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Lead and its inorganic compounds (inhalable fraction) except lead arsenate and lead chromate

MAK Value Documentation, supplement – Translation of the German version from 2022

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Keywords

lead; inorganic lead compounds; neurotoxicity; PBPK model; MAK value; maximum workplace concentration; genotoxicity; human studies; peak limitation; carcinogenicity

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) considering all toxicological end points. After repeated exposure of workers, lead and its inorganic compounds show specific target organ toxicity in the nervous system, kidneys, cardiovascular and haematological system. The most sensitive toxic effects of lead and its inorganic compounds are nervous system disorders. Lead-induced neurological effects are also observed in infants and children and may result in a lifelong reduction of neurological function at low blood lead levels. As lead has a long half-life in humans, the most reliable and specific parameter for determining the internal lead burden is the blood lead concentration. Thus, the BAT value (biological tolerance value) of 150 µg/l blood must not be exceeded and its use is to be preferred over an air limit value. Nevertheless, a maximum concentration at the workplace (MAK value) of 0.004 mg/m^3 for the inhalable fraction was derived by applying an updated and calibrated physiologically based pharmacokinetic (PBPK) model. As the critical effect is systemic, lead has been assigned to Peak Limitation Category II with an excursion factor of 8 due to its long half-life. As it has been demonstrated unequivocally that lead induces damage to the human embryo or foetus and that these effects are to be expected even if the MAK and BAT values are not exceeded, lead has been assigned to Pregnancy Risk Group A. The carcinogenic effects of lead and its inorganic compounds have been demonstrated in animal studies, but the data in humans are inconclusive. The primary mechanism of action is non-genotoxic and genotoxic effects play no or at most a minor part provided that the MAK and BAT values are observed. Lead and its inorganic compounds have thus been classified in Carcinogen Category 4. Skin contact is not expected to contribute significantly to systemic toxicity, but oral absorption via hand-mouth contact continues to be a critical factor. A skin sensitization potential is not expected from the data available. There are no data for sensitization of the respiratory tract.

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MAK value (2021)	**0.004 mg lead/m³ I (inhalable fraction)**
Peak limitation (2021)	**Category II, excursion factor 8**
Absorption through the skin	–
Sensitization	–
Carcinogenicity (2021)	**Category 4**
Prenatal toxicity (2021)	**Pregnancy Risk Group A**
Germ cell mutagenicity (2004)	**Category 3 A**
BAT value (2021)	**150 µg lead/l blood**
BAR (2019)	**30 µg lead/l blood for women** **40 µg lead/l blood for men**
CAS number	7439-92-1 (lead); 1317-36-8 (lead oxide); 301-04-2 (lead diacetate); 7758-95-4 (lead dichloride); 1072-35-1 (lead distearate); 61790-14-5 (lead naphthenate); 7446-14-2 (lead sulfate); 16038-76-9 (lead phosphite); 69011-06-9 (lead phthalate); 10099-74-8 (lead dinitrate)

The documentation is based mainly on the reports from different bodies (AGS 2017; ATSDR 2020 b; ECHA 2020 a; RAC 2020).

Until lead and its inorganic compounds were classified as carcinogenic in animal experiments (Carcinogen Category 3 B (Greim 2004, available in German only), Carcinogen Category 2 (Greim 2009)), a MAK value of 0.1 mg lead/m³ (Greim 2002 b) with Peak Limitation Category II and an excursion factor of 8 (Greim 2002 a) applied. With regard to prenatal toxicity, the substance was assigned to Pregnancy Risk Group B in 1985; a supplement was not published at that time.

The compounds lead distearate, lead diacetate, lead phthalate and lead naphthenate were included in this supplement because, like the inorganic compounds, they can release lead ions.

1 Toxic Effects and Mode of Action

Lead is carcinogenic in animal experiments. In addition to renal tumours with concomitant nephrotoxicity, gliomas were observed, which are rare tumours that do not occur spontaneously. A carcinogenic effect in humans, on the other hand, has not been demonstrated unequivocally; however, clastogenic effects occur in humans at and above about 300 µg lead/l blood as a result of indirect DNA damage.

In humans, the target organs after repeated exposure to lead are the nervous system, the cardiovascular system, the kidneys, the haematopoietic system and the reproductive organs.

Even small increases in the blood lead concentration result in developmental neurotoxicity.

The available data do not provide sufficient evidence to demonstrate that lead causes skin sensitizing effects.

2 Mechanism of Action

A detailed description of the mechanism of action of lead can be found in the earlier supplements (Greim 2002 b, 2009).

The mechanism of action of developmental neurotoxicity is described in the current addendum to the evaluation of the BAT value (Greiner et al. 2022).

Genotoxicity

Studies of the genotoxicity of lead show that indirect genotoxic effects of lead are responsible for the observed damage. These include inhibition of DNA repair mechanisms and thus an enhancement of mutagenic and clastogenic effects triggered by other toxins, as well as oxidative stress induced by lead. The direct interaction of lead with DNA could not be demonstrated to date (García-Lestón et al. 2010).

The influence on the mutation frequency and the inhibition of DNA repair by lead are due to the interaction of lead ions with proteins by binding to SH groups and competition with other essential metals, such as the displacement of zinc from zinc finger structures. Although lead does not interact directly with DNA, genetic damage can occur via the above mechanisms (Beyersmann and Hartwig 2008; Greim 2009).

Four possible binding sites of lead in the minor groove of the DNA double helix were shown in isolated calf thymus DNA, which, according to the authors, can result in a change in the DNA structure (Zhang et al. 2014). For these results, a validation in the physiological system is lacking.

3 Toxicokinetics and Metabolism

Data for the toxicokinetics and metabolism of lead can be found in the BAT evaluation of 2001 (Bolt and Schaller 2005) and the addendum of 2019 (Bolt et al. 2020).

3.1 Absorption, distribution, elimination

After inhalation and oral absorption, lead is distributed throughout the organism by incorporation in erythrocytes. Lead is present in the body in an exchangeable fraction and a fraction that is firmly bound in the bones. The half-life of lead in human bone is about 10 years. The rapidly exchangeable pool correlates with the blood lead concentration. Elimination is mainly via the kidneys. The respective studies were described in detail and evaluated in Greim (2002 b) and in Greiner et al. (2022).

A detailed presentation of the relationship between bone and blood lead levels can be found in the documentation for lead in TRGS 903 (AGS 2017).

In adult male Sprague Dawley rats (n = 4–7 animals), single oral doses of lead diacetate of 1, 10 or 100 mg lead/kg body weight did not result in a dose-dependent proportional increase in blood lead concentrations within the following 25 days. The uptake of lead into the blood, calculated as the area under the curve (AUC), was about 42% at 1 mg lead/kg body weight, about 10% at 10 mg lead/kg body weight and only about 2% at 100 mg lead/kg body weight (Aungst et al. 1981).

After the administration of lead diacetate in the drinking water (0, 5, 50, 500 or 5000 mg lead/l) to adult male Sprague Dawley rats for 14 days, 50 µg lead/l blood and 1 µg lead/g kidney tissue were found in the 50 mg/l group and 245 µg lead/l blood and 4.8 µg/g kidney tissue in the 500 mg/l group (Aungst et al. 1981). The ingestion of lead thus led to a high renal lead burden and not only to an increased blood lead concentration.

Groups of 36 male 50-day-old Long Evans rats were given lead diacetate with the drinking water in concentrations of 0, 100, 300, 500 or 1000 mg lead/l. The lead concentrations in the liver, kidneys, blood and bone were determined in 4 to 6 animals per concentration after 2 and 4 weeks as well as after 2, 4, 8 and 18 months. The lead concentrations of the control animals were not given. According to the data presented in diagrams, blood lead concentrations of about 240 µg/l, 350 µg/l, 450 µg/l and 650 µg/l and bone lead levels of about 18 µg/g, 60 µg/g, 100 µg/g and 130 µg/g, respectively, were obtained after 240 days. The blood lead concentrations reached steady state after about 120 days. The bone

lead levels in the 3 highest concentration groups continued to increase after 8 months. According to the authors, the lead concentrations in the liver and kidneys were erratic and were not presented (O'Flaherty 1991).

In post-mortem examinations (n = 129), similarly high lead concentrations were found in various human organ tissues. The mean lead concentrations in men and women were 0.78 µg/g and 0.55 µg/g in the renal cortex, 0.5 µg/g and 0.38 µg/g in the renal medulla, and 1.03 µg/g and 0.66 µg/g in the liver, respectively. In contrast, very high lead concentrations were observed in the bones with 23.5 µg/g and 15.99 µg/g (for example tibia), respectively, which can be attributed to lead accumulation. The blood lead levels were 200 µg/l and 160 µg/l, respectively (Barry 1975).

In another study, post-mortem lead concentrations in men (n = 46) were reported to be 0.79 µg/g in the renal cortex, 0.48 µg/g in the renal medulla and 0.98 µg/g in the liver. The blood lead level was 210 µg/l (Gross et al. 1975).

In a more recent publication, post-mortem examinations of autopsy material from 20 people (12 men, 8 women, mean age 51 years) who lived in the vicinity of a hazardous waste incinerator in Spain were conducted in 2013. Lead concentrations of 100 µg/g were found in the kidneys, of 1390 µg/g in the bone, of < 0.025 µg/g in the brain, of 180 µg/g in the liver and of 50 µg/g in the lungs (Mari et al. 2014). Blood lead levels were not reported in this study.

A comparison of the human data with the data from the 14-day study in rats (Aungst et al. 1981) shows that about 5 times as much lead accumulates in the kidneys of rats as in the kidneys of humans (this was determined from the following: 200 µg lead/l blood and 0.8 µg lead/g kidney (wet weight) in humans compared with 50 µg lead/l blood and 1 µg lead/g kidney (wet weight) or 245 µg lead/l blood and 4.8 µg lead/g kidney (wet weight) in rats).

In the following, studies are described that address the contribution of dermal exposure to internal lead exposure.

Personal air samples, blood samples and skin wipe samples were analysed for lead content in 7 workers (5 wore gloves, 2 did not) who operated CNC machines at a brass foundry (up to 20% lead in the alloys). The concentrations of lead in the air were < 0.1–3.4 µg/m^3 (mean 1.2 µg/m^3), the concentrations in blood < 7.2–330 µg/l. The lead concentrations on the skin after 2 hours of exposure were 0.16–48 µg/cm^2. In the 4 metal cutting fluid solutions used on this working day, the lead levels were 29–132 mg/kg. The penetration of lead from these solutions into and through pig skin was determined in an in vitro test with Franz cells after 2, 4 and 24 hours. The highest flux rates through pig skin were measured during the first 2 hours and were 0.32–0.97 ng/cm^2 and hour (corresponding to 0.0001%–0.003% penetration). About 2%–4% of the applied lead was found in the skin after 2 hours (mean 4.58 µg/cm^2), and about 2%–10% after 24 hours (mean 7.49 µg/cm^2). On the basis of different assumptions regarding exposure and absorption, a daily uptake of 13.8–26.3 µg lead was calculated to take place by dermal absorption (6.5 µg lead/cm^2; 1070 cm^2 of skin; 0.00197% and 0.00342% absorption after 2 and 4 hours, respectively), 67.5 µg by hand-to-mouth contact and 8.4 µg by inhalation. Using the US EPA's "biokinetic slope factor" (0.4 µg/dl per µg/day) and an assumed number of 220 working days per year, it was calculated that hand-to-mouth contact contributes 162 µg lead/l blood, dermal absorption 34.4–63.3 µg/l blood and inhalation 20 µg/l blood to the steady-state blood lead concentration (Julander et al. 2020). However, the calculations of Julander et al. (2020) seem to be incorrect. The value of 0.00197 corresponds to the percentage uptake and accordingly, under the conditions assumed by the authors of a daily exposure to 6.5 µg/cm^2 and a skin surface of 1070 cm^2 (a daily dose of 6955 µg/1070 cm^2), would not lead to a dermal "uptake dose" of 13.8 µg/day, but to 0.138 µg/day. This would mean that the uptake was overestimated by a factor of 100 and the contribution to the blood level would be significantly lower (0.34 µg/l). Even for 2000 cm^2 of skin and 8 hours instead of 2 hours exposure time, the linearly extrapolated contribution (2.6 µg/l) would not be relevant in view of the BAT value of 150 µg/l.

The lead content in the stratum corneum of 10 workers from a factory that produced lead batteries was determined using the tape-stripping method. Before starting work, a total of 10 (5 × 2) adhesive tapes (1.5 × 8 cm per tape) were stripped from the dorsal skin of the workers' hands after washing with soap and ethanol. As a control, adhesive tapes were stripped from unexposed skin on the lower back and blood samples were taken at the same time. The total amount of lead in the 10 strips was in the range from 20.74 to 86.53 µg for the hand and from 8.94 to 28.32 µg for the back. The lead content in the exposed skin decreased from the outer to the inner layers, with almost 48.4% of the total amount in the first 2 strips (calculated according to data in the publication) or 59% when adjusted for the corresponding values from the control strips (also calculated according to data in the publication). The total amount of lead on the

dorsal skin of the hand and in its stratum corneum correlated with the amount in the blood ($n = 10$, $r^2 = 0.66$, $p < 0.05$, linear regression) (Sun et al. 2002).

A 25-mm membrane filter containing 4.4 ± 0.1 mg (0.5 M) lead dinitrate was attached occlusively to the left forearm of 1 test person for 24 hours. One hour after the start of exposure, the lead concentration in the sweat (induced by pilocarpine iontophoresis) of the right forearm was measured. At the end of the exposure, the filter was removed, the skin was washed, and the lead content was determined in the filter and the washing solution. From the difference between the amount recovered and the amount applied, the authors concluded that 29% of the lead had been absorbed into and through the skin. Another test person was exposed to 5 mg lead in the same way, and the lead level was determined contralaterally in the sweat every hour. In the sweat, the lead level increased from an average of 6 µg/l to a maximum of 174 µg/l within 4 hours after the start of exposure. Within the following 2 hours, the lead level dropped back to the background level. Further subjects received applications of ^{204}Pb as lead dinitrate or lead diacetate occlusively or non-occlusively to the arm and lead was determined in the blood, urine and sweat. Occlusive application increased the contralateral sweat lead level from 46 µg/l to 71 µg/l after lead dinitrate administration. Even after occlusive application, the absolute blood lead concentration was not increased, only the proportion of labelled lead by 0.6 µg/l (or 0.5 µg/l with lead diacetate). The situation was similar for the urine lead levels. The absolute excreted amounts were not affected, only the excretion of ^{204}Pb was increased. The authors calculated that about 6% of the increased ^{204}Pb in the blood was excreted in the urine over 24 hours (Stauber et al. 1994).

Similar results were obtained in preliminary studies by this research group. Here, lead levels of up to 800 µg/l in the iontophoresis-induced sweat of workers in a lead battery factory were reported (Florence et al. 1988; Lilley et al. 1988).

Eight male volunteers were given applications of ^{203}lead acetate (0.012 to 0.0186 mg/cm^2) in 2 hair dyes to the forehead for 12 hours (8 or 10 cm^2) and the quantity of lead absorbed was calculated from blood counts, whole-body counts and urine radioactivity at the end of exposure and 12 hours later and compared with the amounts absorbed after intravenous administration of ^{203}lead chloride. In the whole body 0.058% ± 0.081% of the applied dose and in the blood 0.023% ± 0.021% (0.135 µg in the total blood volume) were found (Moore et al. 1980).

In rats (n = 4/group), the urinary excretion of lead compounds, including lead sulfate, lead oxide, metallic lead powder and lead distearate, was determined before and during 12-day dermal application. In each case, 100 mg of lead was applied occlusively to an area of 2 × 6 cm (8.3 mg/cm^2). Before application, urinary excretion of lead in the rats was in the range from 17.4 ± 5.0 ng to 24.2 ± 3.7 ng per 48 hours. After application of the lead compounds for 12 days, the total lead levels in the 48-hour urine increased in a statistically significant fashion to 146.0 ± 6.4 ng for lead distearate, 123.1 ± 7.2 ng for lead sulfate, 115.9 ± 5.3 ng for lead oxide and 47.8 ± 6.9 ng for lead powder. The control animals excreted 10.3 ± 3.9 ng of lead (Sun et al. 2002).

Nude mice were given 0.6 ml of 0.12 M solutions of lead diacetate or lead dinitrate applied semi-occlusively to an area of 1.5 × 1.5 cm every 24 hours (6.6 mg lead/cm^2), and the lead concentrations in the skin, liver and kidneys were determined. The amounts of lead in the skin after the application of lead diacetate were 2.8 times as high as those after the application of lead dinitrate ($p < 0.05$). The concentrations of lead in the liver were about 3–4 times and in the kidneys about 25 times as high as those in the control animals, but significantly lower ($p < 0.05$) than those in the skin (Pan et al. 2010).

Guinea pigs were given different lead salts (including lead naphthenate in petroleum ether, lead diacetate and lead oxide as an aqueous suspension; 300 mg/kg body weight, calculated as lead, for 7 days) applied occlusively to the shaved dorsal skin every day. Blood, brain, liver and kidney samples were then obtained and their lead levels determined. The levels for lead naphthenate were the highest, followed by those for lead diacetate. Lead oxide yielded lead concentrations that were consistent with background lead concentrations. Overall, the highest levels were found in the kidneys. In further studies, investigations of the absorption through the skin were performed with the same lead salts on human skin from autopsy and guinea pig skin (10 mg lead/1.3 cm^2, for 24 hours at 37 °C, guinea pig skin additionally at room temperature). Within 24 hours, 29.7 ± 2.9 µg lead in the case of lead naphthenate and 5.0 ± 0.9 µg lead in the case of lead diacetate penetrated the human skin. Lead oxide was not detectable in the receptor fluid. The

penetration of lead diacetate, lead naphthenate and lead oxide did not differ significantly between human and guinea pig skin, temperature had likewise no influence (Bress and Bidanset 1991).

The penetration of lead from lead diacetate and lead dinitrate through whole skin of nude mice was determined in Franz diffusion cells (120 mM, 0.5 ml on 0.785 cm^2 (≙ 15.9 mg lead/cm^2)). Physiological phosphate-buffered saline served as the receptor fluid. The lead salts were applied in double-distilled water or artificial sweat (pH 5.5) for 10 hours. With intact skin, the cumulative amount absorbed from water was 0.20 and 0.23 µg lead/cm^2 for lead dinitrate and lead acetate, respectively. When the lead salts were applied in artificial sweat, 0.19 and 0.13 µg lead/cm^2, respectively, were absorbed. Absorption into the skin was 14.4 and 11.1 µg lead/mg skin, respectively (Pan et al. 2010). Determination of the potentially absorbable fraction in the skin according to the OECD test guideline was not carried out.

The penetration of lead oxide through human full-thickness skin (thickness 1 mm) was determined in static Franz diffusion cells. The particle size of the lead oxide was less than 10 µm and 5 mg lead oxide/cm^2 was applied in 2 ml artificial sweat (pH 5.0) for 24 hours and then washed off with water. The total amount of lead that penetrated into the receptor fluid (physiological phosphate-buffered saline) in 24 hours was 2.9 ng lead/cm^2 and that into the skin was 321.3 ng lead/cm^2. The authors stated that for 1-µm particles with the density of lead oxide, a monolayer, and thus the saturation of absorption into the skin, can be achieved at a loading of 50 mg/cm^2. According to the literature cited by the authors, the selected loading of 5 mg/cm^2 is much higher than that occurring at the workplace and thus represents a worst case scenario. Using the US EPA adult lead model, the authors estimate that the concentration of lead in the blood could be increased by up to 74 µg/l when lead oxide remains on the skin for a longer period of time after exposure of 4520 cm^2 of skin (Larese Filon et al. 2006). Under the standard assumptions (2000 cm^2 of skin, exposure for 1 hour), at least 2.9 ng/cm^2 × 2000 cm^2 / 24 hours = 241 ng would be absorbed and 321.3 ng/cm^2 × 2000 cm^2 / 24 hours = 26.8 µg would be stored intradermally. Determination of the potentially absorbable fraction in the skin according to the OECD test guideline was not carried out. Using the US EPA biokinetic slope factor and assuming 220 working days per year, a blood lead concentration of 2.9 ng/cm^2 × 2000 cm^2 = 5.8 µg/day × 0.4 µg/dl/µg/day × 220/365 = 14 µg/l would result, which is below 25% of the BAT value.

Conclusion: Even under worst-case conditions, it cannot be derived from the available studies that dermal absorption of lead contributes significantly to systemic toxicity. However, hand-to-mouth contact can significantly increase the blood lead levels in the case of poor hygiene at the workplace.

3.2 Metabolism

As a metal, lead is not subject to metabolism.

4 Effects in Humans

The current background level of lead in the whole blood of students from Münster, Germany, was recorded in the environmental specimen bank. It fell from over 70 µg/l blood (1981) by about 83% within 26 years to values below 15 µg/l blood (2008). In recent years, lead exposure has remained consistently low, so that the mean blood lead concentration in 2018 was only about 10 µg/l. Similar blood lead levels have now been determined among students at the other sites in Germany, in Halle/Saale, Ulm and Greifswald (Umweltbundesamt 2021).

4.1 Single exposures

After acute intoxication, blood lead levels of more than 1250 µg/l blood led to functional disorders of the kidneys (Greim 2002 b).

4.2 Repeated exposure

After repeated exposure, neurotoxicity, renal toxicity, cardiovascular diseases, fertility disorders and haematological effects have been observed in humans. Detailed descriptions can be found in ATSDR (2020 b), ECHA (2020 a) and Greim (2002 b).

A comparison of the various effects and their corresponding blood lead concentrations shows that neurotoxicity is to be regarded as the most sensitive end point.

A detailed presentation of lead-induced neurotoxicity in case–control studies and cohort studies is given in the addendum to the evaluation of the BAT value (Greiner et al. 2022).

Some recent studies of large cohorts are summarized below.

A cohort study of workers exposed to lead from 3 cohorts in the USA, Finland and the UK, that included more than 88 000 workers with more than 14 000 deaths, found a median blood lead concentration of 260 µg/l. The classification of blood lead concentrations into the 3 categories 200–300 µg/l, 300–400 µg/l and > 400 µg/l revealed a positive trend for chronic obstructive pulmonary disease (COPD; hazard ratio (HR): 1.43, 1.31, 1.84; $p < 0.0001$), stroke (HR: 1.24, 1.49, 1.41; $p = 0.0002$), ischaemic heart disease (HR: 1.14, 1.16, 1.41; $p < 0.0001$) and mortality (HR: 1.15, 1.21, 1.43; $p < 0.0001$), but not for kidney disease. The standardized mortality ratio (SMR) was 1.33 (95% CI 1.16–1.47; $p < 0.05$) for COPD, 1.02 (95% CI 0.96–1.07) for ischaemic heart disease and 0.99 (95% CI 0.87–1.09) for stroke among workers with a blood lead level > 400 µg/l. The SMR was not adjusted for kidney disease. Adjustments were made for sex, year of birth and country. The available data for the smoking behaviour of a subgroup (n = 115) of the cohort from the USA did not reveal a correlation between pack-years and the maximum blood lead levels. There were also no differences in the maximum blood lead levels ($p = 0.80$) between ever smokers and never smokers. The authors point out that the observed effects may be attributed to smoking. Information on the smoking behaviour of the entire cohorts is not available (Steenland et al. 2017).

In a sub-cohort (211 volunteers) of the Adult Blood Lead Epidemiology and Surveillance Program (since 1987), bone lead levels were determined and correlated with the blood lead concentrations. The median bone lead level was 13.8 µg/g (95% CI 9.4–19.5 µg/g), the maximum blood lead level from previous determinations in this programme was 290 µg/l (95% CI 140–380 µg/l), and the participants' current blood lead level was 25 µg/l (95% CI 15–44 µg/l), determined in 2016–2017. A statistically significant association between the blood lead levels and the bone lead levels was determined ($p < 0.0001$). Increased bone lead levels, but not the current blood lead levels, correlated with increased systolic blood pressure. There was no correlation between the glomerular filtration rate and blood lead or bone lead concentrations. Thus, lead had no effect on this renal function (Barry et al. 2019).

A cohort of 58 307 workers who were exposed to lead was followed for a median of 18 years. The maximum blood lead level was 260 µg/l. The incidence of end-stage renal disease (ESRD) was assessed according to the US Renal Data System. There were 524 cases of ESRD and a total of 6527 deaths. An association between ESRD and increasing blood lead levels was not observed (Steenland and Barry 2020).

The evaluation of mortality in a cohort of 58 368 persons occupationally exposed to lead (with a median follow-up period of 12 years) from 11 states in the USA did not reveal any increased SMRs for stroke, COPD, ischaemic heart disease and chronic kidney disease. Subdivision into blood lead levels of 0–49, 50–249, 250–399 and ≥ 400 µg/l revealed relative risks (RR) for stroke of 1.00, 1.12, 1.76 and 1.88 ($p = 0.095$ (trend test)), for COPD of 1.00, 0.30, 0.50 and 0.85 ($p = 0.02$ (trend test)), for ischaemic heart disease of 1.00, 1.13, 1.46 and 1.77 ($p < 0.0001$ (trend test)) and for chronic kidney disease of 1.00, 0.39, 0.73 and 1.52 ($p = 0.04$ (trend test)). The analysis of data from a subgroup of 92 individuals whose blood lead concentrations were studied over 20 years and were above 250 µg/l yielded an SMR of 0.79. After subdivision of this subgroup into blood lead concentrations of 250–399 µg/l and ≥ 400 µg/l, SMRs of 0.43 (95% CI 0.09–1.27; n = 3) and 1.14 (95% CI 0.65–1.85; n = 16) were calculated for COPD. The authors assumed a marked healthy worker effect. In addition, they reported that data for smoking behaviour and workplace history were not collected (Chowdhury et al. 2014).

A follow-up study in a cohort of 4525 workers (3102 women and 1423 men) from 27 printing plants in Moscow did not find a statistically significant increase in the SMRs for circulatory disease, ischaemic heart disease, stroke and

chronic kidney disease. Determinations of lead in the air in 40 printing plants yielded values of 0.001 to 2.7 mg/m^3 (Section 4.7.2; Ilychova and Zaridze 2012).

In a cohort of 1990 male employees of a lead smelter in Idaho, USA, who were employed between 1940 and 1965, a follow-up study of the vital status was performed after 25 years. The update added 13 823 person-years at risk and 721 deaths. After subdividing the cumulative lead exposure into 0–208 mg/m^3-days, 209–757 mg/m^3-days and > 757 mg/m^3-days, dose-dependent increases in cardiovascular diseases (RR: 1, 1.06, 1.19; p = 0.04 (trend test)), chronic kidney diseases (RR: 1, 0.94, 1.76; p = 0.14 (trend test)) and stroke (RR: 1, 1.13, 1.38; p = 0.13 (trend test)) were found. The data were adjusted for age (Bertke et al. 2016).

A cohort of 9122 workers (7770 male, 1352 female) with at least one blood lead determination between 1975 and 1979 was classified according to exposure in relation to the occupational exposure limit (OEL) as low (< 10% OEL), medium (10%–50% OEL) and high (> 50% OEL), with an OEL of 0.15 mg lead/m^3 or 0.1 mg organic lead compounds/m^3. The mean follow-up period was 29.2 years and 3466 deaths were recorded. The SMRs were not increased with statistical significance for kidney disease, but a borderline statistically significant increase was found for circulatory diseases at 1.05 (95% CI 0.99–1.10), ischaemic heart disease at 1.06 (95% CI 0.99–1.13) and cerebrovascular diseases at 1.16 (95% CI 1.00–1.34). The HRs reached statistical significance (p < 0.001) at the mean and maximum blood lead levels with values of 1.30 (95% CI 1.17–1.44) and 1.25 (95% CI 1.14–1.37), respectively, for circulatory diseases and with 1.30 (95% CI 1.17–1.43) and 1.23 (95% CI 1.11–1.34), respectively, for ischaemic heart diseases. The data were adjusted for age, sex and co-exposure to arsenic and cadmium (McElvenny et al. 2015).

Conclusion: Also in recent cohort studies, a significant increase in cardiovascular diseases, and nephrotoxic and haematological effects occurred only above a blood lead level of about 400 µg/l.

4.2.1 PBPK (physiologically-based pharmacokinetic) model for deriving a MAK value

As already described, correlations were found between adverse effects and blood lead concentrations; thus, observance of the BAT value is the decisive parameter for the avoidance of adverse effects caused by lead exposure. Nevertheless, in order to limit exposure also via the air, an additional limit value for airborne exposure is necessary. However, in earlier evaluations based on data for very high exposure levels, the relationship between the lead concentrations in air and blood was found to have a large range of scatter; in addition, determination of the blood lead levels corresponding to the lead concentrations in the air was carried out up to 2 months later (Kentner and Fischer 1994). However, a much more detailed model is now available that allows the derivation of a limit value in air that is intended to ensure compliance with the BAT at the 95th percentile level. With the help of model calculations, the Office of Environmental Health Hazard Assessment (OEHHA) and the California Environmental Protection Agency (CalEPA) (2014) estimated the relationship between airborne and blood lead concentrations under different assumptions and conditions. The Leggett model takes into account the oral and inhalation exposure of the general population. The calculations performed to derive an occupational air exposure limit were carried out using an adapted Leggett model, referred to as Leggett+. Data for the uptake in blood, urine and bone from studies with chronically exposed workers, for the clearance of lead from blood, urine and bone, and data for background exposure in the population were included in the model calculations. In addition to the data required in the Leggett model, exposure conditions at the workplace were included in the Leggett+ model calculation. This includes the respiratory volume (26 m^3/day, of which 14.4 m^3 per 8-hour work shift) and a coefficient that takes into account the transfer of inhaled lead into the blood with 100% absorption of the lead particles deposited in the alveolar region as well as the lead deposited in the upper respiratory tract, swallowed and absorbed in the gastrointestinal tract. This transfer, taking into account the size of the particles (mass median aerodynamic diameter, MMAD 1.3–15.1 µm) at the workplace according to Park and Paik (2002) as well as 5 different activity levels (resting, sitting, light, moderate and heavy activity) of the employees, averages 30% (28%–32%). Thus, a coefficient ("inhalation transfer coefficient", ITC) of 0.3 is used. In order to represent the situation at the workplace well, the background exposure of 15 µg lead/l blood present in the general population in the USA was taken into account; according to the environmental specimen bank, this also corresponds roughly to the current background exposure in Germany. Further assumptions included in the model calculation were: age at

the start of exposure to lead at the workplace of 25 years, duration of exposure at the workplace of 40 years with 250 workdays per year, changes in bone lead levels due to decreasing environmental exposure and a mean body weight of the employees of 73 kg. The Leggett+ model used here assumes a non-linear relationship between blood lead levels and airborne lead concentrations. The authors attribute this non-linear relationship to the saturation of erythrocytes with lead at high blood plasma lead levels. The results of this model calculation led to corresponding values for the lead concentration in air (time-weighted average (TWA) for a reference period of 8 hours) and the blood lead concentration. Table 1 shows the blood lead levels corresponding to airborne lead concentrations (where the blood lead level is not exceeded in 95% of the exposed persons) calculated with the model using the distribution of blood lead levels in the general population. It can be seen from Table 1 that 8-hour exposure to 3.9 µg lead/m^3 does not result in a blood lead level of more than 150 µg/l in 95% of those exposed. Data from a workplace study in workers exposed to lead for many years, which included information on exposure to lead in the air and blood lead values, and a study in volunteers with an exposure duration of up to 123 days and exposure to a low concentration of lead in the air of 3.2 µg/m^3, were compared with the calculated values of this model and showed very good agreement. Thus, the corresponding air and blood lead values calculated by the model have been matched by studies with chronic lead exposures (Leggett 1993; OEHHA and CalEPA 2014; Umweltbundesamt 2021). The Leggett model used by OEHHA und CalEPA (2014) has also been published in a peer-reviewed journal (Vork and Carlisle 2020).

Tab. 1 Relationship between lead concentrations in air and calculated blood lead levels (OEHHA and CalEPA 2014)

8-Hour TWA (µg lead/m^3)	Calculated blood lead level (µg/l) for the 95th percentile
0.5	50
0.8	60
2.1	100
2.4	110
2.8	120
3.9	150
5.0	180
7.5	240
10.4	300

Model calculations of this kind always include assumptions; these must reflect workplace conditions as best as possible. In the present case these were chosen very carefully and justified in great detail (OEHHA and CalEPA 2014). Only the most important parameters are mentioned here. The respiratory volume at the workplace was chosen to be 14.4 m^3/8 hours (equivalent to 30 l/minute); this corresponds to a moderate activity level and is somewhat higher than the value of 10 m^3/8 hours usually assumed when deriving MAK values. Another important parameter was the estimation of the amount of lead absorbed with different lead compounds and particle size ranges. For this purpose, data from 14 different industrial workplaces from 5 industries with a wide range of lead particle sizes were evaluated. In addition, the deposition of the particles as a function of the compound form and particle size was calculated using the MPPD2 model (Multi-path Particle Dosimetry Version 2 model) and the proportion of inhaled lead transferred into the blood was calculated. Finally, the proportion of the blood lead concentration that is absorbed through background exposure (mainly airborne and dietary) was calculated. Both past exposures and current exposures were taken into account; the latter were included in the model calculation with an assumed level of 15 µg lead/l blood and, according to the latest figures from the environmental specimen bank (Umweltbundesamt 2021), also correspond to the current exposure level in Germany. Finally, the model was tested against 2 selected exposure situations for which both determinations of lead in air and the lead levels in blood are well documented. These are a volunteer study and a workplace study, which show excellent agreement with the modelled data. This applies also to the concentration range of the MAK value of 0.004 mg/m^3. Thus, this model substantially refined the wide range of scatter of the values determined on the basis of earlier exposure data by Kentner and Fischer (1994) for the relationship between airborne

and blood lead levels. A detailed presentation of the parameters used in this model calculation and their justification, and a corrected table (Errata sheet "Table A-2: Estimate of fit of predicted to observed BLLs for 47 smelter workers") can be found in OEHHA and CalEPA (2014).

Another PBPK model established by O'Flaherty (1993) was updated using data from blood lead determinations in workers exposed to lead carried out by the Department of Defense (DOD), USA. This resulted in airborne concentrations of 1.1, 4.0, 6.8 and 9.8 µg lead/m^3 for the 95th percentile at blood lead concentrations of 50, 100, 150 and 200 µg/l, respectively. The DOD-O'Flaherty model differs from the Leggett+ model in the different data on which intercompartmental transfer and exposure parameters are based. As it is not possible to model the amount of lead taken up by inhalation, the exposure parameters are included in the calculation by calendar year (Sweeney 2021). The PBPK calculations according to the Leggett+ and the DOD-O'Flaherty model yield airborne lead values of 3.94 µg/m^3 and 6.8 µg/m^3, respectively, for the 95th percentile at a blood lead concentration of 150 µg/l, and are thus close to each other despite the different models and the different assumptions used in the calculation.

4.3 Local effects on skin and mucous membranes

Inorganic lead compounds did not cause skin and eye irritation in several studies carried out according to OECD Test Guidelines 404 and 405 (ECHA 2021 a).

4.4 Allergenic effects

In addition to 3 case reports already described in the supplement from 2000 (Greim 2002 b), only 1 new report is available. In this report, patch tests with lead dichloride as a 0.2% aqueous solution (commercial patch test preparation) and lead diacetate trihydrate as a 0.5% aqueous solution were carried out in 39 persons during investigations for the diagnosis or prediction of allergies to metallic implants. No reaction was observed in any patient (Spiewak 2018).

4.5 Reproductive and developmental toxicity

The developmental toxicity of lead has been known for a long time. The main focus is on disorders in the development of the central nervous system, for which there is sufficient consistent evidence from prospective studies and large cross-sectional studies in children. The following effects have been observed: decreases in neurological functions, including decreases in cognitive functions (learning and memory), changes in behaviour and mood (attention, hyperactivity, impulsivity, irritability, delinquency), and changes in neuromotor and neurosensory functions (visual motor integration, dexterity, balance, changes in hearing and visual thresholds). A NOAEL (no observed adverse effect level) for developmental neurotoxicity could not be established. The detailed data are given in the addendum to the evaluation of the BAT value (Greiner et al. 2022).

4.6 Genotoxicity

In current and very detailed reports by various bodies (AGS 2017; ATSDR 2020 b; ECHA 2020 a; RAC 2020) and the Commission (Greim 2002 b, 2009) numerous studies are described that have found clastogenic effects in workers occupationally exposed to lead. In many studies, the number of participants is below 100 and exposure to other substances cannot be excluded. In addition, the observed effects were often not listed separately according to smoking status, and other confounders (see below) were not taken into account. This makes interpretation of the study results problematic. Thus, the derivation of a blood lead value at which no clastogenic effects are observed or the possibility, despite methodological shortcomings, of deriving a LOAEC (lowest observed adverse effect concentration) becomes difficult.

In the report of ECHA (2020 a), studies from 2000 onwards are described in detail and assessed. Associations between elevated blood lead levels and increases in chromosomal aberrations, micronuclei, sister chromatid exchanges, DNA strand breaks in the comet assay, DNA–protein crosslinks and T-cell receptor mutation frequencies are demonstrated. Uncertainties in the studies due to small case numbers and lack of adjustment for confounders such as smoking

behaviour are pointed out. The uncertainties concern studies in which clastogenic effects occurred at blood lead levels even below 300 µg/l; these studies were therefore classified as not relevant for the evaluation. Based on the available studies, ECHA derived a LOAEC of 300 µg lead/l blood (ECHA 2020 a).

In the report of ATSDR (2020 b), also studies in children/adolescents and environmental studies were included in the evaluation. However, these are not considered in the derivation of MAK values. The studies listed in ATSDR (2020 b) with a mean blood lead concentration of < 300 µg/l in occupationally exposed persons and significant genotoxic effects cannot be considered for the following reasons: no controls given (Kayaaltı et al. 2015), not adjusted for confounders sufficiently (Pinto et al. 2000), blood lead concentrations given as a range that is up to a level of markedly above 300 µg/l for exposed persons, but the genotoxic effects are not assigned to the exact blood lead level (Danadevi et al. 2003), exposed persons not clearly characterized ("workers of construction area"), so that exposure to other substances and overlapping blood lead levels in controls and exposed persons may be assumed (Akram et al. 2019), workers who were exposed to lead from the environment and cadmium and mercury as confounders (Al Bakheet et al. 2013). The other studies were already mentioned in ECHA (2020 a) (ATSDR 2020 a, b).

Table 2 shows the relationship between blood lead concentrations and cytogenetic effects observed in workers occupationally exposed to lead. Table 2 does not include many studies in which genotoxic effects occurred only at significantly higher blood lead levels of > 400 µg/l. This often applies to earlier studies, and it must also be taken into account that the blood lead levels of the controls used to be significantly higher due to environmental pollution. Likewise, Table 2 does not include studies, despite blood lead levels < 400 µg/l, that did not report the genotoxic effects in the exposed persons separately according to smoking status (Duydu and Süzen 2003; Fracasso et al. 2002; Kašuba et al. 2012).

Tab. 2 Selection of statistically significant increases in genotoxic findings in vivo after occupational exposure and the assigned blood lead concentrations (as the LOAEC) (ECHA 2020 a)

Blood lead concentration (LOAEC)	End points	References
250–400 µg/l	micronuclei in lymphocytes	Vaglenov et al. 2001
431.7 µg/l	comet assay in lymphocytes	Olewińska et al. 2010
320 µg/l	ALAD ↓ in erythrocytes, T-cell receptor mutations in leukocytes, micronuclei in leukocytes, comet assay in leukocytes, polymorphism, DNA repair	García-Lestón et al. 2012
301 µg/l	comet assay in lymphocytes, micronuclei in lymphocytes and oral mucosa cells, chromosomal aberrations in lymphocytes	Chinde et al. 2014
285.8 µg/l	comet assay in lymphocytes, DNA repair in lymphocytes	Jannuzzi and Alpertunga 2016
325 µg/l	sister chromatid exchange in lymphocytes, protein–DNA crosslinks in leukocytes	Wu et al. 2002
354 µg/l	micronuclei in lymphocytes	Minozzo et al. 2004
303 µg/l	micronuclei in lymphocytes and oral mucosal cells, comet assay, chromosomal aberrations in lymphocytes	Grover et al. 2010
320 µg/l	micronuclei in lymphocytes	Chen et al. 2006

ALAD: aminolevulinic acid dehydratase activity

Conclusion: Clastogenic effects are observed after occupational exposure to lead. From the available reports with detailed descriptions (AGS 2017; ATSDR 2020 b; ECHA 2020 a) it can be concluded that cytogenetic effects are likely to occur at blood lead levels of 300 µg/l and above. At lower blood lead levels, the data are inconsistent, with heterogeneous individual results and uncertainties concerning the respective findings.

Epigenetics

Hypomethylation and hypermethylation of DNA were observed in workers with elevated blood lead levels (de Araújo et al. 2021; Devóz et al. 2017; Zhang et al. 2019) and a correlation was found between blood lead levels, increasing methylation of tumour suppressor genes and an increased number of micronuclei in the lymphocytes (Yu et al. 2018). In the studies, the blood lead levels were given as ranges. The effects can probably be assigned to the highly exposed workers, but this is not clear from the data; therefore the derivation of a LOAEC is not possible (Yu et al. 2018).

Summaries of the data can be found in the reports of ATSDR (2020 b), ECHA (2020 a) and US EPA (2014).

4.7 Carcinogenicity

4.7.1 Case–control studies

The cases of renal cell carcinomas occurring between 1999 and 2003 in hospitals in Poland, the Czech Republic, Romania and Russia were related to occupational exposure to heavy metals in a case–control study. In 80 persons occupationally exposed to lead, the odds ratio (OR), in relation to 71 control persons, was 1.55 (95% CI 1.10–2.19). The length of exposure and the cumulative exposure to lead were not dose-dependent with regard to the occurrence of renal cell carcinomas, with the exception of the quartile of the workers exposed to the highest levels. Here, the OR was 2.25 (95% CI 1.21–4.19; n = 27). The study data were adjusted for age, sex, smoking behaviour, body mass index, hypertension and co-exposure to other metals (Boffetta et al. 2011).

In a case–control study (INTEROCC, with 7 participating countries: Australia, Canada, France, Germany, Israel, New Zealand and the United Kingdom) with 1906 cases of adult meningioma recruited between 2000–2004 and 5565 people from the general population as a control group, no clear association between lead exposure and cancer was observed. The OR was 1.02 (95% CI 0.79–1.32) (Sadetzki et al. 2016).

The metal levels in brain tissue, whole blood and plasma of glioblastoma patients (n = 47) and control subjects (n = 200) were determined. The concentrations of copper, selenium and cadmium in the blood and plasma of glioblastoma patients were lower ($p < 0.05$) and the concentrations of lead ($p < 0.05$) in the blood were higher compared with the values of the control group. Changes in plasma zinc concentrations were insignificant. The blood lead concentration was directly related to the blood cadmium concentration in the control group ($p < 0.05$). In patients younger than 55 years, the concentrations of lead and cadmium in the blood were lower than in patients older than 55 years ($p < 0.05$). Among glioblastoma patients, higher blood cadmium and lead levels were found in males than in females ($p < 0.05$) (no other details in English; Janušauskaitė 2020; Lithuanian).

4.7.2 Cohort studies

In the following, recent epidemiological studies that found statistically significant increases in the risk for cancer are described in more detail.

In a study already cited in Greim (2009), a statistically significant dose–response relationship between the blood lead level and the occurrence of 16 gliomas was demonstrated in 20 741 workers. In the group of workers with the highest exposure to lead (290–891 µg lead/l blood), the adjusted OR was 11 (95% CI 1.0–630) with a trend test p-value of 0.037. The wide confidence interval is due to the very small sample of 16 cases and thus it is unclear whether the gliomas can be attributed to lead exposure alone (Anttila et al. 1996). A study with significantly higher blood lead concentrations in workers could not confirm this result (Greim 2009; Wong and Harris 2000).

Blood samples were taken from 154 people with kidney tumours and 308 control subjects embedded in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study and the lead concentrations were determined. All persons examined were male and smokers. Classification of the studied subjects into exposure groups of < 250 µg lead/l blood (n = 27, as reference group), 250–330 µg/l (n = 31), 331–466 µg/l (n = 40) and > 466 µg/l (n = 38) yielded ORs for renal cell carcinomas of 1.00 (95% CI 0.6–2.0), 1.1 (95% CI 0.6–32.0), 1.8 (95% CI 1.0–3.6) and 2.0 (95% CI 1.0–3.9) and thus a positive trend

with p = 0.022. Data were adjusted for age, smoking behaviour, body mass index, alcohol consumption, systolic blood pressure, serum calcium concentrations and polymorphisms in the calbindin D28K promoter (Southard et al. 2012).

A study of mortality in workers exposed to lead from 3 cohorts in the USA, UK and Finland found a median blood lead level of 260 µg/l. The study included 88 187 workers with 14 107 deaths, of which 3881 were from cancer. The first blood lead determinations were carried out in 1967, 1977 and 1997 and the last determinations in 2010, 2011 and 2013. 96% of the workers were male. The SMR was greater than 1 ($p < 0.05$) for tumours of the bladder (1.54, 95% CI 1.13–1.88), lung (1.38, 95% CI 1.26–1.48) and larynx (1.80, 95% CI 1.03–2.46) among workers with a blood lead level > 400 µg/l. Classification by blood lead levels of 200–300 µg lead/l blood, 300–400 µg/l and > 400 µg/l yielded HRs with a positive trend for lung cancer ($p < 0.0001$), bladder cancer ($p < 0.06$ (trend test)), brain cancer and larynx cancer (both $p < 0.09$ (trend test)). The analysis of data for the smoking behaviour of a subgroup (n = 115) of the cohort from the USA did not reveal a correlation between pack-years and maximum blood lead concentrations. There were also no differences between "ever smokers" and "never smokers" in their maximum bone lead concentrations ($p = 0.80$). The authors point out that the observed effects could also be attributed to smoking. Information on the smoking behaviour of the entire cohorts is not available. Data were adjusted for sex, birth decade and country (Steenland et al. 2017).

In another study of the cohorts from Finland with 20 752 workers and the UK with 9122 workers exposed to lead, 6790 cancer cases were observed. 13% of the workers were female. The blood lead levels were determined at least once in the workers; the highest blood lead level determined in each case was used as the exposure concentration for subdivision into groups. The combined cohorts had a median maximum blood lead level of 230 µg/l. The workers were divided into 4 groups of < 200 µg/l, 200–299 µg/l, 300–399 µg/l and ≥ 400 µg/l. The < 200 µg/l group represented the control group with an HR of 1. This group included 41% of those exposed. A statistically significant positive trend, calculated using the log maximum blood lead concentration, was found for malignant brain tumours (HR 1.42; 95% CI 1.01–2.00), Hodgkin's lymphomas (HR 1.70; 95% CI 1.01–2.84), lung cancer (HR 1.34; 95% CI 1.21–1.48) and rectal carcinomas (HR 1.30; 95% CI 1.06–1.59). A positive trend, which was not statistically significant, was seen for oesophageal cancer and meningiomas. No positive association with the blood lead level was found for melanomas, stomach, kidney, larynx, bladder and breast cancer. The standardized incidence ratio of the combined cohorts (national rates as the referent) was increased in a statistically significant manner ($p < 0.05$) for lung cancer in the group of workers with the highest exposure (blood lead level ≥ 400 µg/l). When both countries were evaluated individually, however, only the Finnish cohort had significantly elevated results. The data were adjusted for sex, decade of birth and country (Steenland et al. 2019). When the cohorts from Finland and the UK were analysed individually, it was found that the HRs for lung cancer and brain tumours were increased in a statistically significant manner only in the Finnish cohort, although the median blood lead level of 480 µg/l blood in the UK was markedly higher than the median blood lead level in Finland of 190 µg/l.

The evaluation of the mortality in a cohort of 58 368 persons occupationally exposed to lead (with a median follow-up period of 12 years) from 11 states in the USA yielded SMRs of 1.2 (95% CI 1.03–1.39) for lung cancer and 2.11 (95% CI 1.05–3.77) for larynx cancer in the group exposed to ≥ 400 µg lead/l. There were no statistically significant increases in SMRs for other tumours in this group (SMR 0.83 for brain tumours, 0.72 for kidney tumours and 0.92 for stomach cancer), nor in the persons exposed to lower concentrations of lead. Subdivision into blood lead levels of 0–49, 50–249, 250–399 and ≥ 400 µg/l yielded relative risks (RR) for lung cancer of 1.00, 1.34, 1.88 and 2.79 ($p < 0.0001$ (trend test)), for kidney cancer of 1.00, 2.41, 1.31 and 1.70 ($p = 0.62$ (trend test)) and for stomach cancer of 1.00, 0.24, 0.52 and 0.64 ($p = 0.49$ (trend test)). After analysing the data from a subgroup of 92 people whose blood lead levels were studied over 20 years and were > 250 µg/l, the SMR was 0.79 for all causes of death. Subdividing this subgroup into blood lead levels of 250–399 µg/l and ≥ 400 µg/l resulted in SMRs for lung cancer of 0.83 (95% CI 0.40–1.52; n = 10) and 1.35 (95% CI 0.92–1.90; n = 32), respectively. The authors assume a marked healthy worker effect. In addition, data for both smoking behaviour and workplace history were not collected (Chowdhury et al. 2014).

In 2 cohorts of 73 363 female and 61 379 male participants in the Shanghai Women's Health Study and the Shanghai Men's Health Study, 8.9% (6274) and 6.9% (4256), respectively, were occupationally exposed to lead. Depending on the occupation, those exposed to lead were classified in low or high exposure groups. An association between lead exposure and the occurrence of meningiomas was observed with a relative risk (RR) of 2.4 (95% CI 1.1–5.0; n = 9 compared

with n = 38 not exposed) only in the women. The RRs of both sexes combined (which were not statistically significant) were 1.8 (95% CI 0.7–4.8; n = 10) for brain cancer and 1.4 (95% CI 0.9–2.3; n = 17) for kidney cancer. In men, there was a lead-dependent increase in the RR for kidney cancer from 0.5 (95% CI 0.1–3.2; n = 1) in the group with low exposure to an RR of 2.3 (95% CI 1.1–4.7; n = 8) in those with high exposure. There was no association with lead exposure for lung and stomach cancer in this cohort. The data were adjusted for socioeconomic status and smoking behaviour (Liao et al. 2016). Blood lead concentrations were not reported in this study.

A follow-up study of a cohort of 4525 workers (3102 women and 1423 men) from 27 printing plants in Moscow did not reveal a significantly increased risk for any cancer site. In the men and women, the SMRs were 1.24 (95% CI 0.39–3.84) and 0.71 (95% CI 0.23–2.19) for brain tumours (n = 3 and 3, respectively), 1.26 (95% CI 0.46–2.75) and 1.42 (95% CI 0.57–2.93) for kidney cancer (n = 6 and 7, respectively), 0.82 and 0.96 for stomach cancer (n = 24 and 34, respectively) and 0.94 and 0.48 for lung cancer (n = 40 and 7, respectively). Analysis of the air in 40 printing plants in 1974 yielded levels of 0.01 to 2.7 mg lead/m^3 in manual typesetting shops, up to 1.8 mg lead/m^3 in type foundries and 0.001 to 0.88 mg lead/m^3 in mechanical typesetting. In determinations in the 1980s in 20 printing plants, the lead concentrations were < 0.05 mg/m^3 in the manual typesetting shops and type foundries and < 0.01 mg/m^3 in the mechanical typesetting shops. Based on these determinations and the respective employment, individual cumulative exposures were calculated and classified as low (< 10 unit-years), medium (10–29 unit-years) and high (≥ 30 unit-years). Classification of the workers' lead exposure by occupational field and workplace history into low, medium and high lead exposure revealed a dose dependence with increased SMRs for pancreas cancers of 2.32 (95% CI 1.46–3.68) and kidney cancers of 2.12 (95% CI 1.10–4.07) in the high exposure group. Adjustment was made only for age (Ilychova and Zaridze 2012).

In a cohort of 1990 male employees of a lead smelter in Idaho, USA, who were employed between 1940 and 1965, a follow-up study of vital status was carried out after 25 years. 13 823 person-years at risk were calculated and 721 deaths were recorded. The SMRs were 1.29 (95% CI 1.16–1.43) for all tumour cases, 1.56 (95% CI 0.78–2.79) for kidney cancer, 1.31 (95% CI 0.67–2.28) for stomach cancer and 1.94 (95% CI 1.64–2.27) for lung cancer. However, the calculated RRs for the cancers that occurred showed the tumours not to be dependent on the cumulative dose (Bertke et al. 2016).

A cohort of 9122 UK workers (7770 male, 1352 female) with at least one blood lead determination between 1975 and 1979 was classified in low (< 10% OEL), medium (10%–50% OEL) and high (> 50% OEL) exposure groups at an OEL of 0.15 mg lead/m^3 or 0.1 mg organic lead/m^3. The mean follow-up period was 29.2 years and 3466 deaths occurred. The mean blood lead level was 443 µg/l (2.3–3215 µg/l). The SMR for all malignant neoplasms was increased in a statistically significant manner at 1.13 (95% CI 1.07–1.20), as was the SMR for lung cancer at 1.42 (95% CI 1.29–1.57). The SMRs were not significantly increased for brain cancer at 0.92 (95% CI; 0.61–1.38), kidney cancer at 1.30 (95% CI 0.91–1.86; n = 5), stomach cancer at 1.11 (95% CI 0.86–1.43), bladder cancer at 0.95 (95% CI 0.6–1.35) and oesophageal cancer at 1.05 (95% CI 0.78–1.38). The calculated HRs showed the tumours not to be dose dependent; this was true even for lung cancer. The data were adjusted for age, sex and co-exposure to arsenic and cadmium (McElvenny et al. 2015).

In a cohort study of 81 067 workers (54 788 male and 26 279 female) from the lead industry, statistically significant increases were observed in the risks for colorectal cancer in female workers with an RR of 13.42 (95% CI 1.21–149.4; exposure group: 100–200 µg lead/l blood) and for lung cancer with an RR of 10.45 (95% CI 1.74–62.93; exposure group: 100–200 µg/l blood) or an RR of 12.68 (95% CI 1.69–147.86; exposure group: > 200 µg/l blood). There were no statistically significant increases in the risks of all cancers occurring in the male employees. In addition to colorectal cancer and lung cancer, also the risks of developing liver or stomach cancers were investigated (ATSDR 2020 b; Kim et al. 2015).

4.7.3 Meta-analyses

A meta-analysis of 18 cohort or case–control studies of the occurrence of malignant and benign brain tumours after occupational exposure to lead yielded an OR of 1.11 (95% CI 0.95–1.29). If only malignant brain tumours were considered, the OR was 1.13 (Ahn et al. 2020). The significance of the meta-analysis is limited due to methodological problems, such as the multiple inclusion of results from the same study population from different publications.

Further meta-analyses are presented in the supplement from 2007 (Greim 2009).

4.7.4 Evaluations from other bodies

The report of ECHA (2020 a) provides a tabular overview of relevant recent epidemiological studies assessing the association between exposure to lead compounds and cancers of the brain, kidney, stomach and lung. Other studies without statistically significant increases in cancer risks calculated as the HR, OR, RR, SMR or trends in relation to increasing blood lead levels can be found there. Since these studies did not yield statistically significant findings, they are not described in detail here.

RAC (2020) considered the epidemiological data to be inconsistent.

ATSDR (2020 b) likewise presents epidemiological studies of the relationship between the blood lead levels of occupationally exposed persons and cancer incidences in tabular form. The studies listed with statistically significant increases in cancer incidences were already cited in Greim (2002 b, 2009) or described in detail above. A detailed presentation of further studies without statistically significant effects can be found in the reports of the ATSDR (2020 a, b).

ATSDR (2020 b) assessed the data as follows: "Results of occupational exposure studies are mixed and do not establish a pattern of effects of exposure–response relationship. PbBs in these studies generally are >40 µg/dl. ...Although results of these studies are mixed and interpretation may be limited due to confounding factors, associations have been reported between occupational exposure to Pb and cancer, including overall mortality and cancers of the lung, brain, stomach, kidney, and bladder."

4.7.5 Summary

Increased risks for lung, kidney or brain cancer have not been observed in all studies. In some studies with increased risks for lung cancer, smoking behaviour was not considered as a confounder. Also other biases in the cohort studies can be assumed, since data for co-exposures, body mass index, age and socioeconomic factors were not consistently collected. Overall, the studies give no clear indication that lead has carcinogenic effects in humans, even at high exposure levels.

5 Animal Experiments and in vitro Studies

Neurotoxic, nephrotoxic, cardiovascular and immunotoxic effects as well as changes in haematological and reproductive parameters have been observed after repeated administration of lead (Greim 2002 b).

Animal studies of the toxicology of lead play only a minor role compared with the extensive data available for humans. Therefore, only the end points relevant for humans are presented below.

Allergenic effects

Sensitizing effects on the skin

In a local lymph node assay (LLNA) carried out in groups of 4 CBA-Ca mice, already described in the supplement from 2000, a negative result was obtained with 2.5%, 5% and 10% **lead diacetate** in dimethyl sulfoxide (Basketter et al. 1999).

In a recent LLNA with 10%, 25% and 50% **lead dinitrate** in dimethylformamide, only the test with the concentration of 25% yielded a positive result in the first of 2 experiments; this concentration caused severe irritation in the second experiment. Furthermore, also the concentrations of 10% and 50% yielded a positive result in the second experiment, but here without evidence of irritation (ECHA 2018). Due to the lack of plausibility of the test results, no conclusions can be drawn as regards the sensitizing effect of lead dinitrate.

There is also a new maximization test in guinea pigs with negative results available for **lead oxide**, which is included in the ECHA database and described in the registration dossiers for several substances, such as lead (ECHA 2021 a), lead diacetate (ECHA 2021 b) and lead dichloride (ECHA 2020 b). Furthermore, negative maximization test results

are available for **lead phosphite** and **lead phthalate** (ECHA 2021 a). These lead compounds are poorly soluble (for example the water solubility of lead oxide is 70 mg/l (ECHA 2021 c)), therefore the significance of the tests regarding the sensitizing potential of lead and lead compounds is severely limited and the results of these maximization tests are not included in the evaluation.

Sensitizing effects on the airways

There are no data available.

Reproductive and developmental toxicity

The data are listed in the addendum to the evaluation of the BAT value (Greiner et al. 2022).

Genotoxicity

In vitro

In bacterial test systems, lead salts were not found to be mutagenic. In classical mutagenicity tests (HPRT test in V79 or CHO cells (a cell line derived from Chinese hamster ovary)), mostly only weak mutagenic effects were observed. In tests with CHO-AS52 cells, mainly base pair substitutions occurred in the concentration range between 0.1 and 0.5 µM and mainly deletions in the concentration range between 0.5 and 1 µM. The AS52 cells used have an inactive *hprt* gene and have integrated an active bacterial *gpt* gene instead. AS52 cells were particularly sensitive to mutagenicity caused by reactive oxygen species. Micronuclei could be induced in the submicromolar range and co-mutagenic effects in combination with UV radiation (Greim 2009).

A detailed presentation of recent in vitro studies can be found in the documentation for lead in TRGS 903 (AGS 2017) and the reports by ECHA (2020 a) and ATSDR (2020 b). Due to the very high concentrations used in some micronucleus and sister chromatid exchange tests, the results of these studies are not considered relevant to humans. In summary, reactive oxygen species (ROS)-induced strand breaks caused by lead are considered a confirmed mechanism in the reports. In addition, recent studies show that all essential DNA repair systems are inhibited by lead and thus indirect genotoxic effects occur. A direct mutagenic effect of lead has not been observed (AGS 2017; ATSDR 2020 b; ECHA 2020 a; RAC 2020).

In vivo

The evaluation of the Drosophila wing-spot test in 40 wings or 20 flies per concentration group did not reveal an increase in the mutation frequency when the larvae were fed with 0, 2, 4 or 8 mM lead dichloride or 0, 2, 4 or 8 mM lead dinitrate, even after pre-treatment with gamma radiation. With the positive control ethyl methanesulfonate, a significant increase in mutations was found (Carmona et al. 2011).

In the comet assay, Drosophila larvae were fed with 0, 2, 4 or 8 mM lead dichloride or 0, 2, 4 or 8 mM lead dinitrate for 24 hours. Lead dinitrate induced a concentration-dependent increase in DNA strand breaks in haematocytes, but lead dichloride did not (Carmona et al. 2011).

In mice exposed to lead diacetate by inhalation for up to 4 weeks (air concentration 6.8 mg/m^3), DNA strand breaks were observed in various organ systems in the comet assay; compared with the values of the respective organ controls, there was a statistically significant increase in DNA damage after acute exposure only in the lungs and liver (Valverde et al. 2002).

After oral administration of lead compounds, numerous studies found statistically significant increases in chromosomal aberrations in the bone marrow and lymphocytes in monkeys, rats and mice. Also after oral, but not after subcutaneous or intraperitoneal administration, micronuclei were observed in the bone marrow and erythrocytes in rats and mice. In rats and mice, the incidences of sister chromatid exchange (bone marrow) were increased after

intraperitoneal injection and DNA strand breaks in the comet assay (various organs) were increased after oral administration. A detailed presentation of the studies can be found in García-Leston et al. (2010) and Greim (2009).

Recent in vivo studies are described in detail in the documentation for lead in TRGS 903 (AGS 2017) and in the reports of ECHA (2020 a), RAC (2020) and US EPA (2014).

Summary

Lead and its inorganic compounds are not directly mutagenic. The clastogenic effects observed can be explained by lead-inhibited DNA repair or lead-induced ROS.

Carcinogenicity

Almost all carcinogenicity studies were performed with oral administration.

In the supplement from 2007 (Greim 2009), the carcinogenicity studies in animals are presented in detail and evaluated as follows:

"Carcinogenicity studies in experimental animals which meet present requirements are not available. However, the investigations with lead acetate in mice show that kidney tumours also occur without concomitant kidney toxicity. Lead acetate is a pluripotent carcinogen in rats. It caused tumours in the kidney, adrenal gland, testes, prostate, lung, liver, pituitary, thyroid and mammary gland as well as leukaemias, sarcomas of the haematopoietic system and cerebral gliomas. Cerebral glioma is a type of tumour rarely occurring spontaneously."

Oral administration

In a 2-year carcinogenicity study, doses of about 0, 2, 10 or 40 mg lead diacetate/kg body weight and day (0, 50, 250, 1000 mg/l; 0, 31, 156, 625 mg lead/l) in the drinking water led to renal adenomas and carcinomas in 5 of 52 male Fischer rats in each case at 10 mg/kg body weight and day and to renal adenomas in 22 of 41 male rats and to renal carcinomas in 24 of 41 male rats at 40 mg/kg body weight and day. First tumours appeared at the interim sacrifice after 18 months. No renal tumours occurred in the control animals and in the low dose group (no other details, AGS 2017; CalEPA 2002; ECHA 2020 a; RAC 2020). The original study report is not available. The dose of 10 mg lead diacetate/kg body weight and day corresponds to a daily intake of 4 mg lead diacetate/day or about 2.5 mg lead/day in the adult rat (400 g). A drinking water concentration of 150 mg lead/l results in a blood lead concentration of 270 µg lead/l in rats (O'Flaherty 1991). In accordance with the kidney/blood ratio of lead (Aungst et al. 1981), this corresponds to a concentration of 5 µg lead/g kidney in rats. In humans, on the other hand, the concentration in the kidney is only one-fifth as much (Section 3.1).

In other carcinogenicity studies in rats, renal tumours occurred only in dose ranges where very marked nephrotoxicity had already developed (AGS 2017; Greim 2009).

Mice were continuously treated with lead diacetate concentrations of 0, 500, 750 or 1000 mg/l drinking water (about 0, 100, 150 or 200 mg/kg body weight and day) during pregnancy and lactation. In the male offspring, a statistically significant increase in the incidence of renal tumours (5/25) was found in the high dose group, but no chronic nephrotoxicity. Even in the low concentration group of 500 mg/l, tubular hyperplasia (3/25) and 1 renal carcinoma occurred in the male offspring (Greim 2009; Waalkes et al. 1995).

In groups of 25 mice (wild-type metallothionein+) given drinking water with lead diacetate in concentrations of 0, 1000, 2000 or 4000 mg/l, only 1 renal adenoma was found in the high concentration group after 104 weeks (Waalkes et al. 2004).

Gliomas occurred in 3 of 67 male Wistar rats after continuous administration of lead diacetate in the diet for 18 months at a mean dose of about 3 mg/day. No gliomas were found in the female animals. The incidences of carcinomas and

adenomas in the kidneys, adrenal glands, testes and prostate gland were increased in a statistically significant manner (Greim 2009; Zawirska and Medraś 1968).

In another feeding study (lifetime study), gliomas occurred in 10 of 97 animals after continuous administration of about 3 mg lead diacetate/day (8.6 mg lead/kg body weight and day) to male and female Wistar rats. Allocation of the tumours according to sex was not carried out. In addition, the animals had a total of 102 tumours in the kidneys, lungs, and adrenal, pituitary, thyroid, prostate and mammary glands (Greim 2009; Zawirska 1981; Zawirska and Medraś 1972).

Inhalation

After inhalation exposure in whole-animal chambers to lead oxide concentrations of 5.3 ± 1.7 mg/m^3 (5 days/week; 6 hours/day; MMAD 5.1 µm) for 1 year, only 1 renal tumour and no lung tumours were observed in 50 male Sprague Dawley rats (Monchaux et al. 1997). A control group was not included.

Summary

Kidney tumours occurred in rats after the administration of lead diacetate doses of about 10 mg/kg body weight and day (250 mg/l drinking water) for 2 years (CalEPA 2002). Atypical hyperplasia and 1 carcinoma in the kidney were observed in mice at the lead diacetate concentration of 500 mg/l drinking water (Greim 2009; Waalkes et al. 1995). Gliomas were observed in rats after the administration of 3 mg lead diacetate/day for at least 16 months (Greim 2009). Lead and its inorganic compounds are carcinogenic in animal experiments.

6 Manifesto (MAK value/classification)

The critical effects in humans are neurotoxicity, renal toxicity, cardiovascular diseases, haematological effects, clastogenicity and male fertility disorders; sensitive parameters of neurotoxicity are the most sensitive end points. Carcinogenicity studies demonstrated kidney tumours and gliomas in rats and mice at high lead concentrations; in humans, the association with increased tumour incidences is not consistent. Lead caused also developmental neurotoxicity in humans.

MAK value. The best parameter for reflecting lead exposure is the current blood lead level. Therefore, the BAT value of 150 µg lead/l blood must be strictly observed. Nevertheless, in order to derive an additional limit value for lead in air, a PBPK model presented by OEHHA and CalEPA (2014) was used, which calculates a limit value in air based on a blood lead level which is not exceeded in 95% of the exposed persons. Although the initial parameters included in such a model are inevitably of a general nature, these were selected in a very data-based manner and justified in detail, also including different lead compounds and particle sizes at different workplaces. Therefore, the model was considered suitable, especially since it was tested and validated in a volunteer study and a workplace study and thus under real workplace conditions. The results of these studies were in very good agreement with the model.

Based on this model, a limit value for lead in air of 0.0039 mg/m^3 for inhalation exposure alone is estimated, which corresponds to a blood lead level of 150 µg/l (95th percentile) in the PBPK model. A MAK value of 0.004 mg lead/m^3 for the inhalable fraction is derived from this model calculation. At exposure at the level of the MAK value, 0.012 mg lead per day is absorbed during an 8-hour working day assuming absorption by inhalation of 30% and a respiratory volume of 10 m^3.

Peak limitation. Lead is stored in the bone, which results in a very long half-life. Data for irritant effects are not available, but are considered negligible in the concentration range of the MAK value. Lead and its inorganic compounds are classified in Peak Limitation Category II with an excursion factor of 8.

Prenatal toxicity. The developmental toxicity of lead has been known for a long time. The main effects are disorders of the development of the central nervous system, for which there is sufficient consistent evidence from

prospective studies and large cross-sectional studies in children. The following effects have been observed: decreases in neurological functions, including decreases in cognitive functions (learning and memory), changes in behaviour and mood (attention, hyperactivity, impulsivity, irritability, delinquency), and changes in neuromotor and neurosensory functions (visual motor integration, dexterity, balance, changes in auditory and visual thresholds). A NOAEC (no observed adverse effect concentration) for developmental neurotoxicity could not be established. Therefore, lead has been assigned to Pregnancy Risk Group A with a BAT value of 150 µg/l blood (Greiner et al. 2022). The MAK value was derived from the internal exposure at the level of the BAT value of 150 µg/l by means of a PBPK model of the OEHHA and CalEPA (2014), which was tested and adjusted on the basis of workplace exposures. Therefore, the assignment of lead to Pregnancy Risk Group A, which was made for the BAT value of 150 µg/l blood, has been adopted also for the MAK value of 0.004 mg lead/m^3.

Carcinogenicity. Epidemiology provides no clear evidence of carcinogenicity in humans from occupational exposure to lead.

Lead was found to be carcinogenic in animal experiments. Cerebral gliomas are rare in animal experiments and the spontaneous tumour incidence is very low. Significantly increased incidences of gliomas occurred also in an epidemiological study; however, this finding was not confirmed in other studies.

Lead is not directly genotoxic. The observed genotoxicity is due to indirect DNA damage caused by the inhibition of DNA repair or by ROS at blood lead levels higher than those causing neurotoxicity, the most sensitive end point.

If the BAT value and the MAK value are observed, no contribution to the cancer risk in humans is to be expected. Genotoxicity plays no or only a minor role if the BAT and MAK values are observed (Table 2). Therefore, lead and its inorganic compounds have been reclassified in Carcinogen Category 4. The best parameter for reflecting lead exposure is the current blood lead level. Therefore, the BAT value of 150 µg lead/l blood must be strictly adhered to.

Germ cell mutagenicity. In view of the positive findings concerning the clastogenicity of lead in occupationally exposed persons and the bioavailability of lead in germ cells, lead and its inorganic compounds remain in Category 3 A for germ cell mutagens (Greim 2009).

Absorption through the skin. Hand-to-mouth contact and the associated oral exposure can contribute to lead exposure, especially in the case of poor workplace hygiene. In contrast, numerous studies show that direct absorption of lead through the skin is extremely low and does not contribute significantly to workers' internal exposure. Lead and its inorganic compounds have therefore not been designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are only isolated findings in humans suggesting a possible sensitizing potential of lead. In view of the formerly very widespread use of lead diacetate in hair-dye products and medical externals, a significant sensitizing potential of lead or lead salts can be excluded. Lead diacetate yielded negative results in the LLNA. Designation with "Sh" (for substances which cause sensitization of the skin) is therefore not required.

No information is available for sensitizing effects on the airways. The substance has therefore not been designated with "Sa" (for substances which cause sensitization of the airways).

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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