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Lead and its compounds (except lead arsenate, lead chromate and alkyl lead compounds) – Addendum for re-evaluation of the BLW

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 lead [7439-92-1] and its compounds and has derived a biological guidance value at the workplace (BLW) for the blood concentration of lead. Available publications are described in detail. The re-evaluation is entirely based on studies in humans. The following critical health effects were considered: effects on haem synthesis, behavioural toxicity/neurotoxicity, male fertility, developmental toxicity, nephrotoxicity, cardiovascular effects, genotoxicity/carcinogenicity.

Effects on neurobehaviour and nephrotoxicity have been described at blood levels around 300 µg Pb/l and higher. Therefore, a BLW of 200 µg Pb/l blood has been deduced. As investigations of lead-exposed workers show no statistically significant increase in lymphocyte micronuclei at this blood level, it is reasonably expected that the proposed BLW will also minimize a lead-induced genotoxic/carcinogenic risk.

For women a Biological Reference Value (BAR) of 70 µg Pb/l blood is proposed, based on the 95th percentile of lead blood levels of the general population in Germany.

Because of the long persistence of lead in the body, the sampling time is not fixed.

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BLW for women > 45 years and for men (2018)	**200 µg lead/l blood** Sampling time: not fixed
BAR for women (2012)	**70 µg lead/l blood**[a)] Sampling time: not fixed
CAS number	7439-92-1
Formula	Pb
Molar mass	207.2 g/mol
Melting point	327.4 °C
Boiling point	1740 °C
Density at 20 °C	11.3 g/cm^3
MAK value	–
Peak limitation	–
Absorption through the skin	–
Sensitization	–
Carcinogenicity (2006)	Category 2
Prenatal toxicity	–
Germ cell mutagenicity (2004)	Category 3 A

[a)] No longer valid. For the current value see: Göen et al. (2020).

Documentation and several addenda are already available for lead and its compounds.

1981 **Evaluation of a Biological Tolerance Value (BAT value) for women > 45 years and for men:**
700 µg lead/l blood, 15 mg δ-aminolaevulinic acid/l urine
and of a
BAT value for women < 45 years: 450 µg lead/l blood, 6 mg δ-aminolaevulinic acid/l urine
(translated in Schaller et al. 2019)

1987 **Re-evaluation of the BAT value for women < 45 years:**
300 µg lead/l blood, 6 mg δ-aminolaevulinic acid/l urine (translated in Schaller et al. 2019)

2000 **Re-evaluation of the BAT value for women > 45 years and for men:**
400 µg lead/l blood (translated in Bolt and Schaller 2005)

2003 **Re-evaluation of the BAT value for women < 45 years:**
100 µg lead/l blood (translated in Schaller and Bolt 2005)

2005 **Withdrawal of the BAT values** (classification of lead into Carcinogen Category 3 B; withdrawal of the MAK value)
Evaluation of the values as Biological Guidance Values (BLW):
for women > 45 years and for men: 400 µg lead/l blood
for women < 45 years: 100 µg lead/l blood (Bolt 2005)

2012 **Withdrawal of the BLW for women < 45 years** of 100 µg lead/l blood;
Evaluation of a Biological Reference Value (BAR) for women: 70 µg lead/l blood (translated in Bolt 2019 a)

2013 **Lowering of the BLW for lead for women > 45 years and for men** (with consideration of the average value principle):
300 µg lead/l blood (translated in Bolt 2019 b)

This addendum provides an extensive presentation of available data and the re-evaluation of the BLW.

The following occupational medical and toxicological documentation applies to exposure to metallic lead, lead oxides and lead salts. Not considered are exposures to covalent lead compounds, such as alkyl lead compounds, as well as lead salts with an anion, such as lead arsenate and lead chromate, where the special properties of the anion have to be taken into consideration.

1 Metabolism and Toxicokinetics

1.1 Absorption

Several reviews are available for the absorption, distribution, retention and elimination of lead in the human organism. In particular, the reader is referred to AGS (2017), ATSDR (2019), Chamberlain (1985), NTP (2012), Safe Work Australia (2014), Skerfving (1993), US EPA (1986, 2014) as well as WHO (1995).

Lead and its inorganic compounds are absorbed by the human organism via the lungs and the gastrointestinal tract. At the workplace, absorption by inhalation is the most important route.

1.2 Distribution

The absorbed lead immediately enters the bloodstream. About 90% of the blood lead is bound to the membrane of the erythrocytes through which it is distributed in the organism. The lead in the body is available in an exchangeable and in a nonexchangeable (permanently bound) fraction (Baloh 1974).

The rapid exchange pool correlates with the blood lead level, i. e. the lead concentration in blood is in a steady state with the concentration of lead in the soft tissue. The half-life from this compartment is about one month (NTP 2016).

The nonexchangeable pool is determined by the lead deposited in the bones. A detailed description and discussion for this can be found in the documentation on "Lead and inorganic lead compounds" in TRGS 903 (AGS 2017).

Lead easily passes the placental barrier. The lead concentration in foetal blood is therefore almost the same as that in maternal blood (Gulson et al. 2016; Haas et al. 1972; Roels et al. 1978).

Lead also passes the blood-brain barrier, but is said not to accumulate in the brain (Schaller et al. 2019).

About 90% of the lead bound in the body is contained in the bones and teeth. New data on kinetics can be found in Gulson et al. (2016).

As measure for the cumulative blood lead exposure the "cumulative blood lead index" (CBLI; cumulative lead exposure, determined in blood as µg × PbB-years/dl) is used (AGS 2017).

1.3 Elimination

The elimination of the absorbed lead takes place mainly (75–80%) via the urine and to a lesser extent by gastrointestinal excretion (WHO 1977, 1995). The elimination rate is relatively slow. Due to the constantly decreasing availability of the deposit in the bones, it is difficult to provide precise data for the biological half-life of lead. The half-life of lead in human bones is given as about 10–30 years (NTP 2012).

2 Critical Toxicity

The literature on the toxicology of lead and its compounds in animal experiments and in humans has on the one hand been compiled in great detail in the toxicological and occupational medical documentations of the MAK value for "Lead and its compounds, except lead arsenate, lead chromate and alkyl lead compounds" (Greim 2002, 2008; Henschler 1978, available in German only). On the other hand, there are comprehensive reports by ATSDR (2019), NTP (2012), Safe Work Australia (2014), US EPA (2014) and WHO (1995).

Due to the occurrence of genotoxic and carcinogenic effects, lead was classified in Category 3 A for germ cell mutagens and in Category 2 of carcinogenic substances (Greim 2008). The existing BAT values have therefore been withdrawn. However, there are indications that the genotoxic effects of lead are at least partly indirect effects (Silbergeld et al. 2000). In the case of lead, it has to be additionally borne in mind that the previous BAT values (400 µg/l blood for women over 45 years and for men, 100 µg/l blood for women under 45 years) were based mainly on its neurotoxicity (behavioural toxicity), which is of high relevance for occupational safety. The previous BAT values therefore continue to exist as BLWs. Still important is the minimizing of reproductive toxicity. As no effect threshold can be derived for the developmental toxicity of lead, a BAR for women is set on the basis of the general background exposure.

3 Exposure and Effects

3.1 Relationship between external and internal exposure

According to the present state of knowledge, there is no clear relationship between external and internal exposure to lead. There are several causes for this (AGS 2017; European Commission 2002). An essential cause is that, in contrast to the determination of lead in the air (current exposure), the lead concentration in whole blood (PbB) reflects the chronic (long-term) absorption of lead and thus the entire body burden. In addition to absorption by inhalation there can be a significant oral uptake of lead via contaminated hands, beverages and foods. The evaluation of threshold limit values for biological monitoring can therefore not be based on air limit values.

3.2 Relationship between internal exposure and effects

As described above, the neurotoxicity of lead compounds is an essential end point for the evaluation of a biological limit value on the basis of the relationship between blood lead levels and effect parameters. Sensitive toxic effects of lead are the impairment of performance parameters determined using behavioural toxicological methods, and also effects on blood pressure and on reproduction.

3.2.1 Classic lead effects (haem synthesis)

Lead inhibits enzymes of the haem synthesis in a dose-dependent manner; for a number of related parameters threshold values were given in relation to the associated blood lead levels (zinc protoporphyrins: 200 µg/l; coproporphyrin: 400 µg/l; δ-aminolaevulinic acid in blood or urine: 300–350 µg/l; δ-aminolaevulinic acid-dehydratase: 100 µg/l; inhibition of iron chelation: 200–250 µg/l). However, the clinical relevance of biochemical changes in the

low-dose range is controversial. In general, they are not considered as adverse (European Commission 2002). The risk of anaemia increases above blood lead levels of around 500 µg/l (ATSDR 2019; WHO 1995). Minor effects on haemoglobin and erythrocyte count can, however, not be excluded for lower blood lead levels. The calculation of a benchmark dose of the lower 95% confidence limits for effects on haemoglobin and erythrocyte count in 388 male persons exposed to lead yielded benchmark values of around 200 µg lead/l blood (Karita et al. 2005).

3.2.2 Neurophysiological effects

In 2001, on the basis of a fundamental assessment of neurotoxic behavioural effects (Seeber et al. 1997), the Commission has undertaken an extensive re-evaluation of the studies on neurotoxicity and behavioural toxicity available to that date (Bolt and Schaller 2001), taking especially into consideration the meta-analysis by Meyer-Baron and Seeber (2000 a, b), which was confirmed by two further meta-analyses (Seeber et al. 2002). The average current blood lead level at which effects on performance or personality variables (parameters) were observed was between 310 and about 500 µg lead/l blood in the studies evaluated by Meyer-Baron and Seeber (2000 a, b). It was concluded that blood lead levels of 290–530 µg lead/l blood averaged over a longer period of time are associated with statistically significant effects on performance and personality (Bolt and Schaller 2005). Based on the meta-analysis by Meyer-Baron and Seeber (2000 a, b) the concentration level obtained for slight and moderate effects in the given performance dimensions was in the range of 400–450 µg lead/l blood. The meta-analysis showed that, in analogy to age-related changes, the slight effect sizes demonstrated could relate to changes in test performance corresponding to a difference in age of about 10 years. This change was regarded as health-relevant (see also Seeber et al. 1997). It was concluded that generally reproducible effects in the performance range start on average at concentrations of 400 µg lead/l blood. The evaluation of 30 publications, however, showed that three papers pointed to effects occurring in the range of about 300 µg lead/l blood and above. Lindgren et al. (1996) provided indications of the lowest exposure concentrations at which statistically proven effects occurred, however only related to a group comparison. Average current exposure levels at around 280 µg lead/l blood, and long-term ones of 400 µg lead/l blood, produced effects on performance with regard to attention, assignment and sensory motor functions. These showed a dose-response relationship to an index of the cumulative long-term exposure. The results of group comparisons in Chia et al. (1997) with 370 µg lead/l blood and in Mantere et al. (1984) with 300 µg lead/l blood are also to be regarded as indications of effects on performance below the level of 400 µg/l.

In 2013, based on the average value concept, the Commission assumed that early behavioural effects occur at 300 µg lead/l blood and above; this value was therefore derived as BLW (Bolt 2019 b).

Re-evaluation

The individual studies and meta-analyses on the neurotoxicity of lead published since 2000 (in addition to some earlier studies) have been evaluated in detail by the Committee for Hazardous Substances (AGS 2017). This evaluation is presented here in slightly modified and editorially revised form (AGS 2017, Section 5.1).

There are numerous new studies available for the assessment of neurotoxic effects after occupational exposure of adults to inorganic lead compounds. Without any claim to completeness a selection of publications is documented below:

Bleecker et al. (2007 a): *In this study by Bleecker et al. (2007 a) carried out within the framework of different investigations in Canadian lead smelters, 61 occupationally exposed persons of a mean age of 40 years (range: 23–50 years; currently exposed; duration of exposure on average 19 years with a range between 1 and 26 years) were investigated for their lead exposure and white matter changes (WMC) recorded. Changes in the pegboard test were analysed as evidence of possible psychomotor changes. For the results of the pegboard test and the findings of WMC there were significant correlations to lead exposure after adjusting for age and personal cerebrovascular risk factors (multivariance analysis). The current blood lead concentration was on average 291 µg/l ± 68.9 µg/l, the TWA (working lifetime weighted average) 420 (170–590) µg/l, and the mean tibia lead level 38.6 (± 24.4) µg/g. The working lifetime weighted integrated blood lead (IBL) level was 826 µg × years/dl (Bleecker et al. 2007 a). As regards the respective current blood lead value reference*

is made to the previously markedly higher exposure which is reflected in the TWA and which affects the IBL and the tibia-Pb value.

Bleecker et al. (2007 b): *Another study by Bleecker et al. (2007 b) examined both cognitive and motor impairment after occupational exposure to lead. The present exposure of the 112 workers from a metal smelter was about 340 µg lead/l blood (TWA from about 14 years of exposure on average) and the current lead exposure 259–263 µg/l. Workers with high and low cognitive reserve capacity were distinguished. In persons with low cognitive reserve capacity, there was a significant relationship between the blood lead level and the attention/executive factor, the digit symbol and motor speed and dexterity factor. Regarding the cognitive parameters, such differences were not seen in persons with high cognitive reserve capacity. However, there was also a significant relationship with the values for motor speed and dexterity measured in this group. From this study, no threshold concentration can be derived. The correlation is not differentiated according to the levels of exposure. It becomes clear that the motor effects are affected more markedly and independently of the personal cognitive reserve capacity in the blood lead concentration range of interest. It is not clear whether the current blood lead level is of any use with regard to neurotoxic effects. No bone lead concentrations are reported in this study. An IBL as measure for cumulative exposure was recorded, but it was not calculated for a period of 40 years. Therefore, it is not possible to give a CBLI and a corresponding average value of PbB for this study.*

A follow-up publication by Walsh et al. (2010) is available which comprised 358 lead smelter workers. In this collective, the TWA was 390 µg/l (SD (standard deviation): 120 µg/l). As much as 68% of the workers reported about current alcohol consumption. The chronic lead exposure is significantly correlated with the results in the "Rey-Osterrieth complex figure delayed recall" test. The results of workers with good organizational strategies were better than those of workers not having these organizational strategies (influence parameter: executive function). The database for the regression line is not shown exactly; according to these data, however, there is no threshold concentration for the corresponding impairments. In this study, no direct statements on cumulative exposure (CBLI; tibia Pb) are made.

Bleecker et al. (1997): *In one of the earlier publications on the Canadian lead study, 80 persons still actively exposed to lead in their job (average age 44.1 (SD: 8.4) years; exposure duration 4–26 years) were examined with regard to verbal memory and visuomotoric skills. The present lead concentration was 264 (SD: 71) µg/l, the corresponding tibia Pb value 41.0 (SD: 24.4) µg/g bone material. The TWA was given as 423 µg/l. A CBLI was not determined. For visuomotoric impairments there was a correlation with tibia Pb, for verbal memory the correlation with PbB was better than that with tibia Pb.*

Böckelmann et al. (2011): *A study at the University of Magdeburg (Böckelmann et al. 2011) describes long-term effects in male workers who were chronically (at least five years without any relevant interruption) exposed to lead during the processing of copper. A total of 70 exposed persons were compared with 27 controls. The control persons had the same age structure and were not exposed to heavy metals or solvents in the past. Although the premorbid intelligence was not determined, there is no reason to assume a distortion of results because job qualifications and education were the same in the control and in the exposed group. In both groups (exposed, controls), persons with "evidence of nervous lesions or unusual psychic signs, known diabetes mellitus, manifest arterial hypertension or cardiac insufficiency, and abuse of alcohol and/or drugs" were excluded. In a supporting approach, a search analysis for drugs and/or metabolites including caffeine and nicotine was conducted, as the results of performance tests may be modified by such substances. Participation in the tests for blood lead determination was on a voluntary basis. The mean blood lead level of the exposed persons was 306 ± 102 µg/l over the last 12 years. Twenty-one of the persons had a higher (PbB 350 µg/l) and 49 a lower (PbB 350 µg/l) exposure level. Over these 12 years, the exposure of the high-exposed group was 430 ± 61 µg/l and that of the low-exposed 253 ± 63 µg/l. The total reaction time in the single form visual reaction test was 398.4 ± 39.1 milliseconds (ms) (control) or 443.5 ± 66.4 ms (low-exposed group) and 446.0 ± 73.8 ms (high-exposed group); differences to the control were significant even in the low-exposed collective (p 0.001). The movement time in the corresponding test was 91.4 (± 21.6) ms in the control group, 111.0 (± 35.6) ms in the low-exposed group and 115.7 (± 35.4) ms in the high-exposed group. The finding was significant even in the low-exposed workers (p = 0.004). In addition, indications of deviations in the heart rate and sinus arrhythmia were examined as possible effects on the autonomic nervous system. The heart rate was decreased in the exposed workers, and sinus arrhythmia occurred more frequently in the exposed*

workers (with a dose-response relationship between high and low-exposed workers). The authors discussed the results with caution with regard to the comparability of the vagotonic state of the exposed and control groups. The results were interpreted by the German Society of Occupational and Environmental Medicine (Deutsche Gesellschaft für Arbeits- und Umweltmedizin) as indication of early neurological damage (DGAUM 2007). Finally, in the study by Böckelmann et al. (2011) the psychological state level was tested both currently (subjective state level) and in its development during the past 6 months. There were significant changes with regard to fatigue, forgetfulness and lack of energy (the last two parameters were decreased in a concentration-dependent manner).

Chuang et al. (2005): *In a study from Taiwan (Chuang et al. 2005) 27 lead glaze workers were observed prospectively. Their previous blood lead levels were 263 (SD: 120) and those after 4 years 83 (SD: 69) µg/l. The Chinese variant of the neurobehavioral evaluation system 2 (C-NES II) was used. Tests were carried out in 1994, 1996, and 1997. Comparative data with a non-exposed control group (lead = 69 ± 42 µg/l) are available only for 1994. Due to the reduction in lead exposure, there was in some cases an improvement in the neurological findings (finger tapping test, pattern comparison test and pattern memory test). Nevertheless, there were still differences in individual parameters from the control group, so that no effect threshold can be derived from this study. When questioned after 1 year, there were significant deviations from the control group as regards the following questions: "Have you tired more easily than expected for the amount of activity you do?", "Have you had to make notes to remember things?", "Have you had tremor of fingers?", and in the total result of the questioning. Clearly adverse effects have been demonstrated for mean blood lead levels around 263 µg/l, which were, in some cases however, possibly reversible.*

Dorsey et al. (2006): *In a cross-sectional study (n = 652) in 26 plants in Korea the authors investigated the relationship of blood lead and bone (patella, tibia) lead concentrations with cognitive function and with peripheral effects. In 7 of 19 tests, the result was a deterioration of manual dexterity, sensory vibration threshold and depressive symptoms. The average age of the exposed persons was 43.4 (SD: 9.6), the average duration of exposure to lead was 10 (SD: 6.5) years. In some cases, the lead exposure was in the past. The current blood lead level was 309 (SD: 167) µg/l, and the tibia lead concentration was 33.5 (SD: 43.4) µg/g bone material. Patella lead was not regarded as a better indicator of effects.*

Ekinci et al. (2014): *The authors (Ekinci et al. 2014) examined the layer thickness of optical nerve fibres affecting visual effects in 50 battery workers with exposure to lead. A differentiation was made between four groups according to their mean blood lead levels: group 1 (n = 22): 461.8 µg/l, group 2 (n = 16): 293.1 µg/l, group 3 (n = 12): 169.2 µg/l and group 4 (controls; n = 20): 28.5 µg/l. The parameters for the nerve fibre layer thickness determined in a laboratory test were significantly different from the controls even in the lowest-exposed group (with 169.2 µg/l PbB) and decreased in a highly significant and dose-dependent manner with the poorest values in the highest exposure group. The authors suggested further examinations to confirm this effect. From this study, a LOAEC of 169.2 µg/l lead is suspected.*

Hänninen et al. (1998): *The Finnish study in battery lead workers (n = 54) examined results in neurological behavioural tests after previous lead exposure. The workers had been exposed occupationally for more than 20.5 years (in the case of the higher-exposed group) or 12.3 years in the case of the low-exposed workers. The average blood lead level during working life was given as 1.9 (SD: 0.4) µmol/dl (≙ 394 µg/l) for the previously higher-exposed and 1.4 (SD: 0.3) µmol/dl (≙ 290 µg/l) blood for the previously low-exposed group. The blood lead level of the last 3 years was1.6 (SD: 0.4) µmol/dl (≙ 332 µg/l) for the previously higher-exposed and 1.3 (SD: 0.4) (≙ 269 µg/l) blood for the previously lower-exposed group. The tibia lead level was 35.3 (SD: 16.6) mg/kg for the higher-exposed and 19.8 (SD: 13.7) mg/kg for the lower-exposed group. The tibia-Pb levels did not correlate with the test results; based on the blood lead levels, a poorer performance as regards attention test, visual memory and visuoperception was found in the high-exposed group than in the lower exposed group.*

Hsieh et al. (2009 a, b): *In a prospective cohort study, the authors (Hsieh et al. 2009 b) investigated subclinical changes in the brain of 19 workers in a lead paint factory using magnetic resonance spectroscopy (MRS). Between the exposed and the control group (n = 18) there were no significant differences with regard to sex, age, body mass index, smoking habits, betel nut consumption and alcohol consumption. However, the number of milk drinkers among factory workers was significantly higher than that among volunteers. Hsieh et al. (2009 b) found a negative correlation for the*

above-mentioned parameters in relevant brain areas in relation to the blood lead level and interpret these biochemical changes as indication of neurotoxic effects (memory and visual performance). In comparison with the control group there were significant shifts with regard to the diffusion of fluids in the brain (fractional anisotropy). According to the authors, the changes are interpreted as indication of neuronal and axonal damage or loss due to lead exposure. The blood lead values were 114.9 ± 11.5 µg/l (n = 19 exposed workers) compared with 32.3 ± 11.5 µg/l in the control group (n = 18). The changes correlated markedly better with the lead concentration in bone and in the patella than with the blood lead level. The tibia lead concentrations were 51.71 (± 1.79) µg/g in the exposed collective and 20.84 (± 2.88) µg/g in the control group. The high background values and the discrepancy to other studies, however, make a quantitative assessment difficult. In another publication (Hsieh et al. 2009 a), the composition of the exposed group was slightly different (n = 22; 5 females, 17 males) compared with that in Hsieh et al. (2009 a) while the control group was the same. Brain MRS revealed significant biochemical effects (changes in choline:total creatinine ratio and N-acetyl aspartate:total creatinine ratio). Tibia lead levels were 61.55 (± 30.21) µg/g (exposed) and 18.51 (± 22.40) µg/g, blood lead levels 169.9 (± 103.8) µg/l and 34 (± 11.1) µg/l in the exposed persons and controls, respectively.

Iwata et al. (2005): *In this study, 121 lead workers in Japan had lead levels in blood of 400 (SD: 150) µg/l. One year before the exposure level had been similar (430 ± 160 µg/l). The age of the exposed persons was 46.3 (± 11.4) years. There were 60 not exposed control persons (46.6 ± 11 years). In the exposed group postural sway/postural balance occurred with increased incidence. Values of 121–173 (mean value 144) µg/l in the blood were found for the benchmark concentration ($BMDL_{05}$). As BMD_{05} the values are 183–307 µg/l. This effect is regarded as evidence of lead-induced neuromotor dysfunction. The proportion of smokers in the exposed collective was increased in a highly significant manner (66% vs 35%); the assessment, however, was adjusted accordingly (Iwata et al. 2005). The study by Iwata et al. (2005) is also integrated in the assessment by* Murata et al. *(2009) and is used in many current evaluations that are based on a blood lead value as critical effect concentration for occupational lead exposure.*

Khalil et al. (2009 a): *Khalil et al. (2009 a) examined a collective of 83 exposed persons and 51 controls. The lead exposed workers had been employed for 25 (SD: 8) years, they were on average 54 years old (SD: 9). The current blood lead level was 120 (interquartile range 80–190) µg/l and the corresponding tibia-Pb concentration 57 (20–86) µg/g. In the controls the blood lead level was 30 (30–40) µg/l, and the tibia-Pb concentration 12 (8–19) µg/g. The lead exposure of the exposed was on average 6 years ago (interquartile range 0.02–16). Over the years (22 years observation period: 1982–2004) the cognitive function – tested with the Pittsburgh Occupational Exposures Test battery – declined markedly. In 1982, reduced values were found only in the pegboard test in older test participants. In 2004, a decline in cognitive function in old age was shown on the basis of several test results, which was markedly increased by lead.*

Krieg et al. (2005): *In a comprehensive evaluation of neurobehavioural changes in adults on the basis of data from the third National Health and Nutrition Examination Survey (NHANES III) and studies with occupationally exposed collectives (Krieg et al. 2005), relationships between blood lead levels and the tests simple reaction time, symbol-digit substitution, and digit learning were evaluated. After adjustment for co-variables no statistically significant correlation between the test results and the blood lead levels on the basis of the NHANES III data were found. This collective, however, included only 11 persons with blood lead levels of 250 µg/l and only 49 persons with blood lead levels between 150 and 250 µg/l. The blood lead levels of the vast majority of a total of 5662 persons were below 100 µg/l. The collectives with occupational exposure, however, consistently performed worse in the simple reaction time t and the symbol-digit substitution test. From the NHANES data the authors conclude that there is no evidence of behavioural changes in the range below 250 µg/l. However, from this evaluation, no threshold value was obtained for occupationally exposed collectives. Using regression models, evaluation of 18 occupational studies revealed that the mean reaction time was still slightly impaired at a level as low as 100 µg/l; these models showed also still a significant decline in the performance on the symbol-digit substitution test at 100 µg/l PbB based on 27 studies. From the findings made in occupationally exposed collectives (26 studies) with higher exposure levels (240–720 µg PbB/l) the authors concluded that a limit value of 500 µg/l, required by the OSHA for removal of occupationally exposed persons from the workplace in the USA at that time, should be re-evaluated.*

Louis et al. (2003): *In a study with 100 patients with an essential tremor (ET), an association with lead exposure was found at very low concentrations in comparison with the 143 controls. In a smaller subsample bone lead concentrations (tibia) were determined in addition. However, no quantitative results are reported for this. The authors found a correlation between a lead blood level less than 5 µg/dl and ET and a correlation between ET and the bone lead concentration. Reference was made that the cumulative exposure to lead should be analysed in a separate evaluation using bone lead as parameter.*

Note: Due to methodological shortcomings, this study is considered not relevant for the evaluation by the Commission.

Murata et al. (2009): *Murata et al. (2009) carried out a secondary evaluation of several studies on the neurotoxicity of lead. The BMD_{05} and the $BMDL_{05}$ (benchmark dose with and without confidence interval, response 5%) were estimated and it was discussed that these were approximately equal to a LOAEL and a NOAEL (however, the BMD approach is not intended to derive a threshold).*

BMDL and/or BMD were estimated for the following studies (among others):

End point	*Number of exposed persons*	*BMDL – BMD [µg/l] (estimated)*	*Workplace studies*
motor nerve conduction velocity	*n = 38*	*75 – 116*	Araki et al. 1992
motor nerve conduction velocity (tibialis, posterior)	*n = 37*	*82 – 131*	Araki and Honma 1976
median motor nerve conduction velocity	*n = 112*	*84 – 120*	Seppäläinen et al. 1979
cognitive function (P300)	*n = 36*	*61 – 113*	Araki et al. 1992
neuromotor function	*n = 121*	*121–169 (BMDL) – 183–307 (BMD; according to parameter)*	Iwata et al. 2005

From this compilation the authors (Murata et al. 2009) drew the following conclusions: "The neurotoxic effects of lead in workers appear to be initiated at PbB levels below 18.0 µg/dl" and "The present review of lead toxicity in workers suggests that the critical organ is the nervous system and the critical level of PbB is estimated to be between 10.7 and 17.5 µg/dl, although the critical level for higher central or peripheral neuropathy might differ from those for damage of the autonomic nervous system, hypothalamus or cerebellum." Then, differentiated considerations on the reversibility of the effects are put forward. With regard to the motor nerve conduction velocity and other parameters there were clear associations below 200 µg PbB/l as was for P300 (cognitive function).

Qiao et al. (2001): *The authors (Qiao et al. 2001) examined 16 women occupationally exposed to lead (printing works; average age 34.8 years (± 4.9 years), on average 12.7 years (± 5.1 years) employed in the printing area). The exposed group was compared with 36 corresponding control persons. The mean blood lead levels of the exposed were 286 µg/l (± 146 µg/l), those of the control group 124 µg/l (± 47 µg/l). The air lead concentration was on average 25 $\mu g/m^3$ (± 19 $\mu g/m^3$). The Neurobehavioral Core Test Battery (NCTB) of the WHO was used. In the exposed workers, some NCTB scores were significantly changed including "simple reaction time", "digit symbol", "pursuit aiming II" and "correct PA", "profile mood states" (POMS).*

Sahani and Ismail (2005): *In 141 battery workers with an average age of 35.2 (SD 9.6) years employed for 9.1 (SD: 7.1) years the authors from Malaysia found significant correlations between blood lead levels und the results in the digit symbol, the digit forward and digit backward tests as well as in the pursuit aiming and the trail B tests. The blood lead levels (n = 138) were on average 405 µg/l (SD 168; range 49–765). Workers with levels ≥ 400 µg lead/l blood had significantly poorer results in the digit symbol, the digit backward, the Santa Ana preferred hand, the Santa Ana both hands, the Benton, the pursuit aiming and in the trail B tests. A reduction in cognitive, memory and concentration performance were observed at levels below 300 µg/l blood.*

Schwartz et al. (2005): *In a longitudinal study, 576 persons from South Korea occupationally exposed to inorganic lead were examined three times by neurobehavioural tests over a longer period of time (Schwartz et al. 2005). There were consistent associations of blood lead with test scores at baseline and of tibia lead with declines in test scores over the next year, mainly in executive abilities, manual dexterity, and peripheral vibration threshold." The mean blood lead level was 314 µg/l (± 142; range 40 to 760) and the mean tibia lead concentration 38.4 µg/g (± 43; range –7 to 338). Altogether 76% of the persons that were examined three times were male. The average age was 41.4 years (± 9.5 years) at the first examination, and the average duration of their employment 8.5 years (± 6.3 years). Covariables (initial blood lead value; gender; school education) were taken into account for the regression analysis. An increase in the blood lead level from 210 µg/l (25th percentile) to 400 µg/l (75th percentile) was associated with a 11% poorer test result during the first testing in the Purdue pegboard dominant hand test, and the results deteriorated by 6% per year in the repeat tests. An increase in the tibia lead concentration from 140 µg/l (25th percentile) to 470 µg/l (75th percentile) deteriorated the test result by 2% per year in the repeat tests. The authors concluded, that lead is associated on the one hand with an acute effect on the test results due to recent exposure and with a possibly progressive chronic effect (decline in cognitive function) as a function of cumulative lead doses.*

The Committee for Hazardous Substances (AGS 2017) concluded that all available individual studies had their weaknesses and uncertainties, especially because of the sometimes higher previous exposure to lead from occupational and extra-occupational sources. Furthermore, since in this case a LOAEC for occupational collectives should be given, the AGS concluded that, after weighing and assessing all evidence, it could be assumed that a blood lead level of 300 µg/l represents an effect concentration (see AGS 2017, Table 3). The Commission agrees with this view.

3.2.3 Reproductive toxicity

3.2.3.1 Male fertility

The results of a few earlier epidemiological studies suggest an effect of occupational lead exposure of men on the risk of spontaneous abortions, perinatal mortality and lower birth weights (Anttila and Sallmén 1995; Kristensen et al. 1993; Lindbohm et al. 1991). The same is true for reduced fertility and various parameters of sperm quality (Alexander et al. 1996; Assennato et al. 1986; Lancranjan et al. 1975; Lin et al. 1996). In general, such effects occur at blood lead levels above 400 µg/l (Apostoli et al. 1998; European Commission 2002).

3.2.3.2 Developmental toxicity

In the supplement to the MAK documentation of lead (Greim 2002) the findings of prospective studies in children (longitudinal studies) were discussed which determined the relationship between blood levels in prenatal or perinatal maternal blood or in umbilical cord blood and data for postnatal cognitive development. Evaluated were seven birth cohorts which are presented in tabular form in the MAK documentation (Greim 2002, Table 1). Cross-sectional studies, which are primarily relevant for environmental medicine, were not included.

The seven evaluated studies are summarized by Greim (2002) as follows:

The available meta-analyses of the prospective studies, which consider only lead values in blood determined exclusively after birth, cannot contribute much to the question as to how relevant a prenatal/perinatal exposure to lead may be for the later psychomental development (Pocock et al. 1994; WHO 1995).

"In spite of intensive efforts to standardize the methods used (body burden, measurement of effects, relevant confounders), the prospective studies are so different that a truly concurrent picture of the effects of lead cannot really be expected (WHO 1995). The various cohorts differ markedly in the correlates reflecting opportunities for cognitive development. The average maternal IQ in the Boston study cohort was, for example, 121, that in the Cleveland study cohort only 75; this reflects enormous socio-economic and familial differences. The nature of the exposure to lead also differs markedly in the various studies. It includes exposure via paint containing lead in dilapidated slum areas (Cincinnati), exposure mainly via traffic in cities like Sidney and Boston, exposure in the drinking water in one city (Glasgow), and emissions from lead smelters (Port Pirie, Kosovo).

For these reasons it is hardly surprising that the results are discrepant. The results of the seven prospective studies are inconsistent if, as is necessary in the present context, the effect only of the prenatal and perinatal exposure to lead is considered as the predictor for cognitive development. Three of the studies revealed no such relationship (Glasgow, Port Pirie, Sydney). In three other studies (Boston, Cleveland, Cincinnati) a significant negative association was determined at the age of six months. In the Kosovo study, this association was detected in samples from children aged 48 months but not from younger children. In four of the studies (not in Sydney, Glasgow or Cleveland) mainly relationships between cognitive development and postnatal lead exposure were found and these are in accordance in this respect with the results of most cross-sectional studies (not discussed here).

Thus, it is still not clear whether specifically prenatal or perinatal exposure to lead is relevant for a persistent impairment of later cognitive development; the clearest evidence was obtained in the Boston study in which 100 µg/l blood was the effect threshold (Bellinger et al. 1991). The impairment persists, however, for at most 24 months. Prenatal and postnatal blood lead levels are necessarily correlated, so that a negative correlation between prenatal or perinatal blood lead levels and postnatal development could also be detected postnatally. Then it would be justified to doubt that maternal exposure to lead can affect the later cognitive development of her child and to conclude that the developmental toxicological data indicate that changes in the BAT value for women of child-bearing age are not necessary. However, the quantitative situation is unclear and more epidemiological studies are necessary" (Greim 2002).

The available literature shows that a scientifically grounded value, based on a threshold concentration for foetal effects, still cannot be evaluated. Effects can be seen even at low levels of exposure (in some cases around and below 100 µg lead/l blood); a threshold concentration for such effects can probably not be determined. This view of the Commission is further supported by other studies (Canfield et al. 2003; Jelliffe-Pawlowski et al. 2006; Rogan and Ware 2003; Selevan et al. 2003; Walkowiak et al. 1998).

3.2.4 Effects on the kidneys

Experiences with previous high exposures at the workplace show that lead can cause acute tubular kidney damage and chronic interstitial fibrosis. Renal colics have been reported at blood lead levels of about 1000 µg/l and higher (European Commission 2002).

Evans et al. (2010) compared 926 incident cases of chronic renal insufficiency (serum creatinine: men 3.4; women 2.8 mg/dl) with 998 population-based controls in Sweden and could find no significant difference between the two groups with regard to their exposure to lead. Weaver et al. (2009), on the other hand, who examined persons in Korea exposed to lead at the time or previously, using the parameters blood urea nitrogen, serum creatinine and creatinine clearance as well as analyses of blood and bone (tibia) lead, reached the conclusion that there was an association between lead exposure and kidney function. However, it is to be noted that the observed effects could also be due to previously higher occupational exposures to lead, so that a clear dose-related assignment is not possible.

Tian and Jin (2007) examined 135 workers occupationally exposed to lead in a battery factory and 143 control persons with regard to the excretion of the sensitive tubular markers beta-2-microglobulin and NAG (*N*-acetylglucosaminidase). They determined BMD (benchmark dose) levels of about 320 µg lead/l blood for beta-2-microglobulin and of about 300 µg lead/l blood for NAG. The BMDL of about 250 µg lead/l blood for NAG was regarded as the most sensitive tubular marker for the effects of lead. The BMDL determined in the study by Sun et al. (2008) was 101 µg/l. The question of possible effects of previously higher exposures arises here again.

Overall, on the basis of the available data, there is some uncertainty as regards the assessing of the health relevance of these findings. SCOEL (European Commission 2002), for example, concluded that there is no evidence of nephrotoxicity at blood lead levels of 400 µg/l and below. Including the more recent studies, Safe Work Australia (2014) give a limit of 300 µg lead/l blood and more for incipient renal damage.

3.2.5 Cardiovascular effects/Hypertension

Effects of lead on blood pressure have been widely investigated in more and more studies since the 1980s. According to experimental data, lead is able to interfere with the Na-K system, with cAMP, Ca^{2+} and with the renin angiotensin system (European Commission 2002).

The studies available up to then were summarized in the MAK documentation (Greim 2002). Particular reference was made to a meta-analysis of almost all studies then available (a total of 19 studies with 33 141 persons; Staessen et al. 1994). This meta-analysis showed that the association between lead concentration in blood and blood pressure has about the same magnitude in both sexes. Doubling of the blood lead level was associated with an increase in the systolic and diastolic blood pressure by about 1.0 mm Hg. From this it was concluded that, although available data are indicative of a weak positive association between blood pressure and lead exposure, any such relationship may not be causal. Overall, the Commission regarded the observed changes in blood pressure as principally reversible, with no proven causal relationship (Greim 2002).

After evaluation of all studies available up to then (more than 30 population-based cross-sectional and prospective studies comprising over 58 000 adults) the US EPA (2014) described the association between blood lead levels and increase in blood pressure as weak but robust. Uncertainties with regard to the level and length of the respective lead exposure were especially emphasized.

Lustberg and Silbergeld (2002) analysed the mortality data of 4292 participants of the American NHANES II study, which comprised 10 049 persons (*Second National Health and Nutrition Examination Survey,* 1976–1980, with follow-up blood lead analyses up to the end of 1992 in the persons aged between 30 and 74 years). After adjustment for potential confounders, the cardiovascular mortality in persons with blood lead levels of 200–290 µg/l, was increased by 39% (RR (relative risk) 1.39; 95% CI (confidence interval) 1.01–1.91) compared with persons with blood lead levels of 100 µg/l. A similar increase was also found for all causes of mortality.

A subsequently carried out similar evaluation of the data of the following NHANES III study (9757 persons, 1988–1994) compared the cardiovascular mortality of persons with blood lead levels 50 µg/l with that of persons with blood lead levels of 100 µg/l and more, for whom a RR = 1.55 (95% CI: 1.16–2.07) was found. There was likewise a similar increased risk of death from all causes of mortality, and even cancer (Schober et al. 2006).

A clear causal relationship between lead exposure and defined cardiovascular symptomatology cannot be derived from the two NHANES-based studies (Lustberg and Silbergeld 2002; Schober et al. 2006). Thus, the conclusion (Greim 2002) is still valid that the available data were indicative of a weak positive association between blood pressure and lead exposure, but that such a relationship may not been causal.

3.2.6 Genotoxicity and Carcinogenicity

For the genotoxic and carcinogenic effects of inorganic lead, reference is made to the detailed description in the respective MAK documentation (Greim 2008). Animal studies on carcinogenicity meeting present-day requirements are not available. Studies with lead acetate in mice, however, show that renal tumours occur even without simultaneous renal toxicity. In rats, lead acetate is a pluripotent carcinogen. It causes tumours in the kidneys, adrenal glands, testes, prostate, lungs, liver, pituitary gland, thyroid and mammary glands as well as leukaemia, sarcomas of the haematopoetic system and cerebral gliomas. Cerebral glioma is a type of tumour rarely occurring spontaneously. As the release of lead ions is responsible for the toxic effects of all forms of lead, and genotoxicity has been demonstrated both for metallic lead as well as for its inorganic compounds, a carcinogenic effect of lead itself and its inorganic compounds must be assumed. Lead and its inorganic compounds have therefore been classified in Carcinogen Category 2 (Greim 2008).

Parameters of genotoxicity in lead-exposed workers were examined in some studies. Vaglenov et al. (2001) investigated the occurrence of micronuclei in the lymphocytes of 103 persons occupationally exposed to lead and 78 control persons. They reached the conclusion that blood lead levels above 1.2 µM (about 250 µg/l) are associated

with a genotoxic risk. This is compatible with data from other research groups (Duydu et al. 2001; García-Lestón et al. 2012; Kašuba et al. 2012) and in vitro data (Bonacker et al. 2005). The lead-induced formation of micronuclei is mainly an aneugenic effect. In the low dose range, the interaction of lead ions with tubulin and kinesin appears to be important here. These findings were used as arguments for the existence of a threshold dose for the genotoxicity of lead (Bonacker et al. 2005).

4 Selection of the Indicators

There has been a consensus of opinion that the recognition of increased absorption of lead at the workplace must be based on laboratory analysis of specimens from exposed persons. There is principally a wide spectrum of both exposure and effect parameters available for this purpose. These can be classified as follows:

Parameters of internal exposure

Determination of the lead concentration in biological materials:

- blood lead concentration
- amount of lead excreted with the urine
- amount of lead in bones
- amount of lead excreted with the urine after provocation with complexing agents

Parameters of effect

In the past, disturbance of porphyrin synthesis was the main biological parameter used to detect the effects of lead. These disturbances are best recognized in man in effects on haematological parameters.

- in blood: δ-aminolaevulinic acid-dehydratase, erythrocyte porphyrins and zinc protoporphyrins
- in urine: δ-aminolaevulinic acid (ALA-U).

The lead concentration in blood is the most reliable and practicable parameter for monitoring persons exposed to lead. It is the most specific parameter for evaluating the internal exposure to lead. Effect parameters (for example ALA-U) can no longer be recommended, either for methodological reasons, or especially for reasons of low sensitivity in view of the nowadays lower exposure to lead at the workplace compared with in the past.

5 Methods

Quantitative determination of the lead concentration in whole blood can be carried out using atomic absorption spectrometry, voltammetry and ICP-MS (inductively coupled plasma mass spectrometry). Reliable and tested methods for these three analytical techniques have been published by the working group "Analyses of Hazardous Substances in Biological Materials" (available in German only Fleischer and Schaller 1982; Schaller and Pilz 1985; Schramel et al. 1999; Seiler and Angerer 1988). Voltammetric analysis is very sensitive, but also very time-consuming and is therefore not used routinely (Ostapczuk 1992). For a long time, graphite furnace atomic absorption spectrometry (GF-AAS) with Zeeman compensation was used almost exclusively. After dilution and the addition of a matrix modifier, the blood was analysed directly. For a description of GF-AAS methods for determining lead in blood reference is made to the literature (Christensen and Kristiansen 1994; D'Haese et al. 1991; Fleischer and Schaller 1982; Jacobson et al. 1991; Jin et al. 1990; Miller et al. 1987; Parsons and Slavin 1993; Schaller and Pilz 1985; Shuttler and Delves 1986).

Today mainly ICP-MS is used.

The determination of lead in blood must be carried out under conditions of statistical quality control. There are various commercially available control samples for internal quality control (WHO 1996). External quality control programmes, which include the determination of blood lead in the occupational and environmental health field, are offered regularly in Germany as interlaboratory comparison programmes on behalf of the German Society of Occupational and Environmental Medicine (DGAUM) (Göen et al. 2012).

6 Background exposure

In recent years, the internal lead exposure of the general population has considerably declined. For the years 1990/92, the Human Biomonitoring Commission of the Federal Environmental Agency (UBA) gave the following reference values (95th percentiles) for the population of the Federal Republic of Germany:

- Women aged 25 to 69 years: 91 µg lead/l blood
- Men aged 25 to 69 years: 116 µg lead/l blood

The median values were 38 and 54 µg lead/l blood, respectively (Krause et al. 1996).

In Germany, in the meantime, there was a further decline in the blood lead levels. The Environmental Survey of 1998 yielded the following reference values (95th percentiles):

- Women aged 18 to 69 years: 62 µg lead/l blood
- Men aged 18 to 69 years: 79 µg lead/l blood

The median values were in the range from 27 to 36 µg lead/l blood (Becker et al. 2002).

On the basis of the 3rd Environmental Survey, the Human Biomonitoring Commission of the Federal Environmental Agency set the following reference values (UBA 2002):

- Women aged 18 to 69 years: 70 µg lead/l blood
- Men aged 18 to 69 years: 90 µg lead/l blood

International situation

In 1996, within the framework of the "Tracy Project", the lead levels in the blood of the general population were evaluated worldwide. Ten studies were selected which were deemed suitable for evaluation with regard to their analytical methods and definition of the population. The conclusion reached by these studies was that no general reference values for lead levels in blood can be given because the blood lead levels are highly dependent on the sampling time. Possibly due to the elimination of lead from vehicle fuels, the lead levels in blood are in constant decline (Herber 1999). In Sweden, for example, they decreased from 60 µg lead/l blood over a period of about 10 years to 30 µg lead/l blood in 1988. The study revealed that multiple factors such as age, gender, ethnic origin, foods, drinking and smoking habits, hobbies, season and year of sampling, residential area and geographic origin, influence the lead levels of the general population (Gerhardsson et al. 1996). In the NHANES report of the CDC (2003) a 95th percentile of 40 µg lead/l blood was evaluated for the female general population in the USA (n = 4057) and of 60 µg lead/l blood for the male population (n = 3913). The blood samples were obtained in the USA in the period from 1999 to 2000.

7 Evaluation

In Section 3 it was described that the following effects of lead on the human organism (related to the blood lead level) are to be regarded as relevant.

- Classic effects on the *haem synthesis* manifested as anaemia occur above concentrations of 500 µg lead/l blood. Lesser effects and biochemical changes, which however are not regarded as adverse, occur even at lower blood lead levels (Section 3.2.1).
- Incipient *behavioural effects* occur in a range around and above 300 µg lead/l blood (Section 3.2.2).
- Effects on *male fertility* occur at blood lead levels above 400 µg/l (Section 3.2.3.1).
- For *toxic effects on foetal development*, no threshold dose can be derived. Effects are still reported even at very low exposure levels of around and, in some cases, also below 100 µg lead/l blood. Presumably, there is an effect continuum reaching into environmentally relevant lead concentrations (Section 3.2.3.2).
- For incipient *nephrotoxic effects,* a threshold level of 300–400 µg lead/l blood can be assumed (Section 3.2.4).
- C*ardiovascular effects / effects on blood pressure* are reported mainly in population-based studies. There appears to be a weak positive association between blood pressure and lead exposure; a causal relationship is questionable (Section 3.2.5).
- Based on *genotoxicity and carcinogenicity* studies, the MAK Commission classified lead in Category 3 A for germ cell mutagens and in Category 2 for carcinogenic substances (Section 2). An increased incidence of micronuclei in the circulating lymphocytes was observed in workers at blood lead levels above about 250 µg/l, (Section 3.2.6). Mechanistic investigations point to the existence of a threshold level for genotoxicity (Section 3.2.6).

Due to the toxic effects on foetal development, no health-based limit value can be derived for women of reproductive age (up to 45 years). Instead, a biological reference value (BAR) on the basis of the general background exposure is derived.

For women 45 years and for men no BAT value is derived due to the carcinogenic effects (classification of lead in Category 2 for carcinogenic substances), but a BLW which is essentially based on the other effects.

7.1 Derivation of a BAR for women

In 2008, the concept of BARs was established as it had become necessary to include background exposure as orientation in the evaluation of a number of substances. BARs are based on the 95th percentile of the existing background exposure of the general population, without reference to any health effects.

In the past decades the lead exposure of the general population in the industrialized countries continued to decline as a result of the ban of leaded petrol and other measures (Castaño et al. 2012; CDC 2011; Schulz et al. 2009, 2011, 2012). In 1996, using the results of the Environmental Surveys from 1990/92 the Human Biomonitoring Commission of the Federal Environmental Agency derived a reference value for women (25–69 years) of 90 µg lead/l blood (UBA 1996 a). This reference value (RV_{95}) is defined as the 95th percentile of the measured concentrations of the substance in the relevant matrix of the reference population (UBA 1996 b). On the basis of the following 1998 Environmental Survey the reference values (RV_{95}) for lead were updated. For this purpose, the blood lead levels of 4646 persons aged 18–69 years were determined. The analysed concentrations were all between 4 and 380 µg lead/l blood with a geometric mean of 30.7 µg/l. The blood lead levels of men were higher than those in women. Further influencing variables were age, haematocrit, consumption of low-percentage alcoholic beverages and the lead concentration in the residential drinking water. In comparison with the Envrionmental Surveys from 1990/92, the blood lead level in Germany had decreased by about 30% on average. For women (18–69 years) a lead concentration of 70 µg/l blood was determined as 95th percentile (UBA 2002) and in 2003 established as updated reference value (RV_{95}) by the

Human Biomonitoring Commission of the Federal Environmental Agency. This value is still valid at present (Schulz et al. 2011, 2012; UBA 2003, 2012). Like the abovementioned reference value (RV_{95}) of the Federal Environmental Agency the BAR is based on the 95th percentile of the general population. Therefore, a **BAR for women of 70 µg lead/l blood** was set in 2012 (Bolt 2019 a). There is no fixed sampling time.

Note: This BAR is no longer valid. For updates please refer to Göen et al. (2020).

7.2 Derivation of a BLW for women > 45 years and for men

Behavioural effects and nephrotoxicity are to be expected at blood levels of 300 µg lead/l blood and above. Indications of incipient behavioural effects were already found in a range around 300 µg lead/l blood.

Against this background the

BLW of lead for women > 45 years and for men is set at 200 µg lead/l blood.

There is no fixed sampling time.

At the proposed BLW of 200 µg lead/l blood no increase in the incidence of micronuclei in the lymphocytes of workers was found. The proposed BLW is therefore also suited to minimize genotoxic or carcinogenic risks.

8 Interpretation

In the Federal Republic of Germany, occupational health check-ups (or preliminary occupational health examinations) of persons exposed to lead and its inorganic compounds are carried out according to the "Verordnung zur arbeitsmedizinischen Vorsorge" (Ordinance on Occupational Health Care) (BMAS 2016). Intervals for follow-up examinations can be found in the Arbeitsmedizinische Regel (Occupational Medical Regulation, AMR) 2.1 (AfAMed 2016), for biomonitoring in AMR 6.2 (AfAMed 2014), further information in TRGS 505 Lead (AGS 2007). In the case of borderline findings, more frequent check-ups may be indicated.

Due to the long biological half-life of lead in the human organism, there is no fixed sampling time for blood.

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