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Molybdenum and its compounds – Addendum for evaluation of a BAR

Assessment Values in Biological Material – Translation of the German version from 2019

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Abstract

In 2018 the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated molybdenum [7439-98-7] and its compounds. Available publications are described in detail.

In recent publications since the last evaluation in 2005 some authors investigated molybdenum concentrations in blood or urine with respect to occupational molybdenum exposure, however, without a conclusive outcome: The results of the different studies were either contradictory or missed respective exposure data and/or quality control measures. Therefore, no BAT value (biological tolerance value) was derived. However, some studies reported background concentrations in men, women or children, most of them with sufficiently applied quality control. In these studies, it was found that nutrition is the most important contribution to molybdenum in urine. Several studies with quality control means and with sufficient statistical power revealed similar concentration ranges between 34–50 µg/l urine and/or 95th percentiles around 150 µg/l urine. In conclusion, a BAR (biological reference value) of 150 µg molybdenum/l urine was derived.

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BAT value (2018)	**not established**
BAR (2018)	**150 µg molybdenum/l urine**
MAK value (2000)	**not established**
Absorption through the skin	–
Carcinogenicity	–
Prenatal toxicity	–

In 2005, no BAT value (biological tolerance value) could be derived for molybdenum and its compounds due to the data situation. In the present addendum, the data published since then are evaluated with regard to the possibility of deriving a BAT value or a BAR.

The Commission's working group "Analyses in Biological Material" has developed methods for the determination of molybdenum in urine and plasma (Schramel et al. 2001, 2003; Seiler et al. 1997).

Re-evaluation

In the following, publications with publication dates from 2005 onwards are evaluated.

Molybdenum biomonitoring after occupational exposure

Ellingsen et al. (2017) investigated molybdenum concentrations in blood, blood cells, serum and urine of welders from a shipyard in Russia (n = 70) and controls from metal works (fitters without exposure, n = 74). All test persons were healthy according to company medical examination. Exposure to welding smoke particles (SRP) was measured by means of personal sampling of the workroom air during the entire shift. Spectral interference was minimized by high-resolution measurement with inductively coupled plasma sector-field mass spectrometry (ICP-SF-MS); reference materials (seronorm) were also measured. The detection limits in the different samples were 0.088 µg/l (blood), 0.042 µg/l (serum), 0.097 µg/l (blood cells) and 0.048 µg/l (urine). Although the highest median concentration of molybdenum was measured in air (compared with the other elements), no association with the SRP concentration was found for molybdenum.

The following molybdenum concentrations were determined (Table 1):

Tab. 1 Molybdenum concentrations in biological materials (according to Ellingsen et al. 2017)

	Welders ♂ (n = 70)			**Controls ♂ (n = 74)**		
	Median	**Min–Max**	**95th percentile**	**Median**	**Min–Max**	**95th percentile**
Blood [µg/l]	0.74	0.28–5.7	2.7	0.52	0.19–2.8	1.1
Serum [µg/l]	1	0.5–3.3	1.7	0.77	0.16–3.5	2.2
Blood cells [µg/l]	1.7	1.1–2.4	2	1.4	1.1–2.5	1.8
Urine [µg/g crea]	38	12–93	91	27	2.4–382	151

The authors could not establish a statistically significant relationship between the molybdenum concentrations in the biological samples and the molybdenum concentration in the air.

Zeneli et al. (2015) examined blood and serum from 27 unexposed controls of a rural area together with 70 samples from workers of a thermo power plant in Kosovo who were "low to medium" occupationally exposed. The exposure was not quantified in more detail. There was exposure to aluminium, nickel, thallium and uranium, but not to molybdenum. Essential trace elements, including molybdenum, were determined in blood and serum and a relationship with exposure to other elements was investigated. All measurements were performed with ICP-MS. The analytical method was checked by analysis of 12 reference materials in different concentration ranges and matrices (serum, plasma, blood). In both sample groups a very low molybdenum blood concentration was determined, but in the group exposed to other elements the concentration of 0.81 ± 0.3 µg/l was statistically significantly lower ($p = 0.05$) compared with the concentration of 0.94 ± 0.28 µg/l in the controls. The Spearman correlation showed a statistically significant negative correlation between nickel and molybdenum and a statistically significant positive correlation between molybdenum and aluminium.

From the set of the publications with occupational molybdenum exposure only the study by Ellingsen et al. (2017) describes sufficient quality control criteria on the one hand and investigations of molybdenum concentrations of controls and of workers exposed to molybdenum on the other.

Data on Background Exposure

Studies in children

There are studies in children on the molybdenum excretion in urine (Çelik et al. 2014; Moreno et al. 2010*;* Sievers et al. 2001).

Studies in women

Barrios et al. (2017) report molybdenum concentrations in the urine of 124 pregnant Mexican women. The study was conducted to investigate a possible association between maternal exposure to molybdenum and a possible disruption of neuronal development in the children. Dietary habits were recorded by means of a questionnaire. Urine samples were collected in each trimester of pregnancy. In the first and third trimesters of pregnancy, mean molybdenum urine concentrations were determined to be 37.0–40.3 µg/l and 45.7–54.2 µg/g creatinine, respectively. No association with body mass index, age, smoking or other socioeconomic factors was found. After examination of 84 foods, a significant relationship was found only between high chili consumption and molybdenum in urine.

The team of authors led by Rentschler et al. (2018) analysed blood samples for precious metals and molybdenum using high-resolution ICP-sf-MS from 248 women (47–61 years) from nine countries under quality-controlled conditions. From each participating country 24 or 25 samples were available. For molybdenum a median of 2.0 (0.2–16) µg/l in blood samples was reported. Concentrations varied statistically significantly between countries by a factor of 2.9, with Ecuador and China showing the highest values (analytical values not reported). A negative correlation was found between smoking and molybdenum.

In the study by Yoshida et al. (2006), molybdenum intake from food and subsequent excretion was investigated. Only healthy Japanese women aged 18–23 years participated in the study. During the 18-day study, the subjects received only controlled food. The excretion of molybdenum in urine correlated with the molybdenum content in the food consumed.

Studies in men

In a study by Lewis and Meeker (2015), molybdenum concentrations in blood, urine and serum, and their possible correlation to serum testosterone were described in 484 men (18–55 years). The collective and analysis data were taken from the National Health and Nutrition Examination Survey (NHANES) database.

Studies in the general population

In another study by Lewis et al. (2016), data from 1496 adults (♂ 830; ♀ 666) from the NHANES study from the period 2007 to 2010 were used to investigate a potential relationship between bone density and molybdenum concentration in urine. In multivariate models, a statistically significant inverse relationship between *ln*(urinary molybdenum) and lumbar spine or femoral neck bone density was found in women (50–80+ years). The median urinary molybdenum excretion of men was 49.8 µg/l (38.8 µg/g creatinine) in the age group 20–50 years, and 48.4 µg/l (38.2 µg/g creatinine) in the age group < 50 years; for women it was 45.4 µg/l (44.9 µg/g creatinine) in the age group 20–50 years, and 33.7 µg/l (42.9 µg/g creatinine) in the age group < 50 years.

Saravanabhavan et al. (2017) report on a study in the Canadian Health Measures Survey (CHMS) in which blood and urine of three age groups (3–5 years, 6–19 years, 20–79 years) were examined for background exposure to molybdenum. From the 2009/2011 measurement period 95th percentiles for molybdenum in the blood of 2.7 µg/l (1.4–4.0 µg/l) for the age group 3–5 years (n = 495), of 1.7 µg/l (1.3–2.0 µg/l) for the age group 6–19 years (n = 985) and of 1.6 µg/l (1.4–1.7 µg/l) for the age group 20–79 years (n = 1759) were determined. For molybdenum in urine 95th percentiles of 290 µg/l (200–380 µg/l) were determined for the age group 3–5 years (n = 465), of 230 µg/l (180–290 µg/l) for the age group 6–19 years (n = 993) and of 170 µg/l (130–210 µg/l) for the age group 20–79 years (n = 1519).

Zeiner et al. (2006) investigated seven trace elements, including molybdenum, in urine samples of 100 (♂ 50 and ♀ 50; 17–88 years) healthy male and female volunteers from Vienna. The subjects had neither metal prostheses nor occupational exposure. For the entire sample collective, a mean value of 57.7 µg/g creatinine (3.91–745 µg/g creatinine) and a median of 46.2 µg/g creatinine is given. The urinary molybdenum concentrations of men did not differ significantly from those of women (♂ mean value: 61.0 µg/g creatinine (3.91–745 µg/g creatinine), median: 42.3 mg/g creatinine; ♀ mean value: 54.4 µg/g creatinine (12–215 µg/g creatinine), median: 47.2 mg/g creatinine).

Heitland and Köster (2006 a) analysed 37 trace elements in blood samples of 130 (♂ 50; ♀ 80; 18–70 years) non-exposed volunteers from northern Germany. The mean value for molybdenum in the blood is given as 0.43 µg/l (0.06–4.0 µg/l), the 95th percentile with 1.1 µg molybdenum/l blood.

The analysis of 30 trace elements in urine samples from 87 non-exposed adults (Heitland and Köster 2006 b) showed a mean value of 38 µg molybdenum/l urine (4–357 µg/l) and a 95th percentile of 94 µg/l urine.

Studies with sufficient quality control of the background exposure of adults to molybdenum are presented in Table 2.

Tab. 2 Studies with sufficient quality control of the background exposure of adults to molybdenum

Collective	Matrix	n (age)	Molybdenum Mean value	Median	95th Percentile	References
Control collective of an occupational health study; ♂, Russia	blood	74		0.52 µg/l	1.1 µg/l	Ellingsen et al. 2017
♀	blood	248		2.0 µg/l		Rentschler et al. 2018
CHMS, Canada	blood	1759 (20–79 years)			1.6 µg/l	Saravanabhavan et al. 2017
General population, Germany	blood	130	0.43 µg/l		1.1 µg/l	Heitland and Köster 2006 a
General population, Germany	urine	87 (18–65 years)	38 µg/l		94 µg/l	Heitland and Köster 2006 b
Control collective of an occupational health study; ♂, Russia	urine	74		27 µg/g crea	151 µg/g crea	Ellingsen et al. 2017
Pregnant ♀, Mexico	urine	124	37–40.3 µg/l 45.7–54.2 µg/g crea			Barrios et al. 2017
NHANES, USA, ♂	urine	484	41.54 µg/l	46.05 µg/l	141 µg/l	Lewis und Meeker 2015
NHANES, USA, ♂	urine	830				Lewis et al. 2016
		541 (20–50 years)		49.8 µg/l 38.8 µg/g crea		
		289 (50–80+ years)		48.4 µg/l 38.2 µg/g crea		
NHANES, USA, ♀	urine	666				Lewis et al. 2016
		459 (20–50 years)		45.4 µg/l 44.9 µg/g crea		
		207 (50–80+ years)		33.7 µg/l 42.9 µg/g crea		
CHMS, Canada	urine	1519 (20–79 years)			170 µg/l	Saravanabhavan et al. 2017
General population Austria	urine	100	57.7 µg/g crea	46.2 µg/g crea		Zeiner et al. 2006
♂		50	61 µg/g crea	42.3 µg/g crea		
♀		50	54.4 µg/g crea	47.2 µg/g crea		

Re-evaluation of assessment values

In several of the new studies, large and well characterized sample collectives as well as sufficient information for successful quality control of the determinations are available (Barrios et al. 2017; Ellingsen et al. 2017; Heitland and Köster 2006 a, b; Lewis and Meeker 2015; Lewis et al. 2016; Rentschler et al. 2018; Saravanabhavan et al. 2017; Yoshida et al. 2006; Zeiner et al. 2006). No significant differences between the genders were found.

Re-evaluation of a BAT value

Out of the three available publications, only the one of Ellingsen et al. (2017) can be used with regard to occupational exposure. Only this publication mentions sufficient quality control criteria **and** examines molybdenum concentrations of controls and molybdenum-exposed workers. The urinary molybdenum concentration showed **no** correlation with exposure. In the blood of welders, the determined values showed significantly higher molybdenum concentrations, but the authors did **not** find a statistically significant association between molybdenum in the biological fluids and the molybdenum concentration in the air (Ellingsen et al. 2017).

In the study by Zeneli et al. (2015), there was no exposure to molybdenum, but to other metals, so that no association between molybdenum exposure and concentration in biological materials can be established.

Since no studies have been published which demonstrate a clear relationship between exposure and molybdenum concentration in urine, and since values of up to 300 µg molybdenum/l urine can be achieved from predominantly diet-related background exposure,

no BAT value is derived.

Evaluation of a BAR

The more recent studies on biomonitoring of molybdenum confirm the values of background exposure in the general population (Schaller 2010). Relevant studies are presented in Table 2. For the derivation of the BAR, the 95th percentile of the study by Lewis and Meeker (2015) is used, who have analysed the molybdenum concentrations in urine in a non-exposed population sample (NHANES) using modern, reliable analytical procedures with sufficient quality control, as well as the 95th percentiles from the studies by Ellingsen et al. (2017), Heitland and Köster (2006 b) and Saravanabhavan et al. (2017). These studies are additionally supported by similar median values from the studies of Lewis et al. (2016) and Zeiner et al. (2006).

Studies with children (Çelik et al. 2014; Moreno et al. 2010; Sievers et al. 2001) are not considered for BAR evaluation because children's diet is atypical for adults.

From the studies of Ellingsen et al. (2017), Heitland and Köster (2006 b), Lewis and Meeker (2015) and Saravanabhavan et al. (2017)

a BAR of 150 µg molybdenum/l urine

is derived.

The BAR in urine is expressed on a litre basis, as there is no evidence of an advantage of relating molybdenum excretion to creatinine.

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