ОРИГИНАЛЬНАЯ СТАТЬЯ

HAIR SILVER MEDIAN DERIVATIVES FOR THE ASSESSMENT OF THE ENVIRONMENTAL SILVER EXPOSURE, OVEREXPOSURE, AND TOXICITY

ИСПОЛЬЗОВАНИЕ МЕДИАННОГО СОДЕРЖАНИЯ СЕРЕБРА В ВОЛОСАХ ДЛЯ ОЦЕНКИ ЭКОЛОГИЧЕСКОЙ НАГРУЗКИ И ТОКСИЧНОСТИ СЕРЕБРА

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KEYWORDS: hair silver, exposure, overexposure, toxicity, median derivatives, logistic fit.

КЛЮЧЕВЫЕ СЛОВА: анализ волос, серебро, экологическая нагрузка, токсичность, медианное содержание.

ABSTRACT. Silver was analyzed in the hair of 213 occupationally non-exposed subjects (87 men, 126 women) with the inductively coupled plasma mass spectrometry (ICP MS). Median hair Ag concentration was 0.070 µg/g for both sexes combined; but women's hair have more Ag than that of men ($p < 0.05$, Chi square test). The hair silver below 0.010 µg/g and 0.015 µg/g for men and women, respectively, appeared to be toxicologically irrelevant, and to only reflect random silver distribution between the other biochemical compartments of the human body. Above that concentration level hair silver concentration diverges upward, first for men and then for women and rose rapidly in a parallel type biological assay pattern, indicating the physiological saturation mechanism. These two distinct parallel saturation curves for men and women would converge back to the common sigmoid overexposure plateau at 0.210 µg/g and 0.358 µg/g for men and women, respectively. Combined with the medical history, our data indicate the hair silver of 2.00 µg/g to reflect clinical sub toxicity, and its concentrations above 4.00 µg/g an overt neurotoxicity.

РЕЗЮМЕ. Методом масс-спектрометрии с индуктивно связанной плазмой (ИСП-МС) было проанализировано содержание серебра в волосах у 213 пациентов, не имевших производственного контакта с этим химическим элементом (87 мужчин, 126 женщин). Медианная концентрация Ag в волосах в указанной выборке без деления по полу

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составила 0,070 мкг/г, однако у женщин уровень Ag был выше, чем у мужчин ($p < 0,05$ по критерию хи-квадрат). Уровень серебра в волосах ниже 0,010 и 0,015 мкг/г для мужчин и женщин соответственно оказался не имеющим токсикологического значения, а лишь отражающим случайное перераспределение серебра между биохимическими компартментами человеческого тела. Выше этого уровня начинался быстрый рост концентрации серебра в волосах, сначала у мужчин, затем аналогично у женщин, что указывает на наличие маханизмов физиологического насыщения. Затем параллельные кривые насыщения для мужчин и женщин вновь сходились к общему сигмовидному плато на уровне 0,210 и 0,358 мкг/г соответственно. Будучи сопоставленными с историями болезни, наши данные показали, что содержание серебра в волосах на уровне 2,00 мкг/г отражает состояние клинической субтоксичности, а его концентрация выше 4,00 мкг/г соответствует выраженной нейротоксичности.

INTRODUCTION

Silver is a non-essential low-toxic trace element with a strong antibacterial capacity (Emsley, 2001). Classically, occupational inhalation and/or mechanical (imbibition) exposure and ingestion of foods stored in silver utensils may result in silver toxic accumulation in the human body, i.e., the condition named *argyria* (Tomi et al., 2004). Today, silver has been widely used in many applications, from nano electronics to bed blankets and sheets (Reilly, 2005). Therefore, it is to be expected that over the time the population silver human body burden is going to be on increase, whereas a potentially vulnerable segments of the human population remained as yet to be identified. Indeed, we recently reported an increased human hair silver concentration in subjects suffering from mental depression (Momčilović et al., 2006b), indicating that changes in hair silver deposition may shadow the changes of metabolic processes in health and disease.

In this paper we aim to assess the level of current environmental silver exposure in the occupationally non-exposed adult human population of both sexes by using the median derivatives frequency distribution analysis.

SUBJECTS AND METHODS

We studied the hair silver in a randomly selected population of 213 adults (87 men and 126 women), who were not occupationally exposed to silver, most of them living in Zagreb, the capital of Croatia, and who were concerned about their health and well-being. The study was conducted by strict adherence to the Declaration of Helsinki on human subject research (Brown, 2009), and by the complementary Croatian national bylaws and regulations.

The scalp hair was collected over the back of the head at the *protuberantia occipitalis externa*, and analyzed for silver content by the inductively coupled plasma mass spectrometry (ICP-MS) at the Center for Biotic Medicine, Moscow, Russia, an ISO certified high-tech laboratory, as described in great detail previously (Momčilović et al. 2006a). Our detection limit for hair silver is 0.00006 µg/g, and the coefficient of variation was 38.1% (Momčilović et al., 2009).

We studied the frequency distribution of median and its derivatives to assess the silver exposure, overexposure and toxicity. First we assess the median (M_0) hair silver 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 into a series of sequential median derivatives, e.g., we can assess the downward median derivative D_1 by defining the new for D_0 subpopulation, D_2 can be identified by the new median derivative of D_1 subpopulation, and so on ($U_{0,1,2\ ...n}$ and $D_{0,1,2,...}D_n$). For every median derivative of population, the actual hair silver concentration can be graphically identified. Thus, instead of mechanically throwing the percentile grid model upon the data, we inferred the median derivative grid model from the real, naturally occurring observed set of data (Smylevich and Dougherty, 2010). The logic of median derivatives model is outlined in Table 1, and the corresponding actual silver concentrations are shown in Table 2.

Several models of median derivative frequency distribution were tested for their linearity and branch linearity named according to their graphical appearance as Sigmoid and Pyramid, respectively (Fig. 1 and 2) (Brody, 1994). Also, we estimated what would be an expected normal range of hair silver concentrations if the observed current environmental level of silver follows the simple first order kinetics of silver deposition in the hair (Fig. 2). Similarly, we compared the incidence of hair silver in men and women above and below the common median with the Chi square test (Glantz, 2005). The difference of $p < 0.05$ between the groups was considered to be significant.

To further scrutinize the gender difference in hair silver deposition, the frequency distribution of the median derivatives was fitted to the logistic regression analysis function of the general form

$$A_2 + (A_1 - A_2) / (1 + x/x_0)^p,$$

where A_1 is initial value (lower horizontal asymptote); A_2 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). We used the open source Qtiplot 0.9.8.3 – Data Analysis and scientific visualization software http://www.soft.proindependent.com/gbiplot.html.

Table 1. ***The median derivatives model (Population Size, PS = 1.000)***

Median ($M_{0,\ n=213}$ = 0.070 µg/g)	
Downward Branch ($D_{0,\ n=106}$ = PS 0.500)	Upward Branch ($U_{0,\ n=106}$ = PS 0.500)
Descending Median Derivatives (PS)	Ascending Median Derivatives (PS)
$D_1 = D_0/2 = 0.250$	$U_1 = D_0 + U_0/2 = 0.750$
$D_2 = D_0/4 = 0.125$	$U_2 = D_0 + U_0/4 = 0.875$
$D_3 = D_0/8 = 0.062$	$U_3 = D_0 + U_0/8 = 0.937$
$D_4 = D_0/16 = 0.031$	$U_4 = D_0 + U_0/16 = 0.969$
$D_5 = D_0/32 = 0.016$	$U_5 = D_0 + U_0/32 = 0.983$
$D_6 = D_0/64 = 0.008$	$U_6 = D_0 + U_0/64 = 0.992$

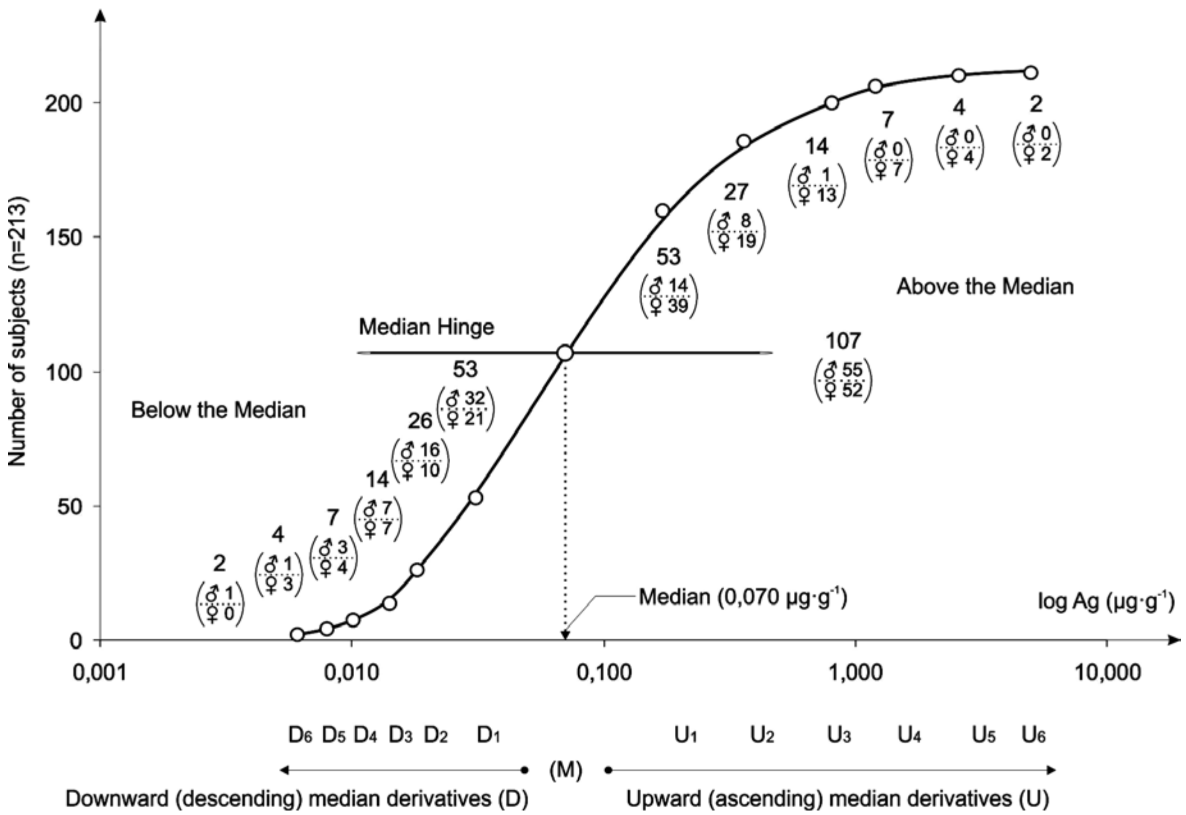

***Fig. 1**. «Sigmoid» model for the hair silver median derivative (both sexes combined).*
M_0 median, D_1–D_6 downward (descending) median derivatives,
U_1–U_6 upward (ascending) median derivatives,
♂ Men, ♀ Women. Below the Median (linear) $Y_{D1–D6} = 1678\ X – 7.2$ ($r^2 = 0.988$),
Above the Median (ln) $Y = 53.7 \ln X + 246.7$ ($r^2 = 0.992$).
See Table 2 for median derivative concentrations

Table 2. ***Actual hair silver median derivatives concentration for men and women combined (μg/g)***

Median (M_0, $_{n = 213}$ = 0.070 μg/g Ag)	
Descending Median Derivatives	Ascending Median Derivatives
D_1 = 0.006	U_1 = 0.170
D_2 = 0.008	U_2 = 0.358
D_3 = 0.010	U_3 = 0.802
D_4 = 0.014	U_4 = 1.190
D_5 = 0.018	U_5 = 2.570
D_6 = 0.031	U_6 = 4.940

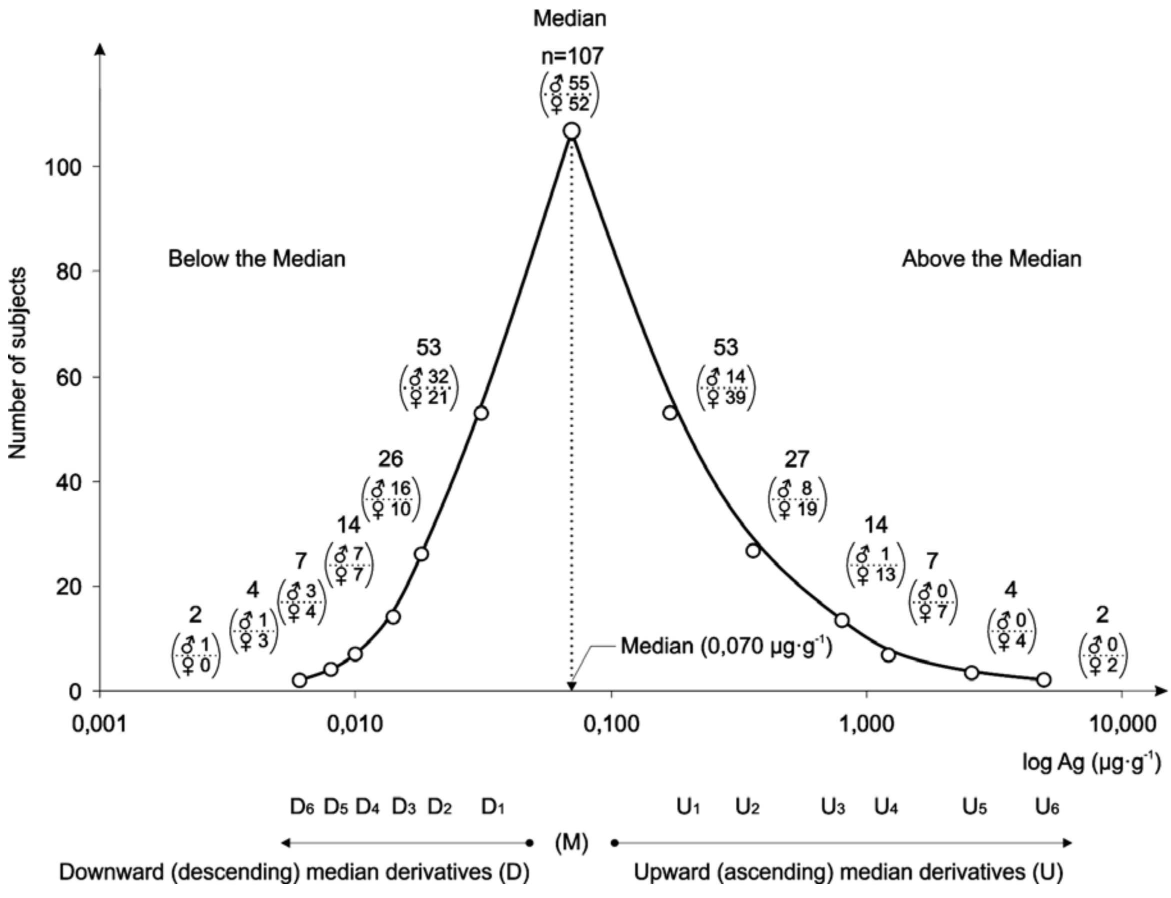

***Fig. 2**. «Pyramid» model for the hair silver median derivatives (both sexes combined).*
M_0 median, D_1–D_6 downward (descending) median derivatives,
U_1–U_6 upward (ascending) median derivatives,
♂ Men, ♀ Women. Below the Median (linear function) $Y_{D1–D6} = 1677.8·X – 7,203$ (r^2 = 0.988),
Above the Median (power function) $Y_{U1–U6} = 7.659·X^{–1,063}$ (r^2 =0,984)

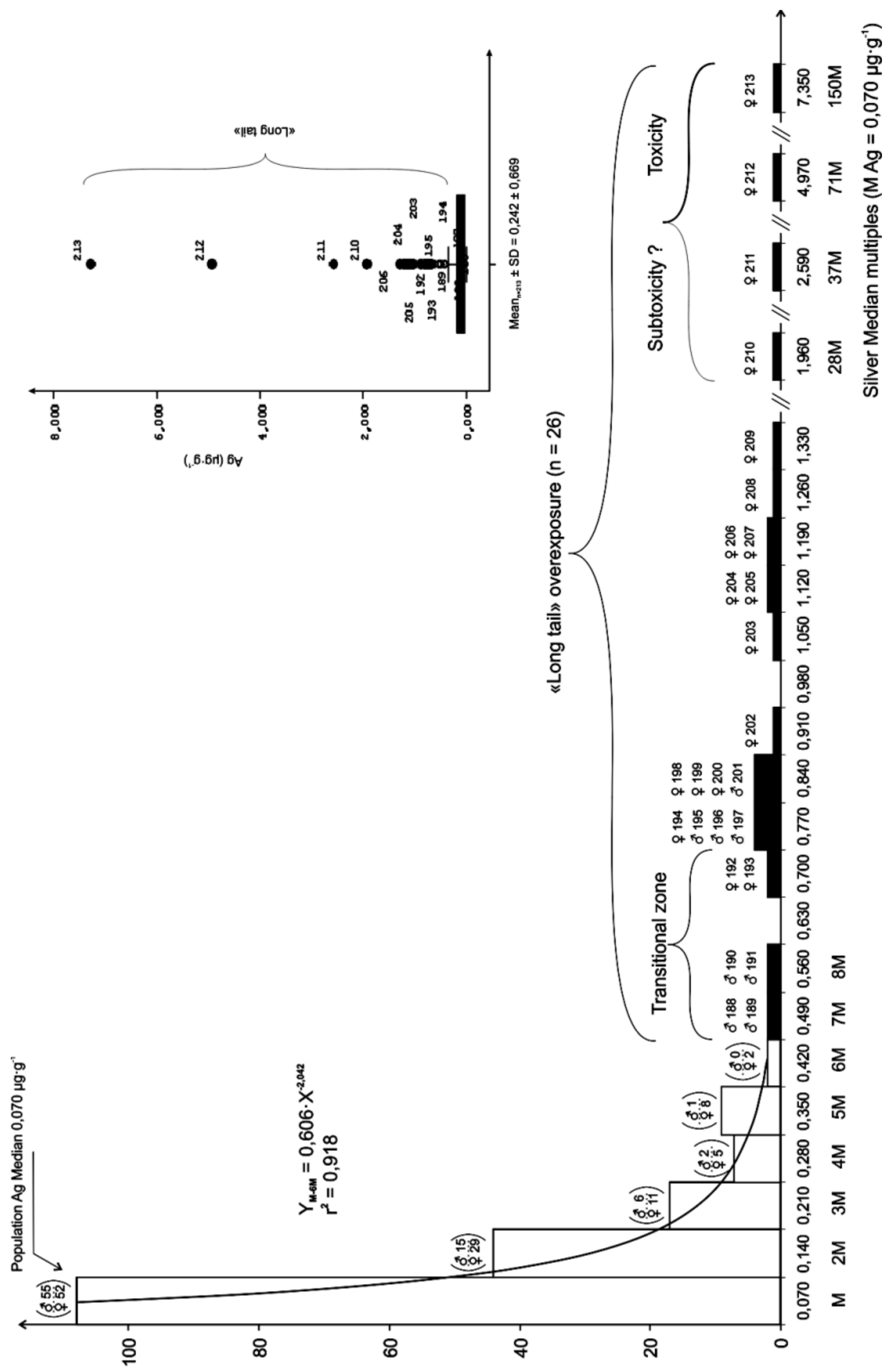

Fig. 3. *«Long tail». The hair silver concentration frequency distribution. Median (M) = 0.070 μg/g Ag). Mean ± SD, subjects (n = 213) are numbered sequentially depending upon the increasing hair silver concentration*

RESULTS

Silver was detected in every one of 213 hair samples and its concentration varied over a wide range of four orders of magnitude, i.e., from 0.006 to 7.350 µg/g, with having a median (M_0) hair silver concentration of 0.070 µg/g for both sexes combined. We used this median (M_0) value as a basic unit of concentration on our x axis (Fig. 3). The hair silver concentration covered the range of six median concentrations (M – 6M), i.e., 0.070 to 0.420 µg/g, and it can be described with the exponential curve having a high correlation coefficient (r^2 = 0.918); adding further multiples of median concentrations would only decrease the value of this correlation coefficient. Hence, hair silver concentrations of 0.420 µg/g (or below) may be considered to reflect the range of the physiological compensatory response. Incidentally, all the silver concentrations above that range were outliers (see the box-plot insert to Fig. 3), comprising our «Long tail» of hair silver concentration (Anderson, 2007). The data indicate that the range between 7M-10M median multiples could be considered as transitional zone, whereas concentrations above 28 M (>1.960 µg/g) may be considered sub toxic, and those above 71 M (>4.670 µg/g) as definitively toxic, respectively.

We have thoroughly re-examined the medical history of the four subjects with the highest hair silver concentration. The respective two sub toxic subjects have an excessive silver exposure due to silver jewelry licking habit (No. 210), and the contact exposure to the silver dental material (No. 211). Moreover, it become apparent that the two subjects having the highest hair silver concentration (No's 212 and 213) were overtly silver poisoned. Analysis of the medical history records revealed that this was not a «guesstimation» (Weinstein and Adam, 2008), since they were already clinically examined for the neurological problems of then unknown origin; nobody thought of them being poisoned with silver.

The sigmoidal («Sigmoid») distribution pattern of hair silver concentration below and above the median hinge, i.e., of respective ascending (upward) and descending (downward) median derivatives, is shown in Fig. 1. Indeed, the hair silver concentrations median derivatives provide the series of dots that can be adequately fitted with the saturation sigmoid curve. However, the descending and ascending branch of the hair silver concentration median derivatives were not symmetrical. The hair silver concentration descending median derivatives (M_0 – D_6) can be described with the linear regression having a high correlation coefficient (r^2 = 0.988), whereas the hair silver concentration ascending median derivatives (M_0 – U_6) are better fitted with the quadratic equation having a comparatively weaker correlation coefficient (r^2 = 0.846). Hair silver concentration median derivatives are shown numerically in Table 2. The visual examination of this curve is in essential correspondence with the previous Fig. 3 since the four highest ascending (upward) median derivatives (U_3–U_6) corresponds with the values above the transitional zone in Fig. 3. Moreover, the two highest hair silver ascending median derivatives (U_5 and U_6) were on the very plateau of the sigmoid curve and what corresponds to the toxicity level. The same graphical solution can be demonstrated by the «Pyramid» of ascending and descending median derivatives (Fig. 2); here it is easier to observe how the population size of each median derivative decreases with the increase of the median derivative number (see subscripts for comparison). Evidently, the downward branches (arms) of the median derivatives are identical for both Fig. 1 and Fig. 2, whereas, the upward arms are obviously different. It should be noted that the median derivatives between the downward and upward branches D_3 – U_2 can be effectively fitted with the linear regression model Y = 53.7 ln X + 246.7 (r^2 = 0.992).

Next, we analyzed the descending branch of the silver hair median derivative concentrations in a greater detail since it appears to be highly linear (Fig. 4). Indeed, if there were no excessive accumulation of silver in the hair, i.e., if the hair silver accumulation follows the first order kinetics, then the ascending branch of the hair silver median derivative concentrations in the «Pyramid model» would mirror its descending branch with the peak at the population Median (M_0) silver concentration. Indeed, if we rotate the observed triangle D_6·Median·M_0 by 180^0 around the Median·M_0 axis, we got the expected mirror image that would satisfy the theoretical premise of the first order kinetics, i.e., if silver won't accumulate excessively in the body (insert to Fig. 4). Therefore, today, the natural environmental hair silver concentration would be close to the current level of 2 M, i.e., about 0.135 µg/g. Indeed, almost 2/3 of all of our subjects would be within this, the most conservatively assessed boundary of the «natural» silver exposure in Croatia, today.

When we compared the number of men and women above and below the median, respectively, then it appears how women had more silver in their hair than men (p < 0.05, Chi square test) (Table 3). Indeed, the hair silver median for 87 men and 126 women were 0.046 and 0.082 µg/g, respectively, and the comparative downward and upward median derivatives for men and women separately are shown in Table 4. Since the slope of the curve depends upon the population size (axis y) we provide the further refinement of the median derivative method by showing the percentage of population belonging to the certain median

Table 3. ***Women retain more silver in the hair than men (median ($M_{0,\ n = 213}$ = 0.070 µg/g Ag)***

	Men	Women
Above the median	32	74
Below the median	55	52

♀>♂ Chi square test (p < 0.01).

derivative (Fig. 5). That would also compensate for the different size of the population studied and for the binning effect (Wainer, 2009). Again, the high upward derivatives accords with that of our Sigmoid curve in Fig. 1. This way of presentation allows for direct visual comparison of populations of different size and for comparison of the different slopes for the different elements.

Table 4. ***Actual hair silver median derivatives concentration (μg/g) for men (D_1–D_6 descending median derivatives, U_1–U_6 ascending median derivatives), and women (d_1–d_6 descending median derivatives, u_1–u_6 ascending median derivatives)***

Men		Women	
Median ($M_{0,n=87}$ = 0.046 μg/g Ag)		Median ($M_{0,n=126}$ = 0.082 μg/g Ag)	
D_1 = 0.0245	U_1 = 0.12	d_1 = 0.04	u_1 = 0.206
D_2 = 0.016	U_2 = 0.2105	d_2 = 0.024	u_2 = 0.358
D_3 = 0.013	U_3 = 0.531	d_3 = 0.015	u_3 = 0.8425
D_4 = 0.0105	U_4 = 0.75	d_4 = 0.0095	u_4 = 1.145
D_5 = 0.008	U_5 = 0.765	d_5 = 0.007	u_5 = 1.2
D_6 = 0.003	U_6 = 0.813	d_6 = 0.006	u_6 = 1.25

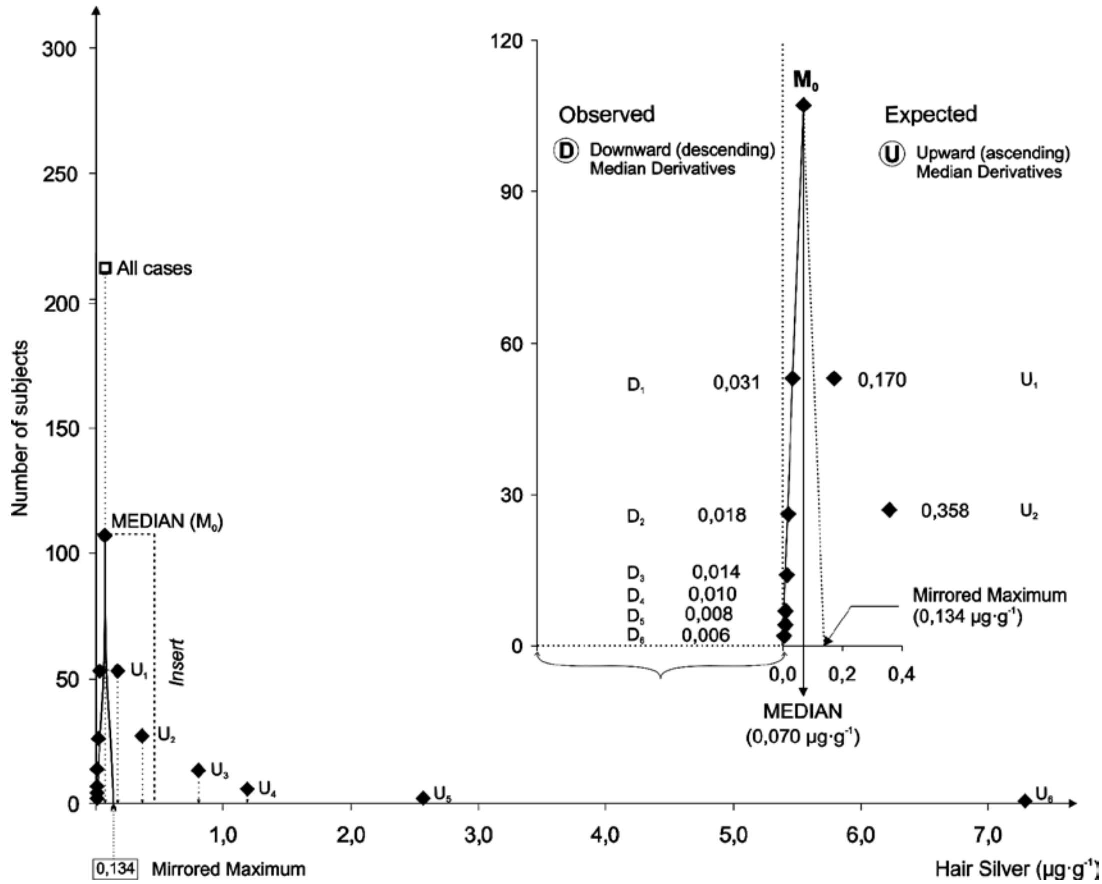

Fig. 4. *«Mirror» image model of the hair silver median derivatives for assessing the tentative level of what would be the «natural» environmental silver exposure today.*
M_0 median, D_1–D_6 downward (descending) median derivatives, U_1–U_6 upward (ascending) median derivatives, ♂ Men, ♀ Women. Observed downward Median Derivatives (M_0 – D_6) $Y = –1698 X + 229.5$ (r^2 = 0.985), Expected upward Median Derivatives (M_0 – U_6) $Y = 1678 X – 7.2$ (r^2 = 0.988)

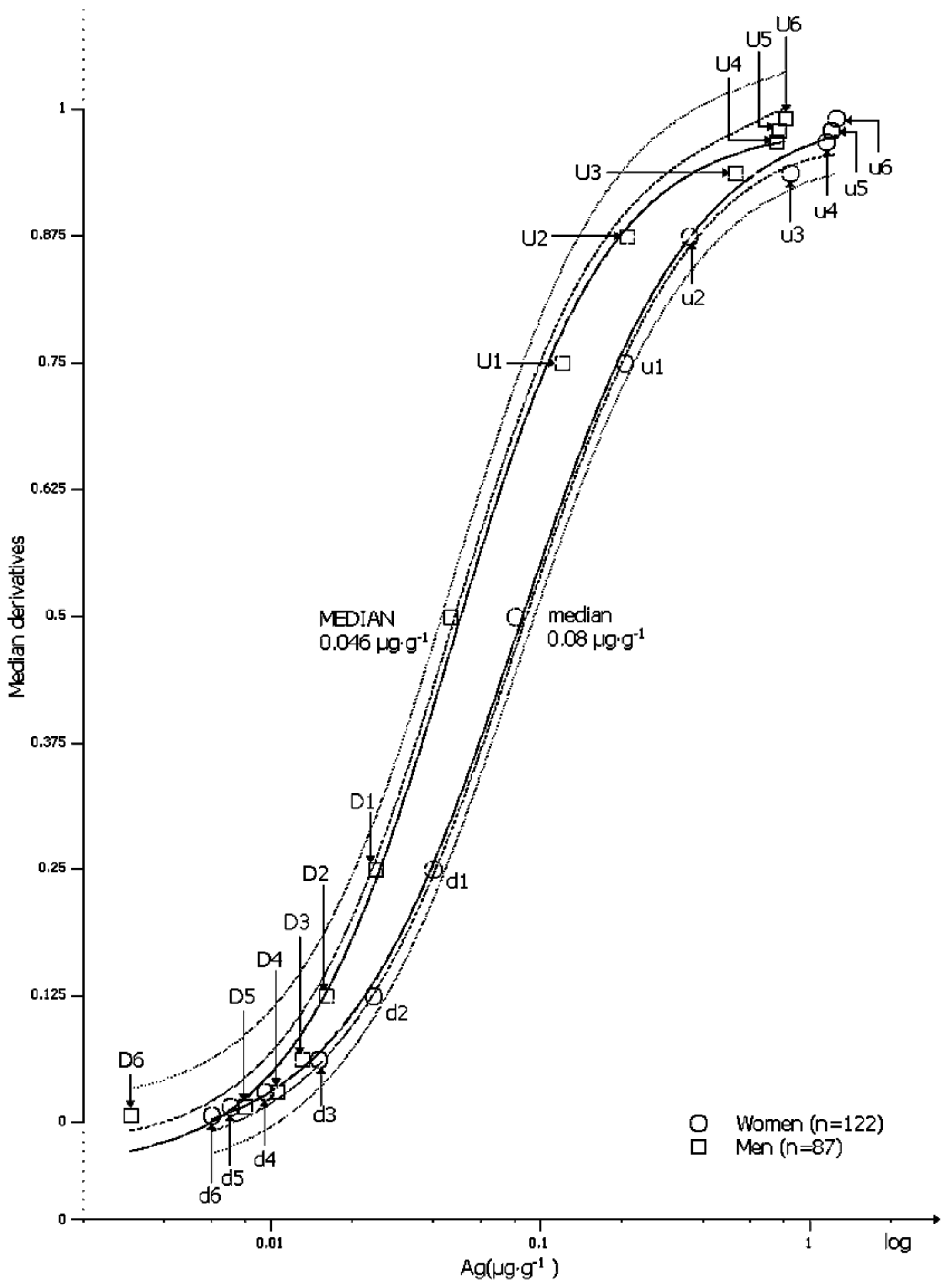

***Figure 5**. The difference between the hair silver median derivatives of Men (□) and Women.(○). D,U Men downward (D) and upward (U) median derivatives, d,u Women downward (d) and upward (u) median derivatives.*

--- Logistic function: $A_2 + (A_1 – A_2)/ 1 + (x/x_0)^p$, - - - 0.95 confidence limit, 0.95 prediction limit.

Men: $Y = 0.983 + (-0.047 – 0.983)/ [1 + (X/0.047)^{1.482}]$.

Women: $Y = 1.001 + (-0.027 – 1.001)/ [1 + (X/0.083)^{1.333}]$

NB. Women No. 209 – 213 (Fig. 1) were excluded from this calculation

The comparative logistic sigmoid curve indicated that the hair silver below 0.010 µg/g and 0.014 µg/g for men and women, respectively, appeared to be toxicologically irrelevant. Being of no observable effective level (NOEL) they may only reflect random silver distribution between the other than hair biochemical compartments of the human body. Above that concentration level hair silver diverges upward, first for men and then for women, and rose rapidly mimicking the parallel type biological assay response pattern, i.e., indicating the physiological saturation mechanism (Harpley et al., 1973). These two distinct parallel saturation curves for men and women would converge to the common sigmoid at the high overexposure plateau starting with 0.210 µg/g and 0.358 µg/g for men and women, respectively. Apparently, men started to accumulate silver in the hair earlier than women, and also reach the saturation point earlier than women. Except for this difference in starting concentrations of hair silver and their concentrations at reaching the saturation point, the rate of accumulation between these two end points appears to be identical regardless of the gender.

DISCUSSION

Our analysis of hair silver concentration median derivatives offers for the new way on how to analyze accurately the samples of a large inherent variability and skewed population distribution. Indeed, the logistic model of the median derivatives presentation allows for the direct visual comparison of populations of different size and of the different slopes among the different elements, respectively.

Thus, this study provided data on current environmental silver exposure, i.e., silver of none occupationally exposed adult population of both sexes in the urban area of Zagreb, the capital city of Croatia. The current level of the population environmental silver exposure, as assessed by analyzing its hair content ($\text{Median}_{n\,=\,213}$ = 0.070 µg/g), appears to be below the environmental silver over exposure level. Indeed, our results indicate that hair silver concentration in non-exposed population up to 0.135 µg/g may be considered harmless by the most conservative first order kinetics Mirror model − 151 subjects (almost three quarters of the tested population) have hair silver concentration within that most conservative safe area. Then, there appears to be a «grey area» between the 0.170 to 0.420 Ag µg/g indicating the increased silver retention and the beginning of the over-exposure. Above that level there is a wide range of silver concentrations (0.420 − 1.330 µg/g) that clearly indicates increased silver exposure, but with no apparent recognizable ill health effects thus far, and what reflects low silver toxicity. Our data indicate that under the condition of presumably oral silver intake, the hair silver concentrations exceeding 1.960 µg/g should be minimally regarded as sub toxic, and those above 4.0 µg/g as definitively neurotoxic. Thus far, we Institute for Medical Research and Occupational Health in Zagreb and at the Center for Biotic Medicine in Moscow, considered that hair silver should not to exceed 0.6 µg/g and 0.8 µg/g, respectively. Now, we think they should be definitively lower, not exceeding about 0.450 µg/g, especially if iodine, selenium, and/or copper are low (Momčilović et al., 2006b).

Indeed, although the hair silver concentration of the most of the tested population was generally low, we were able to identify two cases of overt silver neurotoxicity. These two women (No. 212 and No. 213) having the highest hair silver concentration, showed the clinical neurological signs after consuming silver from the deliberately contaminated food products by another person. The possible neurotoxicity of high doses of silver thus far was «below the radar» of toxicologists and clinicians, although silver is particularly known for its ability to histologically stain the brain neurons (Cajal, 1995). Silver has a strong affinity for the Golgi apparatus that may be found in every cell of the body (Munro, 2011), and such a widespread cellular dispersion of silver may explain its low toxicity. Moreover, adult women have about 20% more fat than men (Shills et al., 1999) what may explain the late onset of silver deposition in the hair of women in comparison with that of men, since their fat metabolic compartment would uptake more silver to get saturated before it became available for hair deposition. On the other hand, since men have less fat but more muscle tissue, more silver would be available to be deposited earlier in the muscle tissue, In other words, the same amount of silver would be more toxic to the lean muscle man than to the obese women.

It is pertinent to note here that there were no correlation between the hair silver and blood silver (data not shown). Since hair reflects a long time unidirectional deposition of silver in the hair, whereas blood silver reflects a short time equilibration period between the various tissues and/or biochemical compartments of the body, any such correlation between the two essentially incommensurable indicator tissue of hair and blood, may be only circumstantial.

ACKNOWLEDGEMENT

This study was supported by the Croatian Ministry of Science, Education and Sport grant No. 292-0222412-2405 (formerly No. 022-0222412-2405). The generous philanthropic support of the RCM, Isle of Man, UK to the first author is greatly appreciated.

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