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Selenium and its inorganic compounds – Addendum for evaluation of BAR

Assessment Values in Biological Material – Translation of the German version from 2021

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated biological reference values (BAR) for selenium [7782-49-2] in plasma and in urine to characterise the internal exposure. Selenium is an essential trace element, which is incorporated in considerable amounts by nutrition. Occupational exposure can lead to an additional selenium uptake. Its metabolism and distribution behaviour are complex. In plasma most selenium is bound to proteins and demonstrates slow kinetics with elimination half-lives of 65–300 days. In contrast, selenium in urine shows faster elimination kinetics than plasma and can display the exposure of the directly preceding work shift.

There are extensive data of the German environmental specimen bank about selenium in plasma of persons not occupationally exposed to selenium at four different geographic regions of Germany, which did not reveal significant differences. These results are in good accordance with those of control groups in studies on occupationally exposed workers in Germany. Therefore, a BAR of 100 µg selenium/l plasma was evaluated. No restriction was made for the sampling time.

Selenium in urine of German adults was determined in several studies, each with limited numbers of participants. They show largely consistent results. Moreover, the German data are in good agreement with two studies in Belgium and the United Kingdom. Selenium excretion in urine is tightly associated with creatinine excretion. In a synopsis of the Western European studies, a BAR of 30 µg selenium/g creatinine was evaluated. As an accumulation has to be considered, the sampling time in case of long-term exposure was set at the end of the shift after several shifts.

BAR (2020)	**100 µg selenium/l plasma/serum** Sampling time: not fixed
	30 µg selenium/g creatinine Sampling time: for long-term exposures: at the end of the shift after several previous shifts
BAT value (2010)	**150 µg selenium/l serum** Sampling time: not fixed
MAK value (2010)	**Selenium and its inorganic compounds:** **0.02 mg selenium/m³ I (inhalable fraction)** **Hydrogen selenide: 0.006 ml/m³ ≙ 0.02 mg/m³**
Absorption through the skin (2010)	Selenium and its inorganic compounds: H Hydrogen selenide: –
Carcinogenicity (1999)	Category 3
Prenatal toxicity (1999)	Group C

In 2010, selenium and its inorganic compounds were evaluated and a biological tolerance value (BAT value) in serum was derived (Rettenmeier 2019). In this addendum, the data for the derivation of biological reference values (BAR) in plasma and urine are evaluated.

1 Metabolism and Toxicokinetics

Selenium is an essential trace element and an essential component of several enzymes, including glutathione peroxidases, thioredoxin reductases and deiodinases (Behne and Kyriakopoulos 2001; Labunskyy et al. 2014). However, adverse effects have been observed with excessive intake, as already described in the available documentations of the maximum workplace concentration (MAK value) and BAT values (Greim 1999, 2001; Hartwig 2014, 2015; Rettenmeier 2019). Selenium is absorbed orally, by inhalation and dermally, with absorption via nutrition being the main route apart from occupational exposure (WHO 1987).

While selenium in plasma mainly reflects longer-term selenium exposure, selenium in urine can display also the exposure of the directly preceding work shift (Göen and Greiner 2018; Greiner et al. 2018, 2020).

Due to differences in metabolism, a distinction must be made between organic and inorganic selenium exposures (Jäger et al. 2016 a, b; Rettenmeier 2019).

2 Critical Toxicity

Information on critical toxicity can be found in the documentations of selenium and its inorganic compounds (Hartwig 2014, 2015; Rettenmeier 2019). The diabetogenic effect is currently considered to be the most critical endpoint.

3 Exposure and Effects

Since the documentation for deriving the BAT value for selenium, new studies have been published.

3.1 Relationship between external and internal exposure

In 17 workers of a selenium-processing company, the selenium concentration in the air was related to the selenium concentration in plasma and erythrocytes after the end of the shift (Greiner et al. 2018). The exposed persons were fifteen men and two women aged 23 to 60 years, eleven of whom were smokers. The median airborne selenium concentration was 319 µg/m³ (range < detection limit (~1.19 µg selenium/m³) to 2394 µg selenium/m³). In 13 of the 17 workers exposure exceeded the currently valid MAK value of 20 µg selenium/m³.

Selenium concentrations in plasma were in the range from 61.7 to 123 µg/l (median 105 µg/l) in the exposed group. For comparison, the selenium concentrations in plasma and erythrocytes were measured in an age-matched control group (18 men, 2 women, 21 to 64 years, 11 smokers) from the same region. Their values were in the range from 70.6 to 115 µg selenium/l plasma (median 76.9 µg/l) and were thus statistically significantly lower than in the exposed group. The BAT value of 150 µg selenium/l was not exceeded in the exposed group. No statistically significant correlation was found between the total selenium concentration in the air and the selenium concentration in the plasma.

The urinary concentrations in the exposed workers of this study ranged from 20.7 to 253 µg selenium/g creatinine (median 50.6 µg selenium/g creatinine) before the start of the shift (Greiner et al. 2020). At the end of the shift, they increased statistically significantly and were 22.1 to 340 µg selenium/g creatinine (median 71.8 µg/g creatinine). In the control group, statistically significantly lower values were found both before and after the shift, ranging from 9.20 to 40.6 µg selenium/g creatinine (median 18.7 µg/g creatinine). Selenium concentrations in post-shift urine correlated statistically significantly with total selenium concentrations in the air ($R^2 = 0.497$, 95% CI (confidence interval): 0.279–0.899). When regarding the difference between selenium in urine before the start of the shift and after the end of the shift, there was a statistically significantly stronger correlation with air exposure ($n = 14$; $R^2 = 0.866$, 95% CI: 0.791–0.978).

During a break from work of two to five weeks, there was a statistically significant drop in selenium concentrations in plasma and urine (Greiner et al. 2018, 2020).

3.2 Relationship between internal exposure and effects

Information on the relationship between internal exposure and effects can be found in the previously available documentations for selenium and its inorganic compounds (Hartwig 2014; Rettenmeier 2019). Among other things, activity changes of selenium-containing enzymes were described, as well as a prolongation of the prothrombin time in a population with a very high selenium concentration in soil and vegetation. An increased risk for the development of diabetes mellitus was observed in particular after oral supplementation with selenium in the case of already previously high selenium concentrations and is considered the most critical end point.

In the study by Greiner et al. (2018), the effect parameters glutathione peroxidase, prothrombin time, glucose, HbA1c and proinsulin were examined. No statistically significant differences were found in the relatively small collective of this cross-sectional study.

4 Analytical Methods

Analytical methods based on atomic absorption spectrometry (AAS) and inductively coupled plasma mass spectrometry (ICP-MS) are available for the determination of selenium in blood and its compartments as well as in urine. Both a method based on hydride AAS for the determination of selenium in blood, plasma and urine (Alt et al. 1988) and a method based on graphite furnace AAS for the determination of selenium in plasma (Heitland and Michalke 2013) were tested and published by the Commission.

In addition to the determination of total selenium in human biological materials, various methods are also available for the specific determination of selenium proteins and low-molecular selenium species.

5 Selection of the Indicators

In humans, increased systemic selenium exposure can be detected in plasma, erythrocytes, urine and other materials such as hair and nails (Göen and Greiner 2018). However, the usefulness of hair and nail analyses is limited, among other things, by the time interval between exposure and the time when the hair breaks through the skin or the nail reaches the tip, as well as by methodological problems (Göen and Greiner 2018; Yaemsiri et al. 2010).

5.1 Selenium in plasma/serum

When evaluating the additional exposure to selenium in plasma/serum, erythrocytes and urine, differences with regard to kinetics have to be considered (Greiner et al. 2018, 2020).

Basically, the selenium concentration in plasma and serum does not differ. In the following, the term "plasma" is therefore used for both matrices.

In plasma, most selenium is bound to proteins. Selenoprotein P accounts for approx. 52% to 56% of the total selenium in plasma, glutathione peroxidase for 19% to 25% and albumin for 12% to 23% (Achouba et al. 2016; Göen and Greiner 2018; Jitaru et al. 2008; Letsiou et al. 2010; Reyes et al. 2003). A link between the kinetics of the total selenium concentration in plasma and the formation and degradation of these proteins can be assumed. Due to this kinetic link, the plasma concentration reflects a longer-term additional exposure to selenium. In line with this, it was shown that the selenium concentration in plasma does not correlate with the exposure in the air in an immediately preceding shift (Greiner et al. 2018; RKI 2006).

5.2 Selen in erythrocytes

Selenium is predominantly immobile also in erythrocytes, so that the kinetics of the selenium content is strongly linked to the life span of the erythrocytes. Consequently, the selenium concentration in the erythrocytes is suitable for reflecting the long-term selenium exposure, but is not suitable for describing the short-term exposure.

5.3 Selenium in urine

Greiner et al. (2020) observed a statistically significantly higher selenium concentration in the urine of occupationally exposed persons before the start of the shift than in the control subjects. In the course of the shift, there was a further statistically significant increase. In contrast to plasma and erythrocytes, there was a correlation between the selenium concentration in the air of the immediately preceding shift and the selenium concentration in urine after this shift, which becomes even better when considering the difference between the pre- and post-shift selenium concentrations in urine. It was thus shown that the occupational selenium exposure of the immediately preceding work shift was better reflected in the urine than in the plasma. However, statistically significantly higher selenium concentrations were found in the pre-shift urine compared to a non-exposed control group from the same region. This indicates rather slow elimination kinetics in urine, so that accumulation may occur over the course of several working days. During a two- to three-week break from work, there was a significant decrease in the concentration in urine, almost reaching the concentration of the control group (Greiner et al. 2020). This is in agreement with previously conducted studies (Göen et al. 2015).

Jäger et al. (2013) showed by means of regression analysis a strong and close linear correlation between the volume-related total urinary selenium and the creatinine content of the individual sample. This is consistent with the results of Hojo (1981, 1982). Therefore, standardisation of the urinary selenium to the creatinine content is necessary to obtain comparable results.

6 Background Exposure

There are significant regional differences in selenium intake and associated selenium concentrations across the world. This is most likely due to geographical differences, agronomic practices and availability and preference of certain foods (Combs 2001; Whanger et al. 1988). Therefore, primarily data from Germany and Western Europe are presented below to derive the BAR.

6.1 Background exposure in plasma/serum

In the documentation for deriving the BAT value (Rettenmeier 2019), a mean selenium concentration in plasma or serum of 70 µg/l with a reference range (5th to 95th percentile) of about 50 to 120 µg/l plasma or serum was presented when considering the background exposure for the adult general population in Germany based on the data of the Robert-Koch-Institute (RKI) (2006). In the meantime, some more recent data on background exposure in Germany are available.

Göen et al. (2015) studied 20 male workers in a selenium-processing company and a control collective of 20 likewise male, age-matched control subjects who had no occupational selenium exposure. The selenium concentration in plasma was determined by AAS according to the method by Heitland and Michalke (2013).

In a group of 20 non-occupationally exposed persons of working age (21 to 64 years) without taking selenium supplementation from the region around Nuremberg, the selenium concentration in plasma was determined by ICP-MS with dynamic reaction cell according to the method described by Jäger et al. (2016 a) (Greiner et al. 2018).

Furthermore, extensive measurement results are available from the Federal Environmental Specimen Bank. For this purpose, students from four German universities (Münster, Greifswald, Halle (Saale) and Ulm) aged between 20 and 29 years were selected in each year of the study, with the number of women and men being roughly equally distributed (UBA 2020). However, it cannot be ruled out that individual test persons have taken dietary supplements containing selenium. The selenium concentration in plasma was determined by ICP-MS.

In two other studies from Germany, selenium concentrations in the plasma of certain patient groups were compared with those of healthy control groups.

For this purpose, Fink et al. (2015) studied a control group of 50 healthy persons without cardiovascular risk and without taking medication. The mean age was 30.4 ± 1.4 years. The selenium concentration in plasma was 109.1 ± 1.3 µg/l.

Weber et al. (2008) compared the serum selenium concentrations of patients with those of 11 healthy control subjects. The control subjects were six men and five women, the median age was 34 years. The selenium concentration in the serum of the control group was 73.95 ± 4.12 µg/l.

A compilation of selenium concentrations in plasma/serum is shown in Table 1, which summarises the median and 95th percentile of the data from the Federal Environmental Specimen Bank as mean values from the results from 2015 to 2018 for clarity.

Tab. 1 Selenium concentrations in plasma/serum of the general population (Germany)

Number of samples	Selenium in plasma/serum [µg/l]			References
	Median	95th Percentile	Range	
11	73.95 ± 4.12[a)]	–	–	Weber et al. 2008
50	109.1 ± 1.3[a)]	–	–	Fink et al. 2015
20 ♂	76	101	52–102	Göen et al. 2015
20	76.9	–	70.6–115	Greiner et al. 2018

Tab. 1 *(continued)*

488 (Münster 2015–2018)	86.5	108	54.2–143	UBA 2020
532 (Greifswald (2015–2018)	85.0	103	45.9–168	
506 (Halle (Saale) 2015–2018)	80.9	102	25.4–127	
496 (Ulm 2015–2018)	83.1	105	49.2–150	

[a] Mean value ± standard deviation

In view of the broad agreement of the analytical results from different German cities (see Table 1), there is no indication of relevant regional differences within Germany.

6.2 Background exposure in urine

Due to the close linear correlation between the volume-related total selenium content in urine and the creatinine content of the individual sample (Jäger et al. 2013; see Section 5.3), values with creatinine reference are used for the consideration of the background exposure in urine. Corresponding studies can be found in Table 2. In the studies by Greiner et al. (2020) and Jäger et al. (2013), only subjects without occupational selenium exposure and without taking selenium supplementation were included in the control groups. In the study by Göen et al. (2015), there was also no occupational selenium exposure in the control group.

Tab. 2 Selenium concentrations related to creatinine in the urine of the general population (Germany)

Method	n	Selenium in urine [µg/g creatinine]			References
		Median	95th Percentile	Range	
ICP-MS	18	18.7	–	9.20–40.6	Greiner et al. 2020
ICP-MS	20 ♂	23	50	12–50	Göen et al. 2015
ICP-MS	47	15.7	30.4	8.5–39.1	Jäger et al. 2013
flameless hydride AAS	18	15.1	–	9–23	Schierling et al. 1982
AAS	24 ♀ + ♂	13.0 ± 3.8[a]		6.3–20.0	Oster and Prellwitz 1990
	16 ♀	13.5 ± 3.8[a]			
	8 ♂	9.8 ± 3.3[a]			

[a] Mean value ± standard deviation

Further data for Germany are available from Heitland and Köster (2006), but without creatinine reference. The selenium content in urine was determined by ICP-MS in 87 samples, with a median of 14 µg selenium/l urine (range 3 to 60 µg selenium/l urine) and a 95th percentile of 24 µg selenium/l urine.

Table 3 shows the most important studies for reference value determinations from Europe. As stated above, regional differences in selenium supply should be considered when looking at data from other European countries.

Tab. 3 Selenium concentrations related to creatinine in the urine of the general population (Europe)

Country	n	Selenium in urine [µg/g creatinine]			References
		Median	95th Percentile	Range	
United Kingdom	132	15.17[a]	29.44[a]		Morton et al. 2014
Belgium	1001	21.6	33.3		Hoet et al. 2013
Slovenia	812	14.1	24.0	1.00–134	Snoj Tratnik et al. 2019
	402 ♂	14.5	24.3	1.57–54.3	
	410 ♀, breastfeeding	13.6	23.6	1.00–134	

[a] calculated

7 Evaluation of a BAR

Given the different kinetics of the two parameters, BARs for selenium in plasma and for selenium in urine are evaluated.

For selenium in plasma, the data are homogeneous within Germany. The data from the Federal Environmental Specimen Bank are the most reliable. Based on the extensive data presented there from four different regions of Germany, it can be concluded that no relevant geographical differences are to be expected within Germany. Longer-term additional exposure to selenium is well reflected in plasma.

Taking into account the studies by Göen et al. (2015) and Greiner et al. (2018), as well as the measurement results obtained in large subject collectives from the Federal Environmental Specimen Bank,

a BAR of 100 µg selenium/l plasma/serum

is set. No restriction was made for the sampling time.

Selenium in urine has a shorter half-life than selenium in plasma. The studies presented above showed that subacute exposures are better reflected by selenium in urine than by selenium in plasma. Furthermore, the studies available for selenium in urine showed indications of accumulation over the working week.

To ensure the reproducibility and comparability of the data (see Section 5.3), the excretion of selenium in urine is related to creatinine. Although only a few studies with a limited number of test persons are available from Germany, the results show a largely uniform picture, also in comparison with the large Belgian study by Hoet et al. (2013). Therefore,

a BAR of 30 µg selenium/g creatinine in urine

is set. For long-term exposures, sampling is to be carried out at the end of the shift after several previous shifts.

8 Interpretation

The BAR in urine relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3 g/l. As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated test persons is recommended (Bader et al. 2016).

When interpreting the study data, the influence of dietary habits and the different kinetics of the parameters must be taken into account.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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