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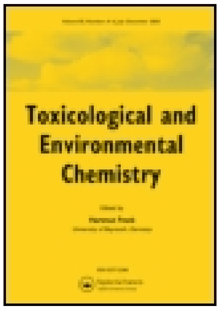

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Environmental Human Silver Exposure

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ENVIRONMENTAL HUMAN SILVER EXPOSURE

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ABSTRACT

Environmental exposure to silver (Ag) was assessed in occupationally non-exposed adult human population by analyzing silver in the hair (H·Ag) and whole blood (WB·Ag). H·Ag was analyzed in 311 (123 men, M; 188 women, W); while WB·Ag was determined in 235 of these individuals (90 M, 145 W). Women had more H·Ag than men (M 0.05 *vs* W 0.076), whereas WB·Ag concentrations in men and women were not significantly different. A natural distribution of the median derivatives was utilized to generate the dataset to fit the logistic sigmoid curve to assess the current human body burden of environmental Ag population exposure for M and W separately. The H·Ag (µg/g^{1}) below 0.0105 for M and 0.0145 for W, reflects low level of environmental Ag exposure. The adaptive physiological saturation phase followed where H·Ag rose rapidly, first for M and then for W in parallel with biological assay. Both parallel saturation curves converged and plateaued at 0.215 for M and 0.965 for W (µg/g^{1}). The current level of human environmental Ag exposure is low, but cases of high Ag exposure occurred sporadically. In conjunction with the medical histories overt clinical neural toxicity may be expected for H·Ag at 4 µg/g^{1}and higher. There were no significant correlation between the H·Ag and WB·Ag.

KEY WORDS. silver, hair, blood, exposure, logistic fit.

INTRODUCTION

Today, silver (Ag) is one of the most used metals in our society that can be found in more than 1000 different applications (S&Q Resource Report 2012). It is a non-essential low-toxic trace element with a potent antibacterial capacity (Emsley 2001). It was claimed that colloidal Ag may serve as an alternative to antibiotics (Undergroundhealthreporter.com 2011) and help treat breast and large bowel carcinoma, respectively (Anonymous 2012). Silver may be toxic at high doses after occupational inhalation exposure, oral ingestion, and mechanical skin irritation (Reilly 2002); in medical terms the condition is known as *argyria* (Tomi et al. 2004). Apparently, Ag has a strong affinity for fat tissue and sulfur containing proteins (Doherty 2004). Today, Ag nanoparticles are extensively used for the study of metabolism (Khan et al. 2011).The widespread use of Ag may increase human environmental exposure and hence body burden. How that may affect human health remains to be elucidated. Recently, Momčilović et al (2006b) reported the increased human hair Ag concentration in subjects suffering from mental depression. The aim of this study was to assess the level of current environmental Ag exposure in occupationally non-exposed adult human population of both genders.

SUBJECTS AND METHODS

This study was approved by the IRES Local Ethical Committee and conducted by strict adherence to the Declaration of Helsinki on Human Subject Research (Brown 2009), and to the complementary Croatian national bylaws and regulations; every subject gave his written consent to participate in the study (Momčilović 2011).

Hair silver (H·Ag) were analyzed in a randomly selected population of 311 adults (123 men and 188 women), who were not occupationally exposed to Ag, most of them living in Zagreb, the capital city of Croatia, and who were concerned about their health. Whole blood silver (WB·Ag) was also analyzed in 235 persons from the same group (90 M, 145 W); the difference in number of hair samples was due to the unfortunate loss because of unforeseen circumstances.

The scalp hair was collected over the easily palpable bony prominence at the back of the head (*protuberantia occipitalis externa),* whole blood was collected by a venous puncture. Both hair and whole blood were analyzed for Ag content with the inductively coupled plasma mass spectrometry (ICP-MS) at the Center for Biotic Medicine, Moscow, Russia (an ISO certified high-tech lab), as already reported by Momčilović et al (2006a). Our detection limit for hair Ag was 0.00006 µg/g^{1}, and the coefficient of variation was 38.1% (Momčilović et al.2009).

The results were expressed as either median or arithmetic mean with standard deviation. The different occurrence of men and women above and below the median was assessed with the Chi square test (Glantz 2005). The difference of $p<0.05$ between the groups was considered to be significant. When there were gender difference between men and women, as assessed by the Chi square test, the frequency distribution of the median derivatives (see Table appendix) for H·Ag concentrations was further scrutinized by fitting the logistic regression analysis function, for men and women separately:

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

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). The Qtiplot – Data Analysis and scientific visualization was used (www.soft.proindependent.com/gbiplot.html).

RESULTS

Silver was detected in all 311 hair samples and its concentration varied over a wide range of 6 orders of magnitude from 0.00006 to 7.350 µg/g^1, with having a median (M_0) hair silver concentration of 0.0695 µg/g^1 for both genders combined. This median (M_0) value was used as a basic unit of concentration on our X axis in Figure.1. The hair Ag concentration covered the range of 9 median concentrations (M – 9 M), i.e., 0.0695 to 0.6290 µg/g^1, and what may be described with the exponential curve $Y = 209\ X^{-2.14}$ (Fig.1) having a high correlation coefficient ($r^2 = 0.94$). Extending the abscise scale (X) beyond the 9 M would only decrease the value of the correlation coefficient. Hence, H·Ag concentrations of up to 0.629 µg/g^1 may be considered to reflect a compensated physiological adaptive response. Indeed, all Ag concentrations above that range were outliers (see the box-plot insert to Figure.1). Apparently, the range between 10 M-70 M may be viewed as transitional zone of gradually increasing overexposure, whereas concentrations above 71 M (>4.67 µg/g^1) we regarded as definitively toxic.

Indeed, the medical history and clinical records of the 5 subjects with the highest hair Ag concentration were thoroughly re-examined. Two of these subjects showed no recognized signs of Ag poisoning, i.e., the subject No.307 was adversely exposed to Ag by compulsive jewelry licking habit and a chronic anemia, and subject (No.308) has occupational contact exposure to Ag and other prosthetic dental alloy metal material (she had surgery for hyperparathyreoidism). However, the three subjects with the highest

H·Ag demonstrated overt clinical symptoms of intoxication. Thus, subject (No. 309) was diagnosed as having a peripheral neuropathy and metal poisoning was already suspected on clinical grounds; later it was revealed that she consumed food stored in Ag utensils. Subject (No.310), a worker in a printing office, was alcoholic until 6 month before he attempted suicide (depression), and subject (No.311) was admitted to hospital due to the acute abdominal emergency (colic). After the H·Ag analysis became available she was found to have ingested homemade sausages stuffed with the high Ag containing polish. She also had some symptoms of *lucor metallicum* (metal madness). All three were clinically hospitalized for the neurological and/or psychiatric problems of then unknown origin; nobody thought of them being poisoned with Ag.

Of 9 subjects having the highest H·Ag, all were women except subject No.310 (Figure.1). When one compared H·Ag concentration of men and women of either being above or below the common median, then it emerged that women had more Ag in hair than men ($p<0.01$, Chi square test) (Table 1). Indeed, the hair Ag median for men and women were 0.05 and 0.0769 μg/g^1, respectively, the comparative downward and upward median derivatives are shown in Table 2 for men and women separately. However, there were no gender differences in WB·Ag. As a matter of fact WB·Ag was below our detection limit for silver of 0.00006 μg/g^1 in about 60% of analyzed samples (Table 3). Moreover, regression analysis showed that there were no correlation between the H·Ag *vs* WB·Ag of matched pairs; $Y = 0.010 X + 0.004$, $R^2 = 0.016$ (Figure.2)

Because of the observed gender differences, the frequency distribution of the median derivatives for H·Ag concentrations was further scrutinized by fitting the logistic regression analysis function, for men and women separately (Figure.3). Data to fit the equation are shown in Table 3.The H·Ag below 0.0105 and 0.0145 $\mu g/g^1$ for M and for W, respectively, reflects low level of environmental Ag exposure. The adaptive physiological saturation phase followed where H·Ag rose rapidly, first for M and then for W in agreement with biological assay. Both parallel saturation curves would converge and plateau at 0.215 $\mu g/g^1$ for M (U_2) and 0.965 $\mu g/g^1$for W (u_1). Indeed, between these end points at the beginning and at the plateau, there were two distinct phase shifts saturation slopes for men and women, respectively. Men started to accumulate Ag in hair earlier than women, and also reach saturation point earlier than women. The comparative logistic sigmoid curve, for men and women separately, showed that, apparently, there were no men to women differences after D_3 and d_3 below the median (M_0), and again above the U_2 for men and u_2 for women above the median, respectively

DISCUSSION

Hair element analysis has its strong advocates and opponents, but hair has a great advantage since it can be obtained in a noninvasive way (Cutler 2004; Wilson 2010). Hair is itself a dynamic tissue structure – some hair follicles are active (anagen phase), some are dormant (telogen phase), and some degenerate only to rise anew some other time (Hordinsky 2003). Our studies showed that hair element analysis is a reliable procedure (Momčilović et al. 2009), and particularly useful to yield an overview of metabolic activities of the body (Momčilović et al. 2010). Indeed, the rate of division of human hair follicle cells is second only to the bone marrow cell, which reflects accurately the metabolic changes within the body (Hordinsky 2003).

This study provided data on current environmental Ag exposure of occupationally exposed adult population of both genders in the urban area of Zagreb, the capital city of

Croatia. The current level of the population environmental Ag exposure, as assessed by analyzing its hair content (Median, $M_{0,\ n = 311} = 0.0695$ µg/g^{1}), appears to be below the environmental Ag toxicity level. Apparently, the concentrations of up to about 9M (0.63 µg/g^{1}) H·Ag may be considered as normal and is in agreement with our previous results (Momčilović et al. 2006b). Above that concentration there appears to be a large "transitional" area between the 0.6 and 4 Ag µg/g^{1} indicating increased Ag retention and over-exposure but with no apparent adverse health effects. Our data indicate that hair Ag concentrations exceeding 4 µg/g^{1} should be regarded as toxic since high doses of Ag may induce clinical neurological and/or psychiatric problems.

Indeed, although the hair Ag concentration of the most of the studied population was generally low, it was possible to identify three cases of overt Ag toxicity. These two women and one man having the highest hair Ag concentration showed clinical neurological and/or psychiatric signs after oral ingestion of Ag contaminated food products. The possible neurotoxicity of high doses of Ag thus far was below the threshold of toxicologists and clinicians, although Ag is particularly known for its attraction to the brain cells as a histological stain for the brain neurons (Cajal and Ramon, 1995). Silver has a strong affinity for the Golgi apparatus of every cell of the body (Munro 2011); such a widespread cellular dispersion of Ag may explain its low toxicity. Silver also has affinity for fat tissue (Doherty 2004), and adult women have about 20% more fat than men (Heymsfield and Baumgartner, 1999). That may explain the delayed onset of Ag deposition in the hair of women in comparison with men, since their fat metabolic compartment would take up more Ag to get saturated before it became available for hair deposition via the hair follicles. In other words, the same amount of Ag would be more toxic to a lean muscle man than to an obese woman.

It is pertinent to note here that there was no correlation between hair and blood Ag. Indeed, hair reflects a prolonged unidirectional deposition of Ag, whereas blood Ag reflects a short time equilibration period between the various tissues and/or biochemical compartments of the body. Thus, any such correlation between hair and blood may be only circumstantial. Our samples were collected from the occupationally non-exposed random population of subjects of presumably various environmental Ag exposures. It is possible if hair and whole blood were sampled at the same time intervals relevant to the onset of the exposure, some correlation between the hair and whole blood Ag may occur.

Silver overexposure may have produced low-intensity adverse effects on various metabolic parameters by affecting other elements. Thus, Ag decreases selenium absorption from the gastrointestinal tract (Jensen 1975) and precipitate lesions of selenium-vitamin E deficiency (Van Vleet 1976). Selenium deficiency increases the genesis of spontaneous mammary tumors (Schrauzer and Ishmael 1974) and thyroid gland malfunction (Arthur et al 1991).

CONCLUSIONS

Hair is the reliable biological material for Ag analysis whereas whole blood Ag was approximately 60% of time below the detection limit. Women accumulate more Ag in hair than men owing to their different body composition. The method of median derivatives brought to the light gender difference in Ag metabolism. There was no correlation between hair and whole blood Ag. Silver toxicity is sporadic under the current environmental Ag exposure.

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This study was approved by the Institute for Research and Development of Sustainable Eco Systems Ethical Committee. No study in this country is possible before the permission of the Croatian Ministry of Science, Education and Sport is granted. Such permission is considered for funding only if it has been approved by the relevant Ethical Committee.

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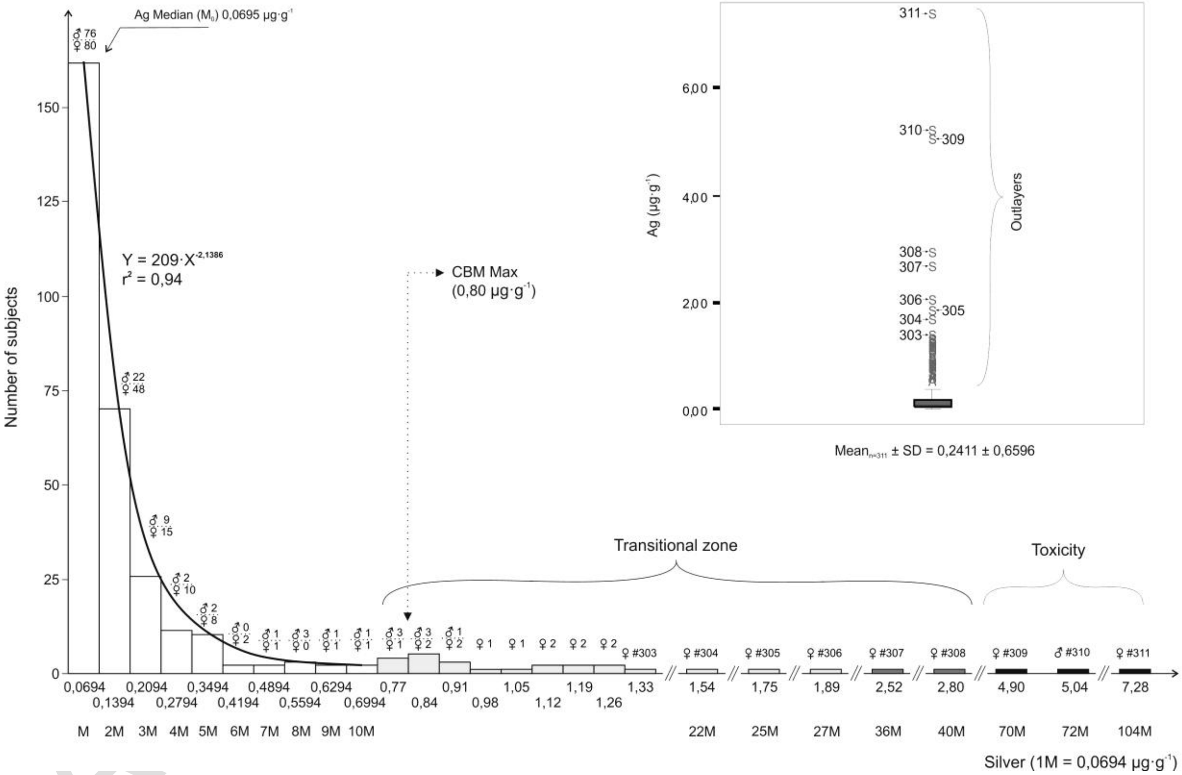
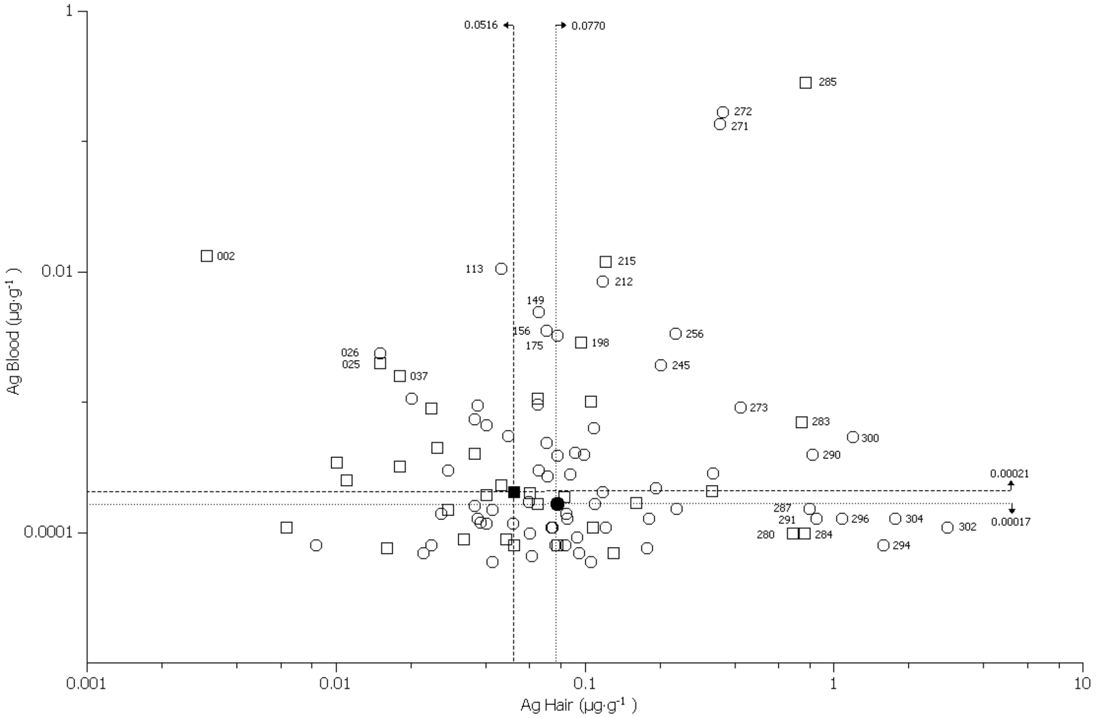
Figure 1. The hair silver concentration frequency distribution.



Median (M) = 0.070 μg ·g^{-1} Ag). ♂ Men, ♀ Women. ▬ $Y_{M\text{-}9M} = 209\ X^{-2.14}$, $r^2 = 0.94$. Insert: Box and whisker plot Mean ± SD, subjects (n = 311) are numbered sequentially depending upon the increasing hair silver concentration.

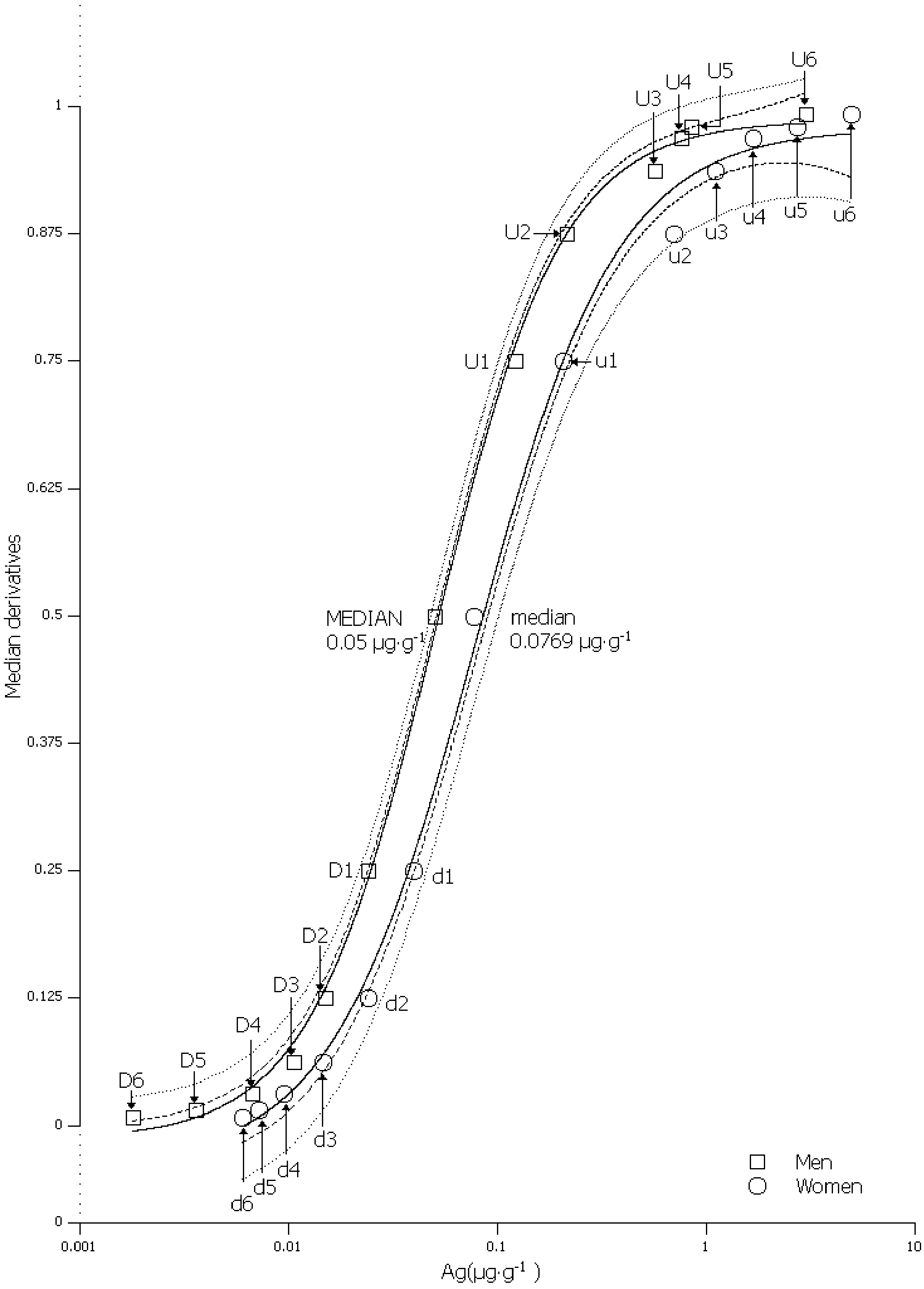
Figure 2. The relationship between the hair silver (H·Ag) and whole blood silver (WB·Ag).



□ Men (n = 34), ○ Women (n = 65), ■ Men median WB·Ag = 0.00021 µg·g^{-1}, H·Ag = 0.0500 ● Women median WB·Ag = 0.00017µg ·g^{-1}, H·Ag = 0.0769 µg·g^{-1}

Numbers denote the subjects in the study.

Figure 3. The difference between the hair silver median derivatives of Men (□) and Women.(○).


Median derivatives
Ag(μg·g^{-1})
0
0.125
0.25
0.375
0.5
0.625
0.75
0.875
1
0.001
0.01
0.1
1
10
MEDIAN
0.05 μg·g^{-1}
median
0.0769 μg·g^{-1}
U1
U2
U3
U4
U5
U6
u1
u2
u3
u4
u5
u6
D1
D2
D3
D4
D5
D6
d1
d2
d3
d4
d5
d6
□ Men
○ Women

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

Men: $0.986 + [(-0.014 - 0.986) / 1 + (x / 0.050^{1.437}]$

Women: $0.979 + [(-0.039 - 0.979) / 1 + (x / 0.078^{1.272}]$

See Table 3. for input values.

Table 1. Gender difference in hair silver (H·Ag, n=311)

	Men (n=123)	Women (n=188)
Above the median[a]	47	108
Below the median[b]	76	80

Median ($M_0 = 0.0695$ μg ·g^{-1} Ag)[a,b]. Women hair has more silver than men ($p < 0.05$ Chi square test).

Table 2. The whole blood silver (WB·Ag)[a]

Gender	No. analyzed	Below detection	Ag detected	Median (detected)
Men	90	56	34	0.00021
Women	145	80	65	0.00017
All	235	136	99	0.00019

[a]There were no gender difference ($p > 0.10$)

Table 3. Hair silver median derivative concentrations (MDC) for Men (D_1-D_6 descending MDC, U_1-U_6 asscending MDC) and Women (d_1-d_6 descending MDC, u_1-u_6 ascending MDC).

MEN Median (M_0)$_{n\ 123}$ = 0,0500 µg·g^{-1}Ag)						WOMEN Median (M_0)$_{n\ 188}$ = 0,0769 µg·g^{-1}Ag)					
MDC	n	Ag	MDC	n	Ag	MDC	n	Ag	MDC	n	Ag
D_1	62	0.0240	U_1	62	0.1209	d_1	94	0.0395	u_1	94	0.2070
D_2	31	0.0150	U_2	31	0.2150	d_2	47	0.0240	u_2	47	0.9650
D_3	16	0.0105	U_3	16	0.5650	d_3	24	0.0145	u_3	24	1.0980
D_4	8	0.0067	U_4	8	0.7625	d_4	12	0.0095	u_4	12	1.6650
D_5	4	0.0036	U_5	4	0.8453	d_5	6	0.0072	u_5	6	2.7085
D_6	2	0.0018	U_6	2	2.9880	d_6	3	0.0060	u_6	3	4.9390

Common Median (M_0)$_{n\ 313}$ = 0.0695 µg·g^{-1} Ag, Capital letters ($D_{1\text{-}6}$, $U_{1\text{-}6}$) Men, Small letters ($d_{1\text{-}6}$, $u_{1\text{-}6}$) Women.

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

Median ($M_{0,\ n=311}$ = 0.0695 µg·g^{-1})

<-->◘<-->

Median Derivative Downward (Descending) Median Derivative Upward (Ascending)

Branch ($D_{0,\ n\ =\ 155}$ = PS 0.500) Branch ($U_{0,\ n\ =\ 155}$ = PS 0.500)

Descending Median Derivatives Ascending Median Derivatives

D_1 $D_0/2$ 0.250 U_1 $D_0 + A_0/2$

0.750

<-------------------------◘---------------------> <-----------------------◘------------------------->

D_2 $D_0/4$ 0.125 U_2 $D_0 + A_0/4$

0.875

<-------------◘-----------> <----------◘------------->

D_3 $D_0/8$ 0.062 U_3 $D_0 + A_0/8$

0.937

<------◘------> <------◘------>

D_4 $D_0/16$ 0.031 U_4 $D_0 + A_0/16$

0.969

<--◘--> <--◘-->

D_5 $D_0/32$ 0.016 U_5 $D_0 + A_0/32$

0.983

<◘> <◘>

D_6 $D_0/64$ 0.008 U_6 $D_0 + A_0/64$

0.992

◘ ◘

We studied the frequency distribution of hair silver (H•Ag) 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 in the same “median of median” way into a series of sequential median derivatives ($U_{0,1,2,3\ \ldots n-1,\ n}$ and $D_{0,1,2,3\ldots n-1,\ nn}$) For every median derivative of the population, the actual hair silver 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 (Smylevich and Dougherty 2010).