The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Manganese and its inorganic compounds – Addendum for re-evaluation of the BAT value and evaluation of a BAR

Assessment Values in Biological Material – Translation of the German version from 2011

M. Bader[1]

[1] *BASF SE, Carl-Bosch-Straße 38, 67056 Ludwigshafen am Rhein, Germany*

email: MAK Commission (arbeitsstoffkommission@dfg.de)

Keywords:

manganese, biological tolerance value, BAT value, bological reference value, BAR, biomonitoring

BAT value (2010)	**not established** Sampling time: at the end of exposure or end of shift; for long-term exposures: at the end of the shift after several previous shifts
BAR (2010)	**15 µg manganese/l blood** Sampling time: at the end of exposure or end of the shift; for long-term exposures: at the end of the shift after several previous shifts
MAK value (2010)	**0.2 mg/m³ I** **0.02 mg/m³ R**
Absorption through the skin	–
Carcinogenicity	–

Citation Note:
Bader M. Manganese and its inorganic compounds – Addendum for re-evaluation of the BAT value and evaluation of a BAR. Assessment Values in Biological Material – Translation of the German version from 2011. MAK Collect Occup Health Saf. 2021 Dec:Doc925. DOI: https://doi.org/10.34865/bb743996eoj21_1ad

Manuscript completed:
26 Feb 2010

Publication date:
14 Dec 2021

Re-evaluation

In correlation to the maximum workplace concentration (MAK value) of 0.5 mg/m³, a biological tolerance value (BAT value) of 20 µg manganese/l blood was derived for manganese [7439-96-5] in 2001 (translated in Triebig et al. 2005). In 2010, the MAK value was lowered to 0.2 mg/m³ I (inhalable fraction) and 0.02 mg/m³ R (respirable fraction) (translated in Hartwig 2015). In this addendum, the data for the derivation of a biological reference value (BAR) are evaluated.

1 Critical toxicity

Manganese and its inorganic compounds act primarily on the airways, the lungs and the central nervous system. Symptoms after inhalation can lead to acute respiratory symptoms and even to symptoms similar to pneumonia (Triebig et al. 2005). The neurotoxic effects of manganese after chronic exposure can result in conditions resembling Parkinson's disease and are termed "manganism". The acute and chronic toxicity of manganese and its compounds is comprehensively presented in MAK and BAT value documentations (Greim 1999; Hartwig 2015; Triebig et al. 2005).

To date, neither sensitizing nor carcinogenic or genotoxic effects have been demonstrated consistently for manganese and inorganic manganese compounds (Greim 1999). No prenatal toxicity is to be expected when the MAK value is observed (Hartwig 2015).

2 Exposure and effects

2.1 Relationship between external and internal exposure

To derive the BAT value for manganese in blood valid up to 2010, air measurement and biomonitoring results from a total of 12 field studies were used and evaluated on a mean value basis by correlation and regression analysis (manganese concentration in blood versus manganese in the inhalable dust fraction) (Triebig et al. 2005). A regression equation of Y [µg/l] = 14.6 × X [mg/m^3] + 8.36 was calculated. Accordingly, with a manganese concentration in the air at the level of the MAK value of 0.2 mg/m^3, a mean manganese concentration in blood within the range of the background exposure is to be expected.

3 Analytical Methods

To analyse manganese in blood, a method tested and recommended by the working group "Analyses of Hazardous Substances in Biological Materials" is available (Bader et al. 2006). Determination is carried out using graphite furnace atomic absorption spectrometry (GF-AAS) from EDTA blood. The detection limit of the method is 0.5 µg manganese/l blood (within-series precision: 5.3%, day-to-day precision: 10.4%, for c = 12.9 µg/l each, accuracy: 98% (relative recovery)). A method for determining manganese in blood using inductively coupled plasma mass spectrometry (ICP-MS) validated in accordance with analytical quality criteria was published (Heitland and Köster 2006). The detection limit is 0.08 µg manganese/l blood (within-series precision: 2.4%, day-to-day precision: 8.3%, for c = 9.6 µg/l each, accuracy: 102% (relative recovery)).

4 Background exposure

In the context of evaluating the BAT value, the manganese concentrations in blood samples of volunteers as well as in the general population were reviewed (Triebig et al. 2005). Thereby it was found that the background exposure in Europeans and North Americans is apparently lower than in persons from Asian countries, possibly due to differences in factors such as geology or eating habits. In addition, since the early 1990s the reported manganese concentrations in blood show a tendency towards lower levels. For these two reasons, it is reasonable to use the relevant background exposure in countries of the European Union as basis for evaluating the BAR.

To derive the BAR as the 95th percentile of a European population of working age not occupationally exposed to manganese, a total of nine studies on background exposure in the general population or in non-exposed reference collectives from occupational medical field studies from 1993–2009 are available. Selection criteria comprised: relevant information on important demographic influence factors such as age ranges, gender distribution and lifestyle factors as well as a sufficient description of statistical data on manganese concentration in blood (for

example mean value and standard deviation, median value, range of measured values, 5th or 95th percentile, sample size). In most studies, GF-AAS with detection limits of approximately 0.5 µg/l was used to determine manganese in blood; ICP-MS with a detection limit of approximately 0.08 µg/l was used in three studies. The results of the studies are summarised in Table 1.

Heinzow (1993) investigated the manganese concentration in the blood of 165 persons from Schleswig-Holstein (age > 45 years) and found a mean value of 8.4 µg/l (median: 8.0 µg/l). The 95th percentile was 12.8 µg/l; the highest individual value was 23.9 µg/l. Among other factors, the purpose of the study was to investigate the possible influence of increased manganese concentrations in the drinking water on those in blood. No differences between the groups were reported, however.

In a study by Kristiansen et al. (1997) in the context of the EURO TERVIHT (Trace Element Reference Values in Human Tissues) project, a mean value of 165 ± 51 nmol manganese/l blood (9.1 ± 2.8 µg/l) was found (median: 157 nmol/l = 8.6 µg/l, maximum: 372 nmol/l = 20.4 µg/l) in a total of 189 reference persons from Denmark (age range: 40–70 years). The central 90% range of values (5th–95th percentile) was between 100 nmol/l (5.5 µg/l) and 271 nmol/l (14.9 µg/l).

Also in an investigation assigned to the EURO TERVIHT project, White and Sabbioni (1998) found a mean value of 7.4 µg manganese/l blood (range: 1.5–22.0 µg/l) in a total of 206 persons from Scotland and England (age range: 16–70 years). The authors obtained a central 95% interval (2.5th–97.5th percentile) according to the definition of the International Federation of Clinical Chemistry (IFCC) (Solberg 1987) amounting to 4.2–12.6 µg manganese/l blood.

In Italy in a workplace study conducted to assess various biomarkers for manganese, Apostoli et al. (2000) found a mean value of 5.99 ± 1.73 µg manganese/l blood in a control group of 87 persons (maintenance personnel in hospitals, age range: 27–62 years). The maximum value was 10.0 µg/l. Under the simplified assumption of a normal distribution a 95th percentile of about 9.5 µg manganese/l can be estimated from these results (5th percentile: 2.5 µg/l).

In 77 persons from Northern Germany (age range: 20–73 years), Bader et al. (2003) found a mean value of 9.6 µg manganese/l blood (median: 9.5 µg/l, range: 2.6–17.2 µg/l). The central 90% range was 5.7–15.0 µg/l.

In an occupational medical study on the manganese exposure of welders by Iarmarcovai et al. (2005) in France using ICP-MS in an external control group of 30 persons (age range: 43 ± 11 years), a mean value of 21.0 ± 7.3 µg manganese/l blood was found (median: 18.2 µg/l). The value range was between 10.0 µg/l and 36.1 µg/l. Based on the mean value and its standard deviation, a 95th percentile of the distribution of measured values of about 35 µg/l can be estimated.

In France, Goullé et al. (2005) investigated the metal concentration of different biological materials of 100 volunteers from the general population using ICP-MS. The median value for manganese in blood was 7.6 µg/l. The 5th and 95th percentiles were 5.0 µg/l and 12.8 µg/l, respectively.

In a study by Heitland and Köster (2006) on trace element concentrations in the blood of a reference population from Northern Germany (n = 130 persons, age range: 18–70 years) using ICP-MS, a mean value of 9.0 µg manganese/l blood was found. The central 90% range of measured values was between 5.7 µg/l (5th percentile) and 14.6 µg/l (95th percentile).

In a comparative population study on manganese exposure from steel plant emissions in Northern Italy, Squitti et al. (2009) found mean manganese concentrations of 7.1 and 8.0 µg/l in the blood of 24 and 52 persons, respectively, from the wider surroundings. The interquartile range (25th–75th percentile) was 5.7–9.8 µg/l or 6.8–8.8 µg/l.

To summarise, the majority of the studies selected show that the mean concentration of manganese in blood is about 9 µg/l and that the 95th percentile of the measured range is about 15 µg/l. This particularly applies for the three studies from the Federal Republic of Germany (Bader et al. 2003; Heinzow 1993; Heitland and Köster 2006). In two of the nine studies, considerably higher (Iarmarcovai et al. 2005) or lower (Apostoli et al. 2000) manganese concentrations were found; in these cases, the selection of volunteers as control group for persons exposed to manganese occupa-

tionally or environmentally could have an influence. All studies agree with each other in reporting that sex, age and tobacco consumption have no statistically significant effect on manganese concentrations in blood. As manganese is an essential trace element, the 5th percentile of the value distribution is of physiological importance; according to the studies cited above, it is about 6 µg manganese/l blood.

Tab. 1 Concentration of manganese in the blood of the general population

Method	LOD [µg/l]	Country	n	Age [years]	Manganese concentration in blood [µg/l]							References
					Mean ± SD	Med	Min	Max	IQR	P5	P95	
GF-AAS		D	165	no data	8.4	8.0	3.8	23.9			12.8	Heinzow 1993
GF-AAS	0.6[a)]	DK	188	40–70	9.1 ± 2.8[a)]	8.6[a)]	4.1[a)]	20.5[a)]		5.5[a)]	14.7[a)]	Kristiansen et al. 1997
GF-AAS	0.60	UK	206	16–70	7.4		1.5	22.0		4.2[b)]	12.6[b)]	White and Sabbioni 1998
GF-AAS		I	87	27–62	5.99 ± 1.73		2.0	10.0		2.53[c)]	9.45[c)]	Apostoli et al. 2000
GF-AAS	0.50	D	79	20–73	9.8	9.5	2.6	17.2		5.7	15.0	Bader et al. 2003
ICP-MS		F	30	43 ± 11	21.0 ± 7.3	18.2	10.0	36.1		6.4[c)]	35.6[c)]	Iarmarcovai et al. 2005
ICP-MS	0.09	F	100	no data		7.6				5.0	12.8	Goullé et al. 2005
ICP-MS	0.08	D	130	18–70	9.0	9.0[d)]	4.8	18.0		5.7	14.6	Heitland and Köster 2006
GF-AAS		I	52	68 ± 7		8.0			6.8–8.8			Squitti et al. 2009
			24	68 ± 11		7.1			5.7–9.8			

[a)] converted from nmol
[b)] 2.5th or 97.5th percentile
[c)] calculated from mean value ± 2 SD
[d)] 60th percentile
D = Germany; DK = Denmark; F = France; I = Italy; IQR = interquartile range; LOD = limit of detection; Max = Maximum; Med = Median; Min = Minimum; P5 = 5th percentile; P95 = 95th percentile; UK = United Kingdom

5 Evaluation

In 2010, re-evaluated MAK values at the level of 0.2 mg/m³ I and 0.02 mg/m³ R were established. However, as a corresponding BAT value derived from the correlation and regression analysis (see Section 2.1) is within the background exposure range, the BAT value is now withdrawn.

From the studies presented in Section 4,

a BAR of 15 µg manganese/l blood

as 95th percentile of the background exposure for the working age population not occupationally exposed to manganese in Central Europe is derived.

Sampling should be carried out at the end of exposure or the end of shift; for long-term exposures: at the end of the shift after several shifts.

6 Interpretation

The BAR corresponds to the 95th percentile of the manganese concentration in the blood of persons not occupationally exposed to manganese. It is therefore suitable as a reference value to assess an additional work-related exposure to manganese and its inorganic compounds.

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.

References

Apostoli P, Lucchini R, Alessio L (2000) Are current biomarkers suitable for the assessment of manganese exposure in individual workers? Am J Ind Med 37(3): 283–290. DOI: 10.1002/(sici)1097-0274(200003)37:3<283::aid-ajim6>3.0.co;2-e

Bader M, Johansson U, Wrbitzky R (2003) Untersuchungen zur Manganbelastung in der Allgemeinbevölkerung vor dem Hintergrund des aktuellen BAT-Wertes für Mangan im Blut. In: DGAUM (ed) 43. Wissenschaftliche Jahrestagung 2003. Gentner Verlag, Stuttgart, 417–422

Bader M, Zimmer H, Heinrich-Ramm R, Begerow J (2006) Manganese. Biomonitoring Method, 2006. In: Angerer J, Greim H (eds) The MAK-Collection for Occupational Health and Safety. Part IV: Biomonitoring Methods, vol 10. Wiley-VCH, Weinheim, 157–168. Also available from DOI: 10.1002/3527600418.bi743996e0010

Goullé J-P, Mahieu L, Castermant J, Neveu N, Bonneau L, Lainé G, Bouige D, Lacroix C (2005) Metal and metalloid multi-elementary ICP-MS validation in whole blood, plasma, urine and hair. Reference values. Forensic Sci Int 153(1): 39–44. DOI: 10.1016/j.forsciint.2005.04.020

Greim H (ed) (1999) Manganese and its inorganic compounds. MAK Value Documentation, 1994. In: Occupational Toxicants, vol 12. Wiley-VCH, Weinheim, 293–328. Also available from DOI: 10.1002/3527600418.mb743996e0012

Hartwig A (ed) (2015) Manganese and its inorganic compounds. MAK Value Documentation, 2011. In: The MAK-Collection for Occupational Health and Safety. Part I: MAK Value Documentations. Wiley-VCH, Weinheim. DOI: 10.1002/3527600418.mb743996e5014

Heinzow B (1993) Bericht der Untersuchungsstelle für Umwelttoxikologie des Landes Schleswig-Holstein, Jahresbericht 1990/91. Ministerium für Natur- und Umweltschutz des Landes Schleswig-Holstein, Kiel, 22–27

Heitland P, Köster HD (2006) Biomonitoring of 37 trace elements in blood samples from inhabitants of northern Germany by ICP-MS. J Trace Elem Med Biol 20(4): 253–262. DOI: 10.1016/j.jtemb.2006.08.001

Iarmarcovai G, Sari-Minodier I, Chaspoul F, Botta C, De Méo M, Orsière T, Bergé-Lefranc JL, Gallice P, Botta A (2005) Risk assessment of welders using analysis of eight metals by ICPMS in blood and urine and DNA damage evaluation by the comet and micronucleus assays; influence of XRCC1 and XRCC3 polymorphisms. Mutagenesis 20(6): 425–432. DOI: 10.1093/mutage/gei058

Kristiansen J, Christensen JM, Iversen BS, Sabbioni E (1997) Toxic trace element reference levels in blood and urine: influence of gender and lifestyle factors. Sci Total Environ 204(2): 147–160. DOI: 10.1016/s0048-9697(97)00155-1

Solberg HE (1987) International Federation of Clinical Chemistry. Scientific committee, Clinical Section. Expert Panel on Theory of Reference Values and International Committee for Standardization in Haematology Standing Committee on Reference Values. Approved recommendation (1986) on the theory of reference values. Part 1. The concept of reference values. Clin Chim Acta 165(1): 111–118. DOI: 10.1016/0009-8981(87)90224-5

Squitti R, Gorgone G, Panetta V, Lucchini R, Bucossi S, Albini E, Alessio L, Alberici A, Melgari JM, Benussi L, Binetti G, Rossini PM, Draicchio F (2009) Implications of metal exposure and liver function in Parkinsonian patients resident in the vicinities of ferroalloy plants. J Neural Transm (Vienna) 116(10): 1281–1287. DOI: 10.1007/s00702-009-0283-0

Triebig G, Ihrig A, Bader M (2005) Manganese and its inorganic compounds. BAT Value Documentation, 2003. In: Drexler H, Greim H (eds) The MAK-Collection for Occupational Health and Safety. Part II: BAT Value Documentations, vol 4. Wiley-VCH, Weinheim, 89–115. Also available from DOI: 10.1002/3527600418.bb743996e0004

White MA, Sabbioni E (1998) Trace element reference values in tissues from inhabitants of the European Union. X. A study of 13 elements in blood and urine of a United Kingdom population. Sci Total Environ 216(3): 253–270. DOI: 10.1016/s0048-9697(98)00156-9