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Assessing Human Environmental Aluminum Exposure by Analysing Frequency Distribution Properties of Hair and Whole Blood Aluminum Concentrations

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ABSTRACT

Aluminum is an omnipresent non-essential trace element in the human diet and an essential component of numerous industrial processes. The Al population exposure risk is increasing, but there is no long-term biomarker for the exposure assessment. We analyzed Al with ICP MS in the hair (^{Al}H) and whole blood (^{Al}WB) in 311 healthy persons (n♂ = 123 and n♀ = 188); the ^{Al}WB was analyzed in 142 women and 90 men. We used the median derivative power function to assess aluminum exposure. ^{Al}H median was higher in men (6.64) than in women (4.74 $\mu g \cdot g^{-1}$) ($p < 0.01$, χ^2-test). ^{Al}WB was below detection limit of 0.09 $\mu g \cdot ml^{-1}$ in over half the men and women. ^{Al}H concentrations below or above the linear segment (Tolerable exposure) of 1.98–14.3 in women and 2.78–17.5 $\mu g \cdot g^{-1}$ in men indicate Low or the Excessive exposure, respectively. ^{Al}WB of 0.09-1.53 $\mu g \cdot g^{-1}$ indicates the Tollerable Al exposure; ^{Al}WB and ^{Al}H were poorly correlated. The Tollerable ^{Al}H exposure can be further differentiated by a 3-component kinetic analysis to reflect the changes of hair aluminum saturation capacity. The median derivative power function for analyzing ^{Al}H frequency distribution is a valuable long-term biomarker for assessing the population environmental aluminum exposure risk.

KEY WORDS

Aluminum; Population Exposure; Biomarkers; Hair; Whole Blood; Median Derivatives; Risk Assessment.

INTRODUCTION

Aluminum is a non-essential element abundantly present in the Earth's crust. It is also widely used in a great number of industrial products and processes - from packaging materials and food additives to water purification, from antiperspirants and gastric antacides to vaccines [1]. Aluminum has a low toxicity, but its ever increasing presence in the human environment became a subject of great public concern [2,3]. Indeed, exposure to high doses of aluminum may impair the brain, blood, bone and kidneys and, also, there is a strong association between the high environmental aluminum exposure and the occurence of Alzheimers's disease and Parkinson's disease [4-7]. The level of the current human aluminum environmental exposure to the general population needs to be accurately assessed so that the adequate health protection measures can be established [8].

Aluminum is omnipresent in all the foods - both fresh and processed - and its concentration therein may vary by a factor of ten worldwide [1]. In the UK the aluminum in the food may vary (mg·kg^{-1} dry weight, dw) from 0.27 in eggs to 78 in miscellaneous cereals [9]. Aluminum absorption from the gastrointestinal tract is of a very low magnitude and of 0.1 - 0.3 % on the average [3].

However, there is no available long term bio-marker to monitor the aluminum exposure of the occupationaly non-exposed general population. Biological monitoring of human aluminum exposure has been conducted with urine, which is thought to indicate recent exposure, and plasma which is thought to better reflect the aluminum body burden. However, neither biomarker is a very good predictor of the aluminum body burden. Thus far, hair aluminum concentration has been described, but its value as an indicator of aluminum body burden has not been demonstrated [3].

In our previous studies we have demonstrated that hair analysis may help to accurately asses the exposure, overexposure, and toxicity of environmental silver, and to accurately estimate the nutritional status of iodine in the human body [10-12]. The aim of this study was to assess the level of current environmental aluminum exposure in an occupationally non-exposed population. We have explored how much aluminum may be found in human hair and whole blood of an apparently healthy population, what was the frequency distribution of the analyzed aluminum concentration in the hair and whole blood, with the aim to estimate the current level and possible risk of aluminum exposure in the population.

Subjects and Methods

This prospective, observational, cross-sectional, and exploratory study was approved by the Ethical Committee of the Institute for Research and Development of the Sustainable Eco Systems (IRES) and conducted by strict adherence to the Declaration of Helsinki on Human Subject Research and to the complementary Croatian national bylaws and regulations [13,14]. Every subject gave his/her written consent to participate in the study and filled out a short questionnaire on his/her health status and medical history (data not shown) [15].

Hair aluminum (^{Al}H) was analyzed in a random sample of 311 apparently healthy adults (123 Men, 188 Women) 47 years old on average (SD 15.7, median 49.0) who were concerned with their health status with respect to their trace element nutritional status and toxic element body burden. They came from a general population from across the country, most of them living in Zagreb, the capital of Croatia. All the subjects were fed their usual home prepared mixed diet, and reported no adverse medical condition. In addtion, the whole blood aluminum was analyzed in 142 women and 90 men (^{Al}WB) from the same cohort.

Hair (^{Al}H) and Whole blood (^{Al}WB) aluminum analysis: Hair and whole blood aluminum were analyzed with the ICP MS (Elan 9000, Perkin Elmer, USA) at the Center for Biotic Medicine (CBM), Moscow, Russia - CBM is an ISO Europe certified commercial laboratory for analysing bioelements (major and trace and ultratrace elements) in different biological matrices [16]. CBM is also a core member of the External Quality Assessment at Surrey EQAS (http://trace-elements-eu) which helps ensure accurate and consistent results of the trace element analysis in biological matrices.

In brief, hair analysis was performed following the International Atomic Energy Agency recomendations and other validated analytical methods and procedures [17,18]. Hair sample of 0.5-0.1 g were stored in envelopes and the vials with whole blood were kept refrigerated at 4°C before they were randomly assigned for analysis. The individual hair samples were cut with the sterilyzed titanium coated scissors (Suvorna Components Private Ltd., Hyderabad, Andra Pradesh, India) prior to chemical analysis to be less than 1 cm long, stirred 10 min in an ethylether/acetone (3:1, w/w), rinsed three times with the redistilled H_2O, dried at 85°C for one hour to constant weight, immersed one hour in 5% EDTA, rinsed again in the redistilled H_2O, dried at 85°C for twelve hours, wet digested in HNO_3/H_2O_2 in a plastic tube, sonicated, and microwaved. Hair was microwave digested with HNO_3 (Fluka #02650 Sigma-Aldrich, Co.) in the Berghof SW-4 DAP-40 microwave system (Berghof Products + Instruments GmbH, 72800 Eningen, Germany), and diluted 1:150 with DDIW, sonicated and run into the ICP MS system.

Whole Blood (^{Al}WB). Whole venous blood was collected into the green-cap Vacuette collecting tubes (#454082 Lot A13030M7, Greiner Bio-On International AG, 4550 Kremsmünster, Austria) which were randomly assigned for ICP MS analysis: whole blood samples of 0.5 ml were digested in a microwave oven with 0.1 ml of HNO_3 (Khimmed Sintez, Moscow, Russia) at 175°C. Blood standards were liophylized Seronorm TM Trace Elements Whole Blood Reference Standards Level 1 (OK 0036), Level 2 (MR9067), and Level 3 (OK0337) for aluminum in the whole blood (SERO AS, Bilingstadt, Norway). Five ml of redistilled H_2O were added to every reference standard and stirred gently at a room temperature for two hours to equilibrate. One ml of such equilibrated standard was pipetted in 25 ml quartz glass vial, dried at 105°C for 24 hours. The microwaved samples were dissolved in 5 ml of redistilled H_2O with 0.1 ml of H_2O added.

All chemicals were proanalysis grade (Khimmed Sintez, Moscow, Russia). We used certified GBW0910b Human Hair Reference Material (Shanghai Institute for Nuclear Research, Academia Sinica, Shanghai 201849, China) (CV [SD/Mean] 0.21) [16,19].

Current CBM hair and whole blood aluminum cut off points (μg·g^{-1}) are 0.00 - 40.0 for men and 0.00 - 15.0 women, respectively; whole blood reference values for allowable aluminum exposure are 0.00 - 0.40 [20]. Values above this range are considered to indicate excessive aluminum exposure; our detection limit for ^{Al}H and ^{Al}WB was 0.039 μg·g^{-1}.

Aluminum belongs to the pleiad of 29 elements sharing the same mass number (number of isotopes//element): 2 Ne, 5 Na, 5 Mg, 8 Al, 5 Sr, 3 P, 1 S [21]. Thus, the pleiad includes all the elements and their isotopes sharing the same mass number.

Median Derivatives

To scrutinize the hair and whole blood aluminum concentration frequency distribution, we used the median derivative model to fit the sigmoid logistic regression analysis function (power function) for men and women separately (Appendix):$A2 + (A1 – A2)/[1+(x/x_0)^p]$where A1 is initial value (lower horizontal asymptote, A2 is final value (upper horizontal asymptote), x_0 is center (point of inflection, in our case it is the median M_0), p is power (the parameter that affects the slope of the area about the inflection point) [10,22]. The Qtiplot Data Analysis and Scientific Visualisation programs were used for this analysis (www.softproindependent.com/qtiplot.html). The same program was used to assess the hair saturation capacity by analysing the exponential functions of a linear part od the sigmoid curve.

RESULTS

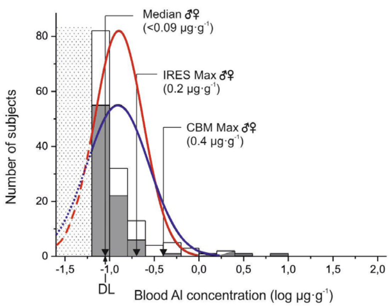
Hair and whole blood aluminum detectability: Aluminum was detected in 304 of 311 of analyzed hair samples, but only in 109 of 232 of the analyzed whole blood samples (Table 1). Thus, over the half of the analyzed whole blood samples were below the detection limits of our ICP MS instrument (0.09 μg·g^{-1}). The frequency distribution of whole blood samples where aluminum could not be detected was not influenced by the sex of the subjects, i.e., the detectability of ^{Al}WB in both sexes was equally affected.

Table 1: Hair and whole blood aluminum detectability.

Whole blood									
Sex	No. analyzed	Below detection	Al detected	Median (in all) (μg·g^{-1} Al)	Mean	SU*	Median (in detected) (μg·g^{-1} Al)	Mean	SU*
Men	90	51	39	0.00 (ND)	0.226	0.094	0.130	0.521	0.209
Women	142	72	70	0.00 (ND)	0.132	0.024	0.143	0.268	0.043
All	232	123	109	0.00 (ND)	0.168	0.040	0.140	0.351	0.081
Hair									
Sex	No. analyzed	Below detection	Al detected	Median (in all) (μg·g^{-1} Al)	Mean	SU*	Median (in detected) (μg·g^{-1} Al)	Mean	SU*
Men	123	2	121	6.54	9.28	0.743	6.58	9.43	0.747
Women	187	4	183	4.74	7.03	0.506	4.86	7.18	0.513
All	310	6	304	5.40	7.92	0.429	5.52	8.08	0.433

*SU – standard uncertainty [23].

Log transformation of aluminum concentrations in the hair (Figure 1, Bottom) and whole blood (Figure 1, Top): DT detection limits IRES·Max and CBM·Max are the maximal allowable concentrations of aluminum in the hair and whole blood at the Institute for the Research and Development of the Sustainable Eco Systems, Zagreb, and Center for Biotic Medicine, Moscow, respectively. After the data were log transformed, the previous skewed and kurtous aluminum data distribution was changed into the standard Gaussian frequency distribution curve. Apparently, men accumulate and retain more aluminum in the hair; there was no difference in whole blood Al between the men and women. The respective ^{Al}H medians



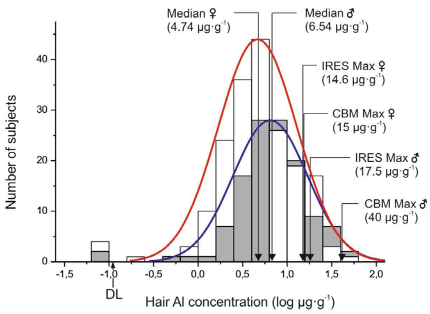


Figure 1: Log transformation of aluminum concentrations in the hair (Bottom) and whole blood (Top). DT detection limits IRES·Max and CBM·Max are the maximal allowable concentrations of aluminum in the hair and whole blood at the Institute for the Research and Development of the Sustainable Eco Systems, Zagreb, and Center for Biotic Medicine, Moscow, respectively.

— Normal distribution curve men and women (column size = 0.2 µg•g^{-1}).

Median derivatives to fit the power function sigmoid (see

were for ♂ = 6.54 and for ♀ = 4.74; and ^{Al}WB medians for both ♂and ♀ (♀♂) = 0.09 (µg·g^{-1} for subjects where aluminum was detectable. Except for the aluminum concentrations in women's hair, we think that the current CBM standards of tolerable aluminum exposure (CBM·Max) are set too high.

Appendix 2): Table 2a Hair, Table 2b Whole Blood: The data to fit the power function sigmoid curve of median derivatives (see Appendix 2) are presented in Table 2. The data on upward and downward arms of the median derivatives are shown for men and women separately. The number of subjects above the linear segment of the sigmoid (segments ♀ u3 – u6 for women and ♂ U3 - U6 for men) involved $^{Al}H_{n=310}$ 30 men and 45 women, whereas $^{Al}WB_{n=232}$ was comprised of 23 men and 35 women. Apparently, somewhat less than 25% of the Croatian population has increased ^{Al}H exposure and 35% of them have increased aluminum in the whole blood (^{Al}WB) according to the criteria graphically presented in Figure 2a and Figure 2b.

Table 2: Median derivatives to fit the power function sigmoid (see Appendix).

Table 2a: Hair

Men (n = 123)						Women (n = 187)					
Median (M_0) = 6.54 µg·g^{-1} Al						Median (M_0) = 4.74 µg·g^{-1} Al					
MDC	n	Al	MDC	n	Al	MDC	n	Al	MDC	n	Al
D_1	62	4.06	U_1	62	10.79	d_1	94	2.89	u_1	94	8.03
D_2	31	2.78	U_2	31	17.49	d_2	47	1.88	u_2	47	14.29
D_3	16	1.89	U_3	16	26.05	d_3	24	1.34	u_3	24	19.05
D_4	8	1.02	U_4	8	28.40	d_4	12	0.93	u_4	12	24.13
D_5	4	0.35	U_5	4	39.10	d_5	6	0.00	u_5	6	28.10
D_6	2	0.00	U_6	2	44.64	d_6	3	0.00	u_6	3	32.94

Note: Common median $(M_0)_{n=310}$ = 5.40 µg•g^{-1} Al, capital letters ($D_1 – D_6$, $U_1 – U_6$) men, small letters ($d_1 – d_6$, $u_1 – u_6$) women.

Table 2b: Whole blood.

Men (n = 90)						Women (n = 142)					
Median (M_0) = 0.000 µg·g^{-1} Al (below DL)						Median (M_0) = 0.00 µg·g^{-1} Al (below DL)					
MDC	n	Al	MDC	n	Al	MDC	n	Al	MDC	n	Al
D_1	45	0.000	U_1	45	0.120	d_1	76	0.000	u_1	76	0.142
D_2	23	0.000	U_2	23	0.160	d_2	36	0.000	u_2	36	0.203
D_3	12	0.000	U_3	12	0.383	d_3	18	0.000	u_3	18	0.455
D_4	6	0.000	U_4	6	1.912	d_4	9	0.000	u_4	9	0.890
D_5	3	0.000	U_5	3	2.910	d_5	5	0.000	u_5	5	1.360
D_6	2	0.000	U_6	2	5.290	d_6	3	0.000	u_6	3	1.660

Note: Common median $(M_0)_{n=232}$ = 0.000 µg•g^{-1} Al (below DL), capital letters ($D_1 - D_6$, $U_1 - U_6$) men, small letters ($d_1 - d_6$, $u_1 - u_6$) women.

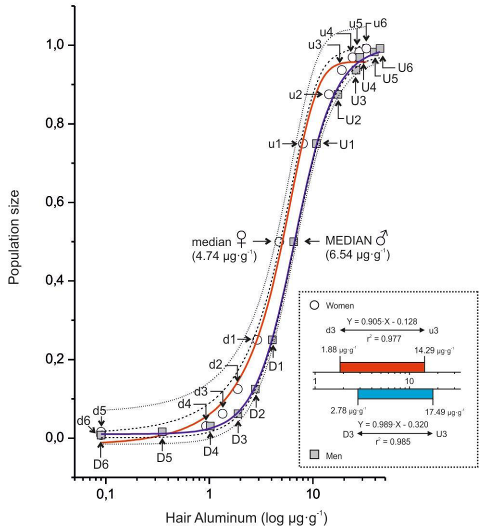


Figure 2: The sigmoid power function curve of median derivatives for hair (Figure 2a) and the whole blood aluminum (Figure 2b). Men in blue, Women in red.

Figure 2a: The difference between the ^{Al}H median derivatives of men $_{n = 123}$ (□) and women $_{n = 187}$ (O) combined.

D, U men downward (D) and upward (U) median derivatives; d, u women downward (d) and upward (u) median derivatives.

— Logistic function $Y = A_2 + (A_1\text{-}A_2)/(1 + (X/X_0)^p)$, - - - 0.95 confidence limit, ••• 0.95 prediction limit.

Men: $Y = 0.997 + (0.010\text{-}0.997)/(1 + (X/6.692)^{2.229})$, $r^2 = 0.999$;

Women: $Y = 0.998 + (0.006\text{-}0.998)/(1 + (X/4.852)^{2.093})$, $r^2 = 0.999$.

Box: Aluminum linear saturation range separate for ♂ and ♀ (log conc).

See Appendix for model and Table 2 for input values.

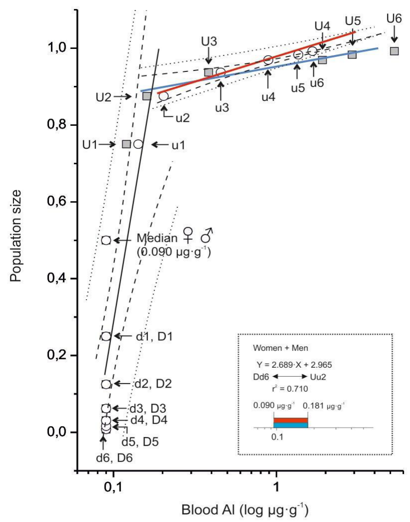


Figure 2b: The difference between the ^{Al}WB median derivatives of men $_{n = 90}$ (□) and women $_{n = 142}$ (O) combined.

D, U men downward (D) and upward (U) median derivatives; d, u women downward (d) and upward (u) median derivatives.

— Linear function Y = A + B·X, - - - 0.95 confidence limit, • • • 0.95 prediction limit.

Men+Women: $Y_{Dd6\text{-}Uu2} = 2.689 \cdot X + 2.965$, $r^2 = 0.710$.

Men: $Y_{U2\text{-}U6} = 0.072 \cdot X + 0.947$, $r^2 = 0.900$;

Women: $Y_{u2\text{-}u6} = 0.125 \cdot X + 0.970$, $r^2 = 0.965$.

Box: Aluminum linear saturation range combined for ♂ and ♀ (log conc) Dd6-Uu2.

See Appendix for model and Table 2 for input values.

The sigmoid power function curve of median derivatives for hair (Figure 2a) and whole blood aluminum (Figure 2b); Men in blue, Women in red: The median derivatives power function of the hair aluminum data is shown in Figure 2a for men $_{n = 123}$ ♂ and women $_{n = 188}$ ♀ separately. Similarly the median derivatives power function of the whole blood aluminum data is shown in Figure 2b for men $_{n = 90}$ ♂ and women $_{n = 142}$ ♀ separately. We define the downward to upward segments ♀$_{d3\text{-}u3}$ and ♂$_{D3\text{-}U3}$ as aluminum exposure Tolerable range. Tolerable hair Al concentrations of the Croatian women population range from 1.88 - 14.3 µg·g^{-1} (median 4.74 µg·g^{-1}), and for Croatian men range from 2.78 - 17.5 µg·g^{-1} (median 6.54). The respective low linear region of the sigmoid power function curve, i.e., the segments d_3-d_6 for women and D_3 - D_6 for men, was defined as a treshold or low environmental aluminum exposure region. Similarly, the respective upper linear region of the sigmoid power function curve above the segments u2 (range u_3-u_6) for women and U_2 (range U_3-U_6) for men we defined as an Excessive aluminum exposure region. Evidently, men retain more aluminum than women. Indeed, when we compare the frequency distribution of aluminum in the hair of men and women above and below the common median (5.40 µg·g^{-1}), men's hair contained more aluminum ($p < 0.01$, Chi square test) (Table 3).

Men's hair contained more aluminum than women's hair (Table 3): We observed no difference in whole blood aluminum concentrations in men and women, but men's hair contained more aluminum than the hair of women.

Table 3: Men's hair contained more aluminum than women's hair.

Hair (n = 310)		
	Men (n = 123)	Women (n = 187)
Above the median[a]	76	79
Below the median[b]	47	108

Note: Men hair has more aluminum than women (*p* = 0.001 Chi square test).

a,bMedian (M_0 = 5.40 µg•g^{-1} Al)

Whole Blood (n = 232)		
	Men (n = 90)	Women (n = 142)
Above the detection limit[a]	39	70
Below the detection limit[b]	51	72

Note: No significant sex dependent difference (p = 0.375 Chi square test)

a,bDetection limit (DL = 0.090 µg•g^{-1} Al)

Aluminum saturation capacity of the hair (Figure 3a) and the whole blood (Figure 3b): To assess the rate of aluminum hair and whole blood deposition and their saturation capacity for aluminum (delta, Δ), we have studied separately a linear segment of the sigmoid power function, i.e., the Tolerable range of the aluminum environmental exposure (Figure 3). When presented on a linear scale, the data fit the clasical Michaelis-Menton three component kinetic exponential curve. Thus, ^{Al}H delta 1 - 11 cover the non-exposed, i.e., the low hair and whole blood saturation capacity, meaning that all the available aluminum is retained in the hair at a constant rate. Segment Δ12 - Δ15 denotes a dynamic interaction of hair with aluminum where the rate of aluminum hair and ^{Al}WB incorporation are exceeding the rate of hair growth so that hair became more and more saturated with the aluminum. The last exponential component (Δ16 - Δ18) is characterized by an even more accelerated rate of aluminum deposition in the hair and ^{Al}WB. The hair is approaching the limits of its capacity to incorporate increasing concentrations of aluminum at an accelerated rate. The concentrations of hair whole blood aluminum above Δ16 is overtly excessive since the proportional rate capacity of Al deposition in the hair and whole blood become saturated.

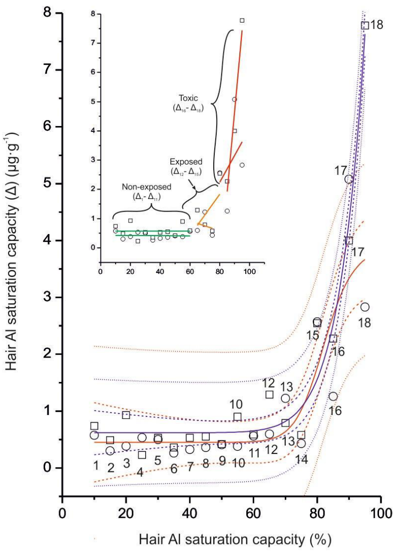


Figure 3: Aluminum saturation capacity of the hair (Figure 3a) and the whole blood (Figure 3b).

Figure 3a. Hair.

Men (□)

— Logistic fit Y = 26712.291+(0.620–26712.291)/(1+(X/192.478)$^{11.677}$), r^2 = 0.954.

- - - 0.95 confidence interval, ••• 0.95 prediction limit; Δ (delta) = following(%)-preceding(%).

Insert:

Linear fit Y (Δ_1- Δ_{11}) = -0.121•X + 0.570, r^2 = 0.167; Linear fit Y (Δ_{12}- Δ_{15}) = 0.071•X-3.854, r^2 = 0.093; Linear fit Y (Δ_{16}- Δ_{18}) = 0.551•X-44.860, r^2 = 0.911.

Women (O)

— Logistic fit Y = 3.910 + (0.450–3.910)/(1+(X/82.188)$^{17.818}$), r^2 = 0.674.

- - - 0.95 confidence interval, ••• 0.95 prediction limit; Δ(delta) = following(%)-preceding(%).

Insert:

Linear fit Y (Δ_1- Δ_{11}) = -3.727•X+0.431, r^2 = 0.107; Linear fit Y (Δ_{12}- Δ_{15}) = -0.017•X+1.905, r^2 = 0.923; Linear fit Y (Δ_{16}- Δ_{18}) = 0.092•X-5.115, r^2 = 0.290.

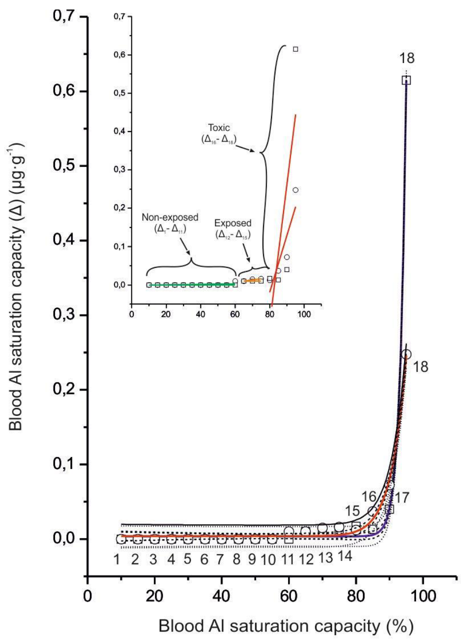


Figure 3b: Whole blood.

Men (□)

— Logistic fit Y = 596.855+(0.004–596.855)/(1+(X/108.519)$^{51.730}$), r^2 = 0.998.

- - - 0.95 confidence interval, ••• 0.95 prediction limit; Δ(delta) = following(%)-preceding(%).

Insert:

Linear fit Y (Δ_1- Δ_{11}) = 0•X, r^2 = -; Linear fit Y (Δ_{12}- Δ_{15}) = 0•X+0.01, r^2 = -;

Linear fit Y (Δ_{16}- Δ_{18}) = 0.036•X-3.016, r^2 = 0.446.

Women (O)

— Logistic fit Y = 675.760 + (0.004–675.760)/(1 + $(X/137.860)^{21.305}$), r^2 = 0.987.

- - - 0.95 confidence interval, ••• 0.95 prediction limit; Δ(delta) = following(%)-preceding(%).

Insert:

Linear fit Y (Δ_1- Δ_{11}) = 0.00009•X -0.002, r^2 = 0.167; Linear fit Y (Δ_{12}- Δ_{15}) = 0.0004•X-0.028, r^2 = 0.742; Linear fit Y (Δ_{16}- Δ_{18}) = 0.015•X-1.207, r^2 = 0.714.

Comparative rates (Δ) of hair and whole blood saturation capacity for aluminium: We also cross compared the rate of hair and whole blood saturation capacity for aluminum (Δ) (Table 4). Indeed, according to the characteristics of its three component exponential kinetic model, the Tolerable (T) range can be divided into its sub-segments: T·Acceptable (Δ1 - Δ11), T·Allowable (Δ12 -Δ15), and T·Borderline (Δ16 - Δ18). Evidently, Tolerable range of aluminum exposure have a changeable quality of adaptive response to the changes of the available aluminum presented to the biomarker and the capacity of the biomaker to receive and incorporate the presented element (Al) concentrations.

Hair and whole blood aluminum are poorly correlated (Figure 4). One of the frequent question regarding the hair bioelement analysis is if you have validated the results in the hair with some other and more often used bioindicator like the whole blood, plasma, urine etc. Perhaps, such objection may be of some interest if you may compare the chosen short term biomarker with some other short term indicator, or long term biomarker with the long term biomarker. Indeed, the data presented in Figure 4 clearly demonstrated that there is no correlation between the short- and long term biomarker of whole blood and hair in assessing aluminum exposure. As a matter of fact, any short term biomarker may be either low, comparable or increased when compared against the long term biomarker, due to the difference on the time scale of comparing the time in days vs the time in months.

Table 4: Comparative rates (Δ) of hair Al and whole blood Al saturation capacity.

HAIR							BLOOD						
	%	Rate	Al ♀ (μg·g⁻¹)	Δ	Al ♂ (μg·g⁻¹)	Δ		%	Rate	Al ♀ (μg·g⁻¹)	Δ	Al ♂ (μg·g⁻¹)	Δ
Non-exposed	10	Δ_1	1.65		2.39		Non-exposed	10	Δ_1	0.000		0.000	
	15	Δ_2	1.95	0.30	2.88	0.49		15	Δ_2	0.000	0.000	0.000	0.000
	20	Δ_3	2.34	0.39	3.81	0.93		20	Δ_3	0.000	0.000	0.000	0.000
	25	Δ_4	2.87	0.54	4.04	0.23		25	Δ_4	0.000	0.000	0.000	0.000
	30	Δ_5	3.37	0.50	4.57	0.53		30	Δ_5	0.000	0.000	0.000	0.000
	35	Δ_6	3.64	0.27	4.93	0.36		35	Δ_6	0.000	0.000	0.000	0.000
	40	Δ_7	3.96	0.33	5.46	0.53		40	Δ_7	0.000	0.000	0.000	0.000
	45	Δ_8	4.32	0.36	6.01	0.55		45	Δ_8	0.000	0.000	0.000	0.000
	50	Δ_9	4.73	0.41	6.43	0.42		50	Δ_9	0.000	0.000	0.000	0.000
	55	Δ_{10}	5.11	0.38	7.33	0.90		55	Δ_{10}	0.000	0.000	0.000	0.000
	60	Δ_{11}	5.67	0.56	7.92	0.59		60	Δ_{11}	0.100	0.100	0.000	0.000
Exposed	65	Δ_{12}	6.27	0.60	9.21	1.29	Exposed	65	Δ_{12}	0.110	0.010	0.100	0.100
	70	Δ_{13}	7.49	1.23	10.00	0.79		70	Δ_{13}	0.125	0.015	0.110	0.010
	75	Δ_{14}	7.92	0.43	10.58	0.55		75	Δ_{14}	0.141	0.016	0.120	0.010
	80	Δ_{15}	10.49	2.57	13.13	2.55		80	Δ_{15}	0.153	0.012	0.137	0.017
Borderline	85	Δ_{16}	11.75	1.26	15.40	2.28	Borderline	85	Δ_{16}	0.190	0.037	0.150	0.013
	90	Δ_{17}	16.83	5.08	19.40	4.00		90	Δ_{17}	0.262	0.072	0.190	0.040
	95	Δ_{18}	19.66	2.83	27.18	7.78		95	Δ_{18}	0.510	0.248	0.805	0.615

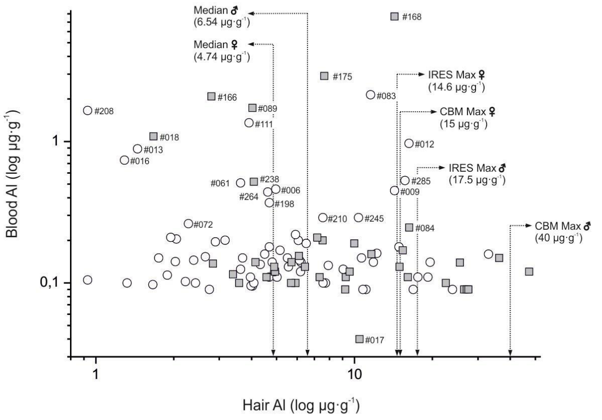


Figure 4: Hair and whole blood aluminum are poorly correlated. ^{Al}H and ^{Al}WB values are shown on the X and Y axis, respectfully. IRES Institute for research and development of the sustainable eco systems, Zagreb, Croatia. CBM Center for biotic medicine, Moscow, Russia.

■Men, ○ Women.

DISCUSSION

Today, hair is considered to be a non-invasive, reliable, reproducible, and affordable biomarker of the human body multi-element status in general population [24-26].

The main advantage of hair for assessing the long-term bioelement status, and toxic element status (body burden) in particular is hair's unidirectional growth. Once a certain bioelement is deposited in the hair, it does not equilibrate further with the body tissues, and thus serves as a permanent time log of environmental exposure. When an element is absorbed into the body, it gets widely distributed between the organs and tissues before it reaches the hair follicle and becomes irreversibly deposited into the hair fibres. With the rate of hair growth of about 1 cm per month, all the homeostatically controlled changes in the bioelement concentrations are irreversibly recorded in the hair [27,28].

However, hair bioelement analysis (macro elements, trace elements, and ultra trace elements, both essential and toxic) is notorious for the large dispersion of the analytical data. Indeed, our results on hair and whole blood aluminum concentrations are easy to compare with those reported by the other researchers because the reported ranges are so wide that it was easy to claim the good agreement. Hence, our hair [24,29-32] and whole blood [24,29-34] aluminum values are in good agreement with the values reported by the quoted authors.

Here presented sigmoid power function of media derivatives allowed us to assess the current level of population aluminum exposure with a resonable accuracy. More large data sets would be necessary to establish a more reliable reference sigmoid power function standards for the benefit of personalized medicine, health practices and in environmental health studies, epidemiology, nutrition, and toxicology. A brief look at our median derivatives input data for the segments u_3-u_6 and $U_3 - U_6$ indicates that already, at the present time, there are some 30% of non-occupationaly exposed persons within the general Croatian population who are overexposed to environmental aluminum. Currently, we do not know how much somebody should be overexposed with aluminum before the clinical signs of toxicity became recognizable. We may only state that the higher the body burden of aluminum, the greater the chance that the adverse signs and symptoms of excessive aluminum exposure would become manifested. The changes in aluminum exposure may also arise from the changes in a health status.

Our approach to assessing environmental hair aluminum exposure by analyzing the median derivatives of a sigmoid power function curve allows us for the first time, to differentiate between the pattern of aluminum hair deposition in men and women. Indeed, women start to accumulate aluminum in the hair earlier than men do, i.e., the aluminum starts to accumulate in hair at lower exposure aluminum concentrations for women. As a matter of fact, that pattern differs from the pattern observed for silver and iodine hair deposition where these two elements tend to accumulate earlier in men than women [11,22]. Such subtle sex dependent differences between the hair deposition of different elements may not be detected by comparing the arithmetic means and by working with the cut off points and/or random sets of unstructured ranges. The tolerable ranges of an element in the hair also differs from element to element, allowing for the possibility of a new insight into the metabolic processes of the human body and of their homeostatic control. However, this new, median derivatives approach to data analysis and data presentation as a sigmoid power function curve would require a wider validation by the other scientists and comparison with other diferent large data sets.

CONCLUSION

Environmental aluminum from food, water and air may enter the human body and accumulate in human hair; this deposition of aluminum in hair is governed by the Power Law function. This study demonstrated that hair is a reliable long term biomarker for assessing the non-occupational human aluminum environmental exposure of general population. By analyzing the frequency distribution of hair aluminum it is possible to differentiate between the Low (non-exposure Treshold), Tolerable, and Excessive level of aluminum population exposure, respectively. More research and larger data sets are required to establish the reliable power function reference curves for use in personalized medicine, environmental health/toxicology, and epidemiology.

DISCLOSURE STATEMENT

The authors declare no conflict of interest.

Appendix. The hair aluminum median derivatives model (Population Size, PS = 1.000)

Median ($M_{0,n=310}$ = 5.40 µg•g^{-1})

<-------------------------------->▣<------------------------------------->

Median Derivative Downward (Descending)		Median Derivative Upward (Ascending)	
Branch ($D_{0,n=155}$ = PS/2 = 0.500)		Branch ($U_{0,n=155}$ = PS/2 = 0.500)	
Descending Median Derivatives			Ascending Median Derivatives
$D_1 = D_0/2$	0.250	$U_1 = U_0 + U_0/2$	0.750
<------------▣-------------->		<--------------▣---------------------->	
$D_2 = D_0/4$	0.125	$U_2 = U_1$ + U0/4	0.875
<------------▣------------>		<------------▣------------>	
$D_3 = D_0/8$	0.062	$U_3 = U_2 + U_0/8$	0.937
<------▣----->		<-----▣------>	
$D_4 = D_0/16$	0.030	$U_4 = U_3 + U_0/16$	0.969
<--▣-->		<--▣-->	
$D_5 = D_0/32$	0.016	$U_5 = U_4$ + U0/32	0. 983
<▣>		<▣>	
$D_6 = D_0/64$	0.008	$U_6 = U_5 + U_0/64$	0.992
▣		▣	

We studied the frequency distribution of hair aluminum (^{Al}H) median and its derivatives to assess the aluminum environmental exposure. First we assess the median (M_0) hair aluminum concentration of our subject population. By definition, one half of the studied population was above the median (upward median branch, U_0), and the other half was below the median (downward median branch, D_0). Hence, the population size (PS) for M_0 is the sum of the respective upward and downward median branches around the central inflection "hinge" M_0, i.e., PS = $U_0 + D_0$ = 0.5 + 0.5 = 1.0. Both the respective upward and downward median branches can be further divided in the same "median of median" way into a series of sequential median derivatives ($U_{0,1,2,3\ ...n-1,\ n}$ and $D_{0,1,2,3,...n-1,\ n}$). For every median derivative of the population, the actual hair aluminum concentration can be identified. Thus, instead of mechanically throwing the preconceived percentile grid upon the observed data, we inferred the median derivative grid out from the data set itself [35].

AUTHOR CONTRIBUTION

Berislav Momčilović concieved the study wrote the paper, Juraj Prejac, Vjeran Višnjević, and Saša Badžek collected the samples and performed statistical analysis of data, Andrey Anatolyevic Skalny and Eugeny Petrovich Serebryansky analyzed the samples, Ninoslav Mimica co-concieved the study and overviewed the paper.

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