International Journal of Advanced Engineering Research and Science (IJAERS)
Peer-Reviewed Journal
ISSN: 2349-6495(P) | 2456-1908(O)
Vol-9, Issue-12; Dec, 2022
Journal Home Page Available: https://ijaers.com/
Article DOI: https://dx.doi.org/10.22161/ijaers.912.54

Exposure to Aluminum and the Prevalence of Anemia in Communities in Barcarena Pará, Brazil

Helenize CM Costalat[1], Nahide P Rodrigues[2], Aline F Ribeiro[3], Ronaldo RM Rocha[4], Rosane P Loiola Rocha[5], Tereza CO Corvelo[6]

[1]Institute of Biological Sciences, Federal University of Pará – UFPA, 01 Augusto Correa St, Belém-PA, 66075-110, Brazil.
[2]Institute of Biological Sciences, Federal University of Pará – UFPA, 01 Augusto Correa St, Belém-PA, 66075-110, Brazil.
[3]SESPA - Secretary of Health of the State of Pará, Tv. Lomas Valentinas, 2190 - Marco, Belém - PA, 66093-677, Brazil.
[4]Pará Public Health Department, Pará Central Laboratory. Rodovia augusto Montenegro. Distrito de icoaraci 66823010 - Belém, PA - Brazil
[5]Pará Public Health Department, Pará Central Laboratory. Rodovia augusto Montenegro. Distrito de icoaraci 66823010 - Belém, PA - Brazil
[6]Institute of Biological Sciences, Federal University of Pará – UFPA, 01 Augusto Correa St, Belém-PA, 66075-110, Brazil.
*Corresponding author

Received: 26 Nov 2022,

Receive in revised form: 16 Dec 2022,

Accepted: 23 Dec 2022,

Available online: 31 Dec 2022

***Keywords*— Anemia, Aluminum, Environmental contamination, Barcarena-PA**

***Abstract*— The city of Barcarena, a major industrial hub, is a city of high demand for mining industry and accidents that involved environmental contamination by heavy metals such as aluminum, subjecting the population to its harmful efFects. Socio-epidemiological data and results of toxicological and hematological tests of 124 individuals were analyzed. The statistical analysis adopting the significance level as $p < 0.05$. Epidemiological data indicate that the majority of the sample was female (71.1%), residents of more than 5 years in the region (90.6%), non-workers with heavy metals and/or mining (81.3%). In the dosage of metals in the blood, about 93.5% of the individuals exhibited aluminum intoxication, which due to the great variability found in the levels of aluminum exposure, the individuals were categorized into the following groups; medium-grade exposure, ranging from 5 ug/dL to 100 ug/dL, high level, more than 100 ug/dL and low detection limit exposure smaller than 5 ug/dL. In addition, the presence of anemia in the population was 64.5%, of which 65.2% were women and 62.5% were men. The relationship between the presence of anemia and high aluminum exposure in the blood was shown to mean (p-value 0.0347) as well as the decrease in hemoglobin and changes in hematimetric indices (p-value > 0.001). This study observed a significant association between aluminum contamination and the presence of anemia, reported that one of the indicators of the toxic action of aluminum on the hematopoietic system, with aluminum as an indicator of apparent hematological changes.*

I. INTRODUCTION

Aluminum (Al) is the metal widely distributed and abundant in the environment (EXLEY et al, 2011) is present in soil, air and water, but despite this, it has no function in any biochemical system of any existing organism (EXLEY, 2013). Every day humans are exposed to Al where dietary and non-dietary sources, even by diet being the main way in which humans are exposed to metal.

Exposure levels of humans to aluminum are increasing, subjecting the population to toxicity, promoting pro-oxidant activities, inflammation, immunogenicity and mutagenic effects, and can accumulate in some organs and tissues and cause changes (OESTERLING et al., 2008; DARBRE et al., 2011).

Recent studies demonstrate that, by causing oxidative stress, there is an interruption of iron (Fe) homeostasis, causing overload (WARD et al., 2001 CONTINI et al., 2007), thereby increasing the concentration of Fe, favoring damage cellular oxidative stress, inducing the emergence of neurodegenerative diseases (TOYOKUNI, 2000; ADZERSEN ET AL., 2003; DEUGNIER, 2003).

When the body detects an increase in serum Fe levels, hepcidine is released in an effort to reduce Fe absorption by the intestine and limit Fe cell eflux from hepatocytes, enterocytes and macrophages (GANZ 2011; BIGNUCOLO et al. 2012). Thus, al toxicity can lead to hematological disorders, such as anemia that has been described in aluminum poisoning, has been inducing iron deficiency anemia via oxidative stress (LI et al, 2021).

Thus, the impacts caused by exposure to aluminum are multiple and the risks of chronic contamination are high. Therefore, this work aims to investigate the levels of exposure to aluminum and the influence on the hematological profile of the communities of the municipality of Barcarena, in the state of Pará, with a history of environmental problems due to mining activities.

II. METHODOLOGY

STUDY DESIGN

This is an epidemiological study of the analytical, observational, cross-sectional type. In this, 124 patients over 18 years and under 60 years of age were included, from whom full blood samples were collected for toxicological, biochemical and hematological evaluation. All individuals were treated at the New Cabanos Basic Health Unit, from spontaneous demand for clinical evaluation, due to acute exposure to mining tailings, due to transhipment of a holding basin of a mining company installed in the industrial pole of the municipality of Barcarena-PA, belonging to the Metropolitan mesoregion of Belém, located in the north of Brazil at a latitude of 01º30'21"south and longitude 48º37'33"west.

ALUMINUM DETECTION IN BLOOD SAMPLES

The collection technique was recommended by the National Human Exposure Assessment Survey Nhexas in 2001. The samples were collected in specific test tubes for metal collection and analyzed according to the adaptation of MASSADEH, et al., 2010. After treatment, the samples were solubilized in 3mL of nitric acid ($HNO_{3} \geq {}^{65\%\ v.v\ -1}$) Biotec with high purity and 1.0 hydrogen peroxide (H_2O_2 30% v.v $^{-1}$) Sigma – Aldrich, following the bergof speed wave four microwave opening schedule. After, the sample solutions were measured for 25 mL using milliQ water. The technique of determination of the elements was optical emission with inductively coupled plasma (ICPOES) using the simultaneous multielementary equipment of Thermo model Cap 7000, LACEN - PA, the details of the methodology adopted in this work are described below.

ANALYTICAL QUALITY CONTROL

The wavelength (λ) of the emission line, the limits of detection and quantification for the above-mentioned element, as well as the parameters of the analytical curve angular, linear coefficient and correlation were determined.

In the present study, the quality control of the determination was performed through the standard addition analysis. Biological monitoring of toxic metal pollution in the environment requires quality control analyses using standard reference materials. A variety of biological tissues are increasingly used for bioaccumulation analysis of elements, but the available Certified Reference Materials (CRMs) are insufficient.

Table 1 presents the control of analytical quality assurance, regulated using standard addition methodology, which consists of adding a known concentration of the study analysis to a matrix sample. All samples processed and standard additions were analyzed in triplicate.

This study was carried out comparing the analytical results for samples extracted in three concentrations. Analyze recovery does not need to be 100%, but the extent of the recovery from the standard addition should be consistent (for all tested concentrations) of 80 % - 120%.

Table 1. Control of analytical quality assurance.

Element	λ (nm)	LD (μg/g)	LQ (μg/g)	a	b	R^2	Recovery MRC NCS DC 73351(%)
Aluminum	396,152	0,004	0,012	39564	3700,8	0,9987	98,10

EVALUATION OF HEMATOLOGICAL PARAMETERS

The blood count was performed at the Central Laboratory of Pará (LACEN), through automated determination, complemented with optical microscopy when necessary, using the reference values as described in Rosenfeld, et al. 2019 according to the patient's gender and age.

CONDUCTING STATISTICAL TESTS

The data were plotted in an Excel® spreadsheet and descriptive analysis was performed in relation to laboratory tests in relation to hemoglobin values, red blood cell count and hematimetric indices, to estimate the prevalence of anemia among individuals in the population.

Finally, binomal tests were applied, which are intended to verify the difference between two independent sample proportions ($p1 \neq p2$), and the linear correlation test, aimed to evaluate the levels of aluminum in the blood, in relation to hematological results. The significance level is considered as $p < 0.05$. The statistical program Bioestat 5.0 (Ayres et al., 2007)

III. RESULTS

EPIDEMIOLOGICAL INFORMATIONS

Among the 124 individuals analyzed, regarding socio-epidemiological data, more than half of the participants are female (71.1%) in the whole reside for more than 5 years in the region (75.0%) and do not work with heavy metals and/or mining (75.8%), as well as the other variables described in Table 2.

Table 2. Demographic variables of the population of Barcarena-PA

Demographic Variables		(N)	%
Genre	Feminine	88	71,1%
	Masculine	36	29,0%
Age	> 18 years	84	67,7%
	≥ 60 years	40	32,2%
Schooling	Illiterate	54	43,5%
	secondary school complete and higher education	70	56,4%
Remuneration	Wage	86	69,3%
	Wage earner	38	30,6%
Residence time/period in years	≤ 5 years	31	25,0%
	≥ 5 years	93	75,0%
Works with mining/metallurgical	Yes	30	21,1%
	Not	94	75,8%

METAL DOSAGE

Regarding the levels of heavy metals in the blood, values above that allowed for aluminum (93.5%) were observed, as shown in Table 3. In individuals who presented Al contamination, an average of 220 ug/L was obtained, about 50 times higher than the reference value (5,396 ug/L) established in the State Council and Territorial Epidemiologists.

Due to the great variability found in aluminum exposure levels, individuals were categorized into the following groups: medium-grade exposure, ranging from 5 ug/dL to 100 ug/dL, of high level, more than 100 ug/dL and those with low detection limit less than 5 ug/dL.

PRESENCE OF ANEMIA IN THE BARCARENA POPULATION

The prevalence of anemia found in the studied population was 64.5% (80/124), and in this group with anemia 75% were women (60/80) and 25% were men (20/80). But in general terms, due to the diagnosis of anemia being commonly differentiated by sex, it should be emphasized that the proportion of anemic women reached more than half of the total 65.2% (60/92), in the same way the frequency among affected men was 62.5% (20/32), however, they did not show meaning between the genders (p-value: 0.3910), as well as hematological parameters did not differ between men and women as shown in Table 4.

Table 3. Measurement of aluminum in the blood of the population of Barcarena

Below detection limit*	Average exposure to Aluminio	High exposure to Aluminio
8 (6 %)	**53 (43 %)**	**63 (51 %)**
Max ± Min	Max ± Min	Max ± Min
4.78 ± 0.064	100.73 ± 6.17	586.07 ± 101.72
Average ± DP	Average ± DP	Average ± DP
2.24 ± 1.51	67.87 ± 27.60	215.80 ± 129.9087

High exposure to Aluminio: X ≥ 100 ug/dL, Average exposure to Aluminio 5 ug/dL < X < 100 ug/dL, below detection limit X ≤ 5 ug/dL * Maximum values allowed according to the Council of State and. Territorial Epidemiologists (CSTE) and World Health Organization: Aluminum: 5,396 ug/L

Table 4- Hematological parameters of the study subjects.

Parameters Hematological	Adult men (*N*)		Adult women (*N*)	
		Max ± Min		Max ± Min
Hematocrit (%)	40.41 %	50.60 ±13.20	39.49 %	58.40 ±27.90
Hemoglobin (g/dL)	12.14 g/dL	16.50 ± 8.00	12.38 g/dL	16.20 ± 8.00
Red Cells (10µL)	4.58 millions/µL	6.0 ± 3.0	4.61 millions/µL	5.0 ± 3.0
VCM (fL)	76.47 fL	97.00 ± 43.2	81.99 fL	95.00 ± 61.00
HCM (pg)	29.46 pg	86.00 ±13.20	26.95 pg	74.00 ±10.00
CHCM (%)	31.97 %	76.00 ± 25.20	32.13 %	51.90 ± 29.60
RDW (%)	16.43%.	19.40 ±14.40	16.70 %.	33.00 ±14.10

Hematocrit (%) 40 – 50%/35 – 45%. Hemoglobin (g/dL) 14 – 18 g/dL/12 – 16 g/dL. RBCs (10µL) 4.5 – 6.1 million/µL/4.0 – 5.4 million/µL. Mean Corpuscular Volume (MCV (fL)) 80 to 100 fL. Mean Corpuscular Hemoglobin (MCH (pg)) 24 – 33 pg Mean corpuscular hemoglobin concentration MHC (%)31 – 36% or g/dL. Red blood cell distribution width (RDW (%)) 11.5 – 14.5%. Renato Failace. Blood count - Interpretation Manual, 6th edition, 2015.

PRESENCE OF ANEMIA IN RELATION TO ALUMINUM EXPOSURE.

When analyzing the relationship between the presence of anemia and aluminum exposure, we observed that in high levels of aluminum in the blood there was a higher occurrence of anemia with 69.8% (44/63) while in exposure considered average only 58.4% (31/53) of the individuals were in anemic state. When we observed only the parameters of high concentration of Al, i.e., greater than 100 ug/dL and the hemoglobin profile, we noticed that according to the gradual decrease in hemoglobin there was a significant increase in aluminum concentration, we obtained a highly significant result, as observed in Figure 1(A), (p-value < 0.001), as well as in the other hematimetric indices, in the decrease of erythrocytes, figure 1(D), decreases in mean corpuscular volume (microcytosis) and mean corpuscular hemoglobin (hypochromia) were significant for both parameters, Figure 1(B) and (C). (p-value < 0.001).

IV. DISCUSSION

This study observed that the average of aluminum levels found in the blood of residents of Barcarena communities was 50 times higher than those allowed by the World Health Organization and the Council of State and Territorial Epidemiologists (CSTE) (Aluminum: 5.396 ug/L), this may have been due to the implementation of aluminum and bauxite mining industry in the region and the numerous mining disasters, registered since 2000 in the municipality of Barcarena (CASTRO, 2018). Recently, the waste leak from the *Hydro Alunorte* depot in February 2018, where several communities reported to the agencies responsible the extravasation of red mud, which contains tailings from the production of aluminum and other chemicals harmful to river beds, reflecting in groundwater contamination due to mining activities, which occur around these communities.

Water is known to be a source of human exposure to Al, (MARTINEZ, 2017). Considering this factor, it is suggested that it is the main form of contamination of the population, according to Oliveira et al (2020), they showed that the waters of the communities of Barcarena-PA presented high concentrations of heavy metals, including aluminum, in the waters of human consumption, a potential risk to human health.

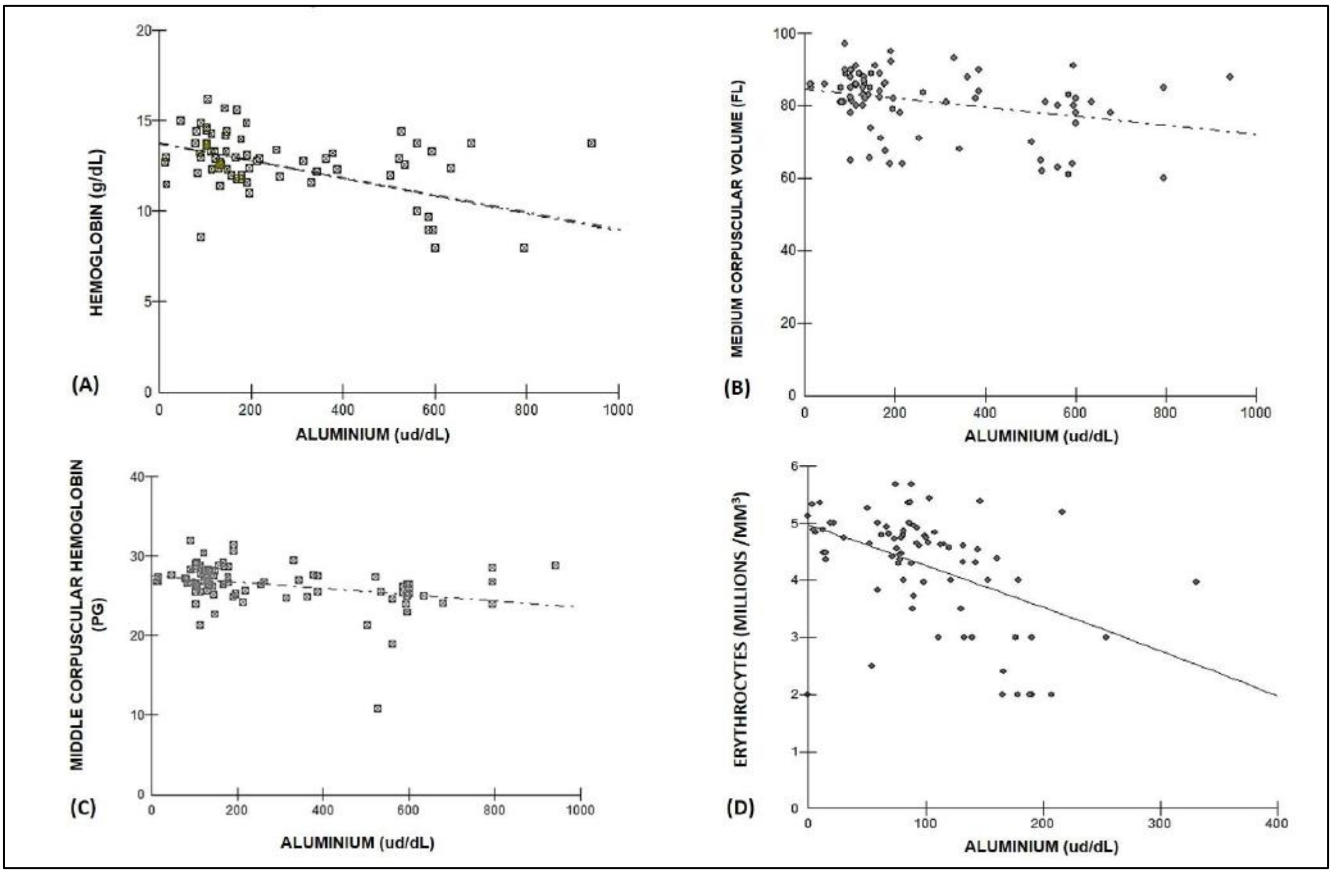

Fig.1. The correlation between aluminum concentration in the blood of exposed individuals and hematological parameters. ***(A)*** *Hemoglobin in relation to blood aluminum concentration (Hb reference value: 11.5g/dl-13.0g/dl);* ***(B)*** *Mean Corpuscular Volume in relation to blood aluminum concentration (MCV reference value: 81.8fl - 100.2fl);* ***(C)*** *Mean Corpuscular Hemoglobin in relation to blood aluminum concentration (HCM reference value: 26.9 pg - 32.4 pg);* ***(D)*** *Erythrocytes in relation to aluminum concentration in the blood (reference value of erythrocytes: 4.3-5.1 million/mm3).*

Studies on aluminum poisoning in the human body describe diverse systemic effects, but such comorbidities of multisystemic intoxications are rarely reported in epidemiological studies (IGBOKWE et al, 2019). Al toxicity is generally observed in experimental animal models (SCHMIDT, 2015; MARTÍNEZ, 2017; BAKOUR ET AL, 2017), however, evidence is lacking in observational studies of human populations.

This study observed that there were hematological alterations in individuals exposed to aluminum, about 64.5% presented anemia. However, because the population studied is composed of the majority of women (71.1%), that is, it is a great differential in the diagnosis of anemia, we emphasize that the proportion of anemia did not differ between men and women, indicating that Al poisoning is a predominant risk factor in the manifestation of anemia states in both genders, however, one limitation of this study should be taken into account, which is the small sample number of the population studied.

Thus, this significant association between aluminum contamination and the presence of anemia is one of the indicators of the toxic action of aluminum on the hematopoietic system. In addition, microcytic, hypochromic anemia is the decrease in the number of red blood cells that reinforce such evidence (BAKOUR et al, 2017; ESPARZA et al, 2018; LI et al, 2021). being parameters already reported in chronic renal patients, with serious aluminum levels higher than 100μg/L (MAHIEU et al, 2000; NASH et al., 2003).

When in contact with metal, mainly orally, aluminum is transported to the gastrointestinal tract, then excreted, but if the load is high, or it is a chronic exposure, a significant amount of aluminum can be absorbed, or it is still carried into the cell interior or, in the case of paracellular transport, the way in which the metal enters the bloodstream and interstitial fluids, and is incorporated forming the Al-transferrin complex. (MARTINEZ, 2017). which is responsible for numerous immediate and long-term deleterious efFects (KREWSKI et al. 2007; PRIEST 2004)

Transferrin, iron carrier protein, acts as *primaprotein*, which Al binds, and aluminum poisoning in hemodialysis patients shows that more than 90% of all Al was associated with transferrin (MLADENOVIC, et al 2019).

Al can cause ruptures in Iron homeotase by dislocation of transferrin, resulting in its release into the bloodstream, serving to confuse, as if there is an increase in serum Fe levels. As a result of an overload, hepcidin is secreted to disrupt the iron absorption, resulting in a decrease in Fe absorption and promoting an anemic state due to iron deficiency (GANZ 2011; BIGNUCOLO et al. 2012).

When the body detects an increase in serum Fe levels, hepcidine is released in an effort to reduce Fe absorption by the intestine and limit the cellular efflux of Fe from hepatocytes, enterocytes and macrophages (NEMETH et al. 2009). Thus, all toxicity can lead to hematological disorders through a hepcidine-mediated process, which is directly linked to the iron synthesis process.

On the other hand, a study on the relationship between Al and the development of anemia demonstrated the presence of massive deposits of Fe in the bone marrow of animals chronically overloaded with Al, with inhibition of the growth of erythroid progenitors and impairment of hemoglobin synthesis. In this sense, the presence of Al reduces the incorporation of Fe in the heme group and inhibits the differentiation of erythroid cells (PEREZ et al, 2005; PEREZ et al, 2001; LIU et al, 2021), in both, the action of Fe is impaired, decreasing its absorption due to the presence of Al, which leads to an anemic process.

V. CONCLUSION

It can be concluded that high levels of aluminum should be the result of years of contamination, to which the population is on exposure, which should have significantly influenced the hematological profile, where it was possible to observe the prevalence of anemia, as well as a correlation between aluminum concentrations in the blood, hemoglobin and hematimetric indices such as MVC and HCM, individuals exposed to aluminum contamination.

Additionally, the presence of anemia did not differ significantly in relation to gender, indicating that Al poisoning is a major risk factor in the manifestation of anemia states in both genders.

Therefore, it is necessary to continue the development of epidemiological studies, in order to be aware, enabling monitoring and elaborate interventions, in order to health interventions, through a better control of environmental contamination.

FUNDING

This work was supported by the Central Laboratory of Pará - Government of the State of Pará.

ETHICS APPROVAL

The study was submitted and approved by the Ethics Committee on research with human beings of the Institute of Sciences and Health of the Federal University of Pará, under opinion no. 4,459,176.

REFERENCES

[1] ADZERSEN KH, BECKER N, STEINDORF.K, FRENTZEL-BEYME R. (2003). **Cancer mortality in a cohort of male German iron foundry workers**. Am J Ind Med 43. DOI: 10.1002/ajim.10187.

[2] AYRES, M., AYRES JR, M. AYRES, DL; SANTOS A.S. (2007). Biostat 5.0. **Statistical applications in the areas of biological and medical sciences**. Mamirauá Institute for Sustainable Development, Belém.

[3] BAKOUR M, AL-WAILI NS, EL MENYIY N, IMTARA H, FIGUIRA AC, AL-WAILI T, LYOUSSI B.J. (2017). **Antioxidant activity and protective efFect of bee bread (honey and pollen) in aluminum-induced anemia, elevation of inflammatory makers and hepato-renal toxicity**. Food Sci Technol. DOI: 10.1007/s13197-017-2889-9.

[4] CASTRO, E.; CARMO, E. D. (Ogrs). (2019). **Dossier: Mining disasters and crimes in Barcarena**. Belém: NAEA: UFPA.

[5] CONTINI MC, FERRI A, BERNAL CA, CARNOVALE CE. (2007). **Study of iron homeostasis following partial hepatectomy in rats with chronic aluminum intoxication**. Biol Trace Elem Res 115. DOI: 10.1385/bter:115:1:31

[6] DARBRE, P. D.; PUGAZHENDHI, D. e MANNELLO, F. (2011). **Aluminium and human breast diseases**.

J.Inorg.Biochem. v. 105, n. 11, p. 1484-1488. DOI: 10.1016/j.jinorgbio.2011.07.017.

[7] DEUGNIER JL. (2003). **Iron and liver cancer**. Alcohol 30: 145–150. https://doi.org/10.1016/S0741-8329(03)00129-0

[8] EXLEY C, MOLD M.J. (2015). **The binding, transport and fate of aluminium in biological cells**. J Trace Elem Med Biol. DOI: 10.1016/j.jtemb.2014.11.002.

[9] EXLEY, C. (2012). **Elucidating aluminium´s exposome**. Curr Inorg Chem 2: 3-7. DOI: 10.1039/C3EM00374D.

[10] EXLEY, C. (2013). **Human exposure to aluminium**. Environ Sci Process Impacts 10: 1807-16. DOI: 10.1039/c3em00374d.

[11] EXLEY, C. (2012). **Reflections upon and recent insight into the mechanism of formation of hydroxyaluminosilicates and the therapeutic potential of silicic acid.** Coordination Chemistry Reviews 256: 82-88. DOI: https://doi.org/10.1016/j.ccr.2011.06.022

[12] EXLEY, C., (1996). BURGESS, E., DAY, J.P., JEFFERY, E.H., MELETHIL, S., YOKEL, R.A**. Aluminum Toxicokinetics** J Toxicol Environ Health 6: 569-584. DOI: https://doi.org/10.1191/0748233702th157oa.

[13] ESPARZA, J.L., GÓMEZ, M. & DOMINGO, J.L. (2019). **Role of Melatonin in Aluminum-Related Neurodegenerative** Disorders: A Review. Biol Trace Elem Res 188, 60–67. DOI: 10.1007/s12011-018-1372-4.

[14] FAILACE, R.; FERNANDES, F.(2015). **Blood count: Interpretation manual**. 6th edition. Porto Alegre: Editora Artmed.Cap. 11.

[15] GANZ T. **Hepcidin and iron regulation**, 10 years later. Blood. (2011) Apr 28;117(17):4425-33. DOI: 10.1182/blood-2011-01.

[16] IGBOKWE, Ikechukwu Onyebuchi. (2019) **Aluminium toxicosis: a review of toxic actions and efFects. Interdisciplinary** toxicology vol. 12,2. DOI: https://doi.org/10.2478/intox-2019-0007

[17] LI M, Nabi G, SUN Y, WANG Y, WANG L, JIANG C, CAO P, WU Y, LI D. (2021) **The efFect of air pollution on immunological, antioxidative and hematological parameters, and body condition of Eurasian tree sparrows. Ecotoxicol** Environ Saf. DOI: 10.1016/j.ecoenv.2020.111755.

[18] MAHIEU S, DEL C. CONTINI M, GONZALEZ M, MILLEN N, ELIAS MM. (2000**) Aluminum toxicity. Hematological effects.** Toxicol Lett. DOI: 10.1016/s0378-4274(99)00184-8.

[19] MASSADEH A, GHARIBEH A, OMARI K, AL-MOMANI I, ALOMARY A, TUMAH H, HAYAJNEH W. (2010). **Simultaneous determination of Cd, Pb, Cu, Zn, and Se in human blood of jordanian smokers** by ICP-OES. Biol Trace Elem Res. DOI: 10.1007/s12011-009-8405-y.

[20] MARTINEZ, Caroline Silveira. (2017). **Effects of Aluminum Exposure on Neurological, Reproductive, Cardiovascular and Biochemical Parameters in Rats**. Doctoral thesis. Federal University of Pampa.

[21] MLADENOVIC J. (2019). **Aluminum inhibits erythropoiesis in vitro**. J Clin Invest 1988 Jun; 81, 6): 1661-5.and sarcopenia vol. 5,1. DOI: 10.1172/JCI113502.

[22] NASH, D. BLOOD L. (2003). **Blood pressure, and hypertension in perimenopausal women**. Jama, v. 289, p. 1523-1532. DOI: 10.1001/jama.289.12.1523

[23] NEMETH E, Ganz T. (2009). **The role of hepcidin in iron metabolism.** Acta Haematol. DOI: 10.1159/000243791.

[24] OECD (ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT). **Aluminium factsheet. In: Material Resources**, Productivity and the Environment. Mechelen: OECD Publishing, 2015.

[25] OESTERLING, E. (2008) **Alumina nanoparticles induce expression of endothelial cell adhesion molecules.** Toxicology Letters, no. 178, p. 160–166. DOI: 10.1016/j.toxlet.2008.03.011.

[26] PEREZ G, GARBOSSA G, DI RISIO C, VITTORI D, NESSE A. (2001). **Disturbance of cellular iron uptake and utilisation by aluminium**. J Inorg Biochem. DOI: 10.1016/s0162-0134(01)00310-5.

[27] PEREZ G, PREGI N, VITTORI D, DI RISIO C, GARBOSSA G, NESSE A. (2005). **Aluminum exposure affects transFerrin-dependent and -independent iron uptake by K562 cells**. Biochim Biophys Acta. https://doi.org/10.1016/j.bbamcr.2004.12.002

[28] SCHMIDT, Patrícia Medeiros. (2015). **Effects of acute exposure to aluminum chloride (AlCl3) on blood pressure, vascular reactivity and oxidative stress in rats**. Master's Dissertation. Federal University of Pampa.

[29] SHAW, C.A.; LI, Y.; TOMLJENOVIC, L. (2013). **Administration of aluminium to neonatal mice in vaccine-relevant amounts is associated with adverse long-term neurological outcomes**. Journal of Inorganic Biochemistry, n. 128, p. 237–244. DOI: 10.1016/j.jinorgbio.2013.07.022.

[30] TOYOKUNI S. (2002). **Iron and carcinogenesis: From Fenton reaction to target genes**. Redox Rep 4: 189–197. DOI: 10.1179/135100002125000596.

[31] WARD R, ZHANG Y, CRICHTON RR. (2001**). Aluminum toxicity and iron homeostasis**. J Inorg Biochem. DOI: 10.1016/s0162-0134(01)00308-7

[32] WHO. **Worldwide prevalence of anemia** 1993-2005. Geneva, 2008. Accessed on May 6.

[33] WILLHITE CC, KARYAKINA NA, YOKEL RA, YENUGADHATI N, WISNIEWSKI TM, ARNOLD IM, MOMOLI F, KREWSKI D. (2014**). Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and anoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts.** Crit Rev Toxicol. DOI: 10.3109/10408444.2014.934439

[34] ZUO Y, LU X, WANG X, SOORANNA SR, TAO L, CHEN S, LI H, HUANG D, NAI G, CHEN H, PAN C, HUANG C, PANG Y. (2020). **High-Dose Aluminum Exposure Further Alerts Immune Phenotype in Aplastic Anemia Patients.** Biol Trace Elem Res. DOI: 10.1007/s12011-020-