Human Hair as a Long Term Biological Indicator for Assessing Strontium Nutritional Status

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ABSTRACT

Strontium (Sr) is a bone seeking trace element that closely parallels calcium metabolism. At the present, there is no available long-term biological indicator for assessing the human Sr nutritional status. In this article, we have presented a novel concept on how to assess the human strontium nutritional status by studying its frequency distribution in the hair and whole blood. In this prospective, observational, cross-sectional, and exploratory epidemiological study, we analyzed hair Sr (^{Sr}H) in 311 apparently healthy adult Croatians (123 men, 188 women); among them, whole blood strontium (^{Sr}WB) was detected in 142 women and 89 men.

Hair and WB samples were analyzed for strontium by the inductively coupled mass plasma spectrometry (ICP MS). The natural frequency distribution of hair strontium obeyed the power law so that the data were analyzed by fitting the logistic bioassay sigmoid curve (ogive) of the median derivatives.

Women have accumulated more ^{Sr}H than men (median men 0.867 µg·g^{-1} vs. median women 3.120 µg·g^{-1}). The normal physiological response range covered by the linear part of the sigmoid curve was 0.418 - 2.950 µg·g^{-1} for men and 0.846 - 7.260 µg·g^{-1} for women. Values below that linear range were considered to denote low Sr nutritional status, whereas values above that range would indicate excessive dietary strontium exposure. The long term biological indicator of hair strontium (^{Sr}H) is incommensurable with that of the short term biological indicator of the whole blood strontium (^{Sr}WB). On the average, women have about three times more strontium in their hair than men, regardless of the age. Analysis of the hair strontium frequency distribution is a valuable long term biological indicator in assessing the population strontium nutritional status.

KEYWORDS

Strontium Nutritional Status; Hair; Long Term Biological Indicator; Women; Men; Age.

INTRODUCTION

Strontium is an osteotrophic (bone-seeking) trace element that is normally present in our diet and our bodies [1]. The pioneers of trace element analysis considered strontium to be an essential trace element for humans , but the conclusive evidence on strontium essentiality for humans has yet to be pro-vided [2, 3]. Strontium was in the limelight in the 50's and 60's of the last century when it was discovered that the metabolism of strontium was closely related to the metabolism of calcium in bone tissue [4]. Indeed, 99% of typical body burden of 320 mg Sr is found in the bone [5]. The atmospheric fallout of fission products after nuclear testing included a long-living bone seeker of ^{90}Sr which has a physical half-life of ~ 27 y and

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a biological T/2 ~ 10 y [6]. Radioactive ^{90}Sr is a powerful beta radiation source and, when lodged in the bones, would act as a strong radio-toxic carcinogen [7]. Moreover, strontium, like calcium, could be transferred from mother to fetus/newborn via the mother's milk and get deposed in their mineralized tissue with possibly deleterious consequences [8, 9]. Later on, the interest in strontium was renewed when Skoryna demonstrated the pharmacological effect of both the stable and ^{89}Sr radiopharmaceutical isotope Metasteron® to alleviate the pain of mammary and prostate carcinoma bone metastases [10, 11]. Today, the most recent research has shown that strontium ranelate [Protelos®, Osseor®] acts as an effective nutritive agent, capable of slowing down mineral bone loss due to old age. Indeed, these strontium compounds are preventing and delaying the onset and progression of osteoporosis, including both femur and vertebral osteoporosis [12-18]. How much such a treatment can affect the strontium body burden and the metabolism of other trace elements in the skeleton remains to be elucidated. Since strontium is not as yet recognized to be an essential trace element, there are no recommended dietary allowances (RDA's) for strontium, and there is also no available long term biological indicator tissue for assessing the strontium nutritional status of the body; the US Environmental Protection Agency has derived an oral recommended dose for strontium of 0.6 mg per kg body weight per day [19].

Today, hair trace element analysis is accepted as a long-term biological indicator for assessing trace element nutritional status and the level of their environmental exposure [20-23]. The aim of this study was to demonstrate how strontium hair analysis (^{Sr}H) may serve as a long term biological indicator tissue for assessing the strontium nutritional status of the human body by analyzing hair strontium frequency distribution properties with a median derivative method. Thus far, we have shown that our innovative approach yielded a reliable assessment of the nutritional status of the essential trace elements iodine and selenium, and in evaluating the exposure to the non-essential elements of silver and aluminium [24-27]. The observed data on hair strontium analysis were compared with that for whole blood strontium (SrWB), i.e., a common short term biological indicator tissue for the assessment of numerous bioelements and other different clinical parameters.

SUBJECTS AND METHODS

This prospective, observational, cross-sectional, and exploratory epidemiological study was approved by the Ethical Committee of the Institute for Research and Development of the Sustainable Eco Systems (IRES), Zagreb, Croatia. The study was conducted in strict adherence to the Declaration of Helsinki

on Human Subject Research and to the complementary Croatian national bylaws and regulations [28]. 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) [29]. Data on hair shampooing were also recorded to control for the possible external strontium contamination, a highly unlikely event in general Croatian population.

Hair strontium (^{Sr}H) was analyzed in a random sample of 311 apparently healthy adults (123 Men, 188 Women), the median age of women and men was 47 and 50 years, respectively. Our population consisted of subjects from the general Croatian population who were concerned about their health status; the majority of them were living in Zagreb, the capital region of Croatia. All the subjects were fed their usual home prepared, mixed mid-European diet and reported no adverse medical conditions. None of our subjects was occupationally or otherwise exposed to some strontium source.

Hair strontium and whole blood strontium was analyzed with the ICP MS (Elan 9000, Perkin Elmer, USA) at the Center for Biotic Medicine (CBM). Moscow, Russia, The CBM is an ISO Europe certified commercial laboratory for analysing bioelements (macro elements, trace elemnts, and ultratrace elements) in different biological matrices [30].

HAIR STRONTIUM (^{Sr}H) ANALYSIS

In brief, hair analysis was performed following the International Atomic Energy Agency recommendations and other validated analytical methods and procedures [31, 32]. A strand of hair 5-7 cm long and weighting less than one gram would be cut with titanium-coated scissors over the anatomically well-defined bone bump at the back of the head (lat. protubarantia occipitalis externa). The individual hair samples were further minced into strands less than 1 cm long prior to chemical analysis, stirred 10 min in an ethylether/acetone (3:1, w/w), rinsed three times with redistilled H_2O, dried at 85°C for one hour to constant weight, immersed one hour in 5% EDTA, rinsed again in 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. We used certified GBW0910b Human Hair Reference Material (Shanghai Institute for Nuclear Research, Academia Sinica, Shanghai 201849, China.

WHOLE BLOOD STRONTIUM (^{Sr}H) ANALYSIS

Whole blood was drawn by vein puncture at the cubital vein. and collected into the green-cup Vacuette collecting tubes (#454082 LotA13030M7m Greineer Bio On International AG, Kremsmunster, Austria), which were randomly assigned for

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the ICP-MS analysis. Whole blood samples of 0.5 ml were digested in a microwave oven with 0.1 ml of HNO_3 at 175°C. Blood standards were liophylised Seronorm TM Trace Elements Whole Blood Reference Standards Level 1 (OK 0036), Level 2 (MR 9067), and Level 3 (Ok 0337) for strontium 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 vials, 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_2 added.

The detection limits for Sr in the hair and whole blood were 0.0009 and 0.00009 $\mu g \cdot g^{-1}$, respectively; strontium was detected in all the 311 hair samples and in all the 212 whole blood samples. All chemicals were proanalysis grade (Khimmed Sintez, Moscow, Russia). Current CBM admissible hair and whole blood strontium ranges ($\mu g \cdot g^{-1}$) are set 0.00 – 6.0 for both men and women, respectively. Values above that range are considered to indicate excessive strontium intake. Strontium belongs to the plead of 143 elements sharing the same mass number (number of isotopes/element): 3 As, 9 Se, 12 Br, 14 Kr, 20 Rb, 18 Sr, 21 Y, 12 Zr, 14 Nb, 8 Mo, 7 Tc, 5 Ru, e.g. there are three arsenic isotopes sharing the same mass number with some 18 strontium isotopes, etc. [33].

MEDIAN DERIVATIVES

To scrutinize the hair strontium 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 1) [25, 34]:

$$A2 + (A1 - A2)/[1+(x/x0)^p]$$

Where A1 is the initial value (lower horizontal asymptote, A2 is final value (upper horizontal asymptote), x0 is center (point of inflection, in our case it is the median $M_{0 \, detected}$, p is power (the parameter that affects the slope of the area about the inflection point) (Appendix 1). The Qtiplot Data Analysis and Scientific Visualisation programs were used for this analysis (www.softproindependent.com/qtiplot.html). The samples below the detection limits were not excluded from the analysis but were treated as having zero strontium concentration.

RESULTS

Strontium was detected in all 311 of analyzed hair samples (188 women and 123 men) whereas ^{Sr}WB was detected in all 231 analyzed samples (142 women and 89 men). After the data were log transformed, the previous skewed and kurtous

strontium data distribution was changed into standard Gaussian frequency distribution curve for both the hair (Figure 1a.) and whole blood (Figure 1b). Apparently, women accumulate and retain three time more strontium in their hair than men. The respective ^{Sr}H medians were for ♂ = 0.867 and for ♀ = 3.120 $\mu g \cdot g^{-1}$. There were no statistically significant differences between men and women in ^{Sr}WB.
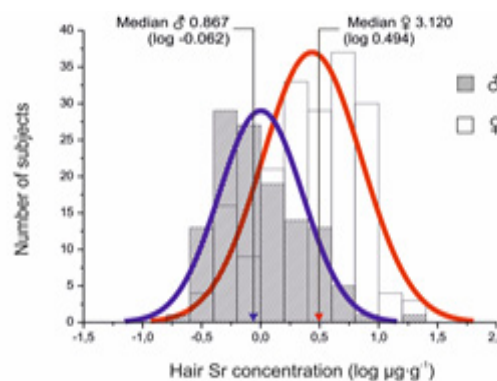

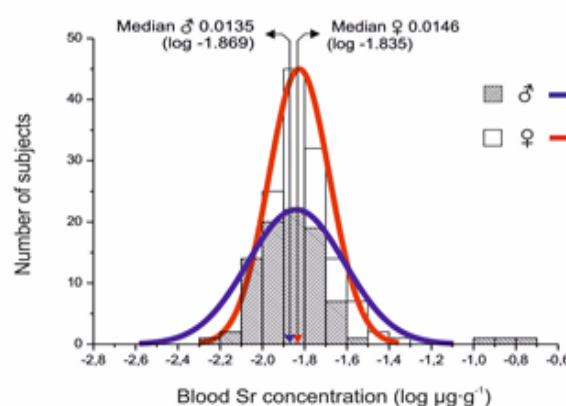**Figure 1a:** Normal hair strontium frequency distribution in 123 men (blue) and 188 women (red) (log $\mu g \cdot g$-1).

Figure 1b: Normal whole blood strontium frequency distribution in 89 men (blue) and 142 women (red) (log $\mu g \cdot g$-1).

Median derivatives (Appendix 2) were used to fit the power function sigmoid curve and they are shown in Appendix 2 (Figure 2a Hair, Figure 2b Whole Blood). The data on the upward and downward arm of the median derivatives are shown separately for men in blue and women in red. Following the principles of bioassay analysis, we have defined the hair linear segments (downward and upward): ♀$_{d2-u2}$ and ♂$_{D1-U1}$ as strontium physiologically normal range [30]. Normal hair Sr concentrations of Croatian women range from 0.85-7.26 $\mu g \cdot g^{-1}$ (median 3.12 $\mu g \cdot g^{-1}$), and that for Croatian men range from 0.42-2.95 $\mu g \cdot g^{-1}$ (median 0.867 $\mu g \cdot g^{-1}$). The respective low linear region of the sigmoid power function curve, i.e., the segments d2-d6 for women and D1-D6 for men, was defined as a low Sr nutritional status range.
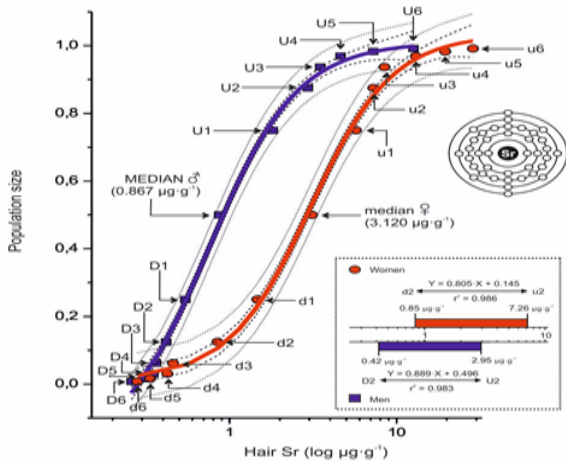
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Figure 2a: The power function sigmoid curve of hair strontium median derivatives. The difference between the ^{Sr}H median derivatives of men n = 123 (blue) and women n = 188 (red). D, U men downward (D) and upward (U) median derivatives; d, u women downward (d) and upward (u) median derivatives.

Logistic function $Y = A2 + (A1-A2)/(1 + (X/X0)^p)$, - - - 0.95 confidence limit, ••• 0.95 prediction limit.

Men: $Y = 1.010 + (-0.207 - 1.010)/(1 + (X/0.754)^{1.644})$, $r^2 = 0.997$;

Women: $Y = 1.033 + (0.010 - 1.033)/(1 + (X/3.045)^{1.773})$, $r^2 = 0.996$.

Box: Strontium linear saturation range for ♂ and ♀ (log conc.). See Appendix 1 for the model and Appendix 2 for median derivatives input values.
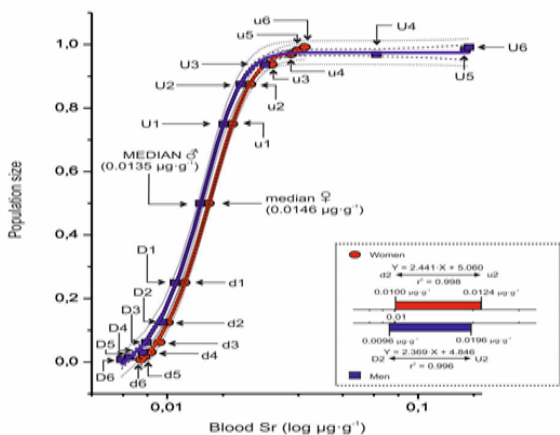

Figure 2b: The power function sigmoid curve of whole blood strontium median derivatives. The difference between the ^{Sr}WB median derivatives of men n=89 (blue) and women n=142 (red).

D, U men downward (D) and upward (U) median derivatives; d, u women downward (d) and upward (u) median derivatives. — Logistic function $Y = A2 + (A1-A2)/(1 + (X/X0)p)$, - - - 0.95 confidence limit, ••• 0.95 prediction limit.

Men: $Y = 0.976 + (-0.008 - 0.976)/(1 + (X/0.013)^{5.514})$, $r^2 = 0.999$;

Women: $Y = 1.000 + (-0.053 - 1.000)/(1 + (X/0.014)^{4.742})$, $r^2 = 0.999$.

Box: Strontium linear saturation range for ♂ and ♀ (log conc). See Appendix 1 for the model and Appendix 2 for median derivatives input values.

Similarly, the respective upper linear region of the sigmoid power function curve above the respective segments u3 for women (range u3-u6) and segment U2 for men (range U2-U6), was defined as an excessively high ^{Sr}H region. Evidently, women retain more strontium than men. There was no correlation between the ^{Sr}H and ^{Sr}WB (Figure 3) and there was no effect of age upon the observed gender difference of ^{Sr}H (Figure 4). Indeed, all the data shown in the Figure's 2a, 3, and 4 demonstrated the higher accumulation of strontium in the hair of women than that of men.
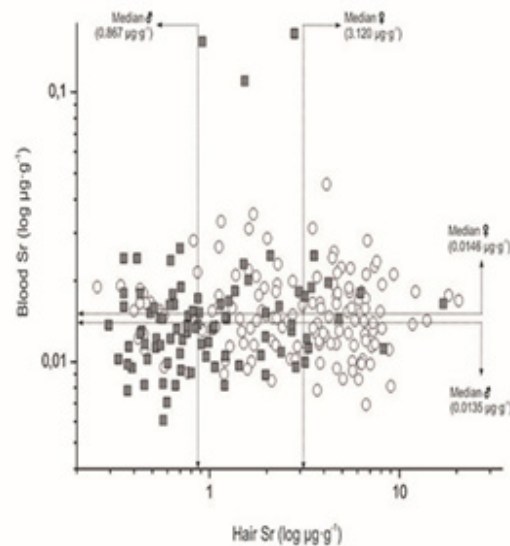

Figure 3: Incommensurability of the hair strontium (long term biological indicator) and whole blood strontium (short term biological indicator). ▢ Women ▢ men
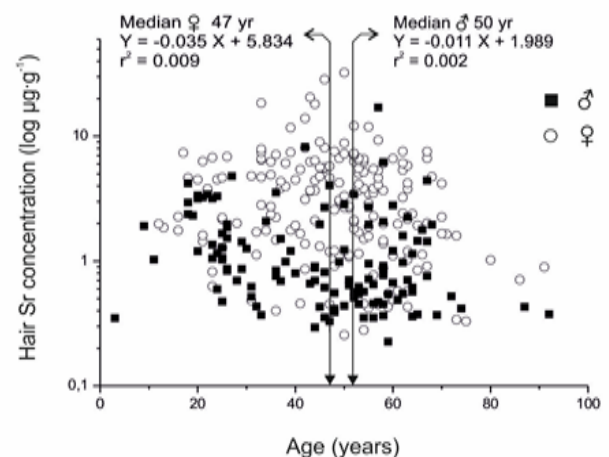
Figure 4: Age does not affect the gender dependent difference in strontium distribution in men and women.

▢ Women ▢ men

DISCUSSION

Our results on hair and whole blood strontium in the linear (adequate, physiological) data range are in good agreement with those obtained by Goulle et al. [35, 36] and Wolowiec et al. [23]. They are considerably lower than that reported by Caroli et al. [20] who, however, have referred on arithmetic means of the highly skewed data distribution (N.B.: The data would be comparable if we did the analysis in such a way).

This study has demonstrated that the strontium nutritional status may be assessed by hair strontium analysis and that hair strontium deposition is distinctly different between men and women, i.e., women tend to accumulate more strontium in their hair than men. It is pertinent to note here that the major osteotrophic elements, i.e., calcium and magnesium, followed the same gender dependent power Law pattern of hair deposition [37]. All the three elements, i.e., calcium, magnesium, and strontium belong to the same 2a column of the Periodic system of elements [38, 39], and they all were substantially higher in the hair of women than that of men. Presumably, the sex dependent hormonal status difference affects strontium hair follicule deposition, their metabolic turnover, throughout and bio mineralization [40]. The

sex dependent preference of Ca, Mg, and Sr deposition observed by these researchers, combined with the identical sporadic observations by other researchers for the respective hair Ca, Mg, and Sr, strongly supports Sr status as an essential bioelement, or at the least, a conditionally essential bioelement where essentiality will depend upon the given inter-relational circumstances[41- 43].

It should be noted that, in difference to the dietary intake data, hair strontium, as well as other trace elements, reflect the individual (personalized) absorption. Indeed, it is well known that different persons may absorb different amounts of trace elements from the same dietary source due to their individual biological variability [20]. We should be aware that one cm of human hair is a reliable metabolic time log that reflects strontium over a period of an entire month [44, 45]. To assess the nutritional status of strontium, by comparing the short term biological indicator of ^{Sr}WB with the long term biological indicator of ^{Sr}H, revealed that these two bioindicators are incommensurabile. Indeed, there is an irrevocable difference in the time base between the short term (^{Sr}WB) and long term (^{Sr}H) bioindicators; the absorbed strontium will be equilibrated between the blood and various body compartments within a period of days, whereas strontium would be uni directionally and irreversibly deposited in the hair [46]. If, for a moment, we put aside a fundamental difference between the equilibration process of ^{Sr}WB with the surrounding tissues and that of the irreversible unidirectional growth of ^{Sr}H, a simple calculation would show that one cm of hair is time-equivalent of a thirty days of cumulative urine collection, i.e., 30 liters of urine. N.B.: Urine is another short term biological indicator like the ^{Sr}WB, which is thus far preferentially used in trace element nutritional studies.

What we are saying in this study is not how much strontium needs to be in the diet, but how much strontium should be found in the hair to claim that strontium nutritional status is adequate for a certain individual subject. Indeed, by using ^{Sr}H median derivatives frequency distribution analysis, we can, for the first time, accurately assess the individual strontium nutritional status and even differentiate the degree of how much is adequate (linear/physiological range of the ogive). Since hair is an easily available biological material that can be collected in a non-invasive way and that hair is easily transported and stored preceding the analysis in some well-equipped analytical laboratory, nutritionists and clinicians have a powerful new tool for assessing strontium and other trace element status in health and disease.

More studies like this, by different researchers and for different elements, are needed before the hair multi-element profile analysis could find its right place in personalized medicine and in public health nutrition in particular.

Strontium was the secret ingredient of the Roman gladiators' potion used to promote bone fracture healing [47].

N.B.: Our short vignette about secret gladiators' potion for promoting bone healing is intriguing since strontium was discovered in 1787, some 15-17 centuries AFTER it was knowingly used by the Roman gladiators [48]. Ancient knowledge lost and rediscovered?

ACKNOWLEDGMENTS

Appendix 1. The hair strontium median derivatives model (Population Size, PS = 1.000)

$$\text{Median } (M_{0,n=312} \; \mu g \cdot g^{-1})$$

<--->•<--->

Median Derivative Downward (Descending)	Median Derivative Upward (Ascending)
Branch ($D_{0,n=156}$ = PS/2 = 0.500)	Branch ($U_{0,n=156}$ = 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 $U_2 = U_1 + U_0/4$ 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 $U_5 = U_4 + U_0/32$ 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 strontium (^{H}Sr) median and its derivatives to assess the strontium nutritional status. First we assess the median (M0) hair strontium 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 M0 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 strontium 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 [49, 50].

Appendix 2: Median derivatives to fit the power function sigmoid (see Appendix). Hair Median Derivative Concentrations (MDC).

HAIR STRONTIUM

Men (n = 123)						Women (n = 188)					
Median (M_0) = 0.867 µg·g⁻¹ Sr						Median (M_0) = 3.120 µg·g⁻¹ Sr					
MDC	n	Sr	MDC	n	Sr	MDC	n	Sr	MDC	n	Sr
D1	62	0.544	U1	62	1.820	d1	94	1.467	u1	94	5.710
D2	31	0.418	U2	31	2.950	d2	47	0.846	u2	47	7.260
D3	16	0.363	U3	16	3.489	d3	24	0.459	u3	24	8.457
D4	8	0.351	U4	8	4.611	d4	12	0.425	u4	12	13.030
D5	4	0.312	U5	4	7.233	d5	6	0.335	u5	6	19.515
D6	2	0.260	U6	2	12.621	d6	3	0.281	u6	3	28.610

WHOLE BLOOD STRONTIUM

Men (n = 89)						Women (n = 142)					
Median (M_0) = 0.0146 µg·g⁻¹ Sr						Median (M_0) = 0.0135 µg·g⁻¹ Sr					
MDC	n	Sr	MDC	n	Sr	MDC	n	Sr	MDC	n	Sr
D1	45	0.0107	U1	45	0.0168	d1	71	0.0117	u1	71	0.0182
D2	23	0.0096	U2	23	0.0164	d2	36	0.0101	u2	36	0.0214
D3	12	0.0083	U3	12	0.0245	d3	18	0.0093	u3	18	0.0261
D4	6	0.0080	U4	6	0.0682	d4	9	0.0086	u4	9	0.0311
D5	3	0.0071	U5	3	0.1540	d5	5	0.0081	u5	5	0.0332
D6	2	0.0066	U6	2	0.1595	d6	3	0.0079	u6	3	0.0353

Capital letters (D1 – D6, U1 – U6) men, small letters (d1 – d6, u1 – u6) women.

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