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THE TOXICOLOGY OF LITHIUM COMPOUNDS

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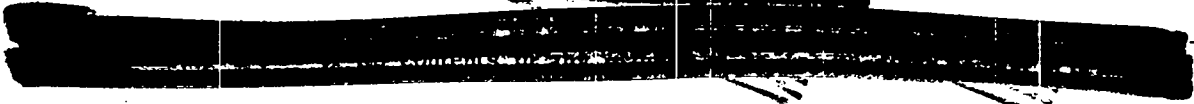
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HEALTH AND SAFETY
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ABSTRACT

The toxicity and pathologic effects produced by lithium chloride, lithium hydroxide and lithium hydride following administration to rats and mice by various routes have been investigated. With oral administration, unneutralized lithium chloride and lithium hydroxide were considerably more toxic than neutralized solutions. Very minute amounts of lithium hydroxide and lithium hydride powder given intratracheally proved lethal to rats because of the extreme causticity of the resulting solution formed in the lungs.

It was concluded that in considerations of air tolerance values for lithium metal, lithium hydroxide, lithium hydride, etc., the caustic effects are the limiting factor rather than the toxicity of the lithium ion per se. Tolerance values for other strong bases should probably apply to these compounds.

A calculation of the radiation hazard from inhaled lithium tritide indicated that the caustic properties of the compound were sufficiently great that long before radiologically dangerous quantities of the material could be inhaled the subject would show severe distress from the liberated lithium hydroxide. It was concluded, however, that monitoring for tritium gas around operations involving lithium tritide should be conducted since water vapor from the air or other sources might cause the liberation of dangerous amounts of tritium.

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Histopathologic studies of the animal material demonstrated minor changes in the kidney from toxic amounts of neutralized lithium chloride and severe damage to the respiratory tract following intratracheal administration of lithium hydroxide or lithium hydride.


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1. INTRODUCTION

The increased use of lithium and lithium compounds in certain manufacturing processes has made considerations of the relative hazard from these materials of increased practical importance.

Although there is a large amount of literature available on the toxicology of the lithium ion itself,* little information exists as to the hazard of certain compounds such as lithium hydroxide, hydride, and tritide, and little information exists as to permissible air tolerance values for these materials.

The present study was undertaken to determine the toxicology and pathology of lithium salts and the strongly basic compounds lithium hydroxide and lithium hydride when these materials were administered by various routes in experimental animals. From the data obtained in the experimental studies, it was considered likely that a theoretical calculation of the toxicity of lithium tritide could be made.

2. LITERATURE REVIEW

The toxic effect of lithium salts (particularly lithium chloride) administered orally to human beings has been

* For excellent reviews of the subject, see Hanlon et al.¹ and Radomski et al.²

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described in detail by a number of authors.^{1,3-7} The lithium ion is readily absorbed,⁸ distributed with the body water^{2,9} including the cerebrospinal fluid,¹⁰ and excreted by the kidney.^{2,8,9,11,12} When lithium chloride was given in excessive amounts as a salt substitute to patients on low sodium diets, the following symptoms were observed: tremors, muscle twitchings, weakness, apathy, confusion, and in some cases coma and death. The toxic effects observed in normal persons and in patients not on low sodium diets included drowsiness, depression, anorexia, gastrointestinal "irritability", and tremors. The amounts of orally administered lithium chloride required to produce any of the above symptoms have varied from 8 g. given in 1 day³ to 0.5 g. given daily for 114 days.¹ Symptoms of toxicity have been found to occur when the lithium concentration in the blood serum reaches 0.7 meq. per liter.⁷ In both human and animal studies the toxicity of lithium has been found to be greater when the patient or animal is given a low sodium diet.²

Severe gastroenteritis has been produced in cats,¹¹ dogs,^{9,11} and rats¹³ by either oral or parenteral administration of lithium chloride. Electrocardiographic changes in dogs^{2,14} and guinea pigs¹⁴ have been reported when these animals were given toxic doses of lithium chloride. The changes observed were thought to be due to increased serum

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potassium levels induced by the lithium ion.² It has been suggested that death in lithium-poisoned animals may be due to a direct toxic action of the lithium on the kidney.² Nerve conduction is known to be depressed by lithium,¹⁵ and aerobic and anaerobic glycolysis by spermatozoa has been shown to be inhibited.¹⁶ Damage to the distal convoluted tubules, collecting tubules, and the terminal portions of the loops of Henle has been demonstrated in the kidney.² Toxic doses of lithium are reported to produce a lymphopenia in dogs² but the specificity of this effect is questionable.

3. EXPERIMENTAL METHODS

3.1 Randomization and Handling of Animals

A total of 620 adult female CF₁ mice weighing 20 to 30 g. and 115 adult male Sprague-Dawley rats weighing 200 to 300 g. were used in the present study. The animals were randomized prior to treatment by using random number tables to assign them to various experimental groups. The rats were maintained 3 to 5 to a cage and the mice maintained 10 to 15 to a cage. All the animals received Purina Laboratory Chow and water ad libitum.

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3.2 Methods of Administration of Lithium

The following lithium compounds were administered to mice and/or rats by the following routes:

LiCl, pH 4, aqueous solution -- intraperitoneally

LiCl, pH 6, aqueous solution -- intraperitoneally

LiCl, pH 7, aqueous solution -- orally and intraperitoneally

LiOH, pH 12, aqueous solution -- orally

LiOH, dry powder -- intratracheally

LiH, dry powder -- intratracheally

The aqueous solutions were prepared by dissolving appropriate amounts of the compounds in water and, in the case of lithium chloride, adjusting the pH to the desired level with sodium hydroxide. The powdered lithium hydroxide was prepared by grinding the material to a fine dust with a mortar and pestle. The lithium hydride was specially prepared by Group CMR-6 of the Los Alamos Scientific Laboratory and had a uniform average particle size of 2 microns. This particular particle size was used to ensure maximum retention of the material by the lungs.

The intraperitoneal injections were made through 23-gauge needles into the left lower quadrant of the abdominal cavity. In the case of oral administration the material was introduced directly into the stomach through a curved steel catheter that


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had previously been introduced through the mouth and esophagus.

Intratracheal insufflation of powdered lithium hydroxide and lithium hydride was performed in anesthetized rats. Prior to anesthesia the rats were injected intraperitoneally with 20 mg. of atropine sulfate per kilogram of body weight to minimize tracheal secretions. Under ether anesthesia a mid-line tracheotomy was performed. A suitable sized section of polyethylene tubing containing a weighed amount of lithium hydroxide or lithium hydride was inserted into the trachea and pushed downward to the bifurcation of the main bronchi. The powder was then blown into the lung by exerting sudden pressure on a syringe attached to the opposite end of the tubing. The incision in the trachea was closed with a single linen suture and the wound in the neck closed with skin clips. To prevent any possible premature reaction between lithium hydroxide and lithium hydride and tracheal secretions, the end of tubing which was inserted into the trachea was sealed with a thin layer of paraffin before its insertion. Sudden pressure on the syringe at the opposite end caused an immediate break in the seal and allowed the lithium compound to be insufflated as a fine dry dust. Because of the extreme toxicity of lithium hydride, it was necessary to dilute it with an inert "filler" in order to increase the accuracy in weighing out the samples to be insufflated. Preliminary

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experiments indicated that cornstarch when given intra-tracheally was nontoxic and produced no microscopically discernible inflammatory reaction. This agent was used, therefore, as a "filler" to dilute the lithium hydride in a proportion of 4 to 1.

Tables 1 and 2 summarize the data on the routes of administration, dosages, and numbers of animals employed in each treatment group.

3.3 Histopathology

Autopsies were performed on all the animals that died spontaneously in the LD₅₀ studies and on a number of serially sacrificed animals. Sections of thymus, lung, liver, kidney, spleen, adrenal, jejunum, ileum, colon, lymph node, bone marrow, and either testis or ovary were fixed in either formalin or Zenker's acetic fixative. Paraffin sections were prepared and stained with either hematoxylin-eosin or azur-eosinate for histological study.

3.4 Statistical Methods

In the cases where LD₅₀ studies were performed, the approximate LD₅₀ was obtained from an eye-fitted plot of the probit regression line on log probability paper.


4. RESULTS4.1 Studies on Lithium Chloride

4.1.1 Toxicology. The data on the toxicology of the lithium ion (LiCl) given by various routes are summarized in Table 1. It can be seen from this table that the lower the pH of the administered solution the greater the toxicity. Presumably, this effect is due to the additive toxic effect of the lithium and the pH of the solution. When neutralized lithium chloride was given orally, the LD₅₀ dose was found to be approximately 200 and 160 mg./kg. for mice and rats respectively; when delivered intraperitoneally, it was 130 and 94 mg./kg.* Tolerance to the compound was much higher when it was given orally.

Signs and symptoms observed in these animals varied somewhat with the dosages employed. Animals given massive doses (sufficient to produce death in 24 hours) of lithium chloride parenterally showed the following sequence of signs: prostration, depressed respiration, cyanosis, dyspnea, diarrhea, clonic convulsions, respiratory failure and death. Smaller doses of the salt given either orally or by intraperitoneal injection caused anorexia, weight loss, diarrhea, dehydration, and occasionally bleeding from the nose.

* Doses are based on the weight of the lithium ion.



4.1.2 Histopathology

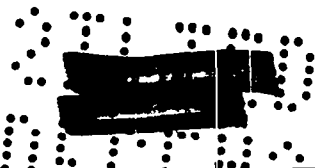
Oral and Parenteral LiCl (94 to 200 mg. Li ion/kg.)

Gross: Animals given high doses of the salt died within a few hours with no gross changes at autopsy. At lower doses, autopsies were obtained at 18 hours, 6 days and 14 days. No remarkable gross changes were seen at these time intervals, except for a moderate hyperemia of the intestines of animals receiving the oral administrations.

Microscopic: At 18 hours, the lymphoid tissues (spleen, lymph node, and thymus) showed marked rhexis and pyknosis of cells in the lymph follicles. No changes were seen in other organs. At 6 days, considerable nuclear debris remained in the lymphoid tissues and a moderate amount of hemosiderin was present in the spleen. The parenchymatous organs showed vascular engorgement. The proximal convoluted tubules of the kidney showed very early and a minimal degree of parenchymatous degeneration. At 14 days, the sections appeared histologically normal.

4.2 Studies on Lithium Hydroxide and Lithium Hydride

4.2.1 Toxicology. Lithium hydroxide, when administered orally to mice, proved considerably more toxic than lithium chloride. The approximate LD₅₀ for mice was 50 mg. Li ion/kg., as compared to 200 mg. Li ion/kg. with neutralized lithium chloride. The reason for this greater toxicity was

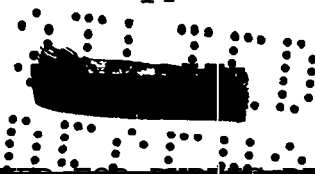




undoubtedly the fact that the solution was extremely caustic (pH 12). These data are shown in Table 1.

In Table 2, the data on rats given lithium hydroxide and lithium hydride intratracheally are summarized. From this table it can be seen that when the toxicity of lithium hydroxide and lithium hydride compared on the basis of the amount of lithium ion given (this value being directly related to the amount of hydroxide ion liberated by the reaction with water), the two compounds are approximately equally toxic. Rats given doses ranging from 0.35 to 3.45 mg. of lithium as LiOH showed a 30-day mortality of 47 per cent. A second group given a somewhat narrower range of doses of lithium as LiH (0.31 to 0.80 mg.) showed a 55 per cent mortality.

No attempt was made to determine the LD₅₀ for intratracheally administered lithium hydride or lithium hydroxide for the following two reasons. The toxic effect of these materials in the lung depends partially on the uncontrollable variable of where the particles lodge (e.g., if for some reason no material lodges in one lobe, the animal is likely to survive). For this reason, dose-response curves are subject to relatively large errors. In the second place, the amount of material administered was determined by weighing a segment of polyethylene tubing containing the compound before and after insufflation into the rat, and from the difference



in weights the exact dose delivered was determined. With a system such as this, it is extremely difficult to reproduce accurately the dose administered to a group of animals.

Rats receiving intratracheal administration of lithium hydroxide or lithium hydride showed immediate signs of respiratory distress. Breathing was rapid and labored and there was considerable "wheezing". Occasionally the animals became very cyanotic. At later times they showed lethargy, weight loss, and ruffling of the fur. Wheezing respirations were present for about 10 days following injection of either material.

4.2.2 Histopathology

Oral LiOH (50 mg. Li ion/kg.)

Gross: Autopsies were obtained at 1, 3, and 6 days. At all these time intervals the intestines were hyperemic but there were no other remarkable changes.

Microscopic: The findings were identical to those described in Section 4.1.2 with the exception that, in addition to these changes, there was microscopic evidence of sloughing of the tips of the villi in the jejunum at all time intervals.

Intratracheal LiOH and LiH (0.31 to 3.45 mg. Li ion)

Gross: Autopsies were obtained at 2, 3, 4, 6, 8, 9, 10, 11, 20, 30, and 40 days after intratracheal

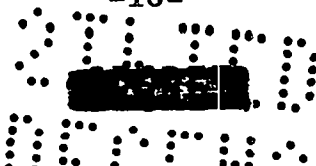



administration of lithium hydroxide and lithium hydride. At all these intervals, the gross changes were confined to the lungs. At the early intervals, the lungs showed massive edema and focal hemorrhages. At later times, these changes had progressed to consolidation, pneumonia, and abscesses. At the last three time intervals, the lungs showed consolidation and fibrosis.

Microscopic: The histologic findings were similar at all the time intervals studied for the first 6 to 8 days. Sections of lung showed focal areas of necrosis, sloughing of bronchial epithelium, hemorrhage, pneumonia, and atelectasis. A small amount of debris was present in lymphoid follicles at these intervals and the spleen showed moderate hemosiderosis. No remarkable changes were seen in the other organs. At 10 days, early reparative changes were present in the lung, and by 20 days, repair was practically complete with resolution of the inflammatory infiltrate and healing of the bronchial epithelium.

5. DISCUSSION

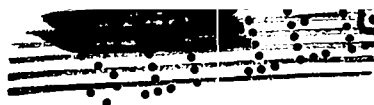
From the data reported in the present study and from the literature concerning human cases of lithium poisoning, it is obvious that the lithium ion itself is not particularly toxic and can probably be disregarded in considerations of air





tolerances for lithium metal or lithium compounds, since other factors such as the acidity or alkalinity of the agents will probably be the limiting factor. Toxic effects from lithium chloride have been reported in human cases following the ingestion of 8 g. of material in 1 day and following the daily ingestion of 0.5 g. for 114 days. If it is assumed that the single dose of 8 g. was given to a man weighing 60 kg., then this toxic dose amounts to 133 mg./kg. In general, mice and rats are considerably more resistant to toxic agents on a weight basis than are human beings. Our values for the LD₅₀ of lithium chloride for mice and rats of 1200 and 960 mg./kg. are, therefore, in reasonable agreement with the value of 133 mg./kg. as a toxic dose for human beings. (The values of 200 and 160 mg./kg. given in Table 1 are based on the weight of the lithium ion. The value for lithium chloride is six times this value because of its molecular weight.)

In the present study, unneutralized lithium chloride and lithium hydroxide produced toxic effects at far lower dosages than did the neutralized lithium salt. The reason for the greater toxicity was undoubtedly the acidity and alkalinity, respectively, of the water solutions. This finding lends support to the thesis that the lithium ion is relatively nontoxic and that in consideration of air tolerance values for lithium metal, lithium chloride, lithium hydroxide, lithium hydride, lithium bromide, etc., the pH of the solution

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resulting from the interaction of these agents with body fluids following inhalation or ingestion presents the limiting factor in air tolerance values.

The portion of the study concerned with intratracheal insufflation of lithium hydroxide and lithium hydride shows conclusively that as far as these agents are concerned their extreme causticity is of primary importance in producing toxic effects. The amounts of lithium ion per se given to these animals intratracheally were negligible and did not enter into the problem of toxicity. On the basis of weight, lithium hydride proved approximately three times as toxic as lithium hydroxide. This factor of 3 would be anticipated on the basis of the molecular weight of the former being one-third that of the latter. Lithium hydride reacts with water to produce molecular hydrogen and lithium hydroxide. Equimolar weights of the two compounds should, therefore, produce equal effects. Such an effect was found.

Since metallic lithium and lithium hydride react with water to produce molecular hydrogen and lithium hydroxide, it is apparent that the toxic effect of metallic lithium, lithium hydroxide, and lithium hydride is produced by their basic properties. Since the lithium ion need not be considered in the air tolerance values in the case of these agents, it follows that the proper value for tolerance should probably be the same as that established for other strong bases.



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In consideration of the relative hazard of lithium tritide, the question arises as to whether the causticity of the compound or the radiation from the tritium presents the greater hazard. In preliminary studies Schulte and his associates¹⁷ have found that an air concentration of $35 \mu\text{g./M}^3$ of lithium hydroxide or lithium hydride (the weight based on weight of the lithium ion) produced extreme discomfort in human volunteers. At this concentration, there was pronounced choking and coughing induced in the experimental subjects. If we consider this concentration the upper limit likely to be encountered in exposures to lithium tritide, then the relative hazard from the tritium may be calculated as follows:

Assume: 1. $\text{LiT} + \text{HOH} \longrightarrow \text{LiOH} + \text{HT (gas)}$

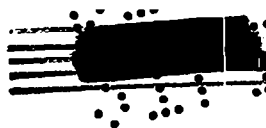
2. Every particle of inhaled lithium tritide comes in contact with a lung surface and reacts as shown in 1.

Then: 3. In $35 \mu\text{g.}$ (measured as lithium) there are about $50 \mu\text{g.}$ of lithium tritide of which tritium constitutes $15 \mu\text{g.}$ In terms of grams, this amounts to $1.5 \times 10^{-5} \text{ g./M}^3$ of air.

4. Since the specific activity of tritium is 1×10^3 curies/g., it follows that in the air concentration being considered there are 1×10^3 curies/g. $\times 1.5 \times 10^{-5} \text{ g./M}^3 = 1.5 \times 10^{-2}$ curie/ M^3 or 1.5×10^{-5} curie/liter.

5. Since the accepted air tolerance for tritium is 1.4×10^{-4} curie/liter, it appears that the tritium evolved

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from the interaction of lithium tritide with body fluids in the lung does not constitute a hazard.

The above calculations, however, do not take into account the fact that in an area contaminated with lithium tritide the majority of the material may react with water vapor in the air or with other moisture in the area to liberate HT. Conceivably, such a situation could lead to concentrations above tolerance values even though the concentration of lithium tritide in the inspired air did not reach uncomfortable levels. On the basis of these considerations, it appears that the hazard from inspired lithium tritide is due to its basicity and not the liberated tritium. The practice of monitoring operations involving lithium tritide for tritium is valid, however, because of the possibility of the liberation of relatively large amounts of tritium by water other than body water.

6. CONCLUSIONS

The following conclusions have been reached based on the present study:

1. The lithium ion per se is relatively nontoxic in animals and man.
2. The toxicity of compounds such as lithium hydroxide and lithium hydride is due primarily to the pH of the solution formed when these compounds react with water.

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Existing tolerance values for strong bases should probably apply for lithium metal, lithium hydride, and lithium hydroxide.

3. Because of the extreme degree of irritation produced by the inhalation of lithium hydride, it appears unlikely that a sufficiently high concentration of lithium tritide could be breathed to constitute a hazard from the tritium liberated by its reaction with water.

4. Monitoring operations for tritium gas should, however, be continued around operations involving lithium tritide because of the possibility of a large amount of tritium being liberated by reaction with water vapor from the air or other sources.


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Table 1

TOXICITY OF LITHIUM CHLORIDE AND LITHIUM HYDROXIDE IN RATS
AND MICE FOLLOWING ADMINISTRATION BY VARIOUS ROUTES

Compound and pH	Route of Adm.	Animals used	No. of Dose Groups	Obs. Period (days)	Approx. LD ₅₀ * (mg./kg.)
LiCl, pH 4	I.P.	160 mice	8	1	103
LiCl, pH 6	I.P.	160 mice	8	30	110
LiCl, pH 7	I.P.	120 mice	6	30	130
LiCl, pH 7	I.P.	25 rats	5	30	94
LiCl, pH 7	Oral	60 mice	6	30	200
LiCl, pH 7	Oral	25 rats	5	30	160
LiOH, pH 12	Oral	80 mice	8	30	50

* Doses are calculated on the basis of the weight of the lithium ion.

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Table 2

TOXICITY OF INTRATRACHEALLY ADMINISTERED LITHIUM HYDRIDE
AND LITHIUM HYDROXIDE IN RATS

No. Rats	Compound	Dosage Range Employed* (mg.)	30-Day Mortality, %
17	LiOH, Powder	0.35 to 3.45	47
25	LiH, Powder	0.31 to 0.80	55

* Doses are calculated on the basis of the weight of the lithium ion.

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