Pediatric reference values for chromium and mercury in urine in the City of Buenos Aires and Greater Buenos Aires

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ABSTRACT
Introduction. Due to the heavy industrialization of the Autonomous City of Buenos Aires and Greater Buenos Aires, the population may have become exposed to metals. To assess the level of exposure to chromium and mercury in children, it is critical to have local reference values (RVs). Our objective was to determine pediatric RVs for chromium and mercury in a single urine sample.
Population and methods: Children who were not exposed to the studied contaminants and who attended the Department of Low Risk Conditions and the Daycare Center Office of Hospital de Pediatría S.A.M.I.C. "Prof. Dr. Juan P. Garrahan" were included. Urinary chromium (UCr), urinary mercury (UHg), and urinary creatinine were measured. The p95 and its corresponding 95 % confidence interval (CI) were estimated based on the RV concept proposed by the German Human Biomonitoring Commission.
Results: The study included 160 patients. A total of 144 samples from children aged 1-17 years (median: 7 years) were collected. UCr was measured in 137 samples and UHg, in 129 samples. The median value of chromium was 0.54 µg/g of creatinine (range, undetectable to 3.06), while that of mercury was 0.49 µg/g of creatinine (range, undetectable to 7.57).
Conclusions: The RVs for UCr were up to 1.5 µg/L [1.2-2.8] and up to 2.2 µg/g of creatinine [1.8-3.0], and for UHg, up to 2.5 µg/L [1.8-4.8] and 3.2 µg/g of creatinine [2.5-4.7].
Key words: *chromium, mercury, urine, pediatrics, reference values.*

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INTRODUCTION

There is a worldwide growing concern for environment protection and its direct action on people's health. Industrial activities have become necessary for modern life and, in developing countries, the resulting environmental hazards are even more serious due to the limited financial, scientific, technological, and human resources. The Autonomous City of Buenos Aires and Greater Buenos Aires comprise a region of heavy industrial development. The Matanza-Riachuelo River Basin (MRRB) encompasses a broad range of industrial facilities that have been declared as contaminating agents: tanneries; electroplating and electroplate-related plants; waste carriers and treatment plants; and rubber, metalworking, plastic, chemistry, glass, electric power, meat processing, food, textile, paper, agricultural, and livestock industries.[1]

In Argentina, in recent years, the population exposed to contamination along the MRRB has been studied. Due to the characteristics of the industries that dump their waste into the river and the environment in general, it was decided to study and monitor the population exposure to heavy metals (lead, chromium, and mercury) and other toxic agents.

The diagnosis and follow-up of lead exposure are done based on blood lead levels, whose reference values (RVs) have been widely studied.[2,3,4] If a subject is suspected to have been exposed to chromium and mercury, a 24-hour urine collection is the sample of choice, and the RVs for this type of sample have been described.[5-8] In addition, at present, a single urine sample is used to assess groups of people and to carry out population studies because it can be collected more easily. This has been recommended by international programs, such as the German Environmental Survey (GerES)[9] in Germany and the National Health and Nutrition Examination Survey (NAHNES)[10] in the United States.

Updated and adequate RVs for our hospital population are critical to interpret laboratory results. The laboratory has three reasons to establish its own RVs and assess those obtained from the international and national bibliography: (1) over the years, the methodologies for metal measurement have advanced in terms of sensitivity and precision;[11] (2) people have different responses to toxic metal exposure due to genetic causes, diet, lifestyle, and demographic characteristics;[12] and (3) there is no evidence in relation to RVs for single urine samples in pediatrics in our country.[13]

The objective of this study was to determine the RVs for chromium and mercury in a single urine sample in the pediatric population of the Autonomous City of Buenos Aires and Greater Buenos Aires.

POPULATION AND METHODS

During 2011 and 2014, the patients who attended the Department of Low Risk Conditions and the Daycare Center Offices of Hospital de Pediatría S.A.M.I.C. "Prof. Dr. Juan P. Garrahan" were invited to participate in the study until reaching a sample size of more than 120 participants. Inclusion criteria were living in the Autonomous City of Buenos Aires or Greater Buenos Aires, age between 0 and 18 years, and voluntarily agreeing to participate; to this end, parents were asked to provide their informed consent and authorization was requested to the Hospital Ethics Committee.

Exclusion criteria were the following:

- Children sharing their household with people who worked in a setting at risk for chromium or mercury contamination or who performed a risk activity in the house or nearby.
- Children who had a chronic disease that may affect liver and kidney metabolism.

Single urine samples were requested after at least 3 hours of the last voiding.

The following levels were measured:

- Urinary chromium (UCr), using a graphite furnace atomic absorption spectrometry (GF-AAS), VARIAN AA240Z-GTA120, limit of detection (LOD): 0.3 µg/L.
- Urinary mercury (UHg), using a cold vapor atomic absorption spectrometry, VARIAN AA240FS with hydride generation, LOD: 0.4 µg/L.
- Urinary creatinine (UCreat), using an automatic kinetic Jaffe method, Cobas 6000, ROCHE. UCreat was measured in all samples for dilution adjustment and to express results in µg/g of creatinine.

Statistical calculations were made using the MedCalc version 12.7 and EPIDAT version 3.1 software. The Kolmogorov-Smirnov test was used to analyze for normal distribution, and a multiple regression analysis, to examine the correlation between outcome measures. A p value < 0.05 was regarded as significant for all tests.

The RVs were determined estimating the 95th percentile (p95) and its corresponding 95 % confidence interval (CI), as defined by the German Human Biomonitoring Commission, based on the recommendations by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the International Union of Pure and Applied Chemistry (IUPAC).[14]

RESULTS

A total of 160 patients were included; none met exclusion criteria *(Figure 1)*. Nine patients did not submit their urine sample to the lab due to personal issues. Out of the 151 samples that were received, 7 were excluded from analysis because UCreat levels were out of the range of validity (between 0.3 g/L and 3 g/L), either because they were too diluted or too concentrated (World Health Organization [WHO], 1996).[15] For the remaining 144 samples, the median UCreat level was 0.97 g/L (range: 0.30-2.84 g/L). UCr and UHg were measured in 122 samples. Only UCr was measured in 15 samples, while only UHg was established in 7, because the sample volume was not enough to measure both metals. The population demographic data are described in *Table 1*.

Results indicated that 18 % of UCr levels and 44 % of UHg levels were below the method's LOD. For statistical calculations, these results were assigned a value equal to half of the LOD.[16]

Figure 2 shows data distribution; none of the data followed a normal distribution ($p < 0.05$). A significant correlation was established between UCr and UHg levels and age ($p < 0.001$), but no correlation to sex was observed. However, when creatinine levels were included in the multiple regression analysis as an independent outcome measure, as suggested by Barr et al., 2004,[17] no relation was observed anymore between metal levels and age.

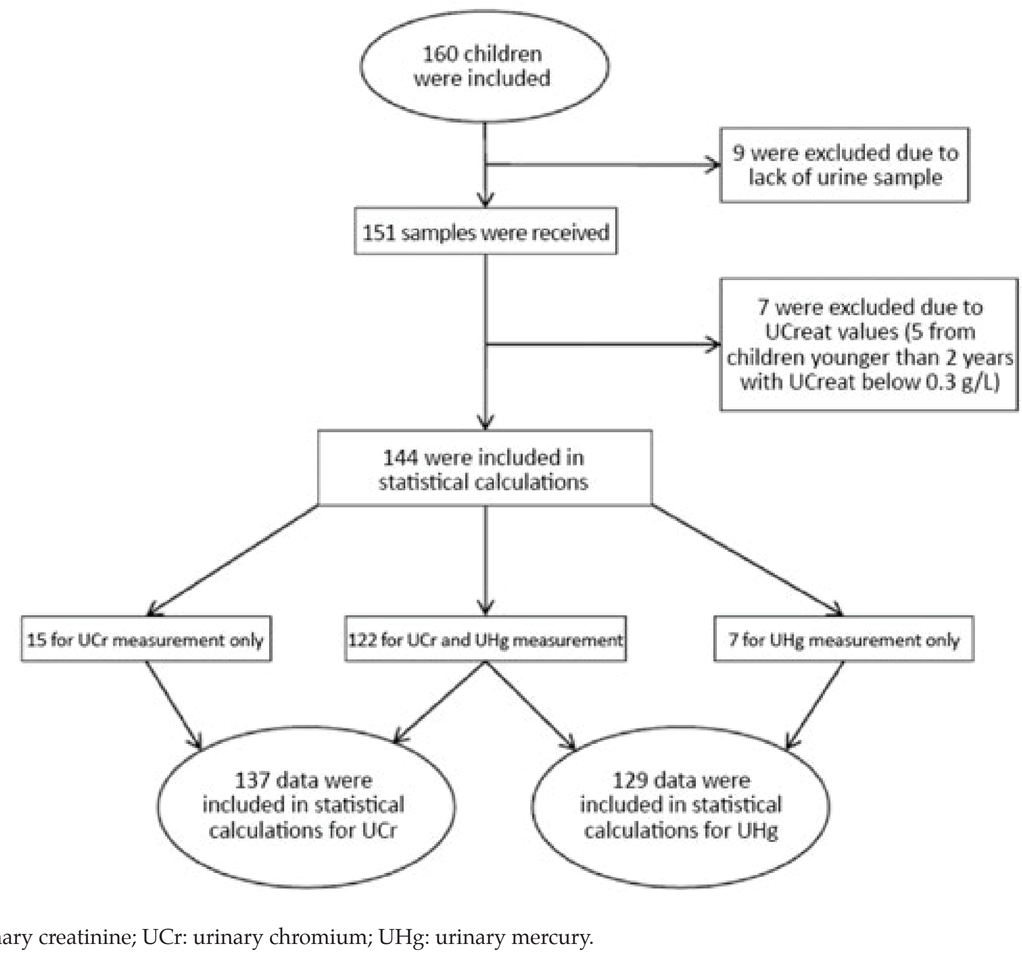
Since values did not show a normal distribution, the median and range were used as measures of central tendency and dispersion. The following percentiles were estimated: p25, p50, p90, p95, and p97.5. *Table 2* shows the analysis of results.

DISCUSSION

In this study, the sample size was at least 120 participants, as suggested by the Clinical & Laboratory Standards Institute (CLSI) (NCCLS-C28-A2),[18] and metal levels were reported in two ways: with and without adjustment for UCreat.

As children grow, their muscle mass increases, so they release more UCreat and, once results are adjusted for it, their metal levels decrease. Future

FIGURE 1. *Flowchart of cases*



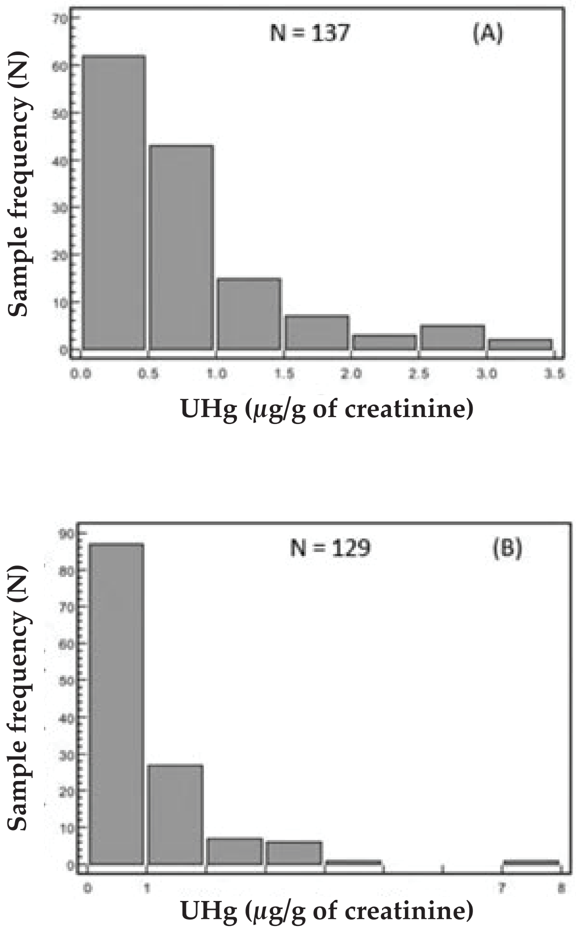
UCreat: urinary creatinine; UCr: urinary chromium; UHg: urinary mercury.

TABLE 1. *Demographic data*

		UCr (n = 137)	UHg (n = 129)
Sex	Female	69 (50.4 %)	65 (50.4 %)
	Male	68 (49.6 %)	64 (49.6 %)
Age (years old)	Median	7	7
	Range	[1-17]	[2-17]
N by age range	1-2 years old	4	1
	3-8 years old	81	75
	9-12 years old	33	34
	13-17 years old	19	19

UCr: urinary chromium; UHg: urinary mercury.

FIGURE 2. *Distribution of urinary chromium (A) and urinary mercury (B) values*



UCr: urinary chromium; UHg: urinary mercury.

studies should assess the RVs in a larger sample to establish differences by age range. The p95 and its corresponding 95 % CI were estimated, which allowed to compare these to the reference values (RV_{95}) proposed by biomonitoring programs, such as the German Environmental Survey (GerES) and the National Health and Nutrition Examination Survey (NHANES), and to studies that used the same criterion. *Tables 3 and 4* show the comparison to the bibliography.

The RV_{95} proposed by the German Human Biomonitoring (HBM) Commission is based on the 95 % CI corresponding to the p95 of the concentration levels in the relevant matrix of the reference population.[19] The RV_{95} has different uses in public health. It provides a basis to identify subjects or subpopulations with high levels of exposure compared to baseline levels in the general population. It also allows to assess temporary changes in exposure to chemical substances, usage patterns, and effectiveness of actions targeted at reducing exposure. If values are above the RV_{95}, it suggests the need for follow-up to establish the cause.[20]

Urinary chromium:

As seen in *Table 3*, only one study was found in Italy, conducted by Alimonti (2000)[21] in the pediatric population using single urine samples. That study found a p95 value, which accounted for half of that observed in this study. The comparison to adult populations was varied. Similarities were observed to a biomonitoring done in France[22] and a study conducted in Buenos Aires,[13] which found, for the p97.5, levels of 1.47 µg/L and 2.68 µg/g of creatinine (close to our values, *Table 2*). A study conducted in the south of Brazil[23] showed considerably higher levels than in our study, contrary to a study done in the United Kingdom,[24] which found a p95 closer to half of that obtained in our study.

Chromium(III) is an essential nutrient from food, necessary for the body in small amounts. Chromium(VI) is a carcinogen that comes mostly from anthropogenic sources. It may be found in the air, soil, and water after it is released by industries that use chromium,

TABLE 2. *Descriptive statistics for chromium and mercury in urine in a single sample*

	UCr		UHg	
	µg/L	µg/g of creat.	µg/L	µg/g of creat.
Median	0.6	0.54	0.48	0.49
Range	< LOD -4.4	< LOD -3.06	< LOD -6.30	< LOD -7.57
p25	< LOD	< LOD	< LOD	< LOD
p50	0.60	0.54	0.48	0.49
p90	1.20	1.66	1.74	2.25
p95	1.47	2.21	2.46	3.20
p97.5	1.70	2.66	3.36	3.69

< LOD: below the limit of detection.
UCr: urinary chromium; UHg: urinary mercury; creat.: creatinine.

such as electroplating plants, tanneries, textile production, and chromium-based manufacturing. It may also be released into the environment through natural gas, oil or carbon burning.[25] Exposure to chromium in the Autonomous City of Buenos Aires and Greater Buenos Aires may be associated with the industrial activities developed in the area.

The differences observed in the RVs may be due to several reasons. These were populations from different countries with different environmental exposures and eating patterns. The pediatric study by Alimonti (2000) and this study were conducted more than 10 years apart. The methodology used in all the studies found in the bibliography is the inductively coupled plasma mass spectrometry (ICP-MS), which is more sensitive than the GF-AAS.

Urinary mercury:

In pediatrics, there is a larger amount of bibliography in relation to UHg. *Table 4* shows that the RVs in this study were higher, except for the study conducted in the Democratic Republic of the Congo (DRC),[26] whose values were five times higher than ours. The data from the DRC are related to the production and use of mercury-containing skin whitening creams and antiseptic soaps.

The Canadian Health Measures Survey (CHMS),[20] in accordance with the latest German Environmental Survey (GerES IV),[27] obtained a

TABLE 3. *Comparison to international reference values for urinary chromium*

Study	Age (years old)	n	p95	[95 % CI]
Argentina (Buenos Aires)	1-17	137	1.4 μg/L	[1.2-2.8]
This study			2.2 μg/g of creat.	[1.8-3.0]
Brazil,(23)	18-74	175 men	6.11 μg/g of creat.	-
2013		65 women	5.19 μg/g of creat.	
France,(22)	20-59	1910	1.60 μg/L	[1.52-1.66]
2008-2010			1.80 μg/g of creat.	[1.71-1.92]
United Kingdom,(24)	18-66	132	0.79 μg/L	-
2014			1.3 μg/g of creat.(a)	
Italy (Rome),(21)	6-10	131	1.07 μg/g of creat.	[0.76-2.06]
2000				

(a) Value reported in μmol/mol (2.89 μmol/mol); a 0.45 conversion factor was used. CI: confidence interval; creat.: creatinine.

TABLE 4. *Comparison to international reference values for urinary mercury*

Study	Age (years old)	n	p95	[95 % CI]
Argentina (Buenos Aires)	2-17	129	2.5 μg/L	[1.8-4.8]
This study			3.2 μg/g of creat.	[2.5-4.7]
Germany (GerES IV),(27)	3-14	1612(a)	0.5 μg/L	[0.39-0.50]
2003-2006		68(b)	1.5 μg/L	-
		39(c)	3.1 μg/L	-
United States (NHANES),(29)	6-11	401	0.89 μg/L	[0.64-1.10]
2013-2014			1.11 μg/g of creat.	[0.71-1.72]
	12-19	452	1.02 μg/L	[0.61-1.81]
			0.85 μg/g of creat.	[0.58-1.07]
Canada (CHMS),(20)	3-5	214	0.58 μg/L	[0.29-0.87]
2007-2013				
DR Congo,(26)	1-14	125	19.3 μg/L	[18.7-20.1]
2015			15.3 μg/g of creat.	[12.8-16.8]
China,(30)	0-6	1072	1.42 μg/L	[1.31-1.51]
2014				

(a) No dental amalgam fillings.
(b) 1-2 dental amalgam fillings.
(c) More than 2 dental amalgam fillings.
CI: confidence interval; creat.: creatinine.

p95 that was five times lower than that observed in this study and in the GerES II 1990/1992[28], which was 3.9 μg/L. The decrease observed in the German population and the findings from Canada are attributed to the reduction in the use of dental amalgam fillings and the more stringent restrictions on fish consumption in the populations included in those studies. One of the limitations of this study is that it did not collect such demographic data about the studied population. Compared to the NHANES values[29] and to the findings of a Chinese study,[30] our results are higher, but to a lesser extent. In 2014, a study was done in Mexico (Mexico City)[31] to analyze UHg levels in children; it estimated the p90 (1.89 μg/L), which was similar to the one found in our study (1.74 μg/L, *Table 2*).

The HBM Commission has established human biomonitoring (HBM-1) values below which there are not risks for adverse effects on health and that, therefore, require no action.[32]In the case of mercury, HBM-1 values were 7 μg/L and 5 μg/g of creatinine (also proposed by the WHO).[33] In this study, the p95 and the upper limit of the 95 % CI were below these recommendations.

The main anthropogenic sources of mercury are releases from fossil-fuel burning (carbon, gas, oil), paper-manufacturing chlor-alkali operations, medical equipment (thermometers, dental amalgam), fluorescent lamps, cement plants, car headlights, waste treatment plants, rubbish dumps, cremation, and paint.[34] These may all be found in the Autonomous City of Buenos Aires and Greater Buenos Aires.

Argentina has adopted different initiatives aimed at reducing the release of mercury into the environment: ratifying the Minamata Convention (whose purpose is to gradually eliminate mercury use and emissions by 2020), reducing dental amalgam use, and implementing policies to stop using mercury-containing medical equipment. The Autonomous City of Buenos Aires has passed Law Nº 1854, known as the Zero Waste Act, which establishes progressive goals to reduce the final disposal of solid urban waste and prohibits waste incineration. It would be desirable for Argentina to implement a national human biomonitoring program to establish baseline values, assess the effectiveness of implemented interventions, and compare values at a regional and international level.

In relation to UCr, no recent pediatric studies were found in the bibliography that would allow us to compare our results. And in relation to UHg, no studies conducted in Argentina were found. This study met the objective of filling a gap regarding pediatric RVs for chromium and mercury corresponding to the Autonomous City of Buenos Aires and Greater Buenos Aires. We encourage the conduct of further studies with the same objective, both in the same area and other regions of Argentina.

CONCLUSION

We propose the following RVs for the studied pediatric population: for chromium, up to 2.2 μg/g of creatinine (1.5 μg/L), and for mercury, up to 3.2 μg/g of creatinine (2.5 μg/L). ■

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