

Lead and its inorganic compounds (except lead arsenate and lead chromate) – Addendum: Evaluation of a BAT value

Assessment values in biological material – Translation of the German version from 2022

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Abstract

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 inorganic compounds (except lead arsenate and lead chromate) and has derived a biological tolerance value (BAT value) at the workplace for the blood concentration of lead and a pregnancy risk group classification. Neurotoxicity is considered to be the most sensitive end point. Neurotoxic effects have been described at concentrations above 180 µg lead/l blood. Therefore, a BAT value of 150 µg lead/l blood was established. Because of the long persistence of lead in the body, the sampling time is not fixed. Since damage to the embryo or foetus in humans by lead has been unequivocally demonstrated and is to be expected even when the maximum workplace concentration (MAK value) and BAT value are observed, Pregnancy Risk Group A was determined.

BAT value (2021)	150 µg lead/l blood Sampling time: not fixed
Prenatal toxicity (2021)	Pregnancy Risk Group A
BAR (2019)	Women: 30 µg lead/l blood Men: 40 µg lead/l blood Sampling time: not fixed
MAK value (2021)	0.004 mg/m³ I (inhalable fraction)
Peak limitation	Category II, excursion factor 8
Absorption through the skin	–
Sensitization	–
Carcinogenicity (2021)	Category 4
Germ cell mutagenicity (2004)	Category 3 A

For lead and its compounds, documentation and several addenda are available:

1981	Establishment of a BAT value for women ≥ 45 years and for men: 700 µg lead/l blood, 15 mg δ-aminolevulinic acid/l urine and of a BAT value for women <45 years: 450 µg lead/l blood, 6 mg δ-aminolevulinic 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-aminolevulinic acid/l urine (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 value (classification of lead in 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 (translated in 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 et al. 2019 a)
2013	Lowering of the BLW of lead for women ≥ 45 years and for men to 300 µg lead/l blood (translated in Bolt et al. 2019 b)
2018	Re-evaluation of the BLW of lead for women ≥ 45 years and for men: 200 µg lead/l blood (translated in Bolt et al. 2020)
2019	Re-evaluation of the BAR: for women: 30 µg lead/l blood; for men: 40 µg/l blood (translated in Göen et al. 2020)

Lead and its inorganic compounds (except lead arsenate and lead chromate) were re-evaluated by the Commission in 2021 and reclassified in Carcinogen Category 4 (translated in Hartwig and MAK Commission 2022). In this addendum,

data on developmental toxicity and neurotoxicity are re-evaluated, as well as a BAT value and its associated pregnancy risk group for lead and its inorganic compounds (except lead arsenate and lead chromate) are derived.

1 Metabolism and Toxicokinetics

The **absorption** of lead and its inorganic compounds occurs via the gastrointestinal tract and the lungs, the latter being particularly relevant at the workplace. **Distribution** throughout the body occurs with the blood, in which 90% of the lead is bound to the erythrocytes. The lead found in the blood and soft tissues is excreted relatively quickly with a half-life of one week to two years. The larger proportion of about 95% in adults and about 73% in children is stored in bones and teeth and is mobilised and excreted very slowly. The elimination half-life of lead from bones and teeth is 10 to 30 years. Lead passes the blood-brain barrier. When tissue samples from 258 deceased people were examined, 0.12% of the total lead was found in the brain, which corresponded to about 1.2% of the lead in soft tissue. There was evidence that more lead is present in brain tissue with increasing age (Schroeder and Tipton 1968). The cumulative blood-lead index ($(\mu\text{g lead/l}) \times \text{years}$) is used as a measure of cumulative lead exposure. **Excretion** takes place mainly with the urine and the faeces, in nursing mothers also with breast milk, and in small amounts with sweat, saliva, hair, nails and seminal fluid (ATSDR 2020; Bolt et al. 2020; Hartwig and MAK Commission 2022).

2 Critical Toxicity

According to current knowledge, the effects on the nervous system are the most sensitive toxicity end point of lead and its inorganic compounds (Bolt et al. 2020; ECHA 2020; Greim 2002). There are no sufficiently robust data on relevant toxic effects on other organ systems occurring at concentrations below those for which neurotoxic effects have been described. Therefore, other end points for critical toxicity are not plausible at present. An evaluation of toxic effects on other organ systems can be found in Bolt et al. (2020).

Numerous studies are available that examine individual aspects of the possible mechanism of action of lead. It is likely that numerous cellular mechanisms are responsible for the lead-induced changes in neurological functions. Thus, lead leads to the impairment of cellular functions by

- displacement of the metal ion cofactor from proteins
- inhibition of enzymes
- inhibition of ion transport
- impairment of cellular and mitochondrial membrane potentials and thus the energy balance
- impairment of intracellular calcium homeostasis
- impairment of neurotransmitter systems
- induction of oxidative stress
- triggering of inflammatory processes
- impairment of endocrine functions

All of these mechanisms have been demonstrated in neuronal tissue, without any particular mechanism dominating (ATSDR 2020).

Lead can exert effects on the nervous system through numerous mechanisms. Important targets are calcium-binding proteins and calcium homeostasis. The reason for this is that calcium is involved as a cofactor in numerous cellular processes (ATSDR 2020). The following interactions are possible:

- a) Pb^{2+} can occupy Ca^{2+} binding sites and the resulting structural modulation inhibits the activity of the affected protein.
- b) Pb^{2+} can mimic Ca^{2+} at the binding sites, thereby falsely activating the affected protein and subsequently perturbing downstream activities.
- c) Pb^{2+} can bind outside the Ca^{2+} binding sites and thereby lead to an allosteric modulation of protein activity (Gorkhali et al. 2016).

3 Exposure and Effects

Various factors of external exposure influence internal exposure. In addition to the air concentration of lead, hand-mouth contact and the resulting oral intake often play an important role at the workplace (ECHA 2020). Therefore, the correlation of the concentration of lead in air with that in the blood is associated with high uncertainties overall. Internal exposure is crucial for the occurrence of chronic effects. Therefore, biomonitoring is essential for the detection of critical exposures. Most studies relate health end points to the lead level in whole blood.

For a detailed description and assessment of studies on the most sensitive end point for lead, neurotoxicity, see the previous documentation (Bolt et al. 2020). This section describes in detail the studies published since the last documentation and selected studies from the last documentation that address the neurotoxic effects of lead in humans.

In a meta-analysis by Vlasak et al. (2019), 22 publications with a total of 3849 participants were analysed. Studies were included that describe associations between lead exposure and cognitive abilities as well as sensorimotor performance. In each case, the effect size in the lead-exposed group and the control group was extracted and subjected to a meta-analysis. Blood lead concentrations of the exposed and control groups were reported in only 13 studies. In the exposed group, the mean blood lead level was $340.8 \pm 136.3 \mu\text{g/l}$, in the control group $121.8 \pm 71.9 \mu\text{g/l}$. The respective difference in the blood lead level between exposed and controls was reported by the authors to be $210.9 \pm 64.4 \mu\text{g/l}$ (minimum $7.0 \mu\text{g/l}$; maximum $330 \mu\text{g/l}$). The authors described a poorer performance that was statistically significant in the group exposed to lead in terms of verbal abilities, visuospatial abilities, memory, attention and psychomotor functions. Considering Cohen's effect size classification, only small effects were reported ($d < 0.5$) and the different functional areas covered by the tests were almost equally affected. The results do not suggest a specific effect of lead exposure on individual functional areas. The authors suggest that due to publication bias, a certain overestimation of the effects of lead exposure on cognitive performance is likely, as statistically nonsignificant results would often not be published. In addition, a differentiation between acute and chronic effects as well as the assessment of a possible reversibility was not possible. The authors could not derive a statement on an absolute effect threshold in $\mu\text{g/l}$; there is only a "relative effect threshold", which is not suitable for deriving a BAT value. For these calculations, the difference in the blood lead concentration between exposed and controls of the respective studies was used and related to the corresponding effect sizes. Taking into account the mean blood lead concentration of the control groups of $121.8 \mu\text{g/l}$, a blood lead concentration of about $220 \mu\text{g/l}$ would be associated with a 10% decrease in test performance.

An extensive study conducted in South Korea (Schwartz et al. 2001) examined 803 lead-exposed workers and 135 controls without occupational lead exposure. The lead-exposed workers were employed in battery manufacturing (13 plants), secondary lead smelting (6 plants), lead oxide manufacturing (3 plants) and car radiator manufacturing (1 plant). Eight exposed persons were retired in the meantime. The unexposed control subjects were employees of an air conditioning manufacturer who did not use lead or other heavy metals and employees of a university. Neuropsychological testing was conducted with a modified version of the WHO Neurobehavioural Core Test Battery. Furthermore, the threshold for peripheral vibratory sensation and hand strength of the non-dominant hand (grip and pinch strength) was determined. The mean blood lead level of the exposed was $320 \pm 150 \mu\text{g/l}$. The control group had a mean blood lead concentration of $53 \pm 18 \mu\text{g/l}$. Compared with the control group, the lead-exposed workers were older, had a lower educational level and a lower proportion of men. After adjustment for age, gender and education (and height or body mass index

(BMI) for the peripheral nervous system measures), the exposed workers performed worse in a statistically significant manner ($p < 0.05$) compared with the controls in the following tests:

- Simple reaction time, standard deviation of simple reaction time
- Digit span (forward, backward)
- Benton Visual Retention (Benton test: immediate memory for visuospatial stimuli)
- Coloured Progressive Matrices (Raven's Progressive Matrices: intelligence test procedure for the non-verbal assessment of cognitive abilities)
- Digit Symbol Substitution (Digit Symbol test from Wechsler Adult Intelligence Test (WAIS))
- Purdue Pegboard (dominant hand, non-dominant hand, both hands, and assembly) (Purdue pegboard test: 30 sec.; right, left, both hands; pin and washer assembly)
- Grip strength
- Peripheral vibration threshold at the big toe

The control group, on the other hand, performed worse in a statistically significant manner than the exposed group in the Pursuit Aiming Test (incorrect responses; motor target tracking test (motor test and part of the WHO NCTB (neurobehavioural core test battery))), in the Pinch Strength Test (usually thumb and index finger) and in the CES-D (depression questionnaire of the Center for Epidemiologic Studies Depression).

In linear regression models including only exposed, blood lead concentration was a statistically significant predictor of poorer performance in the following tests:

- Trail Making Test (number connection test (version B))
- Pursuit Aiming Test (correct and incorrect responses)
- Purdue Pegboard Test (dominant hand, non-dominant hand, both hands, and assembly)
- Pinch strength

Using the Lowess procedure (locally weighted scatterplot smoothing) in the scatterplots of the Purdue Pegboard (assembly) and Trail-Making Test B, the authors suggested a threshold of about 180 $\mu\text{g}/\text{l}$ blood for neurotoxic effects. At higher blood lead concentrations, both the regression lines and the "Lowess lines" showed a decrease in the test scores. The Lowess procedure mathematically determines a "kink point" in the linear relationship, from which an amplification of the effect must be expected.

Ekinci et al. (2014) measured retinal nerve fibre layer thickness, macular thickness and choroidal thickness in 50 battery factory workers and 20 controls using spectral domain-optical coherence tomography (SD-OCT). The employees of the battery factory were divided into three groups according to their activities. Group 1 ($n = 22$) were lead workers, group 2 ($n = 16$) box makers and group 3 ($n = 12$) were assistant personnel. The control group consisted of patients who attended the authors' clinic. Group 1 had a mean age of 27.55 years, group 2 of 28.69 years, group 3 of 32.00 years and the control group of 29.85 years. Statistically significant differences in age were found between group 1 and group 3. The mean exposure duration of the groups was 44, 43 and 49 months, respectively. The blood lead concentrations of the four groups differed in a statistically significant manner: the mean blood lead concentration of group 1 was $461.8 \pm 23.3 \mu\text{g}/\text{l}$, that of group 2: $293.1 \pm 33.0 \mu\text{g}/\text{l}$ and that of group 3: $169.2 \pm 19.8 \mu\text{g}/\text{l}$. In the control group, the mean blood lead concentration was $28.5 \pm 9.8 \mu\text{g}/\text{l}$. The thickness of the retinal nerve fibre layer was reported to be $101.68 \pm 5.32 \mu\text{m}$ for group 1, $119.50 \pm 13.47 \mu\text{m}$ for group 2 and $127.67 \pm 8.92 \mu\text{m}$ for group 3. For the control group, the mean retinal nerve fibre layer thickness was $130.90 \pm 6.63 \mu\text{m}$. The retinal nerve fibre layer thicknesses in group 1 were statistically significantly lower than those in groups 2 and 3. Those in groups 2 and 3 were again statistically significantly lower than those

in the control group, while there was no statistically significant difference between groups 2 and 3. With regard to the macula, layer thicknesses of $94.50 \pm 6.78 \mu\text{m}$ (group 1), $105.63 \pm 5.43 \mu\text{m}$ (group 2), $111.50 \pm 6.74 \mu\text{m}$ (group 3) and $147.95 \pm 6.67 \mu\text{m}$ (control group) were measured for the four groups. For the choroid, the authors determined layer thicknesses of $176.41 \pm 15.39 \mu\text{m}$ (group 1), $222.19 \pm 17.79 \mu\text{m}$ (group 2), $239.17 \pm 15.64 \mu\text{m}$ (group 3) and $251.50 \pm 10.98 \mu\text{m}$ (control group). Regarding the macula and the choroid, the post-hoc tests revealed significant differences between the groups.

Hsieh et al. (2009 b) investigated microstructural changes in the white matter of 19 lead-exposed workers from lead paint production and 18 healthy controls using the diffusion tensor magnetic resonance imaging method. The blood lead concentrations of the exposed were $114.9 \pm 11.5 \mu\text{g/l}$, those of the control group $32.3 \pm 11.5 \mu\text{g/l}$. The lead content of the tibia was reported to be $51.71 \pm 1.79 \mu\text{g/g}$ in the exposed and $20.84 \pm 2.88 \mu\text{g/g}$ in the controls. The used method records the diffusion of water. For one of the effect parameters determined with this method, namely fractional anisotropy, statistically significant differences between the groups were found in several brain regions. Another publication (Hsieh et al. 2009 a) reports on MRS (magnetic resonance spectroscopy) measurements of *N*-acetyl aspartate (neuronal marker), choline (cell membrane marker) and total creatine in the brains of 22 employees of a lead paint factory and 18 control persons. Those exposed had blood lead concentrations and tibia lead levels of $169.9 \pm 103.8 \mu\text{g/l}$ and $61.55 \pm 30.21 \mu\text{g/g}$, respectively. In the control group, the blood lead concentration was $34.0 \pm 11.1 \mu\text{g/l}$ and the tibia lead concentration was $18.51 \pm 22.40 \mu\text{g/g}$. Determining *N*-acetyl aspartate, choline and total creatine, there were statistically significantly lower choline:total creatine ratios and *N*-acetyl aspartate:total creatine ratios in several brain areas in the exposed. A decrease in *N*-acetyl aspartate, which is located in neuronal cell bodies, indicates possible neuronal and axonal damage or loss and is measured relative to the level of creatine, a stable metabolite whose level is constant after neuronal loss (Hsieh et al. 2009 a; van der Knaap et al. 1992). Decreased choline signalling may indicate reduced cell membrane turnover or myelin changes (Cox 1996). Findings from previous studies suggest that the neurotoxic effects of lead alter neuronal transmitters.

In a longitudinal study by Yu et al. (2021), the neurocognitive function of newly hired employees of a lead recycling plant who were previously not exposed to lead was investigated at the start of employment and during the annual follow-up visits. The Digit Symbol test and the Stroop test were used for this purpose, although not all of the workers examined completed both test procedures (total: $n = 267$, digit symbol test: $n = 260$, Stroop test: $n = 168$). The Digit Symbol test measures the following components of cognitive performance: processing speed, working memory, visuospatial processing and attention; the Stroop test measures selective attention. Furthermore, the blood lead concentration was determined.

In the “Digit Symbol test cohort” ($n = 260$), the geometric mean of the blood lead concentration was

- before the start of the activity: $39.7 \mu\text{g/l}$ (5th – 95th percentile 9–143 $\mu\text{g/l}$)
- at the first follow-up: $134 \mu\text{g/l}$ (5th – 95th percentile 37–303 $\mu\text{g/l}$)
- at the second follow-up: $128 \mu\text{g/l}$ (5th – 95th percentile 28–292 $\mu\text{g/l}$).

There were no statistically significant differences between baseline and second follow-up in the digit symbol test, neither for the latency nor for the number of errors.

In the “Stroop test cohort” ($n = 168$), the geometric mean of the blood lead concentration was

- before the start of the activity: $41.3 \mu\text{g/l}$ (5th – 95th percentile 12–130 $\mu\text{g/l}$)
- at the first follow-up: $144 \mu\text{g/l}$ (5th – 95th percentile 46–303 $\mu\text{g/l}$)
- at the second follow-up: $161 \mu\text{g/l}$ (5th – 95th percentile 54–315 $\mu\text{g/l}$).

A statistically significant increase in the mean reaction time for incongruent and congruent trials, for all answers and only for correct answers (always $p < 0.0001$) was found in the course of the follow-up visits. There was no statistically significant difference in the actual effect measure of the Stroop test, the “interference score”.

Furthermore, quartiles were determined using the blood lead concentration ratio at the follow-up to the baseline, and the changes (Δ) in the results of the neurocognitive tests were compared using these quartiles. The tests for linear trend proved not to be statistically significant for the digit symbol test. With regard to the Stroop test, the authors described a trend towards smaller increases in mean reaction time with larger increases in the blood lead concentration. An evaluation according to the lead concentration at follow-up was not carried out.

When looking at associations between changes (Δ) in neurocognitive function and blood lead concentrations, results were presented in three different levels of adjustment:

- a) unadjusted,
- b) adjusted for gender, age at baseline and results of neurocognitive tests at baseline and
- c) additionally adjusted for ethnicity, change in age, BMI at baseline, change in body weight, educational attainment, blood lead concentration at baseline, smoking status at baseline, changes in smoking status during follow-up, alcohol consumption (light, moderate and heavy) and the ratio of total to HDL serum cholesterol.

Association variables were considered in relation to a doubling of the baseline/follow-up blood lead concentration ratio. Without adjustment and with the adjustment described in b), statistically significant associations were found between the increase in blood lead concentrations and latency time in the digit symbol test, and for the change in mean reaction time in the incongruent trial part of the Stroop test for both all responses and correct responses. No statistically significant associations were found in extended adjusted models as described in c).

4 Selection of the Indicators

Different parameters for lead exposure have been discussed in detail earlier. For monitoring lead-exposed individuals, the lead concentration in blood is the most reliable and practical parameter. It is the most specific quantity for detecting internal lead exposure. Exposure parameters (for example δ -aminolaevulinic acid) are no longer recommended either for methodological reasons, but especially due to their insufficient sensitivity with regard to the nowadays significantly reduced exposure to lead at the workplace (Bolt et al. 2020).

5 Analytical Methods

Reliable methods for the quantitative determination of lead concentration in whole blood by atomic absorption spectrometry and ICP-MS (mass spectrometry with inductively coupled plasma) are available and have been tested by the Commission's Working Group "Analyses in biological material" (Fleischer and Schaller 1982; Schaller and Pilz 1985; Schramel et al. 1999). Nowadays, the determination of lead concentration in whole blood is mostly performed by ICP-MS (Bolea-Fernandez et al. 2017; Heitland and Köster 2021).

On behalf of the German Society for Occupational and Environmental Medicine (DGAUM), interlaboratory tests for the determination of lead in blood are regularly offered as external quality assurance programmes in the field of occupational and environmental medicine (Göen et al. 2012).

6 Background Exposure

The internal lead exposure of the general population has reduced considerably in recent years, even though no new representative studies on the lead exposure of the adult population in Germany have been conducted since 1998. However, at least 120 blood and urine samples from young adults (19–29 years) are collected every year for the Environmental Sample Bank at each of the four locations Münster, Greifswald, Halle/Saale and Ulm, and in the so-called real-time monitoring programme lead, among others, in the blood is determined (Göen et al. 2018). An evaluation of the blood lead levels of the Environmental Sample Bank was carried out by the Human Biomonitoring Commission to

update the reference values for lead in women and men with a view to the time trend as well as possible influencing factors (HBM-Kommission 2019; Lermen et al. 2021). A calculation using the full distribution, age profile and time trend of the data in the period from 2010 to 2015 resulted in estimated values of 31.0 µg lead/l blood for women and 39.5 µg lead/l blood for men (HBM-Kommission 2019). Taking these values into account, BAR of 30 µg lead/l blood for women and 40 µg lead/l blood for men were derived. No differentiation was made between smokers and non-smokers (Göen et al. 2020).

7 Evaluation of a BAT Value

Adverse effects of lead and its compounds in humans include neurotoxicity, nephrotoxicity, cardiovascular diseases, haematological and clastogenic effects and male fertility disorders. Lead also leads to developmental neurotoxicity in humans. Carcinogenicity studies revealed kidney tumours and gliomas in rats and mice at high lead concentrations. Neurotoxicity is considered the most critical end point (ECHA 2020).

In the following, the relevant studies published since the last evaluation as well as occupational health studies with neurotoxic effects below 200 µg lead/l blood are assessed.

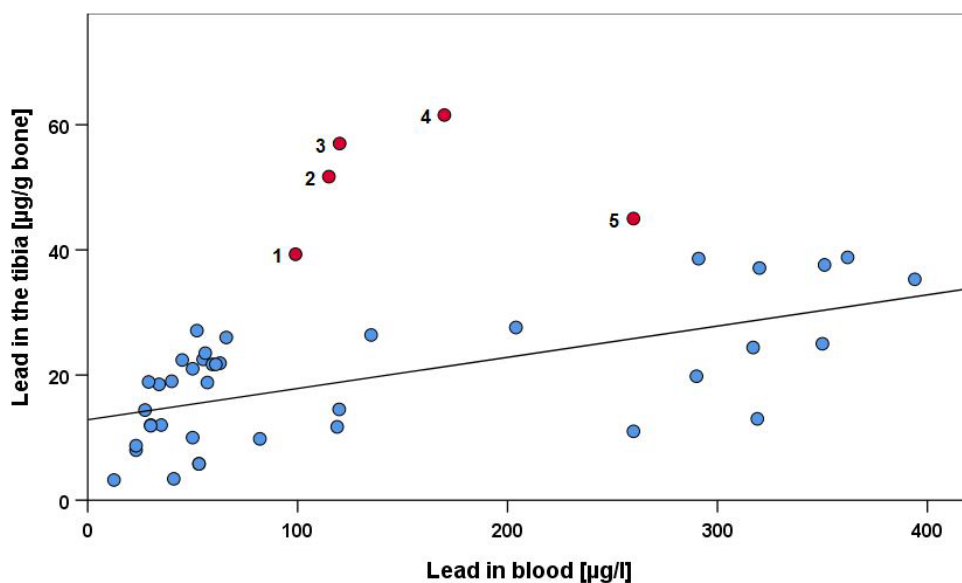
ATSDR (2020) assumes that there may not be a threshold for neurotoxic effects, as neurotoxic effects have been observed even at blood lead levels below 100 µg/l. However, this assessment was based on population-based studies and individual occupational health studies without specific or current lead exposure. Numerous confounders, such as educational level, diseases with effects on the performance of the nervous system or other neurotoxic pollutants cannot be excluded in population-based studies, the effects of which may not be completely controlled even by adjustment. In addition, higher lead exposures in the environmental field which occurred long ago must be taken into account. Older, no longer working collectives are also not decisive for the derivation of a BAT value.

A closer look at the 13 studies considered in the meta-analysis by Vlasak et al. (2019), in which blood lead levels were reported for exposed and control persons, revealed conspicuous features with regard to the exposed and the control groups: in the study by Lindgren et al. (2003), for example, a group of both currently and previously high exposed persons was compared with a group of previously high and currently low exposed persons. In Winker et al. (2006), those currently exposed to lead were compared with those previously exposed to lead. Eight of the fifteen participants in the control group of Milburn et al. (1976) were also previously exposed to lead. In Campara et al. (1984), the high background exposure of the control group of 204 ± 60 µg lead/l blood (range 111–271 µg/l) should be considered. Araki et al. (1986) also found relatively high lead levels in the control group with an average of 130 µg lead/l blood (range 80–200 µg/l), as did Hänninen et al. (1978) with 119 ± 43 µg lead/l blood. Winker et al. (2005) compared employees who had previously been occupationally exposed to lead with a group never exposed to lead. Overall, in their meta-analysis, Vlasak et al. (2019) could not derive a threshold for lead exposure above which cognitive impairment occurs.

In the study by Ekinci et al. (2014) presented in detail in Section 3, in which the effects of lead exposure on the layer thickness of the ocular fundus were investigated, the differences between the control group and the lowest exposed group 3 with a mean blood lead level of 169.2 µg/l are of particular interest. The control group consisted of “clinic patients”. It remains unclear whether these were patients of the eye clinic, possibly also with previous ophthalmological diseases. Age, among others, is discussed as an influencing factor on the layer thickness of the ocular fundus (Curcio et al. 2011; Duan et al. 2010; Ooto et al. 2011). It was striking that the mean age of exposure group 3 was above that of the control group (and also above that of the other exposure groups). However, the post-hoc test showed a statistically significant age difference only between group 1 and group 3, but not between the control group and group 3. An effect on the results could possibly still be taken into consideration. Smoking behaviour is discussed as another factor influencing the recorded layers of the ocular fundus (Teberik 2019; Yang et al. 2019). Smoking behaviour was recorded according to the information in the material and methods section of Ekinci et al. (2014), but the results were not presented. All in all, the decrease in the layer thickness of the ocular fundus is not a neurotoxic finding typically described following lead exposure. It has not yet been established that the cells of the retina would be particularly sensitive to lead-associated effects compared to other neurons (Fox et al. 1997; He et al. 2000). The extent of the effects,

which according to information in the study by Ekinçi et al. (2014) have developed within approximately four years, would give rise to fears of serious disease patterns in the event of linear progression. However, direct visual disturbances, impaired visual acuity or blindness as prominent effects are not known after lead intoxication. So far, this is the only study that describes such effects. The further studies suggested by the authors to verify this have not yet been carried out or published. Another major limitation of this work is the small sample size. The LOAEC (lowest observed adverse effect concentration) of 169.2 μg lead/l blood described by Ekinçi et al. (2014) does not seem plausible overall.

In the studies by Hsieh et al. (2009 a, b), in which effects were observed at blood lead levels of $114.9 \pm 11.5 \mu\text{g}/\text{l}$ (Hsieh et al. 2009 b; significant differences in fractional anisotropy between groups in several brain regions) and $169.9 \pm 103.8 \mu\text{g}/\text{l}$ (Hsieh et al. 2009 a; statistically significantly lower choline:total creatine ratios and *N*-acetyl aspartate:total creatine ratios in several brain regions in exposed persons), high values for lead in bone in comparison to those in blood are conspicuous. This is an indication that the lead exposure must have been higher in the past compared with the current lead exposure. This is illustrated in Figure 1 below showing lead concentrations in blood and bone (tibia) from 27 publications in a scatter plot. Five points (marked red) show a marked deviation from the otherwise clearly recognisable correlation. For three of these data sets, indications of a previous significantly higher exposure than at the time of sampling can be inferred from the respective publications. The data points from the studies of Hsieh et al. (2009 a, b) therefore suggest that the exposure was here also significantly higher previously. It can therefore be assumed that the reported blood lead level does not represent the lifetime exposure that led to the effects. Another limitation of the validity of the studies is that no information is given on possible exposure to other neurotoxic substances.



numbered: ¹Gerhardsson et al. 1993, ²Hsieh et al. 2009 b, ³Khalil et al. 2009, ⁴Hsieh et al. 2009 a, ⁵Bleecker et al. 1995

others: Bergdahl et al. 1998; Bleecker et al. 1995, 2007; Cake et al. 1996; Elmarsafawy et al. 2002; Farias et al. 2005; Gerhardsson et al. 1993; Hänninen et al. 1998; Hernández-Avila et al. 1998; Khalil et al. 2009; Lin et al. 2004; Payton et al. 1998; Popovic et al. 2005; Potula et al. 1999; Rhodes et al. 2003; Rothenberg et al. 2002; Schwartz et al. 2001; Theppeang et al. 2008; Todd et al. 2001; Tsaih et al. 1999; Wang et al. 2017; Watanabe et al. 1994; Weaver et al. 2009; Weisskopf et al. 2004; Wright et al. 2003.

Fig.1 Lead concentrations in blood and bones (tibia) from 27 publications (sometimes several pairs of values per publication)

In the study by Yu et al. (2021) on the neurocognitive function of lead-exposed workers, the statistically significant increase in mean reaction time in the Stroop test could indicate an adverse lead-related effect. However, the effect measure of the test is the interference score and only to a limited extent the reaction time. It should also be considered that some study participants had a higher blood lead level at baseline than at the second follow-up. The further considerations were not based on the absolute blood lead concentrations, but on the quotient of the blood lead concentration at follow-up and at baseline or the change (Δ) of the logarithmically transformed blood lead concentration. For chronic

toxic effects, however, it is not the change from baseline that is decisive, but the absolute level. The missing evaluation with regard to the absolute exposure level limits the usefulness of the study. Regarding associations, different results were given depending on the extent of the adjustment. In addition, the authors describe that they cannot exclude bias due to insufficient standardisation of the investigator-participant assignment and point to investigator effects. The authors themselves concluded that the increase in blood lead level during a two-year exposure was not associated with a relevant decline in cognitive performance. The main limitations of this study, according to the Commission, are that there is evidence of an observer effect, the extent and impact of which cannot be assessed. The evaluation strategy based on the follow-up-to-baseline blood lead level ratio does not allow the derivation of an effect threshold. Furthermore, an over-adjustment of the results must be discussed in part. In summary, it remains unclear whether the effects are due to methodological errors or are related to the lead exposure. In the opinion of the Commission, this study, taking into account its limitations, does not sufficiently substantiate the authors' derivation of an effect at a mean blood lead level of 161 µg/l in view of the results from other studies. The results of a further follow-up announced in the publication remain to be seen.

In the cross-sectional study by Schwartz et al. (2001) with 938 workers, a threshold value was derived at 180 µg lead/l blood for some parameters. Above that level, both the regression lines and the Lowess lines indicate a decline in test scores with increasing blood lead levels. This level of 180 µg lead/l blood is considered the NOAEC (no observed adverse effect concentration) for clinically relevant neurotoxicity and, due to the relatively large number of workers examined, is currently considered the most reliable value for a statement on lead-induced neurological effects in adults (ECHA 2020). This value is supported also by the overall review of the publications listed in the previous BLW evaluation (Bolt et al. 2020).

As already mentioned above, there are studies that provide indications of effects below this value. However, due to their limitations, they cannot be used as a starting point for setting a limit value. Based on the NOAEC of 180 µg lead/l blood in the study by Schwartz et al. (2001),

a BAT value of 150 µg lead/l blood

is set.

If the BAT value is observed, a contribution to cancer risk is not to be expected (see Hartwig and MAK Commission 2022).

Due to the long biological half-life of lead in humans, sampling time is not fixed.

8 Evaluation of a pregnancy risk group for the BAT Value

In 1978, on the basis of mainly epidemiological studies and the higher sensitivity of children compared to mothers, it was deduced that the blood lead level in children should not exceed 250 µg/l or 300 µg/l. Based on the relationship between the lead level in maternal and foetal blood, it was concluded that the blood lead level of occupationally exposed pregnant women should likewise not be significantly higher than 300 µg/l (Henschler 1978). At that time, this level of 300 µg/l roughly corresponded to the background exposure of the general population to lead, which has since been significantly reduced.

Since it is not possible to derive a threshold for the developmental toxicity of lead, no health-based limit value was derived for women of reproductive age (up to 45 years), but a biological reference value (BAR) on the basis of general background exposure (Bolt et al. 2019 a, 2020; Göen et al. 2020).

8.1 Metabolism and toxicokinetics in pregnant women, infants and young children

Since lead readily passes the placental barrier, there is a correlation in the lead concentration between the mother and the foetus. Due to the long half-life in the bone, exposure of the foetus can occur even without acute external exposure to lead during pregnancy (ATSDR 2020; Bolt et al. 2020). At maternal blood lead levels of 10 to 90 µg/l, the ratio of the lead level in cord blood to maternal blood was 0.7 to 1.0 (ATSDR 2020).

In **pregnant women**, a decrease in the blood lead level is observed in the second trimester, and an increase in the third trimester of pregnancy and after birth. This is explained by the storage of lead in the foetal bones in the second trimester and by the greatly increased calcium demand in the third trimester and during breastfeeding, which is accompanied by an increased mobilisation of lead from maternal bones. Isotopic determination of lead in umbilical cord blood suggests that about 80% of the lead in the infant comes from maternal bone stores. Calcium supplementation during the third trimester and after birth counteracts the mobilisation of lead from the mother's body (ATSDR 2020).

In **infants and young children**, isotopic analyses have shown that the main source of lead, regardless of whether the infants/toddlers receive breast milk or breast milk substitutes, is hand-to-mouth activity. Another possible source of lead in infants is neonatal bone turnover, which is very high in the newborn because both bone accretion and bone loss during reshaping of the growing bone are high (CDC 2010).

The ratio of lead concentration in breast milk to maternal blood ranges from less than 0.1 to 0.9 (ATSDR 2020). In a study in 255 breastfed infants and their mothers, lead determinations were carried out on the day of birth (umbilical cord blood; maternal blood) and one month after birth (breast milk, infant blood, maternal blood, patella and tibia). The lead levels in maternal blood were in the range from 1 to 300 µg/l. After adjustment for the lead level in cord blood, infant weight change and information on breastfeeding status, an increase in the maternal milk lead concentration of about 2 µg/l resulted in an increase in the infant blood lead level of 8.2 µg/l (Ettinger et al. 2004). From this, taking into account absorption, distribution and elimination, it was estimated that at maternal blood concentrations of 300, 200 and 20 to 40 µg lead/l, the contribution via breast milk leads to an increase in the infant blood lead level of 37, 25 and 2.5 to 5 µg/l, respectively. The calculation is based on blood lead concentrations that did not exceed 300 µg/l, so extrapolation beyond this value becomes less reliable. These calculations are supported by observational data only in infants at one month of age. At maternal blood lead levels greater than 400 µg/l, the ratio of breast milk to maternal blood lead level increased in a non-linear fashion and breast milk contained disproportionately more lead (CDC 2010).

8.2 Reproductive toxicity – human data

8.2.1 Male fertility

Previous epidemiological studies have described effects of occupational lead exposure of men on the risk of spontaneous abortions, perinatal mortality and lower birth weight. Similar effects have been reported for reduced fertility and various sperm quality parameters. Overall, such effects occurred at blood lead levels above 400 µg/l (Bolt et al. 2020).

A meta-analysis on the effects of occupational exposure to heavy metals, pesticides, organic solvents and other substances on fertility described a correlation between increased lead exposure in men and decreasing reproductive capacity. For this purpose, seven studies were evaluated that correlated either blood lead levels with reproductive capacity (fecundability ratio) or the time to pregnancy. The results of five studies that investigated reproductive capacity are shown in Figure 2. Here, too, clear effects were seen at concentrations of > 400 µg lead/l blood (Snijder et al. 2012).

In the study by Shiau et al. (2004), the time to pregnancy was prolonged if the exposed male had a blood lead level of > 300 µg/l. However, the number of participants in this study was low with about 30 persons per concentration group, so that these results are not very reliable.

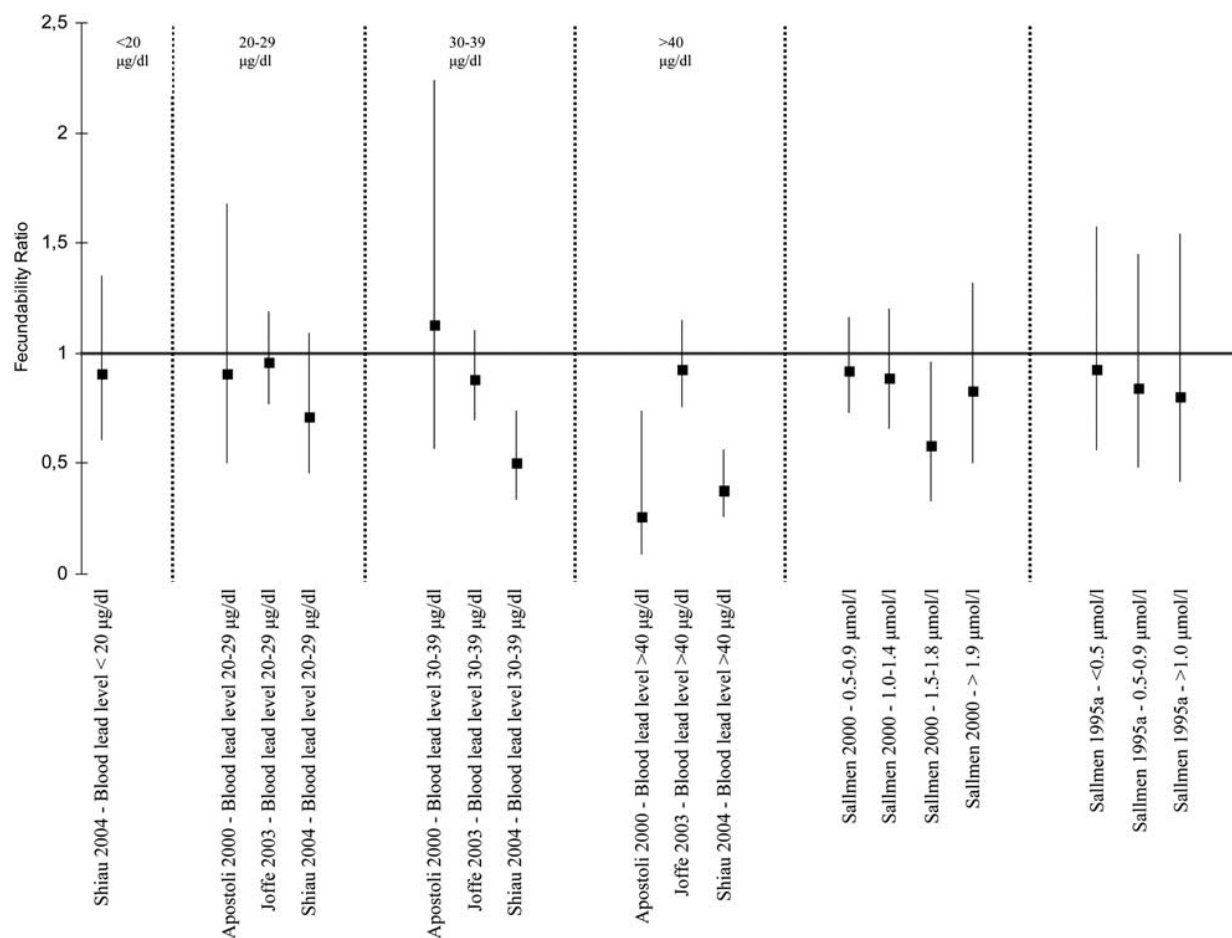


Fig. 2 Effects of elevated lead levels on fecundability (from Snijder et al. 2012; reprinted by permission of Oxford University Press on behalf of the European Society of Human Reproduction and Embryology)

The µmolar blood lead levels in the study by Sallmén et al. (2000), shown in Figure 2, were approximately 100–190 µg/l, 200–290 µg/l, 300–370 µg/l and > 390 µg/l, respectively. The authors stated that their findings provided limited support for the hypothesis that paternal exposure to lead is associated with decreased fertility (Sallmén et al. 2000).

8.2.2 Female fertility

Compared with the studies of effects on the male reproductive organs, there is a smaller database for the effects of lead on female reproductive parameters. In most cases, the epidemiological studies were conducted in populations with mean blood lead levels of less than 100 µg/l. The studies provided evidence of changes in the serum levels of reproductive hormones (oestradiol, luteinising hormone, follicle-stimulating hormone), decreased fertility, increased number of spontaneous abortion and preterm birth, and earlier age at start of menopause. However, the results are inconsistent, with several studies reporting no association between lead exposure and effects on reproductive parameters in females (ATSDR 2020).

8.2.3 Pregnancy hypertension/pre-eclampsia

An association with increased risk of gestational hypertension has been observed for exposure to lead. Uncertainties exist regarding the lead concentration at which the risk increases, the magnitude of the effect, and whether the risk is associated with acute or cumulative exposure. In addition, it is unclear whether lead-induced increases in blood

pressure lead to severe hypertension during pregnancy or pre-eclampsia. Because pre-existing hypertension may lower renal function, leading to retention of lead, the causal relationship has also not yet been established (CDC 2010).

A study of 2067 pregnant workers in ceramic tile production in the Emilia-Romagna region of Italy with follow-up examinations is available. The women were more likely to have high blood pressure, pre-eclampsia, prolonged pregnancy (statistically significant above 50 µg/l) and amniotic cavity problems at blood lead levels above 150 µg/l (ECHA 2020; Paredes Alpaca et al. 2013). However, it is unclear whether these effects can be attributed to the blood lead levels.

8.3 Developmental toxicity

The lead-induced growth retardations, especially in the last stage of pregnancy, are the result of an inhibition of foetal haemoglobin synthesis and/or an effect on placental blood flow and substrate uptake (Gerber et al. 1980).

Foetal haemoglobin (HbF) consists of two α -chains and two γ -chains. In contrast, the most common haemoglobin (HbA0) in adults is composed of two α -chains and two β -chains ($\alpha_2\beta_2$). HbF has a higher affinity for oxygen than HbA0 and can therefore deprive it of oxygen, thereby improving the oxygen supply to the foetus. HbF has a higher affinity for lead than HbA0 (Ong and Lee 1980). Indirect effects on the foetus via inhibition of maternal HbA0 are also possible. Decreased haemoglobin levels result in reduced oxygen transport, which leads to growth retardation in the growing organism with high oxygen and nutrient demand.

The developmental neurotoxicity after lead exposure is well documented in numerous epidemiological studies and has been known for a long time. It is unanimously assumed that no NOAEC can be derived for the developmental neurotoxicity of lead. In children, effects occur even at lead levels below 100 µg/l blood (ATSDR 2020; CDC 2010; ECHA 2020; EFSA 2010; NTP 2012).

The following associations were found between developmental toxic effects and the lead concentrations in prenatal maternal blood or in umbilical cord blood (ATSDR 2020):

Blood lead concentration Developmental toxic effects

≤ 100 µg/l	<ul style="list-style-type: none"> • Effects on birth outcomes (decreased birth weight, head circumference and crown-heel length; study results are inconsistent) • Decreased anthropometric measures in children (body weight, height, head circumference, trunk length, arm length, leg length, BMI; study results are inconsistent) • Delayed puberty in females (breast development, pubic hair development, onset of menarche; corroborated in many studies) • Delayed puberty in males (testicular volume, genitalia development, pubic hair development; few studies with equivocal results)
> 100 µg/l	<ul style="list-style-type: none"> • Preterm birth (study results are inconsistent) • Effect on birth outcomes (low birth weight) • Decreased anthropometric measures in children (weight, height, head circumference, chest circumference) • Delayed puberty in females (breast development) • Delayed puberty in males (reduced testicular size, delayed pubic hair development, delayed penile development)

8.3.1 Foetal growth/low birth weight

According to an evaluation by the CDC in 2010, maternal lead exposure increases the risk of low birth weight. However, data are limited and the blood lead level at which the risk starts to increase is not known (CDC 2010). NTP concluded in 2012 that for maternal blood lead levels of $< 50 \mu\text{g/l}$, there is sufficient evidence of an association with an increased risk of reduced foetal growth (NTP 2012).

The following are examples of studies with a positive association between maternal blood lead levels and effects on foetal growth.

In a prospective cohort study, data were available from 14 541 pregnant women with an expected date of delivery between 1 April 1991 and 31 December 1992 from the Avon Health Authority, United Kingdom; there were 14 062 live births. Adjustment was made for covariates including maternal height, smoking, parity, gender of child and gestational age. 4285 blood samples were analysed. Mean maternal blood lead concentrations were $36.7 \pm 14.7 \mu\text{g/l}$. In multivariate binary logistic models, a blood lead concentration of $\geq 50 \mu\text{g/l}$ statistically significantly increased the risk of preterm birth (adjusted odds ratio (OR) 2.00; 95% confidence interval (CI): 1.35–3.00), but not the risk of having a baby with a lower birth weight (adjusted OR 1.37; 95% CI: 0.86–2.18). In multivariate regression models, increasing blood lead concentration of $10 \mu\text{g/l}$ was statistically significantly associated with reductions in birth weight (-13.23 g ; 95% CI: -23.75 to -2.70 g), head circumference (-0.04 cm ; 95% CI: -0.07 to -0.06 cm (according to publication)) and crown-heel length (-0.05 cm ; 95% CI: -0.10 to 0.00 cm) (Taylor et al. 2015). Using the same database, the working group calculated with the help of an adjusted model that an increase in the blood lead concentration by $10 \mu\text{g/l}$ can be expected to result in a reduction in birth weight by 9.93 g (95% CI: -20.27 to -0.41 g), head circumference by 0.03 cm (95% CI: -0.06 to 0.00 cm) and crown-heel length of 0.05 cm (95% CI: -0.10 to 0.00 cm) (Taylor et al. 2016).

A cohort study included 252 mother-child pairs. The pregnant women were recruited from a rural coastal area in Shandong Province, China, between September 2010 and December 2011. The mean maternal blood lead concentration was $35.3 \mu\text{g/l}$ (range 10.0 – $119.1 \mu\text{g/l}$) and the mean umbilical cord blood lead concentration was $29.2 \mu\text{g/l}$ (range 4.1 – $106.0 \mu\text{g/l}$). In the model, the gender of the child, maternal education, maternal age, gestational age, antenatal BMI, parity and weight gain during pregnancy were used as covariates. After adjustment in the model, there was a statistically significant association between increased maternal blood lead concentrations and reduced birth weight (-148.99 g ; 95% CI: -286.33 to -11.66 g). In addition, a statistically significant decrease in birth length was found with increasing cord blood lead concentration (-0.84 cm ; 95% CI: -1.52 to -0.16 cm). Associations between measured maternal blood lead concentrations and body length and head circumference were not found. This study determined also maternal blood mercury concentrations, which did not exceed $2.14 \mu\text{g/l}$ in any of the study participants (Xie et al. 2013). Other potentially foetotoxic substances were not considered.

In a retrospective cohort study, 43 288 mother-infant pairs from the New York State Heavy Metals Registry from 2003 to 2005 were examined. The mean maternal blood lead concentration was $21 \mu\text{g/l}$. A statistically significant association was observed between the increase in maternal blood lead concentration and a decrease in birth weight. In a linear regression model with fractional polynomials, adjustment was made for the timing of lead determination, gestational age, maternal age, ethnicity, education, smoking, alcohol consumption, drug abuse, marital status, participation in financial assistance programmes, parity and infant gender. In the model, relative to a blood lead concentration of $0 \mu\text{g/l}$, there was an average decrease in birth weights of 61 and 87 g for blood lead concentrations of 50 and $100 \mu\text{g/l}$, respectively. Relative to blood lead concentrations $\leq 10 \mu\text{g/l}$ (lowest quartile), for blood lead concentrations in the highest quartile (31 to $99 \mu\text{g/l}$), the OR for preterm birth was 1.04 (95% CI: 0.89 – 1.22) and the OR for “small for gestational age” was 1.07 (95% CI: 0.93 – 1.23). Clear dose-response trends were not observed in the analysis of all quartiles. The authors concluded that low blood lead concentrations were associated with a small risk of decreased birth weight with a supralinear dose-response relationship (Zhu et al. 2010).

The study by Irgens et al. (1998) with the estimation of occupational lead exposure via a job matrix (Norway, 1970–1993, 1886 children, of which 83 from mothers with high and 1803 from mothers with low/moderate occupational lead exposure determined by means of an exposure matrix of their job) is one of the few workplace studies in which, among other things, birth weight and preterm birth were examined. Women who were exposed to lead during pregnancy had

a marginally higher risk of having a lower body weight baby than women who were not exposed to lead (OR 1.34; 95% CI: 1.12–1.60). Dose-dependent associations were observed for low birth weight and preterm birth (Irgens et al. 1998). Determinations of blood lead concentrations were not carried out.

8.3.2 Spontaneous abortion/preterm birth

In the ATSDR assessment, already blood lead concentrations of ≤ 100 $\mu\text{g/l}$ are associated with increased spontaneous abortions and preterm births, although the study results are inconsistent (ATSDR 2020).

The following are studies with a positive association between spontaneous abortions/preterm birth and blood lead concentrations up to 150 $\mu\text{g/l}$.

An association between maternal blood lead concentrations and an increased risk of spontaneous abortion was shown in a nested case-control study. This detailed prospective study included 668 pregnant women who visited private or public hospitals in Mexico City for pregnancy confirmation or screening between January 1994 and June 1996. There were 35 spontaneous abortions. A detailed control of possible confounders such as age, education, smoking status, alcohol consumption, physical activity, viral serology and diseases was performed. The mean blood lead concentration of the mothers with spontaneous abortions was 120.3 $\mu\text{g/l}$ and that of the controls 100.9 $\mu\text{g/l}$ ($p = 0.02$). Compared with the reference group with a blood lead concentration of < 50 $\mu\text{g/l}$, the ORs (no data for 95% CI) for spontaneous abortions for the groups were 2.3 (blood lead concentration 50–90 $\mu\text{g/l}$), 5.4 (100–140 $\mu\text{g/l}$) and 12.2 (> 150 $\mu\text{g/l}$). The risk of spontaneous abortion in the current pregnancies increased 2.5-fold (95% CI: 0.53–11.7) in women with a previous spontaneous abortion. After multivariate adjustment, there was a 13% increase in the risk of spontaneous abortion per 10 $\mu\text{g/l}$ increase in blood lead concentration; this represents almost a doubling of the risk for a 50 $\mu\text{g/l}$ increase in blood lead (OR: 1.8; 95% CI: 1.1–3.1) (Borja-Aburto et al. 1999).

In a prospective birth cohort study, as already mentioned in Section 8.3.1, in multivariate binary logistic models, a blood lead concentration of ≥ 50 $\mu\text{g/l}$ statistically significantly increased the risk of preterm birth (adjusted OR 2.00; 95% CI: 1.35–3.00), but did not increase the risk of having a newborn with a lower birth weight (adjusted OR 1.37; 95% CI: 0.86–2.18) (Taylor et al. 2015).

8.3.3 Teratogenicity

Very few studies have examined the association between maternal lead exposure and the risk of congenital malformations (ATSDR 2020; CDC 2010; NTP 2012). It was concluded that the data were insufficient to establish an association between maternal lead exposure and congenital anomalies (CDC 2010; NTP 2012). Associations between the blood lead concentration and the occurrence of congenital anomalies have not been shown. For example, a case-control study of 97 cases and 201 controls did not find an increased risk of congenital heart defects. For the highest tertile of cord blood lead concentration (≥ 8.26 $\mu\text{g/l}$), the OR for congenital heart defects was 1.67 (95% CI: 0.88–3.17) (ATSDR 2020; Liu et al. 2018). In the study described in Section 8.3.1, women exposed to lead during pregnancy were found to have an increased risk of having a child with a neural tube defect (OR 2.87; 95% CI: 1.05–6.38) (Irgens et al. 1998).

8.4 Developmental neurotoxicity

The particular vulnerability of the foetus and infant to the neurotoxicity of lead is due in part to immature brain microvessels which affect the blood-brain barrier and the lack of a high-affinity lead-binding protein in the astroglia, which sequester lead (ATSDR 2020). Key processes such as the formation and differentiation of neuronal progenitor cells, followed by growth, migration and differentiation of glial cells and neurons into their subtypes, axonal and dendritic outgrowth, formation and pruning of synapses, myelination, apoptosis, ontogeny of neurotransmitters and receptors, and development of the blood-brain barrier are critical for functional brain development (Bal-Price et al. 2015; Stiles and Jernigan 2010). In humans, neuron formation and migration occur to a large extent prenatally, while glial cell precursor growth and migration continue until after birth, and glial cell differentiation and maturation continue into childhood. Synaptogenesis and myelination are also processes that begin prenatally and continue into

childhood (Semple et al. 2013; Stiles and Jernigan 2010). The complex and dynamic developmental processes differ between different brain regions, which in turn influences the different sensitivity of the developing brain to the same chemical at different time points (Rice and Barone 2000). The integrity of the developmental process depends critically on the availability of the appropriate neural element at the appropriate developmental time (Stiles and Jernigan 2010). Damage that occur early during central nervous system (CNS) development have the potential to cause more widespread impacts throughout the brain, while those insults occurring later in development may only affect specific structures (Bal-Price et al. 2015).

There is an Adverse Outcome Pathway for lead binding as an antagonist to the NMDA (*N*-methyl-*D*-aspartate) receptor during synaptogenesis, resulting in impaired learning and memory. In rodents, Pb^{2+} binds to the NMDA receptor in the developing brain with higher affinity than in the adult brain. Whether this is also true for humans is not known. During synaptogenesis, lead binding to the NMDA receptor in the hippocampus leads to the inhibition of receptor activity and thus to delayed ontogenesis of the NR2A subunit of the receptor, which results in a reduced influx of calcium ions into the neurons and a reduced glutamate release and, at the same time, to a reduced BDNF (brain-derived neurotrophic factor) release. At the cellular level, this results in an abnormal morphology of the dendrites, reduced synaptogenesis, impaired neuronal signal transmission and capacity for long-term potentiation and long-term depression, as well as reduced survival and differentiation of the neurons. At the organ level, there is a reduced formation of the neuronal network and its function, resulting in deficits in learning and memory (supplementary material by Bal-Price et al. 2015).

Numerous changes at the cellular level have been associated with lead-induced developmental neurotoxicity in vitro and/or in vivo:

- Impairment of the differentiation and migration of pluripotent stem cells as well as neural and glial progenitor cells (Deng et al. 2001; Deng and Poretz 2001; Maiuolo et al. 2019; Mansel et al. 2019; Nam et al. 2019; Zawia and Harry 1996)
- Disorders of myelin formation by oligodendrocytes (Deng et al. 2001; Deng and Poretz 2001; Maiuolo et al. 2019; Nam et al. 2019; Zawia and Harry 1996)
- Delayed formation or absence of myelin sheaths of axons (Deng et al. 2001; Deng and Poretz 2001; Jones et al. 2008; Maiuolo et al. 2019; Nam et al. 2019; Zawia and Harry 1996)
- Structural damage to synapses as well as their functional disorders (Ahmad et al. 2020; Gąsowska et al. 2016; Neal and Guilarte 2010; Struzynska et al. 2007)
- Increased apoptosis of astrocytes (Kushwaha et al. 2018)
- Disturbances of the energy balance and oxidative stress (Ahmad et al. 2020; Baranowska-Bosiacka et al. 2017)
- Triggering of inflammatory reactions including the production of cytokines (Chibowska et al. 2016, 2020; Struzynska et al. 2007)

Molecular targets that are associated with lead-induced effects include the following:

- The cell adhesion protein *N*-cadherin, which largely regulates stem cell coalescence and interaction (Mansel et al. 2019)
- The transcription factor Sox2, which is expressed in early neuronal development and plays a role in neurogenesis and gliogenesis (Mansel et al. 2019)
- Osteopontin, which binds to integrin and calcium-binding phosphoproteins and is necessary for neuronal development and axonal myelination (Nam et al. 2019)
- Glucose-regulated protein (GRP78), a chaperone that regulates the secretion of interleukin-6 by astrocytes (White et al. 2007)
- Key enzymes of glycogen metabolism (Baranowska-Bosiacka et al. 2017), binding to critical SH groups of proteins (US EPA 2014)

- Increased formation of amyloidogenic proteins (Bakulski et al. 2020; White et al. 2007)
- Disruption of the communication between different cell types (Bakulski et al. 2020)
- Hypo- and hypermethylation of DNA (Singh et al. 2018; White et al. 2007)

There is sufficient consistent evidence for the developmental neurotoxicity of lead from prospective studies and large cross-sectional studies in children (ATSDR 2020; CDC 2010; ECHA 2020; EFSA 2010; NTP 2012). The following developmental neurotoxic effects in children are associated with blood lead concentrations (ATSDR 2020):

Blood lead concentration Developmental neurotoxic effects

$\leq 100 \mu\text{g/l}$	<ul style="list-style-type: none"> • Decrease in cognitive functions, including full-scale IQ (intelligence quotient) • Changes in behaviour and mood that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviour, conduct disorder and delinquency • Changes in neuromotor and neurosensory functions (gross and fine motor skills, visual-motor integration, changes in auditory thresholds)
$> 100 \mu\text{g/l}$	<ul style="list-style-type: none"> • Decrease in cognitive functions, including full-scale IQ • Changes in behaviour and mood, including attention deficits, hyperactivity, autistic behaviour, conduct disorder and delinquency • Changes in neuromotor and neurosensory functions (gross and fine motor skills, visual-motor integration, changes in auditory thresholds and visual evoked potentials) • Peripheral neuropathy • Encephalopathy

Altogether, the studies demonstrate that cognitive functions are impaired in children following prenatal and/or environmental exposure to low concentrations of lead. Several models predict greater reductions in cognitive function with increases in blood lead concentrations from 10 to 100 $\mu\text{g/l}$ compared with increases above 100 $\mu\text{g/l}$, suggesting a supralinear concentration-response relationship. At higher blood lead concentrations ($> 300 \mu\text{g/l}$), also changes in the function of nerves as well as encephalopathy were observed. With regard to the reduction of cognitive functions, no specific life span could be identified as a critical period so far. It is not clear if the cognitive decrements are related to exposures that occurred in periods of nervous system development like prenatal and childhood exposures or to exposures during adulthood or if effects are due to cumulative exposure (ATSDR 2020). A NOAEC for developmental neurotoxicity could not be derived (ATSDR 2020; CDC 2010; NTP 2012).

There is a large number of prospective studies on neurotoxic effects with the recording of **prenatal exposure** to lead (either maternal blood or umbilical cord blood). From these studies, there is evidence that prenatal lead exposure at a blood lead concentration of $< 50 \mu\text{g/l}$ is associated with declines in general and specific cognitive functions in children. There is evidence for an association between a prenatal blood lead concentration of $< 100 \mu\text{g/l}$ and a decreased IQ score, an increased incidence of attention deficit disorder and antisocial behaviour, and a reduced hearing ability in children (NTP 2012).

The CDC report provides a detailed compilation of studies reporting blood lead concentrations during pregnancy or in umbilical cord blood and neurotoxic effects. From the large number of studies, CDC concludes that there is convincing evidence that prenatal lead exposure impairs the development of the foetal nervous system (CDC 2010).

A limiting consideration is that there may be increased lead uptake in children via breast milk (see Section 8.1) and food, and especially at the age of about 2 years (hand-to-mouth activity, habitual picking up of objects) (ATSDR 2020). Consequently, a reliable differentiation between effects in the child resulting from prenatal exposure (through exposure of the mother at work) or postnatal exposure (environment and breast milk) is not unequivocally possible. This

means that it is not possible to clearly determine which CNS effects result from an insult at which stage of life and whether the prenatal phase is clearly more sensitive than the early postnatal phase.

In 2010, EFSA derived a benchmark dose lower confidence limit of 1% extra risk (BMDL₀₁) of 12 µg lead/l blood as a reference value for the risk characterisation of lead for the assessment of intellectual deficits in children. The full-scale IQ score determined in children was used as end point (EFSA 2010). The benchmark calculation is based on a pooled analysis from seven international population-based longitudinal cohort studies (Lanphear et al. 2005). These included data from Boston, Massachusetts (Bellinger et al. 1992), Cincinnati, Ohio (Dietrich et al. 1993), Cleveland, Ohio (Ernhart et al. 1989), Mexico City, Mexico (Schnaas et al. 2000), Port Pirie, Australia (Baghurst et al. 1992), Rochester, New York (Canfield et al. 2003) and Kosovo (Wasserman et al. 1997). Although the results of the individual studies differ in some respects, perhaps due to the influence of covariates, individual sensitivity and testing methods, the overall evidence after adjusting for possible confounders strongly supports an association between biomarkers of early chronic lead exposure and lower IQ scores and similar neuropsychological measures in school-aged children. Two studies did not reveal a negative effect of lead exposure, although the reasons for this discrepancy are unclear. The three largest studies (Cincinnati, Port Pirie, Kosovo studies) most strongly support the association between lead exposure and developmental neurotoxicity (EFSA 2010).

In the pooled analysis by Lanphear et al. (2005), a total of 1333 children aged 4 to 7 years from seven international studies were included. The full-scale IQ score served as the primary measurement outcome. The maximum geometric mean blood lead concentration in the children was 178 µg/l regardless of the time of determination or age and decreased to 94 µg/l at the age of 5 to 7 years. In total, 244 children had maximum blood lead concentrations less than 100 µg/l, with 103 children having concentrations less than 75 µg/l. IQ point decrements calculated using a log-linear model were 3.9 (95% CI: 2.4–5.3) for an increase in blood lead concentration from 24 to 100 µg/l, 1.9 (95% CI: 1.2–2.6) for an increase from 100 to 200 µg/l, and 1.1 (95% CI: 0.7–1.5) for an increase from 200 to 300 µg/l. For the same increase in blood lead concentration, the IQ score decrement was significantly greater for a maximum blood lead concentration of less than 75 µg/l compared with that of children with a maximum blood lead concentration of at least 75 µg/l ($p = 0.015$) (Lanphear et al. 2005). The analysis also showed that lead-associated intellectual deficits at lower concentrations only became apparent when children born after the ban on the use of leaded fuels were examined. A threshold for such effects could not be identified. The concentration-response curve is steeper at blood lead concentrations of less than 100 µg/l (EFSA 2010).

EFSA commissioned the University of Copenhagen to perform the benchmark calculation for the effects of lead on intellectual function using the complete individual data of all 1333 children from the seven studies. The benchmark calculations were based on standard multiple regression models. After adjustment for possible confounders, model-dependent BMD₀₁ (decrease of one IQ point) values of 3.5 µg lead/l blood and 18.0 µg lead/l blood, respectively, and BMDL₀₁ values of 2.6 µg lead/l blood and 12.0 µg lead/l blood, respectively, were obtained (Jørgensen 2010). These values are in the range of background exposure.

A review article reports on sex-dependent differences in exposure to lead during development. In epidemiological studies, the incidence, manifestation and severity of the effects of lead on the developing brain appear to differ between girls and boys. Gender differences are also observed in animal experiments, but no consistency is seen across the studies. However, most epidemiological studies did not distinguish between genders (Singh et al. 2018).

8.4.1 Neurotoxic endpoints in pre- or perinatal examinations

For a study investigating neural connectivity patterns, functional magnetic resonance imaging (fMRI) examinations were performed on 118 mothers at routine obstetrical appointments to investigate neural connectivity patterns at gestational weeks 23.9 to 39.6. Based on the blood lead concentrations of the newborns, two groups were defined, a lead-exposed group (blood lead concentration 10–110 µg/l, mean 24.3 µg/l (± 6.5); $n = 13$; mean number of gestational weeks at fMRI: 33.69 ± 4.28 ; 7 boys) and a control group (blood lead concentration < 10 µg/l; $n = 13$; mean number of gestational weeks at fMRI: 33.72 ± 4.29 ; 6 boys). Lead-exposed fetuses showed stronger age-related increases in the connectivity of the posterior cingulate cortex to the lateral prefrontal cortex. The control group showed age-related

stronger cross-hemispheric connectivity (Thomason et al. 2019). With a case number of 13, the sample size is very small. However, the method and analysis are considered robust. The presence of other neurotoxic substances in the blood, such as mercury or chlorinated biphenyls, was not tested. Despite limited validity, the study suggests that prenatal lead exposure leads to changes in cognitive development.

A prospective study included spontaneously born infants from a rural area in Sanhe County, Hebei Province, in northern China. The mothers were recruited between November 2009 and November 2011. To correlate with postnatal functional tests, blood samples were taken from the mothers at two time points (approximately week 16 of pregnancy: auditory brainstem response: $n = 343$ and visual acuity: $n = 1038$, week 39 of pregnancy: $n = 362$ and 1058) and cord blood was drawn from the newborns shortly after birth ($n = 321$ and 949). Infants' auditory-induced brainstem responses were measured on the 2nd day of life and visual acuity (measured by plate visual acuity cards) at the age of 6 weeks. High maternal blood lead concentrations in week 39 of pregnancy were associated with auditory-induced brainstem responses and lower visual acuity (Silver et al. 2016). The study indicates that prenatal lead exposure has a negative impact on the development of the auditory and visual sensory systems.

8.5 Results of animal and in vitro studies on reproductive toxicity

8.5.1 Fertility

Groups of three female Wistar rats were given concentrations of 0, 50, 100 or 150 μg **lead acetate**/l drinking water three months before mating until the end of lactation. The males received the drinking water containing lead acetate three months before mating. The litter size was reduced and the gender ratio changed (increased number of female offspring). In addition, delayed vaginal opening and reduced body weight at the time of vaginal opening were reported in the females of the F1 generation (Dumitrescu et al. 2008). However, due to the low animal number of only three animals per group and the small study size, the study cannot be included in the evaluation.

In a one-generation study carried out according to OECD Test Guideline 415 (of 1981) in Wistar rats (30 females and 15 males per group), the animals were given **lead acetate** (0, 1000, 5000, 10 000 mg lead acetate/kg diet; equivalent to about 0, 90, 450, 900 mg lead acetate/kg body weight and day (conversion factor 0.09 (for subchronic exposure according to EFSA 2012)), equivalent to about 0, 58, 288, 576 mg lead/kg body weight and day) and mancozeb (4500 mg/kg diet), a plant protection product. No effects on mating, fertility and gestation were found in the parental generation (Várnagy et al. 2002). Blood lead concentrations were not determined. The presentation of the methods and results is very brief. It is not plausible that no effects were found at such high doses. Additionally, due to the exposure to a mixture of substances, the study is not suitable for assessing the effects of lead on fertility.

8.5.1.1 Fertility studies in male animals

Studies investigating the fertility of male cynomolgus monkeys exposed to **lead acetate** (1500 $\mu\text{g}/\text{kg}$ body weight and day) for up to ten years revealed ultrastructural effects in the testes and seminiferous tubules. Blood lead concentrations were in the range from 320 to 360 μg lead/l and 420 μg lead/l (Cullen et al. 1993; Foster et al. 1993, 1998). In Wistar rats, reduced serum testosterone concentrations and reduced sperm counts were reported after exposure to 0.1% **lead acetate** via drinking water at blood concentrations of 340 to 370 μg lead/l in adult animals (Sokol and Berman 1991). Kunming mice exposed to **lead acetate** via drinking water for 60 days exhibited impaired spermatogenesis and sperm development as well as reduced fertility (no data on blood lead concentrations; Wang et al. 2013). A blood lead concentration without effects on male fertility in rats, mice and monkeys cannot be derived. For Dutch-Belt rabbits, a threshold for impaired semen quality could be derived at 160 to 240 μg lead/l blood after subcutaneous injection of 3.85 mg **lead acetate**/kg body weight for 15 weeks (ECHA 2020).

8.5.1.2 Fertility studies in female animals

In female rats (14 animals per group) treated subcutaneously with 0.05 mg **lead acetate**/kg body weight and day before and during mating and during gestation, no changes in reproductive performance were found (Nampoothiri and Gupta 2008). The study was conducted with only one dose, and the blood lead concentrations appear high compared to other studies with similar exposure.

8.5.2 Developmental toxicity

Numerous studies have documented lead-induced foetotoxicity in sheep, dogs, guinea pigs, hamsters, rats and mice. After injection of lead, specific malformations of the CNS and the skeleton occurred in rats, mice and hamsters, depending on the time of injection (Gerber et al. 1980).

As in the adult animal, impairments of the nervous system in the foetus are the main effects. A large number of studies with pre- and postnatal exposure up to weaning of the rats on postnatal day 21 are available. End points include:

- Cognitive functions in rats and monkeys (impaired learning, spatial memory, working memory, executive functions, ability to learn response sequences and associative abilities); e.g. Altmann et al. 1993; Cory-Slechta 2003; Lassiter et al. 2015; Moreira et al. 2001; Winneke et al. 1977; Yang et al. 2003)
- Motor functions in rodents (effects on endurance, balance and coordination); e.g. Lassiter et al. 2015; Leasure et al. 2008; Winneke et al. 1977)
- Attention and impulsive behaviour in rats (e.g. Brockel and Cory-Slechta 1998; Cory-Slechta 2003; Lassiter et al. 2015; Moreira et al. 2001)
- Effects on neuronal structures and functions in rodents (impairment of neurogenesis, neurite outgrowth and synaptic plasticity), e.g. Lassiter et al. 2015)
- Effects on the release or regulation of neurotransmitters in rats (decrease in GABA release in the hippocampus, effects on serotonin and dopamine; e.g. Lassiter et al. 2015; Leasure et al. 2008)

Table 1 includes studies on behavioural end points with information of blood lead concentrations in dams or offspring at birth. Studies are listed in which animals were treated until the 10th postnatal day according to the gestational lead exposure model (Fox et al. 2008; Leasure et al. 2008; Zhao et al. 2018). The reason for this is that the human brain has a higher degree of maturity at the time of birth compared with that of rodents. This degree of maturity at the time of birth in humans is reached in rodents not before the 10th postnatal day (Semple et al. 2013). In addition, some studies with pre- and postnatal lead exposure are listed as examples.

Tab. 1 Studies with pre- and postnatal exposure to lead or lead compounds (gestational lead exposure (GLE) model, and others)

Species	Exposure	Lead concentration in blood [$\mu\text{g/l}$]	Findings	References
Prenatal or pre- and postnatal treatment up to PND 10				
rat, Sprague Dawley, 8 ♀	GLE model; 2 weeks before mating, entire gestation until PND 10, 0, 0.005, 0.01, 0.02% lead acetate in drinking water, (0, 27, 55, 109 mg Pb/l), brain: PND 30, Morris water maze test: PND 30	<u>offspring, PND 0:</u> about 10 (controls), 180, 230, 480 (from graphic) <u>offspring, PND 30:</u> all dose groups about 10, no determination in the blood of the dams <u>hippocampus, offspring, PND 30:</u> about 0.02, 0.14, 0.2, 0.23 $\mu\text{g/g}$ wet weight (from graphic)	$\geq 180 \mu\text{g/l}$ and above: Morris water maze test: impaired performance (escape latency \downarrow , time in quadrant \downarrow), CA3-CA1 region of the hippocampus: EPSC amplitude \downarrow , CA1 region of the hippocampus: den- dritic spine density of pyramidal cells \downarrow (dose-dependent), NLGN1 expression \downarrow (postsynaptic protein that mediates synaptogenesis); no effects: body weight, hippocampus on PND 30: dendritic complexity of pyram- idal neuron	Zhao et al. 2018

Tab.1 (continued)

Species	Exposure	Lead concentration in blood [µg/l]	Findings	References
Prenatal or pre- and postnatal treatment up to PND 10				
rat , Long Evans Hooded, 12–15 ♀	GLE model; 2 weeks before mating, entire gestation until PND 10, 0, 0.005, 0.01, 0.02% lead acetate in drinking water, (0, 27, 55, 109 mg Pb/l), examination of the retina: PND 90	<u>offspring, PND 0:</u> < 10 (controls), 120, 240, 460	120 and 240 µg/l: retina: ERG supernormality, rod photoreceptor and rod bipolar cell neurogenesis; 460 µg/l: retina: ERG supernormality, loss of rod cells, Zn concentration ↓; non-monotonic dose-response relationships	Fox et al. 2008
mouse , C57BL/6, 10–15 ♀	GLE model; 2 weeks before mating, entire gestation until PND 10 (GLE), PND 0 to PND 21 (PLE), GLE: 0, 0.005, 0.01, 0.02% lead acetate in drinking water, (0, 27, 55, 109 mg Pb/l), PLE: 0, 0.005, 0.01% lead acetate in drinking water examination after 1 year	<u>GLE:</u> <u>offspring, PND 0:</u> ≤ 10 (controls), ≤ 100 (90 from graphic), 270, 420 <u>offspring, PND 30:</u> all ≤ 10	GLE: ≥ 90 µg/l: ♂: spontaneous motor activity ↓, amphetamine-induced motor activity ↑, rotarod: performance ↓; striatum and forebrain: changes in dopamine metabolism (strongest effects at this blood concentration: non-monotonic dose-response relationship); 420 µg/l: ♂: obesity (1 year, ♀ not); PLE: no behavioural toxicity studies carried out	Leasure et al. 2008
monkey , squirrel monkey, 8 ♀	from gestation week (GW) 8.5 or GW 5 until birth (gestation duration: 22 weeks), lead on apple pieces and in drinking water, examination at the age of 5–6 years	<u>dams:</u> exposed animals: 210, 230, 230, 370, 370, 440, 560, 790 (the two latter exposures started at GW 8.5) controls: 65 (40–90) <u>newborns:</u> values close to those of the dams	> 210 µg/l: steady-state behaviour similar to controls, transition behaviour: acquisition: slow progression and 2–4 times more reinforcers needed, i. e. impairment of learning ability; > 400 µg/l: behavioural test with a modified “Lindsley manipulandum”: impairment of steady-state and transition behaviour, i. e. effects on learning	Newland et al. 1994, 1996
Pre- and postnatal treatment				
rat , Wistar, 22 ♀ per group	Maternal group: 50 days before mating, gestation until PND 16 (similar to GLE), Postweaning group: from PND 16 until necropsy, Permanent group: as maternal group continued after PND 16 until necropsy; necropsy of all groups on PND 210, examination on PND 70–210, 0, 745 mg lead acetate/ kg diet, (about 0, 67 mg/kg body weight and day ^{al})	<u>dams:</u> no data <u>offspring:</u> determination in blood during necropsy Maternal group: 2.6 (brain: < 0.01 µg/g wet weight) Postweaning group: 162 (brain: 0.09 µg/g wet weight) Permanent group: 143 (brain: 0.16 µg/g wet weight) Control group: 2.1 (brain: < 0.01 µg/g wet weight)	Maternal group: active avoidance test: impairment of learning, LTP changed; Postweaning group: active avoidance test: no difference to control group, LTP not changed compared with that of controls; Permanent group: active avoidance test: impairment of learning, LTP changed; Conclusion: developing brain more sensitive to lead-induced functional changes compared to exposure after weaning	Altmann et al. 1993

Tab. 1 (continued)

Species	Exposure	Lead concentration in blood [$\mu\text{g/l}$]	Findings	References
Pre- and postnatal treatment				
rat, Wistar, 15–17 ♀ per group	gestation, lactation until PND 21, 0, 500 mg lead acetate/l drinking water, controls: 660 mg sodi- um acetate/l drinking water, examination on PND 23 or PND 70	<u>dams:</u> < 10, 412 <u>offspring, PND 23:</u> < 10, 212 <u>offspring, PND 70:</u> all < 10	412 $\mu\text{g Pb/l}$ (dams) <u>offspring:</u> hyperactivity, open field test according to File and Wardill: explora- tion behaviour ↓, elevated plus maze test: anxiety behaviour, shuttle avoidance task: impairment of learning and mem- ory	Moreira et al. 2001
rat, Wistar, 20 ♀ per group	60 days before mating, 10 weeks of mating, ges- tation, lactation, until weaning about 3 weeks after birth, 0, 745 mg lead acetate/ kg diet, (about 0, 67 mg/kg body weight and day ^{a)}), examination of 40 of the 110 ♂ offspring between PND 100 and 200	<u>dams:</u> prenatal: 240, lactation: 310 <u>offspring:</u> 270–290	240 $\mu\text{g Pb/l}$ (dams) <u>offspring:</u> open field test: locomotor ac- tivity, rearing and grooming behaviour ↑ (hyperactivity); difficult learning task (size discrimina- tion): learned only by control animals, not by lead-exposed animals; simple learning task (orientation dis- crimination): no differences to the con- trol group no stillbirths, no external malformations, no runts	Winneke et al. 1977

^{a)} Conversion factor 0.09 for subchronic exposure according to EFSA (2012)

EPCS: evoked excitatory postsynaptic currents; ERG: electroretinogram; GLE: gestational lead exposure; GW: gestation week; LTP: long-term potentiation; NLGN1: neuroligin 1; PLE: postnatal-only lead exposure; PND: postnatal day

Studies in rats and mice using a gestational lead exposure model showed effects in behavioural tests. For example, newborn rats with blood lead concentrations above about 180 $\mu\text{g/l}$ showed impairment in the Morris water maze test (a test to assess spatial learning and influences on it), reduced evoked excitatory postsynaptic currents in the CA3-CA1 region of the hippocampus, and reduced dendritic spine density of pyramidal cells (Zhao et al. 2018).

In mice, blood lead concentrations of the **newborn** animals above about 90 $\mu\text{g/l}$ resulted in reduced spontaneous motor activity, reduced performance in the rotarod test and changes in dopamine metabolism (Leasure et al. 2008).

In addition, a persistent change in the electroretinogram occurred in the gestational lead exposure model in the offspring of rats. Below 460 $\mu\text{g lead/l}$ blood, this was due to increased neurogenesis of the rods. Above 460 $\mu\text{g lead/l}$ blood, supernormality was seen as rod-selective toxicity (Fox et al. 2008).

In squirrel monkeys, **prenatal** oral lead exposure above a maternal blood lead level of 230 $\mu\text{g/l}$ resulted in impaired learning ability in the offspring (Newland et al. 1994, 1996).

Studies with **pre- and postnatal** lead exposure in rats showed effects on learning ability and memory in the offspring at blood lead concentrations of 143 $\mu\text{g/l}$ and above (Altmann et al. 1993), and hyperactivity, reduced locomotor activity, reduced exploratory behaviour and increased anxiety behaviour at maternal blood lead concentrations of 240 $\mu\text{g/l}$ and higher (Henschler 1978; Moreira et al. 2001; Winneke et al. 1977).

There are several studies demonstrating effects on immune parameters caused by prenatally administered lead compounds. Changes like suppression of the antibody response, altered immunoglobulin levels, altered cytokine production or impaired DTH (delayed type hypersensitivity) were found in the offspring. These effects were observed at blood lead concentrations of about 290 $\mu\text{g/l}$ in sheep, of 1120 $\mu\text{g/l}$ in rats and less than 200 $\mu\text{g/l}$ in mice. Many immune system responses observed in humans after lead exposure can be reproduced in animal studies. However, caution should be exercised when extrapolating these end points from animals to humans, as immune functions are dependent on animal species, gender and developmental stage (ATSDR 2007).

In a carcinogenicity study, C57Bl/6NCr mice were continuously exposed to 0, 500, 750 or 1000 mg lead acetate/l (about 0, 100, 150 or 200 mg/kg body weight and day) via drinking water during pregnancy and lactation. In the offspring, a statistically significantly increased incidence of renal tumours (5/25) was found in the highest dose group, but no nephrotoxicity. Even in the low dose group of 500 mg lead acetate/l, tubular hyperplasia (3/25) and one renal carcinoma occurred in the male offspring (Hartwig and MAK Commission 2022; Waalkes et al. 1995).

8.6 Assessment of the prenatal toxicity of lead

8.6.1 Human data

Numerous epidemiological studies on lead exposure are available. Associations between **developmental toxicity** – such as effects on birth parameters (reduced birth weight, head circumference and crown-heel length) and reduced anthropometric measures in children (body weight, height, head circumference, trunk length, arm and leg length, BMI) – and prenatal maternal blood lead concentrations or cord blood concentrations are already detected below 100 µg/l, although the study results are inconsistent in this concentration range. Above 100 µg/l, there are consistent effects on birth parameters (lower birth weight) and lower anthropometric measures in infancy (body weight, height, head circumference, chest circumference) (ATSDR 2020).

There is sufficient consistent evidence for the **developmental neurotoxicity** of lead from prospective studies and large cross-sectional studies in children (ATSDR 2020; CDC 2010; ECHA 2020; EFSA 2010; NTP 2012). Associations between developmental neurotoxicity in children – such as reduced cognitive functions, changes in behaviour and mood, learning deficits, attention deficits, hyperactivity, autistic behaviour, conduct disorders and delinquency – were found at blood lead concentrations below 100 µg/l. Above 100 µg lead/l blood, there were additional changes in neuromotor and neurosensory functions (gross and fine motor skills, visual-motor integration, changes in auditory thresholds and visual evoked potentials), peripheral neuropathy and encephalopathy (ATSDR 2020). In summary, there is consensus that a NOAEC cannot be derived for the developmental neurotoxicity of lead (ATSDR 2020; CDC 2010; ECHA 2020; EFSA 2010; NTP 2012).

There are several prospective studies on neurotoxic effects in children, in which **prenatal exposure** to lead (either via maternal blood or cord blood) was recorded. CDC concludes that there is convincing evidence that prenatal lead exposure impairs the development of the child's nervous system (CDC 2010). NTP sees limited evidence that prenatal lead exposure at blood lead concentrations of less than 50 µg/l is associated with declines in general and specific cognitive functions in children. There is also evidence of decreased IQ scores, an increased incidence of attention deficit disorder and antisocial behaviour, and reduced hearing ability in children caused by prenatal exposure at blood lead concentrations of less than 100 µg/l (NTP 2012). However, as outlined in Section 8.4, the conclusion that CNS effects in children are due to prenatal lead exposure is complicated by the fact that there is a high correlation between prenatal and postnatal blood lead concentrations in children and that blood lead concentrations determined during childhood are also correlated with such effects (ATSDR 2020; EFSA 2010; Lanphear et al. 2005; NTP 2012). A reliable differentiation between effects in the child caused by prenatal exposure (exposure of the mother at work) or postnatal exposure (environment and breast milk) is not clearly possible, nor is it possible to determine whether the prenatal stage is significantly more sensitive than the early postnatal stage.

A specific life stage (prenatal, early or late postnatal) as a critical period for the lead-induced effects could not be identified (ATSDR 2020; ECHA 2020; NTP 2012).

8.6.2 Experimental animal data

Numerous studies demonstrated lead-induced foetotoxicity in sheep, dogs, guinea pigs, hamsters, rats and mice. After the injection of lead, specific malformations of the CNS and the skeleton occurred in rats, mice and hamsters, depending on the time of injection. The main effects were impairments of the nervous system in rats, mice and monkeys. The following effects were observed: impairment of learning, spatial memory, working memory, executive functions,

ability to learn response sequences, associative abilities and motor functions, effects on attention and impulsive behaviour, effects on neuronal structures and functions, and effects on the release or regulation of neurotransmitters. In rats, in the gestational lead exposure model, impairment in the Morris water maze test, reduced evoked excitatory postsynaptic currents in the CA3-CA1 region of the hippocampus, and reduced dendritic spine density of pyramidal cells were observed at blood lead concentrations in the newborn animals of about 180 µg/l (Zhao et al. 2018). In mice, blood lead concentrations in newborn animals above about 90 µg/l resulted in reduced spontaneous motor activity, reduced performance in the rotarod test, and alterations in the dopamine metabolism (Leasure et al. 2008). It is known from numerous toxicokinetic studies that blood lead concentrations in the newborn offspring are similar to those in the dams (ATSDR 2020; CDC 2010; NTP 2012). Thus, effects in the offspring were observed in the gestational lead exposure model even at the level of the BAT value of 150 µg/l blood. The controlled exposure conditions in animal experiments plausibly support the lead-induced effects observed in humans, such as growth retardation and developmental neurotoxicity.

8.6.3 Assignment to a pregnancy risk group

For the assignment to a pregnancy risk group, also the postnatal period is used for the assessment of the developmental toxicity of lead, because the prenatally generated exposure persists postnatally due to the long half-life of lead and because, as already mentioned, a specific life stage could not be identified as a critical period for the lead-induced effects (ATSDR 2020; ECHA 2020; NTP 2012). For the developmental neurotoxicity of lead, there is sufficient consistent evidence from prospective studies and large cross-sectional studies in children. Animal studies conducted under controlled exposure conditions support the effects observed in children. A NOAEC for the developmental neurotoxicity of lead cannot be derived (ATSDR 2020; CDC 2010; ECHA 2020; EFSA 2010; NTP 2012). Effects can be expected for exposures at the level of the BAT value of 150 µg lead/l blood. Lead and its inorganic compounds are therefore

assigned to Pregnancy Risk Group A at a BAT value of 150 µg lead/l blood.

With regard to toxicokinetics, it should be noted that lead readily passes the placental barrier. During pregnancy, there is an increased mobilisation of lead from maternal bones with the incorporation of lead into foetal bones, so that even without external exposure to lead during pregnancy, there is a transfer of lead to the foetus (ATSDR 2020; Bolt et al. 2020). Therefore, additional lead exposure of pregnant women and women of childbearing age above background concentrations (BAR) is associated with an additional health risk for the newborn infant.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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