of lithium with the major excitatory neurotransmitter in the brain, glutamate, might be behind the mood stabilising effects of lithium.

Lithium, through modulating basic cellular signalling pathways, is capable of modulating several neurotransmitter systems in the brain such as cholinergic, serotonergic, noradrenergic and dopaminergic pathways (13, 160, 179).

Lithium also has a few dramatic interactions with cholinergic drugs and cholinergic compounds, such as organophosphates, that may be relevant to the occupational environment. Several studies implicate that lithium amplifies cholinergic-induced convulsions and associated neuronal phosphoinositide signalling, and greatly increases the likelihood of severe brain damage (67, 68, 70, 83, 137, 138).

9.2.3 Other organs

The mechanism behind the impaired concentrating ability of the kidneys is lithium's inhibition of the action of antidiuretic hormone (ADH), so that the reabsorption of water in the tubuli is hampered (164). Besides inhibiting the response to ADH, lithium inhibits the renal response to aldosterone and this leads to a decreased reabsorption of sodium in the distal tubuli (150, 164) (see chapter 11.3.1). For further readings on possible pathogenesis behind the Li-induced damage to distal tubules, see e.g. (32, 73).

Lithium is concentrated within the thyroid and inhibits thyroid hormone synthesis and release (108, 166). Lithium decreases the sensitivity of the thyroid gland to the thyroid-stimulating hormone (TSH), which causes an increase in plasma levels of TSH. In most cases this is enough to maintain a euthyroid state (49). For further readings on mechanisms of lithium-associated effects of thyroid function, see e.g. (89, 92, 93).

9.3 Summary

Lithium and some lithium compounds e.g. lithium hydride and lithium hydroxide are irritating and corrosive to the respiratory tract, eyes and skin due to alkalinity. Strong reducing properties, as with lithium hydride, may also contribute to the irritant action of a compound. Other lithium compounds e.g. the soluble salts are not particularly irritating.

The pharmacological activity of lithium is dominated by changes in neuro-transmission, neuroendocrine function and renal mechanisms. Interaction or substitution of lithium for sodium, potassium, magnesium and calcium may be fundamental to both the beneficial and harmful effects of lithium. The key mechanisms through which lithium affects the brain include inhibition of cerebral inositol pool, inhibition of adenylate cyclase and cAMP formation, inhibition of GSK3 and apoptosis, and inhibition of activation of glutamatergic N-methyl D-aspartate receptors contributing to neuroprotection. These mechanisms are to various extents operative also in other organs.

10. Effects in animals and in vitro studies

As a vast number of animal and human studies on the toxicity of lithium have been published during the last 50 years *in vitro* toxicity studies are generally not discussed here. However, a great number of *in vitro* studies have been conducted

on the mechanisms of lithium action, see e.g. (25, 50). Furthermore, since there is now abundant information on adverse effects of lithium in patients, only a few animal studies of special relevance for occupational exposure will be referred to in the following.

10.1 Irritation and sensitisation

Groups of rats, mice, guinea pigs and rabbits were exposed to 5-55 mg LiH/m^3 (4–48 mg Li/m^3) at 50% relative humidity for 4-7 hours. All concentrations of lithium hydride caused the animals to sneeze and cough. Levels above approximately 10 mg LiH/m^3 corroded certain areas of the body fur and the skin on the legs. Occasionally severe inflammation and irritation of the eyes were seen and in a few animals the external nasal septum was destroyed. These actions were attributed to the alkalinity of the hydrolysis product, LiOH (156). In the same study some ulceration of nose and forepaws, inflammation of eyes, partial sloughing of mucosal epithelium of trachea and in some lungs emphysema was seen following exposure to approximately 5 mg LiH/m^3 for 5 days (average exposure 4 hours/day), when the animals were killed immediately after or up to 14 days after the end of exposure. No histopathological changes in the lung attributable to lithium hydride exposure were noted 2-5 months post-exposure (156).

In two other studies rats were exposed for 4 hours to aerosols containing 80% lithium carbonate and 20% lithium hydroxide or lithium oxide (aerosol concentration: 620, 1400, 2300, or 2600 mg/m^3), primarily lithium hydroxide and approximately 23% lithium carbonate (aerosol concentration: 570, 840, 1200 or 1500 mg/m^3) or primarily lithium monoxide with some lithium hydroxide and 12% lithium carbonate (aerosol concentration: 500, 750, 1000 or 1500 mg/m^3). The most prominent histopathological changes were ulcerative or necrotic laryngitis, erosive to ulcerative rhinitis often accompanied by areas of squamous metaplasia and in some cases pulmonary lesions, suggested to be secondary to the upper respiratory tract lesions (60, 128). The lesions were seen mainly in the two highest exposure groups (for all three aerosols), indicating that there was some dose-response pattern. However, lithium carbonate produced both fewer and less severe lesions than the other two exposure regimens at similar concentrations. None of the animals (0/16) exposed to 620 mg/m^3 of the aerosol containing 80% lithium carbonate suffered from rhinitis, laryngitis or alveolitis, whereas these lesions were seen in a few animals exposed to the other two aerosols, at the two lowest concentrations.

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. Light and electron microscopy of the lungs, and of macrophages recovered by lung lavage, showed no significant effects with respect to inflammatory changes. Nor were there any significant changes in the oxidative metabolic activity in these macrophages or in the content of phospholipides in lung tissue (77).

10.2 Effects of single exposure

The acute toxicity of lithium chloride in animals is only slightly lower by the oral than by the parenteral routes, indicating a high absorption from the gastrointestinal tract (159). The rat and rabbit oral lethal dose for 50% of the exposed animals at single administration (LD_{50}) for lithium chloride was 757 and 850 mg/kg body weight, respectively (18 and 20 mmol Li/kg body weight). For lithium carbonate, the dog and mouse oral LD_{50} values were 500 and 710 mg/kg body weight (13.5 and 19 mmol Li/kg body weight, respectively) (154, 159).

Prominent symptoms at short-term exposure to lithium compounds are diarrhoea and gastro-enteritis, which have been frequently reported in animal studies (139, 159). In a study on adult beef-type cattle given 250, 500 or 700 mg Li/kg body weight as lithium chloride as a single oral dose via ruminal intubation signs of intoxication, serum levels, and tissue/organ deposition were dose- and time-related (80). None of the animals in the low-dose group died. In the 500 mg Li/kg body weight group 3 of 4 animals died within 7-11 days, and in the 700 mg Li/kg body weight groups all died within 4-7 days. The mean serum Li levels peaked at 8 hours post-treatment and were in the two high-dose groups 5.8 and 7.8 mM. Dominating symptoms were initial salivation, diarrhoea, decreased water and food intake, and finally anuria. In the high-dose group severe depression and ataxia was also seen. The low-dose animals had only initial salivation and a slight transient diarrhoea. Post-mortem and histopathological examination of tissues showed inflammation of the gastrointestinal tract of varying degrees of severity as the most constant and apparent lesion. In the kidneys there was a slight interstitial nephritis with cloudy swelling in the proximal tubules. A cloudy swelling, oedema, and cirrhosis was also seen in the triad area of the liver.

In a study by Greenspan *et al*. rats were exposed for 4 hours to an aerosol that contained approximately 80% lithium carbonate and 20% lithium hydroxide and lithium oxide. A mean 14-day lethal concentration for 50% of the exposed animals at single exposure (LC_{50}) of 1 800 mg/m^3 was calculated (60). At the same laboratory a calculated mean 14-day LC_{50} was 960 mg/m^3 for an aerosol with primarily lithium hydroxide and about 23% lithium carbonate, and 940 mg/m^3 from an exposure atmosphere that was primarily lithium monoxide with some lithium hydroxide and 12% lithium carbonate (128).

10.3 Effects of short-term exposure

In a study on rats, guinea pigs and rabbits no histopathology attributable to lithium hydride was found in the lung, liver, kidney, trachea or lymph nodes 2-5 months after exposure to about 5 mg Li/m^3 for 5 days (average exposure 4 hours/day) (156).

The salt balance is an important determinant in lithium toxicity. Dogs survived daily oral doses of 50 mg LiCl/kg body weight (1.2 mmol Li/kg body weight) throughout the total experimental period (150 days) on normal sodium intake, whereas the same dose was lethal in 12-18 days on a low sodium intake (124). In

rats kept on a sodium-poor diet, treated with various doses of lithium as daily intraperitoneal injections of lithium chloride, a daily dose of 1 mmol Li/kg body weight led to temporary increases in serum lithium concentrations but no accumulation, whereas 3 mmol Li/kg body weight gave a continuous rise in serum lithium levels after a few days. In rats receiving extra sodium the lithium concentration in serum raised continuously in animals treated with 5 mmol Li/kg body weight/day, but not in animals receiving 3 mmol Li/kg body weight/day. However, in all rats with lithium accumulation, the result was an irreversible deterioration of the renal function and finally death. Histological examination revealed acute degenerative changes in proximal tubuli cells. In other tissues including the brain no morphological changes were found, except for moderate vacuolisation in the adrenals. At lower doses the kidney toxicity was reversible if administration of lithium was stopped. From his study Schou concluded that the principal toxic action of lithium was on the kidney function (139). For further reading about the renal toxicity of lithium in animals, see the reviews by Thomsen (163, 164).

10.4 Mutagenicity and genotoxicity

Lithium compounds have been tested in a number of *in vitro* and *in vivo* studies for mutagenicity, DNA damage, chromosome aberrations (CA) and sister chromatid exchanges (SCE); reviews in e.g. (97, 174, 176). Many of these studies have failed to demonstrate an adverse effect of lithium. Positive results have also been obtained, but generally at high doses (doses equivalent to therapeutic doses or higher) (Table 9). Only in a few studies have genotoxic effects been indicated at lower doses (see below). Weiner *et al*. concluded that, in general, the data in multiple mutagenicity tests on a variety of lithium salts support the conclusion that lithium lacks mutagenicity (176).

In an incompletely reported plant assay, the Vicia faba root tip assay, a dose-dependent increase in CA was seen with lithium chloride (5-5000 μg/ml; 8000 μg/ml was toxic) (135). However, the frequency of various types of aberrations was not specified and the significance of the increases was not given in the study. In a study in mice a significant increase in CA in bone marrow cells was reported at all doses when lithium acetate (0.05, 0.5, 5 mg/kg body weight), carbonate (1.2, 12, 120 mg/kg body weight) or chloride (0.2, 2.1, 21.25 mg/kg body weight) was administered perorally, whereas there was no significant elevation of SCE (155). The study failed to define the frequency of various types of aberrations and the number of cells studied. In addition, their negative control values were higher than in other published reports and no positive controls were included (176). When lithium hypochlorite was tested in isolated Chinese hamster ovary (CHO) cells there were significant increases in CA at 25, 50 and 200 μg/ml with S9 and 120 μg/ml without S9 (176). With regard to the hypochlorite ion it must be considered that, both calcium and sodium hypochlorites have been reported to increase CA in Chinese hamster fibroblasts from lung cells (176). Lithium hypochlorite was negative in other mutagenicity/genotoxicity tests (Table 9). In the CHO/HGPRT

Table 9. Genotoxicity tests with different lithium compounds.

Compound	Test system	Endpoint	Test concentrations	Result[a]	Reference
LiCl	Ames test/*S. Typhimurium* TA98, 100, 1535, 1537	gene mutation	100-10 000 μg/ml	-/-	(64)
	B. Subtilis rec-assay	DNA damage	0.005-0.5 M	-/nt	(84)
	B. Subtilis rec-assay	DNA damage	0.05 M	-/nt	(115)
	HeLa DNA synthesis inhibition test *in vitro*	DNA damage	0.07 M	+/nt	(119)
	V. faba root tip assay	CA	5-8000 μg/ml	+/nt	(135)
		micronuclei	5-8000 μg/ml	-/nt	(135)
	Human lymphocytes *in vitro*	CA	50-150 μg/ml	+	(42)
	Mouse bone marrow *in vivo*	CA	0.21-21.25 mg/kg bw	+	(155)
		SCE	0.21-21.25 mg/kg bw	-	(155)
Li-citrate	Ames test/*S. Typhimurium* TA98, 100, 1535, 1537, 1538	gene mutation	≤34 μmol/plate	-/-	(88)
	E. coli K12/343/113	gene mutation	≤10 mM	-/-	(88)
	Host-mediated assay/mouse	gene mutation	≤4 mmol/kg bw	-	(88)
	Sex-linked recessive lethal test/*Drosophila*	gene mutation	20 mM	-	(88)
	Micronuclei/mouse bone marrow *in vivo*	chromosome damage	2·1-3.9 mmol/kg bw	+	(88)
Li_2CO_3	Chinese hamster V79/HGPRT assay	gene mutation	1500-3000 μg/ml	+/+	(153)
	DNA inhibition test/EUE cells *in vitro*	DNA damage	1500-3000 μg/ml	+/+	(153)
	Alkaline elution of DNA/EUE cells *in vitro*	single-strand breaks	150-500 μg/ml	+	(153)
	Human lymphocytes *in vitro*	chromosome damage	Up to doses equivalent to about 10 times the therapeutic dose	-	(167)

Table 9. Cont.

Compound	Test system	Endpoint	Test concentrations	Result[a]	Reference
	Mouse bone marrow and testis cells *in vivo*	chromosomal abnormalities	325-1300 mg/kg bw for 6-30 days	+	(158)
	Mouse bone marrow *in vivo*	CA	1.2-120 mg/kg bw	+	(155)
		SCE	1.2-120 mg/kg bw	-	(155)
Not given	Human leucocytes *in vitro*	CA	1.2-2.4 mM	-	(53)
Not given	Rat bone marrow *in vivo*	CA	86 mg/day for 3 days	-	(23)
Li-acetate	Mouse bone marrow *in vivo*	CA	0.05-5 mg/kg bw	+	(155)
		SCE	0.05-5 mg/kg bw	-	(155)
Li_2SO_4	*S. cerevisiae* D7	gene mutation	0.1 M	+	(151)
	S. cerevisiae D7	gene conversion[b]	0.1 M	+	(151)
LiClO	Ames test/*S. Typhimurium* TA98, 100, 1535, 1537, 1538	gene mutation	5-500 µg/plate	-/-	(176)
	CHO/HGPRT assay	gene mutation	100-800 µg/ml	-/?	(176)
	Unscheduled DNA-synthesis test/rat hepatocytes *in vitro*	DNA damage	1.5-350 µg/ml	-	(176)
	CHO cells *in vitro*	CA	15-200 µg/ml	+/+	(176)
	Rat bone marrow *in vivo*	CA	20-1000 mg/kg bw	-	(176)

+=positive response; -=negative response; ?=equivocal response; nt= not tested

[a] results of tests without/with addition of a metabolic activation system

[b] test considered less relevant to human risk assessment (176)

in vitro assay lithium hypochlorite was negative without metabolic activation and positive at a high dose (675 μg/ml) in one of two trials with metabolic activation (176).

In summary, lithium salts have been tested *in vitro* and *in vivo* for mutagenicity, DNA damage, CA and SCE. Several studies report genotoxic effects of various lithium compounds at high doses, whereas many other studies have failed to demonstrate an effect. Considering the chemical properties of the lithium compounds it is unlikely that they act as direct mutagens. A possible explanation to the apparent genotoxicity may be that it is a secondary effect of increased cell survival caused by lithium's inhibition of GSK3 (see chapter 9.2).

10.5 Effects of long-tem exposure and carcinogenicity

No cancer studies were found.

In a 2-year study on rats ingesting drinking water containing lithium chloride in a concentration of 20 mM no effects on health or behaviour were found, except slight, transitory initial disturbances. The plasma Li levels were 1.5 -2 mM. When administered higher drinking water concentrations, 50 mM LiCl, food and water intake fell within a few days, and the rats became progressively drowsy and asocial on the 3rd to 5th day. Their gait was staggering, and they had a fine muscular tremor. Simultaneously their weight began to drop. The deterioration progressed to stupor and death within 2-3 weeks. The mean plasma Li concentration was 3 mM when behavioural changes were seen, rose to 7 mM during the second week and exceeded 8 mM just before death (168).

10.6 Reproductive and developmental studies

Numerous studies in both lower animals and in mammals have been conducted to evaluate the effects on the developing foetus by lithium exposure during pregnancy; reviews in e.g. (78, 97, 174, 177). In 1969/70 it was reported that cleft palate was a specific teratogenic effect of lithium in mice. In 1973, Weinstein and Goldfield critically evaluated these studies and remarked that the doses of lithium carbonate given were 27 times the usual daily dose in humans and killed 1/3 of the mothers (177). Weinstein and Goldfield also evaluated 5 other teratogenicity studies in rats and mice. Only one reported teratogenic effects, e.g. cleft palate. The authors' conclusion was that teratogenic and toxic effects of lithium were dose-related.

Trautner *et al*. have conducted a teratogenicity study in a group of 52 rats and 100 controls (168). The animals were administered LiCl in a concentration of 20 mM in drinking water producing plasma Li levels of 1.5-2.0 mM. The dose levels were evaluated to be just subtoxic in a fore-going study. These authors found no malformations or other defects in the lithium-exposed litters. Neither were there any differences in size and weight among these and untreated controls. If the young were maintained at the same lithium concentration in the drinking water,

they showed slightly lower growth, but developed finally into adult rats indistinguishable from normal rats.

More recent animal studies following the Environmental Protection Agency (EPA) guidelines for evaluating developmental toxicity confirmed earlier findings that lithium is not uniquely toxic to development (78). In that review a no observed adverse effect level (NOAEL) of 10 mg Li/kg body weight during the critical periods of differentiation and organogenesis was considered to accurately estimate the true no effect level for both developmental and maternal toxicity.

In summary, the adverse foetal outcomes reported from animal studies occur only around levels that are toxic to the mother. Further, malformations were either species specific (like cleft palate in mice) or non-specific effects occurring at exposure to a variety of chemicals at maternally toxic doses. Cardiovascular defects in the offspring were not observed in any of the animal studies (34, 78, 174, 177).

Also fertility has been investigated in animals. The studies were often carried out in such a way that the serum level of lithium in the tested animals was similar to that of treated human patients and general toxicity often resulted in animals at these levels (65). However, in an inadequately reported study effects on reproduction were found in mice at doses at which the animals did not appear to suffer from ill effects. Mating pairs of mice received lithium chloride in their drinking water at concentrations of 10, 20, 30, 50, 100 and 200 mM. In mice given 50 mM LiCl 2 weeks before mating and during gestation and lactation, the reproduction capacity was reduced. The time between litters was increased and the animals did not produce as many litters as controls. The plasma Li level was approximately 0.7 mM. Furthermore, the mortality of the lithium pups between birth and weaning was considerably higher than in controls. When the animals were maintained on 50 mM LiCl from 5 weeks before mating and onwards pups also showed delayed postnatal growth and development. Mice given drinking water containing 100 mM LiCl did not reproduce at all (114).

Significant inhibition of spermatogenesis was found in a study in immature rats after daily subcutaneous injections of 2 mg LiCl/kg body weight (0.05 mmol/kg body weight) for at least 15 days. It was concluded that lithium had an adverse effect on testicular function by reducing serum levels of follicle stimulating hormone, luteinising hormone, prolactin and testosterone. Diminished activity of key enzymes in androgen biosynthesis was also seen. Additionally, administration of lithium chloride for 20 and 25 days decreased the testicular, prostatic and seminal vesicular weights significantly. Serum Li levels were approximately 0.5 mM (57). The same authors showed in a similar study, that a prolactin injection 8 hours after treatment with lithium chloride protected from most of these effects (luteinising hormone and prolactin levels in serum still decreased, compared to controls) (56).

No effect on sperm motility was found in one *in vitro* study with lithium carbonate (98). More recent *in vitro* studies with human sperm reported decreased motility, at concentrations comparable with those reported in semen after oral administration of lithium to patients (126, 147).

To summarise, the adverse foetal outcomes reported occur only around levels that are toxic to the mother. Significant inhibition of spermatogenesis and decreased fertility has been seen in animals at serum lithium levels similar to those reported in patients. However, the amount of evidence and the quality of the human *in vitro* studies is insufficient for a conclusion on the effects on fertility.

11. Observations in man

During the 20th century many epidemiological studies on the medical effects of lithium have been conducted, such as the relation between drinking water lithium concentrations and mental hospital admissions, lithium and cardiovascular mortality, and lithium and dental caries. Most studies have suffered from methodological problems or lack of replicable or substantial results; e.g. in none of the cardiovascular studies was the intake of lithium from foodstuffs examined, although the daily exposure from drinking water is generally less than that from food. Also, comparisons between studies are difficult due to the great variations in measurement techniques and the widely varying levels of lithium considered to be of critical interest (169). In conclusion, there is no clearly established relationship between positive or negative effects and naturally occurring lithium (14, 169).

Most cases of lithium toxicity involve its medicinal use, whereas reports of adverse effects of lithium in industry are rare, although lithium is widely used industrially (46).

11.1 Irritation and sensitisation

Lithium hydride, lithium tetrahydroaluminate and lithium tetrahydroborate have been described as highly corrosive and irritant (24, 97). The only data on this matter found in literature are presented below.

In 1964, Cracovaner called attention to the effect on the mucous membranes by lithium hydride. He described in detail the case history of a young physicist who had been exposed to lithium hydride when a cylinder exploded. The patient had been admitted to the hospital because of burns of the eyes, larynx, nose, esophagus and trachea and developed severe constrictions in both trachea and larynx (39). Chemical pulmonary oedema was reported in another study in a worker following inhalation of fumes of a lithium hydride and argon gas combination for approximately 3-4 minutes (37).

Unpublished studies, referred to in (1) and (16), report effects in workers exposed to very low levels of lithium hydride. Unfortunately, the number of exposed workers and the exposure time are not reported. Beliles (16) reports the results as follows: No effects were observed at the concentration range of 0-0.025 mg LiH/m^3. At 0.025-0.10 mg LiH/m^3, a tickling sensation in the nose was experienced, along with some nasal discharge. This range of concentrations, however, was tolerated by those continuously exposed. When the air concentration reached a range of 0.10-0.50 mg LiH/m^3, a definite nasal irritation with

some coughing was experienced and was not tolerated. At 0.50-1.0 mg LiH/m^3 severe nasal irritation with coughing occurred, and in some workers, eye irritation. Between 1.0 and 5.0 mg LiH/m^3, all effects were severe, and skin irritation occurred. In warmer weather or when sweating occurs, skin irritation appears at lower levels (16). In the ACGIH documentation (1) slightly different information is given: The maximum tolerable concentration in air for brief periods is 0.5 mg LiH/m^3 and workers readily adapt to 0.05 mg LiH/m^3, a concentration that is objectionable to unacclimated individuals. Persons with some degree of adaptation complained of eye and nose irritation at concentrations above 0.1 mg LiH/m^3 and itching of exposed skin areas above approximately 0.2 mg LiH/m^3.

Dust of lithium/aluminium alloys also causes a major irritation of the mucosae. In one study it was stated that at 2 mg/m^3 there was a perceptible irritant action (18).

The frequency of symptoms (based on questionnaires) among workers more or less exposed to alkaline lithium dust was reported in a NIOSH study (134). A comparison between 21 exposed and 23 less exposed workers (57.1% vs. 39.1% were smokers) showed that complaints of sinus problems (42.8% vs. 39.1%), runny nose (38.0% vs. 17.3%), nose bleeds (14.2% vs. 0%), dry throat (52.3% vs. 4.3%), headache (38.0% vs. 8.7%) and skin irritation (38.0% vs. 13.0%) were more frequent among the more exposed workers. The irritant symptoms (especially sinus problems and runny nose) were most troublesome for those involved in hydroxide (pH 12.6) and carbonate (pH 11.2) bagging. Several workers complained of painful skin burns and irritation from exposure to lithium hydroxide at the bagging operation. Lithium levels in total dust obtained at personal sampling in the lithium hydroxide and lithium carbonate bagging areas were 0.02-0.05 and 0.54-1.84 mg Li/m^3, respectively and at stationary sampling 0.02-0.07 and 0.46-0.51 mg Li/m^3, respectively. In the lithium carbonate grinding area the levels were 1.08-3.53 mg/m^3 at personal sampling and 1.31 mg Li/m^3 at stationary sampling (see Table 7).

In another NIOSH study it was reported that workers at a plant producing gear boxes for refrigerator ice makers had noticed irritation (178). The workers had experienced upper respiratory symptoms, headache, skin rash, fatigue, and eye irritation, which were thought to be associated with the use of a lithium containing grease. At an initial visit NIOSH found that over 70% of the workers were experiencing marked nasal and/or respiratory symptoms while working. However, no air sampling was made, and it cannot be decided whether it was the lithium content in the grease that caused the symptoms in the workers.

According to Schou lithium does not act as an allergen (143).

To conclude, occupational exposure to alkaline lithium compounds may cause irritation of the airways, eyes and skin. Some of the compounds, like lithium hydroxide and lithium hydride, are highly irritative and corrosive and cause irritation of the upper respiratory tract at low air levels.

11.2 Effects of single exposure

Acute poisoning at single exposure may occur in individuals who are not being treated with lithium. Typically, this is due to an overdose, when someone has ingested lithium accidentally or intentionally. Acute poisoning generally carries less risk, and patients have milder symptoms than observed in other forms of lithium poisoning, since the elimination half-time is shorter in lithium-naive individuals (166). The serum Li level may be high, above 4 mM, without clinical symptoms of toxicity. However, a large acute dose usually promotes diarrhoea and vomiting and ejection of the lithium dose (24).

11.3 Effects of short-term and long-term exposure

11.3.1 Occupational exposure

In a NIOSH report personal air sampling and biological monitoring for lithium was undertaken at a plant producing battery systems. All serum lithium concentrations were on the order of a 1000 times lower than therapeutic concentrations in patients on lithium medication. Workers in areas where lithium exposure was higher reported fewer health problems than workers in an area where lithium exposure generally was lower. The authors concluded that, if past exposures were similar to exposures during the time of the study (see Table 8), it is unlikely that lithium exposures at the plant caused neither the medical conditions that worried some workers nor known side effects or toxic effects of lithium (85).

11.3.2 Lithium therapy

Side effects, i.e. unwanted and potentially harmful effects, which occur when lithium is administered at therapeutic doses, may be seen at 12-hours serum or plasma Li concentrations of 0.5-1.2 mM (107, 172). Some of the most common side effects at 0.5-0.8 mM are moderate nephrogenic diabetes insipidus (NDI) (prevalence 25%), fine hand tremor (15%), weight gain (10-20%), increased TSH-values (5-10%), hypothyreosis (5%), and diarrhoea (5%) (52). Poisoning can occur in patients whose lithium dosage has been increased or in individuals whose renal function has decreased, resulting in an increase in serum lithium levels (166). In the majority of these patients disorders of water and electrolyte balance preceed the lithium intoxication (24, 62). Lithium intoxication may be categorised as mild (1.5-2 mM Li), moderate (2-2.5 mM) or severe (>2.5 mM). However, the clinical presentation of lithium toxicity is only loosely correlated with serum drug concentrations and there is a great variability in severity associated with a given concentration. Generally serum levels of 1.2-1.6 mM Li or somewhat lower may pose a risk for intoxication, but toxic symptoms may be present even when concentrations are well within the recommended therapeutic range (52, 123, 129, 166).

Renal toxicity

The most common side effect is the polyuria-polydipsia syndrome (increased urine volumes, above 3 l/day, and thirst). Lithium in therapeutic serum levels produces an initial diuresis in as many as 50-60% of the patients (49, 107). Some patients develop NDI, which in most cases seems to be reversible when the patient is no longer treated with lithium (10). Besides inhibiting the response to ADH, lithium inhibits the renal response to aldosterone, which leads to a decreased reabsorption of sodium in the distal tubuli (164). If this results in sodium deficiency there is a compensatory increase of reabsorption, which also leads to a fall of the clearance of lithium. In the end there is a fulminating situation with rapidly increasing plasma lithium levels and neurological toxicity (24, 164).

Whether prolonged administration of lithium causes chronic renal insufficiency has been debated during the last 20 years. Two comprehensive literature surveys on renal function during lithium therapy published in 1983 and 1991 evaluated 23 and 20 studies, respectively (19, 59). Both authors remarked that evaluation of the studies was difficult due to methodological differences such as differing methods to measure renal function, and differences in population, duration of therapy, dosage, serum lithium levels, dose schedule, and type of preparation. In the 1983 survey study serum lithium levels were usually around 0.75-0.95 mM (19), but were not given in the survey from 1991. A common finding was a significant decrease in urine concentrating ability and increases of urine volume. Goodnick and Schorr-Cain found no or only small, non-significant changes in GFR in most of the studies (59). The effects on tubular function were not consistent and were reported to be non-significant in about 1/3 of the studies and decreased in 2/3. Both authors concluded that there continued to be a risk of lithium-induced irreversible renal structural and functional changes during long-term administration of lithium in a minority of patients.

In a report from 1998 3 prospective and 3 cross-sectional studies published 1991-1996 were discussed (79). The maintenance serum lithium levels in the prospective studies were 0.6-0.8 mM. These prospective studies although with a limited number of patients indicated neither a significant effect on GFR (except an age-correlated decrease in one study) nor a significant impairment of tubular function during a follow-up period of up to 10 years. The cross-sectional studies were less informative as maintenance serum lithium levels were not given. In one of them GFR was reduced in 21% and the urinary concentrating capacity in 44% of 142 patients with a mean serum lithium at the examination of 0.65 mM and more than 15 years cumulative lithium exposure. Other medications and somatic diseases and/or episodes of lithium toxicity had influence on the renal function (21).

The conclusion in reports and reviews from the last decade is that progressive impairment of glomerular and tubular function is rare in the vast majority of patients (10, 27, 49, 58, 79, 143). A very small group of patients may develop chronic renal insufficiency, and this is related more to other factors, e.g. lithium intoxication, maintenance plasma lithium levels, the psychiatric disorder *per se* or other drugs than to duration of lithium therapy. Based on single case reports on

NDI persisting after treatment some authors state that lithium-induced NDI may become structural and irreversible over time (58).

In summary, the most common side effect is the polyuria-polydipsia syndrome. Some patients develop NDI, which in most cases seems to be reversible. However, a very small group of patients may develop chronic renal insufficiency. Treatment with lithium affects the reabsorption of sodium and this may lead to a fall of the clearance of lithium and rapidly increasing plasma lithium levels.

Neurotoxicity

The most common neuropsychiatric side effect is hand tremor, which occurs in 25-50% of patients and diminishes with time (123). At 12-hours serum Li values of 0.5-0.8 mM fine hand tremor is seen in 15% of patients (52). Signs of mild toxicity include tremor, lethargy, irritability, muscle weakness and slurred speech. The plasma Li level is usually 1.0-1.5 mM (123). The onset of lithium intoxication may be insidious, and is dependent on the intake of lithium, fluid intake, and renal function. As toxicity develops there is a progressive central nervous system impairment (24, 49). At plasma levels of 1.6-2.5 mM signs of moderate toxicity are disorientation, confusion, drowsiness, restlessness, unsteady gait, coarse tremor, dysarthria and muscle fasciculations. Severe neurotoxicity may occur at plasma Li levels above 2.5 mM, and include impaired consciousness (with progression to coma), delirium, ataxia, generalised fasciculations, extrapyramidal symptoms and convulsions (123). The toxicity may develop during hours to days and in the final stage coma intervenes. Plasma Li levels may be 3.0-5.0 mM. Unless immediate life-saving measures are taken the patient will die. The toxic effects on the nervous system are principally the result of the rapid rise in plasma lithium, due to renal failure (24).

Neurotoxicity may occur at therapeutic plasma lithium levels. In these cases lithium is often administered together with another drug, which can interact with lithium. Emilien and Maloteaux reviewed 41 cases with neurotoxicity at therapeutic lithium levels, published 1979-1994 (51). The most common symptoms were confusion, ataxia, course tremor and dysarthria. The range of serum Li levels was 0.3-1.3 mM. In most cases concomitant medications, such as neuroleptics (n=21), antidepressants (n=9), anxiolytics (n=7) or antiepileptics (n=9) were used. Lithium was withdrawn or the dose lowered in all cases but one. Improvement was seen in 26 cases, where lithium and/or another drug, known to increase the toxicity of lithium, was withdrawn. Single cases of peripheral neuropathy correlated with lithium level and duration of treatment have also been reported (49, 91).

Kores and Lader reviewed 43 cases with irreversible lithium neurotoxicity published 1972-1994, and presented a further 7 cases. The most frequent and prominent signs of long-lasting sequelae were cerebellar abnormalities, especially ataxia (coordination disturbances) and dysarthria (disturbances in articulation). The range of serum Li levels was 0.25-7.4 mM (43 cases) and the mean serum level 2.5 mM. In 22 of the reviewed cases lithium was combined with neuroleptic drugs and in 4 cases with anticonvulsants (91).

To summarise, hand tremor is the most common neurological side effect. Signs of mild toxicity may occur at a plasma Li level of 1.0-1.5 mM and include tremor, lethargy, irritability, muscle weakness and slurred speech. As toxicity develops there is a progressive central nervous system impairment. The toxic effects on the nervous system are principally the result of the rapid rise in plasma lithium, due to renal failure.

Hypothyroidism

Side-effects on the thyroidea are also common (107). Increased levels of TSH are seen in 5-10%, and hypothyreosis in 5% of patients, mainly initially and generally in women above 40 years (52).

Effects on the thyroid function are not clearly dose-related. Goitre may develop within weeks of starting lithium therapy, or months to years of lithium treatment (93). Hypothyreosis is more common in women, the female to male ratio being about 5:1. In a review of 16 reports including 4 681 patients the prevalence of lithium-induced hypothyroidism was 3.4% (range 0-23.6%) (92). The risk of developing hypothyroidism is higher in women with thyroid antibodies, while elevated TSH levels are transitory in most patients (29). Lazarus noted that there was a rise in thyroid antibody titers in patients (mostly women) having these antibodies before lithium administration, whereas there was no induction of thyroid antibody synthesis in other patients (93).

Gastrointestinal effects

Gastrointestinal side effects, such as nausea, diarrhoea, and epigastric pain, tend to occur early in lithium treatment, especially during the first weeks (24, 52, 123, 129). However, vomiting and diarrhoea may also be early signs of lithium toxicity in patients on maintenance therapy (49).

Other effects

Lithium has a weak anti-diabetic effect in both humans and animals (10, 49). This effect may play a role in the weight gain observed in many patients (49). Weight gains of up to 10 kg are seen in 10-20% of the patients (52). Pretibial oedema is seen in some cases, but frequently disappears spontaneously (10). At 12-hours serum Li values of 0.5-0.8 mM oedema is seen in 1-5% (women only) (52). Allergic skin reactions are uncommon, but pre-existing acne, folliculitis, and psoriasis may worsen during lithium therapy (10, 43). Acne and similar eruptions are reported by 1-5% of the patients at serum Li levels of 0.5-0.8 mM (52). Effects on the parathyroid and calcium metabolism have been discussed in many studies. However, the effects of lithium on calcium and parathyroid hormone do not appear to be clinically significant (49). Interference with the electrical activity of the heart and brain causing electrocardiogram and electroencephalogram changes have been seen during prolonged use of lithium (10, 143, 172). Also, a benign increase in circulating polymorphonuclear leukocytes, which is reversed after termination of treatment, is reported during chronic use of lithium (10).

11.4 Genotoxic effects

The vast majority of the studies on chromosomal damage in leukocytes, lymphocytes and bone marrow cells in patients do not indicate any increased risk by lithium therapy for CA or SCE (12, 23, 54, 55, 75, 97, 105, 170, 174, 177). An increase in chromosomal damage in lymphocytes derived from 10 patients on lithium carbonate therapy (many were treated with other drugs as well), compared to 3 controls, was seen in one study (42). In another study significantly higher frequencies of breaks and hypodiploid cells were reported in 3 patients treated with lithium, compared to 11 controls (53). However, no details on methods or number of cells analysed are given in the paper. Weiner (174) concludes that, based on all data on lithium in human, animal and genotoxicity studies, the weight-of-the-evidence indicates that the lithium ion is not mutagenic, does not damage DNA and does not induce CA in patients.

11.5 Carcinogenic effects

Tumour-inducing effects have not been reported, and there is no evidence that lithium treatment has caused an increased incidence of any cancer or tumour type (116).

11.6 Reproductive and developmental effects

Lithium passes the placenta, and the concentrations in maternal and umbilical blood are similar (145). Increased incidence of Ebstein's anomaly (a rare congenital heart defect) has been reported in babies born by mothers on lithium therapy. These reports were based on case reports and on the findings in the Register of lithium babies during the 1970s (10, 129, 143).

Later retrospective case control studies, referred to in Jacobson *et al*. (74), have not confirmed these findings. In 1992, Jacobson *et al*. published a prospective multicentre study of pregnancy outcome after lithium exposure during the first trimester (74). Rates of major congenital malformations did not differ significantly between the lithium and control groups and the authors' conclusion was that lithium was not a major teratogen. In 1994, Cohen *et al*. published a re-evaluation of all controlled epidemiological studies, which had been published since the alarming reports from the Register of lithium babies (34). They found 4 large case-control studies dealing with Ebstein's anomaly and 2 cohort studies, one register-linked from Sweden and the Jacobson *et al*. study mentioned above. In the 4 case-control studies 208 children with Ebstein's anomaly were found. None of the mothers of these children was exposed to lithium during pregnancy. In the Swedish study from 1983 none of 59 lithium-exposed infants had Ebstein's anomaly, but the risk ratio for congenital heart defects was 7.7 (95% confidence interval 1.5-41.2). Cohen *et al*. concluded that the teratogenic risk of first-trimester lithium exposure is lower than previously suggested (34).

In conclusion, later studies show that the risk of foetal cardiovascular malformation at lithium therapy is much lower than previously stated. The risk of Epstein's anomaly was suggested in one study not to be above 1/5000 live births (10). In another study the revised risk for this congenital malformation following first-trimester use of lithium drugs was estimated to be 1/2000 to 1/1000 (3).

Only few studies looking for developmental effects in children exposed *in utero* to lithium have been found. In a follow-up study on 60 children from the Register of lithium babies without congenital abnormalities there was no increased frequency of physical or mental abnormalities as compared with non-exposed siblings (141). "Developmental milestones" were assessed in 22 babies in the Jacobson study (74). Study and control group did not differ in age of attainment of any of these milestones (smiling, lifting head, sitting, crawling, standing, talking, and walking).

Concerning male reproductive ability, a few early case studies have reported impotency, which disappeared when lithium was withdrawn. It is not possible to draw any valid conclusions from these studies. A decrease in sperm viability from 70 to 55%, but no significant change in sperm count or motility was found in a study on 4 patients after 3 weeks of continuous therapy with lithium carbonate (98).

In summary, there is a very low risk, if any, of teratogenic effects of lithium therapy at present therapeutic doses. Available data on effects of male reproductive ability at lithium therapy are insufficient for a conclusion.

12. Dose-effect and dose-response relationships

There is very little information from the work environment on dose-effect and dose-response relationships of lithium compounds. However, there are some data on lithium hydride (Table 10). No irritation was observed in the concentration range of 0-0.025 mg LiH/m^3. Slight irritation in the nose was reported at 0.025-0.10 mg LiH/m^3, whereas definite nasal irritation was found at 0.10-0.50 mg LiH/m^3. At 0.50-1.0 mg LiH/m^3 severe nasal irritation occurred, and in some workers, eye irritation (16). Some data also exist for lithium hydroxide and lithium carbonate. Lithium hydroxide seems to be irritating at approximately the same air levels as LiH. Upper respiratory symptoms and skin irritation was reported at approximately 0.02-0.05 mg Li/m^3 in total dust. Upper respiratory irritation was also reported at exposure to lithium carbonate at 0.54-1.84 mg Li/m^3 in total dust (134).

Other dose-effect and dose-response relationships in humans are derived from patients exposed to lithium by the oral route (Table 11-12). Side-effects may be seen at 12-hours serum or plasma Li concentrations of 0.5-1.2 mM (107, 172). However, there is a narrow gap between therapeutic and toxic concentrations. Generally serum levels of 1.2-1.6 mM Li or somewhat lower may pose a risk for intoxication, but toxic symptoms may be present even when concentrations are well within the recommended therapeutic range (52, 123, 129, 166). The clinical

presentation of lithium toxicity is only loosely correlated with serum drug concentrations and there is a great variability in severity associated with a given concentration (166).

Few animal studies with exposure by inhalation have been found. However, in one study exposure to 5-55 mg LiH/m^3 for 4-7 hours caused the animals to sneeze and cough. Levels above approximately 10 mg LiH/m^3 were irritating to the eyes and airways and corroded certain areas of body fur and skin. Ulceration of nose and forepaws, inflammation of eyes, partial sloughing of mucosal epithelium of trachea and in some lungs emphysema were seen following exposure to approximately 5 mg LiH/m^3, 4 hours/day for 5 days (156). In another study rabbits were exposed to aerosols of lithium chloride containing 0.6 and 1.9 mg Li/m^3 for 4-8 weeks, 5 days/week, 6 hours/day. No significant effects with respect to inflammatory changes were found (77).

Table 10. Dose-effect data for humans exposed to lithium hydride by inhalation.

Exposure level (mg/m^3)	Effect	Reference
0-0.025	No effect	(16)
0.025-0.10	A tickling sensation in the nose, some nasal discharge, tolerated by those continuously exposed	(16)
0.05	Workers readily adapt, objectionable to unacclimated individuals	(1)
0.10-0.50	Definite nasal irritation with some coughing, not tolerated	(16)
>0.1	Eye and nose irritation in persons with some degree of adaptation	(1)
>0.2	Itching of exposed skin	(1)
0.5	Maximal tolerable concentration for brief periods	(1)
0.50-1.0	Severe nasal irritation with coughing, in some workers eye irritation	(16)
1.0-5.0	Severe irritant effects, skin irritation	(16)

Table 11. Dose-effect data in patients on lithium therapy.

Serum/plasma level (mM Li)	Adverse effect	Reference
0.5-0.8	Reversible moderate NDI, fine hand tremor, weight gain, increased TSH values, hypothyreosis, diarrhoea, oedema, acne-like eruptions	(52)
0.6-0.8	No significant changes of tubular function or GFR	(79)
0.75-0.95	Decrease in urine concentrating ability, increased urine volumes	(19)
1.0-1.5	Tremor, lethargy, irritability, muscle weakness, slurred speech	(123)
1.6-2.5	Disorientation, confusion, drowsiness, restlessness, unsteady gait, coarse tremor, dysarthria, muscle fasciculations	(123)
>2.5	Impaired consciousness (with progression to coma), delirium, ataxia, generalised fasciculations, extrapyramidal symptoms, convulsions	(123)

Table 12. Prevalence of side effects from lithium therapy at 12-hours serum Li concentrations of 0.5-0.8 mM (52).

Side effect	Prevalence (%)	Comment
Reversible moderate NDI	25	
Fine hand tremor	15	
Weight gain	10-20	
Increased TSH values	5-10	
Hypothyreosis	5	Mostly initially and in women older than 40 years
Diarrhoea	5	
Oedema	1-5	Only in women
Acne-like eruptions	1-5	

13. Previous evaluations by national and international bodies

Two evaluations on lithium compounds (lithium nitride, lithium boron nitride, lithium stearate) have been performed by the Swedish Criteria Group for Occupational Standards (102, 103). No information was found in the literature

regarding biological effects of these lithium compounds. However, it was stated that lithium nitride, probably gives rise to strongly caustic and irritating substances in contact with moisture on the mucous membranes.

The ACGIH recommend an occupational exposure limit of 0.025 mg/m^3 (as time-weighted average) for lithium hydride to minimise the potential for dermal, nasal and eye irritation (1). The German MAK Committee has concluded, that the toxicological data for lithium hydride provided insufficient foundation for a MAK value (44, 45).

Emergency and continuous exposure guidance levels (EEGL and CEGL) for lithium bromide were developed in 1987 by the Subcommittee on Submarine Air Quality, National Research Council (120). The calculations were based on serum concentrations obtained at administration of lithium carbonate and the conclusion was that a "safe" air level during a 24-hour period would be 70 mg LiBr/m^3. To limit possible respiratory tract irritation a factor of 10 was proposed, yielding a 24-hours EEGL of 7 mg LiBr/m^3. A CEGL of 1 mg LiBr/m^3 for exposure 24 hours/day for 90 days was recommended (including a safety factor of 100) (120). This is equivalent to 80 μg Li/m^3.

In a recent report from the Health Council of the Netherlands, Committee for Compounds toxic to reproduction, it was concluded that the amount of evidence and the quality of human studies were insufficient for a classification of lithium for fertility (65). Based on two animal studies (56, 57) the committee recommended to classify lithium carbonate and lithium chloride for effects on fertility in category 3, i.e. substances which cause concern for human fertility. In view of the amount of evidence in earlier human studies (probably reflecting the high doses of lithium drugs used during the pregnancy at that time, that is about 1800 mg/day or 340 mg Li/day) the committee recommended to classify lithium carbonate and lithium chloride for developmental toxicity in category 1, substances known to cause developmental toxicity in humans. The committee also recommended that lithium carbonate and lithium chloride are labelled for effects during lactation, because lithium ingested by patients is found in breast milk in sufficient amounts to warrant concern.

No IARC or IPCS evaluations on lithium have been found.

14. Evaluation of human health risks

14.1 Assessment of health risks

Irritant effects may occur at occupational exposure to lithium or alkaline lithium compounds. The irritant substances are alkaline *per se* or form alkaline compounds on contact with water e.g. moisture in the airways. Lithium and some lithium compounds, e.g. lithium hydride and lithium hydroxide, are highly irritating or even corrosive to the respiratory tract, eyes and skin and may cause permanent eye damage. Strong reducing properties, as with lithium hydride, may also contribute to the irritant action of a compound. No irritation was reported at

0-0.025 mg LiH/m^3, whereas 0.025-0.10 mg LiH/m^3 was slightly irritating to the respiratory tract. Above 0.1 mg LiH/m^3 a definite nasal irritation and coughing was experienced. Lithium hydroxide seems to be irritating at approximately the same air levels. Upper respiratory symptoms and skin irritation was reported at total dust levels of about 0.02-0.05 mg Li/m^3 (personal sampling). Neutral and non-reactive Li compounds, like lithium chloride, are not particularly irritating.

The lithium concentrations in serum from non-patient populations have been in the order of a 1000 times lower than the concentrations found in patients taking medicines. The few available data on serum values of workers exposed to lithium essentially point in the same direction, that is, very low serum levels of lithium. Occupational exposure to a relatively high level of 1 mg Li/m^3 for 8 hours may result in a dose of 10 mg Li (assuming 10 m^3 inhaled air and 100% absorption). In comparison the defined daily dose in Sweden in lithium treatment of affective disorders is 167 mg Li. For these reasons, systemic adverse effects due to lithium (e.g. NDI, fine hand tremor, weight gain, increased TSH values), including effects on reproduction, are unlikely to occur at occupational exposure to lithium and compounds.

14.2 Groups at extra risk

Factors affecting the GFR have a significant influence on the clearance of lithium. Thus, subjects with chronic renal insufficiency are especially vulnerable to lithium exposure. Other conditions predisposing to lithium intoxication include advanced age, sodium depletion of different origin or use of certain drugs affecting the renal function (see chapter 7.5). However, since the amount of lithium in blood seems to be very low in workers, these factors are not relevant at occupational exposure.

14.3 Scientific basis for an occupational exposure limit

The critical effect of lithium and compounds is irritation of the airways. For most lithium compounds it is not possible to establish a NOAEL or a lowest observed adverse effect level (LOAEL) because the few available data are poorly reported.

For lithium hydride no irritant effects were seen below 0.025 mg LiH/m^3, whereas at higher levels a tickling sensation in the nose was reported along with nasal discharge. At levels above 0.1 mg LiH/m^3 a definite nasal irritation and coughing was experienced.

In workers exposed to alkaline lithium dust, upper respiratory tract symptoms were recorded, e.g. during LiOH bagging at 0.02-0.05 mg Li/m^3 in total dust.

15. Research needs

- Inhalation studies to establish NOAELs and LOAELs for irritation of lithium and different lithium compounds
- Measurements of work-place air levels and the relation to symptoms

16. Summary

Json Lagerkvist B, Lindell B. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 131. Lithium and lithium compounds*. Arbete och Hälsa 2002;16:1-48.

Lithium is a light soft metal. It reacts with water to form lithium hydroxide, but less vigorously than sodium. All lithium compounds are monovalent. In industry lithium and compounds are used e.g. in the manufacture of aluminium, as a flux in glass, enamel and ceramic industries, for manufacturing of lubricants, as a drying agent, as a reducing agent in organic synthesis, and in batteries.

Industrial exposure to lithium and alkaline lithium compounds may give rise to irritation of the respiratory tract, eyes and skin or even corrosive lesions. For lithium hydride no irritant effects were seen below 0.025 mg LiH/m^3, whereas at higher levels a tickling sensation in the nose was reported along with nasal discharge. At levels above 0.1 mg LiH/m^3 a definite nasal irritation and coughing was experienced. Upper respiratory symptoms and skin irritation at exposure to approximately 0.02-0.05 mg Li/m^3 in total dust, as LiOH, has also been reported. No other effects than irritation and corrosive effects have been clearly attributed to occupational exposure to lithium and compounds. However, some lithium compounds are used as drugs in the treatment of affective disorders. Adverse effects of lithium may occur in patients at therapeutic doses. At 12-hours serum lithium concentrations of 0.5-0.8 mM some of the most common side effects are nephrogenic diabetes insipidus, fine hand tremor, weight gain, increased thyroid-stimulating hormone values and hypothyreosis.

Available data indicate very low serum lithium levels in exposed workers, compared to patients receiving lithium drugs.

Keywords: eye damage, health effects, irritation, lithium, lithium hydride, lithium hydroxide, occupational exposure limit, review, risk assessment, toxicity

17. Summary in Swedish

Json Lagerkvist B, Lindell B. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 131. Lithium and lithium compounds*. Arbete och Hälsa 2002;16:1-48.

Litium är en lätt, mjuk metall. Ämnet reagerar med vatten under bildning av litiumhydroxid, men reaktionen sker mindre häftigt än för natrium. Alla litiumföreningar är envärda. Litium med föreningar används industriellt, t ex vid tillverkning av aluminium, som flussmedel inom glas-, emalj- och keramisk industri, vid tillverkning av smörjmedel, som torkmedel, som reduktionsmedel i organisk syntes och i batterier.

Litium och alkaliska litiumföreningar kan vid industriell exponering förorsaka irritation av luftvägar, ögon och hud eller t o m frätskador. För litiumhydrid har inga irritationseffekter rapporterats vid lufthalter under 0,025 mg LiH/m^3, medan kittlingar i näsan och snuva noterats vid högre nivåer. Vid nivåer över 0,1 mg LiH/m^3 har klar näsirritation och hosta rapporterats. Symptom från övre luftvägarna och hudirritation har också rapporterats vid exponering för ca 0,02-0,05 mg Li/m^3 som litiumhydroxid (i totaldamm). Inga andra effekter än irritation och frätskador har kunnat tillskrivas litium och dess föreningar vid yrkesmässig exponering. Några litiumföreningar används dock som läkemedel inom psykiatrin och biverkningar kan uppträda hos patienter vid terapeutiska doser. Några av de vanligaste biverkningarna vid 12-timmarsvärdet 0,5-0,8 mM för serumlitium är nefrogen diabetes insipidus, finvågig handtremor, viktökning, förhöjda värden på tyroideastimulerande hormon och hypotyreos.

Tillgängliga data indikerar att serumnivåerna av litium hos exponerade arbetare är mycket låga, jämfört med de nivåer som uppmätts hos patienter.

Nyckelord: hygieniskt gränsvärde, hälsoeffekter, irritation, litium, litiumhydrid, litiumhydroxid, riskbedömning, toxicitet, ögonskada, översikt.

18. References

1. ACGIH. *Documentation of the threshold limit values and biological exposure indices*. 7th ed. Cincinatti: American Conference of Governmental Industrial Hygienists Inc., 2001.
2. Allison JH, Stewart MA. Reduced brain inositol in lithium-treated rats. *Nat New Biol* 1971;233:267-268.
3. Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J. Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. *Am J Psychiatry* 1996;153:592-606.
4. Amdisen A. Monitoring of lithium treatment through determination of lithium concentration. *Dan Med Bull* 1975;22:277-291.
5. Anderson CE. Lithium in plants. In: Bach RO, Gallicchio VS, eds. *Lithium and cell physiology*. New York: Springer-Ver cop., 1990:25-46.
6. Anderson DK, Prockop LD. Lithium absorption and distribution in body tissues. In: Johnson FN, ed. *Lithium research and therapy*. London: Academic Press, 1975:267-280.
7. Archuleta MM. Toxicity of materials used in the manufacture of lithium batteries. *Journal of Power Sources* 1995;54:138-142.
8. Atkins PW, Beran JA, eds. *General chemistry*. 2nd ed. New York: Scientific American Books, 1992:704-708, 849-851.
9. Attias J, Wissocq J-C, Ripoll C, Thellier M. Compartmental analysis of lithium. In: Thellier M, Wissocq J-C, eds. *Lithium kinetics Vol 1*. Pharmacotherapy Monographs. Carnforth, Lancashire, United Kingdom: Marius Press, 1992:1-15.
10. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. Antimanic mood-stabilizing agents. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman Gilman A, eds. *Goodman & Gilman's The pharmacological basis of therapeutics*. 9th ed. New York: McGraw-Hill, 1996:446-459.
11. Baldwin CM, Safferman AZ. A case of lisinopril-induced lithium toxicity. *DICP, The Annals of Pharmacotherapy* 1990;24:946-947.
12. Banduhn N, Obe G, Müller-Oerlinghausen B. Is lithium mutagenic in man? *Pharmako-psychiatr Neuropsychopharmakol* 1980;13:218-227.
13. Barone P, Palma V, DeBartolomeis A, Tedeschi E, Muscettola G, Campanella G. Dopamine D1 and D2 receptors mediate opposite functions in seizures induced by lithium-pilocarpine. *Eur J Pharmacol* 1991;195:157-162.
14. Barr RD, Clarke WB. Regulation of lithium levels in man: Is there evidence of biological essentiality? *Lithium* 1994;5:173-180.
15. Barr RD, Clarke WB, Clarke RM, Venturelli J, Norman GR, Downing RG. Regulation of lithium and boron levels in normal human blood: environmental and genetic considerations. *J Lab Clin Med* 1993;121:614-619.
16. Beliles RP. Lithium, Li. In: Clayton GD, Clayton FE, eds. *Patty's Industrial hygiene and toxicology Vol 2*. 4th ed. New York: John Wiley & Sons, 1994:2087-2097.
17. Belmaker RH, Livne A, Agam G, Moscovich DG, Grisaru N, Schreiber G, Avissar S, Danon A, Kofman O. Role of inositol-1-phosphatase inhibition in the mechanism of action of lithium. *Pharmacol Toxicol* 1990;66:76-83.
18. Bencze K, Pelikan C, Bahemann-Hoffmeister A, Kronseder A. Lithium/aluminium alloys. A problem material for biological monitoring. *Sci Total Environ* 1991;101:83-90.
19. Bendz H. Kidney function in lithium-treated patients. A literature survey. *Acta Psychiatr Scand* 1983;68:303-324.

20. Bendz H. *Lithium treatment and renal disturbances in patients with affective disorders* [Doctoral thesis]. University of Gothenburg, Sweden, 1991.
21. Bendz H, Aurell M, Balldin J, Mathé AA, Sjödin I. Kidney damage in long-term lithium patients: a cross-sectional study of patients with 15 years or more on lithium. *Nephrol Dial Transplant* 1994;9:1250-1254.
22. Berridge MJ. Inositol trisphosphate and diacylglycerol as second messengers. *Biochem J* 1984;220:345-360.
23. Bille PE, Jensen MK, Kaalund Jensen JP, Poulsen JC. Studies on the haematologic and cytogenetic effect of lithium. *Acta Med Scand* 1975;198:281-286.
24. Birch NJ. Lithium. In: Seiler HG, Sigel H, Sigel A, eds. *Handbook on the toxicity of inorganic compounds*. New York: Marcel Dekker, 1988:383-393.
25. Birch NJ, ed. *Lithium and the cell: Pharmacology and biochemistry*. London, New York: Academic Press Ltd, 1991:351.
26. Birch NJ. Lithium in the cellular environment. In: Birch NJ, ed. *Lithium and the cell: Pharmacology and biochemistry*. London, New York: Academic Press Ltd, 1991:159-171.
27. Birch NJ, Padgham C, Hughes MS. Lithium. In: Seiler HG, Sigel A, Sigel H, eds. *Handbook on metals in clinical and analytical chemistry*. New York: Dekker, 1994:441-450.
28. Birch NJ, Philips JD. Distribution and pharmacokinetics of lithium in tissues and in cells. In: Thellier M, Wissocq J-C, eds. *Lithium kinetics*. Carnforth, Lancashire, United Kingdom: Marius Press, 1992:69-96.
29. Bocchetta A, Bernardi F, Burrai C, Pedditzi M, Loviselli A, Velluzzi F, Martino E, Del Zompo M. The course of thyroid abnormalities during lithium treatment: a two-year follow-up study. *Acta Psychiatr Scand* 1992;86:38-41.
30. Büchner W, Schliebs R, Winter G, Büchel KH. Lithium and its compounds. In: *Industrial inorganic chemistry*. Weinheim, Basel, Cambridge, New York: VCH Verlagsgesellschaft, 1989:215-218.
31. Cade JFJ. Lithium salts in the treatment of psychotic excitement. *Med J Aust* 1949;36:349-352.
32. Christensen EM, Aggernæs H. Prospective study of EDTA clearance among patients in long-term lithium treatment. *Acta Psychiatr Scand* 1990;81:302-303.
33. Clarke WB, Clarke RM, Olson EK, Barr RD, Downing RG. Binding of lithium and boron to human plasma proteins. *Biol Trace Elem Res* 1998;65:237-249.
34. Cohen LS, Friedman JM, Jefferson JW, Johnson EM, Weiner ML. A reevaluation of risk of in utero exposure to lithium. *JAMA* 1994;271:146-150.
35. Cooper TB. Pharmacokinetics of lithium. In: Meltzer HY, ed. *Psychopharmacology: The third generation of progress*. New York: Raven Press, 1987:1365-1375.
36. Corcoran AC, Taylor RD. Lithium poisoning from the use of salt substitutes. *JAMA* 1949;139:685-692.
37. Cordasco EM, Kosti H, Vance JW, Golden LN. Pulmonary edema of noncardiac origin. *Arch Environ Health* 1965;11:588-596.
38. Cox M, Singer I. Lithium. In: Bronner F, Coburn JW, eds. *Disorders of mineral metabolism Vol 1*. New York: Academic Press, Inc., 1981:369-438.
39. Cracovaner AJ. Stenosis after explosion of lithium hydride. *Arch Otolaryngol* 1964;80:87-92.
40. Crowson P. *Minerals handbook 1996-97: statistics and analyses of the world's minerals industry*. London: Macmillan, 1996:209-213.
41. Davie RJ. Gastrointestinal absorption of lithium. In: Birch NJ, ed. *Lithium and the cell: Pharmacology and biochemistry*. London, New York: Academic Press Ltd, 1991:243-248.
42. De La Torre R, Krompotic E. The in vivo and in vitro effects of lithium on human chromosomes and cell replication. *Teratology* 1976;13:131-138.

43. Deandrea D, Walker N, Mehlmauer M, White K. Dermatological reactions to lithium: a critical review of the literature. *J Clin Psychopharmacol* 1982;2:199-204.

44. *DFG. Gesundheitsschädliche Arbeitstoffe. Toxikologisch-Arbeitsmedizinische Begründung von MAK-Werten*. Deutsche Forschungsgemeinschaft. Weinheim: VCH, 1990.

45. DFG. *List of MAK and BAT Values 2002*. Deutsche Forschungsgemeinschaft. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. Weinheim: Wiley-VCH, 2002.

46. DiPalma JR. Lithium toxicity. *Am Fam Physician* 1987;36:225-228.

47. Efalith Multicenter Trial Group. A double-blind, placebo-controlled, multicenter trial of lithium succinate ointment in the treatment of seborrheic dermatitis. *J Am Acad Dermatol* 1992;26:452-457.

48. Ehrlich BE, Diamond JM. An ultramicro method for analysis of lithium and other biologically important cations. *Biochim Biophys Acta* 1978;543:264-268.

49. El-Mallakh RS, Lithium toxicity. In: *Lithium: Actions and mechanisms*. Progress in psychiatry. Washington DC: The American Psychiatric Press Inc., 1996:23-45, 93-140.

50. El-Mallakh RS. *Lithium: Actions and mechanisms*. Progress in psychiatry. Washigton DC: The American Psychiatric Press Inc., 1996:145 pp.

51. Emilien G, Maloteaux JM. Lithium neurotoxicity at low therapeutic doses. Hypotheses for causes and mechanism of action following a retrospective analysis of published case reports. *Acta Neurol Belg* 1996;96:281-293.

52. FASS. *Läkemedel i Sverige. 2001*. Stockholm: Läkemedelsinformation (LINFO). Elanders Publishing AS, 2001.

53. Friedrich U, Nielsen J. Lithium and chromosome abnormalities. *The Lancet* 1969;2:435-436.

54. Garson OM, Latimer NZ, Chiu E, Dixon K. Chromosome studies of patients on long-term lithium therapy for psychiatric disorders. *Med J Aust* 1981;2:37-39.

55. Genest P, Villeneuve A. Lithium, chromosomes, and mitotic index. *The Lancet* 1971;1:1132.

56. Ghosh D, Biswas NM, Ghosh PK. Studies on the effect of prolactin treatment on testicular steroidogenesis and gametogenesis in lithium-treated rats. *Acta Endocrinol* 1991;125:313-318.

57. Ghosh PK, Biswas NM, Ghosh D. Effect of lithium chloride on testicular steroidogenesis and gametogenesis in immature male rats. *Acta Endocrinol* 1991;124:76-82.

58. Gitlin M. Lithium and the kidney: un updated review. *Drug Saf* 1999;20:231-243.

59. Goodnick PJ, Schorr-Cain CB. Lithium pharmacokinetics. *Psychopharmacol Bull* 1991;27:475-491.

60. Greenspan BJ, Allen MD, Rebar AH. Inhalation toxicity of lithium combustion aerosols in rats. *J Toxicol Environ Health* 1986;18:627-637.

61. Gunter BJ. *Health hazard evaluation determination*. US Department of Commerce, National Institute for Occupational Safety and Health (NIOSH). Hazard Evaluation and Technical Assistance Branch, 1980 (HE 80-99-707).

62. Hansen HE, Amdisen A. Lithium intoxication. (Report of 23 cases and review of 100 cases from the literature). *Quartely Journal of Medicine* 1978;47:123-144.

63. Hashimoto R, Hough C, Nakazawa T, Yamamoto T, Chuang DM. Lithium protection against glutamate excitotoxicity in rat cerebral cortical neurons: involvement of NMDA receptor inhibition possibly by decreasing NR2B tyrosine phosphorylation. *J Neurochem* 2002;80:589-597.

64. Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E. Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen* 1983;5, Suppl. 1:3-142.

65. Health Council of the Netherlands: Committee for Compounds toxic to reproduction. *Lithiumcarbonate and lithiumchloride; Evaluation of the effects on reproduction,*

recommendation for classification. The Hague: Health Council of the Netherlands, 2000; publication no. 2000/06OSH.

66. Hirtle B, Teschke K, van Netten C, Brauer M. Kiln emissions and potters' exposures. *American Industrial Hygiene Association Journal* 1998;59:706-714.
67. Hirvonen MR, Paljarvi L, Naukkarinen A, Komulainen H, Savolainen KM. Potentiation of malaoxon-induced convulsions by lithium: early neuronal injury, phosphoinositide signaling, and calcium. *Toxicol Appl Pharmacol* 1990;104:276-289.
68. Hirvonen MR, Paljarvi L, Savolainen KM. Sustained effects of pilocarpine-induced convulsions on brain inositol and inositol monophosphate levels and brain morphology in young and old male rats. *Toxicol Appl Pharmacol* 1993;122:290-299.
69. Hirvonen MR, Savolainen K. Lithium-induced decrease of brain inositol and increase of brain inositol-1-phosphate is transient. *Neurochem Res* 1991;16:905-911.
70. Honchar MP, Olney JW, Sherman WR. Systemic cholinergic agents induce seizures and brain damage in lithium-treated rats. *Science* 1983;220:323-325.
71. Hägg G. Grupp 1, alkalimetaller. In: *Allmän och oorganisk kemi*. 5th ed. Stockholm: Almqvist & Wiksell, 1969:610-619.
72. Höbel M, Maroske D, Glanzmann C, Eichler O. Resorption von Wirksubstanzen aus Aerosolen in Abhängigkeit vom Atmungstyp. Versuche mit LiCl-Aerosolen bei Spontanatmung und künstlicher Beatmung von Ratten. *Arch Int Pharmacodyn Ther* 1972;198:76-84.
73. Jackson BA, Dousa TP. Lithium-induced nephrogenic diabetes insipidus. In: Christensen S, ed. *Lithium and the kidney*. Basel: Karger, 1990:126-133.
74. Jacobson SJ, Jones K, Johnson K, Ceolin L, Kaur P, Sahn D, Donnenfeld AE, Rieder M, Santelli R, Smythe J, Pastuszak A, Einarson T, Koren G. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *The Lancet* 1992;339:530-533.
75. Jarvik LF, Bishun NP, Bleiweiss H, Kato T, Moralishvili E. Chromosome examinations in patients on lithium carbonate. *Arch Gen Psychiatry* 1971;24:166-168.
76. Jezowska-Trzebiatowska B, Kopacz S, Mikulski T. Lithium. In: *The rare elements: Occurrence and technology*. Warszawa: Polish Scient Publ, 1990:403-410.
77. Johansson A, Camner P, Curstedt T, Jarstrand C, Robertson B, Urban T. Rabbit lung after inhalation of lithium chloride. *J Appl Toxicol* 1988;8:373-375.
78. Johnson EM. A summary review and human perspective for developmental toxicity evaluations of lithium in laboratory animals. In: Schrauzer GN, Klippel KF, eds. *Lithium in biology and medicine*. Weinheim, Germany: VCH Verlagsgesellschaft, 1991:101-112.
79. Johnson G. Lithium-early development, toxicity, and renal function. *Neuropsychopharmacology* 1998;19:200-205.
80. Johnson JH, Crookshank HR, Smalley HE. Lithium toxicity in cattle. *Vet Hum Toxicol* 1980;22:248-251.
81. Jope RS. Anti-bipolar therapy: mechanism of action of lithium. *Mol Psychiatry* 1999;4:117-128.
82. Jope RS, Bijur GN. Mood stabilizers, glycogen synthase kinase-3beta and cell survival. *Mol Psychiatry* 2002;7, Suppl. 1:35-45.
83. Jope RS, Song L, Kolasa K. Inositol trisphosphate, cyclic AMP, and cyclic GMP in rat brain regions after lithium and seizures. *Biol Psychiatry* 1992;31:505-514.
84. Kanematsu N, Hara M, Kada T. Rec assay and mutagenicity studies on metal compounds. *Mutat Res* 1980;77:109-116.
85. Kawamoto MM, Echt A, Reh CM. *Health hazard evaluation report*. US Department of Health and Human Services, National Institute for Occupational Safety and Health (NIOSH). Eagle-Picher Industries, Joplin, 1999 (HETA 96-0016-2777).

86. Kersten L. Zur Pharmakokinetik von Lithium bei Ratten verschiedenen Alters. *Acta Biol Med Ger* 1979;38:1331-1345.

87. Kilts CD. The ups and downs of oral lithium dosing. *J Clin Psychiatry* 1998;59, Suppl 6:21-26.

88. King MT, Beikirch H, Eckhardt K, Gocke E, Wild D. Mutagenicity studies with X-ray-contrast media, analgesics, antipyretics, antirheumatics and some other pharmaceutical drugs in bacterial, Drosophila and mammalian test systems. *Mutat Res* 1979;66:33-43.

89. Kleiner J, Altshuler L, Hendrick V, Hershman JM. Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. *J Clin Psychiatry* 1999;60:249-255.

90. Kofman O, Belmaker RH. Ziskind-Somerfeld Research Award 1993. Biochemical, behavioral, and clinical studies of the role of inositol in lithium treatment and depression. *Biol Psychiatry* 1993;34:839-852.

91. Kores B, Lader MH. Irreversible lithium neurotoxicity: an overview. *Clin Neuropharmacol* 1997;20:283-299.

92. Lazarus JH. The effect of lithium on the thyroid gland. In: Weetman AP, Grossman A, eds. *Pharmacotherapeutics of the thyroid gland. Handbook of experimental pharmacology Vol 128*. Berlin: Springer-Verlag, 1997:207-223.

93. Lazarus JH. The effects of lithium therapy on thyroid and thyrotropin-releasing hormone. *Thyroid* 1998;8:909-913.

94. Lehmann K. Die Kinetik von Lithium in Serum, Leber und Gehirn der Ratte. *Acta Biol Med Ger* 1975;34:1043-1047.

95. Lehmann K. Endogenous lithium levels. *Pharmacopsychiatry* 1994;27:130-132.

96. Lenox RH, McNamara RK, Papke RL, Manji HK. Neurobiology of lithium: an update. *J Clin Psychiatry* 1998;59, Suppl 6:37-47.

97. Léonard A, Hantson P, Gerber GB. Mutagenicity, carcinogenicity and teratogenicity of lithium compounds. *Mutat Res* 1995;339:131-137.

98. Levin RM, Amsterdam JD, Winokur A, Wein AJ. Effects of psychotropic drugs on human sperm motility. *Fertil Steril* 1981;36:503-506.

99. Linden D. Lithium batteries. A historical perspective. *4th International seminar on lithium battery technology and applications*. Deerfield Beach, Florida, 1989.

100. Llewellyn A, Stowe ZN, Strader JR, Jr. The use of lithium and management of women with bipolar disorder during pregnancy and lactation. *J Clin Psychiatry* 1998;59, Suppl 6:57-64.

101. Lovell RW, Bunker WW. Lithium assay errors. *Am J Psychiatry* 1997;154:1477.

102. Lundberg P, ed. *Consensus report for some nitrides. Criteria Group for Occupational Standards. Scientific Basis for Swedish Occupational Standards XIV*. Arbete och Hälsa 1993;37:49-51, National Institute of Occupational Health, Solna, Sweden.

103. Lundberg P, ed. *Consensus report for some metal stearates. Criteria Group for Occupational Standards. Scientific Basis for Swedish Occupational Standards XV*. Arbete och Hälsa 1994;30:15-19, National Institute of Occupational Health, Solna, Sweden.

104. Marcus WL. Lithium: a review of its pharmacokinetics, health effects, and toxicology. *J Environ Pathol Toxicol Oncol* 1994;13:73-79.

105. Matsushima Y, Hazama H, Kishimoto A. Chromosome examination of patients under lithium therapy. *Jpn J Psychiatry Neurol* 1986;40:625-630.

106. McCarty JD, Carter SP, Fletcher MJ, Reape MJ. Study of lithium absorption by users of spas treated with lithium ion. *Hum Exp Toxicol* 1994;13:315-319.

107. Mellerup ET, Plenge P, Rafaelsen OJ. Renal and other controversial adverse effects of lithium. In: Melzer HY, ed. *Psychopharmacology. The third generation of progress*. New York:Raven Press, 1987:1443-1448.

108. Meurisse M, Gollogly L, Degauque C, Fumal I, Defechereux T, Hamoir E. Iatrogenic thyrotoxicosis: causal circumstances, pathophysiology, and principles of treatment- review of the literature. *World J Surg* 2000;24:1377-1385.

109. Miller NL, Durr JA, Alfrey AC. Measurement of endogenous lithium levels in serum and urine by electrothermal atomic absorption spectrometry: a method with potential clinical applications. *Anal Biochem* 1989;182:245-249.

110. Moore JA, an IEHR Expert Scientific Committee. An assessment of lithium using the IEHR evaluative process for assessing human developmental and reproductive toxicity of agents. *Reprod Toxicol* 1995;9:175-210.

111. Mora A, Sabio G, Gonzalez-Polo RA, Cuenda A, Alessi DR, Alonso JC, Fuentes JM, Soler G, Centeno F. Lithium inhibits caspase 3 activation and dephosphorylation of PKB and GSK3 induced by K+ deprivation in cerebellar granule cells. *J Neurochem* 2001;78:199-206.

112. Mork A, Geisler A. A comparative study on the effects of tetracyclines and lithium on the cyclic AMP second messenger system in rat brain. *Prog Neuropsychopharmacol Biol Psychiatry* 1995;19:157-169.

113. Morrison JM, Jr, Pritchard HD, Braude MC, D´Aguanno W. Plasma and brain lithium levels after lithium carbonate and lithium chloride administration by different routes in rats. *Proc Soc Exp Biol Med* 1971;137:889-892.

114. Mroczka DL, Hoff KM, Goodrich CA, Baker PC. Effect of lithium on reproduction and postnatal growth of mice. *Biol Neonate* 1983;43:287-296.

115. Nishioka H. Mutagenic activities of metal compounds in bacteria. *Mutat Res* 1975;31:185-189.

116. Norton B, Whalley LJ. Mortality of a lithium treated population. *Br J Psychiatry* 1984;145:277-282.

117. Okawa MT, Wisseman C. *Health hazard evaluation determination*. US Department of Commerce, National Institute for Occupational Safety and Health (NIOSH). Hazard Evaluation and Technical Assistance Branch. Kerr-McGee Chemical Corporation, Trona, 1978 (77-59-49).

118. Okusa MD, Crystal LJ. Clinical manifestations and management of acute lithium intoxication. *The American Journal of Medicine* 1994;97:383-389.

119. Painter RB, Howard R. The HeLa DNA-synthesis inhibition test as a rapid screen for mutagenic carcinogens. *Mutat Res* 1982;92:427-437.

120. Panel on emergency exposure guidance levels. Ammonia, hydrogen chloride, lithium bromide, and toluene. In: *Emergency and continous exposure guidance levels for selected airborne contaminants Vol. 7*. Subcommitte on Submarine Air Quality, Committe on Toxicology, Board on Environmental Studies and Toxicology, National Research Council. Washington DC: National Academy Press, 1987:31-46.

121. Pharmaca, Fennica. *Lääketeollisuusyhdistys, Lääketuojat, Lääketietokeskus (In Finnish)*. Helsinki: Lääketuojat, 2002.

122. Phillips JD, Birch NJ. Lithium uptake and kinetics in body fluids. In: Thellier M, Wissocq J-C, eds. *Lithium kinetics Vol 1*. Pharmacotherapy Monographs. Carnforth, Lancashire, United Kingdom: Marius Press, 1992:54-68.

123. Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med* 1994;331:591-598.

124. Radomski JL, Fuyat HN, Nelson AA, Smith PK. The toxic effects, excretion and distribution of lithium chloride. *J Pharmacol Exp Ther* 1950;100:429-444.

125. Rahil-Khazen R, Henriksen H, Bolann BJ, Ulvik RJ. Validation of inductively coupled plasma atomic emission spectrometry technique (ICP-AES) for multi-element analysis of trace elements in human serum. *Scand J Clin Lab Invest* 2000;60:677-686.

126. Raoof NT, Pearson RM, Turner P. Lithium inhibits human sperm motility in vitro. *Br J Clin Pharmacol* 1989;28:715-717.

127. Rathgeber J, Zielmann S, Kietzmann D, Züchner K, Warnecke G. Sind lithiumchlorid-beschichtete "Heat and Moisture Exchanger" ("Künstliche Nasen") eine Gefährdung für Patienten. *Anaesthesist* 1992;41:204-207.

128. Rebar AH, Greenspan BJ, Allen MD. Acute inhalation toxicopathology of lithium combustion aerosols in rats. *Fundam Appl Toxicol* 1986;7:58-67.

129. Reynolds JEF, ed. *Martindale The extra pharmacopoeia*. 31st ed. London: Royal Pharmaceutical Society, 1996:318-323.

130. Ribas B. Lithium. In: Merian E, ed. *Metals and their compounds in the environment*. 2nd ed. Weinheim: VCH, 1991:1014-1023.

131. Rodushkin I, Ödman F, Olofsson R, Axelsson MD. Determination of 60 elements in whole blood by sector field inductively coupled plasma mass spectrometry. *J Anal At Spectrom* 2000;15:937-944.

132. Rosenthal RC, Koritz GD, Davis LE. Pharmacokinetics of lithium in the dog. *J Vet Pharmacol Ther* 1986;9:81-87.

133. Rosi R, Buscalferri A, Monfregola MR, Criscuolo S, Dal Pra P, Stanca A. Systemic lithium reabsorption from lithium-chloride-coated heat and moisture exchangers. *Intensive Care Med* 1995;21:937-940.

134. Salisbury S, Keenlyside R. *Health hazard evaluation report*. US Department of Commerce, National Institute for Occupational Safety and Health (NIOSH), The Hazard Evaluations and Technical Assistance Branch. Lithium Corporation of America, Bessemer City, 1981 (HHE 80-036-922).

135. Sandhu SS, Acedo GN. Detection of chemically induced aneuploidy by the Vicia faba root tip assay. *Toxicol Ind Health* 1988;4:257-267.

136. Savolainen KM, Hirvonen MR, Tarhanen J, Nelson SR, Samson FE, Pazdernik TL. Changes in cerebral inositol-1-phosphate concentrations in LiCl-treated rats: regional and strain differences. *Neurochem Res* 1990;15:541-545.

137. Savolainen KM, Muona O, Nelson SR, Samson FE, Pazdernik TL. Lithium modifies convulsions and brain phosphoinositide turnover induced by organophosphates. *Pharmacol Toxicol* 1991;68:346-354.

138. Savolainen KM, Nelson SR, Samson FE, Pazdernik TL. Soman-induced convulsions affect the inositol lipid signaling system: potentiation by lithium; attenuation by atropine and diazepam. *Toxicol Appl Pharmacol* 1988;96:305-314.

139. Schou M. Lithium studies. 1. Toxicity. *Acta Pharmacologia et Toxicologia* 1958;15:70-84.

140. Schou M. Lithium studies. 2. Renal elimination. *Acta Pharmacologia et Toxicologia* 1958;15:85-98.

141. Schou M. What happened later to the litihum babies? A follow-up study of children born without malformations. *Acta Psychiatr Scand* 1976;54:193-197.

142. Schou M. Clinical aspects of lithium in psychiatry. In: Birch NJ, ed. *Lithium and the cell: Pharmacology and biochemistry*. London, New York: Academic Press Ltd, 1991:1-6.

143. Schou M. Lithium. In: Dukes MNG, ed. *Meyler's Side effects of drugs. An encyclopedia of adverse reactions and interactions*. 12th ed. Amsterdam-London-New York-Tokyo: Elsevier, 1992:79-85.

144. Schou M. Treating recurrent affective disorders during and after pregnancy. What can be taken safely? *Drug Saf* 1998;18:143-152.

145. Schou M, Amdisen A. Letter: Lithium and the placenta. *Am J Obstet Gynecol* 1975;122:541.

146. Schull, WJ. Trace metals. In: Schull WJ, Rothhammer F, eds. *The Aymara´: Strategies in human adaption to a rigorous environment Vol 2*. Dordrect: Kluwer Academic Publishers, 1990:33-34.

147. Shen MR, Yang RC, Chen SS. Effects of lithium and haloperidol on human sperm motility in vitro. *J Pharm Pharmacol* 1992;44:534-536.

148. Sillence DJ, Downes CP. Lithium treatment of affective disorders: effects of lithium on the inositol phospholipid and cyclic AMP signalling pathways. *Biochem Biophys Acta* 1992;1138:46-52.

149. Simard M, Gumbiner B, Lee A, Lewis H, Norman D. Lithium carbonate intoxication. A case report and review of the literature. *Arch Intern Med* 1989;149:36-46.

150. Singer I. Lithium and the kidney. *Kidney Int* 1981;19:374-387.

151. Singh I. Induction of reverse mutation and mitotic gene conversion by some metal compounds in Saccharomyces cerevisiae. *Mutat Res* 1983;117:149-152.

152. Sittig, M. *McGraw-Hill Multimedia encyclopedia of science & technology*. The McGraw-Hill Companies, Inc. 1998.

153. Slamenová D, Budayová E, Gábelová A, Morávková A, Pániková L. Results of genotoxicity testing of mazindol (degonan), lithium carbonicum (contemnol) and dropropizine (ditustat) in Chinese hamster V79 and human EUE cells. *Mutat Res* 1986;169:171-177.

154. Smyth HF, Jr, Carpenter CP, Weil CS, Pozzani UC, Striegel JA, Nycum JS. Range-finding toxicity data: List VII. *American Industrial Hygiene Association Journal* 1969;30:470-476.

155. Sobti RC, Sharma M, Gill RK. Frequency of sister chromatid exchanges (SCEs) and chromosome aberrations (CAs) caused by three salts of lithium (in vivo). *Cytologia* 1989;54:245-248.

156. Spiegl CJ, Scott JK, Steinhardt H, Leach LJ, Hodge HC. Acute inhalation toxicity of lithium hydride. *Arch Ind Health* 1956;14:468-470.

157. Sposito G. Distribution of potentially hazardous trace metals. In: Sigel H, ed. *Metal ions in biological systems Vol 20*. 4th ed. New York: Marcel Dekker, 1986:1-20.

158. Srivastava S, Sharma A, Talukder G. Effects of lithium carbonate on cellular systems in mice. *Perspectives in Cytology and Genetics* 1986;5:381-386.

159. Stokinger HE. Lithium, Li. In: Clayton GD, Clayton FE, eds. *Patty's Industrial hygiene and toxicology Vol 2A*. 3rd revised ed. New York, Chichester, Brisbane, Toronto: John Wiley & Sons, 1981:1728-1740.

160. Subhash MN, Vinod KY, Srinivas BN. Differential effect of lithium on 5-HT1 receptor-linked system in regions of rat brain. *Neurochem Int* 1999;35:337-343.

161. Thellier M, Wissocq J-C. Methods for the determination of the distribution of lithium at the histological and cytological levels. In: Birch NJ, ed. *Lithium and the cell: Pharmacology and biochemistry*. London, New York: Academic Press Ltd, 1991:59-81.

162. Thellier M, Wissocq J-C, eds. *Lithium kinetics*. Carnforth, Lancashire, United Kingdom: Marius Press, 1992:154.

163. Thomsen K. Renal elimination of lithium in rats with lithium intoxication. *J Pharmacol Exp Ther* 1976;199:483-489.

164. Thomsen K. Renal handling of lithium at non-toxic and toxic serum lithium levels. *Dan Med Bull* 1978;25:106-115.

165. Thornhill DP. The biological disposition and kinetics of lithium. *Biopharm Drug Dispos* 1981;2:305-322.

166. Timmer RT, Sands JM. Lithium intoxication. *J Am Soc Nephrol* 1999;10:666-674.

167. Timson J, Price DJ. Lithium and mitosis. *The Lancet* 1971;2:93.

168. Trautner EM, Pennycuik PR, Morris RJH, Gershon S, Shankly KH. The effects of prolonged sub-toxic lithium ingestion on pregnancy in rats. *Austral J Exp Biol* 1958;36:305-322.

169. Triffleman EG, Jefferson JW. Naturally occuring lithium. In: Bach RO, Gallichio VS, eds. *Lithium and cell physiology*. New York: Springer-Ver cop., 1990:16-24.

170. Turecki G, Smith MC, Mari J de J. Lithium mutagenicity. *Br J Psychiatry*. 1994;165:552-553.

171. Ullrich IH, Lyons MH, Jr, Guy ES. A review of lithium. *W V Med J* 1980;76:111-115.

172. Vestergård P. Clinically important side effects of long-term lithium treatment: a review (Summary of a doctoral thesis from the Copenhagen University, Denmark). *Acta Psyciatrica Scandinavica* 1983;67, Suppl. 305:1-36.

173. Ward ME, Musa MN, Bailey L. Clinical pharmacokinetics of lithium. *J Clin Pharmacol* 1994;34:280-285.

174. Weiner ML. Overview of lithium toxicology. In: Schrauzer GN, Klippel KF, eds. *Lithium in biology and medicine* New York: VCH Publishers, Inc., 1991:81-99.

175. Weiner ML. The human dose response to lithium - from trace to toxic levels. In: Birch NJ, Padgham C, Hughes MS, eds. *Lithium in medicine and biology*. Canforth: Marius Press, 1993:15-25.

176. Weiner ML, Batt KJ, Putman DL, Curren RD, Yang LL. Genotoxicity evaluation of lithium hypochlorite. *Toxicology* 1990;65:1-22.

177. Weinstein MR, Goldfield MD. Pharmacology-Lithium teratology. In: Gershon S, Shopsin B, eds. *Lithium It's role in psychiatric research and treatment*. New York, London: Plenum Press, 1973:147-166.

178. Wilcox T, Ruhe RL. *Health hazard evaluation report*. National Institute for Occupational Safety and Health (NIOSH). The Hazard Evaluations and Technical Assistance Branch. Arkansas General Industries, Bald Knob, 1983 (HETA 81-288-1257).

179. Williams MB, Jope RS. Modulation by inositol of cholinergic- and serotonergic-induced seizures in lithium-treated rats. *Brain Res* 1995;685:169-178.

180. Wissocq JC, Heurteaux C, Thellier M. Estimation of local kinetic parameters of exchange of lithium in various substructures of the mouse brain, using the 6Li(n,alpha)3H-nuclear reaction. *Neuropharmacology* 1983;22:227-232.

181. Wolfson M, Hertz E, Belmaker RH, Hertz L. Chronic treatment with lithium and pre-treatment with excess inositol reduce inositol pool size in astrocytes by different mechanisms. *Brain Res* 1998;787:34-40.

182. Zaldivar R. High lithium concentrations in drinking water and plasma of exposed subjects. *Arch Toxicol* 1980;46:319-320.

19. Data bases used in search of literature

In the search for literature the following data bases were used:

Chemical abstracts
HSELINE
Medline
NIOSHTIC
Toxline

Last search was performed in July 2002.

Submitted for publication December 18, 2002.

Appendix 1

Occupational exposure limits for lithium and lithium compounds in air.

Country	mg/m^3	Comments	Year	Reference
Denmark	0.025	LiH	2000	1
Finland	0.025	LiH	2002	2
	0.075	LiH, STEL[a]	2002	2
Germany	-	LiH	2001	3
Iceland	0.025	LiH	1999	4
Netherlands	0.025	LiH	2001	5
Norway	0.025	LiH	2001	6
Sweden	-	-	2000	7
United Kingdom	0.025	LiH	2000	8
	1	LiOH, STEL[a]	2000	8
USA (ACGIH)	0.025	LiH	2002	9
(NIOSH)	0.025	LiH	2000	10
(OSHA)	0.025	LiH	2000	10

[a] short-term exposure limit (15 min)

References

1. *Grænsverdier for stoffer og materialer*. København: Arbejdstilsynet, 2000 (At-vejledning. C.0.1).
2. *HTP-arvot 2002*. Tampere: Sosiaali- ja terveysministeriö, 2002. ISBN 952-00-1107-2.
3. *MAK- und BAT-Werte-Liste 2001*. Weinheim: Wiley-VCH, 2001. ISBN 3-527-27599-1.
4. *Mengunarmörk og aðgerðir til að draga úr mengun á vinnustöðum*. Vinnueftirlit ríksins, 1999.
5. *Nationale MAC-lijst 2001*. Den Haag: Sdu Uitgevers 1999. ISBN 90-12-08899-2.
6. *Administrative normer for forurensning i arbeidsatmosfære*. Veiledning til arbeidsmiljøloven. Oslo: Direktoratet for Arbeidstilsynet, 2001 (Bestillingsnr. 361).
7. *Hygieniska gränsvärden och åtgärder mot luftföroreningar*. Stockholm: Arbetarskydds-styrelsen, 2000 (AFS 2000:3) ISBN 91-7930-357-9.
8. *Occupational exposure limits 2000*. EH40/2000. Health and Safety Executive, United Kingdom, 2000, ISBN 0-7176-1730-0.
9. *2002 TLVs and BEIs*. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 2002. ISBN 1-882417-46-1.
10. *NIOSH Pocket Guide to Chemical Hazards*. Washington: U.S. Department of Health and Human Services, 2000. CD-ROM. DHHS (NIOSH) Publication No. 2000-130.