Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for lead and its inorganic compounds

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Biological limit value, lead in blood (PbB)	:	30 µg/100 ml
Atmospheric limit values	:	inorganic lead (lead fumes and dusts of < 10 µm)
8 hour TWA:	:	100 µg/m^3
STEL (15 mins)	:	-
Additional classification	:	-

Substance:

Lead Pb

EINECS N° : 231-100 4

EEC N° :

Classification : R61, R62
R20/22, R33

CAS N° : 7439-92-1

MWt : 207.19

Conversion factor (20°C, 101 kPa) : 8.6 mg/m^3 = 1 ppm

1. Occurrence/use

Metallic lead is a lustrous blue-grey metal which rapidly becomes dull in air, and is soft, malleable and ductile. It has a MPt of 327.4 °C and a BPt of 1740 °C. A variety of forms of lead are used industrially, the most common being lead oxide (PbO) and red lead oxide (lead tetraoxide; Pb_3O_4).

Lead is a rare metal in the earth's crust and its deposits are scattered throughout the world. The most common ore is galena (lead sulphide - 87% Pb). Lead is obtained from the ore by smelting to produce lead oxide, which is reduced to lead bullion then refined to remove other metallic impurities. Recycled or secondary lead is also an important source and is produced in a similar manner to primary lead refining. As a result of industrial activity, lead is now a ubiquitous multimedia pollutant. The use of lead in petrol during the past 40-50 years was the most important anthropogenic source of lead for the general population from inhalation (directly proportional to Pb percentage and to petrol consumption) and from fallout and contamination of soil, plants and water (Arnetz and Nicolich, 1990). During the past 10-15 years, directives have been adopted for reducing and replacing lead in petrol in the industrialised countries. As a result, lead in air and in blood dropped: a 3-4 fold reduction of lead in petrol led to a decrease in PbA from 1-2 $\mu g/m^3$ to 0.5-1 $\mu g/m^3$ and blood lead in the general population moved from 15-20 $\mu g/dl$ to 5-10 $\mu g/dl$ or less (Ducoffre *et al.*, 1990). Currently, the general population is exposed to the following sources of the metal: foodstuffs, including alcohol, particularly wine; water; air, resulting from lead still used in petrol and from pollutant industries of activities; "adventitious sources", such as house or street dusts, paint flakes, soil, which are of great importance for particular groups of the population such as children.

The production rate in the EU is in excess of 10^9 tonnes per annum. Occupational exposure occurs in a wide variety of industries, including procedures involved in production of lead metal and its compounds, manufacture of batteries, ceramics, jewellery, glass and pigments, and in the pottery, shipbuilding, construction, demolition and scrap industries. Exposure occurs by inhalation and ingestion, the predominant route varying with the industry and process. Lead can be present in the atmosphere as fume, which is generated at temperatures greater than 500 °C, and as dust. From the main investigations carried out between 1980 and 1995, the mean PbB in occupational exposure groups ranges from 20 to 40 $\mu g/dl$. In the two most important activities using Pb (accumulators, ceramics) median PbB ranges between 25 and 30 $\mu g/dl$, while the percentage of workers with PbB exceeding 40 $\mu g/dl$ lies between 5% and 10%. The risk is concentrated in particular activities (lead scrap foundries, radiator repair, bronze foundries) and in small factories in which preventive measures are inefficient or absent.

In monitoring occupational exposure to lead, two indicators are generally used: Pb in air (PbA) and Pb in blood (PbB). It has been claimed that to determine compliance with limits, PbA is preferable to PbB because of the analytical difficulties in measuring PbB and the different medical and legal implications of the two tests. However, because the adverse health effects of lead correlate better or only with PbB, it was necessary to correlate PbA with PbB, to be able to demonstrate that compliance with a given environmental limit guarantees compliance with the given biological levels of the metal. This approach was suggested until the end of the 1970's and it was argued that standards should be based only or mainly on PbB, and in the last 10 years, diffusion and improvement of analytical methods and instruments have been clearly demonstrated (Alessio and Foa, 1993).

In determining the PbA/PbB ratio in the working environment, the multicompartmental model developed by Bernard (1977) has been widely used, in particular by the OSHA in the so-called "Assumption C", which considers the percentage of particles with diameter less than 1μm, the different percentage for absorption by respiratory and digestive apparatus, the job tenure and the initial level of PbB absorption. The most widely questioned aspects of this assumption are: the definition of the granulometry of the dusts, not confirmed in many working conditions, the predicted percentage of absorption, high only for particles less than 1μm and the failure to assess other variables, such as solubility of Pb compounds in biological media.

The contemporary use of indicators without solving the different aspects of their relationship may generate many of the problems encountered in monitoring Pb exposure. Another order of problems may arise from the use of some effect indicators, currently proposed for in controlling exposed workers. This use follows their suggested and partially demonstrated relationship with PbB and PbA. Urinary δ-aminolaevulinic acid (UALA) for example is well correlated only with PbB levels higher than 60 μg/dl, but there are some problems in determining the correspondence between its limit value and the PbB limit. Applying the most accepted dose effect model to the UALA limit value of 20 mg/g creatinine (from Directive 82/605/EEC), would indicate a PbB level higher than the corresponding PbB limit values of 80 μg/dl. More realistic studies suggest UALA values of 5-10 mg/l correspond to the current limit values of PbB (60-70 μg/dl) as determined by different national regulations within the EU. A good correlation between zinc protoporphyrin (ZPP) and PbB has also been suggested, indicating that ZPP could be a useful parameter for monitoring individual exposure. Exclusive use of ZPP for controlling worker exposure has been criticised mainly for its low sensitivity and for the high percentage of false negatives in predicting PbB of less than 40 μg/dl. For monitoring exposure of this entity, the ZPP is not accurate, and it is preferable to measure PbB directly (Apostoli and Maranelli, 1996; Verschoor *et al.*, 1987; Letourneau *et al.*, 1988).

2. Health effects

The possible PbB levels and related effects in exposed workers are listed in the attached Figure 1.

2.1. General Remarks and Toxicokinetics

There is a vast data-base on human health effects of lead, none of which specifically relates to effects of single exposures, and the majority use blood lead (PbB) as a measure of exposure or body burden. The relationship between PbB and exposure in the workplace is not consistent, and in addition to recent occupational exposure, PbB is determined by other sources of uptake and by endogenous release from bone. Lead and its inorganic compounds have been shown to have diverse biological effects in humans, involving the cardiovascular, nervous, gastrointestinal, haemopoietic and reproductive systems, and only those considered to be most pertinent to occupational exposure are considered here.

The toxicity of lead compounds is thought to be due to the lead cation, and most studies relate effects to the amount of absorbed lead, irrespective of whether the source is metallic lead or an inorganic compound. There are few data on acute toxicity in animals, and no data relating to skin, eye or respiratory tract irritation and sensitisation potential. However, prediction and human experience suggests that these endpoints are not of significant concern in relation to elemental and inorganic lead. The effects of repeated exposure have been extensively investigated in animal models, mainly with

the oral route of administration. Effects on the haemopoeitic, renal, nervous and reproductive systems have been reported.

When inhaled, in most inorganic forms lead deposited in the alveolar regions appears to be almost completely absorbed (Chamberlain, 1985; Morrow *et al.*, 1980) although it is possible that lead compounds of low solubility, such as lead sulphide, may accumulate to some extent in the lung (Gerhardsson *et al.*, 1988). Gastrointestinal absorption of lead is relatively poor in adults (James *et al.*, 1985), but little is known about comparative rates of gastrointestinal absorption of different forms of lead. Dermal absorption is likely to be minimal (Florence *et al.*, 1988). Once absorbed, the toxicokinetic profiles of metallic lead and its inorganic compounds are assumed to be similar. Approximately 94% of the total body burden of adults is located in bone (Barry, 1975), from which it may be mobilised to form a major source of blood lead in persons with previous exposures (Schütz *et al.*, 1987). Lead may also cross the placenta (Ernhart, 1992), and be transmitted to breast milk (Rabinowitz *et al.*, 1985). In humans elimination half-lives for lead in blood and soft tissues have been estimated to be about 30 to 40 days, whereas for bone the half-life is likely to be in excess of 20 years (Rabinowitz *et al.*, 1976). Urine is the primary route of excretion. Recently, the theory has been put forward that genetically determined polymorphisms of enzymes inhibited by lead influence the overall extent of lead binding, and might thereby modify lead toxicity Silbergeld *et al.*, 2000). Specifically, ALAD occurs in two common alleles, ALAD-1 and ALAD-2 (Petrucci *et al.,* 1982). Persons homozygous or heterozygous for ALAD-2 show significantly higher mean lead blood levels at equivalent exposure levels than persons homozygous for ALAD-1 (Petrucci *er al.,* 1982; Wetmur *et al.,* 1991). As an explanation, it has been postulated that ALAD-2 in circulating red blood cells binds lead more avidly than ALAD-1, thus increasing the blood lead level, but at the same time reducing the amount of lead delivered to soft tissues (Smith *et al.,* 1995).

2.2. Genotoxicity and Carcinogenicity

Lead has been tested for genotoxic potential in a range of mutagenicity assays, with equivocal results, which may be related to poor compatibility of the materials with the test systems (Winder and Bonin, 1993). In total, lead is mostly negative in genotoxicity assays, but there is evidence that exposures of cells in culture can induce chromosomal aberrations (Silbergeld *et al.,* 2000). Also, cytogenetic effects (chromosome aberrations and sister chromatid exchanges) have been reported in some, but not all, studies of lead-exposed workers (IARC, 1987). The significance of these effects is not clear. The idea has been put forward that the carcinogenic activity of lead is based on an indirect role in carcinogenises, *e.g.,* in inhibiting DNA repair, rather than in causing alterations in DNA directly (Silbergeld *et al.,* 2000).

Some lead compounds have been shown to be carcinogenic in animals, producing kidney tumours in particular, including carcinomas, at exposure levels that cause chronic renal tissue damage. Tumours at other sites have also been reported. IARC (1987) concluded that there was "sufficient evidence in experimental animals for the carcinogenicity of lead". The mechanism(s) of carcinogenicity is not clearly established; cytotoxicity may well be involved, although the genotoxic potential of lead remains uncertain (v.s.).

The potential carcinogenicity of lead has been investigated in a number of epidemiological studies in lead-exposed workers (IARC, 1987). In 1995, Fu and Boffetta reviewed the epidemiological evidence on the carcinogenicity of inorganic lead, and combined the published data for meta-analysis. Results from all industries entailing exposure to lead at varying intensities, indicated a slight to moderate, but statistically significant excess of deaths from stomach cancer (RR 1.33, 95%CI 1.18-1.49), lung cancer (RR 1.29, 95%CI 1.10-1.50) and bladder cancer (RR 1.41, 95%CI 1.16-1.71), and a

non-significant excess from kidney cancer (RR 1.19, 95%CI 0.96-1.48). The meta-analysis for the studies in industries with heavy exposure to lead (battery and smelter) produced higher risks for cancer of the stomach (RR 1.50, 95%CI 1.23-1.83), lung (RR 1.42, 95%CI 1.05-1.92) and kidney (RR 1.26 95%CI 0.70-2.28). [Only one study reported data for bladder cancer and no meta-analysis was performed]. Because of lack of data, potential confounders as, for example, other occupational exposures, smoking and dietary habits were not explicitly controlled for. Notwithstanding this serious limitation, the increased RR's supporting the hypothesis of an association between stomach and lung cancer and heavy exposure to lead are unlikely to be entirely due to confounding. For bladder cancer, only 4 of the 14 reviewed studies reported relevant results; hence, due to possibly unpublished negative findings, the meta-analysis may have overestimated the risk. By the same token, results for kidney cancer should be considered limited and only suggestive of a true effect.

Some further evidence on the possible carcinogenicity of lead was provided by recent studies in Northern countries and Italy. One study reported on 20,700 Finnish workers biologically monitored for blood lead levels during 1973-83 and grouped by the highest personal blood lead concentration (0.0-0.9 μmol/l; 1.0-1.9 μmol/l; 2.0-7.8 μmol/l). The follow-up of cancer incidence showed increases of overall cancer, digestive cancer, lung cancer (in both men and women), bladder cancer and, suggestively, of cancer of the nervous system (in both men and women) in comparison with the general population. The increases were particularly evident in the intermediate category: all cancers SIR 1.2, 95%CI 1.0-1.4; digestive cancer SIR 1.3 95%CI 0.9-1.8; lung (men) SIR 1.4, 95%CI 1.0-1.9; lung (women) SIR 4.4, 95%CI 0.5-16; bladder SIR 2.0 95%CI 1.0-3.6; nervous system (men) SIR 1.3, 95%CI 0.5-2.7; nervous system (women) SIR 3.8, 95%CI 0.5-14. Few cases occurred in the highest blood-lead group. An internal comparison with workers with blood lead concentration < 1.0 μmol/l confirmed the increase of all malignancies (RR 1.4, 95%CI 1.1-1.8) and lung cancer (RR 1.8, 95%CI 1.1-3.1). The increase was evident in both men and women. In a nested case-control study, the effect of several possible confounders (including smoking) was taken into account. The elevated lung cancer risk appeared to be magnified by concomitant exposure to lead and leaded engine exhaust (Anttila *et al.*, 1995). In a later study, the risk of nervous system cancer was investigated in this same study-base using a within-cohort comparison. In the blood lead exposure groups 1.0-1.9 μmol/l; 2.0-7.8 μmol/l, the results were RR1.6, 95%CI 0.7-3.8, and RR 1.8, 95%CI 0.6-5.8, respectively. The case-referent study included 26 nervous system cancers (16 gliomas). Exposure to > 1.4 μmol/l lead produced an OR 2.2, 95%CI 0.7-6.6 in comparison with exposure to < 0.7 μmol/l. For glioma, the risk associated with the high exposure group was OR 11.0, 95%CI 1.0-626. Adjustment for known confounders changed the results numerically without altering the picture (Anttila *et al.*, 1995).

Wong and Harris (2000) studied the cancer mortality of a cohort of 4518 workers at lead battery plants and 2300 at lead smelters and compared this with the cancer mortality rate of the male U.S. population. In addition, a nested case-control study of stomach cancer was performed. A significant mortality increase from stomach cancer (SMR=147.4, 95%CI: 112.5-189.8) was found. Based on the results of the nested case-control study, this was not regarded as being related to lead exposure. No increased mortality was found for cancers of the kidneys, bladder, CNS, lymphatic and haematopoietic system. A small, but statistically significant increase of lung cancer mortality was ascribed, in absence of an exposure-response, to confoundings from tobacco smoking.

The carcinogenicity of lead was the matter of a recent IARC conference held in Gargnano, Italy (see Landrigan *et al.,* 2000). The results of this conference have been considered by SCOEL. Specifically, an update of the previous epidemiological metaanalysis of Fu and Boffetta (1995) corroborated the earlier conclusions (Steenland

and Boffetta, 2000). It was summarized that most of the epidemiologic studies on the carcinogenicity of lead did not present adequate data on dose-response. The current evidence was considered as "somewhat suggestive of an association between lead, lung and stomach cancers, and weaker in the cases of kidney cancer and brain cancer (Landrigan *et al.,* 2000). In one Swedish cohort consisting of 3979 primary lead smelter workers employed for at least 1 year between 1928 and 1979, followed between 1955 and 1987, there was an increased incidence of lung cancer (SIR 2.9, 95% CI 2.1-4.0) in comparison with the county population. In the sub-cohort study solely exposed to lead, the lung cancer SIR was 3.19 (95%CI 1.7-5.2) and was higher for those exposed before 1950 (SIR 3.7, 95%CI 1.8-6.6). Blood-lead analyses were available since 1950, and the lung cancer incidence was estimated in relation to cumulative lead in blood exposure categories. The results were: blood lead 0-2 μmol/l, no cases observed, 1.4 expected; 2-10 μmol/l, SIR 4.5, 95%CI 1.8-9.3; > 10 μmol/l, SIR 5.1, 95%CI 2.0-10.5. No excess of malignancies other than lung was noted in the lead only exposed sub-cohort (Lundström *et al*., 1997). Another cohort from Sweden, comprising 664 lead-battery workers, was studied for mortality and cancer incidence. Mortality from all cancers (RR 1.65, 95% CI 1.09-2.44) and ischaemic heart disease (RR 1.72, 95%CI 1.20-2.42) was significantly increased. Blood-lead measurements were available, but no dose-response pattern was visible. Compared with the county population, the tumour incidence was slightly elevated mainly due to a nearly twofold increase of gastrointestinal cancers (SIR 1.84, 95%CI 0.92-3.29), affecting mainly those employed before 1970 (SIR 2.14, 95%CI 0.98-4.07) and particularly evident after 15-year latency (SIR 2.44, 95%CI 1.22-4.37). The GI malignancies risk for the quartile of workers with the highest cumulative lead dose was: SIR 2.34, 95%CI 1.07-4.45. No excesses of lung, brain or urinary cancers were found (Gerhardsson *et al*., 1995). In an Italian cohort of 1388 workers in a lead-smelting plant, the risks of bladder (RR 1.45, 95%CI 0.74-2.53), kidney (RR 1.75, 95%CI 0.48-4.49) and brain cancer (RR 2.17, 95%CI 0.57-5.57) were non-significantly increased. Kidney cancer mortality increased with duration of employment, and was significant among smelter workers employed for 21 years or more (2 cases, RR 10.9, 95%CI 1.0-121). Concomitant exposure to cadmium could not be ruled out. No increases were seen for stomach and lung cancer. Deaths due to respiratory disease were significantly in excess; exposure to silica might have been relevant in some work areas of the smelting plant (Cocco *et al*., 1997).

Conclusions: IARC has concluded that the epidemiological evidence is "inadequate" whilst the data from animal experiments provide sufficient evidence of carcinogenicity (IARC, 1987). Taking into account also the evidence of chromosome damage in exposed workers, IARC has classified lead as possibly carcinogenic for humans (group 2B). Based on the results of a recent IARC conference held in Gargnano, Italy, it has been stated that lead should be regarded as a proven animal carcinogen, and that new data on the cancer risk of workers exposed to lead would probably justify a re-evaluation by ARC in the near future (Landrigan *et al.,* 2000).
The studies on mutagenic and carcinogenic effects of lead in humans have been criticised mainly because (a) the differences between lead compounds were not taken into consideration, (b) exposure has not been adequately measured, (c) the predominance of mortality studies which are more suitable for generating hypotheses than for validating them, (d) the failure to adequately account for confounding factors (smoking, alcohol), and other substances (As, Cr, Cd), (e) the insufficient sample size for valid detection of a relatively small excess risk (Copper *et al.*, 1985; Fanning, 1988; Gerhardsson *et al*., 1986; Apostoli *et al.*, 1989). There is also a discrepancy between the suggested sites of tumour formation in humans as opposed to experimental animals (kidneys).

Based on experimental data it seems plausible that the carcinogenicity of lead is based on indirect, rather than on direct genotoxic mechanisms (Silbergeld *et al.,* 2000). This could imply the existence of a practical threshold for the carcinogenic effects, and

would argue in favour of the possibility of setting an health-based OEL for lead. However, further research into the mechanisms of lead genotoxicity and carcinogenicity should be encouraged in order to strengthen this avenue of argumentation.

Effects of Haem Synthesis

In the past 10 years, growing attention has been paid to subclinical effects and indeed to early or subtle health effects, the hypothesis being that these form a physiopathogenic continuum with the clinical or generally overt effects (EPA, 1986; Goyer, 1990).

Lead inhibits enzymes of haem synthesis in a dose-dependent manner (both as regards prevalence and severity) and there are a number of related parameters for which it is possible to tentatively identify PbB levels at which changes cannot be detected; ZPP: 20 μg/dl; coproporphyrin: 40 μg/dl; urinary and blood δ-aminolevulinic acid levels: 30 to 35 μg/dl; δ-aminolevulinic acid dehydrase: 10 μg/dl; inhibition of iron chelation: 20-25 μg/dl. However, the clinical significance of these biochemical changes is uncertain. Although the data-base is weak, there appears to be a risk of developing lead-induced anaemia (haemoglobin concentration < 14 g/dl) at PbB in excess of about 50 μg/dl (IPCS, 1995; ATSDR, 1992; Silbergeld, 1990). Masci *et al*. (1998) have conducted a longitudinal study on workers performing tin/lead alloy welding. Blood lead levels of these workers gradually declined with time to lower values (6-34 μg/dl, accompanied by similar decreases in zinc protoporphyrin concentrations (2-47 μg/dl); thereby it appeared that effects on haem synthesis (which might be regarded as non-adverse) occur even at very low levels of Pb exposure (see Figure 1).

Conclusion: Some subclinical changes in parameters of haem synthesis may occur even below 40 □g Pb / dl blood, but these are not regarded as being "adverse".

Effects on Blood Pressure

The effect of lead on blood pressure has been widely investigated in recent years (Prikle *et al,* 1985; Sharp *et al.*, 1987; Kopp *et al.*, 1988; Micciolo *et al.*, 1994). Experiments have demonstrated that lead effects the soft muscles of the vessels by interfering with the Na-K system, cAMP, Ca and the renin angiotensin system. The biological plausibility of a causal relationship between an elevated blood pressure and lead exposure has been mainly investigated in animal experiments and *in vitro* tests. The most likely mechanisms include interference with the balance between the renin-aldosterone axis and the renal kallikrein system, direct action at the level of the vascular smooth muscle cell and the potentiation of sympathetic stimulation. The available literature suggests that there is a positive association between systolic blood pressure and the blood lead concentration. By contrast, the correlation with diastolic blood pressure was much less consistent across the various studies and in the overall analysis attained statistical significance only because of one strongly positive survey (Gartside, 1988). Whether the association between systolic pressure and blood lead is causal in terms of morbidity or mortality is not proven.

Assuming a causal and reversible relationship between blood pressure and blood lead, the potential health risks of lead exposure were examined in white men via far-reaching extrapolations from the multiple logistic regression models obtained in the Pooling Project and in the Framingham Study. These calculations suggested that a 37% decline in blood lead concentration as observed in the US from 1976 to 1980, would result over 10 years in a 5% fall in the incidence of fatal and non-fatal myocardial infarction, in a 7% decrease in the rate of fatal and non-fatal strokes and in a 5 to 6% decrease in total mortality. None of the epidemiological studies have demonstrated the existence of a

threshold dose in a wide range of "low" doses (7-35 µg/dl) (Prikle *et al,* 1985; Sharp *et al.*, 1987; Kopp *et al.*, 1988; Micciolo *et al.*, 1994).

Conclusion: There is the need of further research on the effects of Pb on blood pressure. Whether low levels of lead (up to 40 □g/dl blood) might cause effects which should be considered as being "adverse" is not clear at present.

Effects on the Peripheral Nervous System

Studies of peripheral nerve toxicity, based upon measurement of nerve conduction velocity (NCV) provide further evidence of a causal relationship between a reduction in NCV and PbB greater than 70 µg/dl, with possible effects at PbB as low as 30 µg/dl (Seppäläinen *et al.*, 1983). This is contradictory to earlier studies by Spivey *et al*. (1980) who did not find NCV changes in lead smelters with blood levels of 60 to 80 µg/dl. Moreover, the data of Seppäläinen et al., (1983) were not confirmed thereafter as more recent studies also demonstrated no effect on NCV at levels below 70 µg/dl PbB (Triebig *et al*., 1984; Ehle, 1986). The peripheral nerve toxicity of lead has been connected with an effect of interaction of Pb/Ca, which has been observed at the level of the neuromuscular junctions, with an antagonism between the two cations in regulating the synaptic transmitter.

Conclusion: There is no consistent proof of effects of Pb on the peripheral nervous system at levels up to 40 □g/dl blood.

Neurobehavioural Studies

Several studies concerned with the neurobehavioural effects of occupational exposure to lead have reported changes in performance in neuropsychological tests at PbBs of around 40 µg/dl and above (Spurgeon, 1994). Effects on performance in neuropsychological tests were found in all studies at blood lead levels well below 70 µg/dl.

Table 1 gives a compilation of studies which were considered relevant and adequate for OEL setting. In generall, mean actual PbB levels of 40-50 µg/dl are a range in which subjective symptoms and objective performance impairments are found. A recent paper of Lindgren *et al*. (1996) reports on the lowest exposures associated with statistically significant effects. A group with mean actual PbB values of 26.9 µg/dl (± 19.5 S.D.) and a mean long-term PbB average of 40 µg/dl showed performance deficiencies. However, no dose-response relationship was seen in this study, and significance was only found following unusual statistical analysis. On the basis of a very recent meta-analysis by Meyer-Baron and Seeber (2000) it appears that neurobehavioural studies indicating effects in the region of 40 □g Pb / dl blood are more convincing. Meyer-Baron and Seeber (2000) have considered 22 human neurobehavioural studies covering lead exposure conditions of <70 □g Pb / dl blood. As a consequence of the use of different test procedures in these studies and isufficiently documented test results only 13 tests out of 12 studies could be included in their meta-analysis. For the tests "Block Design", "Logical Memory" and "Santa Ana" performence deficits were found which may be interpreted as "small"effects in accordance with a convention for evaluating effect sizes. For the example of "Block Design" it was argued that these effects are nevertheless serious. The extent of exposure-related decrease in performance was comparable with those changes in performance which can be expected during aging of up to 20 years.

Conclusion: In total, consistent neurobehavioural effects which are to be considered as "adverse" appear in a multiplicity of studies at lead blood levels of 40 □g/dl and above. The dose-dependency of impairments in performance in neurobehavioural tests, in

relation to PbB levels, may also be drawn from the studies of Mantere *et al.*, (1982) and Stollery *et al.*, (1989, 1991). In general, decreases in global performance are reported at PbB levels >40 μg/dl (Schwartz and Landrigan, 1988; Landrigan, 1990). This is supported by a recent meta-analysis of Meyer-Baron and Seeber (2000). It should be mentioned that no publication addresses the open question of gender specificity in an adequate manner. The behavioural studies have been almost exclusively conducted in males; where (limited numbers of) females are also involved, generally no valid gender-specific data are provided.

2.3. Nephrotoxicity and Gastrointestinal Toxicity

High exposure to lead can induce kidney toxicity involving acute tubular damage and chronic interstitial fibrosis. Kidney toxicity has not been adequately investigated in modern occupationally-exposed groups, but the limited studies available give no clear evidence of lead-induced renal pathological or functional changes at PbBs below 70 μg/dl (Buchet *et al.*, 1980; Pollock and Ibels, 1988). Colic is a recognised symptom of lead-poisoning, associated with PbBs in excess of 100 μg/dl. A number of studies suggest that there is an increased risk of gastrointestinal problems in lead-exposed workers with a PbB in excess of 60 μg/dl (Baker *et al.*, 1979; Lilis *et al.*, 1977), but firm conclusions cannot be drawn because of shortcomings in the study designs.

Conclusion: There is no evidence of nephrotoxic and/or gastrointestinal toxicity at Pb blood levels of 40 □g/dl and below.

2.4. Reproductive Toxicity

A few epidemiological studies have been performed on the association between paternal exposure to lead and adverse reproductive outcome. The results suggest an increased risk of spontaneous abortion, perinatal death and low birth weight following paternal occupational lead exposure (Lindbohm *et al.*, 1991; Kristensen *et al.*, 1993; Anttila and Sallmén, 1995; Min *et al.*, 1996). In a Finnish study, a significant increase was observed in the risk of spontaneous abortion among the wives of men whose PbB was 30 μg/dl or higher during spermatogenesis (Lindbohm *et al.*, 1991). Reduced fertility has also been reported for men with a long duration of lead exposure (Lin *et al.*, 1996). There is limited evidence of an association between reduced semen quality (reduced sperm count and motility and increased morphologically abnormal sperm) and PbB in excess of about 40 μg/dl (Alexander *et al.*, 1996; Assenato *et al.*, 1986; Lancranjan *et al.*, 1975). From a recent review on male reproductive toxicity of lead (Apostoli *et al.*, 1998), it seems evident that only Pb levels above 40 μg/dl in blood are associated with a decrease in sperm count, volume and morphological alterations.

There are no data on female fertility relating to modern occupational exposure levels. Lead is transferred across the placenta during the 12th to 14th weeks of pregnancy.

At birth the blood lead concentration in the umbilical cord of the child is close to the blood lead level of the mother (80-90%). Consequently, the child of a pregnant woman employed in a lead trade may have at birth a blood lead level exceeding considerably that of the unexposed population. Blood lead levels have also been observed to increase during pregnancy despite unchanged or decreasing environmental lead levels. The mobilisation of lead from bone during pregnancy probably explains the increase (Lagerkvist *et al.*, 1996). Studies of the influence of pre- and post-natal low-level environmental lead exposure on *in utero* and childhood development show no evidence of an association between lead exposure and spontaneous abortion or birth defects. Several studies reported a correlation between reduced length of gestation (McMichael *et al.*, 1986; Moore *et al.*, 1982) and reduced

birth weight in full term deliveries (Bellinger *et al.*, 1984; Bornschein *et al.*, 1987) with maternal PbBs as low as about 20 μg/dl, but other studies do not support these observations.

Impaired cognitive development in children exposed to lead during gestation has also been reported at blood lead levels of 15 μg/dl or more in three prospective studies (Bellinger *et al*., 1987; Dietrich et al., 1993; Ernhard et al. 1989) but not in two others (Cooney et al., 1989; Baghurst et al. 1992). Effects of maternal lead exposure cannot be distinguished from early childhood exposure due to other sources but toxicokinetic considerations indicate that effects on neurological and psychomotor development is a possible but uncharacterisable risk from maternal exposure to the fetus or breast-fed infant. It also must be pointed out that in the studies on mental child development umbilical blood lead levels, but not maternal levels throughout pregnancy have been determined.

Conclusions: Signs of male reproductive toxicity appear consistently at Pb blood levels above 40 □g/dl. These effects should be considered as adverse. The effect of reproductive toxicity in females, which is of highest potential impact and which is to be regarded as adverse, is impairment of the cognitive development in newborns and infants. A definite threshold for this effect cannot be derived from the present literature data. However, there are uncertainties and inconsistancies in the present database.

Because of the greater susceptibility of females (particular with regard to these reproductive, but also to haematological effects, it has been suggested that lower limits should be maintained for female workers (Zielhuis, 1985).

Recommendation

The leading toxic effect of lead in males and females is impairment of performance in neurobehavioural tests. Most authors agree that a long-term PbB level of 40 μg/dl probably represents a LOAEL in this respect; since subtle effects have been experienced by some individuals at PbB levels of 40 μg/dl. One particular study (Lindgren *et al*., 1996) reports on neurobehavioural effects at lower concentrations.

Other endpoints of lead toxicity, namely PNS and renal toxicity, are relevant for exposure levels which are consistently higher (*Fig. 1*). The observed experimental carcinogenicity of Pb salts is, in the first instance, directed towards the kidneys as the target tissue. Most probably, these effects are to a great extent based on the renal toxicity of high doses of Pb. There is an ongoing discussion on the human carcinogenicity of lead and lead compounds. Based on experimental findings it seems plausible that lead has no direct genotoxic effect which argues in favour of existence of practical thresholds of carcinogenicity. Hence an OEL based on avoiding functional CNS alterations is expected also to protect against PNS and renal toxicity, including possible renal cancer development. Similar conclusions may probably be drawn with respect to other systemic toxicities, e.g. on haem biosynthesis and on blood pressure, although there is a discrepancy in opinions and more research is needed in this direction.

There is considerable uncertainty concerning impairment of reproductive function by lead. For males, there are valid indications that only PbB levels above 40 μg/dl are connected with impairment of fertility. In females, however, it is relevant that cognitive deficits of the offspring are dose-dependently associated with lead exposure. The question of reversibility of such deficits is not yet satisfactorily resolved. On the basis of the present data no definite NOAEL can be deduced, which calls for a minimization of exposure.

Another aspect to be observed is the existing background levels which result from environmental sources, even without overt occupational exposures. In most EU countries, the background PbB levels have decreased during the last 20-30 years from ~20 µg/dl to ~5 µg/dl. However, there are areas where higher levels are still being found, mainly due to the former use of lead materials in water installations (e.g., in some areas of Eastern Germany).

On this basis, the following recommendation is given:

1. Biological limit values

PbB: 30 µg/100 ml

It should be kept in mind that the recommended BLV is not seen as being entirely protective of the offspring of working women. No threshold for potential central nervous system effects in new born and infants can be identified at present. The exposure of fertile women to lead should therefore be minimised.

2. Occupational Exposure Limits (OEL)

Only part of the occupational exposure occurs by inhalation and a considerable portion is incorporated after oral ingestion. Lead ingestion varies as a function of personal hygiene of the individual and the overall cleanliness of the work environment. In consequence, the setting of an OEL for airborne lead is more difficult than for other compounds.

Based on the field studies on lead battery workers by Lai et al. (1997) and others (see Kentner and Fischer 1993) and using the preferred values approach of SCOEL, an OEL for airborne exposure of 100 µg/m^3 is recommended as consistent with the above biological limit value.

Key Bibliography

Alessio, L. and Foa, V. (1993). Lead. In CEE Monographs on biological monitoring of industrial chemicals, 105-132.

Alexander, B. H., Checkoway, H., van Netten, C., Muller, C. H., Ewers, T. E., Kaufman, J. D. *et al*., (1996). Semen quality of men employed at a lead smelter. Occup. Environ. Med. 53, 411-416.

Anttila, A. and Sallmén, M. (1995). Effects of parental occupational exposure to lead and other metals on spontaneous abortion. J. Occup. Environ. Med. 37, 915-921.

Anttila, A., Heikkilä, P., Pukkala, E., Nykyri, E., Kauppinene, T., Hernberg, S. and Hemminki, K. (1995). Excess lung cancer among workers exposed to lead. Scand. J. Work Environ. Health 21, 460-469.

Apostoli, P. and Maranelli, G. (1996). Impiego della ZPP nel controllo biologico di popolazioni esposte a piombo metallico. Med. Lav. 77, 529-537.

Apostoli, P., Kiss, P., Pozzu, S., Bonde, G. P., Vanhoorne, H. (1998). Male reproduction toxicity of lead in animals and humans. Occup. Environ. Med. 55,

Apostoli, P., Leone, R., Porru, S. and Alessio, L. (1989). Urinary mutagenicity test in lead-exposed workers. Mutat. Res. 222, 245-251.

Arnetz, B. B. and Nicolich, M. J. (1990). Modelling of environmental lead contributors to blood lead in humans. Int. Arch Occup. Environ. Health 62, 397-402.

Assenato, G., Paci, C., Baser, M. E., Molini, R., Candela, R. G., Altamura, B. M. and Giorgino, R. (1986). Sperm count suppression without endocrine dysfunction in lead-exposed men. Arch. Environ. Health 41, 387-390.

ATSDR (1992). Toxicological profile for lead. Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services, Atlanta, Georgia.

Baghurst, P.A., McMichael, A.J., Wigg, N.R., Vimpani, G.V., Robertson, E.F., Roberts, R.J., Tong, S.L. (1992) Environmental exposure to lead and children's intelligence at age of seven years. New England J. Med. 327: 1279-1284

Baker, E. L., Landrigan, P. J., Barbour, A. G., Cox, D. H., Folland, D. S., Ligo, R. N. and Throckmorton, J. (1979). Occupational lead poisoning in the United States: Clinical and biochemical findings related to blood levels. Br. J. Ind. Med. 36, 314-322.

Barry, P. S. I. (1975). A comparison of concentrations of lead in human tissues. Br. J. Med. 32, 119-139.

Bellinger, D. C., Needleman, H. L., Leviton, A., Waternaux, C., Rabinowitz, M. and Nichols, M. L. (1984;). Early sensory-motor development and prenatal exposure to lead. Neurobehav. Toxicol. Teratol. 6, 387-402.

Bellinger, D., Leviton, A., Waternaux, C., Needleman, H. and Rabinowitz, M. (1987). Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. New Eng. J. Med. 316, 1037-1043.

Bernard, S, S. F. (1977). Dosimetric data and metabolic model for lead. Health Phys. 32, 44-46.

Bornschein, R. L., Succop, P. A., Dietrich, K. N., Krafft, K., Grote, J., Mitchell, T., Berger, O., Hammond, P. B. (1987). Pre-natal lead exposure and pregnancy outcomes in Cincinnati lead study. In: Lindberg, S. E. and Hutchinson, R. C. (eds). International Conference: Heavy Metals in the Environment. Vol 1., pp156-158. CEP Consultants, Edinburgh

Buchet, J. P., Roels, H. A, Bernard, A. and Lauwerys, R. (1980). Assessment of renal function of workers exposed to inorganic lead, cadmium and mercury vapor. J. Occup. Med. 22, 740-750.

Chamberlain, A. C. (1985). Prediction of response of blood lead to airborne and dietary lead from volunteer studies with lead isotopes. Proc. Roy. Soc. London B 224, 149-182.

Cocco, P., Hua, F., Boffetta, P., Carta, P., Flore, C., Flore, V., Onnis, A., Picchiri, G. F. and Colin, D. (1997). Mortality of Italian lead smelter workers. Scand. J. Work Environ. Health, 23, 15-23.

Cooney, G.H., Bell, A., McBride, W., Carter, C. (1989) Neurobehavioural consequences of prenatal low level exposure to lead. Neurotoxicol. Teratol. 11: 95-104

Copper, W. C., Wong, O. and Kheifets, L. (1985). Mortality among employees of lead battery plants and lead-producing plants. 1947-1980. Scand. J. Work Environ. Health 11, 331-345.

Dietrich, K., Berger, O., Succop, P., Hammond, P., Bornschein, R. (1993) The developmental consequences of low to moderate prenatal and postnatal lead exposure: Intellectual attainment in the Cincinnati lead study cohort following school entry. Neuratoxicol. Teratol. 15: 37-44

Ducoffre, G., Claeys, F. and Brauax, P. (1990). Lowering time trend of blood lead levels in Belgium since 1978. Environ. Res. 51, 25-35.

Ehle, A. L. (1986). Lead neuropathy and electrophysiological studies in low-level lead-exposure - a critical-review. Neurotoxicology, 7, 203-216.

EPA / U.S. Environmental Protection Agency (1986). Air quality criteria for lead. EPA/600/8-83/028F Final Draft.

Ernhart, C., Morrow-Tlucak, M., Wolf, A., Super, D., Drotar, D. (1989) Low level lead exposure in the prenatal and early preschool years: Intelligence prior to school entry. Neurotoxicol. Teratol. 11: 161-170

Ernhart, C. B. (1992). A critical review of low-level prenatal lead exposure in the human: 1. Effects on the fetus and newborn. Reproductive Toxicology 6, 9-19.

Fanning, D. (1985). A mortality study of lead workers, 1926-1985. Arch. Environ. Health 43, 247-251.

Florence, T. M., Lilley, S. G. and Stauber, J. L. (1988). Skin absorption of lead. Lancet ii 157-158.

Fu, H. and Boffetta, P. (1995). Cancer and occupational exposure to inorganic lead compounds: A meta-analysis of published data. Occup. Environ. Med. 52, 73-81.

Gartside, P. S. (1988). The relationship of blood lead levels and blood pressure in NHANES II: additional calculations. Environ. Health Perspect. 78, 31-34.

Gerhardsson, L., Brune, D., Nordberg, G. F. and Wester, P. O. (1988). Multielemental assay of tissues of deceased smelter workers and controls. Sci. Tot. Environ. 74, 97-110.

Gerhardsson, L., Lundstrom, N. G., Nordberg, G. and Wall, S. (1986). Mortality and lead exposures: a retrospective cohort study of Swedish smelter workers. Br. J. Ind. Med. 43, 707-712.

Gerhardsson, L., Hagmar, L., Rylander, L. and Skerving, S. (1995). Mortality and cancer incidence among secondary lead smelter workers. Occup. Environ. Med. 52, 667-672.

Goyer, R. A. (1990). Lead toxicity: from overt to subclinical to subtle health effects. Environ. Health Perspect. 86, 177-181.

IARC (1987). IARC Monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: An updating of IARC Monographs 1 to 42. Suppl. 7., IARC, Lyon.

IPCS (1995). International Programme on Chemical Safety. Environmental Health Criteria for Lead. No 164.

James, H. M., Hilburn, M. E. and Blair, J. A. (1985). Effect of meals and meal times on uptake of lead from the gastrointestinal tract in humans. Human Toxicol. 4, 401-407.

Kentner, M., Fischer, T. (1993) Biomonitoring bei beruflicher Bleibelastung. Untersuchungen zur Belastungs- und Beanspruchungssituation an 134 Beschäftigten einer Akkumulatorenfertigung im Zeitraum von 1982 bis 1991. Berufsgenossenschaft der Feinmechanik und Elektrotechnik, Köln/Germany

Kopp, S. J., Barron, J. T. and Tow, J. P. (1988). Cardiovascular actions of lead and relationship to hypertension: a review. Environ. Health Perspect. 78, 91-99.

Kristensen, P., Irgens, L. M., Daltveit, A. K. and Andersen, A. (1993). Perinatal outcome among children of men exposed to lead and organic solvents in the printing industry. Am. J. Epidemiol. 137, 134-144.

Lagerkvist, B. J., Ekerydh, S., Englyst, V., Nordberg, G. F. Söderberg, H-Å. And Wiklund, D-E. (1996). Increased blood lead and decreased calcium levels during pregnancy: A prospective study of Swedish women living near a smelter. Am. J. Public Health 86, 1247-1252.

Lai, J. S., Wu, T. N., Liou, S. H., Shen, C. Y., Guu, C. F., Ko, K. N., Chi, H. Y. and Chang, P. Y. (1997). A study of the relationship between ambient lead and blood lead among lead battery workers. Int. Arch Occup. Environ. Hlth 69, 295-300.

Lancranjan, I., Popescu, H. I., Gavanescu, O., Klepsch, I. and Serbanescu, M. (1975). Reproductive ability of workmen occupationally exposed to lead. Arch. Environ. Health 30, 396-401.

Landrigan, P. J. (1990). Lead in modern work place. Am. J. Publ. Health 80, 907-909.

Landrigan, P. J., Todd, A. C. and Wedeen, R. P. (1995). Lead poisoning. Mt Sinai J Med 62 360-364.

Landrigan, P.J., Boffetta, P., Apostoli, P. (2000). The reproductive toxicity and carcinogenicity of lead: a critical review. Am. J. Ind. Med. *(June 2000; pre-print distributed as SCOEL/INF/369)*

Letourneau, G., Plante, R. and Weber, P. (1988).Blood lead and maximal urinary excretion of delta aminolevulinic acid. Am. Ind. Hyg. Assoc. J. 49, 342-345.

Lilis, R., Fischbein, A., Eisinger, J., Blumberg, W. E., Diamond, S., Anderson, H. A., Rom, W., Rice, C., Sarkozi, L., Kon, S. and Selikoff, I. (1977). Prevalence of lead disease among secondary lead smelter workers and biological indicators of lead exposure. Environ. Res. 14, 255-285.

Lin, S., Hwang, S., Marshall, E., Stone, R. and Chen, J. (1996). Fertility rates among lead workers and professional bus drivers: A comparative study. Ann. Epidemiol. 6, 201-208.

Lindbohm, M-L., Sallmén, M., Anttila, A., Taskinen, H. and Hemminki, K. (1991). Paternal occupational lead exposure and spontaneous abortion. Scand. J. Work Environ. Health 17, 95-103.

Lindgren, K., Masten, V., Ford, D. and Bleeker, M. (1996). Relation of cumulative exposure to inorganic lead and neuropsychological test performance. Occup. Environ. Med. 53, 472-477.

Lundström, N-G., Nordberg, G. and Englyst, V. (1997). Cumulative lead exposure in relation to mortality and lung cancer morbidity in a cohort of primary smelter workers. Scand. J. Work Environ. Health 23, 24-30.

Masci, O., Carelli, G., Vinci, F. and Castellino, N. (1998). Blood lead concentration and biological effects in workers exposed to very low lead levels. J. Occup. Environ. Med. 40, 886-894.

Mantere,P., Hänninen, H. and Hernberg, S. (1982). Subclinical neurotoxic lead effect: Two years follow up studies with psychological test methods. Neurobehav Toxicol Teratol 4 725-727.

McMichael, A. J., Vimpani, G. V., Robertson, E. F., Braghurst, P. A. and Clark, P. D. (1986). The Port Pirie cohort study: maternal blood lead and pregnancy outcome. J. Epidemiol. Comm. Health 40, 18-25.

Meyer-Baron, M., Seeber, A. (2000) A meta-analysis for neurobehavioural results due to occupational exposure with blood lead concentrations < 70 □g/100 ml. Arch. Toxicol. 73, in press.

Micciolo, R., Maranelli, G. and Apostoli, P. (1994). Non-occupational lead exposure and hypertension in Northern Italy. Int. J. Epidemiol. 23, 312-320.

Min, Y., Correa-Villaseñor, A. and Stewart, P. A. (1996). Parental occupational lead exposure and low birth weight. Am. J. Ind. Med. 30, 569-578.

Moore, M. R., Goldberg, A., Pocock, S. J., Meredith, P. A., Stewart, I. M., Macanespie, H. and Low, A. (1982). Some studies of maternal and infant lead exposure in Glasgow. Scott. Med. 27, 113-122.

Morrow, P. E., Beiter, H., Amato, F. and Gibb, F. R. (1980). Pulmonary retention of lead: An experimental study in man.

Parkinson, D. K., Hodgson, M. J., Bromet, E. J., Dew, M. A. and Connell, M. M. (1987). Occupational lead exposure and blood pressure. Br. J. Ind. Med. 44, 744-748.

Petrucci, R., Leonardi, A., Battistuzzi, G. (1982). The genetic polymorphism of delta-aminolevulinate dehydratase in Italy. Hum. Genet. 50: 289-290.

Pollock, C. A. and Ibels, L. S. (1988). Lead nephropathy - a preventable cause of renal failure. Int. J. Artif. Organs 11, 75-78.

Prikle, J. L., Schwartz, J., Landis, R. and Harlan, W. R. (1985). The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am. J. Epidemiol. 121, 246-258.

Rabinowitz, M. B., Wetherill, G. W. and Kopple, J. D. (1976). Kinetic analysis of lead metabolism in healthy humans. J. Clin. Invest. 58, 260-270.

Rabinowitz, M., Leviton, A. and Needleman, H. (1985). Lead in milk and infant blood: a dose-response model. Arch. Environ. Health 40, 283-286.

Schütz, A., Skerfving, S., Ranstam, J., Gullberg, B., Christoffersson, J. O. (1987). Kinetics of lead in blood after end of occupational exposure. Scand. J. Work Environ. Health 13, 221-231.

Schwartz, J., Landrigan, P. J. (1988). Threshold effect in lead induced neuropathy. J. Pediatr. 112, 12-17.

Seppäläinen, A. M., Hernberg, S., Vesanto, R. and Kock, B. (1983). Early neurotoxic effects of occupational lead exposure: A prospective study. Neurotoxicology 4, 181-189.

Sharp, D. S., Becker, C. E. and Smith, A. H. (1987). Chronic low-level exposure. Its role in the pathogenesis of hypertension. Med. Toxicol. 2, 210-232.

Silbergeld, E. K. (1990). Toward the twenty first century: lessons from lead and lesson yet to learn. Environ. Health Prospect. 86, 191-196.

Silbergeld, E.K., Waalkes, M., Rice, J.M. (2000). Lead is a carcinogen: experimental evidence and mechanisms of action. Am. J. Ind. Med. *(June 2000)*

Smith, C.M., Wang, X., Hu, H., Kelsey, K.D. (1995). Dehydratase gene may modify the pharmacokinetics and toxicity of lead. Environ. Hlth. Perspect. 103: 248-253.

Spivey, G. H., Bahloh, R. W., Brown, B. L., Browdy, D. S., Campion, D. S., Valentine, J. L., Morgan, D. E. and Culver, B. D. (1980). Subclinical effects of chronic increased lead absorption - a prospective study. J. Occup. Med. 22, 607-612.

Spurgeon, A. (1994). Occupational lead exposure. Do current exposure standards protect workers from harm? A review of neurobehavioral findings since 1978. Inst Environment Health. 3 112-118.

Steenland, K., Boffetta, P. (2000). Am. J. Ind. Med. *(June 2000)*

Stollery, B.T., Banks, H.A., Broadbent, D.E. and Lec,W.R. (1989). Cognitive functioning in lead workers. Br J Ind Med 46 698-707.

Stollery, B.T., Broadbent, D.E., Banks, H.A. and Lec, W.R. (1991). Short term perspective study of cognitive functioning in lead workers. Br J Ind Med 48 739-749.

Triebig, G., Weltle, D. and Valentin, H. (1984). Investigations on neurotoxicity of chemical-substances at the workplace. 5. Determination of the motor and sensory nerve-conduction velocity in persons occupationally exposed to lead. Int. Arch. Occupat. Environ. Health 53, 189-204.

Verschoor, M., Herber, R., Zielhuis, R. and Wibowo, A. (1987). Zinc protoporphyrin as an indicator of lead exposure: precision of ZPP measurements. Int. Arch. Occup. Environ. Health 59, 613-621.

Winder, C. and Bonin, T. (1993). The genotoxicity of lead. Mutat. Res. 285, 117-124.

Wetmur, J.G., Kaya, A.H., Plewinska, M., Desnick, R.J. (1991). Molecular characterization of the human delta-aminolevulinate dehydratase-2 (ALAD-2) allele: Implications for molecular screening of individuals for genetic susceptibility mto lead. Am. J. Hum. Genetics 49: 757-763.

Wong, O., Harris, M.S. (2000). Cancer mortality study of employees at lead battery plants and lead smelters, 1947-1995. Am. J. Ind. Med. *(pre-print distributed as SCOEL/INF/371)*

Zielhuis, R. L. (1985). Biological exposure limits: the fetus and EEC policies. Br. J. Ind. Med. 42, 145-146.

Table 1. Epidemiological studies of occupational exposure to lead which meet the criteria for a discussion of limit values
Key – CG: control group(s); EG: exposed group(s); TWA: "time-weighted average"; IBL: cumulative blood lead; AM: arithmetic mean(s)

Exposed group/control group	Exposure variables	Tests/ variables	Significant group differences	Significant dose-effect relationships	Confounder control	Assessment of examination
Lindgren et al. 1996						
Exposed group: 467 male employees/lead smelting	• Present PbB: 28/8 (AM/SD) Range ? • TWA PbB: 40/4-66 (AM/range) • IBL (cumulative blood lead over entire duration of employment): 765/0.6-1626 µg-dl (AM/range) Low: 269/195 (AM/SD) Medium: 821/122 (AM/SD) High: 1228/145 (AM/SD)	9/14	Not examined	Re IBL: • Digit-symbol test • Logical memory (short-term) • Trail making (two variables) • Purdue pegboard (dominant hand)	No significant differences as regards: • Language • Minor neurological disorders Account taken of significant differences as regards: • Age • Education level • Depression • Alcohol consumption Exclusion criteria • Serious neurological disorders • Pre-existing short-term psychiatric disorders Account of taken of suppresser variable 'employment duration' Examination blind/exposure Examinations at start of shift	• Satisfactory inclusion of all relevant confounders in the analysis

Exposed group/control group	Exposure variables	Tests/ variables	Significant group differences	Significant dose-effect relationships	Confounder control	Assessment of examination
Maizlish et al. 1995						
Exposed group: 43 workers/ lead smelting Control group: 47 workers/glass factory	• Present PbB: EG: 43/12/9-68 (AM/SD/range) CG: 15/6 (AM/SD) < 10 4% 10-25 44% 25-39 20% 40-61 26% 61-81 6% • Maximum PbB (1986-1993): EG: 60/20 (AM/SD) CG: 15/6 (AM/SD) • TWA PbB: EG: 48/12 (AM/SD) CG: 15/6 (AM/SD)	7/14	Exposed Group v. Control group • Symptom indications in year before examination (Concentration; annoyed or agitated without reason; unusual fatigue; aching joints)	Re present PbB>PbB max & TWA Re present PbB: • POMS (tension/fear; hostility; fatigue; depression) Re maximum PbB: • POMS (hostility; depression) TWA-PbB: • POMS (hostility; depression)	Comparability of groups regarding: • Activity • Geographical origin Account taken of influences of: • Age • Education • Alcohol consumption • Earlier exposure to solvents • State of health Examinations not blind	• Satisfactory account taken of confounders • Owing to extensive redundancies of long-term exposed workers shortly before the examination, the representativeness of the sample is questionable ("healthy worker effect"?)

Exposed group/control group	Exposure variables	Tests/ variables	Significant group differences	Significant dose-effect relationships	Confounder control	Assessment of examination
Stollery et al. 1989						
Exposed group: 86 workers/battery factory/printing industry	• Present PbB: Low: <20 Medium: 21-40 High: 41/-80 Range: 5-72 • ALA: Gr 1: 2.5 Gr 2: 4.0 Gr 3: 5.7 Range: 0.5-22 mg/l • ZPP	5/28	High v. Medium + Low • Semantic classification and recollection (identification of distracters) • Serial reaction (number of tests; decision time; motion time)	Re present PbB: • Semantic classification and recollection (three variables) • Serial reaction (fewer tests; decision time; motion time)	Account taken of influences of: • Exposure duration • Age • Age/school-leaving qualifications • Sleep • Alcohol consumption • Activity • Stress/arousal Comparability of groups as regards: • Ethnic origin • Regional origin Computer testing	• Unclear whether account taken of pre-existing diseases • Largely satisfactory account taken of confounders

Exposed group/control group	Exposure variables	Tests/ variables	Significant group differences	Significant dose-effect relationships	Confounder control	Assessment of examination
Yokoyama et al. 1988						
Exposed group: 19 workers/foundry Control group: 12 workers/foundry (same establishment) After 2 years 17/10	• Present PbB: EG: 30-64 (range) CG: 8-20 (range) High: 40-64 Low: 30-39 Control: 8-20 • Present PbB after 2 years High: 26-59** Low: 24-39 Control: 8-14 • Lead in urine (MPb)	5/5	Time 1: High v. Low: • Pictures to be completed High v. Control: • Pictures to be completed Time 2: None found	Exposed workers at time 1: Re present PbB: • Pictures to be completed MPb: • Pictures to be completed ALAD: • Pictures to be completed Exposed workers at time 2: Not reported	Comparability of groups as regards: • Age • Education • Alcohol consumption No exposure to other neurotoxins No significant pre-existing diseases No alcohol or drug consumption on test day	• CG younger • Exposed group drinks more • As performance effect declines with lead level, both points seem to be of subsidiary importance

Exposed group/control group	Exposure variables	Tests/ variables	Significant group differences	Significant dose-effect relationships	Confounder control	Assessment of examination
Parkinson et at. 1986						
Exposed group: 288 workers/3 battery factories Control group: 181 HGV construction	• Present PbB: 40/13 (AM/SD) Range ?? • TWA PbB: 49/12 (AM/SD) • PbB > 60 0.23/0.22 (AM/SD) • ZPP	17/18	None	Re present PbB: • Psychosocial variable (conflicts) Re ZPP: • Psychosocial variable (conflicts) Re TWA-PbB: • Psychosocial variables (conflicts, two variables) • Annoyance • Number of accidents Re max PbB: • Psychosocial variables (conflicts, annoyance at workplace) Re PbB>60: • Psychosocial variable (conflicts) • Number of accidents	Comparability of groups as regards: • Ethnic origin • Psychiatric history • Drug/alcohol abuse Account taken of influences of: • Age • School education • Income CG had no known exposure to neurotoxins Exclusion criteria: • Significant neurological or other disorders	• Despite group comparison, the exposure measurements for the CG are not specific (<=35) • Appropriate inclusion of all relevant confounders in the analysis

Exposed group/control group	Exposure variables	Tests/ variables	Significant group differences	Significant dose-effect relationships	Confounder control	Assessment of examination
Hogstedt et al. 1983						
Exposed group: 49 workers subjected to occupational medical checks/lead smelting/battery factory Control group: 27 industrial workers subjected to occupational medical checks/wire industry/turning shop/ munitions factory:	• Present PbB: EG: 42(AM) CG: 15 (AM) • TWA PbB: EG: 48 (AM) Highest individual value 65 14 persons had > 69 once Range 27-69 High: > 53 Low: 27-52 Control: <21 • ZPP	7/7	Low v. Control: • Memory factor • Learning factor High v. Control: • Memory factor • Simple reaction time High + Low v. Control: • Memory factor • Learning factor • Simple reaction time • Neuropsychiatric symptoms	Significance unclear	Comparability of groups as regards: • Alcohol consumption • Pre-existing illnesses • Solvent exposure Account taken of influence of: • Age Conditions for participation: same school education Comparable testing times for all Examinations not blind as regards difference EG-CG	• Lack of differences in verbal tests testify to comparable premorbid intelligence • Satisfactory account taken of confounders • Differences in proportion of shift workers in exposed group and control group may lead to underestimating of effects, as performance of shift workers was generally inferior

Fig. 1

PbB levels-related effects of lead in exposed workers

Lowest observed effect level (PbB)	Heme synthesis and hematological effects	Neurological effects	Effects on the Kidney	Reproductive function effects	Cardiovascular effects
µg/dl					
100-120		Encephalopathic signs and symptoms	Chronic neophropathy		
80	Frank anaemia				
60				Female reproductive effects	
50	Reduced haemoglobin production				
40	Increased urinary ALA and elevated coproporphyrins	Neurobehavioural impairment	Early signs of kidney malfunctions	Altered testicular function	
30					Elevated blood pressure (White males Aged 40 –55)
25-30	Erythrocyte protoporphyrin (EP) elevation in males				
15-20	Erythrocyte protoporphyrin (EP) elevation in females				
< 10	ALA-D inhibition				?