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AGE DEPENDENCE OF IODINE TO TRACE ELEMENT CONTENT RATIOS IN NORMAL THYROID OF MALES INVESTIGATED BY NEUTRON ACTIVATION AND INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY

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Abstract

Thyroid diseases rank second among endocrine disorders, and prevalence of the diseases is higher in the elderly as compared to the younger population. An excess or deficiency of trace element (TE) contents in thyroid play important role in goitro- and carcinogenesis of gland. The correlations between age and thirty-eight TE, including I, as well as between age and I/TE content ratios in normal thyroid of 72 males (age range 2-80 years) was investigated by two methods: instrumental neutron activation analysis and inductively coupled plasma mass spectrometry. Our data reveal that the Cd, I and Se contents, as well as the I/B, I/Be, I/Cr, I/Ga, I/Li, I/Mn, I/Rb, I/Tb, I/U, and I/Y content ratios increase, while B, Dy, Ga, Mn, U, Y contents and I/Cd and I/Gd content ratios decrease in the normal thyroid of male during a lifespan. Therefore, a goitrogenic and tumorogenic effect at least of excessive Cd and inadequate Cr and Mn levels in the thyroid of males with increasing age may be assumed.

Keywords: thyroid; trace elements; age-related changes; neutron activation analysis; inductively coupled plasma mass spectrometry

Introduction

According to the World Health Organization (WHO), thyroid diseases rank second among endocrine disorders after diabetes mellitus. More than 665 million people in the world have endemic goiter or suffer from other thyroid pathologies. At the same time, according to the same statistics, the increase in the number of thyroid diseases in the world is 5% per year [1]. It has been suggested that risk factors for the development of thyroid disorders may be numerous factors, including genetics, radiation, autoimmune diseases, as well as adverse environmental factors, such as an increase in the content of various chemicals in the environment [2].

Trace elements (TE) are among these various chemicals, because their levels in the environment have increased significantly over the past hundred years as a result of the industrial revolution and the tremendous technological changes that have taken place in metallurgy, chemical production, electronics, agriculture, food processing and storage, cosmetics, pharmaceuticals and medicine. In connection with these changes, the levels and ratio of TE entering the human body from the outside have been significantly disturbed, compared with the conditions in which human societies have lived for many millennia.

More than 50 years ago, we formulated the postulate about the somatic TE homeostasis, which is now generally recognized [3]. According to this postulate, under evolutionary environmental conditions, the mechanisms of homeostasis of organisms maintain the levels and ratios of TE in tissues and organs within certain limits. If the content of TE in the environment changes significantly, the mechanisms of somatic homeostasis may respond inadequately. Inadequate response of homeostasis mechanisms leads to changes in TE levels in tissues and organs, which, in turn, can affect their function and lead to the development of pathological conditions. The correctness of this conclusion was illustrated by us earlier on the example of the study of the role of TE in the normal and pathophysiology of the prostate [4-24]. It was shown, in particular, that a special role in the development of pathological transformations of the prostate is played by disturbances in the relationship between TE in the tissue and gland secretion. Moreover, it was found that changes in the relationship between TE can be used as highly informative markers of various prostate diseases, including malignant tumors [25-40]. These findings stimulated our investigations of TE relationships in thyroid tissue in normal and pathological conditions.

There are many studies regarding TE content in human thyroid, using chemical techniques and instrumental methods [41-64]. However, among the published data, no works on the relationship of TE in the normal human thyroid were found.

This work had three aims. The primary purpose of this study was to determine reliable values for the Ag, Al, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Dy, Er, Fe, Ga, Gd, Hg, I, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Sn, Tb, Ti, Tl, U, Y, and Zn mass fractions in the normal thyroid of subjects ranging from children to elderly males using instrumental neutron activation analysis (INAA) combined in consecutive order with destructive inductively coupled plasma mass spectrometry (ICP-MS) and calculate individual values of I/Ag, I/Al, I/B, I/Be, I/Bi, I/Cd, I/Ce, I/Co, I/Cr, I/Cs, I/Dy, I/Er, I/Fe, I/Ga, I/Gd, I/Hg, I/La, I/Li, I/Mn, I/Mo, I/Nb, I/Nd, I/Ni, I/Pb, I/Pr, I/Rb, I/Sb, I/Sc, I/Se, I/Sm, I/Sn, I/Tb, I/Ti, I/Tl, I/U, I/Y, and I/Zn. The second aim was to compare thirty-eight TE mass fractions in thyroid gland obtained in the study with published data. The final aim was to estimate the correlations between age and TE contents, as well as between age and I/TE content ratios in normal thyroid of males.

All studies were approved by the Ethical Committees of the Medical Radiological Research Centre, Obninsk. All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments, or with comparable ethical standards.

Materials and Methods

Randomly selected tissue samples of the thyroid gland were obtained from autopsies of 72 practically healthy residents (European-Caucasian nationality) of the Obninsk city, who died suddenly. The age of the deceased males ranged from 2 to 80 years. The main causes of sudden death were injuries in car accidents and trauma. Several males have died from suicide, alcohol poisoning, stroke, acute heart failure, and pulmonary embolism. Autopsies were carried out in the forensic medical examination department of the city hospital. In the anamnesis of the deceased males there were no chronic diseases, as well as medications or nutritional supplements that affect the development and function of the thyroid gland,

Thyroid tissue samples were taken from the right lobe of the gland using a titanium scalpel [65] and divided into two parts. One part was subjected to histological examination in order to confirm compliance with the age norm, as well as to exclude the presence of microadenomas and latent cancer. The second part was intended to determine the content of TE in it.

Thyroid tissue samples were delivered frozen to the Medical Radiological Research Center, where they were weighed and stored at -20°C. Subsequently, all samples were lyophilized and homogenized [66]. To determine the contents of the TE by comparison with a known standard, aliquots of commercial, chemically pure compounds were used [67]. Ten subsamples of the Certified Reference Material (CRM) produced by the International Atomic Energy Agency (IAEA) IAEA H-4 (Animal Muscle) and IAEA HH-1 (Human Hair), as well as Polish CRM INCT-SBF-4 Soya Bean Flour, INCT-TL-1 Tea Leaves, and INCT-MPH-2 Mixed Polish Herbs were analyzed to estimate the precision and accuracy of results. The CRM subsamples were prepared in the same way as the samples of dry homogenized thyroid tissue.

The content of I was determined by INAA using short irradiation in a horizontal channel equipped with the pneumatic rabbit system of the WWR-c research nuclear reactor in Obninsk. The neutron flux in the channel was 1.7×10^{13}n cm^{-2} s^{-1}. A vertical channel of nuclear reactor WWR-c with a neutron flux of 1.3×10^{13} $n\times cm^{-2}\times s^{-1}$ was applied to determine the content of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn by long irradiation. Details of sample preparation and used nuclear reactions, induced radionuclides, gamma-energies and semiconductor spectrometry were presented in our earlier publications concerning TE contents in human scalp hair [68,69]. After non-destructive INAA investigation the thyroid samples were decomposed in autoclaves and used for ICP-MS. The content of Ag, Al, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Dy, Er, Fe, Ga, Gd, Hg, I, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Se, Sm, Sn, Tb, Ti, Tl, U, Y, and Zn was determined by ICP-MS using an ICP-MS Thermo-Fisher "X-7" Spectrometer (Thermo Electron, USA). The TE concentrations in aqueous solutions were determined by the quantitative method using multi elemental calibration solutions ICP-MS-68A and ICP-AM-6-A produced by High-Purity Standards (Charleston, SC 29423, USA). Indium was used as an internal standard in all measurements. Information detailing with the ICP-MS methods used and other details of the analysis was presented in our previous publication concerning TE contents in human prostate [70-73].

A dedicated computer program for INAA mode optimization was used [74]. All thyroid samples were prepared in duplicate, and mean values of TE contents were used in final calculation. For TE whose content was determined by two methods, the average value was calculated. The main statistical characteristics of the TE content and the I/TE content ratio of. such as the arithmetic mean, standard deviation, standard error of the mean, minimum and maximum values, median, percentiles with levels of 0.025 and 0.975 were found using Microsoft Office Excel. Pearson's correlation coefficient was used in Microsoft Office Excel to calculate the relationship "age – TE mass fraction" and "age – I/TE mass fraction".

Results

Table 1 depicts the similarity of the means of the Ag, Co, Cr, Fe, Hg, Rb, Sb, Se, and Zn mass fractions in the normal thyroid of male determined by both INAA and ICP-MS methods.

Tables 2 and 3 represents the main statistical characteristics of the Ag, Al, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Dy, Er, Fe, Ga, Gd, Hg, I, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Sn, Tb, Ti, Tl, U, Y, Zn mass fractions and of the I/Ag, I/Al, I/B, I/Be, I/Bi, I/Cd, I/Ce, I/Co, I/Cr, I/Cs, I/Dy, I/Er, I/Fe, I/Ga, I/Gd, I/Hg, I/La, I/Li, I/Mn, I/Mo, I/Nb, I/Nd, I/Ni, I/Pb, I/Pr, I/Rb, I/Sb, I/Sc, I/Se, I/Sm, I/Sn, I/Tb, I/Ti, I/Tl, I/U, I/Y, and I/Zn mass fraction ratios in normal thyroid of males, respectively.

The comparison of our results with published data for contents of all TE in the human thyroid determined in the present study is shown in Table 4.

Pearson's correlation coefficients in Tables 5 and 6 estimate the effect of age on the TE contents and I/TE content ratios, respectively.

Discussion

A good agreement of our results for the Ag, Al, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Dy, Er, Fe, Ga, Gd, Hg, I, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Sn, Tb, Ti, Tl, U, Y, Zn mass fractions with the certified values of CRM IAEA H-4 (Animal Muscle), IAEA HH-1 (Human Hair), INCT-SBF-4 Soya Bean Flour, INCT-TL-1 Tea Leaves, and INCT-MPH-2 Mixed Polish Herbs [68-73] as well as the similarity of the means of the Ag, Co, Cr, Fe, Hg, Rb, Sb, Se, and Zn mass fractions in the normal thyroid of male determined by both INAA and ICP-MS methods (Table 1) demonstrates an acceptable precision and accuracy of the results obtained in the study and presented in Tables 2-6.

The content of TE was determined in all or most of the examined samples, which made it possible to calculate the main statistical parameters: the mean value of the mass fraction (M), standard deviation (SD), standard error of the mean (SEM), minimum (Min), maximum (Max), median (Med), and percentiles with levels of 0.025 (P 0.025) and 0.975 (P 0.975), of the Ag, Al, B, Be, Bi, Cd, Ce, Co, Cr, Cs, Dy, Er, Fe, Ga, Gd, Hg, I, La, Li, Mn, Mo, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Sn, Tb, Ti, Tl, U, Y, and Zn mass fractions (Table 2), as well as I/Ag, I/Al, I/B, I/Be, I/Bi, I/Cd, I/Ce, I/Co, I/Cr, I/Cs, I/Dy, I/Er, I/Fe, I/Ga, I/Gd, I/Hg, I/La, I/Li, I/Mn, I/Mo, I/Nb, I/Nd, I/Ni, I/Pb, I/Pr, I/Rb, I/Sb, I/Sc, I/Se, I/Sm, I/Sn, I/Tb, I/Ti, I/Tl, I/U, I/Y, and I/Zn mass fraction ratios (Table 3) in normal thyroid of males. The values of M, SD, and SEM can be used to compare data for different groups of samples only under the condition of a normal distribution of the results of determining the content of TE in the samples under study. Statistically reliable identification of the law of distribution of results requires large sample sizes, usually several hundred samples, and therefore is rarely used in biomedical research. In the conducted study, we could not prove or disprove the "normality" of the distribution of the results obtained due to the insufficient number of samples studied. Therefore, in addition to the M, SD, and SEM values, such statistical characteristics as median, range (Min-Max) and percentiles P 0.025 and P 0.975 were calculated, which are valid for any law of distribution of the results of TE content in thyroid tissue.

Values obtained for Al, B, Cd, Cr, Cs, Dy, Er, Fe, Gd, Hg, Mn, Nb, Nd, Ni, Pb, Pr, Rb, Sb, Sc, Se, Sm, Tb, Ti, and Zn contents in the normal human thyroid (Table 4) agree well with median of mean values reported by other researches [41-64]. The obtained means for Ag, Co, Mo, Sn, Y, and U were almost one-three orders of magnitude lower median of previously reported means but inside the range of means (Table 4). The mean obtained for Be, Bi, Ce, Ga, La, Li, and Tl were also one-three orders of magnitude lower than the median of previously reported data and outside the range of previously reported means (under a minimal value of published means).

In some published articles, the values of the mass fractions of TE were presented in terms of ash or wet mass of the thyroid tissue. Therefore, we recalculated these data for dry mass basis using published values of 75% for water [55] and 4.16% for ash [75] in adult thyroids. No published data referring to I/Ag, I/Al, I/B, I/Be, I/Bi, I/Cd, I/Ce, I/Co, I/Cr, I/Cs, I/Dy, I/Er, I/Fe, I/Ga, I/Gd, I/Hg, I/La, I/Li, I/Mn, I/Mo, I/Nb, I/Nd, I/Ni, I/Pb, I/Pr, I/Rb, I/Sb, I/Sc, I/Se, I/Sm, I/Sn, I/Tb, I/Ti, I/Tl, I/U, I/Y, and I/Zn mass fraction ratios in human thyroid was found.

With age, the Cd, I and Se contents increase, while B, Dy, Ga, Mn, U and Y contents decrease (Table 5). If we consider the age-related changes in TE in relation to the content of iodine in the thyroid gland, which increases with age, then it can be noted that the I/Cd and I/Gd ratios decrease, while the I/B, I/Be, I/Cr, I/Ga, I/Li, I/Mn, I/Rb, I/Tb, I/U, and I/Y ratios increase. A decrease in the I/Cd ratio indicates that the accumulation of Cd with age is so significant that it is not compensated by an age-related increase in the level of I in the thyroid gland of men. On the other hand, for example, an increase in ratios such as I/Cr and I/Mn reveals an age-related deficiency of Cr and Mn in relation to iodine level. It should be noted that the ratio of such important elements for the function of the thyroid gland as I and Se does not change with age, in other words, the age-related increase in the content of I in the thyroid gland of men is accompanied by an adequate increase in the content of Se.

Previously, it was shown that an increase in the content of such TE as Cd in the tissues of various organs can lead not only to disruption of their normal functioning, but also be the cause of the development of various pathological conditions, including malignant tumors [20]. Deficiency of such intensely involved in the biochemical processes of the body TE as Cr and Mn can also be the cause of pathological conditions of various tissues and organs. including the thyroid gland [3,8]. Thus, in the present study was found multidirectional age-related changes in at least such TEs as Cd, on the one hand, and Cr and Mn. on the other hand, which may be responsible for the increase in the incidence of goiter and thyroid cancer with increasing age of males.

Conclusion

The combination of INAA and ICP-MS is a useful analytical tool for the determination of TE contents in the thyroid tissue samples. This method makes it possible to determine the content of at least thirty-eight TE.

Our data reveal that the Cd, I and Se contents, as well as the I/B, I/Be, I/Cr, I/Ga, I/Li, I/Mn, I/Rb, I/Tb, I/U, and I/Y content ratios increase, while B, Dy, Ga, Mn, U, Y contents and I/Cd and I/Gd content ratios decrease in the normal thyroid of male during a lifespan. Therefore, a goitrogenic and tumorogenic effect at least of excessive Cd and inadequate Cr and Mn levels in the thyroid of males with increasing age may be assumed.

Table 1. Comparison of the mean values (M±SEM) of the chemical element mass fractions (mg/kg, on dry-mass basis) in the normal thyroid of males obtained by both INAA and ICP-MS methods

Element	INAA M_1	ICP-MS M_2	Δ, %
Ag	0.0156±0.0021	0.0121±0.0018	22.4
Co	0.0352±0.0031	0.0334±0.0032	5.1
Cr	0.520±0.041	0.427±0.039	17.9
Fe	222±12	223±15	-0.5
Hg	0.0437±0.0048	0.0970±0.0102	-122
Rb	7.89±0.58	8.38±0.61	-6.2
Sb	0.108±0.010	0.0705±0.0097	34.7
Se	2.36±0.17	2.10±0.17	11.0
Zn	103±5.5	95.4±5.1	7.4

M – arithmetic mean, SEM – standard error of mean, $\Delta=[(M_1 - M_2)/M_1] \cdot 100\%$.

Table 2. Some statistical parameters of thirty-eight trace element mass fraction (mg/kg, dry mass basis) in the normal thyroid of male

Element	M	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Ag	0.0133	0.0122	0.0017	0.0017	0.0789	0.0088	0.00193	0.0321
Al	11.3	14.9	2.3	0.800	69.3	6.4	1.12	58.6
B	0.491	0.473	0.071	0.200	2.30	0.300	0.200	2.03
Be	0.00048	0.00052	0.00008	0.00010	0.00240	0.00025	0.00010	0.00170
Bi	0.00386	0.00511	0.00079	0.00030	0.0245	0.00230	0.00050	0.0217
Cd	2.22	2.13	0.33	0.107	8.26	1.41	0.155	7.95
Ce	0.00773	0.00817	0.00123	0.00100	0.0348	0.00435	0.00123	0.0312
Co	0.0345	0.0238	0.0031	0.0100	0.127	0.0260	0.0124	0.101
Cr	0.474	0.265	0.038	0.130	1.30	0.400	0.152	0.984
Cs	0.0263	0.0177	0.0026	0.0113	0.0924	0.0210	0.0116	0.0806
Dy	0.00108	0.00118	0.00018	0.00030	0.00600	0.00060	0.00030	0.00367
Er	0.00034	0.00028	0.00004	0.00010	0.00110	0.00027	0.00010	0.00110
Fe	222	87	11	52.0	474	224	72.8	406
Ga	0.0318	0.0140	0.0022	0.0100	0.0700	0.0300	0.0100	0.0697
Gd	0.00092	0.00079	0.00012	0.00040	0.00470	0.00060	0.00040	0.00219
Hg	0.0610	0.0394	0.0055	0.0090	0.151	0.0490	0.0105	0.150
I	1486	902	130	220	3744	1337	222	3443
La	0.00454	0.00485	0.00074	0.00040	0.0219	0.00250	0.00040	0.0188
Li	0.0225	0.0168	0.0028	0.00400	0.0977	0.0179	0.00463	0.0547
Mn	1.27	0.47	0.06	0.470	2.30	1.16	0.534	2.21
Mo	0.0856	0.0428	0.0064	0.0305	0.299	0.0804	0.0388	0.156
Nb	0.584	0.952	0.145	0.0130	3.77	0.142	0.0130	3.42
Nd	0.00388	0.00312	0.00047	0.00020	0.0139	0.00295	0.00081	0.0131
Ni	0.467	0.375	0.056	0.0740	1.80	0.345	0.120	1.48
Pb	0.242	0.271	0.040	0.0260	1.60	0.170	0.0450	0.794
Pr	0.00102	0.00080	0.00012	0.00010	0.00350	0.00070	0.00021	0.00345
Rb	8.07	3.96	0.50	3.53	22.6	7.10	3.82	18.5
Sb	0.0895	0.0705	0.0091	0.00470	0.308	0.0662	0.00954	0.291
Sc	0.0390	0.0359	0.0085	0.00050	0.0860	0.0344	0.00093	0.0860
Se	2.23	1.28	0.17	0.530	5.80	1.71	0.810	5.64
Sm	0.00049	0.00047	0.00007	0.00010	0.00210	0.00034	0.00010	0.00150
Sn	0.0674	0.0556	0.0085	0.00900	0.211	0.0507	0.00912	0.199
Tb	0.00020	0.00011	0.00002	0.00010	0.00050	0.00015	0.00010	0.00042
Ti*	3.43	3.36	0.51	0.530	14.5	2.25	0.908	11.9
Tl	0.00099	0.00053	0.00008	0.00029	0.00290	0.00092	0.00030	0.00219
U	0.00040	0.00033	0.00005	0.00010	0.00140	0.00030	0.00010	0.00111
Y	0.00247	0.00221	0.00034	0.00100	0.0100	0.00160	0.00100	0.00818
Zn	99.1	39.4	5.0	34.0	215	92.5	44.0	200

M – arithmetic mean, SD – standard deviation, SEM – standard error of mean, Min – minimum value, Max – maximum value, P 0.025 – percentile with 0.025 level, P 0.975 – percentile with 0.975 level.

Table 3. Some statistical parameters of iodine/trace element mass fraction ratios in the normal thyroid of male

Ratio	M	SD	SEM	Min	Max	Median	P 0.025	P 0.975
I/Ag	246629	216677	32665	6471	916842	211435	10343	827405
I/Al	463	552	91	5.14	2381	226	8.43	1647
I/B	5492	4696	772	367	17855	3753	585	17365
I/Be	6561448	5767441	948161	448980	26480000	5905000	592998	18717500
I/Bi	1493340	2299893	388753	24857	11903333	703750	33890	7670900
I/Cd	1899	3033	513	83.0	16131	903	90.7	10606
I/Ce	478036	433014	72169	10776	1700476	328906	22435	1320005
I/Co	67455	47817	6831	4795	185563	55192	8037	156533
I/Cr	4523	4017	627	373	17005	3300	481	15817
I/Cs	89590	65173	10714	4575	263522	73466	7170	237534
I/Dy	3101253	2720084	447179	81481	11903333	2235000	197148	523560
I/Er	8701775	8954255	1472070	252874	35710000	6600000	523560	30742000
I/Fe	10.6	10.0	1.4	0.60	56.8	7.39	0.92	31.8
I/Ga	61739	46655	7670	3929	192333	56460	7818	155088
I/Gd	2703471	2175673	357678	129412	8927500	2235000	286991	7541500
I/Hg	48998	55726	8703	2529	262813	28085	2840	172417
I/La	824982	820629	136772	12055	4237500	612242	36507	2265590
I/Li	125546	129183	23202	7881	631702	101604	8150	391353
I/Mn	1675	1415	206	200	7066	1334	234	5469
I/Mo	23271	16379	2693	2037	58735	22309	2624	52175
I/Nb	32697	58411	9735	101	274692	8225	168	178039
I/Nd	801763	680477	113413	37183	2483333	559049	53536	2433021
I/Ni	5651	5149	847	327	23807	4566	358	15741
I/Pb	15303	16460	2706	381	67698	9500	668	56214
I/Pr	2708883	2033190	338865	105600	7117500	2255051	204200	6948188
I/Rb	270	211	29	14.5	855	220	27.3	767
I/Sb	28616	26801	3753	2828	132553	21675	3502	93842
I/Sc	384636	528810	132202	3671	1588000	73102	3973	1456287
I/Se	971	765	107	96.0	3708	767	137	3095
I/Sm	7487096	8350864	1411554	240000	35710000	4718333	381100	29556000
I/Sn	48769	46803	7801	1440	182479	34351	3296	165956
I/Tb	11312807	8360862	1374517	523810	34620000	9703333	1148581	30057000
I/Ti*	978	876	146	18.0	3858	811	49.5	2714
I/Tl	2723510	2573438	423071	146667	11159375	2104545	173067	9213211
I/U	7863331	8034124	1320802	273636	35710000	5646000	318540	27403000
I/Y	1150425	962705	158268	36125	3571000	1013333	58423	3472900
I/Zn	21.0	13.4	1.8	2.03	63.4	21.7	2.44	45.7

M – arithmetic mean, SD – standard deviation, SEM – standard error of mean, Min – minimum value, Max – maximum value, P 0.025 – percentile with 0.025 level, P 0.975 – percentile with 0.975 level, *scalpel made od Ti was used in sample preparation

Table 4. Median, minimum and maximum value of means of trace element contents in the normal thyroid according to data from the literature in comparison with our results (mg/kg, dry mass basis)

Element	Published data [Reference]			This work
	Median of means (n)*	Min of means M or M±SD, (n)**	Max of means M or M±SD, (n)**	M±SD
Ag	0.25 (12)	0.000784 (16) [41]	1.20±1.24 (105) [42]	0.0133±0.0122
Al	33.6 (12)	0.33 (-) [43]	420 (25) [44]	11.3±14.9
B	0.151 (2)	0.084 (1) [49]	0.46 (1) [49]	0.491±0.473
Be	0.042 (3)	0.000924(16) [41]	<0.12 (-) [48]	0.00048±0.00052
Bi	0.126 (4)	0.0339 (16) [41]	<0.4 (-) [48]	0.00386±0.00511
Cd	1.68 (20)	0.12 (131) [45]	47.6±8.0 (16) [50]	2.22±2.13
Ce	0.22 (1)	0.22 (59) [41]	0.22 (59) [41]	0.00773±0.00817
Co	0.306 (25)	0.016 (66) [51]	70.4±40.8 (14) [52]	0.0345±0.0238
Cr	0.69 (17)	0.088 (83) [53]	24.8±2.4 (4) [46]	0.474±0.265
Cs	0.066 (6)	0.0112±0.0109 (14) [54]	0.109±0.370 (48) [55]	0.0263±0.0177
Dy	0.00106 (1)	0.00106 (60) [41]	0.00106 (60) [41]	0.00108±0.00118
Er	0.00068 (1)	0.00068 (60) [41]	0.00068 (60) [41]	0.00034±0.00028
Fe	252 (21)	56 (120) [56]	3360 (25) [44]	222±87
Ga	0.273 (3)	<0.04 (-) [48]	1.7±0.8 (-) [57]	0.0318±0.0140
Gd	0.00256 (1)	0.00256 (59) [41]	0.00256 (59) [41]	0.00092±0.00079
Hg	0.08 (13)	0.0008±0.0002 (10) [47]	396±40 (4) [46]	0.0610±0.0394
I	1888 (95)	159±8 (23) [58]	5772±2708 (50) [59]	1486±902
La	0.068 (3)	0.052 (59) [41]	<4.0 (-) [48]	0.00454±0.00485
Li	6.3 (2)	0.092 (-) [48]	12.6 (180) [60]	0.0225±0.0168
Mn	1.62 (40)	0.076 (83) [53]	69.2±7.2 (4) [46]	1.27±0.47
Mo	0.40 (11)	0.0288±0.0096 (39) [47]	516±292 (14) [52]	0.0856±0.0428
Nb	<4.0 (1)	<4.0 (-) [48]	<4.0 (-) [48]	0.584±0.952
Nd	0.0108 (1)	0.0108 (60) [41]	0.0108 (60) [41]	0.00388±0.00312
Ni	0.44 (19)	0.0084 (83) [53]	33.6±3.6 (4) [46]	0.467±0.375
Pb	0.58 (25)	0.021 (83) [53]	68.8±6.8 (4) [46]	0.242±0.271
Pr	0.0034 (1)	0.0034 (59) [41]	0.0034 (59) [41]	0.00102±0.00080
Rb	7.8 (9)	≤0.85 (29) [47]	294±191 (14) [52]	8.07±3.96
Sb	0.15 (10)	0.040±0.003 (-) [61]	≤12.4 (-) [48]	0.0895±0.0705
Sc	0.009 (4)	0.0018±0.0003 (17) [62]	0.0135±0.0045 (10) [47]	0.0390±0.0359
Se	2.32 (21)	0.436 (40) [63]	756±680 (14) [52]	2.23±1.28
Sm	0.00216 (1)	0.00216 (60) [41]	0.00216 (60) [41]	0.00049±0.00047
Sn	0.67 (7)	0.0235 (16) [41]	-≤3.8 (17) [64]	0.0674±0.0556
Tb	0.000224 (1)	0.000224 (60) [41]	0.000224 (60) [41]	0.00020±0.00011
Ti	1.42 (8)	0.084 (83) [53]	73.6±7.2 (4) [46]	3.43±3.36
Tl	<0.2 (2)	0.00138 (16) [41]	<0.4 (-) [48]	0.00099±0.00053
U	0.0060 (11)	0.00014 (66) [51]	0.428±0.143 (10) [47]	0.00040±0.00033
Y	<2.9 (2)	0.00225 (16) [51]	≤5.9 (17) [64]	0.00247±0.00221
Zn	110 (56)	2.1 (-) [43]	820±204 (14) [52]	99.1±39.4

M –arithmetic mean, SD – standard deviation, Min – minimum, Max – maximum, (n)* – number of all references, (n)** – number of samples.

Table 5. Correlations between age (years) and trace element mass fractions (mg/kg, dry mass basis) in the normal thyroid of male (*r* – coefficient of correlation)

Element	Ag	Al	B	Be	Bi	Cd	Ce	Co	Cr	Cs
r	-0.03	-0.29	-0.37[a]	-0.29	-0.11	0.72[c]	0.03	-0.13	-0.13	0.05
Element	Dy	Er	Fe	Ga	Gd	Hg	I	La	Li	Mn
r	-0.35[a]	-0.09	-0.14	-0.37[a]	-0.24	0.09	0.32[b]	0.12	-0.31	-0.35[b]
Element	Mo	Nb	Nd	Ni	Pb	Pr	Rb	Sb	Sc	Se
r	-0.03	-0.17	0.04	-0.18	-0.10	0.10	-0.17	-0.01	-0.03	0.42[c]
Element	Sm	Sn	Tb	Ti	Tl	U	Y	Zn		
r	-0.22	0.18	-0.31	0.01	0.02	-0.46[b]	-0.33[a]	-0.02		

Statistically significant values: [a] $p \le 0.05$, [b] $p \le 0.01$, [c] $p \le 0.001$.

Table 6. Correlations between age (years) and iodine/trace element mass fraction ratios in the normal thyroid of male (*r* – coefficient of correlation)

Element	I/Ag	I/Al	I/B	I/Be	I/Bi	I/Cd	I/Ce	I/Co	I/Cr	I/Cs
r	-0.07	0.26	0.50[b]	0.38[a]	0.26	-0.38[a]	0.01	0.11	0.35[a]	0.20
Element	I/Dy	I/Er	I/Fe	I/Ga	I/Gd	I/Hg	I/La	I/Li	I/Mn	I/Mo
r	0.34	0.24	0.25	0.35[a]	-0.38[a]	-0.02	-0.06	0.33[a]	0.37[a]	0.14
Element	I/Nb	I/Nd	I/Ni	I/Pb	I/Pr	I/Rb	I/Sb	I/Sc	I/Se	I/Sm
r	0.16	-0.18	0.20	0.11	0.01	0.31[a]	0.11	0.10	-0.19	0.23
Element	I/Sn	I/Tb	I/Ti	I/Tl	I/U	I/Y	I/Zn			
r	-0.14	0.39[a]	0.26	0.23	0.34[a]	0.39[a]	0.17			

Statistically significant values: [a] $p \le 0.05$, [b] $p \le 0.01$.

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References

1. Wang H, Jiang Y, Song J, Liang H, Liu Y, Huang J, Tin P, Wu D, Zhang H, Liu P, Zhon D, Wei W, Lei L, Peng J, Zhang J. The risk of perchlorate and iodine on the incidence of thyroid tumors and nodular goiter: a case-control study in southeastern China. Environ Health. 2022; 21: 4.
2. Tang Z, Zhang J, Zhou Q, Xu S, Cai Z, Jiang G. Thyroid Cancer "epidemic": a socio-environmental health problem needs collaborative efforts. Environ Sci Technol. 2020; 54(7): 3725–3727.
3. Zaichick V. Medical elementology as a new scientific discipline. J Radioanal Nucl Chem. 2006: 269: 303-309.
4. Zaichick V. A systematic review of the mercury content of the normal human prostate gland. Archives of Urology 2020; 3(2): 35-45.
5. Zaichick V. A systematic review of the cobalt content of the normal human prostate gland. J Clin Res Oncol. 2020; 3(1): 1-8.
6. Zaichick V. A systematic review of the phosphorus content of the normal human prostate gland. Applied Medical Research 2020; 7(2): 1-7.

7. Zaichick V. A systematic review of the antimony content of the normal human prostate gland. Journal of Hematology and Oncology Research 2021; 4(1): 17-27.
8. Zaichick V. A systematic review of the chromium content of the normal human prostate gland. Innovare Journal of Medical Sciences 2021; 9(1): 1-6.
9. Zaichick V. A systematic review of the nickel content of the normal human prostate gland. Health Sciences 2020; 1(ID 234): 1-6.
10. Zaichick V. A systematic review of the aluminum content of the normal human prostate gland. Advances in Hematology and Oncology Research 2021; 4(1): 69-75.
11. Zaichick V. A systematic review of the lead content of the normal human prostate gland. J Cancer Oncol Res. 2021; 2(1): 1-8.
12. Zaichick V. A systematic review of the arsenic content of the normal human prostate gland. International Journal of Medicine Sciences 2021; 3(1): 1-6.
13. Zaichick V. A systematic review of the calcium content of the normal human prostate gland. Iberoamerican Journal of Medicine 2021; 3(1): 85-94
14. Zaichick V. A systematic review of the tin content of the normal human prostate gland. Journal of Cellular & Molecular Oncology 2021; 3(1): 1-7.
15. Zaichick V. Barium levels in the prostate of the normal human: a review. Universal Journal of Pharmaceutical Research 2021; 6(1): 52-60.
16. Zaichick V. A systematic review of the zinc content of the hyperplastic human prostate gland. Biomedical Research on Trace Elements 2020; 31 (3): 98-116.
17. Zaichick V. Beryllium content of the normal human prostate gland: A systematic review. Acta Scientific Medical Sciences 2021; 5(4): 78-85.
18. Zaichick V. Boron level in the prostate of the normal human: A systematic review. J Nano Nano Sci Rese. 2021; 1(2): 1-9.
19. Zaichick V. Bismuth level in the prostate of normal human: A systematic review. Int J Biopro Biotechnol Advance 2021; 7(1): 264-273.
20. Zaichick V. A systematic review of the cadmium content of the normal human prostate gland. World Journal of Advanced Research and Reviews 2021; 10(01): 258-269.
21. Zaichick V. A systematic review of the strontium content of the normal human prostate gland. Journal of Medical Research and Health Sciences (JMRHS) 2021; 4 (5): 1257-1269.
22. Zaichick V. Thallium content of the normal human prostate gland - A systematic review. Archives of Clinical Case Reports 2021; 2(5): 223-229.
23. Zaichick V. Vanadium content of the normal human prostate gland: A systematic review. Archives of Pharmacy Practice 2021; 12(3): 15-21.
24. Zaichick V, A systematic review of the zinc content of the normal human prostate gland. Biol Trace Elem Res. 2021; 199(10): 3593-3607.
25. Zaichick V, Zaichick S. Ratios of selected chemical element contents in prostatic tissue as markers of malignancy. Hematol Med Oncol. 2016; 1(2): 1-8.
26. Zaichick V, Zaichick S. Ratios of Zn/trace element contents in prostate gland as carcinoma's markers. Cancer Rep Rev. 2017; 1(1): 1-7.
27. Zaichick V, Zaichick S. Ratios of Mg/trace element contents in prostate gland as carcinoma's markers. SAJ Canc Sci. 2017; 2(1): 102.

28. Zaichick V, Zaichick S. Ratios of calcium/trace elements as prostate cancer markers. J Oncol Res Ther. 2017; 2017(4): J116.
29. Zaichick V, Zaichick S. Ratios of cobalt/trace element contents in prostate gland as carcinoma's markers. The International Journal of Cancer Epidemiology and Research 2017; 1(1): 21-27.
30. Zaichick V, Zaichick S. Ratios of cadmium/trace element contents in prostate gland as carcinoma's markers. Canc Therapy & Oncol Int J. 2017; 4(1): 555626.
31. Zaichick V, Zaichick S. Ratios of selenium/trace element contents in prostate gland as carcinoma's markers. J Tumor Med Prev. 2017; 1(2): 555556.
32. Zaichick V, Zaichick S. Ratios of rubidium/trace element contents in prostate gland as carcinoma's markers. Can Res and Clin Oncology 2017; 1(1): 13-21.
33. Zaichick V, Sviridova T, Zaichick S. Zinc concentration in human prostatic fluid: normal, chronic prostatitis, adenoma, and cancer. Int Urol Nephrol 1996; 28(5): 687-694.
34. Zaichick V, Zaichick S. Ratio of zinc to bromine, iron, rubidium, and strontium concentration in the prostatic fluid of patients with benign prostatic hyperplasia. Acta Scientific Medical Sciences 2019; 3(6): 49-56.
35. Zaichick V, Zaichick S. Ratio of zinc to bromine, iron, rubidium, and strontium concentration in expressed prostatic secretions as a source for biomarkers of prostatic cancer. American Journal of Research 2019; 5-6: 140-150.
36. Zaichick V, Zaichick S. Some trace element contents and ratios in prostatic fluids as ancillary diagnostic tools in distinguishing between the benign prostatic hyperplasia and chronic prostatitis. Archives of Urology 2019; 2(1): 12-20.
37. Zaichick V, Zaichick S. Some trace element contents and ratios in prostatic fluids as ancillary diagnostic tools in distinguishing between the chronic prostatitis and prostate cancer. Medical Research and Clinical Case Reports 2019; 3(1): 1-10.
38. Zaichick V, Zaichick S. Using prostatic fluid levels of zinc to strontium concentration ratio in non-invasive and highly accurate screening for prostate cancer. Acta Scientific Cancer Biology 2020; 4(1): 12-21.
39. Zaichick V, Zaichick S. Using prostatic fluid levels of zinc to iron concentration ratio in non-invasive and highly accurate screening for prostate cancer. SSRG International Journal of Medical Science 2019; 6(11): 24-31.
40. Zaichick V. Using prostatic fluid levels of rubidium and zinc concentration multiplication in non-invasive and highly accurate screening for prostate cancer. J Cancer Prev Curr Res. 2019; 10(6): 151–158.
41. Zhu H, Wang N, Zhang Y, Wu Q, Chen R, Gao J, Chang P, Liu Q, Fan T, Li J, Wang J, Wang J: Element contents in organs and tissues of Chinese adult men. Health Phys 98(1): 61–73, 2010.
42. Vlasova ZA: Dynamics of trace element contents in thyroid gland in connection with age and atherosclerosis. Proceedings of the Leningrad Institute of Doctor Advanced Training, 80: 135-144, 1969.
43. Kortev AI, Dontsov GI, Lyascheva AP: Bioelements and a human pathology.

Middle-Ural publishing-house, Sverdlovsk, Russia, 1972.

44. Kamenev VF: About trace element contents in thyroid of adults. In: Trace Elements in Agriculture and Medicine. Buryatia publishing-house, Ulan-Ude, 1963, p.12-16.
45. Stojsavljević A, Rovčanin B, Krstić D, Borković-Mitić S, Paunović I, Kodranov I, Gavrović-Jankulović M, Manojlović D: Evaluation of trace metals in thyroid tissues: Comparative analysis with benign and malignant thyroid diseases. Ecotoxicol Environ Saf 183: 109479, 2019.
46. Reddy SB, Charles MJ, Kumar MR, Reddy BS, Anjaneyulu Ch, Raju GJN, Sundareswar B, Vijayan V: Trace elemental analysis of adenoma and carcinoma thyroid by PIXE method. Nucl Instrum Methods Phys Res B: Beam Interactions with Materials and Atoms 196(3-4): 333-339, 2002.
47. Boulyga SF, Zhuk IV, Lomonosova EM, Kanash NV, Bazhanova NN: Determination of microelements in thyroids of the inhabitants of Belarus by neutron activation analysis using the k0-method. J Radioanal Nucl Chem 222(1-2): 11-14, 1997.
48. Zakutinsky DI, Parfyenov YuD, Selivanova LN: Data book on the radioactive isotopes toxicology. State Publishing House of Medical Literature, Moscow, 1962.
49. Tipton IH, Cook MJ: Trace elements in human tissue. Part II. Adult subjects from the United States. Health Phys 9(2): 103-145, 1963.
50. Uetani M, Kobayashi E, Suwazono Y, Honda R, Nishijo M, Nakagawa H, Kido T, Nogawa K: Tissue cadmium (Cd) concentrations of people living in a Cd polluted area, Japan. Biometals 19(5): 521-525, 2006.
51. Stojsavljević A, Rovčanin B, Krstić D, Jagodić J, Borković-Mitić S, Paunović I, Živaljević V, Mitić B, Gavrović-Jankulović M, Manojlović D: Cadmium as main endocrine disruptor in papillary thyroid carcinoma and the significance of Cd/Se ratio for thyroid tissue pathophysiology. J Trace Elem Med Biol 55: 190-195, 2019.
52. Salimi J, Moosavi K, Vatankhah S, Yaghoobi A: Investigation of heavy trace elements in neoplastic and non-neoplastic human thyroid tissue: A study by proton – induced X-ray emissions. Int J Radiat Res 1(4): 211-216, 2004.
53. Reitblat MA, Kropachyev AM: Some trace elements in thyroid of the Perm Pricam'ya residents. Proceedings of Perm Medical Institute 78: 157-164, 1967.
54. Yamagata N: The concentration of common cesium and rubidium in human body. J Radiation Res 3(1): 9-30, 1962.
55. Katoh Y, Sato T, Yamamoto Y: Determination of multielement concentrations in normal human organs from the Japanese. Biol Trace Elem Res 90(1-3): 57-70, 2002.
56. Ataullachanov IA: Age changes in the content of manganese, cobalt, copper, zinc and iron in the endocrine glands of women. Probl Endocrinol (Mosk) 15(2): 98-102, 1969.
57. Belozerov EC: Gallium contents in some human tissues. Zdravookhranenie Turkmenii 4: 15, 1965.
58. Neimark II, Timoschnikov VM. Development of carcinoma of the thyroid gland in person residing in the focus of goiter endemic. Problemy Endocrinilogii 1978; 24(3): 28-32
59. Zabala J, Carrion N, Murillo M, Quintana M, Chirinos J, Seijas N, Duarte L, Brätter P.

Determination of normal human intrathyroidal iodine in Caracas population. J Trace Elem Med Bio 2009; 23(1): 9-14.
60. Remiz AM: Endemic goiter and trace elements in Kabardino-Balkaria ASSR In: All-Union conference on endocrinology, Medgiz, Moscow, 1962, p. 330-331.
61. Boulyga SF, Becker JS, Malenchenko AF, Dietze H-J: Application of ICP-MS for multielement analysis in small sample amounts of pathological thyroid tissue. Microchimica Acta 134(3-4): 215-222, 2000.
62. Kvicala J, Havelka ., Zeman J, Nemec J: Determination of some trace elements in the thyroid gland by INAA. J Radioanal Nucl Chem 149(2): 267-274, 1991.
63. Stojsavljević A, Rovčanin B, Krstić D, Borković-Mitić S, Paunović I, Kodranov I, Gavrović-Jankulović M, Manojlović D: Evaluation of trace metals in thyroid tissues: Comparative analysis with benign and malignant thyroid diseases. Ecotoxicol Environ Saf 183: 109479, 2019.
64. Forssen A: Inorganic elements in the human body. Ann Med Exp Biol Fenn 50(3): 99-162, 1972.
65. .Zaichick V, Zaichick S. Instrumental effect on the contamination of biomedical samples in the course of sampling. The Journal of Analytical Chemistry 1996; 51(12): 1200-1205.
66. Zaichick V, Zaichick S. A search for losses of chemical elements during freeze-drying of biological materials. J Radioanal Nucl Chem. 1997; 218(2): 249-253.
67. Zaichick V. Applications of synthetic reference materials in the medical Radiological Research Centre. Fresenius J Anal Chem. 1995; 352: 219-223.
68. Zaichick S, Zaichick V. The effect of age and gender on 37 chemical element contents in scalp hair of healthy humans. Biol Trace Elem Res. 2010; 134(1): 41-54.
69. Zaichick S, Zaichick V. (2011) The scalp hair as a monitor for trace elements in biomonitoring of atmospheric pollution. IJEnvH 2011; 5(1/2): 106-124.
70. Zaichick V, Zaichick S (2018) Associations between age and 50 trace element contents and relationships in intact thyroid of males. Aging Clin Exp Res 30(9): 1059–1070.
71. Zaichick S, Zaichick V, Nosenko S, et al. (2012) Mass fractions of 52 trace elements and zinc trace element content ratios in intact human prostates investigated by inductively coupled plasma mass spectrometry. Biol Trace Elem Res 149(2): 171-183.
72. Zaichick V, Zaichick S (2013) Use of neutron activation analysis and inductively coupled plasma mass spectrometry for the determination of trace elements in pediatric and young adult prostate. AJAC 4: 696-706.
73. Zaichick V, Zaichick S (2014) Use of INAA and ICP-MS for the assessment of trace element mass fractions in adult and geriatric prostate. J Radioanal Nucl Chem 301(2): 383-397
74. Korelo AM, Zaichick V. Software to optimize the multielement INAA of medical and environmental samples. In: Activation Analysis in Environment Protection. Dubna, Russia; Joint Institute for Nuclear Research, 1993, pp.326-332.
75. Schroeder HA, Tipton IH, Nason AP. Trace metals in man: strontium and barium. J Chron Dis. 1972; 25(9): 491-517.