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Creatinine as reference parameter for the concentration of substances in urine – Addendum to the conversion of volume- or creatinine-related analytical results

Assessment Values in Biological Material – Translation of the German version from 2020

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M. Bader[1]
T. Jäger[1]
H. Drexler[2,*]
A. Hartwig[3,*]
MAK Commission[4,*]

1 BASF SE, Carl-Bosch-Str. 38, 67056 Ludwigshafen am Rhein, Germany

2 Chair of the Working Group "Setting of Threshold Limit Values in Biological Material", Deutsche Forschungsgemeinschaft, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Henkestr. 9–11, 91054 Erlangen, Germany

3 Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute of Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany

4 Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

* E-Mail: H. Drexler (hans.drexler@fau.de), A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated creatinine as reference parameter for the concentration of substances in urine. The Commission has established factors for the conversion of volume-related into creatinine-adjusted results, and vice versa. A factor (multiplicator) of 0.83 for the conversion of volume-related to creatinine-adjusted data was derived from studies with a balanced gender ratio. The standard factor for conversion of creatinine-adjusted to volume-related results is 1.2. In study groups with predominantly male test persons, the factor for conversion of volume-related to creatinine-adjusted values is 0.71, and 1.4 for converting creatinine-adjusted to volume-related values. In study groups with predominantly female test persons, the conversion factor is 1.0. From the results for spontaneous urine samples, the total excretion of the creatinine parameter cannot be directly extrapolated to a whole day. Calculations relating to 24-h urine samples are based on an average creatinine output of 1.3 g per day (range 1.0–1.6 g) or 20 mg/kg body weight (range 15–25 mg/kg body weight).

Introduction

The creatinine concentration in urine is, besides volume, osmolality, specific gravity and excretion rate, one of the most frequently used adjustment factors to give substance concentrations or amounts in urine. While the excretion rate as part of the clearance is a toxicokinetic key parameter of a substance, other adjustment factors are mainly used to compensate for diuresis-related differences in the dilutions of spot urine samples (Bader et al. 2016; UBA 2005; Weihrauch et al. 1999).

Under normal conditions about 125 ml/min primary urine is formed in the glomeruli of an adult person, which is almost completely reabsorbed (about 60% in the proximal tubule, about 20% in Henle's loop, about 20% in the distal tubules and the collecting ducts) (Heidenreich and Fülgraff 1993). Only about 1 ml of the primary urine per minute goes into the bladder, so that the eliminated amount per hour is about 50–60 ml urine. The total volume of urine excreted per day is on average about 1200–1500 ml; however, it is considerably modified by the amount of beverages consumed and other influencing factors, for example by age, gender, medical drugs, and the individual physiology (Weihrauch et al. 1999). To persons at heat workplaces or such with limited possibilities of beverages supply (for example prolonged working in protective suits) the above-mentioned average data apply only to a limited extent.

The excretion of creatinine in urine depends mainly on the muscle mass of the respective person. Creatinine is a metabolic product of creatine phosphate, which is used for the storage of energy in the muscle. The creatinine amount in urine as well as the urine volume are therefore dependent on individual factors, such as age, gender, nutrition and muscle mass. Especially during exercise and after high-dose creatine supplementation, the creatinine excretion in urine can increase (for example Havenetidis and Bourdas 2003; Kachadorian and Johnson 1971; Kim et al. 2011), but may decrease again at higher physical activity (for example Kachadorian and Johnson 1971). The average amount of creatinine excreted daily in the urine of adult persons in the age group 30–60 years is about 1.0–1.6 g (15–25 mg/kg body weight) (Weihrauch et al. 1999). Due to the on average lower muscle mass of women, their urinary creatinine concentration is also lower (UBA 2007).

The creatinine excretion is not subject to significant variations during the day (Szadkowski et al. 1970). As a result, the plasma level and thus also the absolute renal filtration remain relatively constant, and the creatinine concentration in urine depends directly on the volume of the primary and secondary urine: at higher supply of beverages and increased diuresis, the creatinine concentration in urine will decrease, at dehydration and reduced diuresis, the creatinine concentration will increase. Results of studies, in which the evaluation of biomarkers was both volume- and creatinine-adjusted show that the variability of the excretion of biomarkers can be reduced when creatinine is used as reference (for example Will et al. 2007).

Using a creatinine-related reference is meant to compensate for diuresis-related variations of the concentration in urine, so that an over- or underestimate of the internal exposure by highly diluted or highly concentrated urine samples can be avoided. For most hazardous substances, however, the proportion of tubular reabsorption with regard to the amount of substance eliminated in the primary urine is not exactly known. The relation to creatinine is often established empirically, especially when the biomarker correlates with creatinine (Bader et al. 2007; UBA 2005).

In biomonitoring studies, biomarker concentrations in urine are usually given either in relation to volume or adjusted to creatinine. For this reason, a direct comparison of the results of different studies cannot be made without adjustment to their reference. For this purpose, a general conversion factor is required, which, if possible, considers the special characteristics of study groups from the world of work thus enabling an at least approximate comparison of study results to be made.

Studies on creatinine concentration in urine

Investigations of creatinine concentration in urine samples in larger study collectives from the general population and industry were published by the Federal Environmental Agency (Umweltbundesamt) (Becker et al. 2002), by Barr et al. (2005), Cocker et al. (2011), and Bader et al. (2013) (Table 1).

Tab. 1 Creatinine concentrations in selected study collectives

	Becker et al. (2002) general population Germany	**Barr et al. (2005) general population USA[a)]**	**Cocker et al. (2011) industrial workers United Kingdom**	**Bader et al. (2013) industrial workers Germany**
Number of samples (n)	4730	8150	49 506 (20 433)[g)]	6438
♂ (n)	2384	3820	39 610 (15 111)[g)]	6148
♀ (n)	2346	4330	3207 (1558)[g)]	290
no data (n)	–	–	6689 (3764)[g)]	–
age (years)	18–69	6–>70	16–70	16–79
creatinine ♂ [g/l]				
mean value	1.69	1.44	1.47	1.46
median	**1.60**	**1.33**	**1.36**	**1.37**
5th–95th percentile	0.70[b)]–3.16	0.46[c)]–2.49[c)]	0.42–2.71	0.35–2.86
range	0.70[b)]–4.94	–	0.20[d), e)]–3.51[d), f)]	0.08–9.76
creatinine ♀ [g/l]				
mean value	1.29	1.06	1.11	1.12
median	**1.13**	**0.92**	**1.00**	**1.00**
5th–95th percentile	0.49[b)]–2.66	0.25[b)]–2.06[c)]	0.23–2.38	0.17–2.67
range	0.49[b)]–5.00	–	0.12[d), e)]–3.17[d), f)]	0.08–3.81
creatinine all [g/l]				
mean value	1.49	1.25	1.36	1.45
median	**1.38**	**1.13**	**1.36**	**1.36**
5th–95th percentile	0.57[b)]–2.95	0.31[b)]–2.30[c)]	0.36–2.60	0.33–2.84
range	0.57[b)]–5.00	–	0.17[d), e)]–3.39[d), f)]	0.08–9.76

[a)] non-hispanic whites; [b)] 10th percentile; [c)] 90th percentile; [d)] calculated from original data (mmol/l); [e)] 1st percentile; [f)] 99th percentile; [g)] samples (persons)

In the Third German Environmental Survey 1998 (GerES-III) urine samples from a total of 4630 persons of a population-representative random sample were analysed (Becker et al. 2002, p. 218). The median value for the total collective was 1.38 g creatinine per litre urine (Table 1), the values of men (1.60 g/l) being higher than those of the women (1.13 g/l). In a comparable study within the Third National Health and Nutrition Examination Survey (NHANES-III), Barr et al. (2005) found a lower total median of 1.13 g creatinine/l urine in a study collective of non-hispanic whites from the USA compared with the GerES-III collective. In this case as well, the median of men (1.33 g creatinine/l urine) was above that of women (0.92 g creatinine/l urine). The higher results of the GerES-III collectives compared with the NHANES-III collective can be explained by different sampling times: while morning urine was analysed in the GerES-III collective, no fixed sampling time was specified for the NHANES-III collective. Morning urine samples are on average more concentrated than afternoon or evening samples (Barr et al. 2005; Cocker et al. 2011).

Concerning urine samples collected during occupational health or industrial hygiene investigations, the results of Cocker et al. (2011) and Bader et al. (2013) were consistent with regard to the median values found of 1.36 g creatinine/l urine (total study groups). The median values of the male study subgroups were 1.36 g creatinine/l (Cocker et al. 2011) and 1.37 g creatinine/l (Bader et al. 2013) and thus higher than those in the female subgroup (1.00 g creatinine/l urine in both studies). In both studies, sampling was carried out during the work day, as a rule after a shift or after the end of an exposure and thus randomly distributed over the day in the overall collective.

When reviewing the four studies, the considerably different sex ratios in the study collectives besides the different sampling times have to be taken into account: in the population-related studies by Becker et al. (2002) and Barr et al. (2005) men and women are approximately equally distributed according to the prevalence in the general population. In the collectives by Cocker et al. (2011) and Bader et al. (2013) on the other hand, the percentage of men was more than 90%.

Summary and recommendation

From the above-described studies with balanced gender ratio a median creatinine level of 1.2 g/l urine and thus a

conversion factor (multiplicator) of 0.83

for the conversion of volume-related to creatinine-related data can be derived. This applies in particular to calculations for the derivation of biological tolerance values (BAT-values). Vice versa, the conversion factor is 1.2.

In the case of study groups with predominantly male test persons, the conversion factors are 0.71 (conversion of volume-related to creatinine-related values) and 1.4 (conversion of creatinine-related to volume-related values). In study groups with predominantly female test persons, the conversion factor is 1.0.

From the results for spontaneous urine samples, usually collected in the afternoon after a work shift, the total creatinine excretion cannot be extrapolated to a whole day. Calculations relating to 24-h urine samples are based on an average creatinine amount of 1.3 g (range 1.0–1.6 g) or 20 mg/kg body weight (range 15–25 mg/kg body weight) (Wallach 1986; Weihrauch et al. 1999).

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