

Environmental lithium exposure in the north of Chile - Tissue exposure indices

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ABSTRACT

BACKGROUND: northern Chile has the highest levels of lithium in surface waters in the world which is reflected in very high lithium levels in the plants and animals that depend on these water systems and consequently in the indigenous population.

METHODS: the lithium tissue burdens in populations from two valleys in the extreme north of Chile have been studied. The bulk of this report is based on analyses of lithium levels in urine, hair, and breast milk in the population of several villages. Data on serum levels, some of which had been previously published, are included for the sake of completeness. Since this paper reports studies by several groups of workers samples were analysed by a variety of methods. These include atomic emission, atomic absorption, other photospectroscopic techniques and mass spectroscopy.

RESULTS: in all samples studied the average lithium level (5.3 ppm) was found to be significantly elevated compared to levels reported in the literature and measured in this study for people not exposed to high levels in water and food (0.009-0.228 ppm).

CONCLUSIONS: the people studied represent a unique longitudinal cohort. The work should provide important insights into the potential neuroprotective effects of lithium also help us set guidelines to assess the risks from high dose environmental exposure.

Key words: Chile; Lithium; Urine and tissue levels; Exposure in water and food

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INTRODUCTION

Northern Chile has the highest levels of lithium in surface waters in the world. These arise from natural environmental sources [1].

This is reflected in the very high lithium levels found in the plants and animals that depend on these water systems [2]. The levels of lithium found in the bodily tissues (urine, blood, hair) of the people that have lived in these areas for

generations and have throughout their history relied upon these heavily lithium loaded food and water sources have therefore also been found to be elevated.

The people exposed to high lithium levels in these areas who were studied for this survey lived in villages situated in two valleys in the extreme north of Chile [1]. A few had been found to have very high serum lithium levels forty years ago [3-5]. This was independently confirmed in a larger group of villagers approximately ten years later [6] by Schull and his colleagues [7] between 1973 and 1979 as part of the Multi-Andean Health and Genetic Programme (MAHGP) [8]. The MAHGP also collected numerous samples for analysis from other bodily tissues for lithium content including urine, serum and hair. Since the findings of these studies were never reported, they have been described here in detail.

METHODS

Sample collection

This report is based largely on the unpublished analyses of urine, hair, and breast milk done by Professor Leo Figueroa of the University of Tarapaca. The majority of the samples were urine specimens and a total of 433 urine spot samples were collected. It would have been impossible to collect 24 h urine samples. The validity of measurements from samples collected in this way has been studied (see for example [9]). The samples were collected from 344 people who lived in the two lithium rich valleys of the primary study area [1], the Valle Camarones and the Valle Lluta, and the nearby control valley, Valle Azapa, with low lithium levels [1]. The populations and altitudes of each of the villages were also recorded. Samples were collected from 7 villages in the Valle Camarones, 3 villages in Valle Lluta, and 4 villages in Valle Azapa (see [1]).

Members of the cohort in the Valle Camarones were mostly adults, while in the other two valleys urine was collected from schoolchildren. The protocols for taking the urine samples were laid out in detail in the MAHGP field manuals (available on request).

For the children, the nature of the project was explained to the teacher and her co-operation was requested to explain the

same to her class. A 'urine sample data sheet' was then handed out to the class to complete and a request to provide the urine sample was made. Informed consent forms were completed and signed by each teacher. A water sample was collected from the school tap water. Upon receipt of the urine sample from each child, the cup was numbered and the same number was placed on the child's data sheet. Total urine volume was measured. Each sheet was then inspected to be sure all questions were answered. When the examiner's evaluation for each child was completed, 6 ml of urine was decanted into a plastic tube, 3 drops of 5N HNO₃ were added and the tube securely closed and labelled.

For analysis, one drop of urine was placed on a refractometer and the specific gravity was recorded.

At the time the urine samples were taken, 'additional clinical information' (ACI) was also obtained and entered into bilingual proforma questionnaires completed by each villager and/or their family, since many were children at the time the study was conducted. The questionnaire information included but was not limited to their:

- names and those of their parents;
- place of birth;
- place of residence at the time the samples were taken;
- time spent residing in the area;
- sources of water used at the time the urine samples were taken;
- water lithium concentrations;
- when and what they ate and drank the day before the samples were drawn;
- volume of urine voided, specific gravity, number of times voided day before

Clinical examinations were also performed on each subject [10] and the data from these were entered into another set of questionnaire proformas for correlation with the exposure data. The findings of these correlative analyses will be presented in a future report.

Sample analysis

Urine samples were digested by boiling, first with addition of 65% nitric acid p.a. and

then by means of perchloric acid 70-72% p.a., finally the solution was diluted to a known volume with water. For this and other dilutions and for other analytical operations as necessary distilled water of electrical conductivity <0.5 μ S/cm was used.

Blood samples were first centrifuged to separate the plasma that contains the lithium analyte and then treated similarly.

Measurement of lithium in the urine and blood plasma solutions were by atomic absorption spectroscopy using a hollow cathode lamp, oxidizing flame and following the recommendations in the operation manual for the AAS-Perkin Elmer 503 instrument used. Ionisation effects were suppressed by adding a solution of 0.1% w/v potassium chloride up to a concentration of 1 000 μ g/mL of potassium ion as an ionisation buffer to both samples and calibration standards.

The serum data published by Zaldivar [3] and Barr et al [6] are also included for the sake of completeness. These were also taken from villages in the Valle Camarones and Valle Lluta (see Table 1; also see [6, 11, 12]). Serum data cited as Schull et al. (1979) by Clench et al. [12] and as Schull and Howell (28 Mar 78) in unpublished archival data have also been presented (Table 1). Some ACI (names, age, sex, residence time) was available for 10 subjects with serum data from Valle Lluta (Diez y Sies).

The serum samples analyzed by Zaldivar [3] were done using the photospectroscopic methods of Amidsen et al [13] whilst Barr et al [6] used ultra-sensitive mass spectroscopy [11]. Only two individuals had both urine and blood sampled for lithium content.

TABLE 1

URINE CONCENTRATION DATA FOR INDIVIDUAL VILLAGES OF THE THREE VALLEYS IN THE PRIMARY STUDY AREA

VALLE CAMARONES

VILLAGE	ALT	POP	N1	N2	AVE AGE	Avg Conc.	Conc. Range	Res Time	Cum. Conc.	N3	Ave Conc	Conc Range
Illapata	2 200	32	26	50	23	3 808	683-7 799	13	49 504	31	4 511	1 740-9 460
Esquiña	2 200	71	21	13	36	3 124	479-7 069	23	71 852	26	2 241	810-9 338
Pob. Camarones	1 500	145	49	67	25	2 822	611-6 282	13	36 686	22	8 327	3 310-19 740
Umallane	1 400	ND	5	10	16	5 067	3 096-6 910	12	60 804	ND	ND	ND
Cuartel Viejo	1 300	15	7	14	20	5 754	3 636-8 064	11	53 294	ND	ND	ND
Conanoxa	300	ND	5	10	17	5 582	3 420-7 953	9	50 238	ND	ND	ND
Cuya	100	ND	17	34	37	3 781	158-15 470	5	18 905	ND	ND	ND

VALLE LLUTA

VILLAGE	ALT	POP	N1	N2	AVE AGE	Avg Conc.	Conc. Range	Res Time	Cum. Conc.	N3	Ave Conc	Conc Range
Molinos	550	80	20	35	10	1 713	434-5 069	5	8 565	19	1 763	470-3 400
Poconchile	500	420	51	84	10	1 165	183-2 873	15	18 615	ND	ND	ND
Diez y Seis	200	55	40	44	22	703	112-2 779	30	21 090	ND	ND	ND

VALLE AZAPA

VILLAGE	ALT	POP	N1	N2	AVE AGE	Avg Conc.	Conc. Range	Res Time	Cum. Conc.	N3	Ave Conc	Conc Range
Sobraya	200	ND	25	27	12	187	29-393	6	1 122	ND	ND	ND
San Miguel	200	300	40	37	14	198	57-521	10	1 980	ND	ND	ND
Pago de Gomez	150	ND	41	8	13	140	12-388	14	1 960	24	242	0-2 296

N1: Number of subjects with any identifying information; N2: Number of samples; N3: other cases with urine concentration data only

Lithium analyses were also performed on 11 Chinchorro mummies from Valle Camarones estimated to be 700 to 1 000 years old (Allison unpublished data). The tissues were obtained at autopsy by Prof. Marvin Allison [14] and analyzed by Prof. Figueroa.

Breast milk, urine and serum from 30 pairs of newborn babies and their mothers were collected by Sara Barton and analyzed by Professor Figueroa using photospectrographic methods. The samples were taken shortly after delivery in the Hospital Juan Noe in Arica according to protocols described in detail in the 1973-1974 (Aymara Study Reference Manuals-available upon request). Proforma questionnaires within the manuals were also completed by each participating mother to obtain additional information regarding the 'maternal sample' and the 'cord blood sample' (also within the Reference manuals).

RESULTS

Highly elevated lithium levels were found in those living in Valle Camarones and Valle Lluta for all tissues analyzed. Conversely, those found in those living in the 'control' area, Valle Azapa were low. There was general correlation with lithium levels found in water [1] and food [2] as reported previously. The findings for each tissue are presented below.

Urine Concentrations

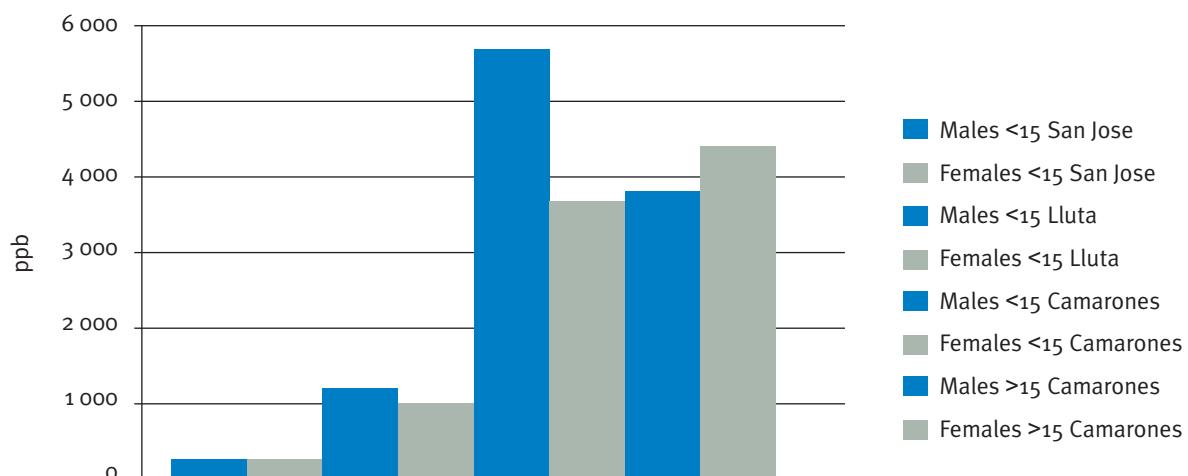
A total of 443 urine samples were taken from 344 subjects. At least one sample was taken from 104 subjects in Valle Azapa; 110 in Valle Lluta; and 130 in Valle Camarones between 1973 and 1979. One sample was taken from each subject. No more than two samples were taken.

Urine samples were taken from 182 males and 164 female subjects. Fifty seven male and 47 female subjects lived in Valle Azapa, 45 male and 65 female subjects in Valle Lluta and 80 male and 50 female subjects in Valle Camarones. Urine concentration data and all of the associated 'ACI' (vs) were available for 158 subjects: Valle Camarones, Valle Lluta, and Valle Azapa (Table 1) Urine concentration data were also available with case ID numbers, age and sex for an additional 77 subjects from Valle Azapa.

The urine concentration data averaged over a 5 year period for four groups from each valley are shown in Figure 1 where San Jose is the area in Azapa where the school was situated. From this it can be seen that there is no significant difference between the sexes and that the highest levels are still found in Valle Camarones followed by Valle Lluta. The average and range of urine concentrations for subjects in villages of the three valleys are shown in Table 1. The data are arranged for

FIGURE 1

LITHIUM URINE LEVELS FROM THREE VALLEYS IN NORTHERN CHILE BY AGE AND SEX



Source: Barton et al, unpublished

villages in their order from the mountains to the coast for each valley.

The highest values were found in Valle Camarones followed by Valle Lluta and then Valle Azapa. For Valle Azapa, there was no significant variation in the urine concentrations found from mountains to coast in contrast to the other two valleys.

The total cumulative urine exposure concentrations incurred by those living in each village, calculated by multiplying average residential time (years) by average concentration (ppb), are shown in Table 1. Those with 'high' (>2 000 ppb) and moderate (250-2 000 ppb) cumulative concentrations apparently demonstrate 'linearity' over time (Figure 2). The 'low' (<200 ppb) cumulative lithium groups do not, probably due to clearance (data not shown). 'Linearity' is also shown in those born in the high exposure valleys as well as those who were not born there (Figure 2).

Serum lithium levels

Zaldivar was the first to demonstrate elevated serum lithium levels in villagers living in the extreme north of Chile (reported in Conference Proceedings [3]). He did so in 30 subjects living in three 'broad ecological niches': the Andean Cordillera (Parinacota) (n=10); the Sierra (Putre) (n=10) and the Coastal Region (Valle Lluta) (n=10). His research was conducted between 1968 and 1970. He also analyzed water from Habitation Camarones and found that it had the highest lithium levels of any surface waters in the world. Zaldivar, however, did not report serum lithium levels from Valle Camarones. This was first done by Barr et al. [6]. On examining the available data at the time, Barr et al. [1993] [6] noted "The blood levels obtained in the present study are closely similar to those reported by Zaldivar [4, 5] and the Houston group [7, 12]"

Lithium serum data for those living in the high exposure areas in the north of Chile have been summarized in Table 2. Data were found for 125 subjects. Thirty two were from Valle Lluta and 10 from Valle Camarones both of which are known to have high levels of lithium in water [1] and food [2]. The serum lithium levels were elevated accordingly (Table 2).

The remaining lithium serum data were from the Andean Cordillera (Parinacota)

(n=25), the Sierra (Putre) (n=24), and Valle Azapa (n=24). All are known to have water [1] and food [2] with relatively low lithium levels consistent with the control lithium levels from unexposed areas (Table 2).

Controls were taken from the Chilean sampling team normally resident in Texas and Santiago. Their lithium levels were very low in keeping with the normal levels reported by Clarke et al. [15] for residents living in Ontario Canada and by Schrauzer [16] for other parts of the world.

Lithium levels in hair

The lithium content of 22 hair samples from people living in the Habitation Camarones, the main village of Valle Camarones was analyzed. The average lithium level (5.3; ND – 9.21 ppm) was found to be significantly elevated compared to normal (0.009-0.228 ppm) [16]. Hair samples were not taken for Valle Lluta or Valle Azapa.

Lithium levels found in the tissues of Chinchorro Mummies

The lithium levels found in various tissues of eleven Chinchorro mummies estimated to be 700 to 1 000 years old (Figure 3a) are shown in Figure 3b. The highest levels were found in muscle, nail and ribs

Lithium levels found in maternal-newborn pairs

The lithium levels found in 30 maternal-newborn pairs were analyzed (Table 3). One mother left without delivery. The mothers had been in Arica from two days to 23 years before delivery. Their ages ranged from 17 to 38 years. Only four were born in Arica. All except one relied on potable water. Maternal venous blood lithium level data were available for 22 women and these ranged from 1 050 to 1 410 ppb. Foetal cord blood and newborn urine lithium concentrations were generally one order of magnitude less than those found in the maternal venous blood (Table 3). Breast milk lithium level were available for 20 women. These were generally two to three times higher than those found in the maternal venous blood ranging from 2 498 to 4 379 ppb. No maternal-newborn pair data were available for women from Valle Lluta or Valle Camarones.

FIGURE 2

LITHIUM CONCENTRATION CURVES

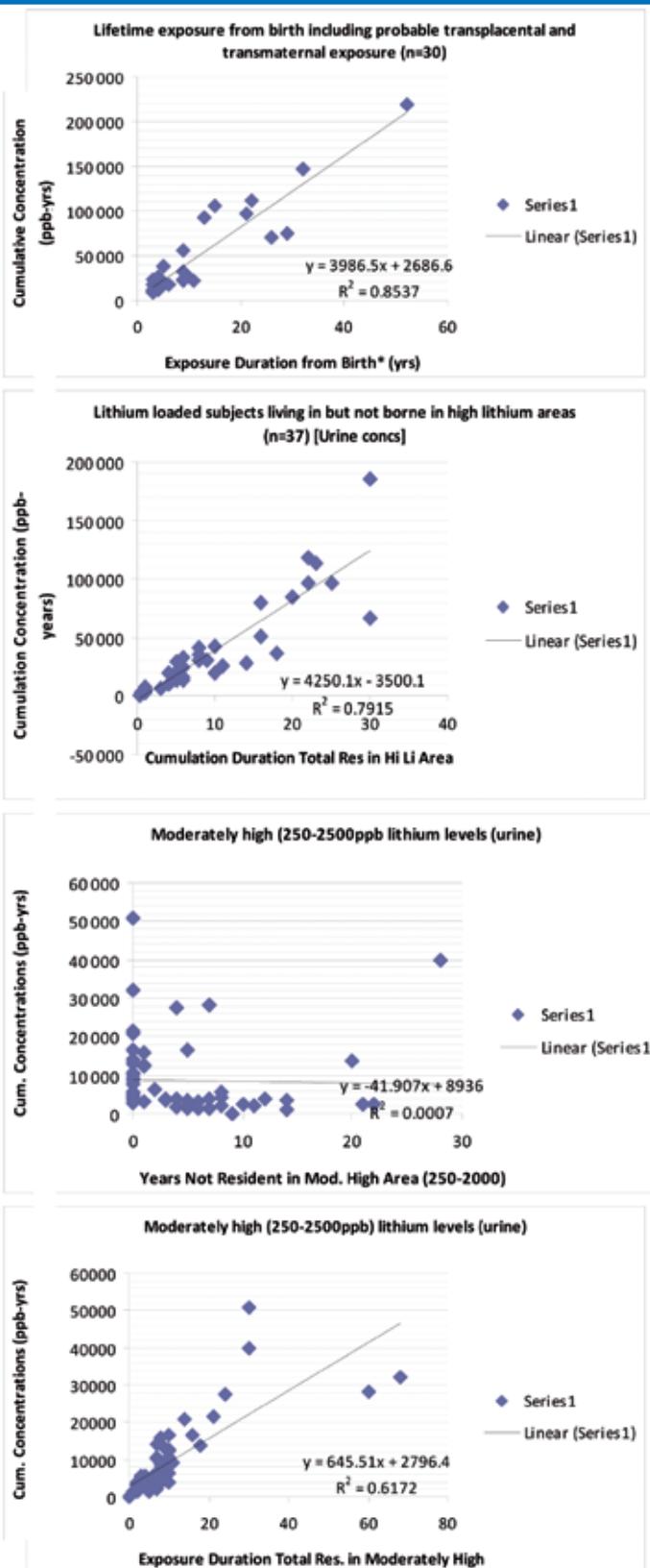


TABLE 2

LITHIUM SERUM DATA						
LOCATION	N	AGE (RANGE) (SEX)	RACE	RT (YEARS)	Li (ppb OR meq/L)	REF.
PARINACOTA (4 300M)	10	NS (5F)	(NS)	NS	0.0038	[Zaldivar, 1980 [4, 5]] ¹
	10	33 (21-59) (4F)		(31) 3-59	9.0 (4.6-15.6) ppb	[Barr et al, 1993] ²
PUTRE (3 400M)	5	18 (8-42) (3F)		ND	0.003-0.004 meq	[Schull & Howell, 1978] ⁴
	10	NS (5F)		NS	0.0057	[Zaldivar, 1980 [4, 5]] ¹
POCHONCHILE (400M) (KM 27)	10	31 (16-86) (5F)		4-86	12.7 (6.4-44.5)	[Barr et al, 1993]
	14	27 (7-52) (8F)	NS		0.003-0.006	[Schull & Howell, 1978]
POCHONCHILE (400M) (KM 27)	10	NS (5F)		NS	0.0148	[Zaldivar, 1980 [4, 5]] ¹
	10	42		27	36	[Barr et al, 1993] ^{2, 3}
	(1)	64M (A)		40	33.8 ppb	
	(2)	24F (C)		10	41.2 ppb	
	(3)	28M (AC)		5	9.8 ppb	
	(4)	38F (A)		38	49.5 ppb	
	(5)	85M (A)		85	46.7 ppb	
	(6)	48F (AC)		5	36.3 ppb	
	(7)	47M (A)		47	53.4 ppb	
	(8)	24F (A)		24	36.6 ppb	
	(9)	43F (C)		10	29.3 ppb	
	(10)	20F (C)		5	22.5 ppb	
	12F	28 (ND)		ND	0.0151 meq/L	[Schull & Howell, 1978]
	(1)	47M			0.029	
	(2)	24F			0.015	
	(3)	30M			0.012	
	(4)	36M			0.010	
	(5)	13F			0.009	
	(6)	8M			0.008	
	(7)	46F			0.008	
	(8)	7M			0.007	
	(9)	66F			0.007	
	(10)	9F			0.006	
	(11)	19F			0.006	
	(12)	34F			0.006	
	(13)	ND			0.053	

RT: Residence Time; n: Sample Number; A: Aymara/C: Caucasian; NS: not stated; ND: no data; NA: not available;

AA: atomic absorption

¹ Zaldivar 1980 [5] 'for obtaining absolute measures, these arithmetic means must be increased by about 20% because of the addition of a cell preservative for collection of the blood specimens'; age range 10-62

² Barr et al. [1993] – Pochonchile is used here to include nearby villages: 'Molinos' (cases 1-3); 'Boca Negra' (cases 4-8); and Pochonchile (cases 9 & 10)

³ Barr et al [1993] urine Li concentrations for all 10 subjects ranged from 943-965 ppb

⁴ Schull & Howell [1978] (unpub) - 8 out of 10 samples simply labelled 'Valle Lluta', their exact sampling site not known; n.b. - 4 entries designated as 'cracked or broken tubes' have not been included here

These results are cross cited in Table 4 of Clench et al. [1981] by Barr et al [1993] but really these are the data produced by Schull et al. [1979 unpublished] reported above as 'Schull and Howell, 1978 unpub]

⁵ Dr & Mrs Schull, 1 sample each; Sara Barton 2 samples; Elena Rothhamer 1 sample

⁶ for Guelph Ontario, Canada [Clark et al, 1987]

DISCUSSION

This report extensively documents the extremely high levels of lithium found in the bodily tissues of those living in the north of Chile as well as those who resided there

thousands of years ago. These reflect the exceedingly high lithium levels found in the water [1] and food [2] upon which they rely found in this area.

To our knowledge, these are the only populations in the world whose historical

TABLE 2 (CONTINUE)

LITHIUM SERUM DATA						
LOCATION	N	AGE (RANGE) (SEX)	RACE	RT (YEARS)	Li (ppb OR meq/L)	REF.
CAMARONES (300M)	10	28		17	109 ppb	[Barr et al, 1993]
	(1)	22F (C)	3		50.3 ppb	[Barr, unpub]
	(2)	30F (C)		12	94.1 ppb	
	(3)	22F (C)		22	72.3 ppb	
	(4)	33F (C)		33	72.9 ppb	
	(5)	27F (C)		1	133 ppb	
	(6)	32F (A)		32	101 ppb	
	(7)	29M (C)		29	175 ppb	
	(8)	27M (C)		3	170 ppb	
	(9)	33M (C)		10	131 ppb	
	(10)	23F (AC)		23	89 ppb	
AZAPA	24	ND (ND)	ND		AA 0.002-0.008	[Schull & Howell, 1978]
CONTROLS 'CHILEAN' SAMPLING TEAM ⁵	4	ND (1M, 3F)		NA	AA 0.003-0.004	[Schull & Howell, 1978]
CLARKE ET AL ⁶ SCHRAUZER 2002	7	ND (ND)		ND	2.6 (1.54-4.42) ppb	[Clark et al, 1987]
					7-28 ppb	

RT: Residence Time; n: Sample Number; A: Aymara/C: Caucasian; NS: not stated; ND: no data; NA: not available;

AA: atomic absorption

¹ Zaldivar 1980 [5] 'for obtaining absolute measures, these arithmetic means must be increased by about 20% because of the addition of a cell preservative for collection of the blood specimens'; age range 10-62

² Barr et al. [1993] – Pochonchile is used here to include nearby villages: 'Molinos' (cases 1-3); 'Boca Negra' (cases 4-8); and Pochonchile (cases 9 & 10)

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⁵ Dr & Mrs Schull, 1 sample each; Sara Barton 2 samples; Elena Rothhamer 1 sample

⁶ for Guelph Ontario, Canada [Clark et al, 1987]

lithium levels have been carefully characterized. They thus represent a unique longitudinal cohort whose historical characteristics have been reconstructed from original archived data and published reports. Cross sectional analysis of these individuals should provide important insights into the potential neuroprotective effects of lithium [17] and also help us set guidelines to assess the risks from high dose environmental exposure.

Urine Data. Most of the data were based on urine samples. Urine is one of the most commonly used methods to assess lithium exposure and has been found to be the most suitable study matrix for doing so [18, 19]. To our knowledge, the only other investigation of environmental lithium exposure aside from this one was conducted by Vahter and

her colleagues at the Karolinska Institutet and University of Lund [19, 20]. Their study was done on a much smaller scale, absent food source, exposure data and historical information. Their study subjects, 200 women from the Argentine Puna (Alt. 3 800 m) were largely non-randomly selected adults (range 12-80; median age 34 years). The range of the urine concentrations was consistent with those reported here though the drinking water levels were generally less (see [1]). They attributed this to additional dietary contributions that could not be accounted for. We would agree with this possibility.

Serum Data. The lithium levels found in the serum paralleled those found in the urine to the extent both are linearly related to the concentration of lithium in the local water

TABLE 3

MATERNAL FETAL SAMPLES
JUAN NOE ARICA HOSPITAL MATERNAL AND NEWBORN SAMPLES (n=30)

ID	AGE	RESIDENCE Nº YEARS	BIRTH PLACE	Nº PREG	Nº CHILD	HOME H ₂ O	1ST μG/L Li ⁺	2ND μG/L Li ⁺	BREAST MILK μG/L Li ⁺	MAT BLOOD μG/L Li ⁺	FET BLOOD μG/L Li ⁺	BIRTH WEIGHT GMS	BIRTH LENGHT MM	GESTATION WKS
1	23	Arica 9	Copíapo	1	0	Potable	201.3	133.9	3 129.9	1 410	146	3 650	50	40
2	24	Arica 4	Copíapo	2	1	Potable	135.3	254	4 379	1 410	73	3 510	48	40
3	36	Arica 14	Vallenar	3	2	Tank Potable	456	09:36	3 130	1 410	110	3 610	50	40
4	36	Arica 4	Santiago	1	0	Tank Potable	186	186.7	3 748	1 050	146	3 700	51	40
5	36	Visviri-in Arica 1 1/2 mo.	Visviri	8	5	Tank Potable	102.7	102.7		1 410	146	3 950	50	40
6	23	Arica 23	Santiago	4	2	Potable	210	204		1 050	146	3 600	52	40
7	Mother left w/o delivery													
8	17	Arica 9	Iquique	1	0	Potable	152	385.9		1 050	146	1 800	42	33
9	20	Tacna-in Arica 3 wks	Tacna	4	1	Potable	238	199.2			110	3 600	51	40
10	25	Pampa Algond Azapa 4	Codpa	3	1	River H ₂ O Tanks	280.4	245		1 050	110	4 100	52	40
11	19	Arica 5	Antofagasta	2	1	Potable	158.9	317.2	4 379.1	1 410	146	3 500	51	40.5
12	23	Arica 1	Antofagasta	1	0	Potable	141.6	140.2	3 129.9	1 050	146	3 250	49	40
13	27	Iquique-10 In Arica-2 wks	Arica	2	1	Potable	140.9	350.5		1 410	73 37	1 800 2 200		35
14	35	Arica 11	Copíapo	7	4	Potable	226.2	226.2	3 747.6	1 410	110	2 680	48	39
15	21	Arica 1	Santiago	4	3	Tank Potable	70.8	279.7	4 379.1	1 050	110	3 200	50	40
16	19	Arica 10	Iquique	1	0	Tank Potable	242.9	109.2	3 747.6	1 410	146	3 150	50	41
17	18	Arica 18	Arica	1	0	Potable	174.9	211.7	3 747.6		73	3 350	52	40
18	20	Arica 5	Chuquicamata	1	0	Tank Potable	141.6	211.7		1 410	37	3 400	50	41
19	27	Arica 23	La Paz	4	3	Potable	340.1	331.7	4 379.1	1 410	37	3 230	50	39
20	37	Arica 10	Potrerillos	4	3	Potable	232.5	158.2		1 050	73	3 550	50	38
21	19	Arica 6 mos.	Quililhue Calama	1	0	Potable	107.6	425.4	2 498.4	1 050	73	2 820	46	38
22	36	Arica 26	Alcereca	8	7	Tank Potable	161.7	636.4	2 498.4	1 410	73	3 300	50	39
23	30	Arica 2	Chuquicamata	6	4	Potable	124.9	479.6	4 379.1		110	4 300	54	40
24	23	Arica 3	Cosapilla Visviri	1	0	Potable	143	268.6		1 050	110	3 250	50	40

TABLE 3 (CONTINUE)

MATERNAL FETAL SAMPLES JUAN NOE ARICA HOSPITAL MATERNAL AND NEWBORN SAMPLES (n=30)														
ID	AGE	RESIDENCE Nº YEARS	BIRTH PLACE	Nº PREG	Nº CHILD	HOME H ₂ O	1ST µG/L Li ⁺	2ND µG/L Li ⁺	BREAST MILK µG/L Li ⁺	MAT BLOOD µG/L Li ⁺	FET BLOOD µG/L Li ⁺	BIRTH WEIGHT GMS	BIRTH LENGTH MM	GESTATION WKS
25	19	Arica 9	Iquique	1	0	Potable	71.5	213.8		1 410	37	2 520	48	36
26	22	Arica 22	Arica	3	2	Potable	321.3	108.3	3 747.6	1 410		3 600	50	39
27	36	Cosapilla-18 Azapa-2 days	Nasahuenta	8	7	Rio Caquena Spring	123.5	266.5	4 379.1		146	3 750	53	40
28	20	Arica 2	Limache	2	1	Potable	72.2	319.2	3 129.9			3 200	47	37
29	16	Arica 16	Arica	1	0	Potable	300.5	143	3 747.6	1 410	0	3 200	48	40
30	38	Arica 10	La Serena	7	5	Potable	72.5	177.7	3 129.9	1 410		3 530	53	40

FIGURE 3a

CHINCHOCORRO MUMMY



<http://www.archaeology.org/image.php?page=online/features/chinchorro/jpegs/chinchorro1.jpeg>

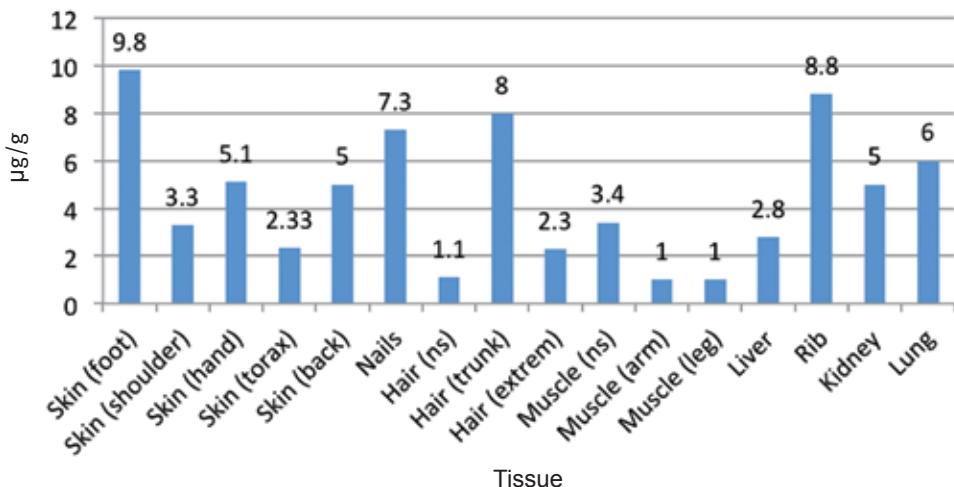
sources (Figure 4). Comparison of the maximal blood lithium levels found in those living in lithium rich valleys with toxic and therapeutic values suggest the latter approach lower recommended maintenance doses for bipolar patients under treatment (Figure 5). This is consistent with the daily lithium ingestion estimates reported by Figueroa et al. [2] for people living in the lithium rich areas.

Control Data. Both 'internal' and 'external' data are cited in this report. The 'internal' data are based on readings in the 'low' (< 200 ppb) lithium areas of Valle Azapa. Some high readings were found in

this valley and in the City of Arica (Gardilcic, pers commun, 2011). There are at least two explanations for this. Firstly, the water supply patterns for the City of Arica are complex since historically much of the water came from wells located in the Azapa and the Lluta valleys. The latter was desalinized using reverse osmosis but this process failed to remove metals and metalloids [21]. Indeed, the sites of high and low exposure from boron (which would in many cases follow lithium) as seen in the City of Arica are mapped out in Figure 2 of the paper by Cortez et al. [21]. Secondly, over the last ten to fifteen years many villagers from Valle Camarones and Lluta have migrated to

FIGURE 3b

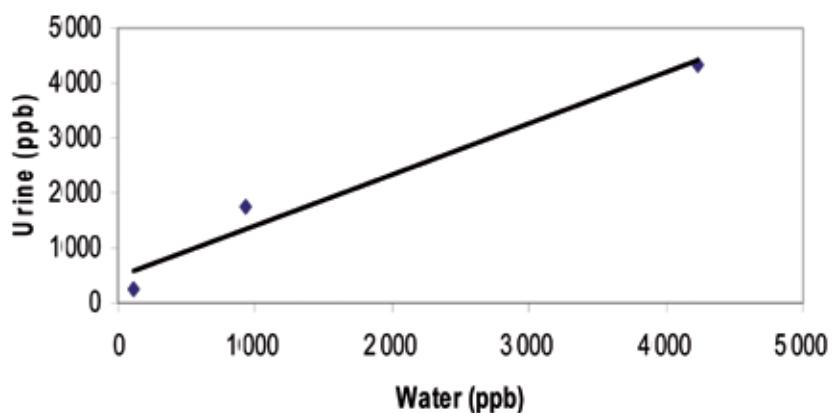
LITHIUM IN CHINCHORRO MUMMY TISSUES FROM THE CAMARONES VALLEY



Source: Figueroa et al, unpublished

FIGURE 4

URINE LITHIUM LEVELS IN PEOPLE LIVING IN THREE VALLEYS WITH HIGH LITHIUM WATER CONCENTRATIONS IN THE NORTH OF CHILE



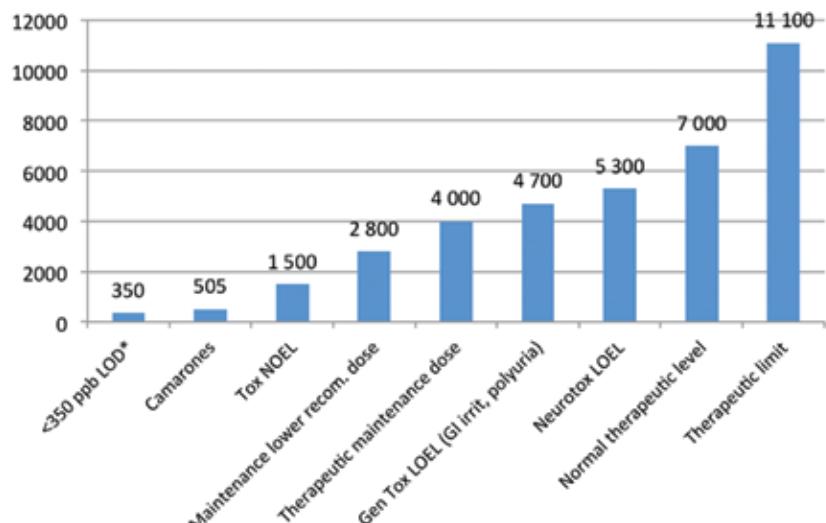
the City of Arica. Many, in turn, visit family and friends in their ancestral homes on a routine basis. Therefore, whilst lithium may be rapidly cleared from the serum in the absence of chronic exposure after several days, returning to their lithium rich valleys can re-establish the high lithium blood levels. Moreover, lithium rich foods from Valle Lluta and Valle Camarones are sold in Arica so these too would be another potentially confounding source of exposure [e.g. see [2]. External serum and urine concentration control data

from the Chilean sampling team and the [11, 15, 16,] are consistent with the ultra-trace levels found by others (as discussed by Cade [22]; also see Dol et al. [23]).

Lithium levels found in maternal-newborn pairs. The lithium levels found in 30 maternal-newborn pairs who delivered their children in the main medical centre in Arica demonstrated that breast milk lithium levels were generally two to three times higher than those found in the maternal

FIGURE 5

COMPARISON OF THE MAXIMAL BLOOD LEVELS FOUND IN THOSE LIVING IN LITHIUM RICH VALLEYS WITH TOXIC AND THERAPEUTIC VALUES



*Highest worker dust exposure 0.83 mg/m^3

venous blood and that the breast could thus potentially concentrate lithium. None of the women appeared to have lived in the two high lithium rich valleys, Valle Camarones and Valle Lluta. Many such women do come to Arica to deliver their children though others have home deliveries. However, getting data under those circumstances could present some logistical difficulties given the remote nature of some of the villages and the attendant lack of facilities.

Newport et al. [24] said 'Lithium has been used during pregnancy for more than four decades, but quantification of foetal lithium exposure and clinical correlations of such exposure are limited'. Indeed, these authors state that 'The management of bipolar disorder during pregnancy remains one of the most daunting challenges of psychiatric practice'. The same group further reported on lithium in breast milk and nursing infants [25] and concluded that breast feeding should be undertaken with caution in women with bipolar disease. To the extent our data appear to demonstrate that the breast does concentrate lithium during pregnancy, we would agree with this conclusion.

Clinical considerations. Virtually all previous studies have relied upon bipolar patients undergoing high dose lithium therapy

to adjudge lithium's toxicity. Since bipolar disease has been found to be a form of neurodegeneration [26], risk assessments based upon bipolar patients are not applicable to the normal population (see e.g. [27]). Neuroradiological studies of the historically lithium loaded populations in the north of Chile should provide unique insights into the role of lithium particularly as a putative hippocampal neurogenic agent [28-34]. The *in vivo* measurement of lithium in such populations using ^{7}Li and ^{1}H -magnetic resonance spectroscopy [35] coupled with structural analyses based on super-sensitive [36] and hyper-specific [37] ^{3}H MRI scans [38] would be an elegant way of investigating lithium's role in neurogenesis.

Comparison to environmental release levels from manufacturing sites and the establishment of regulatory guidelines [39]. Aral and Vecchio noted that "a source of lithium posing impact to the environment is lithium based batteries" particularly as the "lithium ion is highly mobile" [40]. Despite the dramatic increase in the production, storage, transport and disposal of lithium batteries and the increased likelihood of lithium impacting the environment, no environmental release data appear to exist from such activities (see

[1] for discussion]. According to Usuda et al. [41] 'warnings about the risk of exposure from (lithium in) naturally polluted environments' in Chile and Argentina have been given. These workers also say 'the EPA recommended that lithium concentrations in the drinking water supply should not exceed 700 µg/L (ppb)'. Such levels are, however, not based on any scientifically sound evidence and are well below most of the levels described in this report and the two companion papers that precede it [1, 2]. Clearly, reliable health based guideline values to assess the risks potentially posed by such environmental exposures are needed and epidemiological surveys of the historically lithium loaded populations in the north of Chile should be done to fill this data gap. This is feasible since we have now traced many of those surveyed 40 years ago. Epidemiological investigation is further facilitated by the very limited migration from the primary study area due to its remote position, relative 'containment' by border tensions with Bolivia and Peru, the Andean mountain chain, the ocean, a comparatively low cost of living, and nearly perfect year round climate, Arica being the driest city on earth.

CONCLUSIONS

This report extensively documents the existence of very high lithium tissue burdens in populations from two valleys in the extreme north of Chile due to naturally occurring environmental exposures to lithium in water and food stuffs. To our knowledge, these are the only populations in the world whose historical lithium levels have been carefully characterized. They thus represent a unique longitudinal cohort whose historical characteristics have been reconstructed from original archived data and published reports. Cross sectional analysis of these individuals should provide important insights into the

potential neuroprotective effects of lithium and also help set guidelines to assess the risks from high dose environmental exposure.

The effect of lithium at levels measured for this paper should initiate new clinical assessment since virtually all previous studies of lithium's high dose effects have relied upon bipolar patients undergoing high dose lithium therapy to adjudicate lithium's toxicity. Bipolar disease has been found to be a form of neurodegeneration and so any risk assessments based upon such patients are not applicable to the population studied here. Proposed neuroradiological studies, amongst other investigations, of these historically lithium loaded populations in the north of Chile should provide unique insights into the effect of lithium on the brain and, in particular, its potential to stimulate hippocampal neurogenesis. If indeed lithium could accentuate hippocampal growth and demonstrate neuroprotective effects against age related degeneration in this and other parts of the brain, it could serve to prevent the memory loss and other devastating effects found in the setting of Alzheimer's disease and perhaps other forms of neurodegeneration.

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