Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for lithium hydride

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OEL (8-h TWA):	-
STEL (15 min):	0.02 LiH mg/m^3 (inhalable dust)
Additional classification :	None

This summary document is based on the criteria document on lithium and lithium compounds published by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (Json Lagerkvist and Lindell 2002), the consensus report from the Swedish Criteria Group for Occupational standards (Montelius 2003) and key studies therein.

Publications on health effects of lithium hydride are scarce in the scientific literature. Only three relevant studies, all from the 50s and 60s, were found in Pubmed in June 2009.

Substance Identity and Properties

Lithium hydride	LiH
CAS Number:	7580-67-8
EC Number:	231-484-3
Molecular Weight:	7.95
Melting point:	680°C
Autoignition temperature:	200°C
Specific density	0.8
Classification:	Not classified by the European Chemicals Bureau

1. Occurrence and use

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 (Arbejdstilsynet 2000, Büchner et al 1989, Sittig 1998). Lithium hydride decomposes to lithium hydroxide (LiOH) and hydrogen upon contact with water. Airborne dust clouds of lithium hydride may explode on contact with heat (Arbejdstilsynet 2000).

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 (Büchner et al 1989).

Lithium is present at varying concentrations in the earth crust and, hence, also in sea water, plants and animals, including humans. The range in background lithium concentration is normally 0.2-9 µM (1.6 - 70 µg Li/L), depending on geographical location and intake via food and beverages. The daily intake has been estimated to 2-4 mg Li/day and the average body burden to 2.2 mg (Json Lagerkvist and Lindell 2002).

2. Health significance

2.1. Toxicokinetics

Lithium hydride is strongly irritating or even corrosive to the mucosa of the respiratory tract and eyes and to the skin, mainly due to alkalinity. However, the strong reducing properties, as with lithium hydride, may also contribute to the irritant action. The toxicity of lithium hydride differs markedly from that of soluble lithium salts because of its great chemical reactivity, particularly with moisture, producing marked irritancy and corrosiveness to tissues (Arbejdstilsynet 2000, Beliles 1994).

2.1.1. Animal data

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, lithium hydroxide (Spiegl et al 1956).

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 (Spiegl 1956).

2.1.2. Human data

Lithium hydride has been described as highly corrosive and irritant (Birch 1988, Léonard et al 1995). 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 (Cracovaner 1964).

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 (Cordasco et al 1965).

Unpublished studies, referred to by ACGIH (2001) and the 4th edition of Patty´s Toxicology (Beliles, 1994), 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 (1994) 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 (Beliles 1994). Lithium hydride is no longer addressed in the 5th edition of Patty´s Toxicology published in 2001.

In the ACGIH documentation for Threshold Limit Values (2001) it is stated that, according to the American Industrial Hygiene Association hygienic guide series, 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.

2.2. Mutagenicity, genotoxicity and cancer

Lithium salts (but not lithium hydride) have been tested in vitro and in vivo for mutagenicity, DNA damage, chromosomal aberrations and sister chromatid exchanges. Several studies report genotoxic effects of various lithium compounds at high doses, whereas many other studies have failed to demonstrate an effect. Lithium chloride induced chromosomal aberrations in human lymphocytes exposed in vitro at of 50-150 µg/mL, corresponding to 1.2-3.6 mM. The tested concentrations are higher than the therapeutic serum level of 0.5-1.2 mM (De La Torre and Krompotic 1976). Lithium carbonate induced gene mutations in V79 cells and DNA damage in EUA cells in vitro at 1500-3000 µg/mL (37-70 mM) and single strand-breaks were seen at 150-500 µg/mL (3.6-12 mM) (Slamenová et al. 1986). Sobti et al. (1989) studied sister chromatid exchanges (SCEs) and chromosome aberrations (CAs) in mice given three salts of lithium in olive oil or water at three dose levels. CAs were increased compared to control at all doses tested; 0.2-21 mg/kg lithium chloride administered in olive oil, 1.2-120 mg/kg lithium carbonate in olive oil and 0.05-5 mg/kg lithium acetate in water. SCEs seemed marginally increased in the exposed mice (not statistically significant).

Considering the chemical properties of the lithium compounds it is unlikely that they act as direct mutagens. The Nordic Expert Group suggested that a possible explanation to the apparent genotoxicity at high test concentrations may be that it is a secondary effect of increased cell survival caused by lithium's inhibition of glycogen synthase kinase-3 (Json Lagerkvist and Lindell 2002). Similarly, Weiner (1991) concluded 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.

No cancer studies have been found in the literature.

2.3. Reproductive toxicity

Reported adverse foetal outcomes occur only around levels that are toxic to the mother. Weinstein and Goldfield (1973, cited in Json Lagerkvist and Lindell (2002),) critically evaluated these studies and remarked that the doses of lithium carbonate given were 27 times the usual daily dose in humans and killed one third of the mothers. Weinstein and Goldfield also evaluated 5 other teratogenicity studies in rats and mice. Only one reported teratogenic effects, e.g. cleft palate. After reviewing animal studies performed according to modern guidelines, Johnson (1991) concluded that a NOAEL of 10 mg Li/kg body weight during the critical periods of differentiation and organogenesis can be considered to accurately estimate the true no effect level for both developmental and maternal toxicity.

Significant inhibition of spermatogenesis and decreased fertility has been seen in animals at serum lithium levels similar to those reported in patients. Further, decreased motility has been observed in human sperm in vitro at concentrations achieved in semen after therapeutic doses (Raoof et al. 1989, Shen et al. 1992). However, the amount of evidence and the quality of the human in vitro studies is insufficient for a conclusion on the effects on fertility (Json Lagerkvist and Lindell 2002).

Dose-effect data for humans exposed to lithium hydride (unless otherwise stated) by inhalation.

Exposure level (mg/ m^3)	Effect	Reference
0-0.025	No effect	1
0.02-0.05 (n=4)	Irritation symptoms in workers occupied with lithium hydroxide bagging	2
0.025-0.10	A tickling sensation in the nose, some nasal discharge, tolerated by those continuously exposed	1
0.05	Workers readily adapt, objectionable to unacclimated individuals	3
0.10-0.50	Definite nasal irritation with some coughing, not tolerated	1
>0.1	Eye and nose irritation in persons with some degree of adaptation	3
>0.2	Itching of exposed skin	3
0.5	Maximal tolerable concentration for brief periods	3
0.50-1.0	Severe nasal irritation with coughing, in some workers eye irritation	1
0.54-1.84 (n=4)	Irritation symptoms in workers occupied with lithium carbonate bagging	2
1.0-5.0	Severe irritant effects, skin irritation	1

1. Unpunblished studies cited by Beliles (1994).

2. Salisbury and Keenlyside (1981)

3. American Industrial Hygiene Association (1964) Lithium hydride. In: Hygienic guide series. Akron, OH. Cited by ACGIH (2001).

In 1980, NIOSH investigators studied lithium exposures and reported health effects in a plant producing lithium compounds from lithium aluminum silicate. Lithium exposure (area and personal samples) was measured by atomic absorption spectrometry. In addition, dust pH, total and respirable dust, silica and n-hexane were measured. Total dust levels ranged from nondetectable (below 0.01) to 42 mg/m^3, and 3 out of 27 personal samples exceeded 10 mg/m^3. Lithium in total dust ranged from nondetectable (below 0.001) to 3.5 mg Li/m^3, the highest levels being found in lithium hydroxide bagging and lithium carbonate grinding and bagging. Area and personal samples showed similar total dust and lithium concentrations. Lithium in blood was below the detection limit of 0.7 mg/L in all but two samples with levels of 2.1 and 1.0 mg/L blood. Exposure to respirable free silica was below 0.05 mg/m^3. Ten out of 11 air samples were below 5 ppm n-hexane, the one exception reaching 28 ppm (Salisbury and Keenlyside 1981).

A medical questionnaire was administered to 21 lithium exposed and 23 less exposed (jobs outside the plant) workers. The two groups differed with respect to age (31 versus 39 years), employment duration (4.8 versus 8.6 years) and smoking habits (57% versus 39%). Increased frequencies were seen for lower (shortness of breath) and upper (runny nose, nose belleds, dry throat) respiratory symptoms in the exposed compared to the less exposed workers. Also headache and skin irritation was more prevalent among the exposed (no statistical analyses are presented in the report). According to the authors, the irritant symptoms were most troublesome for those involved in hydroxide and carbonate bagging. The lithium levels (personal samples) in these job categories were 0.02-0-05 (n=4) and 0.54-1.84 (n=4) mg Li/m^3, respectively (Salisbury and Keenlyside 1981). Notably, the exposures in the plant were to lithium hydroxide and carbonate. However, as the hydroxide is formed from the hydride under humid conditions, lithium hydroxide and lithium hydride can be assumed to be equally potent with respect to irritant properties.

The lithium concentrations in serum from non-patient populations are approximately 1000 times lower than the concentrations found in patients taking medicines. Even relatively high airborne exposures result in systemic doses far below the therapeutic doses. Thus, daily 8-hour exposures to 0.1 mg Li/ m^3, already a highly irritative level, would theoretically result in a dose of 1 mg Li/day (assuming 10 m^3 inhaled air and 100% absorption), i.e. lower than the estimated background intake via food and water and far below the defined daily dose in Sweden in lithium treatment of affective disorders of 167 mg Li/day. The few available data on workers exposed to lithium essentially point in the same direction, that is, nondetectable increases in serum lithium. For these reasons, systemic adverse effects due to lithium (e.g. nephrogenic diabetes insipidus, fine hand tremor, weight gain, increased thyroid-stimulating hormone level), including effects on reproduction, are unlikely to occur at occupational exposure to lithium and lithium compounds.

Recommendations

The critical effect of lithium and compounds is irritation of the airways. 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.

Lithium hydroxide may be formed from lithium hydride under humid conditions. In workers exposed to alkaline lithium dust, upper respiratory tract symptoms were recorded, e.g. during lithium hydroxide bagging at 0.02-0.05 mg Li/ m^3 in total dust.

In view of the lack of airway irritation below 0.025 mg LiH/m3, a STEL of 0.02 mg/m^3 is proposed. There is no data upon which an 8-h OEL can be set, however, based on experience from patients on lithium therapy, systemic adverse effects due to lithium, including effects on reproduction, are unlikely to occur at any occupational exposure.

No skin notation is necessary, since dermal exposure is not expected to give rise to significant systemic doses.

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