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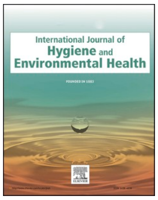

Normal variability of 22 elements in 24-hour urine samples – Results from a biobank from healthy non-smoking adults

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ABSTRACT

Background: Urine is often used for biomonitoring the exposure to elements. However, most studies report concentrations in spot urine samples, which may not accurately mirror the "gold standard" of complete 24-h (24 h) urine samples. There are relatively few data published for 24 h samples, and little information on the within- and between person variability.

Objectives: The present study aimed at assessing variability within and between individuals in 24 h excretion for a number of elements in adults from the general population and the typical 24 h excretion of these elements. In addition, we assessed concentrations adjusted for creatinine and specific gravity (SG), and associations between elements.

Methods: 60 healthy non-smokers (31 women and 29 men) from Sweden, aged 21–64 years, collected all urine during 24 h (split into six separate samples) on two occasions, about one week apart. Concentrations of As, Br, Cd, Co, Cr, Cu, Fe, Hg, Li, Mn, Mo, Ni, P, Pb, S, Sb, Se, Sn, U, V, W, and Zn in urine were analyzed by inductively coupled plasma sector-field mass spectrometry (ICP-SF-MS) and 24 h excretion rates were calculated for each day. The ratio of between-individual variance and the total variance, the intra-class correlation (ICC) was calculated based on natural log-transformed 24 h excretion. Correlation coefficients were calculated between excretion rates (mass/24 h), and concentrations adjusted for creatinine and SG.

Results: Geometric means (GM), and 90-percentiles are presented for each element. The 24 h excretion was higher in men than in women for most elements, and the difference was statistically significant for Cr, Cu, Fe, Li, P, Pb, S, Se, U, V, and Zn. However, for Cd and Co, the excretion was higher in women. Variability between days was low for Cd, Co, Hg, Pb, Sn, Se, V, and Zn (ICC 0.75–0.90), highest for Cr (ICC = 0.3) and Sb (ICC = 0.18), and moderate for the other elements. Spearman's rank correlation coefficients were about 0.8–0.9 for 17 elements, and 0.3–0.7 for Br, Cu, P, S, Se. Excretion of P and S were highly correlated, and also associated with excretion of most of the other elements, especially Cu, Se, V, and Zn. A high correlation was also found between As and Hg, between Mo and W, as well as between Cr, Fe and Mn.

Conclusions: These data present normal variability of 24 h excretion of a number of elements, and can also be used as updated reference levels for elements with no or limited previous literature available. Information on variability within- and between individuals is important to know when designing studies with urine levels of elements used as exposure biomarker in studies of associations with health outcomes.

Abbreviations: SG, specific gravity; BMI, body mass index; GM, Geometric mean; ICP-SF-MS, inductively coupled plasma sector-field mass spectrometry; DL, detection limit; ICC, intra-class correlation.

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1. Introduction

Urine is often used for biomonitoring the exposure to metals and metalloids in occupational and environmental health surveillance and scientific studies. In contrast to blood sampling, urine collection has the advantage of being a non-invasive method. However, most studies in the literature report results for concentrations of elements in spot urine samples, which may not accurately mirror the "gold standard" of concentration in complete 24-h (24 h) urine samples, and there are relatively few data published for 24 h samples (Smolders et al., 2014). Some studies on multiple elements in 24 h urine have focused on occupationally exposed groups, and some on samples from the patients or general population samples, e.g. in Japan (Araki et al., 1986), US (Komaromy-Hiller et al., 2000), the UK (Sieniawska et al., 2012), Belgium (Smolders et al., 2014), and China (Wang et al., 2016). In addition, there are some studies on 24 h urine excretion of single elements such as zinc (Henderson et al., 1996; Ilich et al., 2009), cadmium (Hotz et al., 1999; Uno et al., 2005; Lampe et al., 2008; Akerstrom et al., 2013, 2014), mercury (Akerstrom et al., 2017), chromium (Nomiyama et al., 1980), sulphur (Magee et al., 2004) and phosphorus (Palomino et al., 2013). Older studies may have used analytical methods with limited sensitivity.

There is normal variability between days in 24 h excretion of elements, but few studies did repeated sampling, so there is little information on the relation between within- and between person variability for 24 h excretion. We identified only two studies using repeated sampling of normal excretion in 24 h urine in a limited number of individuals. Four male-female couples in Belgium were examined over six consecutive days (Smolders et al., 2014), and 11 men in China were examined on eight separate days over a 3-month period (Wang et al., 2016, 2019; Chen et al., 2019).

Adjustment for urine dilution is often performed using urinary creatinine or specific gravity (SG) when using spot samples, and it has been discussed which best reflects the long-term excretion (Barber and Wallis, 1986; Suwazono et al., 2005; Smolders et al., 2014; Hoet et al., 2016; Hsieh et al., 2019). There is, however, limited data on impact of adjustment in 24 h urine samples (Sienawska et al., 2012; Wang et al., 2016, 2019; Chen et al., 2019).

The present study aimed at assessing variability within (between days) and between individuals in 24 h urine samples for a number of elements in adults from the general population. In addition typical 24 h excretion, and concentrations adjusted for creatinine and SG are presented, as well as associations between elements. We selected nutritional elements and well recognized toxic elements for analysis, taking into account also the experience of the laboratory with analysis of the respective elements, and other analytical issues.

2. Methods

2.1. Subjects and urinary sampling

A description of the study population and sample collection has been described elsewhere (Sallsten and Barregard, submitted). Briefly, the study was performed in a convenience sample of 60 healthy non-smokers (31 women and 29 men) from Gothenburg, Sweden, not occupationally exposed to metals (Table 1). They were 21–64 years of age (mean 34 years), 52 were never smokers and eight were former smokers. The mean body mass index (BMI) was 24, and 63% (n = 38) were born in Sweden. The frequency of certain food items are shown in Table 1. Only one person was vegetarian. The participants collected all urine (in six separate consecutive samples) during 24 h on two separate days, about one week apart. The mean urinary volume (mean of two days) was 1.7 L (range 0.84–3.7), and the mean creatinine concentration in the 24 h urine samples was 1.1 g/L (0.8 g/L for women and 1.3 g/L for men). The study was approved by the Ethics Review Board at the University of Gothenburg, and all participants signed a written informed consent to participate in the study. The biobank is open for researchers examining normal variability of their favorite biomarker(s).

Table 1
Background data in the 60 individuals providing samples for the varfiability biobank.

	Mean or %	Range
Age	34	21–64
Sex, % women	52%	
Born in Sweden	63%	
Body mass index	24	19–44
Exercise, at least 2 × 30 min/week	78%	
Amalgam fillings	20%[a]	
Meat, meals per week	4.7	0–14
Fish, meals per week	1.8	0–7
Rice, meals per week	2.3	0–10

[a] The percentage for amalgam fillings are based on N=50 (missing data for 10 individuals).

2.2. Analyses of elements in urine

Trace elements analyses in urine were performed at the National Institute of Occupational Health in Oslo, Norway (NIOH). Urine specimens were heated for 1 h at 80 °C prior to analysis in order to prevent laboratory acquired infections and to dissolve urine precipitates. One hundred μL of an internal standard solution containing 2.0 μg mL^{-1} of gallium, germanium, indium and thallium were added to 1 mL of urine in a 15 mL polypropylene tube before dilution to 5 mL with deionized water. The DI water used was prepared by a Milli Q System (18.2 MΩ cm, Millipore Corp., Billerica, USA). The prepared solutions were analyzed by inductively coupled plasma sector-field mass spectrometry (ICP-SF-MS) using an Element 2 mass spectrometer (Thermo Electron, Bremen, Germany) calibrated with urine matrix matched standard solutions. Seronorm™ (Sero AS, Billingstad, Norway)Trace Elements human urine quality control materials were used for quality assurance (Seronorm L1 (LOT 1403080), Seronorm L2 (LOT 1403081). The range (due to more than one analytical run) of the obtained detection limits (DLs) and number of samples below DL for trace elements in urine are shown in supplemental Table S1. The detection limits were calculated daily as three times the standard deviation of "water blank" (see supplemental material) concentrations.

The laboratory is regularly taking part in external quality assurance schemes, which include: Proficiency Testing Program for Blood Lead, EP and Trace Elements organized by Wadsworth Center, New York State Department of Health; German External Quality Assessment Scheme organized by Institute and Outpatient Clinic for Occupational-, Social- and Environmental Medicine, Friedrich-Alexander University Erlangen-Nuremberg; PCI: Interlaboratory Comparison Program for Metals in Biological Matrices organized by The Centre de toxicologie du Québec.

Details on blanks used and operation conditions of the ICP-SF-MS equipment are described in the supplemental material (text and table S2 and S3).

2.3. Data analysis

From the six spot samples the 24 h excretion rates (mass/time) were calculated (one for each day and participant) by adding element masses (obtained from concentrations and volumes) for each spot sample. For one person, two spot samples were erroneously merged, leading to a total number of 719 analyzed samples. For all elements, the detection limit (DL) was determined for each individual measurement. Values below the detection limits were replaced by $DL/\sqrt{2}$, as the geometric standard deviation was always <3 (Hornung and Reed, 1990). For each element, the range of DLs and the number of samples below DL are shown in Table S1.

Concentrations of elements in 24 h urine adjusted for creatinine were calculated by dividing the 24 h mass of each element by the 24 h mass of creatinine. Concentrations in 24 h urine were also adjusted to a specific gravity of 1.015 (close to the median SG of 1.016 in the present study). The SG of the 24 h urine sample was calculated from the SGs in the spot samples, weighted for urine volumes of the six separate samples.

Differences in the 24 h excretion rates between men and women were tested with the Mann-Whitney-Wilcoxon test, and significance was assumed for a p-value <0.05.

Between- and within-individual (inter-day) variability was calculated based on natural log-transformed 24 h excretion rates. Individual variance components were estimated using the PROC MIXED procedure in SAS. Sex was first included in the models as a fixed effect.

Three different variance structures were compared: common between- and within-person variances for men and women, distinct between-person but common within-individual variances, and distinct between- and within-individual variances, using a likelihood ratio test (significance level; $p < 0.05$) where the difference in -2loglikelihood follows a chi square distribution (Rappaport and Kupper, 2008).

The estimated ratio of the between-individual variance to total observed variance, the intra-class correlation (ICC) for the two 24 h urine samples was calculated. If either within- or between-individual variance or both was significantly different in men and women, separate estimates by sex were calculated for ICC. If common variances could be used, they were calculated without sex in the models.

Spearman's rank correlation coefficients were calculated between excretion rates (mass/24 h), and concentrations adjusted for creatinine and SG. In addition, rank correlations between 24 h excretion rates for the 22 elements were calculated.

Calculations were carried out with R version 3.3.1 (R Core Team, 2016) or SAS, version 9.4 (SAS institute, Cary, NC, USA).

3. Results

The 24 h excretions of 22 elements are listed in Table 2. Since the distribution was skewed for many elements, results are presented as GM, 90-percentile, minimum and maximum. As shown in the table, for most elements the difference in GMs for day 1 and 2 was $<5\%$. On the individual level, day-to-day variation was, however substantial for several elements, see below.

The geometric mean 24 h excretion was higher in men than in women for most elements, with a statistically significant difference for Cr, Cu, Fe, Li, P, Pb, S, Se, U, V, and Zn. However, for Cd and Co, the excretion was significantly higher in women. These differences were the same in Day 1 and 2 (data not shown).

Adjustment for urinary creatinine or specific gravity is usually performed, to adjust for urinary dilution in spot samples. Concentrations of the 22 elements in 24 h urine samples adjusted for creatinine and specific gravity are shown in Tables 3 and 4. Since urinary creatinine excretion is lower in women than in men, concentrations adjusted for creatinine are higher in women than in men for most elements, statistically significant for Br, Cd, Co, Cu, Ni, P, and Se (Table 3). When concentrations instead were adjusted for specific gravity (normalized to SG = 1.015) they were higher in women for Cd, and Co, but higher in men for S, V, and Zn (Table 4).

Variability between days was low for Cd, Co, Hg, Pb, Sn, Se, V, and Zn, having within-person (inter-day) variabilities of only 10–25% of total variability (intra-class coefficients 0.75–0.90). It was moderate for As, Br, Cu, Fe, Li, Mn, Mo, Ni, P, S, U, and W (ICC 0.35–0.75), and highest for Cr (ICC = 0.31) and Sb (ICC = 0.18), for details see Table 5 and example plots in Figures S1 – S8. For Co, Fe and U the likelihood ratio test showed that distinct between- and within-person (inter-day) variance should be used and for Cd distinct between-person but common within-person variance. For all other elements the test showed a common variance structure.

The 24 h concentrations of elements adjusted for creatinine or specific gravity, or unadjusted concentrations were highly correlated with the 24 h excretion, as could be expected. Spearman's rank correlation coefficients were about 0.8–0.9 for all elements except for Br (0.53–0.77), Cu (0.34–0.69), P (0.46–0.71), S (0.48–0.75), and Se (0.52–0.78). In the total study population correlations after adjustment for SG were slightly higher than after creatinine adjustment, but the reverse was true after stratification for sex, which removed the impact of higher creatinine excretion in men.

There were many significant associations between the 24 h excretion of the various elements (Figure S9). Excretion of P and S were highly correlated, and also associated with excretion of most of the other elements, especially Cu, Se, V, and Zn. A high correlation was also found between As and Hg, between Mo and W, as well as between Cr, Fe and

Table 2

Excretion of 22 elements in 60 healthy non-smokers in 24 h urine collected on two different days, one week apart. The units are µg/24 h, apart from Br, P, and S with the units are mg/24 h and U where it is ng/24 h. Significant differences (5% level) between men or women are marked in bold.

	Mean of two days							Day 1				Day 2			
	All (N = 60)		Men (N = 29)		Women (N = 31)		P-value men vs. women	All (N = 60)				All (N = 60)			
Element	GM	90%	GM	90%	GM	90%		GM	90%	Min	Max	GM	90%	Min	Max
As	48.1	244	47.9	246	48.3	203	0.76	41.0	199	4.64	935	39.4	234	4.21	1301
Br	3.27	5.04	3.56	5.57	3.03	4.62	0.18	3.20	4.84	0.83	8.50	3.25	5.48	0.92	8.31
Cd	0.12	0.34	0.087	0.28	**0.16**	0.40	0.011	0.12	0.33	0.012	0.49	0.12	0.33	0.012	0.48
Co	0.38	1.20	0.30	1.34	**0.47**	1.02	0.019	0.36	1.16	0.059	2.90	0.38	1.37	0.11	2.99
Cr	0.11	0.19	**0.13**	0.24	0.097	0.16	0.012	0.12	0.24	0.021	0.74	0.097	0.18	0.036	0.38
Cu	8.76	11.9	**10.2**	15.4	7.62	9.81	<0.001	8.67	12.9	3.58	16.4	8.71	12.4	4.65	20.6
Fe	4.36	11.8	**5.42**	11.9	3.55	8.35	0.011	4.34	12.9	1.19	56.0	3.76	10.5	1.08	37.8
Hg	0.23	0.49	0.24	0.48	0.22	0.49	0.67	0.22	0.53	0.068	1.99	0.23	0.46	0.055	1.25
Li	17.5	36.2	**22.2**	37.3	14.0	20.6	<0.001	16.9	38.5	3.57	107	16.6	31.9	4.35	161
Mn	0.18	0.39	0.20	0.39	0.16	0.37	0.086	0.18	0.44	0.027	1.35	0.15	0.39	0.046	0.64
Mo	54.2	101	62.6	104	47.3	101	0.081	50.8	130	10.1	236	53.0	100	12.0	248
Ni	1.47	2.88	1.58	2.98	1.38	2.13	0.31	1.46	3.28	0.35	5.21	1.38	2.66	0.53	8.06
P	867	1286	**1008**	1327	753	1084	<0.001	840	1277	242	2135	871	1281	507	2993
Pb	0.50	0.83	**0.60**	0.96	0.43	0.63	0.001	0.50	0.98	0.15	1.26	0.50	0.76	0.14	1.53
S	744	1146	**903**	1467	620	864	<0.001	756	1157	195	1836	715	1176	323	3245
Sb	0.080	0.28	0.082	0.28	0.079	0.23	0.58	0.068	0.21	0.0098	0.64	0.072	0.24	0.018	14.8
Se	22.6	31.9	**26.3**	50.4	19.7	25.1	<0.001	22.6	36.1	8.81	89.7	22.2	30.2	12.8	123
Sn	0.36	0.90	0.39	1.26	0.33	0.69	0.47	0.36	1.08	0.042	9.49	0.33	0.78	0.084	5.11
U	3.01	5.17	**3.64**	5.42	2.52	4.65	0.007	2.93	5.21	0.46	15.1	2.94	5.60	0.86	9.53
V	0.023	0.042	**0.032**	0.054	0.017	0.025	<0.001	0.023	0.043	0.0036	0.16	0.022	0.043	0.0063	0.20
W	0.079	0.18	0.087	0.14	0.071	0.26	0.23	0.072	0.19	0.015	0.58	0.072	0.19	0.015	0.61
Zn	352	727	**493**	881	258	438	<0.001	335	782	54.8	1143	357	717	83.8	1820

Table 3
Concentrations adjusted for creatinine of 22 elements in 60 healthy non-smokers in 24 h urine collected on two different days, about one week apart. Units are μg/g creatinine, apart from Br, P, and S (mg/g) and U (ng/g). Significant differences between men and women are marked in bold.

	Mean of two days							Day 1				Day 2			
	All (N = 60)		Men (N = 29)		Women (N = 31)		P-value men vs. women	All (N = 60)				All (N = 60)			
Element	GM	90%	GM	90%	GM	90%		GM	90%	Min	Max	GM	90%	Min	Max
As	31.6	143	24.7	130	39.7	143	0.12	26.8	130	3.25	543	25.9	144	2.33	867
Br	2.14	3.24	1.84	2.64	**2.47**	3.92	<0001	2.09	3.10	0.60	5.37	2.14	3.47	0.62	4.80
Cd	0.079	0.25	0.045	0.11	**0.13**	0.28	<0001	0.078	0.23	0.0055	0.45	0.077	0.22	0.0073	0.40
Co	0.25	0.75	0.16	0.64	**0.38**	0.87	<0001	0.24	0.84	0.056	1.40	0.25	0.74	0.067	1.30
Cr	0.073	0.11	0.068	0.12	0.079	0.11	0.10	0.077	0.13	0.026	0.45	0.064	0.12	0.021	0.25
Cu	5.72	7.59	5.26	7.30	**6.18**	7.62	0.008	5.67	7.81	3.20	9.64	5.24	7.54	3.47	10.7
Fe	2.85	5.71	2.83	5.78	2.87	5.45	0.85	2.84	7.73	1.15	27.6	2.48	5.60	0.72	18.8
Hg	0.15	0.33	0.12	0.24	0.18	0.46	0.052	0.15	0.31	0.041	1.25	0.15	0.40	0.034	0.83
Li	11.4	19.8	11.5	20.9	11.4	19.1	0.75	11.1	19.7	3.61	75.8	10.9	18.2	3.8	80.7
Mn	0.11	0.25	0.10	0.21	0.13	0.25	0.23	0.12	0.31	0.019	0.77	0.097	0.23	0.028	0.51
Mo	35.4	70.2	32.6	50.2	38.3	71.9	0.19	33.2	72.1	8.5	128	34.9	59.9	10.5	131
Ni	0.96	1.71	0.81	1.54	**1.12**	1.87	0.027	0.96	1.80	0.25	5.26	0.91	1.65	0.24	3.85
P	567	750	522	649	**612**	832	0.014	549	760	131	1031	574	729	325	1032
Pb	0.33	0.53	0.31	0.51	0.35	0.53	0.49	0.32	0.56	0.093	0.94	0.33	0.55	0.11	0.67
S	485	636	466	595	503	662	0.092	494	649	259	905	471	647	281	855
Sb	0.052	0.17	0.042	0.17	0.064	0.16	0.086	0.044	0.15	0.013	0.35	0.048	0.16	0.012	11.5
Se	14.8	20.7	13.6	22.7	**16.0**	19.7	0.009	14.8	20.5	7.77	50.5	14.6	22.0	8.34	40.6
Sn	0.23	0.58	0.20	0.69	0.27	0.54	0.11	0.23	0.72	0.056	8.34	0.22	0.56	0.049	3.97
U	1.97	3.30	1.89	3.31	2.05	3.29	0.28	1.91	3.26	0.51	7.93	1.93	3.61	0.63	7.13
V	0.015	0.025	0.017	0.028	0.014	0.019	0.34	0.015	0.026	0.0059	0.079	0.014	0.023	0.0063	0.11
W	0.051	0.12	0.045	0.067	0.058	0.17	0.23	0.047	0.12	0.012	0.36	0.047	0.10	0.013	0.53
Zn	231	417	255	442	210	367	0.10	219	414	35.0	564	235	416	62.8	661

Table 4
Concentrations adjusted for specific gravity of 22 elements in 60 healthy non-smokers in 24 h urine collected on two different days, about one week apart. Units are in μg/L, apart from Br, P, and S (in mg/L) and U (in ng/L). Significant differences between men and women are marked in bold.

	Mean of two days							Day 1				Day 2			
	All (N = 60)		Men (N = 29)		Women (N = 31)		P-value men vs. women	All (N = 60)				All (N = 60)			
Element	GM	90%	GM	90%	GM	90%		GM	90%	Min	Max	GM	90%	Min	Max
As	28.3	124	24.6	124	32.2	123	0.26	23.7	114	2.43	472	23.4	146	1.37	734
Br	1.91	2.56	1.81	2.40	2.00	2.56	0.27	1.85	2.53	0.62	5.20	1.93	2.72	0.66	3.45
Cd	0.071	0.22	0.045	0.12	**0.11**	0.26	<0.001	0.069	0.22	0.0062	0.35	0.069	0.21	0.0094	0.36
Co	0.22	0.69	0.15	0.69	**0.31**	0.69	<0.001	0.21	0.78	0.057	1.65	0.23	0.69	0.048	1.52
Cr	0.066	0.11	0.067	0.11	0.064	0.10	0.86	0.068	0.12	0.022	0.46	0.058	0.11	0.020	0.19
Cu	5.13	7.26	5.21	6.79	5.06	7.25	0.86	5.01	6.87	2.40	9.76	5.18	7.66	3.09	9.35
Fe	2.55	5.69	2.78	5.71	2.34	5.14	0.26	2.51	6.67	0.74	24.0	2.24	4.95	0.67	15.5
Hg	0.13	0.28	0.12	0.25	0.15	0.29	0.35	0.13	0.31	0.040	1.17	0.13	0.29	0.032	0.71
Li	10.2	17.2	11.3	19.5	9.22	16.1	0.084	9.77	21.3	3.14	51.6	9.85	17.9	2.49	85.7
Mn	0.10	0.24	0.10	0.24	0.10	0.25	0.81	0.10	0.26	0.023	0.58	0.088	0.21	0.024	0.41
Mo	31.8	59.7	32.3	55.9	31.3	63.4	0.94	29.4	60.7	8.09	114	31.5	64.2	11.7	118
Ni	0.86	1.52	0.81	1.43	0.91	1.57	0.51	0.84	1.72	0.18	4.24	0.82	1.47	0.14	4.08
P	506	632	514	632	498	618	0.42	485	620	152	753	518	659	328	807
Pb	0.29	0.45	0.30	0.49	0.28	0.43	0.35	0.29	0.48	0.085	0.72	0.30	0.44	0.12	0.77
S	432	508	**459**	534	409	472	0.002	437	503	201	787	425	506	236	715
Sb	0.047	0.15	0.042	0.16	0.053	0.14	0.39	0.039	0.11	0.010	0.32	0.043	0.15	0.0096	9.15
Se	13.2	18.3	13.4	17.8	13.1	18.3	0.51	13.1	19.0	8.20	50.1	13.2	17.5	6.95	35.5
Sn	0.21	0.51	0.20	0.57	0.22	0.46	0.94	0.21	0.62	0.044	7.85	0.20	0.52	0.054	3.17
U	1.76	2.84	1.86	2.72	1.67	2.82	0.69	1.69	2.60	0.45	10.4	1.75	3.45	0.53	7.09
V	0.013	0.022	**0.016**	0.030	0.011	0.018	0.006	0.013	0.023	0.0037	0.072	0.013	0.023	0.0047	0.11
W	0.046	0.098	0.045	0.073	0.047	0.14	0.94	0.042	0.11	0.0098	0.25	0.043	0.099	0.013	0.49
Zn	207	402	**251**	423	172	316	0.003	193	391	28.0	549	212	365	43.9	623

Mn.

4. Discussion

The present study presents results for excretion of 22 elements in repeated full 24 h samples in 60 adult non-smokers from the general population. For several elements there are few previous data in the literature, and for some of them such data are lacking completely.

4.1. 24 h excretion of 22 elements and differences between men and women

This section compares our results with previous studies, with some comments on sources and differences between men and women. Elements for which urinary elimination is not important, as well as sulphur and phosphorous are discussed together in the end of the section.

4.1.1. Antimony

Sb is a non-essential element with a short half-life in urine. Milk and seafood are examples of dietary sources (Tylenda et al., 2015). The 24 h GM excretion was only about 0.08 μg, similar in men and women. This is

Table 5
Intra-class correlation (ICC; ratio between-individual variance/total variance) for 24 h excretion of 22 elements in 60 healthy non-smokers. Samples were collected on two separate days, about one week apart. All data were log-transformed before calculation of ICC. If either within-or between-individual variance was significantly different in men and women, Separate estimates of ICC are presented.

Element	ICC	ICC women	ICC men
As	0.52		
Br	0.63		
Cd		0.81	0.91
Co		0.82	0.95
Cr	0.31		
Cu	0.66		
Fe		0.22	0.69
Hg	0.91		
Li	0.39		
Mn	0.38		
Mo	0.56		
Ni	0.55		
P	0.56		
Pb	0.81		
S	0.71		
Sb	0.18		
Se	0.76		
Sn	0.83		
U		0.59	0.66
V	0.75		
W	0.43		
Zn	0.81		

lower than the median of 0.29 μg/24 h reported from a renal stones clinic in the UK by Sienawska et al. (2012) and 0.15 μg/24 h in Chinese young men (Wang et al., 2019).

4.1.2. Arsenic

The GM amount of total As was 48.1 μg/24 h with no significant difference between men and women. This is higher than previously reported medians of 36 μg/24 h (Sieniawska et al., 2012) and 20 μg/24 h (Wang et al., 2016). The urinary concentration of total As is strongly related to the consumption of seafood (Smolders et al., 2014). This may explain the differences in 24 h urinary As excretion. It has also been shown that the As concentration in fish muscle differs substantially between species (Sobolev et al., 2019). Only a minor part of the As exposure in the general population is inorganic As. For example, Hinwood et al. (2002) found that 70% of Australian adults had a concentration of inorganic As in 24 h urine samples below the detection limit, which was 2 μg/L. On the individual level it is not possible to assess inorganic As without speciation.

4.1.3. Bromine

The GM in the present study was 3.3 mg, with no difference between men and women. We found only one previous report in the literature on Br in 24 h urine. Wester (1974) reported a mean of 3.2 mg/24 h in six hypertensive adults.

4.1.4. Cadmium

For Cd, smoking is a strong predictor of exposure, and the mean level in the present study of non-smokers was only 0.12 μg/24 h. We found few studies reporting 24-h excretion of Cd in in non-smokers. The 24 h urinary Cd was reported to be 0.4 μg in elderly US non-smokers in the 1990s (Lampe et al., 2008), and 0.17 μg in 40-year old non-smokers in Sweden in the 2000s (Akerstrom et al., 2014). In combined groups of smokers and non-smokers the median Cd level was about 1 μg/24 h in Japan (Uno et al., 2005), 0.9 μg/24 h in UK patients (Sienawska et al., 2012), and 0.8 μg/24 h in the Belgian Pheecad population where one third were smokers (Hotz et al., 1999). Urinary Cd levels are known to be higher in Japan than in Europe and the US due to rice consumption (Nordberg et al., 2015), and also high in Belgium due to contamination from zinc smelters (Hotz et al., 1999). The excretion of Cd was about two-fold higher in women than in men. This difference between non-smoking women and men has been shown previously (Akerstrom et al., 2014) and is considered a result of higher gastrointestinal absorption of cadmium in women due to lower iron stores (Nordberg et al., 2015; Berglund et al., 1994; Meltzer et al., 2010).

4.1.5. Chromium

The GM urinary content of Cr was 0.11 μg/24 h, slightly higher in men than in women. This is somewhat lower than the median amount of 0.25 μg/24 h reported previously (Sieniawska et al., 2012) and much lower than the median of 2.6 μg/24 h reported by Komaromy-Hiller et al. (2000) in US patients, and by Chen et al. (2019) in eleven Chinese men.

4.1.6. Cobalt

The Co excretion was 0.38 μg/24 h, and significantly higher in women than in men. This may be due to higher prevalence of iron deficiency in women, as iron deficiency may substantially increase the uptake of Co (Meltzer et al., 2010). The 24 h Co excretion reported by Sieniawska et al. (2012) was higher, 1.4 μg/24 h, while Komarory-Hiller et al. found 0.7 μg/24 h, and Wang et al. (2016) 0.24 μg Co/24 h, results which are more in agreement with ours.

4.1.7. Lead

The geometric mean 24 h excretion of Pb was 0.5 μg which is much lower than reported in some previous studies in non-occupationally exposed adults after year 2000; 2.0 μg in the US (Komaromy-Hiller et al., 2000), 2.4 μg in the UK (Sienawska et al., 2012), and 3.1 μg in China (Wang et al., 2016). Likely explanations are that Pb exposure has decreased substantially in the last couple of decades, that levels still differ between countries, and that the present study included only non-smokers. Studies of U–Pb in spot urine samples from adults in Germany (Heitland et al., 2006), Sweden (Sommar et al., 2014), and the US (Buser et al., 2016), have shown levels consistent with the 24 h excretion in the present study. The 24 h excretion was somewhat higher in men than in women.

4.1.8. Lithium

Li is a non-essential metal used in the manufacturing of batteries, ceramics, glass, and medicines. Environmental exposure occurs mainly through food and drinking water. The average dietary exposure to lithium in a recent study from New Zealand was estimated to be between 0.14 and 0.31 μg/kg body weight/day among adult male and female, with the highest concentrations in fruits, vegetables, crustaceans and shellfish (Pearson et al., 2020). Elevated lithium exposure (>1,000 μg/L) through drinking water has been reported in some areas in Austria and South America (Kapusta et al., 2011; Zaldivar, 1980; Concha et al., 2010). In Sweden, Li concentrations in well water are generally low (median 6.7 μg/L; Harari et al., 2017). Bottled water may contribute to elevated Li exposure as certain brands have shown to contain lithium concentrations of up to 5,000–10,000 μg/L (Krachler and Shotyk, 2009). The daily dose of Li, prescribed for mood disorders ranges between 300 and 1,300 mg. The GM Li excretion in this study was 18 μg/24 h and statistically significantly higher among men (22.2 vs 14.0 μg/24 h among women). Our results are very similar to the median of 19 μg/24 h in UK patients (Sienawska et al., 2012). Li is readily absorbed from the intestinal tract, and at high intake it is mainly excreted in urine (95%) with a half-life of 1–4 days (Davanzo et al., 2011). Toxicokinetics at low-dose Li from environmental sources are, however, largely unknown.

4.1.9. Nickel

The GM excretion of the essential element Ni was 1.5 μg/24 h, similar in men and women. This is lower than 5.1 μg/24 h reported in patients from the UK (Sieniawska et al., 2012) and 3.3 μg/24 h from US patients (Komary-Hiller et al., 2000), but similar to the median of 1.9

μg/24 h in Chinese men (Wang et al., 2016). Urine is the major elimination pathway of Ni, and the half-life of U–Ni is about one day (Klein and Costa, 2015).

4.1.10. Mercury

The 24 h excretion of Hg was 0.23 μg and very similar in men and women. This is lower than reported in a few previous studies. Sienawska et al. (2012) found a median U–Hg of 0.7 μg/24 h in UK adults, Komaromy-Hiller et al. (2000) 1.0 μg/24 h in US adults, and Akerstrom et al. (2017) 1.9 μg (mean) in Swedish adults. The number of dental amalgam fillings has, however, a strong impact on U–Hg, and in the study by Akerstrom et al. (2017) >90% had dental amalgam fillings, while that was the case in a minority of the individuals in the present study.

4.1.11. Selenium

The excretion of Se was 26.3 and 19.7 μg/24 h in men and women, respectively. These levels are very similar to the results of around 26 and 18 μg/24 h in men and women reported from UK patients by Sieniawska et al. (2012). They are, however, much lower than the median levels of 128 and 109 μg/24 h reported in men and women from Japan (Yoneyama et al., 2008), and around 162 μg/24 h reported in an American population (Longnecker et al., 1996). Chen et al. (2019) found a low median of 9.4 μg/24 h in eleven Chinese men. Substantial differences in urinary Se levels were observed in an experimental study of subjects on a diet high in Se (114 μg/24 h) compared to low (14.9 μg/24 h) (Hawkes et al., 2003). The dietary intake of Se from food is dependent on the soil from where crops for human and animal consumption are grown (Alexander, 2015), which is the likely explanation of differences between countries.

4.1.12. Tungsten

The GM 24 h urinary excretion of W was only 0.08 μg, similar in men and women. This is slightly lower than the median reported in Chinese men (Wang et al., 2019) and substantially lower than the GM of around 9 μg/24 h reported in UK patients (Sieniawska et al., 2012). Recent studies of spot urine samples have reported median concentrations of 0.04 μg/g creatinine and 0.07 μg/L in occupationally unexposed populations (De Palma et al., 2010; Ellingsen et al., 2017). Moreover, Alimonti et al. (2005) found a GM of 0.05 μg/L in spot samples from 50 Italian individuals. This suggests that the W levels reported by Sieniawska et al. (2012) are too high.

4.1.13. Uranium

Urine is the major elimination pathway for U, but human exposure is normally low. Therefore 24 h U levels were below the detection limits in previous studies from the UK and the US (Sieniawska et al., 2012; Komary-Hiller et al., 2000). Uranium in diet often originates from dirt contaminating potatoes or certain vegetables (Keith et al., 2015). Table salt is another source, and in areas with high U content in rock and soil, drinking water levels of U may be high (Kurttio et al., 2002). In the present study the GM of U was 3 ng/24 h. This is consistent with reports from the US of U levels of 7–8 ng/gC in spot samples (Keith et al., 2015), but much lower than the median of 55 ng/24 h reported by Wang et al. (2019) in eleven Chinese men. A study in a Finnish population consuming drinking water from drilled wells in granite bedrock showed a median U level in overnight urine samples of 78 μg/L (Kurttio et al., 2002), i.e. >10 000 times higher than in the present study.

4.1.14. Vanadium

The GM urinary V excretion of 0.02 μg/24 h is substantially lower than the median amount of 1.9 μg/24 h reported in a previous study (Sieniawska et al., 2012). As for W, there is little information published on 24 h urinary excretion of V. However, spot urine samples of non-occupationally exposed individuals have shown concentrations of 0.05 μg/g creatinine (Ellingsen et al., 2017) or around 0.1–0.2 μg/L (Barceloux, 1999; Gruzewska et al., 2014). This may indicate that also the V levels reported by Sieniawska et al. (2012) are too high.

4.1.15. Iron, manganese, tin, copper, zinc and molybdenum

For the essential elements Fe, Mn, Sn, Cu, Zn and Mo, excretion in feces (mainly via bile) is more important than elimination in urine (Lucchini et al., 2015; Ellingsen et al., 2015; Ostrakhovitch, 2015; Sandstead 2015; Tallkvist et al., 2015). This limits the importance of urine biomonitoring for these elements. However, increased levels of Cu in urine are found in Wilson's disease, and in other conditions with disturbed copper transporters. The GM 24 h excretion of Fe (4.4 μg), Mn (0.18 μg), Sn (0.36 μg), and Cu (8.8 μg) were lower than reported in UK patients (Fe: 12 μg, Mn: 0.7 μg, Sn: 2.3 μg, Cu: 22 μg) by Sieniawska et al. (2012) and in Chinese men (Fe: 38 μg, Mn: 1.9 μg, Cu 11 μg) by Chen et al. (2019) and Wang et al. (2019). The GM excretion of Zn was 352 μg/24 h, and higher in men than in women. The results for Zn are similar to those found in the UK (Sieniawska et al., 2012), in the US (Komary-Hiller et al., 2000), as well as in Chinese men (Chen et al., 2019). Homeostasis of Zn is maintained by regulating gastrointestinal absorption as well as urinary excretion. For Mo, the GM in the present study was 54 μg/24 h, with no difference between men and women. Similar results were found in UK patients (66 μg/24 h) (Sieniawska et al., 2012) and in Chinese men (96 μg/24 h) (Wang et al., 2016). Mo excretion in bile is more important than excretion in urine. Cereals and dairy products are the most important sources (Swedish National Food Agency, 2012).

4.1.16. Sulphur and phosphorous

The 24 h excretions of S (GM 744 mg) and P (GM 867 mg) are in agreement with previous literature (Magee et al., 2004; Palomino et al., 2013). Dietary intake of S and P is mainly derived from protein, but for S also inorganic sulfates and sulfites contribute (Magee et al., 2004). Urine is the major elimination route for both elements.

4.2. Variability within and between individuals

Urinary excretion of elements varies over the day (Smolders et al., 2014; Wang et al., 2016, 2019) and therefore the within-person variance is reduced in 24 h urine samples compared to spot samples. In spite of this we found considerable within-person variability in 24 h samples for many elements. This was, however, not the case for Pb, Cd and Hg, for which the low within-person (inter-day) variability and high ICCs reflect the long half-lives of these elements. For Cd this is in agreement with previous findings by Akerstrom et al. (2014) and Wang et al. (2016). For Pb, Wang et al. (2016) found high within-person variability in Chinese men, and a very low ICC of 0.01. In the present study ICC was high (≥0.75) also for Co, Se, Sn, V, and Zn. This is in agreement with the study in Chinese men for Co (Wang et al., 2016) and Zn (Chen et al., 2019), while the ICC for Se was much lower in that study (Chen et al., 2019). For Sn and V we found no published studies on ICC. ICC values approaching or exceeding 0.75 are desirable for good to excellent reliability in exposure classification, while an ICC below 0.4 indicates that a single sample (in our case a 24 h urine sample) will not provide reliable exposure classification (Rosner, 2015).

We found low ICC (<0.4) for Sb, Cr and Mn in agreement with the study in Chinese men (Wang et al., 2016, 2019; Chen et al., 2019). For Li we found no previous published study on ICC. For Mo, Ni, U, W and P) the ICCs were around 0.5 in our study, which is much higher than the ICCs presented for Mo, Ni, U, and W in the Chinese study (Wang et al., 2016, 2019). ICC around 0.5 indicate fair to good reproducibility (Rosner, 2015).

There seem to be very disparate results for some of the elements, especially for Pb and Se but also for Cu, Mo, Ni and U. Further investigations on variability of metals in urine for 24 h samples, first morning samples as well as for spot samples from different time of the day are needed in order to provide reliable exposure assessment in epidemiological studies on health effects. For elements with long half-life the associations between concentrations adjusted for creatinine or specific gravity can be expected to be quite strong. This has been demonstrated in some studies, which include both first morning urine and 24 h urine samples, e.g. Pearson correlation coefficients of 0.75 for cadmium (Akerstrom et al., 2013), and 0.84 for mercury (Akerstrom et al., 2017). We hope to be able to present such data also for other elements and other day-time sampling times.

4.3. Impact of adjustment for creatinine or SG

It is not surprising that excretion of elements in mass/24 h was highly correlated with concentrations adjusted for creatinine or specific gravity, or unadjusted concentrations. Such adjustment is mainly done to take into account variability in urinary flow rate, which is less relevant in 24 h samples. The fact that creatinine-adjusted 24 h concentrations for some metals are higher in women is a natural result of the lower average 24 h excretion of creatinine in women.

4.4. Associations between elements – common sources

The most important route of exposure for all elements examined is diet. Excretion of S and P is largely affected by intake of protein, with meat, fish and dairy products a s important sources. This likely explains the high correlation between excretion of S, P, and Se, and also moderate associations between these elements and Fe, Cu, Zn, and V (Swedish National Food Agency, 2012). For Cu, Zn, Fe and Mn, also cereals are important dietary contributors (Swedish National Food Agency, 2012), contributing to intercorrelations. The high correlation between As and Hg is likely due to fish consumption (Swedish National Food Agency, 2012).

4.5. Strengths and limitations

The present study is moderately sized (N = 60) and limited to Sweden. On the other hand, the individuals had mixed ethnic origin. The study included only non-smokers, which is a strength if impact of dietary sources is examined, but a limitation if there is a focus on the impact of smoking. It adds to the knowledge of levels and variability in 24 h excretion of many elements, since for most of the elements the only prior data on ICC was derived from repeated samples in 11 young Chinese men (Wang et al., 2016, 2019; Chen et al., 2019).

4.6. Implications and conclusions

Information on variability within- (inter-day) and between individuals is important when designing studies where urine levels of elements are used as exposure biomarker in studies of associations with health outcomes. A high ICC is necessary in such studies if only a single 24 h sample is available since otherwise the true exposure-response associations will be attenuated (Rappaport and Kupper, 2008). These data on 24 h excretion of a large number of elements can also be used as updated reference levels, especially for a number of elements with no or limited previous data available.

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Ethics approval

The study was approved by the Ethics Review Board at the University of Gothenburg, and all participants signed a written informed consent to participate in the study.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2021.113693.

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