MICHIGAN DEPARTMENT OF NATURAL RESOURCES AND ENVIRONMENT

INTEROFFICE COMMUNICATION

To: **File for Lithium (CAS#7439-93-2) and lithium compounds**

From: Mary Lee Hultin and George Eurich

Date: June 6, 2011

Subject: **Screening level for Lithium (CAS#7439-93-2) and lithium compounds**

The screening level for lithium is 35 ug/m3 based on 24 hour averaging.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH) Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), Michigan Department of Natural Resources and Environment (DNRE) library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) online (1968-Feb 2008), National Library of Medicine (NLM) - Toxline, and National Toxicology Program (NTP) Status Report. The CAS and NLM searches were performed in March 2010.

There are no EPA RfC or RfD values for lithium or lithium compounds, nor are there published toxicity data sufficient to derive an RfC. There is an ACGIH TLV for lithium hydride of 0.025 mg/m3. The basis for the lithium hydride TLV is to prevent ocular, dermal and respiratory irritation from the corrosive effects of lithium hydride hydrolysis products. Lagerkvist and Lindell [1] reviewed the key study used by ACGIH in the derivation of the TLV for lithium hydride. They report that the corrosive effects, inflammation and irritation in the study animals resulted from the alkalinity of the hydrolysis product lithium hydroxide. Lithium hydroxide has been reported to be irritating at approximately the same air levels as LiH. The pH of lithium hydroxide is 14. The pH of many other lithium salts is considerably lower and therefore not likely to cause the same corrosive effects upon inhalation as either lithium hydride or lithium hydroxide. Therefore, it is not appropriate to use the TLV for risk assessment of lithium compounds aside from the hydrides and hydroxides.

Due to the widespread use of lithium as a pharmaceutical, a fairly substantial body of literature exists on the toxicity of the compound from oral exposure. However, the inhalation route has not been well studied aside from the hydride data noted above. The impact of the rout of administration on lithium pharmacokinetics was examined by Saratikiov, et al, 1971. The authors administered lithium carbonate via s.c., i.p., or gavage to rats and mice. They found that distribution, accumulation and elimination were not affected by rout of administration. However, the full article was not available for examination as it is published in Russian.

Oral lithium has been associated with reproductive and developmental effects. A number of human and animal studies have been published which analyzed the teratogenic potential of lithium. When used as a drug for major affective disorders, in-utero exposures in women has been associated with cardiac anomolies, particularly a condition termed Ebstein's anomaly (Nyuyen H.T., et al, 2008). Animal studies with lithium using doses comparable to human therapeutic serum levels have not reported any abnormalities. (Giles and Bannigan, 2006).

Studies have indicated that chronic lithium exposure has the potential to affect renal, nervous, cardiac and endocrine systems. The critical endpoints from lithium exposure, however, appear to be the potential for embryotoxicity or teratogenicity. The placental barrier appears to be insufficient for protection of the fetus from adverse impacts of lithium. Maternal lithium serum concentrations have been found to be similar to fetal serum levels. A number of epidemiologic studies have used the Registry of Lithium Babies in examining effects of lithium exposure (Nora et al., 1974; Schou et al. 1973; Weinstein, 1976; Linden and Rich, 1983).

Bush and Mackenzie-Taylor (1997) of this Department previously developed an oral reference dose using the work of Jacobson, et al. as the key study. The Jacobson study included a prospective cohort analysis of 148 women exposed to lithium carbonate (LI_2CO_3) during the first trimester of pregnancy. The study assumed a maternal bodyweight of 62 kg. A significant increase in birth weight (macrosomia) was noted as the LOAEL at a mean daily dose was 927 mg. Uncertainty factors included 10 for intraspecies sensitivity and 10 for LOAEL rather than NOAEL. It was noted that the maximum UF for LOAEL was partially based on the steep dose-response curve for lithium (premature birth, kidney toxicity, thyroid toxicity). An additional UF of 3 is used in the ITSL determination for the study treatment duration of only the first trimester of pregnancy.

The ITSL derivation for Lithium is based on the Jacobson, et al. Lithium Carbonate study and is described below:

ITSL = Oral RfD x 70 kg/20m3

927 mg Li_2CO_3 contains 174 mg Li

174 mg Li/62 kg body weight/ (UF 10-LOAEL to NOAEL, 10-interspecies sensitivity, 3-less than chronic study duration)

174 mg Li/ 62 kg/(300 UF) = .01 mg Li/kg

ITSL = 0.01 mgLi/kg x 70 kg/20m3 x (1000 ug/mg)
= **35 ug/m3 based on a 24 hour average.**

References:

Jacobson, S.J., et al., 1992, **"**Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester.", Lancet, v. 339, p. 530-533.

Lagerkvist, B.J. and B. Lindell, 2002, "The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals, No. 131., Lithium and lithium Compounds, Nordic Council of Ministers, http://www.niwl.se/

Giles, J.J. and J.G. Bannigan, 2006, "Teratogenic and developmental effects of lithium.", Curr Pharm Des. 12(12):1531-41.

Nora, J.J., et al., 1974, "Lithium, Ebstein's anomaly, and other congenital heart defects", Lancet, v. 2:594-595.

Schou, M., et al., 1973, "Lithium and pregnancy – I. Report from the register of lithium babies." Br. Med. J. 2:135-136.

Linden and Rich, 1983, "The use of lithium during pregnancy and lactation." J. Clin. Psychiatr. 44:358-361

Weinstein, M.R., 1976, "The international register of lithium babies.", Drug Information Journal, v. 10:94-100.