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Provisional Peer Reviewed Toxicity Values for
Lithium
(CASRN 7439-93-2)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR LITHIUM (CASRN 7439-93-2)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).
2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.
3. Other (peer-reviewed) toxicity values, including:
 - ▶ Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
 - ▶ California Environmental Protection Agency (CalEPA) values, and
 - ▶ EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and

circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Lithium (Li), an alkali metal, exists in two isotopic forms (^7Li and ^6Li) and is naturally present in soil and water. Lithium has numerous industrial and commercial uses including as a cell additive in electrolytic aluminum production, a catalyst of chemical reactors, a component of fluxes and brazing alloys, a component of batteries, specialized glass and ceramics, and a sanitizing agent for swimming pools, hot tubs and spas (Leonard et al., 1995; Moore, 1995). Lithium carbonate and lithium citrate are also used for the therapeutic treatment of psychiatric disorders, primarily in the acute and long-term maintenance treatment of bipolar mood disorders.

A reference dose (RfD) or reference concentration (RfC) for lithium are not available on the Integrated Risk Information System (IRIS) (U.S. EPA, 2007), the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997), or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2004). The U.S. Environmental Protection Agency's (EPA) Chemical Assessments and Related Activities (CARA) (U.S. EPA, 1994) lists only Reportable Quantity (RQ) documents for lithium chromate and lithium hydride; the RQ documents (U.S. EPA, 1983, 1988) for these two compounds state that the data are not sufficient for derivation of an RQ as there are no subchronic or chronic studies. Neither the Agency for Toxic Substances Disease and Registry (ATSDR) (2006), the National Toxicology Program (NTP) (2006), the International Agency for Research on Cancer (IARC) (2006), nor the World Health Organization (WHO) (2006) has produced documents regarding lithium. The following sources were also consulted: Chemical Hazard Information Profiles (U.S. EPA, 1980), National Occupational Health Survey of Mining (NIOSH, 1990) and Information Profiles on Potential Occupational Hazards - Classes (NIOSH, 1978). Literature searches were conducted from 1965 to August 2006 in TOXLINE

(including NTIS and BIOSIS updates), CANCERLIT, MEDLINE, CCRIS, GENETOX, HSDB, EMIC/EMICBACK, DART/ETICBACK, RTECS and TSCATS.

REVIEW OF PERTINENT LITERATURE

Human Studies

Oral Exposure

Overview of the Therapeutic Use of Lithium – Lithium carbonate, and more recently, lithium citrate have been used since 1949 in the treatment of bipolar affective (manic-depressive) disorder; thus, extensive clinical literature on the beneficial and adverse effects of lithium is available. Lithium is therapeutically used in the treatment of bipolar affective disorder as a sole therapy or in combination with other antidepressant drugs and in the treatment of schizophrenia in combination with anti-psychotic drugs. Although lithium is effective in the treatment of bipolar affective disorders, adverse effects are associated with therapeutic dose levels, resulting in a low therapeutic index (e.g., ratio of dose associated with therapeutic efficacy to dose associated with adverse effects). Thus, lithium is not simply prescribed by dose, but is monitored based on serum concentrations. For the treatment of bipolar disorder, the desired therapeutic serum concentrations range from 0.6 to 1.4 mmol Li/L, although concentrations of 0.8-1.0 mmol Li/L are generally accepted as providing optimal therapeutic effects (Physicians Desk Reference, 2006; Baldessarini and Tarazi, 2001).

Although the precise mechanism of action has not been established, it is unlikely that a single mechanism of action is responsible for the therapeutic and adverse effects of lithium. Several mechanisms for the therapeutic effects of lithium have been proposed. Since the chemical properties of lithium are similar to those of sodium, lithium can be substituted for sodium in generating action potentials and in some sodium transport processes across membranes. Lithium also appears to alter neurotransmitters, enhances some actions of serotonin, has variable effects on norepinephrine, augments the synthesis of acetylcholine and increases norepinephrine and dopamine turnover. Lithium also alters brain inositol phosphate levels, affecting second messenger responses for α -adrenergic and muscarinic transmission. A decrease in functioning brain protein kinases has also been identified as a consistent effect of lithium. Lithium also interacts with nuclear regulatory factors that affect gene expression (Baldessarini and Tarazi, 2001).

The potential for lithium to cause toxicity has been of significant concern due to its use on a maintenance basis for a lifelong disorder; thus, a large body of clinical literature on lithium-induced toxicity exists, including several reviews (Gitlin, 1999; Berk and Berk, 2003; Markowitz et al., 2000; Moore, 1995; McIntyre et al., 2001; Awad et al., 2002; Presne et al., 2003; Jefferson, 1998). Effects that are associated with therapeutic use of lithium include: neurological and psychiatric effects (tremor, choreoathetosis, motor hyperactivity, ataxia, aphasia, fatigue, cognitive impairment); decreased thyroid function; hyperparathyroidism; renal effects (nephrogenic diabetes insipidus, nephritis, chronic progressive renal disease); edema (related to sodium retention); cardiovascular effects (T wave flattening); acniform skin eruptions;

benign leukocytosis; and gastrointestinal effects (nausea, vomiting, abdominal pain, diarrhea). Since all therapeutic serum concentrations are associated with adverse effects, long-term treatment strategies for individual patients must balance the beneficial effects of lithium therapy with the risks and severity of toxicity. Although available data are not sufficient to define dose-response relationships, it is generally accepted that severity of adverse effects is related to serum lithium levels.

Adverse renal effects associated with lithium therapy have received extensive focus due to their serious nature and frequency of occurrence. Thus, lithium-induced renal toxicity has been the subject of numerous clinical and animal studies. The most common adverse renal effect is nephrogenic diabetes insipidus (NDI), which occurs over the range of therapeutic serum lithium concentrations (e.g., 0.6-1.4 mmol Li/L). The development of NDI involves lithium-induced down-regulation of the vasopressin-regulated water channel aquaporin-2, expressed on the apical plasma membrane of principal cells of the collecting duct (Markowitz et al., 2000). The consequence of this effect is to reduce the capacity of the kidneys to preserve free water, resulting in impaired renal concentrating ability and the production of excessively dilute urine. Clinically, this manifests as polyuria, with secondary thirst, and volume depletion. Although other mechanisms may also contribute to polyuria, interference with vasopressin-induced antidiuresis is considered the most important cause (Gitlin, 1999). It has been estimated that renal concentrating ability is impaired in at least 50% of patients undergoing lithium treatment, with polyuria and polydipsia in approximately 20% of patients (Presne et al., 2003; Gitlin, 1999; McIntyre et al., 2001). In a review of data from several studies published between 1979 and 1986, impairment of concentrating ability was seen in at least 54% of 1105 patients on chronic lithium therapy, with polyuria observed at serum lithium concentrations ranging from 0.6 to 1.2 mmol/L (Botton et al., 1987). Thus, periodic measurement of serum creatinine, creatinine clearance, 24-hour urine volume and urine protein has become integral to the management patients on long-term lithium therapy (Jefferson, 1998).

NDI appears to be reversible early in treatment, but may be progressive during the first decade, leading to irreversible damage over time (Gitlin, 1999). A small percentage of patients show progressive renal failure indicated by a pronounced decrease in glomerular filtration rate (GFR) and renal insufficiency, with little or no proteinuria (Markowitz et al., 2000). Severe decreases in GFR have resulted in the need for maintenance hemodialysis, typically after 10 or more years of lithium therapy. Results of renal biopsy on patients with chronic renal effects showed interstitial fibrosis, tubular atrophy, focal sclerosis, acquired renal cystic disease and cytoplasmic swelling with glycogen deposits in the distal convoluted tubules and collecting ducts (Markowitz et al., 2000; Gitlin, 1999). Confounding factors (other medical disorders such as hypertension, heart disease) may contribute to susceptibility and severity of irreversible damage (Gitlin, 1999).

Studies on Adverse Effects in Patients Treated with Lithium: Renal Effects – The results of retrospective and prospective studies and findings of case reports summarized below focus on adverse effects observed in patients maintained on chronic lithium therapy for the treatment of affective mood disorders. As expected based on the established pharmacological profile of therapeutic lithium, decreased renal concentrating ability is the most frequently reported adverse effect, although neurological, dermal, cardiovascular and endocrine effects are

also observed. Interpretation of results from clinical studies is difficult due to many factors, including the lack of baseline data prior to lithium use, absence of control groups, presence of pre-existing renal and other diseases and use of concomitant medications. Furthermore, since clinicians rely upon serum lithium concentrations, rather than daily doses, to evaluate the dose-response relationships between lithium treatment, efficacy and adverse effects, daily lithium doses often are not reported nor were the results of male vs. female dosing reported separately. However, the clinical literature provides consistent evidence that the kidney is a primary target organ for lithium in men and women, and supports that adverse renal effects occur over the range of desired therapeutic serum concentrations (0.6-1.4 mmol Li/L).

In a prospective study, a cohort of 373 patients who started receiving lithium therapy at various times between 1979 and 1987 were given pre-treatment examinations to establish baseline levels for renal parameters (Schou and Vestergaard, 1988; Vestergaard and Schou, 1988). Patients were examined once before and on the average 3.3 times during lithium therapy. Patients who had been treated with lithium prior to entry into the cohort and patients taking neuroleptic agents during lithium therapy were excluded from analysis. On examination days, urine was collected every 24 hours and data were disregarded if less than 75% of the daily lithium dose was recovered. The desamino-8-D-arginine vasopressin (DDAVP) test was used to determine renal concentrating ability. The mean lithium dose was 23.2 mmol Li/day and the mean lithium serum concentration was 0.68 mmol/L. Because of a high drop-out rate (for various reasons), especially among men, and because the dosing durations of the full cohort ranged from 5 months to 7 years, data from a subcohort of 39 patients who received lithium therapy continuously for 4 years were compared with the data for the whole cohort to guard against errors due to selective sample attrition. The ratio of men to women in the whole cohort and in the subcohort remained constant.

Patients in the whole cohort developed a moderate rise in urine volume and a moderate fall in renal concentrating ability (Schou and Vestergaard, 1988; Vestergaard and Schou, 1988). Urine volume increased by 7% (not statistically significant) for the whole cohort and 23% for the subcohort ($p=0.05$). For the whole cohort, urine volume was positively correlated with lithium dosage ($r=0.29$, $p<0.001$). Renal concentrating ability fell by 7% ($p<0.01$) for the whole cohort and by 10% for the 4-year subcohort ($p<0.01$). Changes in renal concentrating ability took place within the first 1-2 years of lithium therapy for members of the whole cohort, with no additional changes in renal function when treatment duration was extended more than 2 years. There was no correlation between concentrating ability and lithium dosage in the whole cohort. Glomerular function, as determined by measurement of serum creatinine concentrations and urine creatinine concentrations, was not affected by lithium therapy in the whole cohort. In addition, there was no change in the incidence of proteinuria associated with lithium treatment. Complaints of increased thirst, frequent urination and nocturia were made more often during lithium therapy than before lithium therapy in both the cohort and the subcohort. Therefore, the results from the subcohort support the results from the entire cohort. Assuming that the average body weight was 70 kg, patients were exposed to 2.32 mg Li/kg-day. This study identifies a lowest-observed-adverse-effect level (LOAEL) of 2.32 mg Li/kg-day for increased urine volume and decreased urine concentrating ability.

A group of 53 patients (20 men and 33 women) was examined prior to starting long-term lithium therapy and again after 4 and 12 months on lithium (Smigan et al., 1984). Twenty-five patients of this cohort had previously received lithium, but treatment had been withdrawn for 27 months before the start of the present treatment. Over the course of the study, 13-28% of the 53 patients received neuroleptics. Lithium carbonate dosages were not provided, but serum lithium levels were maintained at approximately 0.6 mmol/L. A clinically significant change in renal concentrating ability (defined as having a urine osmolality below 600 mOsm/kg water) was observed in a small group (n=6) of patients after 12 months on lithium treatment. Of these six patients, five had been treated previously with lithium and had some signs of impaired renal concentrating ability at the start of the present treatment. Multiple regression analysis determined that concurrent treatment with neuroleptics did not contribute to the decline of renal function.

Polyuria and/or decreased urine concentrating ability were found among 112 women and 125 men (average weight, 76.2 kg) exposed to 12-57 mmol/day of lithium (mean dose of 32.6 mmol/day of lithium or 3.0 mg Li/kg-day) for 0.5-17 years (mean duration, 5.2 years) in a retrospective study by Vestergaard et al. (1979). Serum lithium concentration ranged from 0.2 to 2.0 mmol/L. Baseline renal function prior to lithium therapy was not assessed, since all patients were on maintenance lithium therapy prior to the start of the study. The majority of patients were also receiving concomitant therapy with other medications, such as neuroleptics and/or antidepressants, and 37% the patients received concomitant therapy with hypnotics or anxiolytics. In a follow-up study, 184 of the original 237 patients were re-examined 2 years later (Vestergaard and Amdisen, 1981). The 184 patients were divided into two groups; those patients who continued with lithium (147) and those who discontinued (37). Lithium-treated patients were compared with 68 manic-depressive patients that were about to receive lithium. Glomerular function did not change over the 2-year period. In patients who had discontinued lithium treatment, there was an improvement in renal concentrating ability when compared with the patients who continued with lithium therapy. However, maximal urine osmolality did not reach the level found in the control (pre-lithium treatment) group, although the urine volume approached levels in the control group. There was a further increase in urine volume and decreased in urine osmolarity for those patients that continued with lithium therapy.

In a study involving 116 men and 152 women who took an average of 1322 mg/day of lithium carbonate (3.57 mg Li/kg-day) for an average period of 37.6 months, maximum concentrating ability was lower in all patients receiving lithium than in 59 control patients not receiving lithium (Gelenberg et al., 1987). However, differences did not achieve statistical significance. A major limitation of this study is that baseline data were not available.

Results of a biopsy study in patients receiving lithium maintenance therapy provide evidence of lithium-induced histopathological changes to the kidney (Hestbech et al., 1977). Fourteen manic-depressive patients received an average of 42 mmol Li/day as lithium carbonate (4.2 mg Li/kg-day) for 1.5-15 years. Serum lithium concentrations ranged from 0.6 to 1.3 mmol/L. Thirteen age-matched patients without renal disease served as the source of kidney biopsy specimens for control observations. Impaired urine concentrating ability and polyuria was observed in lithium patients. Histopathological examination of the kidney biopsy samples revealed a pronounced degree of focal nephron atrophy and/or interstitial fibrosis in 13 of the

14 patients examined. Semiquantitative assessment of renal lesions revealed significantly greater degrees of focal cortical fibrosis, diffuse medullary fibrosis, mononuclear cell infiltrates and distal tubular dilatation in the patients than in the controls. Quantitative assessment revealed significantly greater percentages of totally sclerotic glomeruli, fibrous cortical tissue and unidentifiable and atrophic renal tubules in patients than in controls.

Hansen et al. (1979) also reported impaired renal concentrating ability in 14 patients (7 men and 7 women) treated with 36 mmol/day of lithium (3.6 mg Li/kg-day) for 1.3 to 12 years. Serum lithium concentrations ranged from 1.75 to 4.50 mmol/L. Results of renal biopsy showed interstitial fibrosis and tubular atrophy. Baseline levels were not available and controls were not used. There was a significant negative correlation between the degree of tubular atrophy and renal concentrating ability.

Walker et al. (1982) examined renal function and biopsy samples in 47 patients (18 men and 29 women) who were receiving an average of 1250 mg/day of lithium carbonate (3.38 mg Li/kg-day) for an average of 5 years. The median serum lithium concentration was 0.84 mmol/L. Thirty-two patients not receiving lithium therapy were used as the controls. Decreased urine concentrating ability and impaired urinary acidification, indicative of distal nephron dysfunction, were observed in patients receiving lithium relative to controls. Lithium-treated patients also exhibited decreased glomerular filtration rate, as measured by significantly increased serum creatinine, increased β_2 -microglobulins, and decreased Cr-EDTA clearance, compared to controls. Histological examination of kidney biopsy samples did not reveal abnormalities.

Hansen and Amdisen (1978) reported effects on the kidneys in a case study of 23 patients who were exposed to therapeutic doses of 24-56 mmol Li/day (2.4-5.6 mg Li/kg-day) for 6.1-8.5 years. Patients were hospitalized due to severe lithium intoxication. Pre-exposure baseline levels were not available. Impaired renal concentrating ability was a consistent finding. Abnormal electroencephalography (EEG) was also reported. There was no relationship between the severity of symptoms of lithium intoxication and the serum lithium concentration on admission to the hospital. Many of the patients (22 out of 23) included in the Hansen and Amdisen (1978) study experienced frank adverse effects, including renal insufficiency in 17 patients, mental and neurological symptoms (decreased alertness or slight apathy) in 18 patients, muscular rigidity and/or muscular fasciculations in 14 patients, slight ataxia in 6 patients, and stupor and latent convulsive movements in 14 patients. Severely abnormal electroencephalograms were observed in 19 patients. Two patients died and two patients developed persisting neurological sequelae.

Studies on Adverse Effects in Patients Treated with Lithium: Other (Non-Renal) Adverse Effects – Neurological effects, including tremors, are commonly reported in patients treated with lithium. Neurological effects of lithium were evaluated in 28 patients (15 men and 13 women) with bipolar affective disorder receiving 1012 mg/day of lithium carbonate (2.74 mg/kg-day) for 4.1 years. The mean serum lithium level was 0.68 mmol/L. Although patients did not develop overt neurological effects, nerve conduction velocities were prolonged (Chang et al., 1990). Electrodiagnostic tests revealed a slowing of motor and sensory nerve conduction velocities and prolonged central neural conduction times obtained from somatosensory and brainstem auditory evoked potentials that correlated with serum lithium levels. Another patient

developed polyneuropathy after being exposed to 1.62 mg Li/kg-day for an unspecified period (years) (Tomasina et al., 1990). The patient had a sensorimotor peripheral neuropathy with mostly axonal degeneration. The patient improved after the lithium therapy was discontinued. Levine and Puchalski (1990) have also described two cases of pseudotumor cerebri syndrome in patients that were exposed to 900-1200 mg/day of lithium carbonate (2.43-3.24 mg Li/kg-day) for 4-8 years. The serum lithium concentration did not exceed 1.0 mmol/L. This syndrome is characterized by chronic headaches, bilateral papilledema and increased intracranial pressure in the absence of any localized neurological signs or symptoms.

Hagino et al. (1995) observed adverse effects on 20 children aged four through six exposed to oral lithium for the treatment of aggressive and/or mood-disordered children. All children were hospitalized during the course of the study as part of the medical intervention program. Daily lithium doses were adjusted to maintain serum lithium concentrations between 0.6 and 1.2 mmol/L and ranged from 12.2 to 48.9 mg/kg-day. Patients remained on lithium therapy for up to 37 days. Adverse effects to the central nervous system (tremor, drowsiness, ataxia, confusion) were the most commonly observed effects, reported in approximately 60% of patients. Other effects observed included gastrointestinal effects (nausea, vomiting, abdominal discomfort) in 25% of patients, renal effects (polyuria) in 10% of patients and blurred vision in 10% of patients. No adverse effects were observed in the cardiovascular, pulmonary, autonomic, hematological or integumental systems. The potential contribution of concomitant medications was not ruled out by the study authors. Sixteen of the 20 children also received one or more psychoactive medications and six children received antibiotics for infections.

Adverse effects on thyroid function, primarily asymptomatic hypothyroidism, have been reported in patients treated with lithium. Thyroid effects may be secondary to altered renal clearance of iodine, rather than to direct effects of lithium on the thyroid (Moore, 1995). A retrospective study was conducted involving 129 patients (46 men, 83 women) who were on lithium therapy for 2-180 months and 21 patients who served as controls (Bocchetta et al., 1991). Most of the patients receiving lithium had previously received or were receiving medication (antipsychotics and antidepressants) other than lithium. Serum lithium concentrations ranged between 0.5 and 1.0 mmol/L. Palpable and/or visible goiter was found in 51% of the patients receiving lithium ($p < 0.01$), compared with 9.5% occurrence in the control group. Based on elevated thyroid stimulating hormone (TSH) levels, subclinical hypothyroidism was diagnosed in 19% of the patients on lithium compared with 9.5% in the control group. There were no differences in thyroid function tests between patients receiving lithium alone or receiving additional medication. The researchers noted that lithium-induced subclinical hypothyroidism may be transient and recommended that repeated determinations of TSH is required. Joffe et al. (1988) reported that 20% of the 42 patients receiving lithium carbonate therapy for 3 months required thyroid replacement or had evidence of subclinical hypothyroidism. Cowdry et al. (1983) also reported that 12 of 24 patients who were on lithium therapy for 12 months developed hypothyroidism. Only those patients with a median serum lithium concentration of 0.6 mmol/L were used in the study. When 22 women received lithium therapeutically for more than 2 years, there was evidence of subclinical hypothyroidism in 32% of these patients (Bartalena et al., 1990).

Hyperparathyroidism with progressive hypercalcemia was reported to occur in a patient who received lithium for 6 years (Graze, 1981). The daily dosage was not reported by the author. The patient had progressive hypercalcemia for the duration of the therapy and a parathyroid adenoma.

Raouf et al. (1989) demonstrated a concentration-dependent inhibition by lithium chloride on human sperm motility *in vitro* at semen concentrations that would be expected from therapeutic doses of lithium. However, Raboch et al. (1981) found no abnormality in sperm count, motility or morphology in semen samples obtained from 14 patients that were using lithium for an average of 4.1 years. The mean serum lithium level was 0.64 mmol/L and the mean lithium level in the semen was 1.48 mmol/L.

A group of 16 men and 4 women were treated with 1008 mg/day of lithium carbonate (2.72 mg Li/kg-day) as either a once-daily dose or as a divided twice-daily dose for an average of 4.4 years (Abraham et al., 1992). An elevated white cell count, increased serum phosphate, and elevated serum ionized calcium were observed in the study group receiving the once-daily lithium treatment. These effects were not seen in the study group that received lithium twice a day. No evidence of polyuria was observed in either group and no significant differences were observed between the two treatment regimens with respect to mental status, serum lithium or electrocardiograms.

Adverse effects on cardiac conductivity, including sinoatrial block, sinus bradycardia and junctional escape rhythm, have been reported in patients taking therapeutic lithium (Moore, 1995). A patient who received 600 mg/day of lithium carbonate (1.62 mg Li/kg-day) for 4 months (serum lithium concentration 1.3-2.0 mmol/L) developed symptomatic sinus node dysfunction, which disappeared after discontinuation of lithium therapy (Riccioni et al., 1983). Roose et al. (1979) also reported cardiac sinus node dysfunction during lithium treatment in several patients exposed to at least 8.6 mg/kg-day of lithium for 10 years.

Studies on Developmental Effects of Lithium Treatment During Pregnancy – The potential for lithium-induced developmental effects was the subject of an assessment conducted by Moore and an Institute for Evaluating Health Risks (IEHR) Expert Scientific Committee (Moore, 1995). Data from 139 references, including registries, prospective studies and case histories were reviewed. This assessment determined that sufficient evidence is available to conclude that therapeutic use of lithium causes developmental effects in offspring when maternal serum lithium concentrations are within the therapeutic range. Review of developmental effects reported in birth registries revealed reports of cardiovascular defects associated with lithium treatment. Reports of Ebstein’s anomaly (a structural defect in which there is a downward displacement of the tricuspid valve into the right ventricle, and valvular redundancy with adherence of some cusps to the right ventricular wall; affected individuals may have right ventricular failure or conduction abnormalities), in particular, were in “substantial excess among all malformations.” Although the magnitude of the increase could not be determined from birth registry reports, data indicate that first-trimester lithium exposure increases the risk of cardiac malformations. Other studies reviewed by Moore (1995) also report an association between maternal lithium treatment and cardiovascular defects in offspring. The literature reviewed also suggests a possible association between maternal lithium treatment and neonatal mortality.

There are also reports that newborn infants of mothers on lithium therapy may exhibit symptoms of acute lithium toxicity such as cyanosis, hypotonia and cardiac toxicity. However, the available data regarding developmental effects in humans are limited by insufficient dose-response information.

Jacobson et al. (1992) prospectively recruited and followed 148 women using lithium during the first trimester of pregnancy. Each study patient was matched with a woman (control) of similar age (within 2 years). The mean lithium dose was 927 mg/day of lithium carbonate (2.5 mg Li/kg-day); the authors did not report serum lithium concentrations. No significant differences between the exposed group and the controls were observed for congenital defects (3% in lithium patients and 2% in controls) and spontaneous abortions (9% in lithium patients and 8% in controls). Kallen and Tandberg (1983) identified a cohort of 350 mothers who were treated with lithium during their pregnancy. The authors reported that the total delivery outcome was poorer than expected, with high perinatal death and malformation rates compared to the national average expected rates in Sweden. Congenital heart defects occurred in 6 cases compared with the national expected number of 2.1 cases ($p < 0.05$). However, the sample size was relatively small and the difference between delivery outcome in women on lithium and in women on other psychotropic drugs was not statistically significant. Weinstein and Goldfield (1975) reviewed 143 cases of lithium use during pregnancy collected by the Register of Lithium Babies. There were 13 malformed infants (9.1%) among the 143 in the register. Of these 13 malformed infants, 11 were born with significant malformations of the cardiovascular system. As was the case with the previous study, the daily lithium dosage was not reported and at least 6 of the 13 mothers who delivered malformed babies were exposed to other medications in addition to lithium. Krause et al. (1990) reported a case of severe polyhydramnios that developed from the 26th week of gestation. Except for weeks 6-13 of gestation, the mother was maintained on lithium (serum level, 0.7 mmol/L) prior to the diagnosis. Ang et al. (1990) described a similar case report in a woman who was exposed to lithium during pregnancy. The infant displayed symptoms of lithium toxicity, including polyuria.

Studies on the Carcinogenic Potential of Therapeutic Lithium – Controlled studies on the potential of therapeutic lithium to induce cancer have not been reported. Although a few case studies have reported associations between lithium therapy and recurrence of cancer, data are inadequate to establish any association between lithium and the development or recurrence of cancer in humans. Furthermore, given that the widespread clinical use of lithium as a long-term maintenance treatment in patients with affective mood disorders has not revealed an increased incidence or recurrence of cancer, it is unlikely that lithium is carcinogenic in humans. Nonetheless, the few studies examining potential carcinogenic effects of lithium are briefly reviewed below.

Several case reports that suggest an association of lithium-induced leukocytosis with induction or reinduction of acute and chronic leukemia. Orr and McKerna (1979) reported the recurrence of acute monocytic leukemia in a 64-year-old woman who was previously in remission. This patient received 600 mg/day of lithium carbonate for 7 weeks before the leukemic relapse occurred. Nielsen (1980) reported the development of acute myeloid leukemia in one male and one female patient administered lithium for a duration of 1 and 12 years, respectively. Jim (1980) reported the occurrence of chronic monocytic leukemia in a patient

who received 900 mg/day of lithium carbonate for 11 months prior to the diagnosis of leukemia. A 37-year-old woman developed chronic granulocytic leukemia after receiving 600 mg of lithium carbonate 3 times/day for 5 years (Schottlander et al., 1980).

Contrary to anecdotal reports that attempt to associate an increased risk of leukemia with lithium intake, the limited epidemiological information suggests no increased risk. Resek and Olivieri (1983) examined the relationship between leukemia and chronic lithium therapy during 1971-1980 by examining hospital records of 187 leukemia patients to determine whether these patients were receiving lithium medication prior to their illness. Only 7% of these patients had received psychiatric services and in all cases, these patients were not treated with lithium. The authors reported that there was no association between lithium therapy and leukemia. In a 14-year ecological study, one human population in El Paso exposed to lithium via drinking water (66 µg/L) was compared with another human population in Dallas-Fort Worth that was not exposed to lithium in drinking water (Frenkel and Herbert, 1974). There was no difference in the incidence of chronic or acute granulocytic leukemia in the two populations.

Only two separate cases have been reported in the literature of the possible association of lithium with cancers other than leukemia. Brownlie et al. (1980) reported the occurrence of papillary cell carcinoma of the thyroid in a 55-year-old woman after 3.5 years of lithium therapy. McHenry et al. (1990) also reported three cases of thyroid carcinoma occurring in association with chronic (9 years) lithium therapy.

Studies of Adverse Effects of Lithium in Healthy Volunteers – The effect of lithium therapy on short- and long-term memory was assessed in healthy volunteers exposed to daily oral lithium for 3 weeks (Stip et al., 2000). Groups of 15 healthy men and women were randomized into placebo or lithium treatment groups. Subjects in the lithium group were administered lithium twice daily at doses ranging from 1050 to 1950 mg/day (197 to 366 mg Li/day) in order to achieve a mean serum lithium concentration of 0.8 mmol/L. The form of the lithium was unstated but the dose is consistent with lithium carbonate. Actual serum lithium concentrations were not reported. Cognitive performance (attention and memory) was assessed in each subject at 3 times during the study: baseline, after 3 weeks of treatment and 2 weeks after discontinuation of treatment. After 3 weeks of treatment, performance scores for short-term memory tasks (assessed using an auditory digit span) for subjects taking lithium were significantly lower ($p < 0.03$) compared to placebo. Results of long-term memory assessments (using recall tests) showed adverse effects in lithium-treated subjects compared to controls. Performance on short- and long-term memory tests improved 2 weeks after discontinuation of treatment. Results indicate that lithium produces effects in the central nervous system in healthy subjects at exposure levels corresponding to the target therapeutic serum concentrations. The mean dose, 1569 mg/day (295 mg Li/day) was a LOAEL in this study.

Effects on the hemopoietic system and clotting have also been reported in healthy volunteers exposed to lithium (Stein et al., 1981). Groups of at least five non-psychiatric volunteers received 900 mg/day lithium carbonate (2.43 mg Li/kg-day). Granulocyte count, expressed as a percent of baseline, was significantly increased by 25% ($p < 0.05$), 32% ($p < 0.001$), and 42% ($p < 0.001$) after 1, 2 and 3 weeks of exposure. Volunteers administered 0, 300, 600, 900, 1200 or 1500 mg/day of lithium carbonate (0, 0.8, 1.62, 2.43, 3.24 or 4.05 mg Li/kg-day)

orally for 1 week developed increased granulocytosis at doses ≥ 2.43 mg Li/kg-day. Granulocyte count was increased by 26, 55 and 43% of baseline values in the 2.43, 3.24 and 4.05 mg Li/kg-day groups, respectively. Decreased bleeding times were also observed in the 3.24 and 4.05 mg Li/kg-day dose groups, although there was no apparent treatment effect on platelet count. Serum lithium concentrations were not reported.

The use of lithium as a therapeutic agent to reverse chemotherapy-induced neutropenia and thrombocytopenia has been explored in humans, with studies providing conflicting results. Richmon et al. (1984) reported an increase in neutrophil and thrombocyte production in five cancer patients who received 900 mg/day of lithium carbonate (169 mg Li/day) for an unspecified duration. Twenty-two patients with oligoblastic leukemia receiving 900 mg/day of lithium carbonate for an unspecified time remained cytopenic without evidence of lithium-induced bone marrow proliferation (Barlogie et al., 1984). In another study, Friedenbergl and Marx (1980) reported that lithium increased the granulocyte count in eight healthy volunteers who had received 900 mg/day of lithium carbonate for 1 week. Despite the observed increase in granulocyte number, there was a reduction in bactericidal capacity (function) of granulocytes in these individuals.

Inhalation Exposure

No studies on the effects of inhaled lithium in humans were identified.

Animal Studies

Oral Exposure

Subchronic and chronic oral exposure studies evaluating comprehensive toxicity endpoints in laboratory animals are not available. Few animal studies have investigated the adverse effects of chronic oral exposure to lithium. The primary purpose of animal studies has been to evaluate specific adverse effects associated with the therapeutic serum lithium concentration range, with most studies focusing on lithium-induced renal toxicity. The available data in animals provide supporting evidence that subchronic and chronic oral exposure to lithium induces similar adverse effects as those associated with the therapeutic use of lithium in patients. However, insufficient data are available to determine dose-response relationships for adverse effects.

Cancer Bioassays – No long-term animal bioassays examining the carcinogenicity of lithium were identified. An abstract by Prolov and Pliss (1991) reported that lithium carbonate promoted bladder carcinogenesis in rats previously exposed to N-butyl-N-(4-hydroxybutyl)-nitrosamine; no additional publications of this finding were identified. Although Hori and Oka (1979) stimulated cell multiplication of mammary gland explants with lithium in C3H/HeN virgin female mice, Ziche et al. (1980) were unable to demonstrate any growth promoting effect of lithium on primary carcinomas induced by two chemical carcinogens (7,12-dimethylbenz[α]anthracene and N-nitrosomethylurea) in Sprague-Dawley and Buffalo/N female rats.

Adverse Renal Effects – Chronic renal failure was induced in male and female Wistar rats fed diets containing 0 or 40 mmol lithium chloride/kg diet (0 or 3.58 mg Li/kg-day) from birth for 55 to 56 weeks (Christensen and Ottosen, 1986). Plasma lithium concentration ranged from 0.6 to 0.7 mmol/L after 16 weeks and from 1.0 to 1.1 mmol/L after 48 weeks of treatment. Mortality was 51% in lithium-treated rats compared to only 6% in control rats. Mean plasma urea concentration was elevated by 74% after 16 weeks and 175% after 48 weeks, compared to controls. After 55 weeks of treatment, inulin clearance was reduced by 62% and lithium clearance was reduced by 39% compared to controls. Lithium-treated rats also had polyuria and diminished renal concentrating ability (assessed by failure to respond to exogenous vasopressin). No treatment-related effects on systolic or diastolic blood pressure were observed. Morphological examination of the kidneys of lithium-treated rats revealed large cortical cysts, dilated distal tubules and collecting ducts, and widespread interstitial fibrosis. Glomerular volume and proximal tubular mass were significantly reduced. Comprehensive toxicity endpoints were not examined in this study. A LOAEL of 3.58 mg Li/kg-day for adverse renal effects was identified; a NOAEL was not established.

Two groups of six male Wistar SPF rats were exposed to a diet containing 0 or 40 mmol LiCl/kg diet (0 or 4.5 mg Li/kg-day) for 3 weeks and then 0 or 60 mmol LiCl/kg (0 or 6.7 mg Li/kg-day) for an additional 18 weeks (Christensen et al., 1982). The time-weighted average daily dose was 6.4 mg Li/kg-day, with mean serum lithium concentrations of 0.7-0.8 mmol/L. Rats exposed to lithium developed polyuria and lowered renal concentrating ability after 2 weeks of exposure to diets containing lithium. Focal microscopic changes in distal convoluted tubules and collecting ducts were also observed. Focal basal vacuolization of the cytoplasm was observed after 2-4 weeks of lithium exposure. After 8 weeks of treatment, all rats had severe nuclear polymorphism, nuclear hyperchromasia and cellular polymorphism with tubular giant cells. In addition to these cellular changes, dilatations of the tubular lumen and focal atrophy of the tubular cells were observed in rats exposed to lithium for 21 weeks. Renal concentrating ability was significantly decreased after 2 weeks of dietary exposure. After lithium was withdrawn for 8 weeks, structural changes persisted, but concentrating ability was normalized. Based on their experimental findings, the authors concluded that the use of urinary concentrating ability as an index of lithium-induced structural damage may underestimate lithium-induced effects on the kidney. A LOAEL of 4.5 mg Li/kg-day for adverse renal effects observed after 2 weeks of treatment was identified; a NOAEL was not established.

Polyuria and vasopressin-resistant diabetes insipidus developed within 3 weeks of exposure to dietary lithium (Kling et al., 1984). Two groups of 12 male Wistar rats were exposed to 0 or 90 mmol/kg diet of lithium carbonate (11.6 mg Li/kg-day) for 126 days. Serum lithium concentration was maintained at 0.8 mmol/L. Early lesions were associated with the cortical collecting tubules and distal tubules, extending into the medullary collecting tubules by week 3 of treatment. There were alterations in nuclear size and shape and cytoplasmic basophilia of tubular cells, focal dilation and thinning of the tubular epithelium, and occasional sloughing of cells into the tubular lumen. In this study, early tubular lesions correlated with the polyuria. However, polyuria remained constant while morphological changes deteriorated for several more weeks of lithium exposure. A LOAEL of 11.6 mg Li/kg-day for adverse renal effects was identified; a NOAEL was not established.

Two groups of seven male Wistar rats were exposed to a control diet or a diet containing lithium for 112 days (Marcussen et al., 1969). Due to poor reporting of methods and results, the concentration of lithium in the diet or daily dose of lithium could not be determined. Rats exposed to lithium developed uremia and reduced body weight. All kidneys were polycystic in the cortical areas, and distal tubules and cortical collecting ducts were dilated. Severe fibrosis was observed in the interstitial space. Tubular glomeruli (67%) and some hypertrophic glomeruli were also observed. The hypertrophic glomeruli did not compensate adequately for other impaired glomerular function, as indicated by an overall decrease in GFR.

Other (Non-Renal) Adverse Effects – Reductions in body weights were observed in rats exposed to dietary lithium (Ehlers and Koob, 1985). Twenty-nine male Wistar rats were exposed to 0, 30 or 40 mmol Li/kg diet (0, 19 or 26 mg Li/kg-day) for 56 days. In the 40 mmol Li/kg diet group, body weight was reduced by 37% ($p < 0.001$). A significant increase ($p < 0.05$) in brain theta wave activity in the 6-8 Hz range in all lithium-treated animals was also observed. A LOAEL of 19 mg Li/kg-day for adverse effects to the central nervous system was identified; a NOAEL was not established.

The effect of dietary lithium on thyroid function was examined in two groups of 10 male Wistar rats exposed to 0 or 1100 mg lithium carbonate/kg diet (0 or 20 mg Li/kg-day) for 120 days (Dhawan et al., 1985). Serum lithium levels ranged from 0.44 to 0.65 mmol/L. There was a significant decrease ($p < 0.01$) in circulating levels of T_4 and T_3 after 1 month of exposure to lithium. There was also a marked decrease ($p < 0.001$) in thyroid hormone levels after 4 months of lithium treatment. A LOAEL of 20 mg Li/kg-day for adverse thyroid effects was identified; a NOAEL was not established. Etling et al. (1987) investigated the effect of lithium on thyroid hormone levels in rats exposed to 0, 300 or 600 mg lithium carbonate/L in drinking water (0, 12.8 or 25.6 mg Li/kg-day) for 5 weeks. Decreases in serum T_3 and T_4 were observed only in the 600 mg/L group. A NOAEL and LOAEL of 12.8 and 25.6 mg Li/kg-day, respectively, for adverse thyroid effects were identified.

The effect of 90-day dietary exposure to lithium on male reproductive organs was evaluated by Thakur et al. (2003). Groups of 20 sexually mature Wistar rats were exposed to lithium carbonate at dietary concentrations of 0, 500, 800 or 1100 mg/kg diet for 90 days (equivalent to 0, 6.6, 10.6 or 14.2 mg Li/kg body weight-day). Serum lithium concentrations were not reported. Assessments included weight of reproductive organs, histopathology of testis, epididymis, seminal vesicle, and prostate, testicular interstitial fluid volume, testosterone level, sperm morphology and fertility index. Weights of the testes and epididymis, sperm number from cauda epididymis, daily sperm production, serum testosterone and interstitial fluid volume were significantly reduced in the mid- and high-dose groups, compared to controls. Seminal vesicle and prostate secretions were completely blocked in the mid- and high-dose groups. The percentage of abnormal sperm was significantly increased in all lithium treatment groups. Histopathological assessments revealed degeneration of spermatogenic cells and vacuolization of Sertoli cell cytoplasm in the high-dose treatment groups. A LOAEL of 6.6 mg Li/kg body weight-day for increased percentage of abnormal sperm was identified; a NOAEL was not established.

Sharma and Iqbal (2005) evaluated the effects of oral exposure of male Wistar rats to lithium nitrate for 7 weeks. Groups of 12 rats were exposed to 0 or 20 mg Li/kg body weight by gavage on alternate days (10 mg Li/kg-day) for 7 weeks and examined for effects on blood chemistry and hematology at the end of the treatment period. Serum lithium concentration was not reported. Numerous blood chemistry and hematology parameters were significantly different from controls: decreased hemoglobin and erythrocyte count, elevated white cell count, elevated erythrocyte sedimentation rate, elevated glucose, decreased protein and elevated blood urea nitrogen (BUN), calcium and phosphorous. Histopathological effects observed in the kidney included ruptured epithelial lining of the proximal and distal tubules of the medulla, renal tubular necrosis, thickened capsular wall of the glomerulus and cytoplasmic vacuolization in the corticomedullary region. Comprehensive toxicity endpoints were not examined in this study. A LOAEL of 10 mg Li/kg body weight for hematological and renal effects was identified; a NOAEL was not established.

Developmental Effects – The review by Moore and an IEHR Expert Scientific Committee (Moore, 1995) on lithium-induced developmental effects included available data from studies in animals using a variety of experimental designs. The data in animals are of limited usefulness to providing a comprehensive picture of lithium-induced developmental effects because of limitations of available studies. Issues with some of the studies include small number of animals, inability to ascertain litter incidence, inadequate reporting, administration of only a single dose, and failure to report or describe chemical characteristics of test materials. Despite these limitations, sufficient data are available to suggest that prenatal developmental toxicity can occur in studies with rats and mice in which lithium is administered during pregnancy and fetuses are examined just before birth. Doses associated with adverse developmental effects ranged from 2.71 to 12.67 mmol/kg body weight-day. Evidence of maternal toxicity was often present. Specific cardiac developmental effects have not been reported in animal studies; however, it does not appear that rigorous assessments of cardiac morphology have been conducted. Results of selected animal developmental studies are briefly summarized below.

Hoberman et al. (1990) evaluated the developmental effects of lithium hypochlorite administered by gavage once daily to groups of 25 Sprague-Dawley rats on days 6 through 15 of gestation at dosages 0 (vehicle), 10, 50, 100 or 500 mg/kg-day (0, 0.4, 2.1, 4.2 or 21 mg Li/kg-day). Six of the 25 rats in the 500 mg/kg-day group died between days 12 and 20 of gestation. Decreased fetal body weight, wavy ribs and delayed ossification of the thoracic vertebrae (bifid centra), forepaw and hindpaw phalanges, and metatarsal and metacarpal bones were observed in the offspring of the highest exposure group. Maternal NOAEL and the developmental NOAEL for lithium hypochlorite were determined by the authors to be 100 mg/kg-day of lithium hypochlorite (4.2 mg Li/kg-day). The LOAEL for developmental toxicity is 500 mg/kg-day (21 mg Li/kg-day) and the maternal frank effect level (FEL) is 500 mg/kg-day (21 mg/kg-day).

Twenty albino Sprague-Dawley rats were exposed to 0 or 100 mg/kg-day (0 or 18.8 mg Li/kg-day) lithium carbonate on days 16 through 20 of gestation (Fritz, 1988). Signs of maternal toxicity, including reduced weight gain and feed consumption, polyuria and polydipsia, were observed. Enlarged renal pelvises were observed in 50% of the fetuses in the lithium-exposed

group. Exposure of rats to a lower daily dose of lithium carbonate (11.3 mg Li/kg-day) on gestational days 16 through 20 induced similar maternal effects and some prenatal mortality; however, no signs of impaired renal development for the young offspring that survived were observed. A LOAEL of 11.3 mg Li/kg body weight for maternal effects was identified; a NOAEL was not established. For fetal effects, NOAEL and LOAEL values were identified as 11.3 and 18.8 mg Li/kg-day, respectively.

Developmental toxicity was evaluated in the offspring of 44 pregnant Wistar rats exposed to 0, 50 or 100 mg/kg-day of lithium carbonate (equivalent to 0, 9.5 or 19 mg Li/kg-day) by oral gavage on gestational days 6 through 15 (Marethe and Thomas, 1986). Reduction in the number of implantations, number of live fetuses and fetal body weights and a higher number of resorptions were reported in the 100 mg/kg-day group. A developmental NOAEL for lithium carbonate is 50 mg/kg-day (9.5 mg Li/kg-day) and a LOAEL of 100 mg/kg-day (19 mg Li/kg-day) was determined.

Statistically significant reductions in total body weights of the fetus and the fetal length were observed in the offspring of albino rats exposed to 7 mg/kg-day of lithium carbonate (1.3 mg Li/kg-day) for the first 10 days of gestation (Sharma and Rawat, 1986). The authors did not report the number of animals used in the study, but rather the number of abnormal developmental observations and expressed these as a percentage of control. The authors also reported a high incidence of cleft palate abnormalities (46%), fetal brain liquification (46%), hepatomegaly (46%) and non-ossification of upper and lower digits (30 and 37%, respectively). Lower incidences of cardiomegaly (3%) and hydronephrosis (3%) were observed. A LOAEL of 1.3 mg Li/kg body weight for adverse developmental effects was identified; a NOAEL was not established.

Groups of 12 female Sprague-Dawley rats were fed 0 or 1000 ppm lithium carbonate (0 or 18.5 mg Li/kg-day) in the diet throughout gestation (Ibrahim and Canolty, 1990). Following parturition, the dams were exposed to the same concentration of lithium and were also allowed to nurse the pups for an additional 21 days. Dietary lithium resulted in decreased growth in both the dams and the offspring, as well as increased mortality of the offspring. Litter size was decreased 25% and mean pup weight was decreased by 10%. The highest mortality was observed in the group of pups that were exposed to lithium during both gestation and lactation. Gross malformations were not observed in the newborn animals. A LOAEL of 18.5 mg Li/kg body weight for adverse developmental effects was identified; a NOAEL was not established.

Groups of three to six mice (HmM/ICR strain) were exposed to 0, 200 or 465 mg/kg-day of lithium carbonate (0, 37.8 or 87.9 mg Li/kg-day) on gestational days 6 through 15 (Szabo, 1970). The human equivalent dose for mice, based on lithium plasma levels of 0.6-1.6 mmol/L, was calculated by the authors as 465 mg/kg-day. The highest dose, 465 mg/kg-day, caused an increased incidence of maternal (37%) and fetal (32%) deaths. Nineteen percent of the surviving fetuses had cleft palate. The 200 mg/kg-day dose (37 mg Li/kg-day) did not cause maternal or fetal deaths; the incidence of cleft palate in fetuses was 0.4%, which was not statistically significantly elevated relative to controls. Cleft palate was not observed in any of the 181 fetuses in the control group. NOAEL and LOAEL values for maternal effects and developmental effects were identified as 37.8 and 87.9 mg Li/kg-day, respectively.

Inhalation Exposure

Only three studies that evaluated the effect of inhaled lithium in animals were identified (Johansson et al., 1988; Greenspan et al., 1986; Rebar et al., 1986). Greenspan et al. (1986) exposed groups of eight male and eight female F344/Lov rats to an aerosol mixture containing lithium carbonate (80%) and lithium hydroxide (20%) at concentrations of 0, 620, 1400, 2300 or 2600 mg Li/m³ once for 4 hours (Greenspan et al., 1986). The 14-day LC₅₀ values were estimated to be 1700 mg Li/m³ for the males and 2000 mg Li/m³ for the females from the single exposure. No clinical signs of toxicity were observed in animals exposed to 620 mg Li/m³. At concentrations \geq 1400 mg/m³, signs of acute effects on the respiratory system included respiratory distress and bronchospasms. At necropsy, severe congestion of the lungs was observed in 14 out of the 16 animals in the two highest exposure groups. Three of 16 animals at 1400 mg Li/m³ showed congestion in the lungs. Histopathologic lesions in the respiratory tract were seen in the \geq 1400 mg/m³ groups, and were found only in animals dying within 12 days of exposure. Lesions were characterized as necrotizing rhinitis, necrotizing laryngitis and secondary suppurative bronchiolitis and bronchopneumonia. There was congestion of the thymus and tracheobronchial lymph nodes in almost half of the animals exposed to lithium aerosols. Similar observations were reported by Rebar et al. (1986) in groups of eight male and eight female rats that were exposed to an aerosol mixture of lithium monoxide and lithium hydroxide at concentrations of 0, 570, 840, 1200 or 1500 mg Li/m³ for 4 hours. The 14-day LC₅₀ value was 940 mg/m³. In this same study, the 14-day LC₅₀ value for a 4-hour exposure to an aerosol containing only lithium hydroxide was 960 mg Li/m³. Clinical signs and pathological changes were similar to those described in the Greenspan et al. (1986) study. Exposure to the lithium hydroxide/lithium monoxide aerosol mixture at concentrations of 570 Li mg/m³ and greater resulted in upper respiratory tract and pulmonary lesions.

No adverse respiratory effect were observed in groups of eight male rabbits exposed to aerosols of 0, 0.1 or 0.32 mg Li/m³ as lithium chloride for 6 hours/day, 5 days/week for 4-8 weeks (Johansson et al., 1988). Inhalation of lithium chloride produced no adverse effects on lung morphology or phospholipid content. The number of alveolar macrophages in lithium-treated animals was not different compared to controls.

Supporting Studies

Toxicokinetic

The clinical pharmacokinetics of lithium has been extensively studied. Reviews and clinical pharmacology text books provide summaries of the pharmacokinetic profile of therapeutic lithium (Ward et al., 1994; Baldessarini and Tarazi, 2001; Potter and Hollister, 2001). The bioavailability of oral lithium preparations ranges from 80 to 100%, although it is generally accepted that the oral bioavailability of lithium is 100%. Peak plasma concentrations are typically reached within 2 hours of administration of lithium. Lithium does not bind to plasma proteins. The volume of distribution of lithium is calculated as 0.66 L/kg. Although lithium is distributed into total body water, lithium distribution is not uniform in all tissue compartments. As an element, lithium is not metabolized and is excreted intact, primarily by the kidney; elimination through sweat, saliva and feces is negligible. Approximately 80% of the filtered load

of lithium is reabsorbed by the kidney and elimination correlates with renal function. Excretion follows first-order kinetics, with an average half-life of 22 hours and an average clearance of 0.35 mL/min-kg (0.5 L/day-kg).

Genotoxicity

Moore (1995) reviewed genotoxicity data as part of their assessment of the developmental effects of lithium and concluded that there is no evidence demonstrating genetic toxicity of lithium in bacterial or *in vitro* mammalian test systems. Garson et al. (1981) reported no increase in the occurrence of chromosome breaks in 23 human subjects under continuous lithium treatment for a period of 1-8 years when compared with 19 healthy age-matched controls. Lithium hypochlorite was not mutagenic in the Ames test nor did it induce DNA damage in the unscheduled DNA synthesis assay using rat primary hepatocytes or increase chromosome aberrations when tested orally in rats at maximally tolerated doses (Weiner et al., 1990).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC RfD VALUES FOR LITHIUM

The use of lithium as a long-term maintenance therapy in the treatment of bipolar affective disorders has led to an extensive body of literature on the adverse effects associated with oral lithium therapy. Adverse effects, which are observed in several organs and systems, are associated with the entire target therapeutic serum lithium concentration range, leading to treatment strategies based on a risk-benefit assessment for individual patients. The available clinical data identify the lower bound of the therapeutic serum lithium concentration range (0.6 mmol/L) as a LOAEL; the clinical literature does not identify a NOAEL for adverse effects associated with therapeutic lithium. Data reported in humans studies are not sufficient to define the relationship between serum lithium concentrations and the development or severity of adverse effects, although it is generally accepted that the severity of adverse effects is related to serum lithium levels. Given the lack of adequate dose-response data, a single critical effect cannot be identified for lithium. Occupational and environmental oral exposure studies in humans are not available.

Adverse renal effects associated with lithium therapy have received extensive focus due to their serious nature and frequency of occurrence. The most common adverse renal effect is impaired renal concentrating ability and the production of excessively dilute urine. Clinically, this manifests as polyuria, with secondary thirst, and volume depletion. The onset of impaired renal concentrating capacity typically is within the first 2 years of treatment. Although altered renal function appears to be reversible early in treatment, it may be progressive during the first decade of lithium treatment, leading to irreversible damage over time.

Lithium therapy produces side effects in a number of organs and systems other than the kidney. The most frequent neurologic side effects are lethargy, fatigue, weakness, tremor and cognitive impairment. Endocrine glands such as the thyroid and parathyroid can also be affected. Although serious cardiovascular effects are rare, they do occur, the most common

being changes in the EKG. Gastrointestinal side effects include nausea, vomiting, diarrhea and abdominal cramping. The most frequently observed hematological reaction is a benign leukocytosis. Developmental effects, primarily involving the heart, undoubtedly represent the most serious type of unwanted effects.

The available animal data provide supportive evidence that lithium produces adverse effects in several organs and systems at exposure levels that result in serum lithium concentrations in same range as that targeted for therapeutic use in humans. However, available studies do not evaluate comprehensive toxicity endpoints or identify a NOAEL for adverse effects. Thus, although results of toxicity studies in animals are consistent with the adverse effects profile in humans exposed to therapeutic lithium, data are not suitable as the basis for the provisional subchronic and chronic RfD.

The lower bound of the therapeutic serum lithium concentration range of 0.6 mmol/L is selected as the basis for derivation for the provisional RfD and subchronic RfD (p-RfD; p-sRfD). Given that the adverse effects profile of therapeutic lithium is similar for patients on short- and long-term lithium therapy, an RfD based on the LOAEL of 0.6 mmol Li/L is applicable for subchronic and chronic exposures. Based on the pharmacokinetic considerations detailed below, to achieve a serum lithium concentration of 0.6 mmol Li/L, the daily ingestion of lithium by a 70-kg individual is calculated as approximately 1.8 mg Li/kg-day.

At steady state,

$$D = \frac{C_p \cdot Cl}{f}$$

where D is the dose (mg/kg-day), C_p is the plasma concentration (mg/L), Cl is the plasma clearance (L/kg-day) and f is the fraction of the dose absorbed. Assuming values of 0.5 L/kg-day for Cl and 1 for f (Baldessarini and Tarazi, 2001), a steady-state plasma concentration of 0.6 mmol/L (4.2 mg Li/L) corresponds to a daily dose of 2.1 mg Li/kg-day.

The provisional subchronic and chronic RfD for lithium was derived from the LOAEL of 2.1 mg/kg-day for adverse effects in several organs and systems. Dividing the LOAEL of 2.1 mg/kg-day by an uncertainty factor of 1000 yields a subchronic and chronic **p-RfD of 0.002 mg/kg-day or 2 µg/kg-day**.

$$\begin{aligned} \text{p-RfD} &= \text{LOAEL} \div \text{UF} \\ &= 2.1 \text{ mg/kg-day} \div 1000 \\ &= 0.002 \text{ mg/kg-day or } 2 \text{ } \mu\text{g/kg-day} \end{aligned}$$

The composite uncertainty (UF) of 1000 includes a factor of 10 to extrapolate from a LOAEL to a NOAEL, a factor of 10 to protect susceptible individuals and a factor of 10 to account for database insufficiencies as follows:

- A default 10-fold UF for extrapolation from a LOAEL to a NOAEL was used because the lower bound of the therapeutic serum lithium range is associated with the development of adverse effects in several organs and systems; a NOAEL for adverse effects of therapeutic lithium has not been established in the clinical or animal literature.
- A default 10-fold UF was used to account for potentially susceptible individuals in the absence of quantitative information on the variability of response to lithium in the human population. Since lithium adversely affects several organs and systems, numerous pre-existing disease states (e.g., renal disease, cardiovascular disease, endocrine disease) may increase susceptibility to lithium.
- A UF of 10 was applied for database uncertainties. The renal effects of lithium have been extensively studied in humans and animals. However, much less information is available on the effects of lithium in other systems, including the cardiovascular, neurological and endocrine systems, and subchronic and chronic exposure studies in animals assessing comprehensive endpoints are not available. Furthermore, although lithium appears to produce developmental effects in humans, the database lacks well-controlled epidemiology studies and multi-generation reproduction studies in animals.

A wide range of estimates for daily dietary intake of lithium has been reported. Several authors report estimates for the average daily dietary intake of lithium, ranging from 0.24 to 1.5 $\mu\text{g}/\text{kg}\text{-day}$ (Noel et al., 2003; Clarke et al., 1987; Hamilton and Minski, 1973; Evans et al., 1985; Clark and Gibson, 1988). A much higher estimate for daily intake from food and municipal drinking water ranging from 33 to 80 $\mu\text{g Li}/\text{kg}\text{-day}$ was reported by Moore (1995). The source of the discrepancy between these estimates is unknown. The p-RfD of 2 $\mu\text{g}/\text{kg}\text{-day}$ is above most estimates of daily dietary intake, but below the range estimated by Moore (1995).

Confidence in the LOAEL value is low-to-medium. Since the clinical literature has focused on the therapeutic treatment of patients, information on effects observed below the minimally effective dose is lacking. Confidence in the database is also low-to-medium. Although there is an extensive database demonstrating the adverse effects of chronic exposure to therapeutic lithium, information regarding the dose-response relationship of lithium to the development of adverse effects is lacking. Thus, the relative sensitivity of the different target organs cannot be identified based on human data. Furthermore, since most animals studies have been designed to evaluate specific adverse effects associated with the therapeutic serum lithium concentration range, NOAEL and LOAEL values have not been established in animals studied for comprehensive toxicity endpoints. The database also lacks well-controlled epidemiology studies and multi-generation reproduction studies in animals, even though there is evidence of developmental effects in lithium patients. Low-to-medium confidence in the p-RfD is the result.

FEASIBILITY FOR DERIVING A PROVISIONAL SUBCHRONIC RfC FOR LITHIUM

No studies investigating the effects of acute, subchronic or chronic inhalation exposure to lithium in humans were identified. The available studies in animals did not evaluate comprehensive histopathological, biochemical and clinical endpoints of inhalation exposure.

Thus, due to the lack of data, derivation of a provisional subchronic or chronic RfC for lithium is precluded.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR LITHIUM

Weight of Evidence Descriptor

Cancer studies in humans and cancer bioassays in animals exposed to lithium by the oral or inhaled routes were not found. Results of *in vitro* and *in vivo* studies in bacterial and mammalian systems indicate that lithium is not genotoxic. Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the hazard descriptor, "data are inadequate for an assessment of human carcinogenic potential," is appropriate for lithium.

Quantitative Estimates of Carcinogenic Risk

Due to the lack of data, derivation of an oral cancer slope factor and an inhalation cancer unit risk are precluded.

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