NR 2005:3

Criteria Document for Swedish Occupational Standards

Inorganic lead

– an update 1991–2004

*Staffan Skerfving**

* Department of Occupational and Environmental Medicine,
University Hospital, SE-221 85 Lund, Sweden

ARBETE OCH HÄLSA | VETENSKAPLIG SKRIFTSERIE

ISBN 91-7045-743-3 ISSN 0346-7821

Arbetslivsinstitutet
National Institute for Working Life

Arbete och Hälsa

Arbete och Hälsa (Work and Health) is a scientific report series published by the National Institute for Working Life. The series presents research by the Institute's own researchers as well as by others, both within and outside of Sweden. The series publishes scientific original works, dissertations, criteria documents and literature surveys.

Arbete och Hälsa has a broad target-group and welcomes articles in different areas. The language is most often English, but also Swedish manuscripts are welcome.

Summaries in Swedish and English as well as the complete original text are available at www.arbetslivsinstitutet.se/ as from 1997.

ARBETE OCH HÄLSA
Editor-in-chief: Staffan Marklund
Co-editors: Marita Christmansson, Birgitta Meding, Bo Melin and Ewa Wigaeus Tornqvist

National Institute for Working Life
S-113 91 Stockholm
Sweden

ISBN 91–7045–743–3
ISSN 0346–7821
http://www.arbetslivsinstitutet.se/
Printed at Elanders Gotab, Stockholm

Preface

The Swedish Criteria Group for Occupational Standards (SCG) of the Swedish National Institute for Working Life (NIWL) has engaged Professor Staffan Skerfving at the Department of Occupational and Environmental Medicine, University Hospital, Lund, Sweden, to write this criteria document concerning inorganic lead. Based on this document the Criteria Group will present a report to be used as the scientific background material by the Swedish Work Environmet Authority in their proposal for an occupational exposure limit.

Johan Högberg
Chairman
Criteria Group

Johan Montelius
Secretary
Criteria Group

Abbreviations

α_1-MG	α_1-Microglobulin=protein HC
AAS	Atomic absorption spectroscopy
ACGIH	American Conference of Governmental Industrial Hygienists
ALA	δ-Amino levulinic acid
ALAD	δ-Amino levulinic acid dehydratase
ALS	Amyotrophic lateral sclerosis
As	Arsenic
ß$_2$-MG	ß$_2$-Microglobulin
BAT	Biologische Arbeitsstofftoleranzwert
BEI	Biologic Exposure Index
bm	Bone mineral
BMI	Body mass index
B-ALAD	Activity of δ-amino levulinic acid dehydratase in blood
B-Cd	Blood cadmium concentration
B-Hg	Blood mercury concentration
Bone-Pb	Lead concentration in bone
B-Pb	Blood lead concentration
BUN	Blood urea nitrogen
bw	body weight
B-ZPP	Zinc protoporphyrin cencentration in blood
Ca	Calcium
Calcaneus-Pb	Heal-bone lead concentration
CAS	Chemical Abstract Service
Cd	Cadmium
Crea	Creatinine
Cu	Copper
cf	see further
CHD	Coronary heart disease
CI	95% confidence interval
CNS	Central nervous system
CP	Coproporpyrin
CRC	Chemical Rubber Company
DALY	Disability-adjusted life year
DMSA	Dimercaptosuccinic acid
ECG	Electrocardiogram
EDTA	Calcium disodium ethylenediamine acid (edetate)
EEC	European community
EEG	Electroencephalography
eg	For example
Ery-ALAD	Activity of δ-amino levulinic acid dehydratase in erythrocytes
etc	*etcetera*, and so on
EU	European Union
FAO	Food and Agriculture Organization
Fe	Iron
FEP	Free erythrocyte protoporphyrin
Finger-bone-Pb	Finger-bone lead concentration
FSH	Follicle stimulating hormone
GABA	Gamma-aminobutyric acid
GFR	Glomerular filtration rate
γ-GT	γ-Glutamyl transpeptidase
GI	Gastrointestinal
GM	Geometric mean

Hg	Mercury
HPLC	High performance liquid chromatography
HRV	Heart rate variability
ia	*inter alia*, among others
IARC	International Agency for Research on Cancer
ICP-MS	Inductively induced plasma mass spectrometry
ICRP	International Commission on Radiological Protection
ICPS	International Programme on Chemical Safety
ie	that is
IQ	Intelligence quotient
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
LH	Luteinizing hormone
LOAEL	Lowest observed averse effect level
MAK	Maximale Arbeitsplatzkonzentration
Milk-Pb	Breast milk lead concentration
M-Pb	Mobilized lead (urinary lead excretion after administration of chelating agent)
Na+, K+ATPase	Na+, K+ adenosinetriphosphatase
NADS	Nicotinamide adenine dinucleotide synthetase
NAG	*N*-acetyl-ß-D-glucosaminidase
NOAEL	No observed adverse effect level
OEL	Occupational exposure level
8-OhdG	8-hydroxy deoxyguanosine
OR	Odds ratio
P-ALA	δ-amino levulinic acid concentration in plasma
Patella-Pb	Knee-cap lead concentration
Pb	Lead
PIMS	Poison information monographs
PNS	Peripheral nervous system
P5N	Pyrimidine 5´-nucleotidase
PBGS	Porphobilinogen synthase (=ALAD)
PP	Protorphyrin
P-Pb	Plasma lead concentration
Protein HC	Human complex-forming protein=α_1-microglobulin
PTWI	Provisional tolerable weekly intake
RBP	Retinol-binding protein
ROS	Reactive oxygene species
RR	Realtive risk
RTECS	Registry of Toxic Effects of Toxic Substances.
SCE	Sister chromatid exchange
SD	Standard deviation
SEM	Standard error of the mean
SFR	Standardized fertility ratio (=relative fecundibility ratio)
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
S-Pb	Serum lead concentration
Swedish NBOSH	Swedish National Board of Occupational Safety and Health
Tibia-Pb	Shin-bone lead concentration
TLV	Threshold limit value
TWA	Time-weighted average
U-ALA	δ-Amino levulinic acid concentration in urine
U-Cd	Urinary cadmium concentration
U-CP	Urinary coproporphyrin concentration
U-Hg	Urinary mercury concentration
U-Pb	Urinary lead concentration
UK	United Kingdom

UK MRC	United Kingdom´s Medical Research Council
US, USA	United States of America
US ATSDR	United State´s Agency for Toxic Substances and Disease Registry
US CDC	United State´s Center for Disease Control and Prevetion
US EPA	United State´s Environmental Protection Agency
US NAHNES	United State´s National Health and Nutrition Examination Survey
US NIOSH	United State´s National Institute for Occupational Safety and Health
US NRC	United State´s National Research Council
US OSHA	United State´s Occupational Safety and Health Agency
VDR	Vitamin D receptor
vs	*versus*
ww	Wet weight
WHO	World Health Organization
XRF	X-ray fluorescence
Zn	Zinc
ZPP	Zinc protoporphyrin

Contents

Background

The literature on lead (Pb) is enormous. Pb is certainly the most extensively studied toxic agent. A criteria document on inorganic Pb was written in 1991 (Skerfving 1992 and 1993). Since then, a wealth of new information has been published. The intent of this update paper is to summarize this, mainly as a basis for decisions on occupational exposure limits (OELs).

However, the review will not try to comprehensively cover all information; rather it will focus on issues identified in the 1991 document to be critical for the establishment of occupational exposure standards. In addition, some other new information of importance for the risk assessment will be dwelt upon. The documents covers information up to April 30, 2004.

Each section will start with a brief summary of the "state of the art 1991", as described in the criteria document (Skerfving 1992 and 1993). Then, new data will be quoted and further treated in the section 10. Discussion and assessment.

Several reviews of the toxicology of inorganic Pb have occurred during the last decade (*eg*, PIMs 1994; American Academy of Pediatrics 1995; Skerfving et al 1995; WHO/ICPS 1995 [contains references up to 1994]; Goyer 1996; US ATSDR 1999; Landrigan et al 2000; WHO 2000b; US CDC 2002; RTECS 2003).

Concentrations will be given as presented in the papers, with one exception, that blood-Pb concentrations (B-Pb) expressed in μg/dL (very common in the US) have been changed to μg/L.

The number of decimals given for information on concentrations in the papers have been kept, in spite of the fact that they are not always warranted by the analytical technique. For bone-Pb, the negative values are sometimes obtained (*ie*, lower than the standard) and reported in the papers (not to skew the distribution).

Also, the original number of decimals for effect estimates have been kept, in spite of the sometimes large uncertainties.

1. Physical and chemical properties

Lead (Pb)	
CAS registry number:	7439-92-1
Molecular weight:	207.19 (4 isotopes: 204, 206, 207 and 208).
Density:	11.3 g/cm^3
Melting point:	327.5 ˚C
Boiling point:	1,740 ˚C
Valences:	In its inorganic compounds, Pb usually has the oxidation state +2, but +4 also occurs.
Conversions factors:	1 μg=0.004826 μmol. 1 μmol=207.2 μg.

Solubility: Metallic Pb is very insoluble, but will dissolve in nitric acid and concentrated sulphuric acid. Most Pb (II) salts are difficult to dissolve (*eg,* Pb sulphide and Pb oxides), with the exception for Pb nitrate, Pb chlorate, and – to some extent – Pb sulphate and Pb chloride. In addition, some salts with organic acids are insoluble, *eg* Pb oxalate.

Further information on physical and chemical properties of lead compounds may be obtained in, *eg*, CRC Handbook of Chemistry and Physics (1989).

2. Exposure

2.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993) it was noted, that the main origins of Pb is occupational exposure, leaded gasoline, Pb paints, industrial Pb emissions, Pb pipes and Pb solders in drinking water systems, cans with Pb-soldered side-seams, Pb-glazed ceramic ware and hobby equipment.

In accordance with this, occupation, place of living, food, alcohol and smoking habits and age, gender and socioeconomic status are determinants for the exposure. Families of Pb workers are exposed in their homes through Pb unintentionally brought home by the worker. Some exposure occurs through alcoholic beverages and tobacco (including environmental tobacco smoke).

The main routes of Pb exposure in Sweden are food and - to a lesser extent - air. In some other countries, ingestion of soil and dust by children are very important, in some areas inhalation and ingestion of drinking water. Uptake of Pb occurs through the gastrointestinal (GI) tract and inhalation.

It was estimated that an adult Swede, without occupational exposure, ingested about 0.5 μg/kg/day (Skerfving 1992 and 1993). The “background” inhalation exposure was far less. The exposure in modern man is two orders of magnitude higher than in prehistoric subjects (Nubian skeletons).

2.2 Update

There seems to be some skin absorption of soluble Pb species (Stauber et al 1994).

Most of the information on exposure is based on measurements of the Pb concentration in blood (B-Pb) (Skerfving et al 1993; WHO/ICPS 1995; WHO 1996). Hence, this will mainly be used as an index. The occupational exposure to Pb in the Swedish work life decreased during the 1970s and 1980s. For example, in a primary smelter the mean B-Pb in 1950 was 3.0 μmol/L, in 1987 1.6 μmol/L (Lundström et al 1997). Further, in the register over legally prescribed surveys of B-Pb in Pb-workers, the mean concentration was about 1.4 μmol/L in 1977, about 1 μmol/L in 1989 (Figure 1) (Swedish NBOSH 1993), although there may be a sampling bias. In 1989, about 100 subjects in the four main exposing factories were removed from exposure because of B-Pb ≥2.5 μmol/L (Järvholm 1996). Unfortunately, after 1989, there is no national Swedish register.

After 1991, there has been a dramatic decrease of B-Pbs in the general Swedish population (Strömberg et al 1995 and 2003; Bárány et al 2002b; Lundh et al 2002; Wennberg et al, submitted), certainly mainly as a result of elimination of Pb from gasoline. In accordance with this, the exposure gradient from the rural to urban environment has decreased (Strömberg et al 2003).

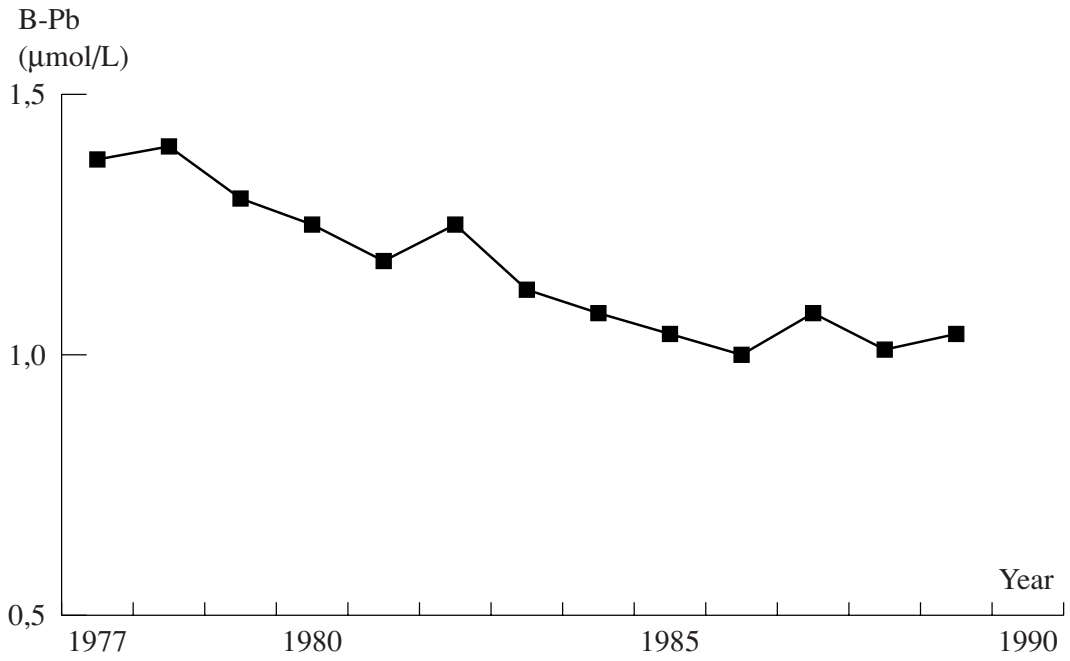

Figure 1. Blood lead levels 1977-89 in lead workers registered in the national Swedish register (Swedish NBOSH 1993).

Living close to a Swedish Pb-emitting industry (mining and smelting) may have caused exposure in adults (Lagerkvist et al 1993; Hallén et al 1995) and children (Strömberg et al 1995; Gerhardsson et al 1997a; Farago et al 1999), but it seems that this has decreased (Berglund et al 1994 and 2000b; Strömberg et al 2003). The impact of alcohol intake and smoking has been confirmed (Bensryd et al 1994; Micciolo et al 1994; Ehrlich et al 1998; Åkesson et al, submitted), including that of environmental tobacco smoke (Willers et al 1992 and 1993; Osman et al 1998a; Berglund et al 2000b).

There has been an almost complete elimination of Pb-soldered side-seams in food cans. As a curiosity, crystal glass may contaminate its liquid content (Nilsson 2002). Shooting at indoor firing ranges (Svensson et al 1992), as well as outdoor hunting (Bensryd et al 1994) cause exposure to Pb. Gun bullet wounds may cause a remarkable increase of B-Pb (Gerhardsson et al 2002).

Acid precipitation may cause an increase in the concentration of Pb in water from private wells (Bensryd et al 1994; Gerhardsson et al 1997a; Rosborg et al 2003a and 2003b). However, there were no relationships between acidity of drinking water or its Pb content, on the one hand, and B-Pb, on the other (Bensryd et al 1994).

In 16 Swedish women having a mixed diet, the median fecal elimination of Pb was 31 (range 14-118) μg/day (Vahter et al 1992). Since the GI absorption is low, this should correspond to an ingestion of about 0.5 μg/kg body weight (bw)/day, thus confirming the 1991 estimate. In other countries, food basket studies in the 1980s have indicated intakes up to 60 μg/kg bw/week (WHO 2000b). When there were data for both children and adults, the former had a 2-3 times higher intake than the latter.

A lot of the data on risks associated with Pb exposure relate to environmental exposure in various other countries. Then, the exposure may be much higher. For example, in Mexico City, the population of which has been studied frequently, the exposure is high due to heavy traffic and high concentrations of Pb in the petrol (Hernandez-Avila et al 1998) and consumption of foods cooked in Pb-glazed pottery (Téllez-Rojo et al 2004). The exposure in some areas has decreased as a result of reduction/elimination of Pb from gasoline (Thomas et al 1999; Ikeda et al 2000a and 2000b). Hence, the air concentration of Pb at selected monitoring sites across the US decreased by 94% 1980-99 and by 60% 1990-99 (US EPA 1999; US CDC 2003). In Sweden, the air-Pb now is a few ng/m^3 (Nilsson 2003).

In areas, where the air levels of Pb were low, food is the dominating source of Pb uptake, while high air concentration mean that half of the absorbed amount originated from inhalation (Ikeda et al 2000a).

Pb plumbing (leaded water pipes and Pb-soldered joints) in the drinking-water system may still be a problem (Potula et al 1999; Fertmann et al 2004), as may living close to Pb-emitting industries (Bernard et al 1995; Osman et al 1998a; Skerfving et al 1999; Counter et al 2000; Fischer et al 2003; Wasserman et al 2003). Also, dust and soil contaminated by deteriorating Pb-based paint is a major concern (Elhelu et al 1995; Mielke & Reagan 1998; Manton et al 2000; Haynes et al 2003). Pb-glazed low-temperature fired ceramic pottery is a problem in some

countries (Brown et al 2000; Hernandez-Avila et al 1996). In the last decade, heavy non-occupational exposure through cosmetics and herbal preparations in some population strata have been stressed (Markowitz et al 1994). In 1979-1998 there were 200 deaths from Pb poisoning in the US (Kaufmann et al 2003). The rate had decreased during the period. Ingestion of "moonshine" (illegally produced whiskey) and Pb paint (in children) and occupational poisoning were major causes in 1979-1988 (Staes et al 1995).

"Background"/"reference"/"normal" concentrations for B-Pb are discussed below (section 3.1. Blood lead).

2.3. Summary

In Sweden, the occupational exposure to Pb has decreased in the last decades, as has exposure from leaded gasoline. The main route of Pb exposure in the general population in Sweden is food. Alcohol beverages, smoking and drinking water are other sources of background exposure. Acid precipitation increases Pb in well water. Swedes ingest about 0.5 μg/kg bw/day, which is a low figure from an international point of view.

In other geographical areas, occupation, industrial Pb emissions, dust from Pb-paints, Pb pipes for drinking water, Pb-soldered cans and Pb-glazed ceramicware are important sources.

3. Metabolism and biomonitoring

3.1. Blood lead

3.1.1. State of the art 1991

B-Pb is traditionally used for biomonitoring of Pb (Skerfving et al 1993). In 1991 (Skerfving 1992 and 1993), it was noted that other indices [urinary-Pb=U-Pb, chelated Pb (sometimes called mobilized Pb=MPb) and bone-Pb] had been used, but only to a limited extent. Serum/plasma-Pb (S-Pb/P-Pb) has some advantages over B-Pb, but the analytical problems were great. As regards B-Pb, it was stressed that: (1) The relationship between uptake and B-Pb is not rectilinear, the relative increase of B-Pb decreases with rising exposure. This is probably the reason why some effects (*eg*, on heme metabolism) display non-linear relationships with B-Pb; it does not mean that there is a threshold. (2) There is a large inter-individual variation in kinetics of B-Pb. (3) There also seemed to be a great variation in the effects suffered by different individuals at the same B-Pb. There were some indications that this might be due to variations in binding of Pb.

The "background" B-Pb in Swedish males in 1991 was assumed to be about 0.4 μmol/L, somewhat lower in females. In an international perspective, these were low concentrations.

3.1.2. Update

3.1.2.1. Erythrocytes/whole blood

δ-Aminolevulinic acid dehydratase (ALAD; porphobilinogen synthase=PBGS; EC 4.2.1.24) is an enzyme present in all cells, including the erythrocytes (review: Kelada et al 2001). It is the second enzyme in the heme pathway, promoting the asymmetric addition of two molecules of δ-aminolevulinic acid (ALA) to form the monopyrrole porphobilinogen. ALAD is a 250 kDa homo-octameric enzyme, containing four active sites, reactive cysteines, and two different types of zinc (Zn)-binding sites (Jaffe et al 2000). Pb can replace some of the Zn (Jaffe et al 2001); the binding of Pb is about 20 times tighter than for Zn (Simons 1995). The association of Pb causes slow-acting inhibition of the enzyme activity.

In the red cells, ALAD binds about 80% of the Pb (Bergdahl et al 1996 and 1998b; Bergdahl 1998). However, the binding capacity is limited. This is the explanation of the well-known non-rectilinearity of the relationship between B-Pb and exposure (Skerfving et al 1993). Other proteins in the erythrocyte also bind Pb, though to a much lesser extent (Bergdahl et al 1998b). Hence, a 45-kDa protein carries only about 20% of the B-Pb and a <10 kDa one <1%, while no binding to hemoglobin was found.

In northern Sweden, the range of Pb in erythrocytes (Ery-Pb) in *adults* (age 25-74) in the period 1990-1999 was 11-750 μg/L; the median in males was 63, in females 45 μg/L (Lundh et al 2002; Wennberg et al, submitted). The highest median concentration (71 μg/L) was seen among males in the age *stratum* 45-54 years. If one assumes a 45% packed cell volume, this corresponds to a B-Pb of 29 μg/L. The Ery-Pb was higher in men than in women (maximum median 52 μg/L at age 55-64).

In 176 men and 248 women from central Sweden, the B-Pb was lower at 50 than at 70 years of age; after 70, there was an increase, probably because of higher exposure 10-30 years ago, which had been retained in the skeleton (Baecklund et al 1999). In 730 women aged 53-64 years from the south of Sweden sampled in 1997, the median B-Pb was 22 (range 7-81) μg/L (Åkesson et al, submitted). Further, in 762 elderly (age above 75, mean 88.2±4.9 years), subjects from Stockholm city, the average B-Pb was 0.18±0.11 (range 0.01-1.41) μmol/L (Nordberg et al 2000). Men had higher B-Pb than women (0.22 vs. 0.17 μmol/L, respectively).

In 314 15-year-old *adolescents* from Central Sweden (Uppsala and Trollhättan), the median B-Pb 1993/94 was 16 (range 3.5-170) μg/L (Bárány et al 2002a; Bárány & Oskarsson 2002). Boys had higher B-Pb than girls (medians 20 *vs* 15 μg/L) (Bárány et al 2002b). In 7-year-old *children* sampled in southern Sweden 1995-2001, the geometric mean B-Pb was 21 (range 6-80) μg/L (Strömberg et al 2003).

B-Pbs have decreased in many countries during the last decades (Skerfving et al 1999; Thomas et al 1999; Meyer et al 2003b). Hence in Sweden, the decrease has been about 6% per year in both children in the south (Strömberg et al 1995 and

2003), see Figure 2**,** and adults in the north (Lundh 2002; Wennberg et al, submitted); there was also a decrease in adolescents (Bárány et al 2000b). The decrease is parallel to the elimination of leaded gasoline (Strömberg et al 1995 and 2003). Decays of B-Pb have also been reported in Germany (Meyer et al 2003a), Poland (Jarosinska & Rogan 2003) and the United Kingdom (UK) (Delves et al 1996) and the US (Pirkle et al 1998). In some areas, it has been shown, that the decrease reflects air-Pb concentrations (Thomas et al 1999).

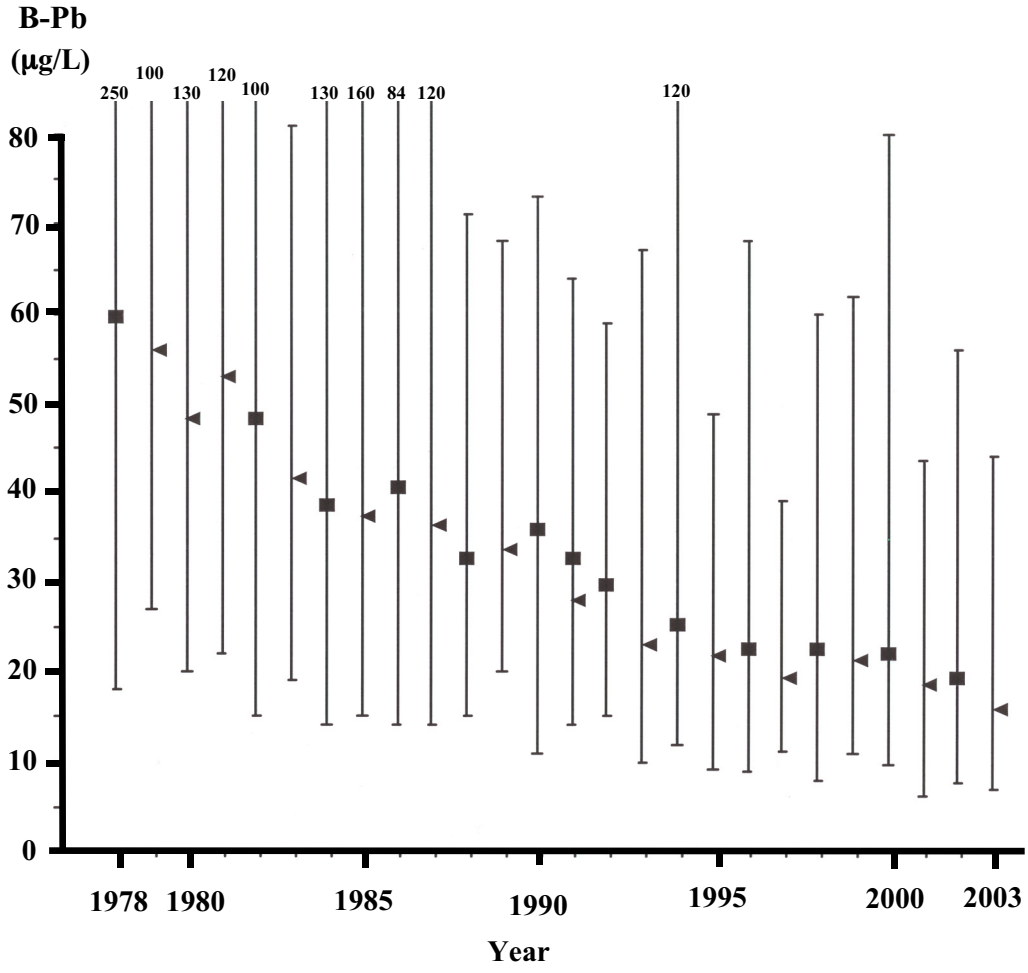

Figure 2. Blood lead levels (geometric means and ranges, which have been truncated at 83 μg/L) in 3,306 Swedish children 1978-2003 (Landskrona=squares, Trelleborg= triangles) (Strömberg et al 2003 and to be published).

Table 1. Blood lead concentrations in urban children and adults (B-Pb, in different areas, WHO regions) (Fewtrell et al 2004).

Area	WHO region	Surveyed countries	B-Pb (μg/L)	
			Children	Adults
Africa	D	Nigeria	111	116
	E	South Africa	98	104
Americas	A	Canada, USA	22	17
	B	Argentina, Brazil, Chile, Jamaica, Mexico, Uruguay, Venezuela	70	85
	D	Ecuador, Nicaragua, Peru	90	108
Eastern Mediterranean	B	Saudi Arabia	68	68
	D	Egypt, Morocco, Pakistan	154	154
Europe	A	Denmark, France, Germany, Greece, Israel, Sweden	35	37
	B	Turkey, Yugoslavia	58	92
	C	Hungary, Russia	67	67
South East Asia	B	Indonesia, Thailand	74	74
	D	Bangladesh, India	74	98
Western Pacific	A	Australia, Japan, New Zealand, Singapore	27	27
	B	China, Philippines, Korea	66	36

In a review of B-Pbs measured in different regions, there was a remarkable variation, with one order of magnitude (Fewtrell et al 2004), see Table 1.

However, in many countries, the B-Pbs are still high. Some examples: Even in the Baltic area, there are considerable variations (Skerfving et al 1999). Hence, in some geographical areas, the B-Pbs are high: In the Katowice area, Poland, the median B-Pb in children was 0.27 (range 0.09-1.9) μmol/L (Osman et al 1998a). In some areas of Kosovo, the median B-Pb in children is 120 (range 42-260) μg/L (Gerhardsson et al 2001). In Montevideo, Uruguay, the mean B-Pb was 96 (range 47-191) μg/L (Schütz et al 1997). In the Ecuadorian Andes, B-Pbs up to 1,100 μg/L were encountered in children in families engaged in tile production (Counter et al 1997; Vahter et al 1997).

In samples obtained 1999-2000 (National Health and Nutrition Examination Survey III=NHANES III) in adult US males, the median B-Pb was 18 and in females 13 μg/L (US CDC 2003). In US children aged 1-5 years, the median was 27 μg/L; however, 4.4% had ≥100 μg/L (Pirkle et al 1998). There was a gradient from non-hispanic whites, over Mexican Americans to non-hispanic blacks. High levels occur in urban settings, old buildings, lower socioeconomic groups, immigrants and refugees. (Kaufmann et al 2000). In many areas, the fraction of children with B-Pb ≥100 μg/L is high. Hence, in New Orleans, Louisiana, USA, 29% had such concentrations (Rabito et al 2003), in Wuxi City 27% (Gao et al 2001),

in Johannesburg, South Africa 78% (Mathee et al 2002) and in Dhaka, Bangladesh, 87% (Kaiser et al 2001).

Guidelines for sampling (Cornelis et al 1996) and presentation of "normal" values for toxic metals in blood and urine (Vesterberg et al 1992) have been published, as well as reference values for B-Pb (Gerhardsson et al 1996; Ewers et al 1999; Herber 1999). However, it was not possible to establish generally valid reference values for B-Pb. The B-Pbs are widely distributed within any population, and generally appear to have a log-normal distribution, which is skewed towards higher concentrations. As a result, many people are exposed to high concentrations of Pb, even when the mean is low.

There is some diurnal variation in B-Pb, with the lowest values in the night (Yokoyama et al 2000; Soldin et al 2003). In children, season of sampling for B-Pb seems to be of importance (higher in summer) (Mielke & Reagan 1998; Gulson et al 2000a; Kaufmann et al 2000), probably mainly because the varying fraction of time they spend outside.

B-Pbs were associated with the serum level of selenium (Se) (Osman et al 1998b; Bárány et al 2002c), as well as with glutathion peroxidase and selenoprotein P in serum (Osman et al 1998b). This may indicate an effect of Se on Pb metabolism, which may be of particular interest in Sweden, since it is a Se-deficient area.

The relationship between B-Pb and skeletal Pb is discussed below (Section 3.2. Skeletal/bone lead).

3.1.2.2. Plasma/serum

Pb is present in blood plasma and serum (P-Pb/S-Pb). The P-Pb makes up only about 1% of the total B-Pb (Schütz et al 1996; Bergdahl et al 1998b and 1999; Skerfving et al 1998; Smith et al 1998; Hernandez-Avila et al 1998; Bárány et al 2002c; Bergdahl 2002; Smith et al 2002).

In plasma, most of the Pb has been claimed to be present in a low molecular weight fraction, supposed to represent an ionic form (Sakai et al 1998). Possibly, some of the Pb is bound to cystein, which is in accordance with *in vitro* binding (Al-Modhefer et al 1991). Also, there is some binding to a high molecular weight protein, which is neither globulin, nor albumin, in spite of *in vitro* binding to the latter.

Serum/plasma is readily transported to target organs and may thus constitute the majority of the bioavailable Pb in the circulation. This should make S-Pb/P-Pb optimal measures of exposure and risk. However, because of the low concentrations, determination of Pb in plasma/serum has long been analytically complicated.

However, the development of inductively-induced plasma mass spectrometry (ICP-MS) has made determinations sensitive (detection limit about 0.01 μg/L), accurate and relatively simple (Schütz 1993; Schütz et al 1996; Bárány et al 1997; Smith et al 1998). For example, in 43 Swedish Pb-smelter workers, the median P-Pb was 1.2 (range 0.3-3.6) μg/L, while the B-Pb was 281 (60-530) μg/L. In seven unexposed controls, the corresponding values were 0.15 (0.1-0.3) and 40 (24-59)

μg/L, respectively (Schütz et al 1996). Contamination at sampling or analysis is no major problem. However, severe hemolysis may cause spuriously high concentrations (Smith et al 1998; Bergdahl et al, submitted). There was no swift variation from day-to-day depending on the variations in exposure.

As said above, because of the saturation of ALAD binding, the relationship between B-Pb and P-Pb is non-rectilinear (Bergdahl et al 1997c; Smith et al 2002). Possibly, the B-Pb/P-Pb relationship varies between individuals (Hedmer et al 2001; Smith et al 2002; Bergdahl et al, submitted).

P-Pb after chelation has been proposed as an index of body burden (Sakai et al 1998), but has only occasionally been used.

3.1.3. Summary

Traditionally, B-Pb is used for biomonitoring of Pb. A major advantage of B-Pb is the wealth of information. However, it has problems: (1) The relationship between uptake (and effects) and B-Pb is not rectilinear. (2) There is a large inter-individual variation in kinetics of B-Pb.

There has been a dramatic decrease of B-Pb during the last decades. The "background" average B-Pb in adult Swedish males is now about 0.15 μmol/L, lower in females, adolescents and children. In an international perspective, these are low concentrations.

In the erythrocytes, Pb is mainly bound to the enzyme ALAD. The binding capacity is limited, which is the explanation of the non-linear behaviour of B-Pb.

Serum/plasma-Pb (S-Pb/P-Pb) amount to only 1% of the B-Pb. They have some advantages over B-Pb (closer relation to target tissue concentration). The analytical problems are no longer unsurpassable. However, there is still limited information. Hence, we have to rely on B-Pb.

3.2. Skeletal/bone lead

3.2.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was concluded, that Pb accumulates in the skeleton, which contains several Pb pools; trabecular bone has a faster turnover than cortical. Pb is released from the skeleton, whereby it may cause endogenous exposure, which may go on for decades after end of occupational exposure, and may be responsible for a major fraction of B-Pb. The bone-Pb might constitute a risk of poisoning, if rapidly released. Thus, skeletal accumulation should be avoided, especially in girls and fertile women, since it will cause exposure of the fetus and breast-fed infant. Also, there were indications of a mobilization of Pb from the skeleton at menopause.

3.2.2. Update

Methods for *in vivo* measurement of Pb by K-shell X-ray fluorescence (XRF) in fingerbone (Skerfving & Nilsson 1992; Nilsson & Skerfving 1993; Mattsson et al 2002), cortical tibia (Erkkilä et al 1992; Todd & Chettle 1994), as well as the

mainly trabecular bones, calcaneus (Erkkilä et al 1992; Todd & Chettle 1994), and patella (Hu et al 1991, 1996c and 1998; Watanabe et al 1994) have been extensively used in the last decade. Occasionally, determinations have been reported for ulna and sternum, but the measurements were less precise (Erkkilä et al 1992). There is a reasonably good correlation between the different bone sites (Gerhardsson et al 1992; Erkkilä et al 1992; Tell et al 1992). The concentrations in tibia and calcaneus may be used to calculate the total bone Pb burden, which averaged about 100 mg in Pb workers and 8 mg in occupationally unexposed subjects (Erkkilä et al 1992). Measurements by L-shell XRF have been used only occasionally, because of its inability to assess deep parts of the bone.

A long series of studies of bone-Pb in Pb workers have been published in the last decade (*eg*, Erkkilä et al 1992; Gerhardsson et al 1992, 1993 and 1998; Börjesson et al 1997a and 1997b; Olsson et al 2000; Schütz et al, submitted). Their levels are much higher than in occupationally unexposed subjects. Usually, the highest concentrations have been recorded in retired workers, as compared to active ones (Gerhardsson et al 1993), due to longer exposure duration and higher exposure intensity (and the slow elimination of Pb from bone, see below!).

Also, many studies of bone-Pb in the general population have appeared (*eg*, Gamblin et al 1994; Kosnett et al 1994; Hoppin et al 1995, 1997 and 2000; Hu et al 1996b; Kim et al 1997; Roy et al 1997; Aro et al 2000; Wasserman et al 2003; Lin et al 2004). Determinations are possible for tibia, calcaneus and patella, at least in populations with a relatively high exposure. However, for fingerbone, the sensitivity is not sufficient. The tibia-Pb in Canada was higher than in northern Sweden and Finland, similar to southern Sweden, but lower than in England (Roy et al 1997). There is an increase in bone-Pb with age (Kosnett et al 1994; Watanabe et al 1994; Hu et al 1996b; Lin et al 2004).

There are associations between bone-Pb, on the one hand, and both B-Pb (Erkkilä et al 1992; Börjesson et al 1997a and 1997b; Gerhardsson et al 1998; Wasserman et al 2003) and S-Pb/P-Pb (Bergdahl et al 1998a; Gerhardsson et al 1998; Hernandez-Avila et al 1998), on the other. Women immigrating to Australia, from areas where the exposure was to Pb of a different $^{206}Pb/^{204}Pb$ ratio than that in Australia, have been studied for changes in the B-Pb isotopic ratios (Gulson et al 1995). This confirmed that release from bone made up a significant fraction (45-70%) of total B-Pb. Similar data have been published for the US general population (Smith et al 1996). In Pb workers, about 1.7 μg/L per μg/g bm in tibia seemed to originate from endogenous exposure (Bleecker et al 1995). The association between bone-Pb and B-Pb is particularly close in retired workers, but less in active ones, in whom the current exposure is superimposed on the endogenous one from bone (Erkkilä et al 1992; Gerhardsson et al 1992 and 1998; Börjesson et al 1997a and 1997b). It has been estimated, that a constant occupational exposure corresponding to a B-Pb of 2.4 μmol/L for 38-63 years would result in a B-Pb of 1 μmol/L after retirement (Erkkilä et al 1992).

Pb is lost from the bone by diffusion (heteroionic exchange), as well as by resorption. The trabecular (spongy, *eg*, in calcaneus, patella and vertebrae) bone-

Pb has a more rapid turnover than the cortical (Hu et al 1991 and 1998; Kim et al 1997). From relationships between tibia-Pb and calcaneus-Pb, on the one hand, and time-integrated B-Pb, on the other, it was estimated that the half-times were 13 and 12 years, respectively. In a similar approach, the corresponding half-times were 16 and 27 years (Gerhardsson et al 1992). In a recent study, the tibia-Pb half-time was estimated to 15 (95% confidence interval=CI 9-55) years (Brito et al 2000). There are indications that young subjects have a shorter half-time than older ones, and that high exposure means a slower turnover than a low (Brito et al 2000 and 2001). For fingerbone-Pb, the half-time was estimated to 5.2 (range 3.3-13.3) (Börjesson et al 1997a) and 14 (Börjesson et al 1997b) years.

By direct, long-term measurement of finger-bone-Pb by XRF in Pb-workers for up to 18 years after end of exposure, the half-time was 16 (95% confidence interval=CI 12-23) years (Nilsson et al 1991). The corresponding decline of B-Pb could be described by a three-exponential model, with half-times of 34 (29-41) days, 1.2 (0.9-1.8) years and 13 (10-18) years, respectively, Figure 3 (Skerfving et al 1993 and 1998) and Figure 4 (Skerfving et al, to be published). The fast

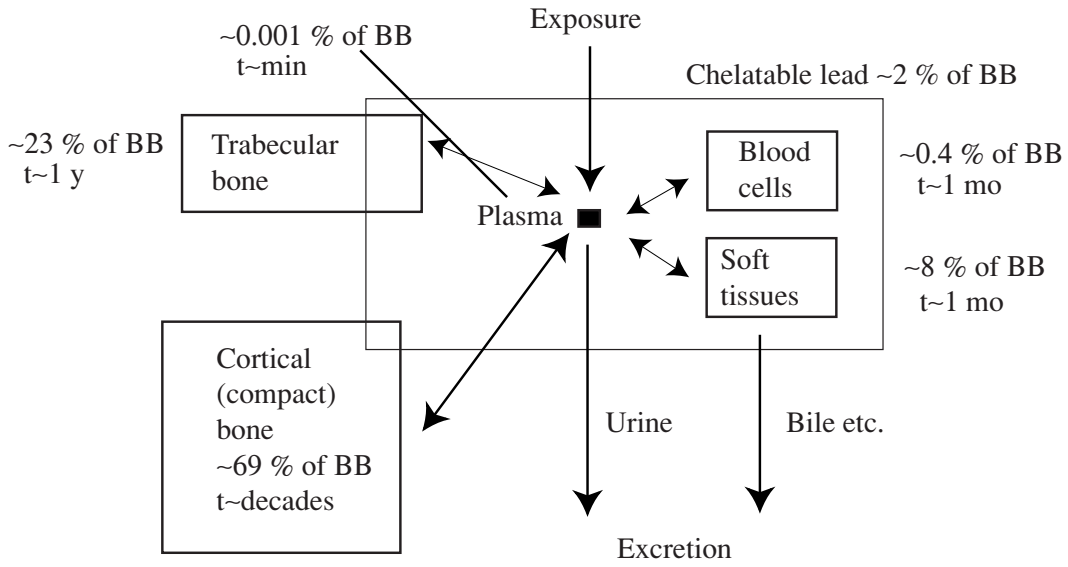

Figure 3. Metabolic compartment model for lead in an adult man (Skerfving et al 1995). The figures shown for the percentage of body burden in different compartments are those corresponding to approximately steady state conditions (*ie*, the situation after regular exposure during long time). The areas of the boxes are not proportional to the sizes of the compartments. "Chelatable lead" denotes the amount available for binding to a chelating agent in a mobilization test. BB=total body burden; t=biological half time; y=year; mo=month; min=minute.

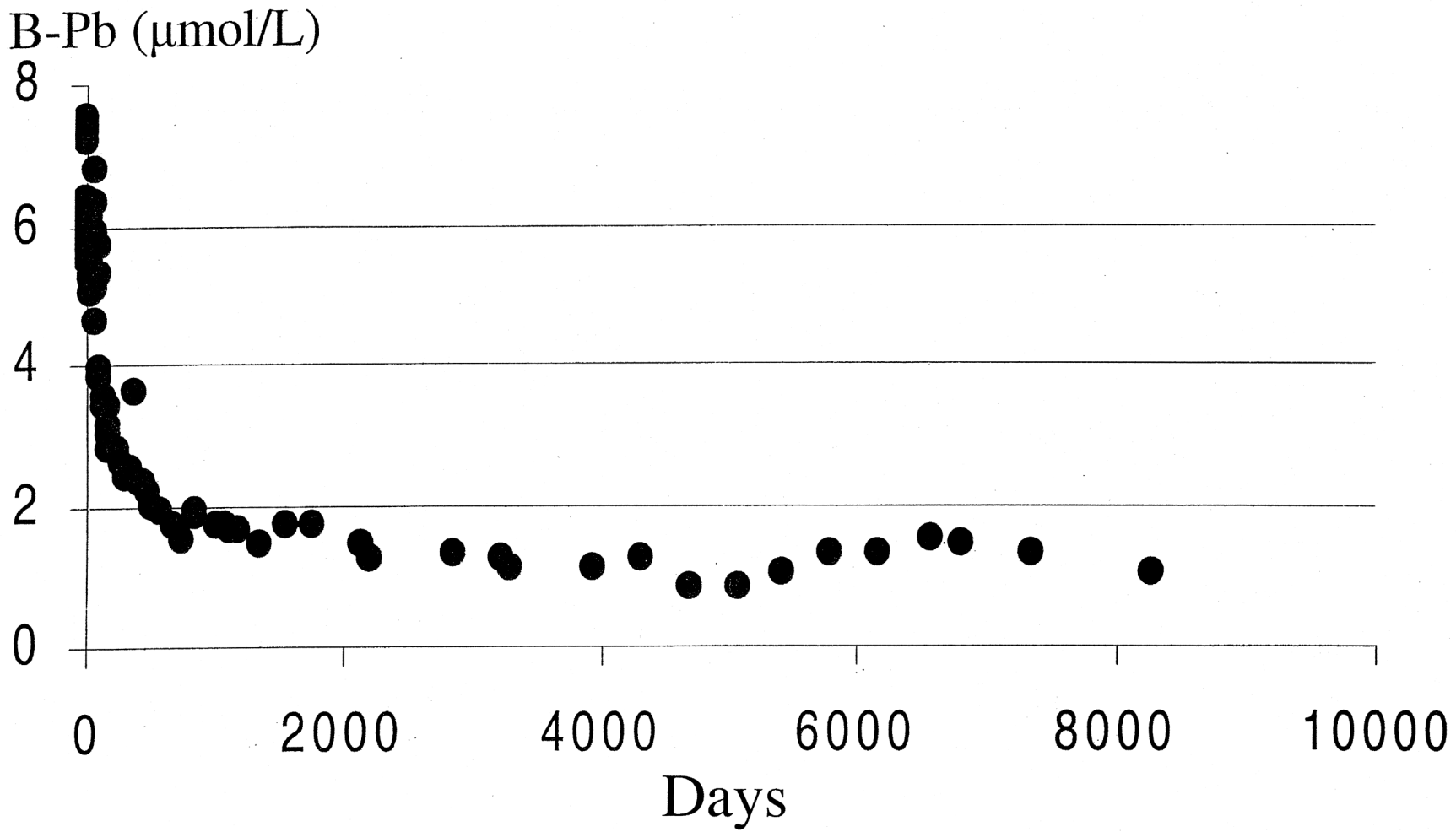

Figure 4. Blood lead level (B-Pb) in a worker during 23 years after end of heavy exposure. In the worker, it is possible to identify three different compartments, representing soft tissues, trabecular bone and cortical bone (Skerfving et al, to be published). Note: At the end of the period, the mean B-Pb in the "background population" was about 0.15 μmol/L.

component definitely reflects soft tissues, the second probably trabecular bone and the last one cortical bone.

In particular, evidence suggests mobilization of Pb from the skeleton during bone demineralisation. Women loose as much as half of the trabecular bone and a third of cortical peak bone mass during their later lifetime. Estrogen supplementation may decrease the Pb mobilization (Webber et al 1995; Korrick et al 2002; Latorre et al 2003). Increased B-Pb has been observed during pregnancy and lactation (section 8. Reproduction and effects in infants/small children), menopause (Grandjean et al 1992; Lagerqvist et al 1993; Symanski et al 1995; Nielsen et al 1998; Berglund et al 2000a; Hernandez-Avila et al 2000; Korrick et al 2002; Latorre et al 2003), old age (Webber et al 1995; Tsaih et al 2001), thyreotoxicosis (Goldman et al 1994) and primary hyperparathyroidism (Osterloh & Clark 1993). Other bone disease may also increase the bone-Pb (Berlin et al 1995; Adachi et al 1998).

There is a strong interaction between season and bone-Pb (patella) on B-Pb; hence, the bone-Pb exerted an almost two-fold greater influence on B-Pb during the winter months than in the summer (Oliviera et al 2002). The explanation was supposed to be enhanced bone resorption, because of decreased exposure to sunlight, resulting in lower levels of activated vitamin D.

Because of its slow turnover, bone-Pb reflects long-term Pb exposure (and total body burden), which may be of importance for chronic toxicity. Hence, in Pb workers, there were close correlations between tibial and calcaneal Pb, on the one hand, and duration of exposure to inorganic (Todd et al 2001) and organic (Swchwartz et al 1999) Pb and time-integrated B-Pb in workers exposed to inorganic Pb (Bergdahl et al 1998a), on the other.

The relationships between exposure time, B-Pb and bone-Pb are described in Figure 5. They are non-rectilinear (Fleming et al 1997; Brito et al 2002). When recent exposure has been low, meaning a relatively low current B-Pb, a high bone-Pb may indicate previous higher exposure, which may affect the relationship between effects and B-Pb in the direction of an underestimate of risk.

In a study of bone-Pb, Cake et al (1996) found a somewhat stronger correlation with S-Pb than with B-Pb. In accordance with this, among Mexicans, bone-Pb (in particular trabecular) had a B-Pb-independent effect on P-Pb (Hernandez-Avila et al 1998). Further, in pregnant women, estimated P-Pb varied independently of B-Pb, and was assumed to be affected mainly by maternal bone-Pb (Chuang et al 2001).

On the basis of such observations, it has been speculated, that the endogenous Pb from bone may cause a constant inflow of Pb into serum/plasma, which may elevate the S-Pb/P-Pb continuously over extended periods of time, thus leading to a great transfer of Pb into target organs and high P-Pb/B-Pb ratio (Cake et al 1996; Hu et al 1998). In contrast, Pb from exogenous sources (ingested or inhaled), which may enter the circulation in a discontinuous fashion, depending on the exposure pattern, was believed to cause a lower target organ exposure and P-Pb/B-Pb ratio. Similar conclusions were made on basis of studies of U-Pb, which was used as a proxy for P-Pb (Tsaih et al 1999).

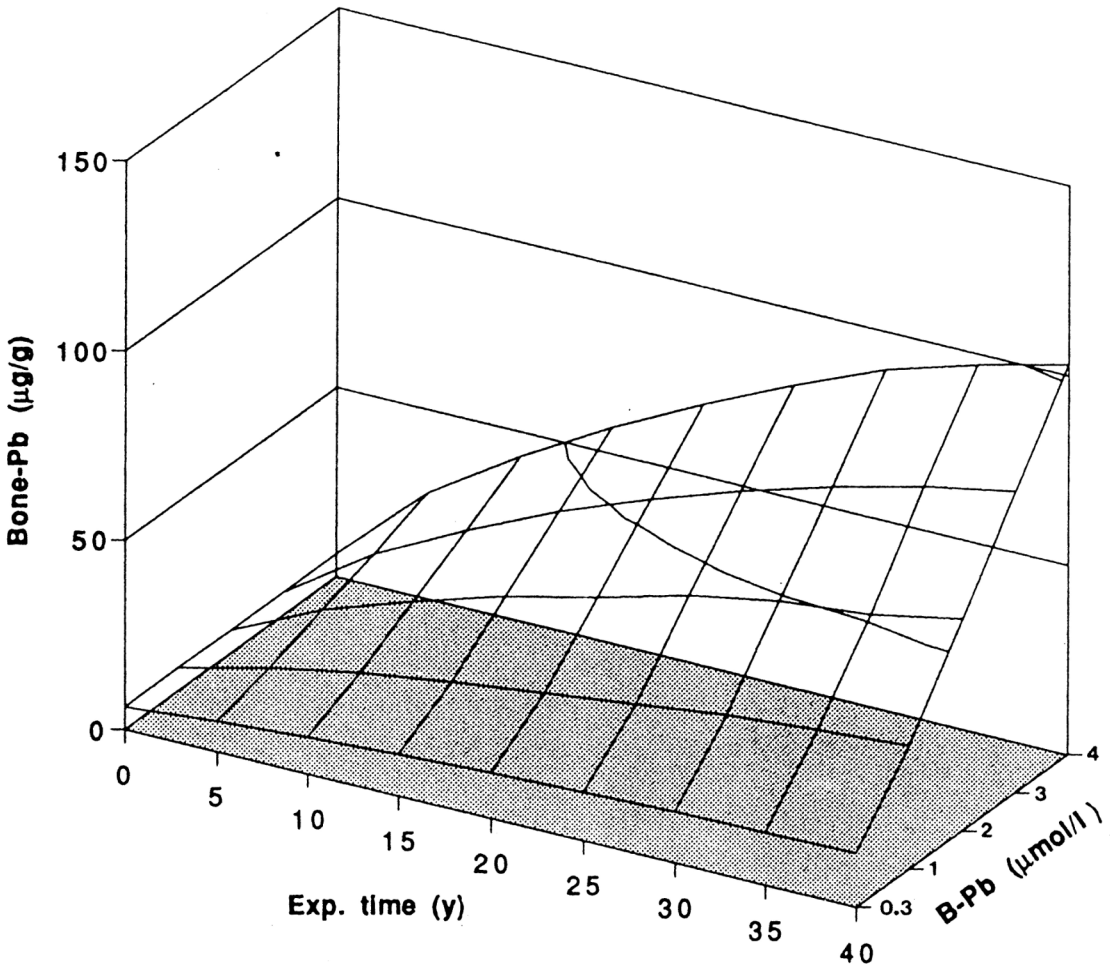

Figure 5. Relation between bone (Bone-Pb) and blood (B-Pb) lead concentration, assuming that the worker´s exposure is constant over time. It is assumed that the exposure starts at age 17 years and that the B-Pb in an occupationally unexposed subject is 0.3 μmol/L (Börjesson et al 1997b).

However, no support for a preferential effect of bone-Pb on P-Pb was found, neither in a study of B-Pb, P-Pb and bone-Pb among Swedish active and retired smelter workers (Bergdahl & Skerfving 1997), nor in studies of Pb-isotope ratios in pregnant and lactating women (Gulson et al 1998b, 2000b and 2003). This is also in accordance with the rapid equilibrium between plasma and erythrocytes (Simons 1993).

The above-mentioned observations, that S-Pb or P-Pb may reflect bone-Pb better than B-Pb, or at least contribute in models of bone-Pb and B-Pb, have a much simpler explanation in the fact that they are all inter-correlated. Any exchange between bone and blood occurs *via* plasma. Therefore, in modelling of bone-Pb, B-Pb is merely a proxy for P-Pb. Bearing in mind that P-Pb, at the same B-Pb, can vary by a factor 2-3, it is natural that P-Pb contributes

significantly in models of B-Pb and bone-Pb. Moreover, the curved relation between B-Pb and P-Pb might be paralleled by a similarly non-rectilinear one between B-Pb and bone-Pb (Brito et al 2002), which would invalid the linear regression model. Hence, there is no evidence that the endogenous exposure from bone-Pb should pose a threat different from the external one.

Deciduous tooth-Pb in children predicts bone-Pb decades later (Kim et al 1996a). Of course, the turnover is slow (Gulson and Gillings 1997). There was an association between B-Pb and dental caries (Moss et al 1999; Gemmel et al 2002). This might be because of Pb-modified enamel is more susceptible, but there are several other possibilities, including residual confounding by socioeconomic factors.

3.2.3. Summary

Pb accumulates in the skeleton, which contains about 95% of the body burden, and which has several Pb pools; trabecular bone has a faster turnover (half-time about one year) than cortical (half-time decades). Pb is released from the skeleton, whereby it may cause endogenous exposure, which may go on for decades after end of occupational exposure, and may be responsible for a major fraction of B-Pb. It has been claimed, that P-Pb is particularly affected by this release; however, this is far from well founded.

The bone-Pb might constitute a risk of poisoning, if rapidly released. Thus, Pb accumulated in the skeleton of girls and fertile women, will cause considerable exposure of fetuses and breast-fed infants. Also, there is mobilization of Pb from the skeleton at menopause.

Skeletal Pb may be measured by *in vivo* XRF. There is a lot of information on tibial, calcaneal and patellar Pb levels in Pb workers and general populations. The bone-Pb reflects the long-term B-Pb pattern (time-integrated or cumulated B-Pb).

3.3. Urinary lead and chelatable lead

U-Pb has sometimes been used as a proxy for biomonitoring of exposure and risk of Pb (Skerfving 1992 and 1993).

In a study of 646 women aged 52-63 years from the south of Sweden, there was a relatively close association between B-Pb (median 22, range 11-46 μg/L) and U-Pb (r_S=0.67; p<0.0001) (Åkesson et al, submitted). However, the variation is too large (Erkikilä et al 1992; Skerfving et al 1993; Bergdahl et al 1997c; Börjesson et al 1997a and 1997b; Gulson et al 1998a; Paschal et al 1998; Fukui et al 1999; Higashikawa et al 2000; Shimbo et al 2000), to allow a prediction on an individual B-Pb from U-Pb. Also, the association, due to the above-mentioned saturation of B-Pb, is non-linear (Fukui et al 1999; Tsaih et al 1999). Further, the necessary adjustment for variations in dilution of spot samples is difficult to manage (Sata et al 1995; Sata & Araki 1996); *eg*, the creatinine excretion, which is often used, is dependent upon muscle mass. Also, there is some diurnal variation in the excretion, with the lowest concentrations in the night, due to some diurnal variations in P-Pb and in glomerular filtration rate (GFR) (Yokoyama et al 2000). Since

creatinine excretion also varies in parallel, creatinine-adjusted U-Pb concentrations vary less.

In contrast to B-Pb, P-Pb seems to be rectilinearly related to "basal" U-Pb (Hirata et al 1995; Bergdahl et al 1997c; Gerhardsson et al 1998), as well as to the urinary excretion of Pb after chelation (Gerhardsson et al 1999).

Urinary excretion of Pb after administration of a chelating agent has often been used as an index of risk and total body burden. After administration of calcium disodium ethylenediamine tetraacetic acid (EDTA), the P-Pb increases, because of the presence of a Pb-EDTA complex, which is filtrated into urine (mobilized Pb=M-U-Pb; *chelatable Pb/chelated Pb/mobilized Pb)* (Sakai et al 1998). After such chelation there is only a marginal (6%) decrease of erythrocyte Pb (and thus of B-Pb). The Pb excretions after the major chelating agents (EDTA and dimercaptosuccinic acid (DMSA) differ (Lee et al 1995).

Chelatable Pb (Figure 3) has been used as an index of the total body burden. However, it is not a good measure. It mainly reflects Pb concentrations in blood and soft tissues (Tell et al 1992; Gerhardsson et al 1998; Schwartz et al 1999), and possibly trabecular bone (Tell et al 1992), while it is not a good index of total body burden, and thus not of long-term accumulation, which mainly occurs in cortical bone. Accordingly, chelation did not cause any decrease of neither tibia-Pb, nor calcaneus-Pb (Tell et al 1992). The bone-Pb available for chelation seems to decrease with increasing age (Schwartz et al 1999; Todd et al 2001).

In summary, U-Pb has only been used to a limited extent, partly because of the problems with adjustment for diuresis. However, U-Pb after administration of chelating agents (chelatable Pb) has been fairly widely used as an index of risk and the body burden. However, it does not reflect the bone-Pb, which is the major pool. Further, the major advantage of chelation lies in the fact that it increases the concentration of Pb in urine, which makes the Pb determination easier. However, with modern analytical methods, this is no longer as important. Further, renal impairment may decrease the excretion of the complex.

3.4. Other indices

Pb is excreted in the saliva, which is probably the explanation of the gingival Pb seam sometimes seen in Pb workers (Skerfving 1992 and 1993). In Singaporean Pb workers ,the mean B-Pb was 266 μg/L, while the saliva-Pb was only 0.77 μg/L; there was a non-rectilinear relationship, reflecting the saturation of B-Pb at high exposure (Koh et al 2003). The authors conclude that saliva Pb should not be used for biomonitoring. Pb is also excreted into sweat; there is a correlation with B-Pb, although - as always in the case of B-Pb - non-rectilinear (Omokhodion & Crockford 1991).

Pb grows out into hair (Skerfving 1992 and 1993). In Pb workers in Singapore (GM B-Pb 341 μg/L), the GM hair-Pb was 641 μg/g (Foo et al 1993). There was a correlation between hair-Pb and B-Pb, though non-linear. However, due to the risk of external contamination, hair-Pb is not a reliable index of the internal dose.

3.5. Toxicokinetics

3.5.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was noted, that there was a good deal of data on the metabolism of Pb.

Of particular importance is the relationship between exposure and B-Pb, as most of the information on exposure-response relationships relate to B-Pb. Generally, in industry, there had been poor correlations between air-Pb measurements and B-Pb, probably because: (1) Limited data on air-Pb concentrations. (2) Most of the sampling had been of the area mode, not personal sampling in the breathing zone of the worker. (3) Variations in particle sizes and solubility of the Pb species. (4) The "background" Pb exposure (through food, water and air) may vary. (5) Exposure through alcoholic beverages and tobacco had not been accounted for. (6) Inter-individual variation in Pb metabolism had not been considered. (7) The endogenous exposure from the skeletal Pb pool may be of importance. (8) The curvilinear relationship between B-Pb and Pb exposure (saturation of B-Pb at high exposures). Hence, other sources of information were used. Then, a B-Pb of 1.5 μmol/L was estimated to correspond to an uptake of 700 μg/week.

As said above, the "background" B-Pb in Swedish males was assumed, at that time, to be about 0.4 μmol/L, somewhat lower in females. The Swedish "background" uptake – mainly from foods, to some extent also from water, air and tobacco – was about 35 μg/week. In other parts of the world, the "background" is much higher. If 1.5 μmol/L should not be exceeded, the uptake from occupational exposure should be ≤670 μg/week. If an occupational exposure was entirely through inhalation, the particle size ≤1 μm (Pb fume), the pulmonary deposition 40% (which was assumed to be fully absorbed) and 60% of the Pb was cleared to the GI tract (where 15% was absorbed), then the inhaled amount should be ≤1,370 μg/week. At an inhalation at work of 50 m^3 per week (10 m^3 per day in males), this corresponds to about 30 $\mu g/m^3$, and a B-Pb of 0.75 μmol/L to about 15 $\mu g/m^3$. The uncertainty of these estimates was stressed.

3.5.2. Update

3.5.2.1. Models

Since 1991, several advanced metabolic models have been presented - two physiologically based pharmacokinetic (PBPK) models (Legett 1993; O´Flaherty 1993) and one classical compartment (US EPA 1994 and 2002) one. A simple compartment model is presented in Figure 3.

The Legett (1993) model is an expansion of an International Commission on Radiation Protection (ICRP 1993) age-specific one. It will not be discussed here.

In 1994, US Environmental Protection Agency published an "Integrated Exposure Uptake Biokinetic Model for Lead in Children" (IEUBK), a detailed, classical compartment model (US EPA 1994 and 2002; White et al 1998). In a four-step process, it mathematically and statistically links several sources (soil, house dust, drinking water, air and food) of environmental Pb exposure to B-Pb

in children, 0-84 months of age. It takes into account indoor and outdoor air-Pb, time spent outdoors, ventilation rate and lung absorption. The drinking-water data includes the fraction of total water intake consumed as first draw and Pb concentration in that, as well as flushed water, and the fraction consumed from fountains and concentration in that. The GI bioavailability is expressed in relation to Pb acetate in pigs. Also, the *in utero* transfer is estimated from maternal B-Pb. The body compartments are lungs, GI tract, plasma/extracellular fluid, red blood cells, kidney, liver, other soft tissues and trabecular and cortical bone. The elimination occurs through urine, feces and skin/hair/nails. The transfer rates were based in part on kinetic data in baboons. Certain non-linearities, specifically capacity-limited binding in the red cell and absorption from the GI tract, are built into the model.

The accuracy of the model in prediction of B-Pb has been verified (Choudhury et al 1992). Further, a probabilistic (of exposure parameters) version has been developed (Goodrum et al 1996). A key input in the model is the assumption of the variability of B-Pb (expressed as geometric standard deviation) in populations of children (Griffin et al 1999). The use of a high absorption rate (40-50%, even at age 7), has been criticized (Gulson et al 1997a).

A PBPK model of Pb kinetics has been developed and validated for adults with a wide range of exposures from a variety of sources (O´Flaherty 1993). It has been supplemented with a Monte Carlo probabilistic module (Beck et al 2001). The model has also been tested and calibrated for B-Pb in children (O´Flaherty 1995), as well as bone-Pb in Pb workers (Fleming et al 1999). Both B-Pb and bone-Pb are very labile in early childhood; they respond rapidly to increases in exposure, and decrease almost as rapidly to near-preexposure concentrations, when exposure returns to background levels (O´Flaherty 1995). From the peak in adolescence and into early adulthood, the rate of bone turnover drops dramatically and, hence, the ability to reverse bone-Pb accumulation relatively rapidly is lost.

Despite some qualitative and quantitative differences in Pb uptake, the O´Flaherty and IEUBK models give predicted B-Pbs that are not greatly dissimilar (O´Flaherty 1998). This is not unexpected, since both models were calibrated against the same types of data for B-Pb in US urban children.

3.5.2.2. Relationship between lead concentrations in air and blood

In a series of studies, the relationship between B-Pb and air-Pb concentrations have been scrutinized. Most studies show the well-established non-rectilinear relationship, with a saturation of B-Pb at rising air-Pb (Figure 6). It is also obvious that the curves vary between the studies. It seems that workers in Pb-battery factories, where the exposure is to soluble Pb oxide and sulphate, have higher B-Pb than crystal-glass industry-workers, where the Pb is less soluble. Most studies entailed high air-Pb levels. However, US (Ulenbelt et al 1990; Hodgkins et al 1992) and Italian (Masci et al 1998) workers exposed at low intensities also fit. In a study of 20 Spanish smelter workers, the slope of the curve is in accordance with the figures in the low range (De Medinilla & Espigares 1991).

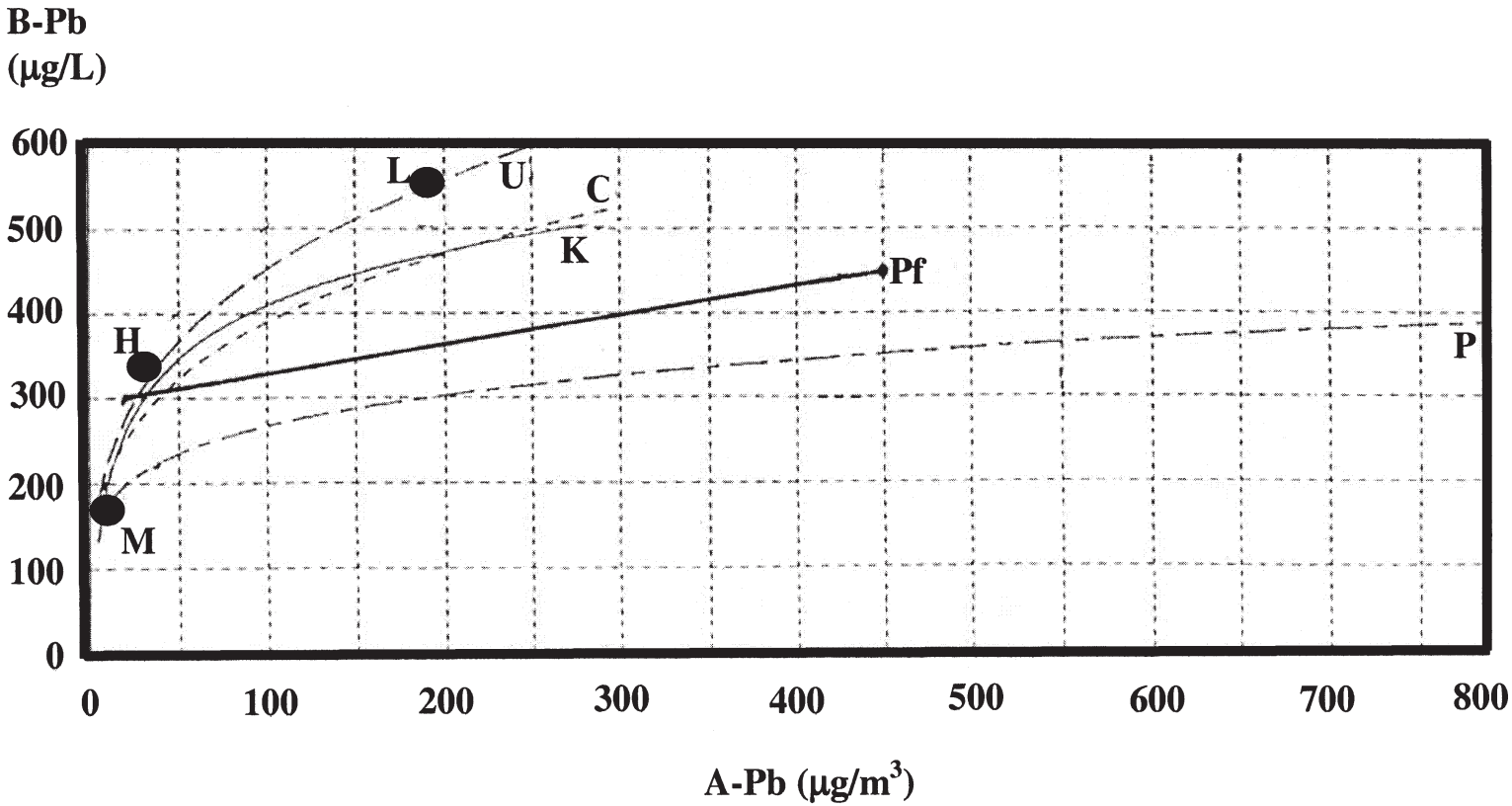

Figure 6. Relationships between lead (Pb) concentrations in blood (B-Pb) and air (A-Pb) in different studies. *Pb battery workers*: C= Chavalitnikul et al 1984; logB-Pb (µg/dL)=1.042 + 0.273 X logA-Pb (µg/m^3). U=Ulenbelt et al 1990; logB-Pb (µg/L)=2.045 + 0.305 X logA-Pb (µg/m^3); "background" B-Pb not given. H=Hodgkins et al 1992; mean B-Pb about 340 µg/L at an air-Pb of 30 µg/m^3; "backgrund" B-Pb not given. K=Kentner and Fischer 1994; B-Pb (µg/dL)=62.183 + 21.242 X logA-Pb (mg/m^3); "background" B-Pb not given. L=Lai et al 1997; mean B-Pb 569 µg/L, air-Pb 190 (µg/m^3); "backgrund" B-Pb not given. *Copper smelter workers*: Pf=Pfister et al 1994; "control group: B-Pb 56±13 µg/L. *Crystal industry workers*: Pi=Pierre et al 2002; logB-Pb (µg/L)=2.13 + 0.161 X logA-Pb (µg/m^3); unexposed referents: B-Pb: GM=92 (range 55-178) µg/L. *Pb/tin soldering*: M=Masci et al 1998; mean B-Pb 190 µg/L, mode air-Pb about 10 µg/m^3; "general population": B-Pb: GM 82 (range 50-160) µg/L. Modified from Kentner and Fischer (1994) and Pierre et al (2002), with several additions.

When using the relationships specifically for Swedish occupational conditions, one must consider the background exposure outside work, which is low in Sweden, as compared to many other countries (Skerfving et al 1999). Also, the endogenous exposure from the skeleton, caused by the Pb-exposure history, affects the air-Pb/B-Pb relationship (Schwartz et al 1994 and 1995). Further, the hygienic standard of the worker (in particular eating and smoking at work) influences the B-Pb (Hodgkins et al 1992; Far et al 1993; Maheswaren et al 1993; Chuang et al 1999). Hence, there may be a wide variation in the same factory of B-Pb on air-Pb.

3.5.3. Summary

Several metabolic models for Pb have been designed and tested, both compartment and physiologically-based ones. They allow prediction of concentrations in biomarkers at varying exposure.

The models, as well as studies of occupationally exposed workers, show a non-rectilinear relationship between air concentrations and B-Pb. This means that, at the low air-Pbs relevant for the present Swedish exposure within and without workplaces, even a minor increase in the exposure will cause a substantial increase of B-Pb.

They also indicate a wide variation in the relationship, which is probably mainly due to variations in particle sizes and solubility of the Pb species, exposure through contaminated food and tobacco, as well as varying "background" exposure. Also, there is an inter-individual variation in Pb metabolism. Because of the accumulation of Pb in the skeleton, endogenous exposure from that pool will differ between workers with varying exposure history.

The present "background" B-Pb in Swedish males is about 0.15 μmol/L, lower in females, adolescents and children (Section 3.1. Blood lead). It seems that the average Swedish worker would just not reach a B-Pb of 1.5 μmol/L if he is exposed to 200 $\mu g/m^3$ of Pb with low solubility (sulphide, dust from crystal glass, *etc*) or to about 30 $\mu g/m^3$ with high (sulphate, nitrate, *etc*), assuming small particle sizes. However, there is a wide inter-interindividual variation of B-Pb at a certain air-Pb.

3.6. Gene-environment interaction

3.6.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was noted that, in addition to the age- and sex-related variations in vulnerability, there was a large inter-individual differences in sensitivity to Pb, but the basis of this was largely unknown.

3.6.2. Update

Since 1991, a wealth of new information has been published on ALAD, which is encoded by a single gene on chromosome 9q34. Human ALAD is a polymorphic enzyme. Eight ALAD variants have been described. The allele contains a site-

directed mutagenesis, a G→C transversion at position 177 of the coding region, resulting in the substitution of asparagine for lysine at amino acid 59 (proteins K59 and N59, respectively). These amino acids have different charges, and electrophoretic separation may be used to identify the polymorphism, and the phenotype of individuals. However, genotyping has mostly been employed. The human *ALAD* gene was cloned and sequenced more than 20 years ago. The enzymatic specific activity of K59 was twice that of N59 (Jaffe et al 2000).

The enzyme is codominant, in that both these alleles are expressed if a copy is present. Hence, there are three distinct isoenzyme phenotypes: K59-K59 (ALAD 1-1), K59-N59 (ALAD 1-2) and N59-N59 (ALAD 2-2). Below, the first one will be denoted as $ALAD^1$, and the latter two as $ALAD^2$. In Caucasian populations, approximately 80% of the individuals have ALAD 1-1, 19% ALAD 1-2 and 1% ALAD 2-2 (Bergdahl et al 1997b; Kelada et al 2001). Asian and African populations have lower frequencies of $ALAD^2$.

As said above, ALAD is the major binding site for Pb in red cells (Bergdahl et al 1996, 1997b and 1998b). Experimentally, there was neither differential displacement of Zn by Pb for K59 relative to N59, nor inhibition of activity by Pb (Jaffe et al 2000). However, in erythrocytes, the $ALAD^2$ gene product seemed to bind Pb more tightly than the $ALAD^1$ one (Bergdahl et al 1997c). Hence, genetic polymorphism in *ALAD* may affect the metabolism of Pb.

Among 1,051 environmentally exposed individuals (primarily children) in New York City, $ALAD^2$ subjects had higher B-Pb than $ALAD^1$ ones (Wetmur et al 1991; Wetmur 1994). However, the design of the study has been challenged. In a population-based study of 660 Taiwanese subjects, $ALAD^2$ subjects had higher B-Pb than $ALAD^1$ ones (78.3 *vs* 59.5 μg/L), but the difference was not statistically significant (Hsieh et al 2000). This may be because of the relatively low B-Pb and the few $ALAD^2$ subjects.

In 202 German Pb-exposed workers, the $ALAD^2$ subjects had higher B-Pb than the $ALAD^1$ ones (means 470 *vs* 384 μg/L) (Wetmur et al 1991). In accordance with this, in 134 smelter workers, there was a (statistically non-significant) difference in B-Pb between $ALAD^1$ and $ALAD^2$ subjects (means 231 *vs* 284 μg/L) (Alexander et al 1998). Also, in 381 Canadian smelter workers, $ALAD^2$ subjects had higher B-Pb (means 251.8 vs 228.5 μg/L) and S-Pb than $ALAD^1$ ones (Fleming et al 1998). In another Korean battery plant (308 currently exposed workers), $ALAD^2$ subjects more often had high B-Pb, and they were 2.3 times more likely to have worked for more than 6 years and, accordingly, they were over-represented in the workforce (Schwartz et al 1995). The finding was confirmed in a study of 798 Korean Pb workers and 135 unexposed controls (Schwartz et al 2000c).

However, the information is not consistent. Hence, in 726 middle-age and elderly US men, $ALAD^2$ subjects (mean B-Pb 62 μg/L) did not differ from $ALAD^1$ ones (Hu et al 2001). Moreover, in 691 US construction workers (mean B-Pb only 77.8 μg/L), there was no difference in B-Pb (Smith et al 1995a). Further, in another study, of Japanese Pb workers (N=192; 125 controls), there was no ALAD-genotype dependent difference in B-Pb (Sakai et al 2000). Moreover,

in 201 Japanese porcelain paint workers, there was no statistically significant difference in B-Pb between *ALAD*^{2} and *ALAD*^{1} subjects (means 89, range 18-307 vs 78, range 14-270 μg/L) (Zhang et al 1998). Also, among 72 Turkish battery workers, the 29.2% who were *ALAD*^{2} did not differ in B-Pb from *ALAD*^{1} ones (means 349 *vs* 344 μg/L) (Süzen et al 2003). However, in the *ALAD*^{1} subjects, the U-Pb was higher in relation to B-Pb, as compared to *ALAD*^{2} ones (means 78.5 *vs* 80.6 μg/g crea), though the difference was not statistically significant.

Any effect of *ALAD* genotype on Pb metabolism, might explain ethnic differences noted in B-Pb in a study of battery workers (Chia et al 1991). However, there are other possible explanations. Further, gene-environment interactions, as described above, may – at least partly - explain the association between B-Pbs seen in women (but not in men) in a Swedish study of mono- and dizygotic twins (Björkman et al 2000). The genetic influence was as high as 58%.

It has been hypothesized, that one link is *via* genetics of bone metabolism (Vahter et al 2002). The *ALAD* genotype seems to affect the Pb kinetics in calcified tissues. In US children, there were indications that *ALAD*^{2} subjects had lower dentine-Pb (Bellinger et al 1994a). They also were less likely to have high tibia-Pb. This is in accordance with a study of US middle-aged and elderly men, in whom it also seemed that *ALAD*^{2} subjects had lower patella-Pb (but not tibia-Pb) (Hu et al 2001). In accordance with this, in US cases of amyotrophic lateral sclerosis (ALS; motor neuron disease) and referents, *ALAD*^{2} subjects had lower patella-Pb and tibia-Pb (but did not differ in B-Pb) (Kamel et al 2003). Also, another *ALAD* polymorphism was associated with low bone-Pb. In 122 US construction workers, there were no *ALAD*-dependent differences in patella- or tibia-Pbs (Smith et al 1995a). Also, in 89 Swedish Pb-smelter workers, there was no polymorphism-dependent difference in B-Pb or bone-Pb (Bergdahl et al 1997a). Neither did, among 381 Canadian smelter workers *ALAD* genotype affect tibia- or calcaneus-Pbs (Fleming et al 1998 and 1999). However, *ALAD*^{2} subjects seemed to have a lower increase of bone-Pb on cumulated B-Pb. Hence, the results differ between studied populations. This may be because the selection may vary, depending on the exposure and health surveillance systems. Also, the effect seems to be exposure-dependent.

In 57 Korean battery workers, the *ALAD*^{1} individuals had a higher urinary excretion of Pb after DMSA-chelation (Schwartz et al 1997a). Studies in US former organo-Pb workers (Schwartz et al 1997b) and Swedish smelter workers (Gerhardsson et al 1999) corroborated this. Intriguingly, Schwartz et al (1997b) claimed that creatinine clearance was an important predictor of the excretion and that the *ALAD* genotype modified this interaction; *ALAD*^{2} subjects had larger increase of chelated Pb with rising creatinine clearance.

There is a rare hereditary ALAD deficiency (for some reason denoted plumboporphyria by some authors), which may constitute an inborn error of Pb metabolism, making the subject vulnerable, and predispose for severe toxic effects at relatively low exposure (and low B-Pb) (Dyer et al 1993).

Among 57 Korean battery workers, *ALAD*^{1} subjects had higher hemoglobin A_1 levels, which, in turn, was associated with high DMSA-chelatable Pb (Schwartz et al 1997a). The authors concluded that hemoglobin A_1 (in addition to ALAD) binds Pb. However, as said above, Bergdahl et al (1998b) found no binding of Pb to hemoglobin.

Calcium (Ca) status affects Pb absorption; this is mediated through Ca-binding proteins, which are, in turn, affected by the blood-borne form of vitamin D (calcitrol), which binds to the vitamin D receptor (VDR). In 781 Korean battery workers, there was a difference in B-Pb between *VDR* genotypes (Lee et al 2001b). Also, there was a non-significant difference in bone-Pb. Interestingly, the authors found an association between *VDR* and *ALAD* genotypes, which varied by exposure status (but with no interaction). This may indicate a genotype selection. Among 504 US former organo-Pb workers, the *VDR* genotype also modified the kinetics of bone-Pb (Schwartz et al 2000a). However, in US cases of ALS and referents, *VDR* polymorphism did not affect bone-Pb (Kamel et al 2003).

In 275 2-year old US children, there was an interaction between B-Pb and polymorphism in the *VDR-Fok1* gene; in those with the *FF* genotype, B-Pb increased more with rising floor-dust Pb, than in *Ff* individuals; the *ff* subjects were too few to allow firm conclusions (Haynes et al 2003). The authors thought that the effect was due to Pb´s mimicry of Ca, and a more efficient Ca absorption in *FF* subjects. B-Pb was inversely associated with B-Pb, but there was no significant modification of this relationship by *VDR* genotype.

Low iron status increases the GI absorption of Pb. Hence, there is an inverse relationship between iron intake (Cheng et al 1998b), serum ferritin (the iron-transport protein) (Berglund et al 1994; Osman et al 1998b; Lundh et al 2002; Wennberg et al, submitted; Bárány et al, submitted), and red cell mean corpuscular volume (Wrigth et al 1999 and 2003), on the one hand, and B-Pb, on the other.

Subjects who were homozygous for the mutation which induces hereditary hemochromatosis, with increased absorption of iron (and iron overload), had increased B-Pb (homozygous 56, heterozygous 41 and wild-type 36 μg/L, respectively) (Barton et al 1994). However, this finding was not corroborated in a Swedish study; however, the B-Pbs were lower (Åkesson et al 2000).

3.6.3. Summary

For centuries it has been known, that there is a large inter-individual variation in sensitivity to Pb, but the basis for this has been largely unknown. Possible explanation of – at least some – this variation has now been revealed. ALAD, which is a major binding site for Pb, is polymorphic. Two genotypes have been focussed upon: *ALAD*^{1} (80% in the Swedish population) and *ALAD*^{2} (20%). It seems that the gene product of *ALAD*^{2} binds Pb tighter than *ALAD*^{1}, and that the former subjects have higher B-Pb than the latter at the same exposure, at least at high exposure intensities, and lower chelatable Pb. The tendency to reach higher B-Pb may lead to an selection by a surveillance system based on B-Pb checks;

workers with some *ALAD* genotypes may leave Pb-exposing workplaces. It is likely, that the genotype affects the Pb accumulation pattern of the skeleton; $ALAD^2$ subjects accumulate less.

There are some indications of an interaction between polymorphism in the *VDR* gene and B-Pb.

Subjects with iron deficiency (mainly women) absorb a larger fraction of ingested Pb.

4. Organ effects

4.1. Nervous system

4.1.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was noted, that very severe Pb toxicity, with clinical encephalopathy, may occur in some adults at B-Pbs about 4 μmol/L. There was evidence of slight effects on the central nervous system (CNS; symptoms and neurobehavioural testing at exposures corresponding to B-Pbs of 2.5 μmol/L; limited data indicated effects already at 1.5 μmol/L). Infants are probably more sensitive than adults. The health impacts of slight CNS effects were not fully clear; however, it seems reasonable to consider them adverse.

Severe Pb exposure causes peripheral neuropathy with axonopathy. Slight peripheral nerve dysfunction (reduced nerve conduction velocities at neurophysiological examination, but no signs or symptoms) may occur in adult subjects; limited information indicated that this may occur at B-Pbs as low as 1.5 μmol/L. It was not known whether the reduced conduction velocities are really subclinical signs of the clinical neuropathy - it might be that they signify a more harmless disturbance of the ion transport over the cell membrane of the nerve cell. Also, there were some indications of reversibility. However, in light of the severe neuropathy that may affect heavily Pb exposed subjects, the conduction velocity disturbances were considered adverse. Effect on the autonomic nerve system had been recorded at similar B-Pbs.

4.1.2. Update

A wealth of new information has occurred since 1991. Several reviews have been published (Spurgeon 1994; Balbus-Kornfeld et al 1995; Albers & Bromberg 1995; Araki et al 2000; Meyer-Baron & Seeber 2000; Goodman et al 2001; Seeber et al 2002; Lidsky & Schneider 2003).

4.1.2.1. Central nervous system

Neuropsychological tests

Occupational exposure

A long series of studies of *neurobehavioural* CNS effects in Pb workers have been published.

Ehle and McKee (1990) reviewed 14 studies published 1978-86. The authors concluded, that the data suggested that Pb-exposed workers, even at B-Pbs <600 μg/L, have more difficulty performing tasks that require: (1) attention/concentration/memory; (2) visuospatial and visuomotor skills; (3) speed of learning and problem-solving ability; and that deficits appear to be associated with degree of exposure. Further, it was considered possible, that increased irritability, fatigue, tension, depressed mood and interpersonal problems were effects of Pb exposure. As to psychomotor and psychophysiological testing (critical flicker fusion, eye movements, reaction time and psychomotor performance), there was unsufficient support of associations.

In 17 Japanes gun metal foundry workers (median B-Pb 400, range 300-640 μg/L) and 10 controls (B-Pb 120 μg/L), there was an association between B-Pb and impaired performance in one out of a series of psychological tests (Yokoyama et al 1988). At a second examination, 2 years later, when an exhaust ventilation system had been introduced, and the B-Pb had decreased among the 11 most heavily exposed workers (medians 460 to 380 μg/L), their performance in that test had improved, while the others had not changed. This was claimed to indicate reversibility.

When 70 UK male Pb workers (battery and printing industries; median B-Pb about 300, range <20-800 μg/L) were followed for 8 months, those with B-Pb in the range 410-800 μg/L performed less than the lower ones in sensory motor reaction time and some cognitive tests and they had more difficulties in remembering incidental information (Stollery et al 1991).

In 98 Belgian battery factory workers (mean 510, range 400-750 μg/L) and 85 "controls" (B-Pb 209, range 44-390 μg/L), there was no statistically significant difference in flicker fusion (Gennart et al 1992a).

In 43 Venezuelian Pb smelter (mean B-Pb 2 μmol/L) and 45 "unexposed" (B-Pb 0.73 μmol/L) workers, there were associations between current B-Pb (less so with peak B-Pb or time-weighted B-Pb) and some aspects of a mood scale (tension-anxiety, hostility, depression, difficulties in concentrating) and joint pain (adjusted for age, education, alcohol intake, solvent exposure and exposed/unexposed status, which might have caused an over-adjustment), while a series of neurobehavioural tests did not reveal clear associations (Maizlish et al 1995).

Among Canadian current (N=11) and former (N=30) smelter workers (mean time-weighted B-Pb during an average of 52.51 months was 527.5, range 300-660 μg/L) and 37 "non-smelter workers" (B-Pb not given) there was no obvious association between exposure, on the one hand, and cognitive and motor functions, on the other (Braun & Daigneault 1991). However, most tests were made after end of exposure, and there was a heavy selection of the examined subjects.

In 109 German copper-smelter workers there was an association between time-weighted averages of B-Pb (range about 190-570 μg/L) and air-Pb (average 0.14±0.11, range about 0.025-0.45 mg/m^3) (Pfister et al 1994). At neuropsychological examination, there were no clear differences between the performance in these workers (median B-Pb at time of examination 312, range about 90-590

μg/L; median during the last 5 years 238±104 μg/L) and 27 unexposed workers (assumed B-Pb about 50 μg/L). Possibly, the most heavily exposed workers (average B-Pb >350 μg/L) performed less, but there was a selection.

Twenty-six German non-ferrous smelter workers (partly the same as above?; mean B-Pb 377±71 μg/L; mean air-Pb 0.13±0.05 mg/m^3) differed from 48 "unexposed controls" as regards psychoneurovegetative, neurologic, irritability and concentration symptoms (Pfister et al 1999). Also, there was an association between individual estimates of air-Pbs and symptoms. In neurobehavioural test batteries, concentration and IQ differed (but not other tests); however, there were indications of a pre-exposure difference in IQ.

In a study of 467 male current and former Canadian Pb workers, who were employed in a Pb smelter, which had operated for 26 years, and in which, due to hygienic measures and personal protection, the exposure had decreased significantly 12 years ago, there were no associations between the current B-Pb (mean 275, SD 84; range not given) μg/L or time-weighted average (TWA) B-Pb and 13 neuropsychological tests (Lindgren et al 1996). However, the time-integrated B-Pb (mean 7,652, range 6-16,257 μg/L x year) was associated with impairment of five tests (visuomotor skill, psychomotor speed and dexterity and verbal memory) after adjustment for age, education, alcohol use, and – less obviously why - time of employment and depressive symptoms. The authors suppose that the effect was due to previous high exposure. They do not give any estimate of the corresponding B-Pb, but it seems that it should have been about 600 μg/L in average.

In a study of 80 of current Canadian smelter workers (partly the same?), there were significant adjusted associations between B-Pb (mean 264, range 130-430 μg/L), TWA B-Pb, cumulated B-Pb and tibia-Pb (mean 41, range –12 to 90 μg/g bm), on the one hand, and one to four out of five neuropsychological tests (verbal and visuomotoric abilities), on the other (Bleecker et al 1997a). It seemed, that young workers were less susceptible than older (ages 44-64) ones (effect at tibia-Pb >20 μg/g bm).

In a Finnish study of 54 storage battery workers with well known exposure to Pb (mean recent B-Pb 1.3±0.4 μmol/L; tibia-Pb 19.8±13.7, calcaneus-Pb 78.6±62.4 μg/g bone mineral=bm), those who had never exceeded 2.4 μmol/L still had a decrement in visuospatial and visuomotor function, attention and verbal comprehension (Hanninen et al 1998).

Several critical reviews of studies up to 1999 have been published. In a survey of 21 studies of neurobehavioural testing in Pb-exposed, it was concluded, that the best three ones indicated a greater effect of recent exposure (B-Pb) than of time-integrated exposure (Balbus-Kornfeld et al 1995). In a summary of two meta-analyses (including studies by Braun et al 1991; Bolla et al 1995; Lindgren et al 1996; Chia et al 1997; Maizlish et al 1995; Hanninen et al 1998; Pfister et al 1999; quoted here), the authors concluded that "These test results provide evidence for subtle deficits being associated with average blood lead levels between 370 and 520 μg/L." (Seeber et al 2002). Critics were published (Goodman et al 2001). As

a consequence, a third meta-analysis was made; the authors withheld their conclusion (Seeber et al 2002).

In another review, about 140 studies were scrutinized, and 22 ones with B-Pb <700 (B-Pb means 240-630 in exposed subjects, <280 in "unexposed" ones) μg/L and 22 tests were selected on basis of strict criteria (information on potential confounders, *ia* age, education and alcohol use) for a meta-analysis (Goodman et al 2002). Only two of the tests showed unequivocal significant difference between exposed and control groups. The results were sensitive to selection of studies, inclusion or exclusion of tests, adjustment for reliability and choice of statistical analysis. A problem was lack of control of the wide inter-personal variability (pre-exposure capacity). Prospective studies were thus urged. This review has attracted several comments, it has, *eg*, been accused of bias because of industrial funding (Seeber & Meyer-Baron 2003; Schwartz et al 2002). In response to the critics the authors made new approaches, but stayed with their conclusion (Goodman et al 2003).

Contrary, in another meta-analysis, which evaluated 12 tests, using similar selection criteria, but with a different analytical approach, three of the tests showed significant effects (Meyer-Baron & Seeber 2000). The authors concluded that "The evidence of neurobehavioural deficits at a current blood lead concentration of ~40 μg/100 ml is obvious". The controversy well illustrates the problems associated with evaluation of this kind of studies.

In a study of 50 Chinese Pb battery plant workers (geometric mean=GM B-Pb 371, range 132-646 μg/L) and 97 referents (B-Pb 61, range 24-124 μg/L), the former had poorer performance in neurobehavioural tests (manual dexterity, perceptual motor speed and motor steadiness in the WHO Neurobehavioural Core Test Battery) (Chia et al 1997). The cumulated B-Pb correlated better than current B-Pb with tests of perceptual and motor skill.

In a Swedish study, 38 male workers at a secondary smelter were divided into a high (median fingerbone-Pb 32, range 17-101 μg/g; B-Pb 1.8, range 0.9-2.4 μmol/L) and a low (median fingerbone-Pb 16, range –7 to 49 μg/g; B-Pb 1.6, range 0.8-2.6 μmol/L) bone-Pb group (Österberg et al 1997). Also, 19 referents were studied (median fingerbone-Pb 4, range –4 to 18 μg/g; B-Pb 0.18, range 0.07-0.34 μmol/L). There were no association between the Pb exposure (including time-integrated B-Pb) and results in a neuropsychological test battery.

In a study of 803 Korean workers (mean B-Pb 320±150 μg/L; tibia-Pb 37.1±40.3 μg/g bm) and 135 controls (mean B-Pb 53±18 μg/L; tibia-Pb 5.8±7.0 μg/g bm), there were associations between B-Pb and DMSA-chelatable Pb, on the one hand, and some of the WHO neurobehavioural core battery tests, on the other (Schwartz et al 2001). Tibia-Pb did not show such associations. In a fraction of the workers, erythrocyte protein kinase C (PKC) activity modified the relation between neurobehavioural test results and B-Pb (Hwang et al 2001). Further, tibia-Pb (but not B-Pb) was associated with PKC (Hwang et al 2002).

47 German male battery plant workers (current mean B-Pb 308, range 106-621 μg/L, time-integrated B-Pb 4,6135, range 110-213,300 μg/L x year) differed in

several neurobehavioural tests from 53 referents (steel workers; B-Pb 43.2, range 16-126 μg/L) (Barth et al 2002). There were associations between current B-Pb and the cognitive tests, but not with time-integrated B-Pb.

General population

In adult middle-aged and elderly US *general population* men (mean B-Pb 55 μg/L, patella-Pb 31.7 and tibia-Pb 22.5 μg/g bm) men with higher B-Pb were less good in cognitive tests than those with low (Payton et al 1998).

Stokes et al (1998) examined 281 young (age 19-29), who had from 9 months to 9 years lived near a US Pb smelter, and 287 referents. Their current mean B-Pb was 29 and 16 μg/L, respectively, tibia-Pb 4.6 *vs.* 0.6 μg/g bm. A fraction of the exposed subjects had an average of 493 μg/L as infants/children. Almost all adjusted results of a long series of tests of CNS function and symptoms were poorer in the exposed than in the control group. However, there was a considerable selection, and no significant associations with tiba-Pbs, which the authors think is because of lack of precision in the tibia-Pb determinations, or to a lack of correlation with the actual historical exposure.

In 762 elderly (age above 75, mean 88.2±4.9 years), subjects from Stockholm city, there was no association between B-Pb (mean 0.18±0.11, range 0.01-1.41 μmol/L) and adjusted cognitive function (Mini-Mental State Examination= MMSE) (Nordberg et al 2000).

In a construction carpenter, clinically severely Pb-poisoned through cutting of steel while dismantling a bridge, EDTA-chelation therapy 2 years later was claimed to improve neuropsychological tests and postural sway test performance (Linz et al 1992). However, the causal relationship is doubtful.

Other effects

In a study of 60 Finnish Pb-battery workers, alpha and beta activities of the electroencephalogram (EEG) were more abundant in subjects with higher long-term exposure (Kovala et al 1997). Their mean current B-Pb was 1.3 (range 0.5-2.2) μmol/L, time-integrated B-Pb 26 μmol/L x years, exposure time 16 years, long-term B-Pb 1.6 μmol/L and maximum B-Pb 2.5 μmol/L. Their mean tibia-Pb was 26, and calcaneus-Pb 88 μg/g bm.

In a kind of population-based case-referent study in the US, there were associations between work with Pb and Cu, and Pb and iron (mainly electricians, vehicle mechanics and machine operators), as recorded in an occupational-hygienist administered questionnaire, and clinically well-defined Parkinson´s disease (Gorell et al 1999). However, the exposure is ill-defined.

Similarities between the primary motor neuropathy caused by Pb, and ALS have been noted. In a US case-referent study of ALS, the risk was associated with self-reported occupational exposure to Pb (odds ratio=OR 1.9, CI 1.3-3.3) (Kamel et al 2002). Further, among 107 cases and 41 referents, a risk was associated with B-Pb (range <10-140, median about 40 μg/L; OR 1.9, CI 1.4-2.6 per 10 μg/L increase). Such an effect may be spurious, because low physical activity may mobilize bone-Pb to the blood. However, the risk was also related to patella-Pb

and tibia-Pb (<4-107 and <7-61 μg/g bm, respectively). But the matter may be complicated since there were indications that two different *ALAD* polymorphisms were associated with decreased bone-Pbs, and - at the same time - with non-significantly either increased or decreased ALS risks (Kamel et al 2003).

4.1.2.2. Autonomous nervous system

Among 172 Japanese Pb storage battery-factory and Pb-refinery workers mean B-Pb 360, range 50-760 μg/L), there was an association between electrocardiographic (ECG) heart rate variability (HRV) and B-Pb, which was obvious at B-Pbs >300 μg/L, but probably also present at >200 μg/L (Teruya et al 1991). The workers were exposed to antimony, arsenic (As) and tin at "negligible concentrations". The data indicate an effect of Pb on parasympathetic nerve function.

Between 98 Belgian battery-factory workers (mean 510, range 400-750 μg/L) and 85 "controls" (B-Pb 209, range 44-390 μg/L), there were no statistically significant differences in HRV (Gennart et al 1992a). Neither was there any association with B-Pb.

In the above-mentioned 16 gun-metal foundry workers (mean B-Pb 340, range 160-600 μg/L), a study of the autonomous nervous system, revealed that the HRV at deep breath was significantly depressed, as compared to 16 unexposed workers (B-Pb not given), indicating an effect of Pb on parasympathetic activity (Murata et al 1991). In 22 gun-metal foundry workers (partly the same?; median B-Pb 300, range 120-590 μg/L), the HRV was also significantly depressed, as compared to 14 unexposed workers (Murata et al 1993).

Between 36 female Chinese glass (mean B-Pb 556, range 258-793 μg/L) and 15 control (B-Pb 63 μg/L) workers, there were significant differences in HRV, indicating effects on the sympathetic and parasympathetic (less) nervous systems, possibly on the brain-stem level (Murata et al 1995). However, the exposed workers had more subjective symptoms than the unexposed ones.

4.1.2.3. Peripheral nervous system

Nerve conduction

Among 31 Taiwanese battery workers (mean B-Pb 630, range 170-1,860 μg/L), 25 had mild distal extensor weakness of the upper limb, prolonged motor latency of the median nerve and signs of denervation in the electromyogram (EMG), as compared to 31 referents (B-Pbs not given!) (Yeh et al 1995). There were also neurophysiological effects in the tibial and sural nerves, which correlated with the cumulative (but not current) B-Pb.

In a study of 16 male Japanese gun-metal foundry workers (mean B-Pb 340, range 160-600 μg/L), both the motor and sensory nerve conduction velocities in the distal median nerve were significantly slowed, as compared to 16 "unexposed" controls (B-Pb not given) (Murata et al 1991). In accordance with this, in 22 gun-metal foundry workers (median B-Pb 300, range 120-590 μg/L), both the motor and sensory nerve conduction velocities in both the distal radial and median nerves were significantly slowed, as compared to 14 "unexposed" controls (B-Pb

not given) (Murata et al 1993). There were some indications that Zn and Cu antagonized the subclinical neurotoxic effects of Pb (Arakai et al 1993). It seems that fast sensory fibers are more sensitive to Pb than slow ones (Sata et al 1993; Fujimura et al 1998).

In 41 Japanes Pb workers (production of Pb-glass based colors, Pb pipes and electrode platers and Pb-bronze; mean B-Pb 433, range 130-700 μg/L; air-Pb <2.69 mg/m^3) and 39 unexposed workers (B-Pb not given!), there was a B-Pb associated, adjusted effect on radial nerve motor and sensory conduction velocities (Hirata & Kosaka 1993).

In Israel, 21 battery-factory workers (mean B-Pb 285±52 to 525±52 μg/L in subgroups) had longer visual event-related potentials than 40 unexposed controls (77 μg/L), did not differ in sensory nerve conduction velocities (Solliway et al 1994).

In 72 Chinese battery workers (mean current B-Pb 369, range 73-685 μg/L) and 82 referents (B-Pb 105, range 44-198 μg/L), there were significant differences in sensory and motor conduction velocities, distal latency and amplitudes of the median nerve, while in the radial nerve only distal latency were affected (Chia et al 1996b). The findings correlated with cumulative B-Pb. However, workers with cumulative B-Pbs <400 μg/L x year did not differ from the referents. Similar findings were made during a follow-up each 6 months during 3 years (Chia et al 1996c).

Further, in the above-mentioned study of 60 Finnish Pb-battery workers, peripheral sensory thresholds and - to a lesser degree - motor conduction velocities, showed negative correlations with time-integrated B-Pb and exposure time (Kovala et al 1997). Vibration threshold in the arms were related to the recent exposure, in the leg to the long-term one. The mean current B-Pb was 1.3 (range 0.5-2.2) μmol/L, long-term B-Pb 1.6 μmol/L and maximum B-Pb 2.5 μmol/L. Their mean tibia-Pb was 26, and calcaneus-Pb 88 μg/g bm.

On the other hand, in a study of 80 of current Canadian smelter workers, there were no significant associations between B-Pb (mean 264, range 130-430 μg/L), TWA B-Pb, cumulated B-Pb or tibia-Pb (mean 41, range –12 to 90 μg/g bm), on the one hand, and current perception thresholds in fingers or toes, on the other (Bleecker et al 1997a). In the same workers, there was a non-linear, U-shaped relationship between adjusted, simple reaction time and B-Pb (Bleecker et al 1997b). The authors believe that Pb causes activation. They further claim that the B-Pb originating from endogenous exposure from the skeleton has less effect than that from recent uptake; however, that conclusion seems doubtful, due to imprecise estimates and low levels.

In 17 male Japanese gun-metal workers (mean B-Pb 402, range 220-590 μg/L), studied twice at a 1-year interval, there was a decrease in sensory nerve conduction velocity of large fibers in the median nerve, parallel to an increase of EDTA-chelated Pb (but no association with change of B-Pb) (Yokoyama et al 1998). These workers differed from non-exposed referents.

In a study of 95 Korean Pb workers (smelting, polyvinyl chloride and battery production; mean B-Pb 446, range 214-784 μg/L) and 13 controls (B-Pb 59, range

40-72 μg/L), there were associations between B-Pb and DMSA-chelatable Pb, on the one hand, and subjective symptoms (tingling or numbness in arms or legs and muscle pain), on the other (Lee et al 2000).

Other

Among 151 Latvian battery workers, 46 subjects with symptoms and signs of peripheral neuropathy (mainly sensory, with paresthesiae, pain and impaired sensitivity to pain and vibration) had higher mean B-Pb (639 μg/L) than the others (B-Pb 492 μg/L) (Rubens et al 2001). In accordance with this, the neuropathy group had "abnormal" sensory nerve neurophysiology, while motor conduction velocities were within the "normal" range; there were no correlations with B-Pbs.

In a study of 803 Korean workers (mean B-Pb 320±150 μg/L; tibia-Pb 37.1±40.3 μg/g bm) and 135 controls (mean B-Pb 53±18 μg/L; tibia-Pb 5.8±7.0 μg/g bm), there were associations between B-Pb and DMSA-chelatable Pb, on the one hand, and peripheral motor strength (pinch and grip strength), on the other (Schwartz et al 2001). Tibia-Pb did not show such associations.

Moreover, in 206 Taiwanese Pb-battery workers (current average B-Pb 283±127 μg/L), there were associations between the vibration perception threshold in the feet (but not the hands) and the average B-Pb during the last 5 years; there seemed to be a threshold at 310 μg/L (Chuang et al 2000).

In a Japanese vinyl chloride resin factory, which had used Pb-stearate stabilizer, in one worker, who had severe Pb poisoning (B-Pb 1,000 μg/L), with advanced motor neuropathy, including hand muscle atrophy, chelation with EDTA for one year caused a significant clinical and neurophysiological improvement (Kajiyama et al 1993).

No data on gene-environment interaction as regards neurotoxicity in adults have been published.

4.1.2.4. Other effects

Evoked potentials

In a series of studies, evoked potentials have been assessed in relation to Pb exposure. Disturbances on evoked potentials may mean effects in different areas of the nervous system. Hence, visual evoked potentials involve both the visual nerve and the cerebral cortex, auditory brainstem evoked potentials the auditory nerve, the brain stem and the cortex, and somatosensory evoked potentials the afferent sensory nerves of the PNS, the plexus, the brain stem and the cortex. Auditory or visual event-related evoked potentials also assess cognitive functions.

In 49 Pb-exposed Italian workers (battery factory workers, ceramic industries and miscellaneous; four of them exposed through consumption of Pb-contaminated wine!; mean B-Pb 546 μg/L) and 49 controls (B-Pb not given), there were differences in auditory brainstem evoked potentials (Discalzi et al 1992). Workers who had a mean B-Pb <500 μg/L during he last 3 years differed from those >500 μg/L.

In 22 male Japanese gun-metal foundry workers exposed to Pb, Zn and copper (Cu; median B-Pb 300, range 120-590 μg/L), latencies of auditory event-related

and somatosensory and auditory evoked potentials were associated with B-Pb, as compared to 14 unexposed workers (Araki et al 1992; Murata et al 1993).

In the 41 above-mentioned Japanese Pb workers (production of Pb-glass-based colors, Pb pipes and electrode platers and Pb-bronze; mean B-Pb 433, range 130-700 μg/L; air-Pb <2.69 mg/m^3) and 39 unexposed workers (B-Pb not given!), there was a B-Pb-associated, adjusted effect on visual evoked and short-latency somatosensory evoked potentials and auditory brainstem response, but not on the electroretinogram (Hirata & Kosaka 1993). The authors claim that the effect is greater on the PNS component of somatosensory and auditory pathways than on CNS, while the opposite is true for the visual pathway.

In 36 female Chinese glass (mean B-Pb 556, range 258-793 μg/L) and 15 control (B-Pb 63 μg/L) workers, there were no effects on visual or brainstem auditory evoked potentials (Murata et al 1995).

In Israel, 21 battery-factory workers (mean B-Pb 285±52 to 525±52 μg/L in subgroups) had longer visual event-related potentials than 40 unexposed controls (77 μg/L) (Solliway et al 1994). Among the Pb workers, the effect correlated with B-Pb. In a second study, visual event-related potentials while performing a target detection, as well as memory scanning tasks, differed between 31 Pb workers (B-Pb 414, range 230-530 μg/L) and 56 non-exposed controls (B-Pb 78, range 10-130 μg/L) (Solliway et al 1995a and 1995b). The findings correlated with U-ALA; the authors suspected that this was due to ALA-induced inhibition of gamma-aminobutyric acid (GABA) release, or competitive binding of ALA to GABA receptors, which has been shown experimentally.

In 300 Italian males, there was an association between B-Pb and visual evoked potentials (Abbate et al 1995). The effect seemed to appear already in a group with a mean B-Pb of 295±38.9 μg/L. It is not clear how the subjects were recruited, or how they were exposed. However, since the highest sub-group had a mean B-Pb of 557 μg/L, they must reasonably have been exposed occupationally.

In a study of seven Ecuadorian *children* with extremely high Pb exposure (B-Pb 648-833 μg/L), auditory brainstem evoked potentials were "normal" (Counter et al 1997).

In a study of 155 children aged 4-14 in the Katowice area in Poland, some aspects of the auditory brainstem evoked potential differed between children with B-Pbs above and below 100 μg/L (0.48 μmol/L) (Osman et al 1999a).

Postural stability

Postural stability is a complex function. It involves exteroceptors and proprioceptors, sensory nerves of the PNS, the spinal medulla, the brain stem, the visual nerves, the cerebellum and the cerebral cortex.

In 60 Chinese Pb-battery workers (B-Pb mean 360, range 64-645 μg/L) and 60 controls (B-Pb 63±2.4 μg/L), there was an increased postural sway (Chia et al 1994c). In the Pb workers, the postural sway parameters were not significantly correlated with current B-Pb or total cumulated B-Pb (Chia et al 1996a). This indicates reversibility, though the interpretation is complicated by the fact that B-

Pb had decreased over time. However, the cumulated B-Pb during the latest 2 years was associated with all parameters.

Twenty-nine Chinese female glass workers (B-Pb mean 557, range 260-790 μg/L) differed in posturography in relation to 14 unexposed referents (B-Pb mean 61, range 50-90 μg/L) (Yokoyama et al 2002a). In the Pb workers, there was a relationship between the effect and B-Pb.

In 49 male Japanese workers exposed to Pb stearate in a chemical factory (current mean B-Pb 180, range 70-360 μg/L; past B-Pb 477, range 110-1,100 μg/L), differed from unexposed controls (B-Pbs not given!) as to different parameters of posturography (Yokoyama et al 1997 and 2002b). These findings indicated an effect on the anterior cerebellar lobe and the vestibulo-cerebellar and spinocerebellar afferent systems.

In 109 6-year-old *children*, there were a statistically significant association between postural sway and B-Pb during the first five years of life (GM 119±15 μg/L) (Bhattacharya et al 1993).

Other

Effects of Pb on auditory and visual functions have been reviewed (Otto & Fox 1993).

In a study of 155 children aged 4-14 in the Katowice area in Poland (median B-Pb 72, range 19-281 μg/L=0.34, range 0.09-1.4 μmol/L), the hearing threshold increased with rising B-Pb, even below 100 μg/L (0.48 μmol/L) (Osman et al 1999a). Above that B-Pb, there was also a change of brainstem auditory-evoked potential.

In Pb-workers and referents, there was an association between impaired visual contrast and B-Pb (median 280, range 60-610 μg/L and 70, 20-210 μg/L, respectively) (Lucchini et al 2000). This was considered to be a sensitive indicator of neurotoxicity.

In an audiometry study of Ecuadorian *children* with high environmental Pb exposure (median B-Pb 526, range 99-1,100 μg/L) and a referent group of 14 (B-Pb 64, range 39-120 μg/L), there were no Pb-associated effects (Counter et al 1997). However, the testing facilities may not have been optimal.

In a recent review of 102 papers on neurotoxic effects in Pb workers, it was concluded, that, on a group basis, effects on peripheral nerve conduction velocity, event-related evoked EEG potential, postural balance and HRV occurred at group mean B-Pbs of 300-400 μg/L, on somato-sensory, visual and brainstem auditory evoked EEG potentials, as well as on distribution of nerve conduction velocities, at 400-500 μg/L (Araki et al 2000).

4.1.2.5. Organolead

In a study of US current organo-Pb (tetramethyl and tetraethyl Pb, which are rapidly dealkylated in the body) workers (exposed to a mixture of organic and inorganic Pb; "lifetime" mean B-Pb 261 μg/L), there were plenty of neurological findings (Mitchell et al 1996); however, the group was selected. Among 222 workers (air-Pb: inorganic 4-119, organic 1-56 $\mu g/m^3$; weighted average B-Pb 240

μg/L), manual dexterity and verbal memory/learning (Schwartz et al 1993) and simple visual reaction time (Schwartz et al 1995) were related to the exposure intensity (and U-Pb). Among the Pb workers, 42.6% had "subnormal" scores in a symptoms questionnaire, vs 7.6% in a referent group of unexposed workers from the same factory (B-Pbs not given) (Bolla et al 1995). The neurobehavioural and symptoms pictures were similar to that in workers exposed to organic solvents (Schwartz et al 1993; Bolla et al 1995).

In 543 US former (average 17.8 years since last exposure) organo-Pb workers, there were associations between current (mean 14.4, range –1.6 to 52.0 μg/g bm) and peak (calculated concentrations at the end of occupational exposure, assuming a half-time of 27 years; mean 23.7, range –2.2 to 105.9 μg/g bm) tibia-Pb, on the one hand, and adjusted performance in a series of neuropsychological tests (particularly in the domains manual dexterity, executive ability and verbal intelligence and memory), on the other (Stewart et al 1999). The associations were somewhat closer with peak levels than with current ones. There was almost no correlation with cumulated occupational exposure (μg/m^3; data not given) or current DMSA-chelated Pb. The authors claim that the results indicate a cumulative and persistent effect. However, the selection of workers was great. Further, the back-calculation did not take into account the current "background". B-Pbs were not given, but in a sub-population, the current average concentration was 46 μg/L (Tassler et al 2001).

Interestingly, the Apolipoprotein E genotype (which has associations with Alzheimer´s disease) interacted with tibia-Pb to explain findings (Schwartz et al 2002). The authors argue, that the tibia-Pb after end of exposure (*ie*, through endogenous exposure) may be of importance (Links et al 2001).

Also, they followed the workers for up to 4 years (Schwartz et al 2000b). Then, there was a decline of function in some tests, which was proportional to "peak" tibia-Pb. The authors claim that earlier external exposure may cause a progressive decline in cognitive functions. Contrary, sensory and motor tests in the hands did not deviate (Schwartz et al 2001). These important findings have some limitations, though, because the workers had been exposed to organo-Pb (though the tibia accumulates and releases inorganic); further, there is a multiple inference problem.

In 490 of the US former (average 16 years since last exposure) organo-Pb workers, there were no associations between current B-Pb (mean 46 μg/L) and DMSA-chelated Pb and current (mean 14.7 μg/g bm) and peak (calculated concentrations at the end of occupational exposure, assuming a half-time of 27 years; mean 24.1 μg/g bm) tibia-Pb, on the one hand, and peripheral nervous function in hands (sensory pressure threshold in index fingers) and pinch and grip strengths), on the other (Tassler et al 2001). The only exceptions were (for unclear reasons) associations with pressure threshold in the little finger.

Effects on cognitive and behavioural effects in infants and children are discussed in section 8. Reproduction and effects in infants/small children.

4.1.3. Mechanisms

The mechanism behind Pb-induced neurotoxicity is not clear (Rice & Silbergeld 1996). However, several possibilities have been proposed. Hence, Pb interferes with heme synthesis, which may impair the energy metabolism in the nervous system. Further, ALA is neurotoxic.

Also, Pb interferes with Ca-dependent processes, *ia*, such related to neuronal signalling and intracellular signal transduction (Rice & Silbergeld 1996). Pb perturbs intracellular Ca cycling, altering releasability of organelle stores, such as endoplasmic reticulum and mitochondria. In some cases, Pb inhibits Ca-dependent events, such, including Ca-dependent release of several neurotransmitters and receptor-coupled ionophores in glutamateric neurons; in other cases, Pb appears to augment Ca-dependent events, such as protein kinase C and calmodulin.

Experimentally, Pb can induce significant function impairment *in vivo* in the nervous system at doses below those associated with cytotoxicity (Rice & Silbergeld 1996). For instance, exposures that significantly and persistently alter both neurochemical parameters and behaviour, are associated with little quantitative changes in brain weight, size, regional cytoarchitecture or markers of neural or glial numbers.

4.1.4. Summary

Heavy Pb exposure (B-Pb ≥4 μmol/L) to inorganic Pb may cause clinical *encephalopathia*, which is to a large extent reversible if adequately treated (Table 2, see page 80). Slight CNS symptoms have been reported in groups of workers with mean B-Pb of about 1.5-2 μmol/L, or higher.

Neurobehavioural effects may occur at B-Pbs of 1.5-2.0 μmol/L (tibia-Pb 40 μg/g bm), or higher (Table 2). There are many problems associated with the interpretation of these data: For example, several indices of exposure and a wide variety of tests have been used; only some in each study have been positive, which may lead to a bias of multiple inference. Also, the reference groups had often relatively high B-Pbs, in the same range that has, on basis of limited data, been claimed to cause disturbances of neurobehavioural tests in the general population.

There are some reports of associations between occupational Pb exposure, on the one hand, and Parkinson´s Disease and ALS, on the other.

Severe Pb exposure causes *peripheral neuropathy*, which is reversible, if adequately handled. Slight sensory symptoms and signs of decreased strength have been noted at mean B-Pbs about 1.5 μmol/L, or higher (Table 2). Neurophysiological disturbances of motor and sensory nerve conduction velocities and of vibrations sense have repeatedly been associated with mean B-Pbs of about 1.5 μmol/L (tibia-Pb 30-40 μg/g bm), or higher.

Subclinical effects on vision and hearing, as well as on visual and auditory evoked potentials, have been reported at mean B-Pbs of 1.5 μmol/L, or higher, and at even lower B-Pbs in children (Table 2). Subclinical effects on postural stability have been recorded at B-Pbs of 1.5 μmol/L, or higher. All these effects may be due to disturbances of different parts of the nervous system.

Several studies indicate effects on the *autonomous nervous system* (mainly HRV) at mean B-Pbs of about 1.5 μmol/L, or higher (Table 2).

For all these effects, it is not clear whether they are mainly dependent upon recent or long-term exposure (reflected by time-integrated B-Pb or bone-Pb). However, there is some evidence that some of these effects may be reversible at a reduction of exposure.

4.2. Blood and blood-forming organs

4.2.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was recognized, that heavy Pb exposure may cause anemia. Such is usually associated with B-Pbs of 3 μmol/L. The main mechanism is inhibition of several enzymes in the heme (ALAD and heme chelatase, the inhibition of which causes a rise of zinc protoporphyrin [ZPP] in blood) and hemolysis. There was limited data indicating an effect on the hemoglobin concentration at a mean of 2.5 μmol/L.

Further, the nucleic acid metabolism in erythrocytes is Pb sensitive. Hence, pyrimidin-5´-nucleotidase (P5N) activity is inhibited. An advantage with P5N over ALAD determinations was that it is less sensitive as to time after sampling.

There is slight enzyme inhibition in the bone marrow/red cells at low B-Pbs. Probably, effects on the enzymes ALAD and P5N in red cells are proportional to the B-Pb, right down to the B-Pbs in subjects without particular Pb exposure, even at the low B-Pbs seen in Sweden at that time (mean B-Pb about 0.3 μmol/L). At B-Pbs about 1.0 μmol/L, the ALA concentrations in plasma and urine and ZPP in erythrocytes start to increase. Disturbance of heme metabolism is more pronounced in women than in males.

However, it was not known whether such slight effects have health consequences. Neither was it known whether corresponding inhibition of heme synthesis occurs in other tissues at similarly low exposure. However, considering the central position of heme in the energy metabolism (CNS inclusive) and in handling of organic xenobiotics by the tissues, the effect was considered to be potentially important. However, there was not sufficient evidence for classifying such effects as definitely adverse.

There were some indications that subjects with certain types of inborn errors of metabolism (porphyria) are particularly sensitive to Pb, and that hemoglobin disorders could predispose.

4.2.2. Update

4.2.2.1. Heme metabolism

Determination of ALAD activity has considerable method problems (Jaffe et al 1991). ALAD activity (especially the fraction of the activity restored by Zn or dithiothreitol) is more sensitive than disturbances in ALA concentrations (Sakai & Morita 1996).

In Pb workers, ALA increases earlier in plasma (P-ALA; but not in red cells) than in urine; there is an exponential increase of P-ALA with rising B-Pb (Morita et al 1994; Sakai & Morita 1996; Sakai et al 1998), which is most likely due to the saturation of the Pb binding in the red cells.

P-Pb without (Hirata et al 1995) and after (Sakai et al 1998) chelation is associated with ALA concentrations in plasma and urine and coproporhyrin in urine; it displays closer correlations than B-Pb. In Israeli battery workers, smokers had higher U-ALA than nonsmokers, in spite of the fact that B-Pbs did not differ (Solliway et al 1996). The authors argue (without data), that creatinine adjustment of U-ALA is not valid, since ALA excretion is dependent upon the pH of the urine.

In Japanese workers with B-Pb <400 μg/L, the "benchmark dose" (excess risk 5%) was calculated to B-Pbs of 27 μg/L for Ery-ALAD, 33 μg/L for P-ALA and 88 μg/L for U-ALA (Murata et al 2003).

By cytometry, ZPP may be determined in individual red cells, which may be an advantage when evaluating the time pattern of Pb poisoning, as it reflects the B-Pb at the time of formation of the cell (Markowitz et al 1994). B-ZPP is less sensitive to Pb exposure than P-ALA (Sakai & Morita 1996).

There are indications of gene-environment interaction: In Japanese Pb workers, there was no genotype-associated difference in basic B-ALAD activity, but restoration of activity by chelator was less efficient in *ALAD*^{2} subjects than in *ALAD*^{1} ones (Sakai 2000), which may be a result of the tighter binding of Pb. However, contrary to what might be expected from the higher affinity of Pb to *ALAD*^{2} than to *ALAD*^{1}, elevated P-ALA was shown in Korean (Schwartz et al 1997b), Thai (Sithisarankul et al 1997) and Japanese (Sakai et al 2000) Pb workers with homozygous *ALAD*^{1} genotype, as compared to *ALAD*^{2} subjects. Moreover, among 72 Turkish battery workers, the *ALAD*^{1} subjects had higher U-ALA than the *ALAD*^{2} ones (29.2%), especially at B-Pbs >500 μg/L (Süzen et al 2003).

Since there seems to be no clear genotype-dependent difference in basic ALAD activity in erythrocytes (Zhang et al 1998; Sakai et al 2000; Süzen et al 2003), the above-mentioned rise of P-ALA may be caused by an induction of ALA synthetase, caused by negative feed-back regulation due to lack of heme, which is a result of inhibition of ferrochelatase-mediated incorporation of Fe^{3+} into heme in the mitochondria, because Pb is not as efficiently sequestered by the ALAD protein in *ALAD*^{1} subjects, as compared to *ALAD*^{2} ones.

Moreover, among the above-mentioned Korean, Thai and Japanese Pb workers, those with *ALAD*^{1} had higher ZPP, when controlling for B-Pb (Schwartz et al 1995; Sakai et al 2000). The same finding was claimed to be present in 119 Canadian smelter workers (Alexander et al 1998).

However, the picture is not clear: In 201 Japanese porcelain paint workers, there was no statistically significant difference in U-ALA between *ALAD*^{2} and *ALAD*^{1} subjects, though the latter had higher values numerically (Zhang et al 1998). Further, in 798 Korean Pb workers (mean B-Pb 320, range 40-860 μg/L; tibia-Pb 37.2, range –7 to 338 μg/g bm) and 135 controls (mean B-Pb 53, range

20-100 μg/L; tibia-Pb 5.8, range –11 to 27 μg/g bm), there was no clear effect modification of *ALAD* (nor *VDR*) genotype of the effect of Pb (B-Pb and DMSA-chelatable Pb) on neither ALA, nor ZPP metabolism (Lee et al 2001b).

4.2.2.2. Nucleotide metabolism

The enzyme P5N is present in the cytosol of erythrocytes. It catalyzes, as a step in degradation of ribosomal RNA, hydrolytic dephosphorylation of pyrimidine-5´-monophosphates, but is ineffective on purine nucleotides, which are kept as a source of ATP.

Hence, inhibition of P5N leads to accumulation of pyrimidine nucleotides in red cells (Ichiba et al 1992; Kim et al 1995a), which is believed to shorten the life span of the cells. However, the inhibitory effect of Pb on ALAD is higher than on P5N (Kim et al 1995a). Nicotinamide adenine dinucleotide synthetase (NADS) activity is also inhibited by Pb (Morita et al 1997), but has only occasionally been used for monitoring.

4.2.2.3. Hemoglobin/anemia

Hu (1991a) studied 21 US adults in the general population (mean current B-Pb 0.29 μmol/L), who had 1930-1942 suffered from Pb-poisoning as children, and matched referents (B-Pb 0.36 μmol/L). The cases still had lower blood hemoglobin levels.

It has been claimed, that reserve capacity for new blood formation is a more sensitive index of toxic effect than the hemoglobin level (Grandjean 1991).

In 98 Belgian battery factory workers (mean 510, range 400-750 μg/L) and 85 "controls" (B-Pb 209, range 44-390 μg/L), there were associations between hemoglobin concentration and hematocrit, on the one hand, and B-Pb, on the other, although only 6% of the variance was explained (Gennart et al 1992a).

In a study of 31 Israelian Pb workers (B-Pb 414, range 230-530 μg/L) and 56 non-exposed controls (B-Pb 78, range 10-130 μg/L), the latter had lower, and weakly B-Pb associated, red blood cell count, while the haemoglobin concentrations did not differ (Solliway et al 1996). Also, there was an exposure-dependent elevation of glutathione peroxidase activity, which the authors attributed to reticulocytosis (not assessed) and Pb-induced free radical formation, with lipid peroxidation. Acetyl-cholinesterase activity in blood cells did not differ.

In the above-mentioned 798 Korean Pb workers (mean B-Pb 320, range 40-860 μg/L; tibia-Pb 37.2, range –7 to 338 μg/g bm) and 135 controls (mean B-Pb 53, range 20-100 μg/L; tibia-Pb 5.8, range –11 to 27 μg/g bm), tibia-Pb (but neither B-Pb, nor chelatable Pb) was associated with lower hemoglobin/ (packed cell volume), although the explained variance was small (<1%) (Lee et al 2001b). The authors suppose, that while the effect on ALA and ZPP depends on recent exposure, the effect on hemoglobin is a long-term one.

In a study of US construction workers without particular exposure to Pb (mean B-Pb 0.40 μmol/L=83 μg/L), the patella-Pb (but neither B-Pb, nor tibia-Pb) was associated with a decrease of hemoglobin and hematocrit (Hu et al 1994). The authors assumed that this indicated an effect on hematopoesis (direct on the bone

marrow?). However, there was no effect modification by *ALAD* genotype (Smith et al 1995b).

In a study from Brazil (of Caucasians and mulattoes), 60 subjects exposed to Pb in a pottery manufacturing plant (mean B-Pb 534±12.1 μg/L), as compared to 30 controls (police preparatory school students; B-Pb 63±2.3), besides increased U-ALA, had higher fraction of blood methemoglobin and urinary chemiluminiscence, as well as activity of superoxide dismutase (SOD) in blood (Costa et al 1997). The latter finding correlated with B-Pb, the first two ones with U-ALA. The authors believe, that the effects were due to a pro-oxidant effect of ALA, causing oxidative stress with production of reactive oxygene species (ROS), resulting lipid peroxidation, leading to excretion of chemofluorescents and induction of the antioxidant defence, which is in agreement with experimental findings (including decrease of glutathione). However, they do not account for age, or smoking and alcohol habits, which may confound the results.

In 13 Pb-smelter workers, there was inverse relationship between hemoglobin level and P-Pb (median 1.4, range 0.9-3.0 μg/L), which may indicate the inhibition of the heme synthesis (Bergdahl et al, submitted). The dose-response relationship of such an effect may be blurred if B-Pb (median 390, range 320-450 μg/L) is used, because of reverse causation (Pb induces a decrease of the red cell volume, which binds Pb).

4.2.3. Summary

Heavy Pb exposure (about 3.0 μmol/L, or more) may cause clinical anemia, caused by inhibition of heme synthesis and hemolysis (Table 2).

Slight effects on blood hemoglobin concentrations and hematokrit have been reported at mean B-Pbs of 2.0-2.5 μmol/L (Table 2). However, B-Pb has particular limitations as an index of exposure when effects on the blood are assessed, since a reduced voume of red cells will limit the possibilities of Pb binding in blood. P-Pb may have advantages, but the information is yet scanty. Further, there are some data, indicating that bone-Pb may be more closely associated with blood effects than is B-Pb, perhaps through a local effect on the bone marrow. Any effect on the hemoglobin concentration is adverse.

The main target in the heme synthesis is ALAD, the activity of which seems to be inhibited at B-Pb right down to those in general populations with low exposure (about 0.10 μmol/L; Table 2). This results in increases of ALA concentrations in plasma (documented at about 0.15 μmol/L) and urine (about 0.4 μmol/L). At higher B-Pbs, there is inhibition of heme syntethase, resulting in an increase of blood ZPP, and of P5N of the nucleotide metabolism. The relations between all these effects and B-Pb are exponential, because of the saturation of the erythrocytes at high exposure. Disturbance of heme metabolism is more pronounced in women than in males.

It is not known whether such slight effects on heme synthesis and nucleic acid metabolism have health consequences. Neither is it known whether corresponding inhibition occurs in other tissues at similarly low exposure. However, considering

the central position of heme in the energy metabolism (CNS inclusive), and in handling of organic xenobiotics by the tissues, the effect on the heme metabolism is potentially adverse. Also, it must be considered that ALA is neurotoxic and induces formation of free radicals.

There are indications of a gene-environment interaction, in that one of the *ALAD* genotypes ($ALAD^1$) is associated with a greater effect on the heme metabolism (than in $ALAD^2$ subjects). Subjects with certain types of inborn errors of metabolism (porphyrias) may be particularly sensitive to Pb, and that some hemoglobin disorders may predispose.

4.3. Kidneys

4.3.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was concluded, that Pb may induce kidney damage, with interstitial nephritis, often combined with hypertension, hyperuricemia and gout. Since there was no evidence of overproduction of uric acid, it was assumed that there was an impairment of the tubular secretion of urate.

The information on exposure-response was incomplete. However, severe effect were assumed to occur mainly a long time after high exposures, though there was evidence, that slight effects on the tubular epithelium, with enzymuria, occurs at considerably lower exposures, probably already at B-Pbs of about 1.5-2.0 μmol/L. The health effects of slight enzymuria were not known; there was some information indicating reversibility after end of exposure. However, considering the severe kidney effects that Pb-exposed individuals may suffer, the subclinical findings were considered adverse. Pb also affects vitamin D and Ca metabolisms. In children, such disturbances had been documented already in the B-Pb range 0.75-1 μmol/L. However, adults seem to be less sensitive.

4.3.2. Update

Since 1991, a lot of new data have been published (reviews: Nolan & Shaikh 1992; Batuman 1993; WHO/ICPS 1995; Loghman-Adham 1997). In one review, the proofs for the existence of Pb-induced nephropathy in man was questioned and considered to be, at best, circumstantial (Nuyts et al 1991). Hence, it was claimed, that the morphological picture is unspecific and the temporal relationship between exposure and onset of disease obscure (exposure history often not reported). Further, it was suspected, that Pb merely aggravates a pre-existing kidney disease. Also, a healthy worker selection (before employment, or during exposure, because of the medical survey system or selective quitting because of disease) probably exists. However, these conditions would rather cause a bias towards the null. Moreover, the risk of counfounding, from cadmium (Cd) and mercury (Hg) nephrotoxicity, as well as socioeconomic factors, was stressed, which is a true problem. However, organic solvents, which were also mentioned as a potential confounder, only seldom occur in the same occupational settings. Further, the health importance of microproteinuri and enzymuria was challenged.

Since 1991, more evidence from animal experiments has been published, again showing nephropathy with nuclear inclusion bodies in proximal tubuli, microproteinuria and enzymuria and - finally - tubular atrophy and interstitial fibrosis (Khalil-Manesh et al 1992a and 1992b).

4.3.2.1. Occupational exposure

Kidney function

In 98 battery factory workers (mean 510, range 400-750 μg/L) and 85 "controls" (B-Pb 209, range 44-390 μg/L), there were no statistically significant differences in serum concentrations of creatinine or β_2-microglobulin ($ß_2$-MG), predicted creatinine clearance (calculated from serum creatinine, sex, age, and body size) or urinary excertion of albumin, $ß_2$-MG, retinol-binding protein (RBP) or the lyzosomal enzyme *N*-acetyl-ß-D-glucosaminidase (NAG; age-adjusted) (Gennart et al 1992a). Neither was there any association with the B-Pb. There was no difference in U-Cd. However, the Pb exposure in the "controls" was remarkable.

In 70 current (median B-Pb 1.54, range 0.24-2.29 μmol/L; tibia-Pb 48.6 μg/g bm) and 20 retired (B-Pb 0.48 μmol/L; tibia–Pb 100.2 μg/g) Swedish smelter workers and 41 referents (B-Pb 0.2 μmol/L; tibia-Pb about 20 μg/g), there was no difference as regards plasma creatinine, creatinine clearance, or urinary excretion of albumin, $ß_2$-MG or NAG (Gerhardsson et al 1992).

In 87 active and 16 former battery plant workers, 38 clerks at the factory and 26 unexposed referents, there were no correlations between parameters reflecting short- (mean B-Pb 0.18-1.45 μmol/L in the four groups) or long-term (time-integrated B-Pb; tibia-Pb –3.5 to 21.1; calcaneal-Pb 1.2 to 76.6 μg/g bm) Pb exposure, on the one hand, and urinary activity of NAG or concentration of RBP, on the other (Erkkilä et al 1992), although the reporting of data was very brief.

When a battery of 22 potential markers of renal changes were applied to a cohort of 41 Belgian smelter workers, moderately exposed to Pb (mean B-Pb 480, range 360-650 μg/L; exposure ≥1 year), and 41 controls (average B-Pb 167, range 63-343 μg/L), the only effect observed were associations between urinary excretion of eicosanoids (lower 6-keto-prostaglandin F_1 and higher tromboxane B_2) and B-Pb, which was considered to reflect a disturbance of their synthesis in the kidney (Cárdenas et al 1993). The urinary excretion of some tubular antigens was associated with duration of Pb exposure (but not B-Pb). There was no correlation between Pb exposure, on the one hand, and markers of glomerular (including albumin), proximal (including $ß_2$-MG, RBP and NAG) and distal tubular, and collecting duct/interstitial markers, on the other. The Pb-exposed workers also had some Cd retention, as compared to the controls (mean U-Cd 0.88 *vs* 0.40 μg/g creatinine=crea), while they had lower U-Hg (1.7 *vs* 2.3 μg/g crea).

Eicosanoid disturbances may affect the renal hemodynamics. Accordingly, in 76 Belgian smelter workers (GM B-Pb 430, range 259-679 μg/L; tibia-Pb 66, range <15-69 μg/g bm), and 76 referents (B-Pb 141 μg/L; tibia-Pb 21 μg/g), there was a slight positive association between creatinine clearance after protein challenge and tibia-Pb (Roels et al 1994). The authors hypothesize, that Pb

induces a slight hyperfiltration (as has also been seen in experimental animals) (Khalil-Manesh et al 1992a and 1992b). The Pb-workers excreted more NAG, but this was associated with a slight difference in U-Cd (1.04 *vs* 0.53 μg/g crea). There were no other differences in kidney function (urinary albumin, transferrin, β_2-MG or RBP).

In 99 Japanese Pb-solder and Pb-smelter workers (B-Pb 39-1,077 μg/L), subjects with high B-Pb (means 276 μg/L and higher) had increased urinary excretion of α_1-microglobulin= α_1-MG; adjusted for age, but not for Cd), while serum concentration of α_1-MG was not affected (Endo et al 1993).

Among 166 Spanish Pb-battery workers (median B-Pb 368 μg/L) there was a clear increase of urinary NAG (but not of the brush-border enzymes alanine-aminopeptidase and γ-glutamyl-transpeptidase=γ-GT, albumin or total protein), as compared to 60 controls (B-Pb 116 μg/L) (Santos et al 1994). In the whole group, B-Pb correlated with U-NAG.

In an interesting study of 128 workers exposed to Pb oxide and stearate in a Pb-stabilizer factory and 152 controls, there was no difference in total urinary NAG (Chia et al 1994b). Further, there was no association between NAG and current (median B-Pb 296, range 39-666 *vs* 87, range 32-164 μg/L) or time-integrated B-Pb. However, the relative (but not absolute) change of B-Pb during the last 6 months was correlated to NAG. Moreover, when the two species of NAG - NAG-A and NAG-B - were studied separately, the association was only with the latter, which is heat stable, linked to the lysosomal membrane of the proximal tubular cell and excreted at epithelial turnover, as a result of necrosis, cell breakdown or loss of brush-border vesicles, while the intralysosomal NAG-A is excreted through exocytosis. Hence, the data indicate that there is damage, dependent upon recent exposure, which indicates reversibility. Also, there were indications of a difference between Chinese and Malays.

In another report on 128 (partly the same?) Pb-workers (mean current B-Pb 326, range 76-662 μg/L) and 93 controls (B-Pb 90, range 32-67 μg/L), there was a significant difference in urinary α_1-MG (Chia et al 1995a). Also, that tubular protein was associated with B-Pb, but more strongly with time-integrated B-Pb, and in particular with B-Pb peaks >600 μg/L. Similar - but less definite - increases were seen for serum β_2-MG and urinary albumin, while urinary β_2-MG and RBP only correlated with the time-integrated B-Pb. There was no effect of recent changes of B-Pb. Interestingly, there was an effect-modification by age; the effect was more pronounced in workers employed >30 years. Importantly, there was no effect of U-Cd (1.21, range 0.05-2.07 μg/g crea in the exposed group).

In a study of 154 mainly Malayan and Indian workers (partly the same?) in a Pb-stabilizer factory, there were associations between the urinary excretion of a proximal tubuli brush-border antigen, on the one hand, and time-integrated B-Pb, number of peaks >400 μg/L and relative change of B-Pb during the last 6 months, on the other; current B-Pb also correlated, but less (Chia et al 1994a). Further, the brush border protein excretion was associated with – in order of association -

urinary α_1-MG, NAG-B, β_2-MG and RBP, which strongly supports a toxic effect on the proximal tubuli.

In 137 Pb-exposed mainly Malayan and Indian workers (partly the same?) in a Pb-stabilizer factory and 153 postal workers (current B-Pbs not given!), the Pb workers had higher serum α_1-MG and urinary albumin, while there was no difference in serum creatinine or creatinine clearance (Chia et al 1995b). It is difficult to follow the data treatment. However, it seems, that Pb workers >30 years of age more often had abnormally (not defined) high serum β_2-MG. Also, the time-integrated (but not current) B-Pb correlated with serum α_1-MG, irrespective of age and with abnormal serum creatinine and β_2-MG and urinary albumin at >30 years; for the latter two markers, the number of B-Pb peaks above >600 and >400 μg/L seemed to be of importance. The findings may indicate a decrease of GFR and tubular protein reabsorption. The Cd retention (B-Cd ≤1.92 and ≤2.0 μg/L in the exposed and unexposed groups, respectively; U-Cd ≤2.07 and ≤1.2 μg/g crea) did not seem to confound.

In 22 Indian automechanics (mean B-Pb 409, range 300-690 μg/L), urinary NAG and β_2-MG were increased, as compared to 27 referents (B-Pb 232±98 μg/L) (Kumar & Krishnaswamy 1995). Further, there was a significant association between B-Pb and NAG (but not β_2-MG). There was a marginal impairment of 4-h creatinine clearance, but not statistically significant.

In 382 South African Pb battery plant workers (mainly coloured; current mean B-Pb 535, range 23-1,100 μg/L), there was no association between blood pressures and B-Pb (Ehrlich et al 1998). In 40 subjects studied (later), the median tibia-Pb was 60.9, range 22.6-179.4 μg/g bm.

In 80 active (median B-Pb 1.6, range 0.7-2.8 μmol/L; tibia-PB 25, range –5 to 193 μg/g bm) and 73 retired (B-Pb 0.9, range 0.4-1.6 μmol/L; tibia-Pb 75, range 17-169 μg/g bm) Swedish Pb-smelter workers and 24 referents (median B-Pb 0.2, range 0.1-0.7 μmol/L; tibia-Pb –6 to 36 μg/g bm), there was an increased excretion of urinary NAG in the active subjects, and a correlation between NAG and tibia-Pb; no such associations were seen in the retired individuals (Tell et al 1998). The groups did not differ in U-Cd. There were no differences in excretion of albumin or β_2-MG.

Out of 22 Swedish smelter workers (11 active, 11 retired; median B-Pb 1.2, range 0.37-2.4 μmol/L; fingerbone-Pb 48, 20-99 μg/g ww) and 11 referents (B-Pb 0.20, 0.10-0.34 μmol/L; fingerbone-Pb 2, -2 to 16 μg/g ww), one active and five retired showed signs of kidney dysfunction (urinary NAG, protein HC, β_2-MG and/or albumin above the upper reference limits) (Gerhardsson et al 1998). However, there was a concomitant low exposure to Cd (Pb-workers: B-Cd 8.6, 1.9-53 nmol/L, kidney-Cd 24, 5-61 μg/g; referents: B-Cd 2.6, 0.9-16 nmol/L, kidney-Cd 10, 3-28 μg/g), although this was considered to be of less importance.

In 382 South African Pb battery plant workers (mainly coloured; current mean B-Pb 535, range 23-1,100; historical B-Pb 573, range 140-963 μg/L), there was an association between serum creatinine and urate (but not urinary NAG, RBP,

alkaline phosphatases, Tamm-Horsfall glycoprotein, epidermal growth factor or albumin), on the one hand, and current and historical B-Pb exposure, on the other (Ehrlich et al 1998). In 40 subjects studied (later), the median tibia-Pb was 60.9, range 22.6-179.4 μg/g bm, in 56 was the median B-Cd <0.5, range up to 1.2 μg/L.

In 803 Korean Pb workers (mean B-Pb 320±150 μg/L; tibia-Pb 37.2±40.4 μg/g bm) and 135 controls, there were associations between some aspects of impaired kidney function, and the biomarkers of Pb exposure (Weaver et al 2003), although the picture was not coherent. The effect was modified by age (worse in old workers). Interestingly, the blood urea nitrogen (BUN) and serum creatinine decreased, and measured and estimated creatinine clearances increased, with rising Pb markers. U-Cd (mean 1.1 μg/g crea) was associated with U-NAG. However, tibia-Pb (but not the other Pb biomarkers) was correlated with U-NAG after adjustment for Cd; a 0.5 μg/g crea increase in U-Cd had the same effect as a 66.9 μg/g bm rise of tibia-Pb.

Deaths

In a study of 1,900 US smelter workers (average duration of Pb exposure 9.9 years), there was an increase of deaths from chronic kidney disease, which was most pronounced in those with long-time exposure (standardized mortality ratio=SMR=2.79, 95% confidence interval=CI 0.75-7.15) (Steenland et al 1992). However, the work had entailed a certain exposure to Cd as well.

In a study of mortality 1950-1992 among 1,388 workers and laborers in an Italian primary Pb smelter (air-Pb in 1977-78; GM 47.6, range 1-1,650 $\mu g/m^3$), there was no increase of all causes (SMR=89; CI=82-95; national rates) (Cocco et al 1997). Regional rates were higher, but were only available from 1965 on (SMR=105; CI=97-114). There was an increase of deaths from “saturnism” (among those exposed for >20 years RR=38.5; CI=4.4-340; mostly among maintenance workers and labourers), and of deaths from geneto-urinary system diseases (SMR=126; CI=78-192 and SMR=135; CI=74-227, respectively; all among workers employed before 1946; 52% from renal failure). The latter risk was associated with duration of exposure (>20 years RR=6.6; CI=1.7-26.1; adjusted for calender year and age). There was concurrent exposure to Cd (28% of air samples >10 $\mu g/m^3$).

4.3.2.2. General population

Adults

In a cross-sectional study in Belgium (random samples from two areas with substantial environmental Cd exposure, and two with lower; 965 men and 1,016 women; the Cadmibel study), measured and estimated creatinine clearances were slightly and inversely related to B-Pb (males: mean 114, range 23-725 μg/L; females: 75, range 17-603 μg/L) (Staessen et al 1992 and 1996). Importantly, the relation was neither altered by adjustment for Cd levels in blood or urine, nor hypertension. Further, a 10-fold increase of B-Pb was associated by a raised risk of substantially reduced GFR (<52 mL/min in males, <43 mL/min in females; OR=3.76, CI=1.37-10.4). There were associations between B-Pb and B-ZPP,

on the one hand, and urinary β_2-MG, on the other, while γ-GT displayed no such associations. B-Pb was increased in subjects who reported heavy metals at work.

In a cross-sectional study of 744 Caucasian middle-aged and elderly US men out of the general population, with an average B-Pb of 81 (range <40-260) μg/L, there was (after adjustment for a series of potential confounders, including blood pressure and smoking) a significant negative association between creatinine clearance (measured or estimated) and B-Pb (Payton et al 1994). A 100 μg/L increase of B-Pb was associated with a 10.4 mL/min decrease in logarithm of creatinine clearance. There was also an association between patella-Pb (mean 32.1±19.5 μg/g bm) and estimated creatinine clearance (Wu et al 2003a).

In a follow-up of 777 middle-age and elderly men from the general US population, the association between patella-Pb and serum urate was confirmed (Shadick et al 2000). Gouty arthritis had been diagnosed in 6.7%; however, neither B-Pb, nor bone-Pb predicted this diagnosis. Further, in a 6-year follow-up of 448 of the men, longitudinal, adjusted increases in serum creatinine were non-significantly associated with baseline B-Pb (mean 65±42 μg/L), patella-Pb (32.4±20.5 μg/g bm) and tibia-Pb (21.5±13.5 μg/g bm) (Tsaih et al 2004). The rise of serum creatinine was dependent upon a statistically significant interaction between baseline tibia-Pb and hypertensive status. An interaction was also present between B-Pb and bone-Pb, on the one hand, and diabetes, on the other (a change from the lest to the highest tibia-Pb was associated with a 17.6 times higher increase in diabetics, as compared to non-diabetics).

Further, in a longitudinal (1979-1994) study in the above-mentioned population (459 US men), there was an association between concurrent serum creatinine and B-Pb, even at B-Pbs ≤0.48 μmol/L (<100 μg/L) (Kim et al 1996b). The creatinine/B-Pb relationship was curvilinear, with a steeper slope in the low B-Pb range. An increase of B-Pb by 1 μmol/L meant an average rise of serum creatinine by 2.89 μmol/L. The effect was greater in older age strata. A tenfold increase of B-Pb meant a serum-creatinine increase corresponding to 20 years of aging. More important, there was a relationship between the B-Pb at one point in time and the change in serum creatinine until next sampling, although this was only borderline statistically significant. There was no significant impact of hypertension.

In a study of 64 Spanish patients with chronic renal failure (mean±SEM creatinine clearance 41.4±3.7 mL/min), hypertension and gout, but without known Pb exposure, B-Pb was somewhat higher than in 30 control subjects (mean B-Pb 211 *vs* 167 μg/L), but 56.1 *vs* 0% had a high urinary Pb excretion after EDTA administration (Sánches-Fructuoso et al 1996). In the latter, there was an association between chelatable Pb and serum creatinine. Comment: Since the EDTA-Pb complex is excreted through glomerular filtration, any such association would be partly obscured. In those subjects, there was also a correlation to transiliac bone-Pb (mean 27.8 μg/g ww). No associations with Pb biomarkers were seen for other cases of chronic renal failure. The selection of patients is not clear.

Within the US NAHNES III cross-sectional survey (15,211 adult subjects), there were, among hypertensives (but not normotensives), associations between B-Pb (mean 42.1 μg/L), on the one hand, and serum creatinine (adjusted OR between the highest and lowest B-Pb quartiles 2.41) and chronic kidney disease (GFR <60 mL/min/1.73 m^2 estimated from the serum creatinine; OR=2.60), on the other (Muntner et al 2003). However, the association was only present among non-smokers. There was an indication of an interaction with diabetes. The relationship was curvilinear, with the greatest effect at low B-Pbs.

In a study of the population around a battery factory in Taiwan, there was a decreasing gradient of B-Pb from the plant and outwards (means 163.3, 134.5 and 74.8 μg/L) (Lin et al 1993). Between the most and least exposed groups, there was a significant difference in urinary NAG. However, within the most exposed group, there was no clear association between NAG and chelatable Pb.

In a study of 820 women aged 52-63 years from the south of Sweden, there were significant associations between B-Pb (median 22, range 11-46 μg/L), on the one hand, and serum concentrations of creatinine and cystatin C (indices of GFR), as well as urinary Ca (index of tubular function), on the other (Åkesson et al, submitted). Further, U-Pb was associated with urinary levels of α_1-MG, NAG and Ca. However, there was a correlation between biomarkers of Pb and Cd. Thus, when adjustment was made, only cystatin C remained as significantly associated with B-Pb.

In a series of Taiwanese papers, effects of Pb mobilization (elimination) on kidney function has been addressed: In one of these studies, the progression of chronic renal insufficiency (serum creatinine 15-39 mg/L; GFR 12.7-72.7 mL/min/1.73 m^2) of varying etiology (mainly glomerulonephritis and hypertension) during 24 months was to some (limited) extent dependent upon the "body lead burden" (or rather, EDTA-chelatable Pb; mean 104 μg) in subjects who had a mean B-Pb of 53 μg/L (0.26 μmol/L) (Lin et al 2003). During 27 months, half of 64 patients with high "body lead burdens" (80-530 μg) were treated with EDTA (1 g weekly). Then, the "body lead burden" decreased (from 151 to 43 μg; B-Pb from 61 to 39 μg/L) and the GFR increased by 11.9%, while GFR decreased by 3.6% in the non-treated controls. After end of the chelation, the "body lead burden" and B-Pb increased again, most probably because of "refilling" of endogenous Pb from the bone pool. This may indicate a potentiating effect of Pb on renal disease of other basal etiology. However, the mechanism is not known. One obvious possibility is the decrease of Pb, but another one is scavering by EDTA of ROS. A third one (less probable) is chelation of Cd, and a fourth confounding via alcohol intake and consumption of analgetics (Elinder 2003; Elinder & Alvestrand 2003). The same research group has published other papers on the same issue, with fewer patients and shorter chelation and follow-up times (Lin et al 1999 and 2001b). It is not clear whether the patients were the same.

In another study (different material?), of 101 patients with chronic renal insuffiency (again mainly because of chronic glomerulonephritis and hypertension), there were significant correlations between "body lead stores" (but not

significantly with hemoglobin-adjusted B-Pb, which was 52-545 μg/L), on the one hand, and serum urate and urate clearance, on the other (Lin et al 2001a). In accordance with this, 67 patients with a history of gouty arthritis had higher levels than the 34 others (means: serum urate 99 *vs* 86 mg/L; B-Pb 536 *vs* 43.9 μg/L; "body lead store" 138.1 *vs* 64.2 μg). Similar results have been reported earlier in smaller patient materials (partially the same?). In the first one, it was shown that subjects with essential hypertension and renal insufficiency had increased "body lead burden" (Lin & Lim 1994), in the second one relations between urate metabolism and this burden (Lin & Huang 1994). Moreover, EDTA-chelation therapy weekly during one month in a random half of 30 gout patients with "high body lead stores", markedly increased the urate clearance. The mechanism was probably Pb elimination (Lin et al 2001a).

Chelation therapy by DMSA improved the renal function in Pb-treated experimental animals (Khalil-Manesh et al 1992b).

Children

Some recent papers have reported data on Pb and kidney effects in children: A Pb-associated increase of urinary RBP was seen in a group of children from the Czech Republic with B-Pbs ranging 123-354 μg/L (Bernard et al 1995). Further, urinary NAG was increased in Romanian children with a mean B-Pb of 342 μg/L (Verberk et al 1996).

In 162 Polish children (age 4-14), there were statistically significant associations between decreasing estimated creatinine clearance, and increasing serum cystatin C and urinary α_1-MG, on the one hand, and B-Pb (median 0.35, range 0.09-1.36 μmol/L), on the other (Osman et al 1999b). These associations were present even in subjects with B-Pbs <0.7 μmol/L. Cd and Hg levels in blood were not associated with the kidney markers.

A very detailed study of 62 children in a contaminated Polish area (mean B-Pb 133 μg/L, previously 210 μg/L) and 50 controls (B-Pb 39 μg/L), the former had higher (and B-Pb associated) urinary excretions of glomerular (transferrin, prostaglandins and thromboxane B, but not albumin), proximal ($ß_2$-MG and Clara cell protein, but not α_1-MG or NAG) and distal (epidermal growth factor) tubular, as well as collecting duct/interstitial cell (prostaglandin) markers (Fels et al 1998). In total, no less than 29 markers were studied. The urinary Cd levels were 0.88 and 0.43 μg/g crea, respectively.

In an Australian study among subjects with no reported history of heavy Pb exposure, there were no differences in B-Pb in those with normal renal function, or mild or severe renal dysfunction (Emmerson 1991). In contrast, B-Pbs were higher among adults with renal failure and a history of childhood Pb poisoning.

Hu (1991a) studied 21 US adults (mean B-Pb 0.29 μmol/L), who had 1930-1942 suffered from Pb-poisoning as children, and carefully matched referents (B-Pb 0.36 μmol/L). Surprisingly, the plumbism cases had *increased* mean adjusted creatinine clearances and *low* serum creatinine concentrations.

In 62 adult US subjects with severe childhood Pb poisoning (mean initial B-Pb 1,503±771, range 1,000-4,701 μg/L) and 19 aged-matched siblings, studied 17-23 years (mean B-Pbs in both groups 74 μg/L) after chelation therapy, there were no differences in renal function parameters, including serum creatinine and urinary $ß_2$-MG clearance (Moel & Sachs 1992). In a follow-up study of 454 US children, who had been hospitalized for Pb poisoning in the period 1923-1966, there were (up to 1991) no increase in deaths from chronic nephritis (McDonald & Potter 1996).

4.3.2.3. Gene-environment interaction

An important issue is, whether *ALAD* genotype may interact with Pb as regards nephrotoxic effects. In 691 US construction workers (mean B-Pb 77.8 μg/L), there was an association between BUN and B-Pb; subjects with $ALAD^2$ had higher (sic!) BUN than the $ALAD^1$ ones (Smith et al 1995a). They also had a tendency of higher serum urate concentration, but there was no difference in serum creatinine.

In a study of 89 smelter workers and 32 referents, serum creatinine was slightly higher in $ALAD^2$ individuals, but the difference was not statistically significant (Bergdahl et al 1997a). They also excreted more Ca, but there were no differences as regards excretion of β_2-MG or NAG.

In a recent update of 709 subjects in one of the above-mentioned surveys of middle age and elderly Caucasian US men (Payton et al 1994), serum urate concentration were, as mentioned above, associated with patella-Pb, but more clearly in $ALAD^2$ genotype individuals (already at >15 μg/g bm) than in $ALAD^1$ ones (only at >101 μg/g bm). There also seemed to be an interaction between tibia-Pb and the $ALAD^2$ genotype as regards serum creatinine concentration.

In a small study of smelter workers from northern Sweden, there was no interaction between Pb and *ALAD* genotype as regards GFR or serum creatinine (Gerhardsson et al, to be published).

4.3.3. Summary

Heavy Pb exposure may cause renal dysfunction characterized by glomerular and tubulointerstitial changes, resulting in chronic renal failure, hypertension, hyperuricemia and gout. There are indications that a fraction of such patients, at least in some areas, have an occult Pb exposure, and that elimination of Pb by chelation therapy may be beneficial.

At low-level Pb-exposure, there are associations between B-Pb and bone-Pb, on the one hand, and increased serum levels of urate and urinary excretion low molecular weight proteins and lysosomal enzymes, on the other. This indicates an effect on the proximal tubuli (although hyperuricemia may also reflect oxidative stress) (Waring et al 2001). The effect on α_1-MG is more evident than on $ß_2$-MG, which may be due to the problem by destruction of the latter at low urinary pH, as well as the fact that it has a lower molecular weight, which might make it less sensitive to inefficient reabsorption in the proximal tubuli.

Such effects have been seen in occupational groups with mean B-Pb of about 1.5 μmol/L, or higher (Table 2). In a few studies changes have been seen in workers with mean bone-Pbs of about 40 μg/g bm, or higher.

Limited data indicate that corresponding effects may occur in general populations of children with B-Pb of about 0.5 μmol/L, or higher; in one study even lower.

However, these slight effects are sensitive to confounding. Then, a particular problem is Cd, which is well known to cause proximal tubular effects, even at low exposures. Hence, smelter workers – one of the most frequently studied categories - are often exposed to both Pb and Cd. This may cause a bias – overestimation of any Pb effect. Also, there is a possibility of a Pb/Cd interaction/sum effect. On the other hand, effects have been seen in workers in occupational setting (mainly battery factories) with less likelihood of Cd exposure.

As to glomerular effects, the picture is less clear. There were also associations between B-Pb, on the one hand, and serum concentrations of creatinine, BUN, cystatin C and urate and estimated and measured creatinine clearance, on the other. Such effects have been reported in adult general populations with mean B-Pb of 0.5 μmol/L, or higher; in a couple of studies even lower (Table 2). There are limited indications of interactions between Pb exposure, on the one hand, and diabetics and hypertensive status, on the other.

This may indicate an effect on the GFR. However, since urate and creatinine are excreted by tubular secretion, this may – at least partly – also be due to tubular damage. Also, there is a possibility that a decrease of GFR may result in an accumulation of B-Pb (reverse causality). This possibility has not been conclusively addressed. There are no data indicating Pb-induced albuminuria. Glomerular effects have only to a limited extent been studied in workers, and have then sometimes indicated hyperfiltration.

There are some indications, that the *ALAD*^{2} genotype is particularly associated with Pb-associated increase of serum creatinine.

A problem in the interpretation of data from the occupational studies is the health surveillance that Pb workers are often subject to, meaning that subjects with history or signs of kidney disorder or hypertension are selected before and during employment, which would cause an underestimate of the risk, in particular if the role of Pb is aggravation of other kidney disease.

It is not known whether recent or long-term (continuous or peaks) Pb exposure is the most relevant determinant of risk. Further, the relationship between the sensitive urinary tests and later clinical chronic renal disease is not clear. There is limited evidence of increased mortality from kidney disease in Pb workers, but Cd confounding precludes firm conclusions.

4.4. Cardiovascular system

Relationships between Pb and blood pressure in pregnant women will be discussed in section 8. Reproduction and effects in infants/small children.

4.4.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was noted, that Pb causes an increase of blood pressure in experimental animals. The exposure-response relationship is unusual: The effect is probably more pronounced at low exposures than at high ones. Also, several studies of samples from the general population indicated that a similar effect may occur in man. Then, it seemed that the slope of the B-Pb/blood pressure curve is steepest at low B-Pbs, levelling off at higher ones. In the B-Pb range of the general population in many countries, there was an increase of systolic and diastolic blood pressure by 1-2 mm Hg (0.133-0.266 kPa) for each doubling of B-Pb. This is a rather small effect from an individual risk point of view.

However, from a population health point of view, it might be important, since an effect on the blood pressure may have impacts on the cardiovascular system, mainly cerebrovascular disease and coronary heart disease (CHD). Hence, each mm Hg rise is associated with an increase of ischemic heart disease by about 1%. It has been proposed that Pb is the background of the association in the general population between soft drinking water and CHD. However, Pb is certainly not a major contributor to risk of cardiovascular disease. Thus, any association between Pb exposure in the general population and risk of cardiovascular disease had not been empirically demonstrated. Moreover, the available information did not allow firm conclusions on whether the association between B-Pb and blood pressure in man is causal; there might be methodological problems (reverse causality and residual confounding).

It was also concluded, that several studies indicated a blood-pressure effect in heavily exposed Pb workers. It is possible that these effects are associated with kidney damage, and different from the effect at lower exposures, which may mainly be due to effects on vascular reactivity. Increased risk of cerebrovascular (perhaps also CHD) had been reported in some studies of Pb workers.

4.4.2. Update

4.4.2.1. Blood pressure

In particular, the inconsistencies between studies of occupationally Pb-exposed populations and general populations have attracted several reviews and provoked controversy regarding the effect (Hertz-Picciotto & Croft 1993; Staessen et al 1994, 1995 and 1996; Nawrot et al 2002; Den Hond et al 2003).

Occupational exposure

In 410 male US textile workers exposed to carbon disulphide (CS_2) and – to some extent – Pb at soldering during maintenance operations, there were associations between B-Pb and logarithms of systolic (0.63 mm Hg per 100 μg/L; adjusted for *ia* alcohol intake) and diastolic blood pressures (Egeland et al 1992). A problem in the interpretation is an association between B-Pb and the CS_2-exposure. The B-Pbs were low (means 0.44-0.82 μmol/L in various CS_2-exposure groups).

In 809 UK Pb-battery workers (mean B-Pb 316 μg/L), there was a significant association between systolic (but not diastolic) blood pressure and B-Pb, which, however, disappeared after adjustment for confounders (Maheswaran et al 1993).

Between 166 Brazilian battery-factory workers (median B-Pb 368 μg/L) and 60 controls (116 μg/L), there was a difference in diastolic (but not systolic) blood pressure (Santos et al 1994). Further, in multivariate models (adjusted for age and body mass), there were associations between systolic and diastolic blood pressures, on the one hand, and B-Pb, on the other.

However, in 382 South African battery-plant workers (mean historical B-Pb 573, range 140-963 μg/L), there was no association between blood pressure and Pb exposure (Ehrlich et al 1998).

In a study of 543 male former (≥18 years since last exposure) US workers in an *organo-Pb* plant, there was an association between adjusted systolic and diastolic blood pressures and B-Pb (mean 46, range 10-200 μg/L, explained variance 1.3%); the authors claim that an association was present down to 50 μg/L (Schwartz & Stewart 2000), but this seems doubtful. Tibia-Pb displayed no such association. In a prospective follow-up during 4 years of 496 of the former workers (mean B-Pb 46±26 μg/L; tibia-Pb 14.7±9.4 μg/g bm), there was an increase of systolic blood pressure, which was dependent upon the Pb biomarkers (0.64 and 0.73 mm Hg for each standard deviation increase for B-Pb and tibia-Pb, respectively (Glenn et al 2003). In 220 of the subjects, the gene for the alpha 2 subunit of Na(+)-K(+)ATPase seemed to modify the relation between B-Pb and blood pressure (Glenn et al 2001). There was a great difference in genotype prevalence between African Americans and Caucasians.

General populations

Most of the recent studies have been made in general populations: Møller & Kristensen (1992) found, in 1,052 Danes, a rise of systolic blood pressure by 1.86 (cross-sectional) or 0.90 (longitudinal) mm Hg at a rise of B-Pb by 100 μg/L (B-Pb means 1976: men: 136, range 50-600; women 96, 40-390 μg/L). In a German population, there were also statistically significant associations between B-Pb (median 83 μg/L in 1,703 men, and 60 μg/L in 1,661 women) and systolic (1.45 mm Hg per 100 μg/L; adjusted for, *ia,* alcohol intake and hematocrit) and diastolic blood pressures (Hense et al 1993).

In the cross-sectional Belgian CadmiBel study (2,327 subjects), there was no evidence of an association between B-Pb and blood pressure or hypertension (Dolenc et al 1993; Staeseen et al 1996). In a prospective follow-up of the population, which had a mean B-Pb of 87 μg/L in 1985-1989, and 29 μg/L after an average follow-up time of 5.2 years, there was no consistent association between changes of blood pressure and of B-Pb (Staessen et al 1996). Neither the baseline B-Pb, nor ZPP predicted the development of hypertension during the follow-up.

In 254 male and 271 female Italians, there was a correlation between B-Pb and hypertension (Apostoli et al 1992). Further, in 630 Italian males (patients at general practitioners and blood donors; mean B-Pb 148, range 43-469 μg/L), there

were univariate associations with systolic and diastolic blood pressures and with hypertension, but when potential confounders (age, BMI and alcohol intake) were adjusted for, these were lost (Micciolo et al 1994). However, it is not obvious that this is not an over-adjustment.

In a study of 507 male Austrian law-enforcement officers (policemen, prisons officers, *etc*) without significant occupational exposure to Pb (mean B-Pb 80±35 μg/L), there was a significant effect of B-Pb on diastolic (but not systolic) blood pressure, even when the potential confounders alcohol intake and erythrocyte count were taken into account (Wolf et al 1995).

In 798 middle-aged and elderly US men (median B-Pb 56, range 5-350 μg/L), an increase of 27 μg/L (sic!) was associated with rise of adjusted diastolic blood pressure by 1.2 mm Hg (Proctor et al 1996). Also, there was, in addition, an association between blood pressure, on the one hand, and patella-Pb and tibia-Pb, on the other (Hu et al 1996a). In a third study of the same basic population (N=519), there was no association between B-Pb and blood pressure, but there was one between blood pressure and patella-Pb (Cheng et al 2001).

In middle-aged women from the same US area, there was also an association between patella-Pb (mean 13.3 μg/g bm) and risk of hypertension, but no such associations for B-Pb (mean 0.15 μmol/L) or tibia-Pb (Korrick et al 1999).

In 762 elderly (age above 75, mean 88.2±4.9 years), subjects from Stockholm city, there was no association between B-Pb (mean 0.18±0.11, range 0.01-1.41 μmol/L), on the one hand, and adjusted (age and BMI) systolic or diastolic blood pressure, on the other (Nordberg et al 2000).

In a Croatian population (N=154), B-Pb (median 57, range 25-254 μg/L) was associated with adjusted both systolic and diastolic blood pressures (Telisman et al 2001).

Nash et al (2003) in 2,165 perimenopausal women from the general US population (NHANES III), found that an increase of B-Pb from 10 to 64 μg/L was associated with a rise of systolic blood pressure by 1.7 mm Hg, and of diastolic blood pressure by 1.4 mm Hg. Also, there were relationships with systolic and diastolic (odds ration 8.1, 95% confidence interval 2.6-25) hypertension. The effects were most evident in postmenopausal women. The Pb effect was much more prominent in black men and women than in white subjects (Vuppituuri et al 2003). Hence, there seemed to be an effect modification by race, the reason of which is unclear. However, in another analysis of the NHANES III data, no association between B-Pb and blood pressure was found (Den Hond et al 2002).

Hu (1991a) studied 21 US adults (mean B-Pb 0.29 μmol/L), who had during 1930-1942 suffered from Pb-poisoning as children, and matched referents (B-Pb 0.36 μmol/L). There was a large increase of the risk of hypertension (relative risk=RR 7.0, CI 1.2-42.3). In 62 US subjects with severe childhood Pb poisoning (mean initial B-Pb 1,503±771, range 1,000-4,7010 μg/L) and 19 aged-matched siblings, studied 17-23 years (mean B-Pbs in both groups 74 μg/L) after chelation therapy, there were no differences in blood pressure (Moel & Sachs 1992).

Schwartz (1995) made a meta-analysis of 15 studies in men published 1985-1993. He estimated that an increase of B-Pb from 50 to 100 μg/L was associated with an increase 1.5 mm Hg in systolic blood pressure.

Steassen et al (1994, 1995 and 1996) have made several other meta-analyses. In the latest one (Nawrot et al 2002), 31 studies (19 general and 12 occupational populations; 58,518 subjects), a two-fold rise of B-Pb was associated with a 1.0 (CI +0.5 to +1.4) mm Hg increase of systolic, and a 0.6 (CI +0.4 to +0.8) mm Hg of diastolic blood pressure, with no sex difference, though the effect in females is less well documented than in males. The authors concluded that the association was weak.

In a study of 282 *children* (age 5.5 years) from a Pb-industry town in Kosovo (mean B-Pb 373 μg/L) and an "unexposed one (B-Pb 87 μg/L), there were non-significant associations between adjusted systolic (0.5, CI –0.2 to 1.3 mm Hg/100 μg/L) and diastolic (0.4, CI –0.1 to 0.9 mm Hg) blood pressures, on the one hand, and B-Pb, on the other (Factor-Litvak et al 1996). Use of twelve B-Pb determinations since birth gave similar results.

Gene-environment interaction

There might be gene-environment interactions: In 798 Korean Pb workers (mean B-Pb 320, range 40-860 μg/L; tibia-Pb 37.2, range -7 to 338 μg/g bm) and 135 controls (mean B-Pb 53, range 20-100 μg/L; tibia-Pb 5.8, range –11 to 27 μg/g bm), B-Pb, tibia-Pb and DMSA-chelatable Pb were all predictors of systolic blood pressure, but only tibia-Pb of diastolic. There was no clear effect modification of neither *ALAD*, nor *VDR* genotype of the effect of Pb (B-Pb and DMSA-chelatable Pb) on neither blood pressure, nor hypertension (Lee et al 2001a). However, VDR genotype *per se* was associated with blood pressure. In accordance with these results, in 691 US construction workers (mean B-Pb 77.8 μg/L), there was no difference in blood pressure with *ALAD* genotype (Smith et al 1995a).

Mechanisms

The mechanism(s) behind the likely association between Pb exposure and blood pressure is not known. Several possibilities have been proposed: Direct effects on the excitability and contractibility of the heart, alteration of the compliance of the vascular smooth muscle tissue (perhaps through interaction with Ca signalling), altered vascular reactivity to α-adrenergic agents, interference with the renal synthesis of eicosanoids (resulting in depletion of prostaglandins with enhancement of sodium retention and the pressor response to angiotensin II and vasopressin), effects on the renal ion transport processes, and action on the parts of the CNS responsible for blood pressure regulation (Loghman-Adham 1997). In US males, there was an association between B-Pb and excretion of epinephrine (but not norepinephrine) (Payton et al 1993).

Pb may cause a modification of the renin-angiotensin system. Also, other effects mediated through kidney toxicity must be considered. Hence, although there was no association between renal markers of Pb toxicity and blood pressure

in two studies (Staessen 1995; Nash et al 2003), in a third one there was an association between B-Pb and serum creatinine concentration (Kim et al 1996b). Also, reverse causality may exist: hypertension reduces glomerular filtration, which may decrease urinary Pb excretion and cause a rise of B-Pb. Further, the variance of blood pressure explained by B-Pb is very minor.

4.4.2.2. Heart disease and stroke

Hypertension is a major risk factor for cardiovascular disease. As said above, for an individual, the blood pressure effects associated with Pb have limited importance. However, on a population basis, the effect on cardiovascular disease is considerable. Thus, a 2 mm Hg reduction of systolic blood pressure would be expected to result in a 17% reduction of the prevalence of hypertension, a 15% decrease of the risk of stroke and transient ischemic attacks and a 6% reduction of the risk of CHD (Mulrow 1999).

Occupational exposure

Studies of HRV have been discussed above (section 4.1.2.2. Autonomous nervous system).

In a survey of 1,261 New York City typesetters with low exposure to Pb (air levels <50 $\mu g/m^3$), there was a slight increase of cerebrovascular deaths (total cohort: SMR=1.35, CI=0.98-1.82; subjects exposed >30 years: SMR=1.68, CI=1.18-2.31; based on local rates) (Michaels et al 1991).

In a study of 1,990 US smelter workers (average duration of Pb exposure 9.9 years, the intensity assumed to be high, average 3.1 mg/m^3), there was no significant increases (compared to national rates) of ischemic heart or cerebrovascular diseases (Steenland et al 1992). The exposures to Cd and As were reported to be "relatively low" (averages 14 and 113 $\mu g/m^3$, respectively).

Swedish primary smelter workers, who had died from cardiovascular or cerebrovascular diseases did not have higher levels if Pb in lung tissue than other smelter workers (but they differed from unexposed controls) (Gerhardsson & Nordberg 1993; Gerhardsson et al 1995a).

In 664 male workers in a Swedish secondary smelter handling mainly Pb batteries, there was increased mortalities from ischemic heart disease (SMR 1.72, CI 1.20-2.42) and totally (SMR 1.44, CI 1.16-1.79) (Gerhardsson et al 1995b). However, smoking was not controlled for.

In a study of mortality 1950-1992 among 1,388 workers and laborers in an Italian primary Pb smelter (air-Pb in 1977-78; GM=47.6, range 1-1,650 $\mu g/m^3$), there was no clear increase of total cardiovascular, ischemic heart (SMR=34; CI=77-115; national rates) or cerebrovascular (SMR=95; CI=77-115) disease (Cocco et al 1997).

In a case-referent study of Swedish glass-industry workers, there was no association between cardiovascular death and Pb exposure (Wingren & Axelson 1993).

Among a cohort of 3,979 Pb-exposed Swedish primary-smelter workers, followed 1955-1987, there was no increase of deaths from cardiovascular disease

(ischemic heart or cerebrovascular), as compared to the county population (SMR=0.9, CI=0.8-1.0; mean B-Pb 1950: 3.0 μmol/L; 1987: 1.6 μmol/L) (Lundström et al 1997). This was also true for the subgroup with the highest exposure.

In a study of first-time, non-fatal myocardial infarction in Stockholm, there was no increase of adjusted risk in subjects with a history of occupational Pb exposure (air-Pb estimated by an occupational hygienist ≥0.04 mg/m^3; RR=1.03, CI=0.64-1.65) (Gustavsson et al 2001).

General population

In 775 middle-aged and elderly US men, bone-Pb (in particular tibia-Pb; mean 22.2 μg/g bm) was associated with ECG-changes (intraventricular block), while B-Pb (mean 58 μg/L) was not (Cheng et al 1998a).

In a population-based survey of 1,052 Danish men and women born in 1936 and living in Copenhagen, after adjustment for potential confounders (sex, tobacco use, serum cholesterol, physical activity), B-Pb (means 1976: men: 136, range 50-600, women 96, 40-390 μg/L) was associated with CHD at follow-up (Møller & Kristensen 1992). However, after adjustment for potential confounders, there was only left an association with total deaths.

Further, in the US general population, elevated B-Pb was associated with a dose-related increase in deaths due to hypertension-related CHD and stroke in both men and women (Lustberg & Silbergeld 2002). Hence, the RR for circulatory disease was 1.39 (CI=1.01-1.91), in subjects in the B-Pb range 200-290 μg/L, as compared with those <100 μg/L. There was a numerical increase even in the range 100-190 μg/L. The all-cause mortality was also increased in that range (RR=1.46, CI=1.14-1.86).

In a follow-up study of 454 US children, who had been hospitalized for Pb poisoning in the period 1923-1966, there were (up to 1991) significantly increases of all-cause mortality (RR=1.7, CI=1.4-2.2) and cardiovascular (RR=2.1, CI=1.3-3.2) and cerebrovascular (women: RR=5.5, CI=1.1-15.9) deaths (McDonald & Potter 1996).

Also, even moderate increases of blood pressure affects the GFR, as indicated by associations with serum creatinine in a cross-sectional study of the US general population (NHANES III) (Coresh et al 2001), and – more importantly – in a prospective study over 12-15 years (Perneger et al 1993).

4.4.3. Summary

As said above (section 4.1.2.2. Autonomous nervous system), there were some indications of ECG effects (reduced HRV) at B-Pbs of 1.5 μmol/l, or higher (Table 2).

There is considerable evidence that Pb absorption, at least in predisposed individuals, may lead to hypertension. Hence, several studies indicated a blood-pressure effect in Pb workers, although the picture is far from consistent (Table 2).

There are also clear indications of an effect of Pb on blood pressure at lower exposures. Thus, in the B-Pb range of the general population (mean B-Pbs 0.4 μmol/L, or higher; Table 2), there was an increase of systolic and/or diastolic blood pressure by about 1 mm Hg for each doubling of B-Pbs in the low range (although the picture is not consistent), less at higher.

The available information does not allow firm conclusions on whether the association between B-Pb and blood pressure is really causal. Thus, epidemiological studies of determinants of blood pressure are complicated, since there are many potential confounding and effect-modifying factors. For example, alcohol intake may cause confounding. However, in the latest studies, these problems seem to be reasonably well under control. Still, there is a risk of both residual confounding and over-adjustment, which may result in over- or under-estimates of the effect. The problems are well illustrated by the partly diverging results obtained in analyses of the same data-base. Also, there might be other methodological problems, in terms of reverse causality, mediated through a blood-pressure dependent decrease of GFR with reduced Pb excretion.

It is possible that any effect on the blood pressure, at the high exposures in Pb workers, is associated with Pb-caused kidney damage, although hypertension seems to occur even in workers without obvious kidney disorder. This mechanism may be different from the effect at lower exposures, which may mainly be due to effects on vascular reactivity.

The effect on blood pressure is not a health outcome *per se*, but is a risk factor for cardiovascular and cerebrovascular disease. This risk is rather small from an individual subject risk point of view. However, in a population, it might be important. Indeed, some (but far from all) studies showed increased risk of cerebrovascular (perhaps also CHD) in Pb workers. In those studies, the referents were from the general population. This may be a problem, since there are indications of an effect already at such low B-Pbs.

In an attempt to calculate the global burden of disease (ischemic heart, cerbrovascular, hypertensive and other cardiac) because of an effect of Pb on blood pressure, it was estimated that 2% of the world-wide cardiovascular disease burden was due to Pb exposure (annually 229,000 deaths and 3.1 million disability-adjusted life years [DALYs], *ie,* the sum of years of life lost due to death and years of life with disability) (Fewtrell et al 2004).

4.5. Endocrine system

4.5.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was concluded, that there were some indications of various effects of occupational Pb exposure (mean B-Pbs about 1.5-2.0 μmol/L, or higher) on the hypothalamus-pituitary-thyroid/adrenal axes.

4.5.2. Update

Male Swedish Pb-smelter workers (mean B-Pb 332, range 83-932 μg/L) did not differ from unexposed referents (B-Pb 8-62 μg/L) as regards thyroid stimulating hormone or serum levels of thyroid hormones (basal and after challenge) (Erfurth et al 2001). Sex hormones are discussed under section 8. Reproduction and effects in infants/small children.

In 98 Belgian battery-factory workers (mean 510, range 400-750 μg/L) and 85 "controls" (B-Pb 209, range 44-390 μg/L), there were no statistically significant differences in serum concentrations of follicle-stimulating hormone, thyroid-stimulating hormone, thyroxine or triiodothyronine (Gennart et al 1992a). Neither was there any association with the B-Pb.

In a study of Pb smelter workers and referents, there were no significant differences in hormone concentrations depending upon *ALAD* genotype (Bergdahl et al 1997a).

In Italian Pb-workers and referents, there was an association between serum prolactin and B-Pb (median 280, range 60-610 μg/L and 70, 20-210 μg/L, respectively) (Lucchini et al 2000). Possibly, an effect was present down to about 100 μg/L. Increased prolactin can be ascribed to impaired modulation of pituitary secretion by the tubero-infundibular dopaminergic system, and may thus be an early sign of neurotoxicity. Similar results were reported in another study, with higher B-Pbs (mean 553 μg/L) (Manzo et al 1996), while another one (mean 367 μg/L) (Telisman et al 2000) revealed no such effect.

4.5.3. Summary

There are some indications of various effects of occupational Pb exposure (B-Pb 1.5-2.0 μmol/L) on the hypothalamus-pituitary-thyroid/adrenal axes.

5. Immunotoxicology

5.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was noted, that there was limited information on immunotoxic effects of Pb. Possibly, there are various effects on the humoural and cellular immunity in groups of Pb workers with B-Pbs about 2 μmol/L, or higher. The health implications of some of these effects was not clear, but an increased sensitivity to infections had been reported in one study.

5..2. Update

Reviews of the immunotoxicology of Pb has been published (Fischbein et al 1993a; McCabe 1994).

Further, some new studies have been published since 1991: Hence, varying effects on immunoglobulins in serum (Horiguchi et al 1992a; Queiroz et al 1993 and 1994; Undeger et al 1996; Pinkerton et al 1998) and saliva (Queiroz et al

1994; Pinkerton et al 1998) have been reported in Pb workers. Further, serum concentrations of C3 complement have been found to be unaffected (Pinkerton et al 1998).

Moreover, in Pb-exposed workers, varying effects on leucocyte and lymphocyte subtypes and function have been described (Valentino et al 1991; Fischbein et al 1993b; Queiroz et al 1994; Undeger et al 1996; Sata et al 1997; Pinkerton et al 1998).

There was a slight increase of colds in Japanese Pb-refinery workers, as compared to referents (Horiguchi et al 1992b).

All these effects have been noted at B-Pb about 2 μmol/L, or higher.

5.3. Summary

There is fairly limited information on immunotoxic effects of Pb. The picture is not consistent. Some of the inter-study discrepancies may be due to the variations in exposure intensity and methodologic differences. There is no evidence of a very marked immunotoxic effect of Pb at the exposure levels studied. However, there are probably various effects on the humoural and cellular immunities. Their health implications are not clear, but there are some indications of increased sensitivity to infections. The information is not easy to interpret in terms of exposure-response. However, various effects have been reported in groups of Pb workers with mean B-Pbs about 2 μmol/L, or higher (Table 2).

6. Mutagenicity

6.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was noted, that genotoxic effects (chromosome aberrations in peripheral lymphocytes) had been reported in Pb workers exposed at levels corresponding to average B-Pbs of about 2 μmol/L, or higher. However, the available information was conflicting. Further, the health significance of such findings was not known.

6.2. Update

In a recent review, it was concluded, that experimental evidence shows that Pb accumulates in the cell nucleus. There, it may cause clastogenic activity (induction of chromosomal aberrations, micronuclei and sister chromatid exchanges) (Silbergeld et al 2000). However, there is only limited evidence of direct genotoxic or DNA-damaging effects, except for Pb chromate, where hexavalent chromium is probably the cause. Hence, Pb has mostly been negative in *in-vitro* gen-tox assays.

Rather, Pb-induced non-genotoxic/epigenetic mechanisms seem to affect DNA. Pb exposure may increase the susceptibility to genotoxic agents. Hence, Pb may

bind to, and deplete, glutathione (a free-radical scavenger) (Hunaiti et al 2000), interfere with DNA repair (Hartwig 1994) and bind to histones, thus decreasing their DNA protection (Quintanilla-Vega et al 2000). In accordance with this, there was a multiplicative effect for co-exposure in occupational settings to Pb (mean air level 3, range 1.6-50 $\mu g/m^3$) and cobalt and Cd, as regards induction of DNA single strand breaks (Hengstler et al 2003).

Pb-induced ALA accumulation can also generate ROS (Silbergeld et al 2000). Further, experimental evidence shows, that Pb can substitute for Zn in several proteins that function as transcriptional regulators, including protamines. Pb also reduces the binding of these proteins to recognition elements in genomic DNA, which suggests an epigenetic involvement of Pb in altered gene expression.

32 male workers in a Turkish metal powder-production factory (mean B-Pb 138±92 $\mu g/L$) and 20 controls (B-Pb 23.7±9.0 $\mu g/L$) differed slightly as to sister chromatid exchange (SCE) frequency in lymphocytes from peripheral blood (Dönmez e t al 1998). The effect did not seem to be dependent upon age or smoking.

Among a Bulgarian study, the frequency of micronuclei in peripheral blood lymphocytes was 2-3 times higher in 22 battery workers (mean B-Pb 2.94, range 0.78-3.94 $\mu mol/L$; air-Pb 447, range 130-711 $\mu g/m^3$) than in 19 "internal" (in the same factory; B-Pb 1.33, range 0.78-2.40 $\mu mol/L$; air-Pb 58, range 22-86 $\mu g/m^3$) and 19 "external" (B-Pb 0.88, range 0.72-1.20 $\mu mol/L$; air-Pb 73, range 130-711 $\mu g/m^3$) referents (Vagenlov et al 1998). Further, after the workers had been treated for 4 months by a "polyvitamin-polymineral complex" drug (composition and dose not given), there was a dramatic decrease of the effect; however, no un-treated control group was studied. In a second study, of 103 Pb-workers and 78 controls, there was a gradual increase of binucleated cells with micronuclei in peripheral blood lymphocytes from a group with <1.20, over 1.20-1.91, and 1.92-2.88, to >2.88 $\mu mol/L$ (Vaglenov et al 2001).

120 Slovenian Pb-Zn miners (mean B-Pb 279, range 37-800 $\mu g/L$) differed from two control groups (B-Pb 72±8.4 $\mu g/L$) as to the frequencies of structural chromosomal aberrations, micronuclei and SCEs in lymphocytes from peripheral blood (Bilban 1998). However, there was no correlation with B-Pb, but only with radon exposure.

31 Turkish battery workers (mean B-Pb 363, range 222-525 $\mu g/L$) differed from 20 matched controls (B-Pb 111, range 81-147 $\mu g/L$) in SCE frequency, even at B-Pbs <400 $\mu g/L$, possibly even at <300 $\mu g/L$ (Duydu et al 2001). There were correlations between B-Pb and U-ALA (better), on the one hand, and SCEs, on the other. The authors suspect that ALA generates oxidative stress with DNA damage.

In 11 Chinese battery workers (median B-Pb 276, range 79-578 $\mu g/L$; median TWA air-Pb 1.22, range 0.19-10.32 $\mu g/m^3$), the adjusted frequencies of SCEs and DNA-protein cross links were higher than in 11 controls (B-Pb 33, range 15-70 $\mu g/L$) (Wu et al 2002). The air-Pb levels are very high in relation to the B-Pbs.

6.3. Summary

There is only limited evidence for a direct genotoxic effect of Pb. However, non-genotoxic/epigenetic mechanisms seem to damage DNA. Hence, Pb may affect mechanisms handling free radicals and the metabolism of genotoxic xenobiotics, as well as DNA repair.

Pb has a clastogenic effect, inducing chromosome aberrations, micronuclei and SCEs. An increased occurrence of such has been shown in peripheral lymphocytes of Pb workers exposed at levels corresponding to average B-Pbs of about 1.5-2 μmol/L, or higher (Table 2).

All these effects may increase the risk of cancer (see below, section 7. Cancer). Indeed, it has now become clear, that structural chromosome aberrations – as had been assumed for a long time – are really associated with an increased risk of later cancer (Hagmar et al 1998). For micronuclei and SCEs, the picture is less clear.

7. Cancer

7.1. State of the art 1991

Animal experiments have shown a tumourogenic effect of Pb (Skerfving 1992 and 1993). Hence, soluble Pb salts such as Pb acetate and subacetate have produced kidney and brain tumours, and Pb phosphate kidney tumours, in rodents after oral or parenteral administration. Synergistic effects exist for the development of cancer between Pb acetate and oxide, on the one hand, and some organic carcinogens, such as benso(a)pyrene and nitrosoamines, on the other. In general, epidemiological studies did not support a carcinogenic effect of inorganic Pb in humans, although the exposure in several studies had been high (B-Pb >3 μmol/L); the small increases seen in some studies could well be explained by confounding.

7.2. Update

The carcinogenicity of Pb has recently been reviewed (Vainio 1997; Landrigan et al 2000; Silbergeld 2000). In animals, exposure to some inorganic Pb species are associated with increased risks of carcinogenesis, even at doses which do not cause organ toxicity. There are also limited indications of transplacental carcinogenicity. Possible mechanisms of cancer have been discussed above (Section 6. Mutagenicity).

7.2.1. Occupational exposure

A series of investigations of occupational and other cohorts have been published since 1991: In a study of 1,990 US smelter workers (average duration of Pb exposure 9.9 years), there was no significant increases of deaths from total cancers or lung cancer, but an increase of kidney cancer, which was most

pronounced in those with high (SMR=2.39, CI=1.03-4.71) and long-time exposure (Steenland et al 1992).

In a meta-analysis of 10 case-control and cohort studies of humans exposed to Pb, there was an excess risks of total (RR=1.33, CI=1.18-1.49), stomach (RR=1.33, CI=1.18-1.49), lung (RR=1.29, CI=1.10-1.50) and bladder (RR=1.41, CI=1.16-1.71) cancers (Fu & Boffetta 1995). However, no adjustment for potential confounders was made. In a meta-analysis of 20 populations (out of 92 studies made 1969-98 covering 121 populations), there was no association between risk of pancreatic cancer and exposure to Pb and Pb compounds (RR=1.1, CI=0.8-1.5) (Ojajärvi et al 2000).

In 664 male workers in a Swedish secondary smelter, handling mainly Pb batteries, there was an increased mortality from all malignant neoplasms (SMR=1.65, CI=1.09-2.44; county rates), but no dose (employment time)-response relationship (Gerhardsson et al 1995b). In the most exposed quartile, there was an increased risk of gastrointestinal tract cancers (SMR=2.34, CI=1.07-4.45).

In a study of workers in a Swedish primary smelter, exposed to Pb and employed for at least 1 year in 1928-1992, the total deaths from cancers were not increased (Gerhardsson et al 1997b; Lundström et al 1997; Englyst et al 2001). However, there were increased risks of lung cancer, both in the total cohort of 3,797 subjects and in the 710 workers who had ever been employed in the Pb department (SIR=2.42, CI=1.16-4.45; county rates). 85 deceased workers had increased levels of Pb in their lung tissue, as compared to 25 urban and rural controls (Gerhardsson & Nordberg 1993). However, the cases also had a significant exposure to arsenic (As); the concentrations of this element were also raised (Gerhardsson & Nordberg 1993). The highest Pb levels were recorded in lung-cancer cases. Increased Pb levels in relation to unexposed controls have also been recorded in liver, kidney (both associated with time-integrated B-Pb) and brain (Gerhardsson et al 1995a).

In 20,741 Finnish workers, who had been monitored for B-Pb in 1973-83, there was a 1.4-fold increase of total cancer incidence, and a 1.8-fold of lung cancer, among those who ever had a B-Pb ≥1.0 μmol/L (Anttila et al 1995). In a nested case-referent study (handling potential confounders, *eg*, smoking), the risk for lung cancer was increased at concomitant exposure to Pb and diesel exhaust, even when the B-Pb had only been slightly increased. Further, there was an excess of gliomas (Anttila et al 1996). Hence, in a nested case-referent study, workers with B-Pb >1.4 μmol/L had an increased risk, as compared to those with <0.7 μmol/L (OR=11, CI=1.0-630).

Wong and Harris (2000) found no significantly increased all-cancer mortality (SMR=103.8, CI=97.1-110.8) in a US cohort of 4,518 battery and 2,300 smelter workers. However, stomach (SMR=147.4, CI=115-189.8) and lung (SMR=116.4, CI=103.9-129.9; unadjusted for smoking) cancers were increased, although there were no exposure-response relationships. No rises of kidney, bladder, CNS, lymphatic or hematopoetic tumors were observed.

In studies of Sardinian female (Cocco et al 1994a) and male (Carta et al 1994; Cocco et al 1994b) Pb- and Zn-mineworkers, there were no increases of total mortality, but rises of lung cancers. However, no data on Pb exposures were given. Further, smoking and exposure to polycyclic aromatic hydrocarbons and As were not fully accounted for. The cancer risk seemed to be associated with exposure to quartz (increased risk of non-malignant respiratory disease) and radon daughters.

In a study of cause-specific mortality in 1950-1992 among 1,388 workers and laborers in an Italian primary Pb smelter (air-Pb in 1977-78; geometric mean=GM=47.6, range 1-1,650 $\mu g/m^3$), there was no increase of all cancers (SMR=69; CI=58-81; national rates) (Cocco et al 1997). Regional rates were higher, but were only available for 1965 and on (SMR=93; CI=78-110). The risk of lung cancer was low (SMR=62; CI=43-86 and SMR=82; CI=56-116, respectively), in spite of the fact that there was an increased risk of pneumoconiosis. There was a non-significant increase of kidney cancer (SMR=142; CI=46-333 and SMR=175; CI=48-449, respectively), and an association between exposure time and risk (>20 years RR=10.9, CI=1.0-121; adjusted for calendar year and age). Non-significant increases were reported for cancers of the liver and biliary tract, bladder and brain. There was concurrent exposure to Cd (28% of samples >10 $\mu g/m^3$); the As levels were low (<1 $\mu g/m^3$).

In a case-referent study of glass-industry workers, there was some association between death from stomach and colon cancer (but not lung cancer) and the Pb consumption of the glass work, but there was co-exposure to a multitude of other elements (Wingren & Axelson 1993). The mean level of Pb in air was 61 $\mu g/m^3$ in the foundry of a heavy crystal glasswork; oven inlay work resulted in up to 72 $\mu g/m^3$ in both crystal and semicrystal works (Andersson et al 1990). In 1993, IARC (IARC 1993) evaluated the manufacture of art glass, glass containers, and pressware to entail exposures that are probably carcinogenic to humans (Group 2A).

In a job-exposure matrix study of 413,877 Finnish women with blue-collar occupations in 1970, there was no significant increase of cancer risk associated with assumed Pb exposure (Wesseling et al 2002).

7.2.2. General populations

In a follow-up study up to 1991, of 454 US children, who had been hospitalized for Pb poisoning in the period 1923-1966, there was no increase of deaths from total cancers, but two deaths from pancreatic cancer (RR=10.2, CI=1.1-36.2) and two from non-Hodgkin´s lymphoma (RR=13.0, CI=1.5-46.9) (McDonald & Potter 1996).

In the US general population (NHANES III), elevated B-Pb was associated with a dose-related increase in total cancer deaths; RR was 1.68 (CI=1.02-2.78, adjusted for multiple potential confounding, including smoking) in subjects in the B-Pb range 200-290 $\mu g/L$ (as compared to <100 $\mu g/L$) (Lustberg & Silbergeld 2002). There was a numerical increase even in the B-Pb range 100-190 $\mu g/L$.

Increased (but statistically non-significant) risks were seen for both lung and non-lung cancers. Possibly, there was an interaction between B-Pb and smoking.

7.3. Summary

Experiments in rodent have demonstrated a carcinogenic effect of some Pb compounds, with increased risk of kidney and brain tumours after oral or parenteral administration. Synergistic effects exist between Pb and some organic carcinogens.

In a series of epidemiological studies, Pb workers had increased risks of total, kidney, lung or stomach cancers. Also, there is limited support for a synergism with other carcinogens. The studied cohorts of Pb workers have had a high exposure (mean B-Pbs >3 μmol/L), at least in most of the studies. There is some data indicating that Pb exposure in the general population is associated with cancer risk. Then, the exposure has been lower.

However, the pattern is not consistent and there are major problems in terms of confounding, *eg,* as regards concomitant exposure to As and Cd in the occupational cohorts. Also, there may be selection bias. Hence, Pb-workers may differ in many ways besides the Pb exposure. In particular, confounding by smoking is a problem, which has only occasionally been tackled. Also, they may be physically fit and may have different diet.

8. Reproduction and effects in infants/small children

8.1. Female

8.1.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was concluded, that exposure to Pb in a woman during pregnancy causes Pb accumulation in the placenta. Further, Pb passes the placenta; the B-Pb in cord blood is about 85% of maternal B-Pb.

Pb is embryotoxic/fetotoxic in experimental animals. The information in man was considered incomplete, but there were indications of several types of effects. However, there was little information available on occupationally exposed women.

The information did not firmly support a teratogenic effect (malformations) in man. However, several studies had shown effects on the fetus, including reduction of gestational age, birth weigth and disturbance of heme synthesis. Further, retardation of neurobehavioural development and growth, as well as EEG and hearing changes, had been reported in infants and children. Slight effects on the mental and motor development had repeatedly been claimed to be associated with exposures corresponding to low B-Pbs, prenatally and/or early in life. In spite of many methodological problems in such studies, there were indications, that effects may occur even at B-Pbs in the pregnant woman and infant of only 0.5-0.75 μmol/L. However, the fraction of the total variance of the CNS function that was explained by Pb was marginal.

Further, it was concluded, that the breast-fed infant may be exposed to significant amount of Pb, although there is a large inter-individual variation in milk-Pb. It was noted that the absorption of Pb from the GI tract probably was enhanced in the lactating woman, that there is probably a mobilization of Pb from the skeleton during lactation, that the Pb absorption is higher in infants than in adults, and that the Pb absorption may be enhanced when the Pb is ingested in milk. Further, the penetration of Pb into the CNS is probably more effective in infants than in adults. It was not known to what extent the reported effects in infants/children are due to prenatal exposure, to exposure via milk and/or to later exposure. Also, the reversibility of the effects was not known.

Moreover, in addition to the effects through germ cells (and placenta and breast milk), secondary exposure may occur in children of both male and female Pb workers, as a result of contamination of the infant/child´s environment.

8.1.2. Update

Effects on reproduction (Andrews et al 1994; Landrigan et al 2000) and children (Lidsky & Schneider 2003; US CDC 2004) have been reviewed. Rice and Silbergeld (1996), in a review of monkey and human data, concluded that the CNS effects (behavioural impairment) may be dependent upon the time and pattern of exposure, that the infant is vulnerable and that the effects seem not to be reversible.

8.1.2.1. Fertility

In a US study (NHANES III) of sexual maturation in girls and exposure to Pb, B-Pb was significantly associated with the attainment of pubic hair and menarche, but not breast development (Wu et al 2003b). For example, at age 12, 68.0% of girls with B-Pb 7-20 μg/L had reached menarche, 44.3% at 21-49 μg/L and 38.5% at 50-217 μg/L.

In a Finnish study, there were indications that occupational exposure to Pb in an exposure-related way increased time to pregnancy (ORs: unexposed=1.0, <0.48 μmol/L=0.93, 0.48-0.99=0.84, ≥1.0=0.80) (Sallmén et al 1995).

8.1.2.2. Lead metabolism during pregnancy and lactation

There is a U-shaped time trend for B-Pb (West et al 1994; Lagerqvist et al 1996; Rothenberg et al 1994 and 2000; Schnell et al 2000) and P-Pb (Téllez-Rojas et al 2004) during pregnancy. This is because there is first hemodilution, and later mobilization of Pb from the skeleton (Pires et al 2001; Téllez-Rojo et al 2004), possibly also increased Pb absorption in the GI tract. In a series of studies, employing high-precision measurements of Pb isotopic composition in Australian and immigrant women, it was seen that B-Pb rose by 20% during pregnancy, and that about 30% of the B-Pb originated from the skeleton (Gulson et al 1997a, 1997b and 1998b). Low Ca intake was associated with high P-Pb (Téllez-Rojo et al 2004) and B-Pb and patella-Pb (Hernadez-Avila et al 1996). However, when the Pb load was small, there was no increase of B-Pb (Berglund et al 2000a;

Vahter et al 2002) or P-Pb (Téllez-Rojo et al 2004). Pb was present in the placenta, but also passed into the fetus (Lutz et al 1996; Osman et al 2000).

There is a transfere of Pb to the fetus. A significant positive, relatively close correlation was observed between the B-Pbs in maternal and cord blood in women from Singapore (Ong et al 1993). It has been claimed that the skeletal Pb is mobilized to plasma, and that this is particularly available for transfer to the fetus (Chunang et al 2001). However, as said above (section 3.5. Toxicokinetics), this is doubtful.

During *lactation*, there is also an increase of maternal B-Pb. The maternal B-Pb seems to increase more in women who practice breast-feeding than in others (Téllez-Rojo et al 2002). In Swedish women (rise of mean from 11 to 18 μg/L), this was probably due to increased skeletal turnover (as judged from rises of serum osteocalcin and urinary crosslinked N-terminal telopeptide of type I collagen=NTx) (Berglund et al 2000a), although bone mineral density did not correlate with B-Pb (Osterloh & Kelly 1999).

Pb is transferred into milk (reviews: Oskarsson et al 1995; Abadin et al 1997). In Australia (mean B-Pb 30 μg/L), the milk-Pb was 0.09-3.1 μg/kg, with large day-to-day variations (Gulson et al 2001). Similar milk-Pb levels have been reported from northern Sweden (Hallén et al 1995), Austria (Tiran et al 1994), the US (Pires et al 2001; Soweres et al 2002) and Mexico (Ettinger et al 2004a and 2004b). Much higher concentrations have been reported from Mexico (Namihira et al 1993), Egypt (Saleh et al 1996) and China (Li et al 2000), partly due to high exposure, but probably also because of methodological problems. Milk-Pb is proportional to maternal B-Pb (non-linearily; Namihira et al 1993; Ettinger et al 2004a) and bone-Pb (Ettinger et al 2004a) and skeletal mobilization (Sowers et al 2002). Further, the infant´s B-Pb correlated with maternal B-Pb and milk-Pb (Ettinger et al 2004b).

During the pregnancy and lactation periods, an average of 0.9-10 μg Pb/day was mobilized from the skeleton in Australians, more during lactation than in pregnancy (Gulson et al 1999 and 2000b). There was no increase of maternal GI Pb absorption rate. Half of the milk-Pb originated from the skeleton, the rest from the maternal diet (Gulson et al 2001). Possibly, there is some reduction of skeletal mobilization by Ca supplementation (Hernandez-Avila et al 2003). No less than 79% of the mobilized Pb reached the baby (Gulson et al 2003). As expected, there is a correlation between the milk-Pb and the infant´s B-Pb (Gulson et al 1998b).

8.1.2.3. Effects in the pregnant woman or embryo/fetus

Among 1,627 US women in their third trimester, an increase of B-Pb from 5th to 95th percentile (90 to 620 μg/L) was associated with a rise in *blood pressure* (2.8 and 2.4 mm Hg for systolic and diastolic, respectively) in immigrants (almost only Latin Americans), while no significant increase was seen in nonimmigrants (Rothenberg et al 1999a). The authors hypothesize that the difference is due to prior Pb exposure. Indeed, in the same cohort, an increase by 10.7 µg Pb/g bm in trabecular bone (patella; GM 10.7 μg/g) was associated with a rise of OR for

hypertension by 1.86 (CI 1.04-3.32) (Rothenberg et al 2002). Cortical tibia-Pb displayed no such association, possibly because Pb is mobilized mainly from trabecular bone during pregnancy. However, only a small fraction of the variation in blood pressure (1% of systolic) was explained by Pb (Rothenberg et al 1999a). Still, in the US population, such a Pb-associated effect (assuming a causal relationship) would push a considerable fraction of high normotensive/borderline hypertensive pregnant women into clear hypertension.

Hertz-Picciotto (2000) made a critical review of the information on maternal exposure to Pb and risk of *spontaneous abortion*. She concluded, that most studies (including Murphy et al 1990; Laudanski et al 1991; Tabacova and Balabaeva 1993; Driscoll 1998) were biased due to small sample sizes, bad ascertainment of outcome, lack of confounding control and/or deficiencies in exposure assessment (ecological rather than individual). In a prospective study in Mexico City, most of these problems were handled (Borja-Aburto et al 1999). Then, a exposure-response relationship was seen, from women with B-Pb <50 μg/L over the exposure categories 50-90 (OR=2.3), and 100-140 (OR=5.4) to >150 (OR=12.2) μg/L (test for trend P<0.03; it is not clear at which level there is a formal statistical significance).

In a study of preterm labor, there was no indication of an increased risk in Swedish (mean B-Pb 11 μg/L) and Polish (B-Pb 38 μg/L) women (Fagher et al 1993). Neither did Pb concentrations in the myometrium or placenta (mean 0.3 μg/g dry weight) predict this effect.

In north-west England there were significant associations between Pb in placentas (mean 2.3 μg/g wet weight), on the one hand, and gestational age of the newborn, birth weight and head circumference, on the other (Ward et al 1990).

Among 349 African American women, who were sampled in the third trimester of pregnancy, B-Pbs (mean 63.6, range 27-126 μg/L) were associated with low gestational age, birth weight (though not fully significantly) and birth length in relation to weight (West et al 1994), though the information is scarce. However, B-Pbs were positively associated with serum Ca and phosphorous. Women who took vitamineral supplement had lower B-Pbs than those who did not, and there were negative correlations with serum levels of vitamins C and E; however, the latter may be explained by confounding by life style/vitamin supplement.

Further, in a study of about 200 mother-infant pairs in Mexico City, low birth weight (Gonzalez-Cossio et al 1997), birth length, head circumference (Hernandez-Avila et al 2002) and infant weight gain during the first month of life (Sanin et al 2001) were associated with biomarkers of Pb (mean umbilical cord B-Pb 67, range 12-216 μg/L; maternal tibia-Pb 9.8 μg/g bm, patella-Pb 14.4 μg/g). Moreover, B-Pb and bone-Pb were also associated with low scores on a mental development scale at age 2 years (Gomaa et al 2002). The bone-Pb had an effect independent of B-Pb, which indicates that exposure during the whole pregnancy is of importance. There was no significant effect on motor development.

Similar findings of association between B-Pb and birth weight were made in a study of Norwegian (mean maternal B-Pb 0.06 μmol/L) and Russian (0.14 μmol/L) mother/infant pairs (Odland et al 1999). However, there is an obvious

risk of confounding. Effects on the size of the infant were also reported from South Carolina (37% of B-Pb in infants/children >0.48 μmol/L=100 μg/L) (Recknor et al 1997).

In a study of 199 mother-newborn pairs in Mexico City, an increase of B-Pb at gestational week 36 from 10 to 350 μg/L (0.05 to 1.68 μmol/L) was associated with an average reduction of the adjusted head circumference by 1.9 (CI 0.9-3.0) cm at age 6 months (Rothenberg et al 1999b). Also, at age 36 months, there was a negative association with the children´s B-Pb at age 12 months.

In 106 Swedish mother-child pairs, there were associations between birth weight, length and head circumference, on the one hand, and cord-blood B-Pb (median 54 nmol/L, range 4.3-590 nmol/L), on the other (Osman et al 2000). An increase of 54 nmol/L corresponded to an adjusted decrease in the infant´s weight by 100 g and length by 0.5 cm. The maternal B-Pb was almost the same as in cord blood, which correlated with placenta-Pb (median 26 nmol/kg=5.2 ng/g wet weight), which, in turn, was associated with the mothers´ wine intake. Further, as expected, the birth weight was dependent upon the smoking habits of the pregnant woman. Hence, there is a wealth of possible confounding. Also, there might be co-precipitation of Ca and Pb in a degenerating placenta.

In a Norwegian study of the reproductive outcome as reflected in the birth register in offspring of parents who were occupationally exposed to Pb, as judged from the population census records, offspring to women potentially exposed to Pb had a significantly increased risk of low birth weight (RR=1.34, CI 1.12-1.60) and neural tube defects (RR=2.87; CI 1.05-6.38) (Irgens et al 1998). However, the study is fairly blunt, since job titles (the exact procedure is not described) were used as a surrogate to measure degree of Pb exposure, which is open to mis-classification. Further, some of the job titles used were obtained 10 years before conception. Moreover, there is a risk of confounding by smoking and occupational exposure to other chemicals. Also, there is a risk of multiple inference, since many associations were tested. Risk of neural tube defects were also associated with Pb in drinking water (25% increase for each 10% increase of houses in the area with >10 μg Pb/L; the origin of Pb was pipes, lined tanks or solder) in Lancashire, UK, though the risk estimate was reduced by inclusion of socioeconomic deprivation in the epidemiological model (Bound et al 1997). The authors speculated that the mechanism was interaction with zinc, which impairs folate absorption.

In a review of studies on maternal occupation and birth defects, it was concluded that the associations were equivocal and often controversial (Shi & Chia 2001). Many reported associations were only suggestive and hampered by methodological problems. As to Pb, there was almost no valid information.

8.1.2.4. Neurobehavioural and other effects in the offspring

US adults, who had suffered Pb encephalopathia below age 4, were inferior to controls in cognitive tasks, and they had a lower lifetime occupational status (White et al 1993). Also, they had higher proportions of spontaneous abortions and stillbirth, and their children more often had learning disabilities (Hu 1991b).

In a series of meta-analyses, using data from some of the cross-sectional studies off school-age children reviewed in 1991 (Skerfving 1992 and 1993), it was concluded, that a decrease of one IQ point was seen for every 20-40 μg/L change in B-Pb, with a steeper slope (*ie,* a greater effect) at high B-Pbs than at low ones; an increase of B-Pb from 100 to 200 μg/L was associated with a decrease by approximately 2.6 IQ points (Schwartz 1994). A shortcoming of the analysis was a lack of analysis of population variation or uncertainty. The analysis showed no threshold, down to a B-Pb of 10 μg/L. Similar estimates have been reported later, with a net decrease of 3.4 (CI 1.1-5.0) IQ points at 150 μg/L (WHO 2000b). A working group of the US CDC (2004) concluded that, while available evidence did not permit a definite causal interpretation of the observed associations between higher B-Pbs in the range <100 μg/L and adverse health indicators, the weight of the available evidence favored, and did not refute, the interpretation that these associations were, at least partial, causal, though the possibility of residual confounding and other factors left considerable uncertainty.

Since 1991, a series of additional cross-sectional studies of general populations, with varying exposure intensities, have been reported [in Denmark (Damm et al 1993; Nielsen et al 2000); New Zealand (Ferguson et al 1993); Germany (Walkowiak et al 1998); China (Shen et al 1998); NHANES III (Lanphear et al 2000); Croatia (Prpic-Majic et al 2000); Saudi Arabia (Al-Saleh et al 2001); Mexico (Calderón et al 2001); Pakistan (Rahman et al 2002); Taiwan (Wang et al 2002)]. The studies examined 80-4,853 infants or children, up to age 16. Mean B-Pb ranged 29.4-973 μg/L. However, taken together they add little to the understanding of low exposure to Pb on cognitive functions (Koller et al 2004).

In a cross-sectional study of 301 children (age 11) from Pittsburgh, Pennsylvania, USA, there was a slight, but statistically significant, association between tibia-Pb class and assessments of delinquent behavior (Needleman et al 1996). Curiously, in that study, the IQ was positively correlated with tibia-Pb (although this effect was entirely due to Afro-Americans). Further, 194 arrested and adjudicated youths aged 12-18 had higher tibia-Pb than 146 non-delinquent controls (11.0±32.7 *vs* 1.5±32.1 μg/g bm) (Needleman et al 2002). The adjusted OR to have high tibia-Pb was 4.0 (CI 1.4-11.1). In this connection, it may be mentioned, that in the US, there is an ecological relationship (at county level) between B-Pb levels and homicide rate (Stretesky & Lynch 2001).

Several prospective studies have been published since the review in 1991 (Skerfving 1992 and 1993).

In the Cincinatti Lead Study, Ohio, USA, there were, in 245 6-year-old children, significant negative associations between the covariate-adjusted achievements in a comprehensive neuromotor assessment battery, on the one hand, and maternal first trimester (mean 0.406 μmol/L), neonatal (0.233 μmol/L) and postnatal (maximum at 2 years, 0.824 μmol/L) B-Pbs, on the other (Dietrich et al 1993).

In a prospective study in Boston, Massachusetts, USA, in 48 children, whose B-Pb had never exceeded 100 μg/L at birth or at age 6, 12, 18, 24, 57 or 120 months, there was a negative association between adjusted IQ at age 10 and B-Pb,

although the precise shape of the dose-effect relation remained uncertain (Bellinger et al 1992 and 1994b; Kim et al 1995b; Bellinger 2000; Bellinger & Needleman 2003).

Around the smelter in Port Pirie, Australia, B-Pb (GM 83 μg/L at birth) in 375 children was negatively associated with adjusted cognitive performances at 2, 4 and 7 years of age (Baghurst et al 1992; Tong et al 1996, 1998 and 2000). In connection with a decrease of mean B-Pb from 1.02 μmol/L (212 μg/L) at age 2, to 0.38 μmol/L (79 μg/L) at age 11-13, there was no significant relationship between the individual´s B-Pb decrease and its IQ change. The data may indicate a long-lasting effect of damage caused in the fetus and/or infant.

In the Yugoslavia Prospective Lead Study, IQ at 3, 4, 5, 7 or 10-12 years in 390 children to women living in a smelter (mean B-Pb 309 μg/L at age 10-12) and a control (B-Pb 61 μg/L) town displayed a negative association with prenatal and postnatal B-Pb (Factor-Litvak et al 1999; Wasserman et al 2000 and 2003). A doubling of the average lifetime B-Pb (*eg*, an increase from 30 to 60 μg/L) was associated with a decrease of full-scale IQ by 1.6 points. The association with tibia-Pb (range –14.4 to 193.5 μg/g bm) at age 10-12 was closer than with B-Pb.

In the Mexico City Prospective Lead Study, 112 children were followed between 3 and 5 years of age (Schnaas et al 2000; Gomaa et al 2002). B-Pbs (-Pb GM about 100 μg/L) measured in cord blood (*eg*, 50 to 100 μg/L) was negatively associated with adjusted intellectual function, while postnatal B-Pbs were not. This had also been seen in other studies.

In an important study of 172 children in Rochester, New York, USA, in whom B-Pbs were measured serially between the ages 6 months to 5 years, 101 did not have a recorded B-Pb >100 μg/L (Canfield et al 2003; additional information in Koller et al 2004). Strong and significant negative associations between B-Pb and adjusted IQ (0.74 points per 10 μg/L) were observed at 3 and 5 years. There were indications that the effect was larger at lower B-Pbs than at higher ones.

In 79 infants from Atlanta, Georgia, USA, memory at age 7 months was negatively associated with maternal B-Pb (7.2±8.8 μg/L) (Emory et al 2003). However, the authors urge caution because of the small number of infants.

In a thorough review of some of the recent prospective studies of children, it was concluded, that even at B-Pbs consistently <100 μg/L, there was intellectual impairment (Koller et al 2004). However, Pb exposure was believed to account for only a small amount (1-4%) of the total variation in cognitive ability, social and parenting factors for 40%, or more.

Critics have questioned the importance of such a small decrements of IQs of individual children. However, the tests are blunt instruments for detecting subtle changes in brain function. Further, even small changes of IQ in large numbers of children will dramatically increase the proportion of children with low (*eg*, <80), and decrease the fraction with high (>120).

It should be stressed, that the confounding and effect-modification issues are very complicated (Bellinger 2000). Hence, over- and/or under-adjustment or incorrect inference may easily occur. Also, the limits of the precision of analytical and psychometric measurements increase the uncertainty of any estimate of effect,

especially at B-Pbs <100-150 μg/L. Hence, if a threshold exists, it is unlikely to be detected.

In a study of neuropsychological performance in 19-20 year-olds, those who had had high deciduous tooth-Pb performed less in several tests, while there were few associations with current patella-Pb or tibia-Pb (Bellinger et al 1994a). Five children with the *ALAD*^{2} genotype had low dentine-Pb and consistently better performance (for some reason adjusted for dentine-Pb), as compared to 67 children with *ALAD*^{1}, though the effects were small.

Pb-associated declines in mental development are not reversed by chelation (Rogan et al 2001; Liu et al 2002). However, conflicting results have been reported (Ruff et al 1993 and 1996), although that study has been severely criticized.

In Boston, deciduous dentine-Pb (but not tibia-Pb) was associated with body mass index (BMI) at age 13 (Kim et al 1995b). In a case-referent study in Baltimore, Maryland, USA, there were no clear association between estimated occupational exposure to Pb in the mothers from conception through age 9 months and strabismus in the offspring (Hakim et al 1991).

8.1.3. Summary

There is some information indicating an effect of Pb on female sexual maturation. Also, limited information may mean that Pb causes a delay of time-to-pregnancy. Pb is embryotoxic and fetotoxic in experimental animals. Pb exposure in man is associated with spontaneous abortion. It seems that such effects may occur already at B-Pbs about 0.5 μmol/L (Table 2), although there is a risk of confounding. The mechanism for inducing pregnancy loss is not clear. Besides preconceptional chromosome damage (in the egg cell or in the testis, see below) or a direct teratogenic effect on the fetus, interference with the maternal/fetal hormone environment or developmental toxicity to the embryo/fetus are possible. Also, vascular effects on the placenta are plausible; elevated blood pressure during pregnancy means increased risks to both the mother and fetus (reduced birth weight, *abruptio placentae* and perinatal mortality).

During pregnancy, Pb is is mobilized from the skeleton of the pregnant woman, causing an increase of B-Pb. A large part of that amount, and of recently absorbed Pb is transferred through the placenta into the fetus. The available information does not support a teratogenic effect (malformations) in man. However, several studies had shown effects on the fetus, including reduction of gestational age, birth weight and disturbance of heme synthesis. Associations between Pb exposure and size of the newborn have occasionally been reported at mean B-Pb in the mothers even <0.1 μmol/L (Table 2). However, again unadjusted confounding may be a problem. Reduced fetal growth is of particular interest, since it may predict later cardiovascular, neurologic and metabolic disorders.

Further, retardation of neurobehavioural development and growth, as well as electrophysiological and hearing changes have in a long series of studies of infants and children been shown to be associated with B-Pbs in the mother,

newborn, infant and child. It is not known which period that is most critical. For example, the *in utero* exposure is often related to postnatal uptake of Pb.

During lactation, there is also a mobilization of Pb from the skeleton of the woman. Pb is excreted into the milk. A large fraction of the Pb is absorbed by the infant and transferred into the fetal CNS.

Although there are many methodological problems in such studies, there were indications, that effects may occur even at B-Pbs in the pregnant woman and infant of only 0.5 μmol/L, perhaps even lower (Table 2). Although the effect in the individual is small, as is the fraction of the total variance of the CNS function explained by Pb, the effect is definitely adverse. The reversibility of the effects is not adequately known, but they seem to be at least partly irreversible.

In an attempt to calculate the global burden of disease because of Pb-induced mild mental retardation, the estimate was 9.8 million DALYs, mostly in the West Pacific, South East Asia and Central and South America regions (Fewtrell et al 2004).

8.2. Male

8.2.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was concluded that Pb had caused disturbances of the hypothalamic-pituitary-testis endocrine axis, testis damage and sperm defects in experimental animal studies. The studies in man were few and not fully conclusive. However, there were some indications of various effects of occupational Pb exposure on the hypothalamus-pituitary-testis axis. Moreover, decreased libido, sperm quality and concentration and other effects on the testis had been indicated. It seemed reasonable to assume, that B-Pbs of about 2-3 μmol/L, or higher, are associated with both endocrine dysfunction and sperm changes.

8.2.2. Update

Effects of paternal Pb exposure on reproduction has been reviewed (Tas et al 1996).

8.2.2.1. Endocrine function

122 Chinese Pb workers (mean B-Pb 352, range 96-774 μg/L) had slightly higher plasma levels of luteinizing (LH) and follicle stimulating (FSH) hormones (but not testosterone or prolactin) than 49 non-exposed ones (B-Pb 83, range 26-148 μg/L) (Ng et al 1991). In the B-Pb range 100-400 μg/L, the LH and FSH concentrations increased.

In a study of 98 Pb workers (mean B-Pb 367, range 119-659 μg/L) and 51 unexposed referents (B-Pb 103, 67-208 μg/L), parameters of prostate secretory function and serum testosterone and estradiol displayed associations with B-Pb (Telisman et al 2000).

Male Swedish Pb workers (mean B-Pb 332, range 83-932 μg/L) also displayed minor changes in their male endocrine function (lower serum levels of FSH levels after challenge with gonadotrophin-releasing hormone) than unexposed referents (B-Pb 8-62 μg/L) (Erfurth et al 2001). There were no effects on basal serum levels of sex-hormone binding globulin or testosterone. The data indicate an effect of Pb on the pituitary level.

8.2.2.2. Effects on sperms

In five Taiwanese occupationally Pb-exposed battery workers (mean B-Pb 436±112 μg/L), the total semen-Pb was 411±274 μg/L, while in eight controls (B-Pb 105±77 μg/L), it was 219±165 μg/L (Kuo et al 1997). As in all semen studies, there was a considerable selection of workers willing to participate.

In a study of 38 battery workers (mean B-Pb 656, range 405-980 μg/L) and 30 referents (235, 176-260 μg/L), there were significant reductions (about 30%) of sperm count and motility, as well as a decrease of dead and an increase (two times) of abnormal sperms, but no dose-response relationship within the exposed group (Lerda 1992). On the other hand, in another battery-worker study (current B-Pb 280-930 μg/L), there was no association between the Pb exposure and sperm concentration or count (Robins et al 1997). However, the number of workers with low B-Pb was limited; hence, the exposure contrast may have been too small.

In a study of 98 Pb workers (mean B-Pb 367, range 119-659 μg/L) and 51 unexposed referents (B-Pb 103, 67-208 μg/L), there were dose-dependent decreases in sperm concentration, and motile, viable and morphologically normal sperms, as functions of B-Pb (Telisman et al 2000). B-Pb correlated with semen-Pb, and on the same level, which is in accordance with findings in Thai battery workers (Aribarg et al 1996). However, in the latter ones there was no association between semen-Pb and quality, which was neither the case in Finnish workers without occupational Pb exposure (Hovatta et al 1998).

In a European study, of 362 male Pb workers (mean B-Pb 310, range 46-645 μg/L) employed in 10 companies (battery factories, Pb smelter, Cu alloy foundries) and 141 referent workers (44-198 μg/L), the median sperm concentration was reduced by 49% in subjects with B-Pb >500 μg/L (Bonde et al 2002). There seemed to be a threshold at about 440 μg/L. Abnormal sperm chromatin structure was not related to B-Pb. Neither was there any relation between time-integrated B-Pb (up to about 5,090 μg/L x year) and effects. A problem with the study (as in any sperm investigation) was the low participation rate (18%), which may have caused selection bias. In the 165 workers studied, there were strong associations between Pb in seminal plasma (average 19 μg/L), spermatozoa (320 μg/L) and blood (280 μg/L). There was a significant decline of sperm count and semen volume with rising spermatozoa-Pb, and some indications of deterioration of sperm chromatin at high concentrations.

In a longitudinal study of 19 Danish battery workers, significant improvements were seen in the proportion of motile semen cells and in egg penetration parallel to a decrease of B-Pb from 2.03 to 0.96 μmol/L, but no change of sperm cell concentration or morphological abnormalities (Viskum et al 1999).

In 106 smelter workers, the log values of total sperm count was inversely correlated with B-Pb (mean about 230 μg/L), but this association did not vary significantly by *ALAD* genotype, although there was a tendency of lower values in $ALAD^1$ subjects (Alexander et al 1998). However, the selection was tremendous.

Among 35 Chinese males of the *general population* attending a andrology clinic, there was no difference in B-Pb between asthenozoospermic (72±62 μg/L) and normozoospermic (51±24 μg/L) subjects (Chia et al 1992). The authors believe (for unclear reasons), that the difference is due to chance.

In 76 Singapore non-occupational exposed males, the mean level of Pb in blood was 82.6 (range 33.0-184) μg/L and in *seminal plasma* 12.4 (8.1-19.0) μg/L, without any correlation (Xu et al 1994). In 221 men, there were no correlations between sperm density, motility, morphology or semen volume and B-Pb (mean B-Pb 77.2±31.3 μg/L) or seminal plasma Pb (12.7±2.9 μg/L) (Xu et al 1993). In 56 males, the GM seminal Pb was 7.8 μg/L (CI 4.6-13.1) μg/L (Xu et al 2003). When seminal Pb was >10 μg/L, there were a reduction of sperm density and sperm number per ejaculum. However, a weak correlation was seen between oxidative DNA damage (8-hydroxy deoxyguanosine=8OHdG).

In 64 "apparently healthy men" of a university clinic staff, there was an inverse association between sperm viability and seminal plasma-Pb (mean 125±80 to 60±20 μg/L in different groups) (Dawson et al 1998). Similar patterns were seen for Cd and aluminum.

8.2.2.3. Fertility

Among 681 Italian healthy adult males, who submitted a semen sample because of couple infertility, there was no increase of men who, in a questionnaire, reported occupations with plausible exposure to Pb (Figà-Talamanca et al 1992). However, the bluntness of the approach precludes any conclusion.

In a French battery-factory, 229 Pb-exposed male workers (exposure ≥1 year; mean B-Pb 463±152 μg/L) did not differ with regard to fertility (live births during an average follow-up time of 4.1 years) from 125 non-exposed ones (B-Pb not defined!) (Coste et al 1991). ORs adjusted for factors claimed to be potential confounders (including age and exposure to heat, but not contraceptives) ranged 0.79-1.20 in different B-Pb groups.

In 74 Belgian battery factory workers (mean B-Pb 463, range 240-750 μg/L) and 138 "unexposed" controls (B-Pb 104, 44-190 μg/L), the probability of a live birth was somewhat greater in the Pb exposed subjects before the onset of exposure (adjusted OR=1.31, CI 0.98-1.76), while a decrease in fertility was observed during the period of exposure (OR=0.65, CI 0.43-0.98) (Gennart et al 1992b). However, none of the variables reflecting exposure duration or intensity were found to be significantly associated with fertility, although there was a tendency of decreased fertility with increasing duration of exposure.

Lin et al (1996) examined the standardized fertility ratio (SFR) 1981-92 in 4,256 New York State workers exposed to Pb, as compared to 748 bus drivers. There was no association between B-Pb (mean 372±110 μg/L) and fertility. However, in Pb workers employed for >5 years, the likelihood of having a

child was reduced, irrespective of B-Pb (adjusted SFR=0.38; CI=0.23-0.61). The authors pledge careful interpretation, since there is a possibility of confounding (*eg,* by marital status).

In 251 Italian Pb-workers and 119 controls, the time to pregnancy was shorter (sic!) among the exposed subjects (although non-significantly longer among the most heavily exposed ones), and the number of children greater (Apostoli et al 2000). However, the participation rate was low. Among Finnish Pb-exposed men, there was an exposure-associated decrease of SFR (B-Pbs <0.5 μmol/L=1.0, 0.5-0.9=0.92, 1.0-1.4=0.89, 1.5-1.8=0.58, ≥1.9=0.83) (Sallmén et al 1992 and 2000).

8.2.2.4. Effects on the embryo/fetus/offspring

In a review of epidemiological studies of paternal Pb exposure on risk of *spontaneous abortion*, it was concluded, that there were indications of such an effect (Anttila & Sallmén 1995). Issues surrounding male-mediated reproductive toxicity for Pb have been more thoroughly reviewed by Apostoli et al (1998). Further, in a general review of paternal exposures and birth defects, it was concluded that in painters and painters and printers – occupation with a potential exposure to Pb, though not exceptionally high - run an increased risk (Chia & Shi 2002).

In a study of Norwegian printers, there were increased risks of early *preterm birth* (exposure to Pb: adjusted OR= 2.0, CI=0.5-8.7; Pb and solvents: OR=8.6, CI=2.7-27.3) and *perinatal deaths* (Pb: OR=2.4, CI=1.2-4.9), as compared to national rates (Kristensen et al 1993). Paternal exposure had little impact on birth weight, intrauterine growth or total and specific birth defects. There is an obviuos risk of confounding, *eg*, by life style factors.

In a case-referent study in Baltimore, US, there was a gradual rise of the risk of low *birth weight* by increasing paternal occupational Pb exposure 6 months prior and during pregnancy (interview; classification by industrial hygienist) (Min et al 1996). In the most heavily exposed group, the adjusted OR was 4.72 (CI=1.10-20.23; 10 out of 12 of the fathers were painters). Pb seemed to affect both intrauterine growth and preterm birth. Adjustment was made for maternal smoking, but there is a clear risk of confounding.

In a study of occupations in fathers of 268,109 children borne in Cumbria, UK, 1950-89, a hypothesis that Pb-exposure had affected the testosterone levels, and thus the *sex distribution* of the children, could not be verified (Dickinson & Parker 1994). However, the Pb exposure in the studied occupations (professional drivers) was probably low.

In a study of the offspring of US firemen, who had an assumed exposure to Pb during firefighting, there was an increased risk of *malformations* (septal defects of the heart) (Olshan et al 1990). In a case-referent study in Baltimore, Maryland, USA, there were no clear association between estimated occupational exposure to Pb in the fathers (from conception through age 9 months) and strabismus in the offspring (Hakim et al 1991). Both studies have very weak data on Pb exposure and obvious risks of confounding.

In a large US study of cardiovascular malformations, paternal Pb soldering during 6 months preceding pregnancy (as reported in an interview), was associated with pulmonary atresia (Correa-Villaseñor et al 1993). However, such soldering causes only low air-Pb levels. Also, paint stripping (causing organic solvent exposure) correlated with coarctation of the aorta and ventricular septal defects.

In a study of male printers, potentially exposed to Pb (compositors, monotype casters and stereotyping workers; B-Pb may have been as high as 1.5-3 μmol/L), there was no significant increase of cancers in their offspring (Kristensen & Andersen 1992).

In a Norwegian study of the reproductive outcome as reflected in the birth register in offspring of parents who were occupationally exposed to Pb, as judged from the population census records, offspring to fathers potentially exposed to Pb had no increased risk for any of the analysed birth defects (Irgens et al 1998). Surprisingly, and opposite to exposed women (above), there was a decreased risk of low birth weight (RR=0.91, CI 0.86-0.96).

The studies of malformations and cancers among offspring are open to methodological problems, since the father´s occupation was often obtained from birth certificates and job titles (sometimes 10 years before conception) were used as a surrogate to measure degree of Pb exposure, which is open to misclassification. Moreover, there is a risk of confounding by smoking and alcohol, exposure to other chemicals and maternal exposure. Also, multiple comparisons were made.

8.2.3. Summary

In experimental animals Pb exposure may cause effects on the male endocrine system, as well as on the testis and sperms. In Pb-workers, semen-Pb is correlated with B-Pb.

Pb workers have shown disturbances of the hypothalamic-pituitary-testis endocrine axis and sperm quality. Some data may also indicate decreased libido and decreased fertility, as well as increased risk of spontaneous abortion and decreased birth weight in their offspring. Some of these effects (in particular endocrine, sperm and fertility effects) have been reported at mean B-Pbs as low as 1.5-2.0 μmol/L (Table 2). However, there are methodological problems in most studies, especially as regards selection (very low participation rate and confounding).

9. Needs for further research

In spite of centuries of investigations into the toxicology of Pb, there is a large number of theoretically and practically important questions which are still unsolved. Here, only a few ones will be mentioned.

The mechanism of Pb toxicity is still not well understood. Pb competes with Zn in proteins (ALAD and others). Also, it interferes with Ca turnover in several

ways. Hence, there are numerous possibilities for toxic interference. More information is needed on which aspects that are really crucial for different effects.

There is a controversy on whether the endogenous exposure from bone-Pb is a particular risk because it affects P-Pb, which in turn hits the target organs. This important issue should be solved.

The information on exposure-response relationships for many of the effects is incomplete. Hence, more information is needed.

Further, while a series of routes to perform deterministic risk assessments have been tried, there is a lack of probabilistic ones, which might contribute more reliable and detailed estimates (Bridges et al 2003). In only a couple of papers (WHO 2000b; Murata et al 2003) has a probabilistic approach been used.

10. Discussion and assessment

10.1. State of the art 1991

In 1991 (Skerfving 1992 and 1993), it was noted, that exposure to Pb may affect many functions in the body: the nervous system, blood, kidney, cardiovascular, endocrine, and immuno systems and female and male reproduction and the GI tract. Also, there was evidence of mutagenicity and some indications of cancer.

It was stressed that there were many problems with interpretation of the available information. Most studies were cross-sectional, which means that there might have been a selection. Also, even in the most ambitious analyses, there was a risk of residual confounding. Moreover, information on history of exposure was missing. Further, many of the reported effects were subclinical and their relationship to clinically relevant disease was unclear. Also, there was only rarely detailed information on the low-exposure part of the exposure-response curve, which is a problem, since the potential lowest observed adverse effect level (LOAEL) is close to the "background".

It was noted, that there are sensitive groups. Hence, there seemed to be a sex difference in the metabolism of Pb. Further, Fe and Ca deficiencies, which are more prevalent in women than in males, will increase the GI absorption of Pb. Such deficiency is particularly prevalent during pregnancy, Ca deficiency during pregnancy and lactation. Moreover, disturbance of heme metabolism is more pronounced in women than in males. There were some indications that subjects with certain types of porphyrias are particularly sensitive to Pb. Also, subjects with "non-Pb" anemias, hypertension, kidney disease, disorders of the nervous system and – possibly – some immunodeficiencies were assumed to be particularly vulnerable.

For almost all information on exposure-response was the exposure information in terms of B-Pb. It was concluded that sensitive adult subjects could suffer slight - but potentially adverse - effects on the CNS and PNS and kidney at an average B-Pb in a group of exposed subjects of about 1.5-2.0 μmol/L, or higher. Sperms were believed to be affected at about 2 μmol/L. It was considered likely that

fetuses suffer effects on the CNS at even lower exposures, perhaps already at 0.5-0.75 μmol/L in the pregnant woman. There were some indications of effects on the blood pressure at similarly low exposures.

It was estimated, that an average B-Pb of 1.5 μmol/L in subjects with a low "background" exposure (as in Sweden) would be reached at an air level in the occupational setting of about 27, 0.75 μmol/L at about 13 $\mu g/m^3$.

It was concluded, that some chemical forms of Pb were animal carcinogens and that there were some indications of mutagenicity in man, but no firm support for carcinogenicity in man.

10.2. Update

Since 1991 an enormous amount of new information has been published. Pb is certainly the by far most extensively studied toxic agent. Large Pb-worker and general populations have been investigated. Then, some types of effects have been reported in general population strata with low exposures, indeed in the range of the referent groups in many studies of Pb workers. This is a problem.

Also, explanations of the formerly intriguing differences in sensitivity have begun to appear in terms of gene-environment interactions, mainly as regards *ALAD* genotype. $ALAD^2$ has a higher binding capacity for Pb, so that such subjects seem to have a higher B-Pb at the same exposure intensity (at least when it is not low). However, in spite of their higher B-Pb, they may be protected from at least some adverse effects, and may tolerate higher exposure. These phenomena may induce selection at the work place. Hence, if B-Pb is surveyed, $ALAD^2$ subjects are more likely to be removed. On the other hand, if there is no such surveillance, $ALAD^1$ subjects may quit selectively because of early symptoms. Moreover, the prevalences of the genes differ between races, making it less obvious to use information from other parts of the world for evaluation of risks for Caucasians. Pre-employment screening for *ALAD* genotype has been proposed. However, this seems premature.

Moreover, while selection and confounding are often addressed, effect modification has rarely been considered (Bellinger 2000), especially not in meta-analyses. This has become all the more critical, when genetic influence on the toxicity is realised.

One problem is that most studies do only allow conclusions about differences between groups with varying exposure; hence, it is not possible to define a no observed adverse effect level (NOAEL) or LOAEL. Also, the number of occupationally exposed subjects have often been low. On the other hand, when discrete exposure measures (B-Pb) are used in large populations, effects may be shown at low exposures, but then at a low rate.

At the same time, very sensitive methods have been employed. Then, the question whether the effects should really be considered adverse (*ie,* indicating a health risk, and thus a basis for risk assessment) becomes more complicated.

There is still far too little information on the relationship between air-Pb and effects. Hence, biomarkers have to be used. However, the choice of biomarkers to

define the exposure may seem less obvious than earlier. Hence, in the last decade, the use of *in vivo* determination of skeletal Pb has exploded. Thus, bone-Pb has sometimes shown relations to effects, when B-Pb has not. This has been taken as an indicator that the endogenous exposure is of particular importance for the exposure of target organs (Hu & Hernandez-Avila 2002). However, it might as well be an illustration of the well-known limitations of B-Pb (saturation at high exposure).

Some information relating effects to P-Pb has occurred. P-Pb may have advantages over B-Pb. However, P-Pb data are still too limited to make it possible to use it in a risk assessment. As to U-Pb, there are several problems, in particular at low exposure; also, the information on exposure-response is limited and mostly obsolete. Further, chelatable Pb (after dosing of EDTA or DMSA, which differ), in spite of the fact that there is quite a lot of information as regards some effects, is not possible to use in practice, mainly because it is too complicated for risk surveillance.

Thus, because of the wealth of information, we still have to use B-Pb, keeping its limitations in mind. An important - and still mostly unsolved - problem, is the time aspect of the toxic effects. Hence, it is possible that the current B-Pb is less interesting than the time-integrated/cumulated B-Pb (or bone-Pb, which is related to it) or the peak B-Pb. Further, the reversibility of most of the critical effects is not known. It is perfectly clear, that some effects (kidney damage by heavy exposure during childhood) stays for life, in spite of reduction of exposure, but it is possible that others – at least partly - disappear.

From the above review of effects on different organs, it is clear that the focus, from the point of view of the occupational setting, should be on two discrete effects: Toxicity in the fetus and/or breast-fed infant, and on the blood pressure. In the general population, neurotoxicity in children must also be considered. These effects are adverse. It is not possible to define an overall NOAEL or LOAEL. It might well be, that in some areas of the world, a considerable fraction of the general population suffers effects. However, it is also clear, that the fraction of the variance explained by Pb then is low. On an individual level, the effect of Pb on disorders and disease processes may be subtle. However, on the population level, Pb exposure may contribute an important fraction to the mortality associated with theses disease processes.

10.3. Conclusion

A summary of the B-Pbs associated with various adverse and non-adverse effects is given in Table 2.

Table 2. Overall summary of information on at which lowest blood concentrations (average in studied populations; μmol/L) various adverse, slight effects of lead have been reported with some consistency. ? = Limited data, inconsistent results and/or possible/ probable confounding. - = Not relevant or not sufficiently studied.

		Population		
			General	
Organ	Effect	Occupational	Adults	Children
Nervous system				
Central	Encephalopathia[1]	>4.0	>4.0	>4.0
	Slight symptoms	1.5-2.0	-	-
	Neurobehavioural	1.5-2.0	-	<0.5[2]
Peripheral	Symptoms	1.5	-	-
	Neurophysiological	1.5	-	-
Complex effects	Evoked potentials	1.5	-	-
	Posture	1.5	-	-
	Hearing	-	-	0.5
Autonomous	Heart rate variability	1.5	-	-
Blood	Anemia[1]	>3.0	>3.0	>3.0
	Hemoglobin concentration	2.0-2.5	-	-
	Heme metabolism	0.1-0.3	-	-
	Nucleotide metabolism	≈0.3	-	-
Kidneys	Tubular	1.5	-	0.5?
	Glomerular	2.0?	0.5?	0.5?
Cardiovascular	Blood pressure	1.5-2.0?	0.4	1.8?
	Heart rate variability	1.5	-	-
Endocrine system[3]	Hypothalamus/pituitary/ thyroid/adrenal axes	1.5-2.0	-	-
Immune system	Immunosuppression	2.0	-	-
Mutagenicity	Chromosome aberrations, Micronuclei, SCEs	1.5-2.0	-	-
Cancer	Kidney, lung[4]	?	-	-
Reproduction				
Female	Abortion	?[5]	0.5?	-
	Fetal growth	-	0.1?	-
	Neurobehavioural	-	-	<0.5[2]
Male	Endocrine function	1.5	-	-
	Sperm quality	2.0	-	-
	Fertility	2.0?	-	-
Gastro-intestinal tract[1]	Obstipation, abdominal pain	>3.0	>3.0	>3.0

[1] See Skerfving 1992 and 1993.
[2] Uncertainty whether effects are mainly due to exposure in utero or after birth.
[3] Except for reproduction.
[4] Uncertain.
[5] Levels not clear, probably high.

The CNS of the fetus and the breast-fed infant seems to be affected already at a mean B-Pb in the pregnant/lactating woman of 0.5 μmol/L, probably even much lower (Table 2). In the last decade, the importance of the mobilization of Pb from the skeleton of the pregnant and lactating women has become perfectly clear. This is a major source of exposure of the offspring. Considering its sensitivity, Pb exposure in girls and fertile women should be as low as possible. Hence, before menopause, women should not be exposed in the workplace.

Effects on blood pressure in general populations have been shown at average B-Pbs about 0.4 μmol/L (Table 2). Effects on the kidney may perhaps start already at a mean B-Pb of 0.5 μmol/L, a level present in many general populations.

However, there is better evidence for slight effects on the kidney at a mean B-Pb of 1.5 μmol/L (Table 2), which is a level often present in Pb-workers, and in the general population in some areas with high Pb exposure. Adverse effects on the nervous and endocrine systems and male reproduction may occur at a mean B-Pb of 1.5-2.0 μmol/L.

There is some evidence of mutagenicity (clastogenicity) and effects on the immune system at a mean B-Pb of 1.5-2.0 μmol/L (Table 2). Adverse effects on blood formation seem to start at about 2.0-2.5, on the GI tract at about 3 μmol/L.

Because of the dramatic decrease of B-Pb in the general population in many areas (to about 0.2 μmol/L in the average adult Swedish male), it may be argued that the space for occupational exposure has increased somewhat.

It is not easy to translate these B-Pbs into Pb concentrations in air. Part of the uptake in occupational settings occurs *via* oral ingestion. Further, it is clear that there is a wide difference between Pb species with varying solubilitie and particle sizes. Also, the "background" exposure (which is low in Sweden, in an international perspective) and the endogenous exposure from skeletal Pb depots, caused by earlier exposure, must be considered. However, from the data presented above (section 3.5. Toxicokinetics), it seems that the average worker would just not reach 1.5 μmol/L if exposed to 200 μg/m^3 of Pb with low solubility (sulphide [solubility 0.86 mg/L] [CRC 1989], dust from crystal glass, *etc*) or to about 30 μg/m^3 with high solubility (sulphate [42.5 mg/L], nitrate [376,500 mg/L], *etc*), assuming small particle sizes (Figure 6). The metabolic models give the same picture.

Several human studies indicate limited evidence that Pb is carcinogenic in man, but definite proof is lacking. Pb chromate and arsenate are carcinogenic in man, but that is not due to the Pb moiety.

11. Exposure standards and classifications

11.1. Occupational exposure limits

The present Swedish OEL is 50 μg/m^3 for respirable dust and 100 μg/m^3 for total dust (Swedish NBOSH 2000). As to biological exposure/risk monitoring, Pb work is considered to be present when samples from at least one out of ten workers

show a B-Pb ≥0.8 μmol/L (Swedish NBOSH 1992). Such workers shall be surveyed medically (occupational and medical history, physical examination, blood pressure and blood hemoglobin and Pb and urinary protein concentrations). Such periodical examination of Pb workers shall be organized within 1 month after start of work, and then each third month (if ≤1.5 μmol/L three times each sixth month). A worker with >2.5 (women <50 years >1.5, since Pb is classified as a reproductive toxin) μmol/L, is not allowed to work with Pb until the B-Pb is <2.0 (<1.2) μmol/L. The same applies to workers who have >2.0 (>1.2) μmol/L at three consecutive examinations. Pregnant and lactating women are not allowed to work with Pb. Chromates (including Pb chromate) and inorganic As compounds (including Pb arsenate) are classified as carcinogens.

The OEL in the European Union is 150 $\mu g/m^3$ (EU 1998a). Medical surveys shall be made if the air-Pb is >75 $\mu g/m^3$ (TWA during a 40-hour week) or if the B-Pb is >400 μg/L in an individual worker. However, the Scientific Committee on Occupational Exposure Limits (EU SCOEL, in press) has recommended an OEL of 100 $\mu g/m^3$ (fumes and dust) and a biological limit value for B-Pb of 300 μg/L (for both males and females). It is noted, that it is not easy to set an OEL for airborne Pb, since a considerable fraction of the Pb is ingested orally. Further, the B-Pb is not seen as entirely protective for the offspring of working women; no threshold for potential CNS effects in newborn and infants could be identified.

In Norway (Norwegian Directory of the Labour Inspectorate 2003) and Denmark (Danish Labour Inspectorate 2002), the OEL is 0.05, in Finland 0.1 (Finnish Social Wellfare and Health Agency 2002), and in the United Kingdom 0.15 (UK Health and Safety Executive 2002) mg/m^3.

In Germany, the air limit (Maximale Arbeitsplatzkonzentration; MAK) is 0.1 mg/m^3 (for Pb and its inorganic compounds, except Pb arsenate and chromate; excursion factor 2 for a maximum of 15 min, maximum four per shift with an interval of 1 h) and the biological limit value (Biologischer Arbeitsstofftoleranz-wert; BAT) 400 μg/L. A BAT of 100 μg/L for women <45 years has been proposed, based on the background load in the general population (Deutsche Forschungsgemeinschaft 2003). Pb was classified as animal carcinogen and potentially fetotoxic.

In the US, ACGIH (2001 and 2003) has given a threshold limit value (TLV) for Pb and its inorganic compounds of 0.05 mg/m^3 and consider them to be confirmed animal carcinogens with unknown relevance to humans. Pb chromate has the same TLV, but is listed as a suspected human carcinogen. Pb arsenate has a TLV of 0.15 mg/m^3 as the total compound, in order to also protect from the toxic effects of As. The recommended Biological Exposure Index (BEI) for elemental and inorganic Pb is 300 μg/L blood, with a special warning, that women with a B-Pb >100 μg/L are at risk of delivering a child with a B-Pb over the US CDC (1997) guideline of 100 μg/L, which should not be exceeded.

The US OSHA (1998) permissible exposure limit is 50 $\mu g/m^3$ (action limit 30 $\mu g/m^3$). There is a requirement for monitoring of B-Pb, medical surveillance and reduction of exposure when the worker B-Pbs are ≥400 μg/L; at ≥600 μg/L the worker should be removed from exposure. There are no additional restrictions for

women. It may be mentioned, that in the US, the current goal of the Department of Health and Human Services is to eliminate all occupational exposures resulting in B-Pb >250 μg/L (1.2 μmol/L).

In Japan, the OEL is 0.1 mg/m^3 and the occupational exposure limit based on biological monitoring 400 μg/L (Japan Society for Occupational Health 2002).

11.2. Other assessments

11.2.1. Environmental exposure

In the US, the Centers for Disease Control and Prevention in 1991 identified a goal to reduce children´s B-Pb below 100 μg/L (US CDC 1991). Interventions for individual children were recommended at levels of 150 μg/L and above.

The WHO *B-Pb* level of concern is 200 μg/L (WHO/ICPS 1995). Later, a critical B-Pb level of 100 μg/L was given (WHO 2000a).

In Germany, as to "human biological monitoring values" for B-Pb for the general population, no risk was assumed at 100 μg/L in children <12 years and women in the reproductive age, and 150 μg/L in men >45 years, increased risk of adverse effects at 150 and 250 μg/L, respectively (Ewers et al 1999).

The EU (1999) *ambient air* quality guideline for Pb is 0.5 μg/m^3 on an annual basis. This is to be met 2005; in the immediate vicinity of specific industrial sources, the value is 1 μg/m^3 until 2010. In the US, the ambient air quality standard is 1.5 μg/m^3 (quarterly average) (US EPA 2003). The level 0.5 μg/m^3 has been adopted by Sweden (Ministry of the Environment 2001).

A provisional tolerable weekly intake (PTWI) of 25 μg/kg bw through *food and drinking water* has been established for all age groups by the Joint FAO/WHO Expert Committee on Food Additives (JEFCA 1999; WHO 2000b).

The tolerable concentration of Pb in drinking water in the EU (1998b) and Sweden is 10 μg/L (National Swedish Food Agency 2001). This is based on a health-based guideline value for bottle-fed infants (provisional tolerated weekly intake 25 μg/kg bw=3.5 μg/kg bw/day; bw 5 kg; 50% allocation to water; 0.75 L/day; rounded figure) (WHO 2003).

11.2.2. Cancer and reproduction

International Agency of Research on Cancer (IARC 1987), on the basis of animal experiments, determined that Pb is possibly a human carcinogen (Group 2B).

A series of inorganic Pb species have been classified as having (Repr1), or possibly having (Repr3), effects on fertility (R60, R62) and the human embryo/ fetus/offspring (R6, R63) by the EU and Sweden (KemI 2001).

Pb acetate, Pb chromate, Pb chromate molybdenum sulphate, Pb chromate sulphate and Pb hydrogen arsenate have been classified as possibly carcinogenic to man (Canc3; R40) by the EU and Sweden (KemI 2001).

12. Summary

Pb is certainly the most extensively studied toxic agent. Occupational exposure occurs in a wide variety of settings. However, the exposure levels have decreased considerably in the last decades. There is also exposure in the general environment. For many years, the US ATSDR (1999) has considered Pb to be the toxicant that poses the greatest risk. After the ban of Pb addition to petrol, there has been a dramatic decrease of the exposure in several parts of the world. From an international perspective, Swedes have a low exposure.

Exposure to Pb is most often assessed by biological monitoring, mainly often by determination of B-Pb. This index has limitations, especially since there is saturation at high exposure. P-Pb has advantages, but the experience is too meagre yet. Pb is accumulated in the skeleton, where the concentration reflects long-term uptake, and where it may be determined by *in vivo* methods.

At Pb exposure, there are toxic effects on the CNS and PNS, the blood (including inhibition of heme synthesis, which will also affect all other cells), the kidney, the cardiovascular, endocrine, immune systems and the GI tract. There are also effects on male reproduction (sperm quality).

Pb passes the placenta barrier and may cause toxic effects on the nervous system of fetuses. Slight (but adverse) effects on the mental development of infants have repeatedly been reported at a mean B-Pb of 0.5 μmol/L, or even less, in the pregnant woman. As Pb is accumulated in the skeleton, mobilized during pregnancy and lactation, and is transferred to the fetus/infant, premenopausal women are a group of great concern.

Epidemiological studies of exposure-response relationships for slight toxic effects of Pb suffer methodological problems, *eg,* in terms of selection bias and confounding. However, they permit conclusions on the relationships between different effects and B-Pb.

The current average B-Pb in adult Swedish males is about 0.2 μmol/L, lower in women, adolescents and children.

Effects on the heme synthesis occur at the B-Pbs in general populations with low exposure. There are indications of slight effects on the blood pressure right down to a mean B-Pb of about 0.4 μmol/L. On a population basis, this may mean an increased risk of coronary heart and cerebrovascular diseases.

There is evidence for slight effects on the kidney at a mean B-Pb of 1.5 μmol/L, which is a level often present in Pb workers, as well as in the general population in some areas of the world with high Pb exposure. Adverse effects on the nervous and male reproduction may also occur at a mean B-Pb of 1.5 μmol/L.

There is some evidence of mutagenicity (clastogenicity) and effects on the endocrine and immune systems at a mean B-Pb of 1.5-2.0 μmol/L. Adverse effects on blood formation seem to start at about 2.0-2.5, on the GI tract at about 3 μmol/L.

The average worker would just not reach 1.5 μmol/L if exposed to 200 $\mu g/m^3$ of Pb with low solubility (sulphide, dust from crystal glass, *etc*), or to about 30 $\mu g/m^3$ with high (sulphate, nitrate, *etc*), assuming small particle sizes.

Pb is carcinogenic in animal experiments, but there is only limited evidence for carcinogenicity in humans.

13. Summary in Swedish

Av alla toxiska substanser är bly utan tvekan den mest undersökta. Yrkesmässig exponering för bly förekommer i många olika arbetsmiljöer. Exponeringsnivåerna har emellertid minskat väsentligt det senaste årtiondet. Exponering förekommer även i omgivningsmiljön. I många år ansåg amerikanska myndigheter att bly var den toxiska substans som utgjorde den största risken för hälsan (US ASTDR 1999). Efter det att blytillsatser i bensin förbjöds, har det i stora delar av världen skett en dramatisk minskning av exponeringen för bly. I ett internationellt perspektiv har vi i Sverige låga exponeringsnivåer för bly.

Blyexponering uppskattas oftast med biologisk exponeringsmätning, vanligast är att mäta halten bly i blodet. Emellertid har detta mått begränsningar, bl.a. mättas blodbly vid högre exponeringar. Att i stället mäta bly i plasma har vissa fördelar men erfarenheten av detta exponeringsmått är än så länge begränsad. Bly ackumuleras i skelettet och skeletthalten som kan mätas med in vivo-metoder speglar långtidsexponeringen.

Blyexponering kan orsaka effekter på centrala och perifera nervsystemet, blodet (inkluderat hämning av hemsyntesen vilket också påverkar alla celler i kroppen), njurarna, mag-tarm-kanalen, hjärt-kärl- och immunsystemet samt det endokrina systemet. Effekter ses också på det manliga fortplantningssystemet (spermie kvalitén).

Bly passerar placentabarriären och kan skada nervsystemet hos fostret. Lätta, men ändock skadliga, effekter på den mentala utvecklingen hos barn har rapporterats i ett flertal studier när modern under graviditeten haft en medelhalt av blodbly på 0,5 μmol/L, kanske även t.o.m. lägre. Eftersom bly ackumuleras i ben, frigörs under graviditet och amning och transporteras till fostret/det diande spädbarnet, utgör flickor och fertila kvinnor en grupp som är speciellt viktig att ta hänsyn till med tanke på effekter på avkomman.

Epidemiologiska studier av dos-responssamband för lätta toxiska effekter av bly är behäftade med metodologiska problem, t.ex. selektionsbias och confounding. Det går dock att dra slutsatser om förhållandet mellan blodblyhalt och olika effekter.

Hos svenska män är för närvarande medelvärdet för blodbly ca 0,2 μmol/L. Medelvärdet är lägre hos kvinnor, ungdomar och barn.

Hemsyntesen påverkas vid halter av blodbly som förekommer vid låg exponering i den allmänna befolkningen. Det finns tecken på att blodtrycket påverkas vid medelblodblyhalter ända ner till 0,4 μmol/L. På populationsbasis kan detta innebära en ökad risk för hjärt-kärlsjukdom.

Det finns belägg för att lätta effekter på njurarna uppträder vid en medelblodblyhalt på 1,5 μmol/L. Detta är en blodblynivå man ofta finner hos blyarbetare och i den allmänna befolkningen i områden av världen med hög blyexponering. Skadliga effekter på nervsystemet och manlig fortplantningsförmåga uppträder också vid en blyblodhalt på 1,5 μmol/L.

Det finns en del belägg för att bly är mutagent (klastogent) och att effekter på det endokrina systemet och immunsystemet uppträder vid en medelblodblyhalt på 1,5-2,0 μmol/L. Skadliga effekter på blodbildningen och på mag-tarmkanalen verkar börja uppträda vid en blodblyhalt på 2,0-2,5 respektive 3 μmol/L.

Det har uppskattats att personer som är yrkesmässigt exponerade för blyföreningar med liten partikelstorlek ($\leq$1 μm) och låg vattenlöslighet (t.ex. sulfid, damm från kristallglas m.m.) sällan uppnår en blodblyhalt på 1,5 μmol/L vid en luftexponering på 200 $\mu g/m^3$. Motsvarande luftvärde för blyföreningar med hög vattenlöslighet (t.ex. sulfat, nitrat, etc.) är 30 $\mu g/m^3$.

Bly är carcinogent på försöksdjur, men endast begränsade belägg för carcinogenicitet hos människa föreligger.

14. Acknowledgements

Some of the data presented in this review have been obtained within studies supported by the Swedish Environment Protection Agency, the National Swedish Work Environment Fund, the Swedish Council for Working Life and Social Research, the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning, the Swedish Medical Research Council, the National Swedish Occupational Safety and Health Agency, the County Councils of Southern Sweden and the Medical faculty, Lund University.

Dr. Ingvar Bergdahl, DMedSci, and Dr. Johan Montelius, PhD, have reviewed the text. Ms Gertrud Lennartsson, Ms Lina Bamsaite and Ms Mette Kronqvist have been of enormous help in finding literature.

15. References

Abadin HG, Hibbs BF, Pohl HR. Breast-feeding exposure in infants to cadmium, lead and mercury: A public health viewpoint. *Toxicol Ind Health* 1997;13:495-517.

Abbate C, Buceti R, Munaò F, Giorgianni C, Ferreri G. Neurotoxicity induced by lead levels: an electrophysiological study. *Int Arch Occup Environ Health* 1995;66:389-392.

ACGIH. *Documentation of TLVs and BEIs*. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists 2001.

ACGIH. *TLVs and BEIs. Based on the Documentation of the Threshold Limits Valuse for Chemical Substances and Physical Agents & Biological Exposure Inices*. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists 2003, 206 pp. ISBN 1-882417-49-6.

Adachi JD, Arlen D, Webber C, Chettle DR, Beaumont LF, Gordon CL. Is there any association between the presence of bone disease and cumulative exposure to lead. *Calcif Tissue Int* 1998;63:429-432.

Åkesson A, Stal P, Vahter M. Phlebotomy increases cadmium uptake in hemochromatosis. *Environ Health Perspect* 2000;108:289-291.

Åkesson A, Lundh T, Vahter M, Bjellerup P, Lidfeldt J, Nerbrand C, Samsioe G, Strömberg U, Skerfving S. Tubular and glomerular kidney effects in women with low environmental cadmium exposure – thew WHILA/CAD study. Submitted.

Albers JW, Bromberg MB. Chemically induced toxic neuropathy. In: Rosenberg NL, ed. *Occupational and environmental neurology*. Boston: Butterworth-Heinemann, 1995: p 175-233. ISBN 0-7506-9515-3.

Alexander BH, Checkoway H, Costa-Mallen P, Faustman EM, Woods JS, Kelsey KT, van Netten C, Costa LG. Interaction of blood lead and δ-aminolevulinic acid dehydratase genotype on markers of heme synthesis and sperm production in lead smelter workers. *Environ Health Perspect* 1998;106:213-216.

Al-Modhefer AJA, Bradbury MWB, Simons TJB. Observation on the chemical nature of lead in human blood serum. *Clin Sci* 1991;81:823-829.

Al-Sahle I, Nester M, DeVol E, Shinwari N, Munchari L, Al-Shahria S. Relationships between blood lead concentrations, intelligence, and academic achievements of Saudi Arabian schoolgirls. *Int J Hyg Environ Health* 2001;204:165-174.

American Academy of Pediatrics. Committee on drugs. Treatment guidelines for lead exposure in children. *Pediatrics* 1995;96:155-160.

Andersson L, Wingren G, Axelson O. Some hygienic observations from the glass industry. *Int Arch Occup Environ Health* 1990;62:249-252.

Andrews KW, Savitz DA, Hertz-Picciotto I. Prenatal lead exposure in relation to gestational age and birth weight: A review of epidemiologic studies. *Am J Ind Med* 1994;26:13-32.

Anttila A, Sallmen M. Effects of parental occupational exposure to lead and other metals on spontaneous abortion. *J Occup Environ Med* 1995;37:915-921.

Anttila A, Heikkila P, Pukkala E, Nykyri E, Kauppinen T, Hernberg S, Hemminki K. Excess lung cancer among workers exposed to lead. *Scand J Work Environ Health* 1995;21:460-469.

Anttila A, Heikkila P, Nykyri E, Kauppinen T, Pukkala E, Hernberg S, Hemminki K. Risk of nervous system cancer among workers exposed to lead. *J Occup Environ Med* 1996;38:131-136.

Apostoli P, Maranelli G, Micciolo R. Is hypertension a confounding factor in the assessment of blood lead reference values. *Sci Total Environ* 1992;120:127-134.

Apostoli P, Kiss P, Porru S, Bonde JP, Vanhoorne M. Male reproductive toxicity of lead in animals and humans. ASCLEPIOS Study Group. *Occup Environ Med* 1998;55:364-374.

Apostili P, Bellini A, Porru S, Bisanti L. The effect of lead on male fertility: a time to pregnancy (TTP) study. *Am J Ind Med* 2000;38:310-315.

Araki S, Murata K, Yokoyama K, Uchida E. Auditory event-related potential (P300) in relation to peripheral nerve conduction in workers exposed to lead, zinc and copper: effects of lead on cognitive function and central nervous system. *Am J Ind Med* 1992;21:539-547.

Araki S, Murata K, Uchida E, Aono H, Ozawa H. Radial and median nerve conduction velocities in workers exposed to lead, copper, and zinc: a follow-up study for 2 years. *Environ Res* 1993;61:308-316.

Araki S, Sato H, Yokoyama K, Murata J. Subclinical neurophysiological effects of lead: A review on peripheral, central, and autonomic nervous system effects in lead workers. *Am J Ind Med* 2000;37:193-204.

Aribarg A, Sukcharoen N. Effects of occupational lead exposure on spermatogenesis. *J Med Assoc Thai* 1996;79:91-97.

Aro A, Amarasiriwardena C, Lee ML, Kim R, Hu H. Validation of K x-ray fluorescence bone lead measurements by inductively coupled plasma mass spectrometry in cadaver legs. *Med Phys* 2000;27:119-123.

Baecklund M, Pedersen NL, Björkman L, Vahter M. Variation in blood concentrations of cadmium and lead in the elderly. *Environ Res* 1999;80:222-230.

Baghurst PA, McMichael AJ, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ, Tong SL. Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study. *N Engl J Med* 1992;327:1279-1284.

Balbus-Kornfeld JM, Stewart W, Bolla KI, Schwartz BS. Cumulative exposure to inorganic lead and neurobehavioural test performance in adults: an epidemiological review. *Occup Environ Med* 1995;52:2-12.

Bárány E, Oskarsson A. Whole blood and serum levels of toxic and essential trace elements in adolescents. In: Skerfving S, ed. *Toxicology of metals. A symposium in memory of Andrejs Schütz*. 2002:55-62.

Bárány E, Bergdahl IA, Schütz A, Skerfving S, Oskarsson A. Inductively coupled plasma mass spectrometry for direct multi-element analysis of diluted human blood and serum. *J Anal Atomic Spectrometry* 1997;12:1005-1009.

Bárány E, Bergdahl IA, Bratteby L-E. Lundh T, Samuelson G, Schütz A, Skerving S, Oskarsson A. Trace element levels in whole blood and serum from Swedish adolescents. *Sci Total Environ* 2002a;286:129-141.

Bárány E, Bergdahl IA, Bratteby L-E, Lundh T, Samuelson G, Schütz A, Skerfving S, Oskarsson A. Trace elements in blood and serum of Swedish adolescents: Relation to gender, age, residential area and socioeconomic status. *Environ Res* 2002b;89:72-84. http://www.idealibrary.com/links/doi/10.1006/enrs.2002.4351/pdf

Bárány E, Bergdahl I, Bratteby L, Lundh T, Samuelson G, Schütz A, Skerfving S, Oskarsson A. Relationships between trace element concentrations in human blood and serum. *Toxicol Lett* 2002c;134:177-184.

Bárány E, Bergdahl IA, Bratteby L-E, Lundh T, Samuelson G, Skerfving S, Oskarsson A. Iron status influences trace element levels in human blood and serum. Submitted.

Barth A, Schaffer AW, Osterode W, Winker R, Konnaris C, Valic E, Wolf C, Rüdiger HW. Reduced cognitive abilities in lead-exposed men. *Int Arch Occup Environ Health* 2002;75:394-398.

Barton JC, Patton MA, Edwards CQ, Griffen LM, Kushner JP, Meeks RG, Leggett RW. Blood lead concentrations in hereditary hemochromatosis. *J Lab Clin Med* 1994;124:193-198.

Batuman V. Lead nephropathy, gout, and hypertension. *Am J Med Sci* 1993;305:241-247.

Beck BD, Mattuck RL, Bowers TS, Cohen JT, O'Flaherty E. The development of a stochastic physiologically-based pharmacokinetic model for lead. *Sci Tot Environ* 2001;74:15-19.

Bellinger DC. Effect modification in epidemiologic studies of low-level neurotoxicant exposures and health outcomes. *Neurotoxicol Teratol* 2000;22:133-140.

Bellinger DC, Needleman HL. Intellectual impairment and blood lead levels (letter). *N Engl Med J* 2003;249:500-502.

Bellinger DC, Stiles KM, Needleman HL. Low-level lead exposure, intelligence and academic achievement: A long-term follow-up study. *Pediatrics* 1992;90:855-861.

Bellinger D, Hu H, Titlebaum L, Needleman HL. Attentional correlates of dentin and bone lead levels in adolescents. *Arch Environ Health* 1994a;49:98-105.

Bellinger D, Leviton A, Allred E, Rabinowitz M. Pre- and postnatal lead exposure and behavior problems in school-aged children. *Environ Res* 1994b;66:12-30.

Bensryd I, Rylander L, Högstedt B, Aprea P, Bratt I, Fåhraéus C, Holmén A, Karlsson A, Nilsson A, Svensson B-L, Schütz A, Thomassen Y, Skerfving S. Effect of acid precipitation on retention and excretion of elements in man. *Sci Tot Environ* 1994;145:81-102.

Bergdahl IA. Lead-binding proteins – a way to understand lead toxicity? *Analusis Magazine* 1998;26:81-85.

Bergdahl IA. Lead concentration in plasma as a marker of exposure and health risk – how far have we come? In: Skerfving S, ed. *Toxicology of metals. A symposium in memory of Andrejs Schütz* 2002.

Bergdahl IA, Skerfving S. Partition of circulating lead between plasma and red cells does not seem to be different for internal and external sources of lead. Letter to the editor. *Am J Ind Med* 1997;32:317-318.

Bergdahl AI, Schütz A, Grubb A. Application of liquid chromatography - inductively coupled plasma mass spectrometry to the study of protein-bound lead in human erythrocytes. *J Anal Atomic Spectrometry* 1996;11:735-738.

Bergdahl IA, Gerhardsson L, Schütz A, Wetmur JG, Skerfving S. Delta-aminolevulinic acid dehydratase polymorphism. Influence on lead levels and kidney function in humans. *Arch Environ Health* 1997a;52:91-96.

Bergdahl IA, Grubb A, Schütz A, Desnick RJ, Wetmur JG, Sassa S, Skerfving S. Lead binding to ∂-aminolevulinic acid dehydratase (ALAD) in human erythrocytes. *Pharmacol Toxicol* 1997b;81:153-158.

Bergdahl IA, Schütz A, Gerhardsson L, Jensen A, Skerfving S. Lead concentrations in human plasma, urine and whole blood. *Scand J Work Environ Health* 1997c;23:359-363.

Bergdahl IA, Strömberg U, Gerhardsson L, Schütz A, Chettle DR, Skerfving S. Lead concentrations in tibial and calcaneal bone in relation to the history of occupational lead exposure. *Scand J Work Environ Health* 1998a;24:38-45.

Bergdahl IA, Sheveleva M, Schütz A, Artamonova VG, Skerfving S. Plasma and blood lead in humans: Capacity-limited binding to ∂-aminolevulinic acid dehydratase and other lead-binding components. *Toxicol Sci* 1998b;46:247-253.

Bergdahl IA, Vahter M, Counter SA, Schütz A, Buchanan LH, Ortega F, Laurell G, Skerfving S. Lead in plasma and whole blood from lead-exposed children. *Environ Res* 1999;80:25-33.

Bergdahl IA, Liljelind IE, Nilsson L, Skerfving S. Plasma-lead concentration. Investigations into its usefulness for biological monitoring of occupational lead exposure. Submitted.

Berglund M, Lind B, Lannero E, Vahter M. A pilot study of lead and cadmium exposure in young children in Stockholm, Sweden: methodological considerations using capillary blood sampling. *Arch Environ Contam Toxicol* 1994;27:281-287.

Berglund M, Akesson A, Bjellerup P, Vahter M. Metal-bone interactions. *Toxicol Lett* 2000a;112-113:219-225.

Berglund M, Lind B, Sörensen S, Vahter M. Impact of soil and dust lead on children´s blood lead in contaminated areas of Sweden. *Arch Environ Health* 2000b;55:93-97.

Berlin K, Gerhardsson L, Börjeson J, Lindh E, Lundström N, Schütz A, Skerfving S, Edling C. Lead intoxication caused by skeletal disease. *Scand J Work Environ Health* 1995;21:296-300.

Bernard AM, Vyskocil A, Roels H, Kriz J, Kodl M, Lauwerys R. Renal effects in children living in the vicinity of a lead smelter. *Environ Res* 1995;68:91-95.

Bhattacharya A, Shukla R, Dietrich KN, Miller J, Bagchee A, Bornsschein RL, Coc C, Mitchell T. Functional implications of postural disequilibrium due to lead exposure. *Neurotoxicology* 1993;14:179-180.

Bilban M. Influence of the work environment in a Pb-Zn mine on the incidence of cytogenetic damage in miners. *Am J Ind Med* 1998;34:455-463.

Björkman L, Vahter M, Pedersen NL. Both the environment and genes are important for concentrations of cadmium and lead in blood. *Environ Health Perspect* 2000;108:719-722.

Bleecker ML, McNeil FE, Lindgren KN, Masten VL, Ford DP. Relationship between bone lead and other indices of lead exposure in smelter workers. *Toxicol Lett* 1995;77:241-248.

Bleecker ML, Lindgren KN, Ford DP. Differential contribution of current and cumulative indices of lead dose to neuropsychological performance by age. *Neurology* 1997a;48:639-645.

Bleecker ML, Lindgren KN, Tiburzi MJ, Ford DP. Curvilinear relationship between blood lead level and reaction time. Differential association with blood lead fractions derived from exogenous and endogenous sources. *J Occup Environ Med* 1997b;39:426-431.

Bolla KI, Schwartz BS, Stewart W, Rignani JE, Agnew J, Ford P. Comparison of neurobehavioral function in workers exposed to a mixture of organic and inorganic lead and in workers exposed to solvents. *Am J Ind Med* 1995;27:231-246.

Bonde JP, Joffe M, Apostoli P, Dale A, Kiss P, Spano M, Caruso F, Giwercman A, Bisanti L, Porru S, Vanhoorne M, Comhaire F, Zschiesche W. Sperm count and chromatine structure in men exposed to inorganic lead: lowest adverse effect levels. *Occup Environ Med* 2002;59:234-242.

Bound JP, Harvey PW, Francis BJ, Awwad F, Gastrell C. Involvement of deprivation and environmental lead in neural tube defects: a matched case-control study. *Arch Dis Childhood* 1997;76:107-112.

Borja-Aburto VH, Hertz-Picciotto I, Rojas Lopez M, Farias P, Rios C, Blanco J. Blood lead levels measured prospectively and risk of spontaneous abortion. *Am J Epidemiol* 1999;150:590-597.

Börjesson J, Gerhardsson L, Schütz A, Mattsson S, Skerfving S, Österberg K. In vivo measurements of lead in fingerbone in active and retired lead smelters. *Int Arch Occup Environ Health* 1997a;69:97-105.

Börjesson J, Mattsson S, Strömberg U, Gerhardsson L, Schütz A, Skerfving S. Lead in fingerbone: A tool for retrospective exposure assessment. *Arch Environ Health* 1997b;52:104-112.

Braun CMJ, Daigneault S. Sparing of cognitive executive function and impairment of motor functions after industrial exposure to lead: A field study with control group. *Neuropsychology* 1991;5:179-193.

Bridges JW, Klein W, Knudsen I, Kroes R, Le Neindre P, O´Gara FT, Paoletti R, Schaefer H, Skerfving S, Taragona TV, Maijala R, Verger P, Wester P. *The future of risk assessment in the European Union. The second report on the harmonisation of risk assessment procedures*. Adopted by the Scientific Steering Committee at its meeting of 10-11 April 2003. European Commission, Health & Consumer Protection Directorate-General, Directorate C – Scientific Opinions. C1 – Follow-up and Dissimination of Scientific Opinions, Brussels, 2003.

Brito JA, McNeill FE, Chettle DR, Webber CE, Vaillancourt C. Study of the relationships between bone lead levels and its variation with time and the cumulative blood lead index, in a repeated bone lead survey. *J Environ Monit* 2000;2:271-276.

Brito JA, McNeill FE, Stronach I, Webber CE, Wells S, Richard N, Chettle DR. Longitudinal changes in bone lead concentration: implications for modelling of human bone lead metabolism. *J Environ Monit* 2001;3:343-351.

Brito JA, McNeill FE, Webber CE, Wells S, Richard N, Carvalho ML, Chettle DR. Evaluation of a novel structural model to describe the endogenous release of lead from bone. *J Environ Monit* 2002;4:194-201.

Brown MJ, Hu H, Gonzales-Cossio T, Peterson KE, Sanin LH, de Luz K. Palazuelos E, Aro A, Schnaas L, Hernandez-Avila M. Determinants of bone and blood lead concentrations in the early postpartum period. *Occup Environ Med* 2000;57:535-541.

Cake KM, Bowins RJ, Vaillancourt C, Gordon CL, McNutt RH, Laporte R, Webber CE, Chettle DR. Partition of circulating lead between serum and red cells is different for internal and external sources of lead. *Am J Ind Med* 1996;29:440-445.

Calderón J, Navarro ME, Jimenez-Capdeville ME, Santoz-Diaz MA, Golden A, Rodriguez-Leyva I, Borja-Aburto V, Diaz-Barriga F. Exposure to arsenic and lead and neuropsychological development in Mexican children. *Environ Res* 2001;85:69-76.

Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 microg per decilitre. *N Engl J Med* 2003;348:1517-1526.

Cárdenas A, Roels H, Bernard AM, Barbon R, Buchet JP, Lauwerys RR, Roselló J, Ramis I, Mutti A, Franchini I, Fels LM, Stolte H, De Broe ME, Nuyts GD, Taylor SA, Price RG. Markers of early renal changes induced by industrial pollutants. II Application to workers exposed to lead. *Brit J Ind Med* 1993;50:28-36.

Carta P, Cocco P, Picchiri G. Lung cancer mortality and airways obstruction among metal miners exposed to silica and low level radon daughters. *Am J Ind Med* 1994;25:489-506.

Chavalitnitikul C, Levin L, Chen LC. Study and models of total lead exposures of battery workers. *Am Ind Hyg Ass J* 1984;45:802-808.

Cheng Y, Schwartz J, Vokonas PS, Weiss ST, Aro A, Hu H. Electrocardiographic conduction disturbances in association with low-level lead exposure (the Normative Aging Study). *Am J Cardiol* 1998a;82:594-599.

Cheng Y, Willett WC, Schwartz J, Sparrow D, Weiss S, Hu H. Relation of nutrition to bone lead and blood lead levels in middle-aged to elderly men. The normative aging study. *Am J Epidemiol* 1998b;147:1162-1174.

Cheng Y, Schwartz J, Sparrow D, Aro A, Weiss ST, Howard H. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension. *Am J Epidemiol* 2001;153:164-171.

Chia SE, Chia KS, Ong CN. Ethnic differences in blood lead concentration among workers in a battery manufacturing factory. *Ann Acad Med Singapore* 1991;20:758-761.

Chia SE, Ong CN, Lee ST, Tsakok FH. Blood concentrations of lead, cadmium, mercury, zinc, and copper and human semen parameters. *Arch Androl* 1992;29:177-183.

Chia KS, Mutti A, Alinovi R, Jeyaratnam J, Tan C, Ong CN, Lee E. Urinary excretion of tubular brush border antigens among lead exposed workers. *Ann Acad Med Singapore* 1994a;23:655-659.

Chia KS, Mutti A, Tan C, Ong HY, Jeyaratnam J, Ong CN, Lee E. Urinary N-acetyl-beta-D-glucosaminidase activity in workers exposed to inorganic lead. *Occup Environ Med* 1994b;51:125-129.

Chia SE, Chua LH, Ng TP, Foo SC, Jeyaratnam J. Postural stability of workers exposed to lead. *Occup Environ Med* 1994c;51:768-771.

Chia KS, Jeyaratnam J, Lee J, Tan C, Ong HY, Ong CN, Lee E. Lead induced nephropathy: relationship between various biological exposure indices and early markers of nephrotoxicity. *Am J Ind Med* 1995a;27:883-895.

Chia KS, Jeyaratnam J, Tan C, Ong HY, Ong CN, Lee E. Glomerular function in lead workers. *Toxicol Lett* 1995b;77:319-328.

Chia SE, Chia HP, Ong CN, Jeyaratnam J. Cumulative concentrations of blood lead and postural stability. *Occup Environ Med* 1996a;53:264-268.

Chia SE, Chia HP, Ong CN, Jeyaratnam J. Cumulative blood lead level and nerve conduction parameters. *Occup Med* 1996b;46:59-64.

Chia SE, Chia HP, Ong CN, Jeyaratnam J. Three-year follow-up of serial nerve conduction among lead-exposed workers. *Scand J Work Environ Health* 1996c;22:374-380.

Chia SE, Chia HP, Ong CN, Jeyaratnam J. Cumulative blood lead levels and neurobehavioral test performance. *Neurotoxicology* 1997;18:793-803.

Chia SE, Shi LM. Review of recent epidemiological studies of paternal occupations and birth defects. *Occ Environ Med* 2002;59:149-155.

Choudhury H, Peirano WB, Marcus A, Elias R, Griffin S, De-Rosa CT. Utilization of uptake biokinetic (UBK) model to assess risk in contaminated sites. In: *Superfund risk assessment in soil contamination studies*. ASTM, Philadelphia PA, 1992, pp. 193-204.

Chuang HY, Lee ML, Chao KY, Wang JD, Hu H. Relationship of blood lead levels to personal hygiene habits in lead battery workers: Taiwan, 1991-97. *Am J Ind Med* 1999;35:595-603.

Chuang HY, Schwartz J, Tsai SY, Lee MLT, Wang JD, Hu H. Vibration perception thresholds in workers with long term exposure to lead. *Occup Environ Med* 2000;57:588-594.

Chuang HY, Schwartz J, Gonzales-Cossio T, Lugo MC, Palazuelos E, Aro A, Hu H, Hernandez-Avila M. Interrelations of lead levels in bone, venous blood, and umbilical cord blood with exogenous lead exposure through maternal plasma lead in peripartum women. *Environ Health Perspect* 2001;109:527-532.

Cocco P, Carta P, Flore MV, Picchiri GF, Zucca C. Lung cancer mortality among female mine workers exposed to silica. *J Occup Med* 1994a;36:894-898.

Cocco P, Carta P, Belli S, Picchiri G, Flore MV. Mortality of Sardianian lead and zinc miners: 1960-88. *Occup Environ Med* 1994b;51:674-682.

Cocco P, Hua F, Boffetta P, Carta P, Flore C, Flore V, Onnis A, Picchiri GF, Colin D. Mortality of Italian lead smelter workers. *Scand J Work Environ Health* 1997;23:15-23.

Coresh J, Wei L, McQuillan G, Brancati FL, Levey AS, Jones C, Klag MJ. Prevalence of high blood pressure and elevated serum creatinine level in the United States. *Arch Int Med* 2001;161:1207-1216.

Cornelis R, Heinzow B, Herber RF, Christensen JM, Poulsen OM, Templeton DM, Thomassen Y, Vahter M, Vesterberg O. Sample collection guidelines for trace elements in blood and urine. IUPAC Commission of Toxicology. *J Trace Elem Med Biol* 1996;10:103-127.

Correa-Villaseñor A, Ferenc C, Loffredo C, Magee C. Paternal exposures and cardiovascular malformations. *J Exp Anal Environ Epidemiol* 1993;3:173-185.

Costa CA, Trivelato GC, Pinto AMP, Bechara EJH. Correlation between plasma 5-aminolevulinic acid concentrations and indicators of oxidative stress in lead-exposed workers. *Clin Chem* 1997;43:1196-1202.

Coste J, Manereau F, Pessione M, Coste J, Mandereau L, Pessione F, Bregu M, Faye C, Hemon D, Spira A. Lead-exposed workmen and fertility: a cohort study on 354 subjects. *Eur J Epidemiol* 1991;7:154-158.

Counter SA, Vahter M, Laurell G, Buchanan LH, Ortega F, Skerfving S. High lead exposure and auditory sensory-neural function in Andean children. *Environ Health Perspect* 1997;105:522-526.

Counter SA, Buchanan LH, Ortega F, Amarasiriwardena C, Hu H. Environmental lead contamination and pediatric lead intoxication in an Andean Ecuadorian village. *Int J Occup Environ Health* 2000;6:169-176.

CRC. *Handbook on Chemistry and Physics, 1989-90*. The Chemical Rubber Co, Cleveland, OH, 1989.

Damm D, Grandjean P, Lyngbye T, Trillingsgaard A, Hansen ON. Early lead exposure and neonatal jaundice: relation to neurobehavioral performance at 15 years of age. *Neurotoxicol Teral* 1993;15:173-181.

Danish Labour Inspectorate. *Grænsævrdier for stoffer og materialer*. Arbejstilsynet, Copenhagen, 2002.

Dawson EB, Ritter S, Harris WA, Evans DR, Powell LC. Comparison of sperm viability and seminal plasma metal levels. *Biol Trace Element Res* 1998;64:215-219.

Delves HT, Diaper SJ, Oppert S, Prescott-Clarke P, Periam J, Dong W. Blood lead concentrations in the United Kingdom have fallen substantially since 1984. *Br Med J* 1996;313:883-884.

De Medinilla J, Espigares M. Environmental and biological monitoring of workers exposed to inorganic lead. *J Soc Occup Med* 1991;41:107-112.

Den Hond E, Nawrot T, Staessen JA. The relationship between blood pressure and blood lead in NHANES III. *J Hum Hypertension* 2002;16:56-58.

Den Hond E, Nawrot T, Staessen JA. Hypertension and low-level lead exposure: a scientific issue or a matter of faith? *Hypertension* 2003;42:e9.

Deutsche Forschungsgemeinshaft. *List of MAK and BAT valuses 2003*. Wiley-VCH, Weinheim, Germany, 2003.

Dickinson H, Parker L. Do alcohol and lead change the sex ratio? *J Theor Biol* 1994;169:313-315.

Dietrich KM, Berger OG, Succop PA. Lead exposure and the motor developmental status of urban six-year-old children in the Cincinatti prospective study. *Pediatrics* 1993;91:301-307.

Discalzi GL, Capellaro L, Bottalo L, Fabbro D, Mocellini A. Auditory brainstem evoked potentials (BAEPs) in lead-exposed workers. *Neurotoxicology* 1992;13:207-210.

Dolenc P, Staessen JA, Lauwerys RR, Amery A. Short report: low-level lead exposure does not increase the blood pressure in the general population. Cadmibel Study Group. *J Hypertens* 1993;11:589-593.

Dönmez H, Dursun N, Özkul Y, Demirtas H. Increased sister chromatid exchanges in workers exposed to occupational lead and zinc. *Biol Trace Elem Res* 1998;61:105-109.

Driscoll RJ. *Health hazard evaluation report 93-1035-2686, Section 2: Epidemiologic study of adverse reproductive outcomes among women in the U.S. Forest Service*. U.S. Department of Agriculture, U.S. Forest Service, Washington D.C., 1998.

Duydu Y, Suzen HS, Aydin A, Cander O, Uysal H, Isimer A, Vural N. Correlation between lead exposure indicators and sister chromatid exchange (SCE) frequencies in lymphocytes from inorganic lead exposed workers. *Arch Environ Contam Toxicol* 2001;41:241-246.

Dyer J, Garrick DP, Inglis A, Pye IF. Plumboporphyria (ALAD deficiency) in a lead worker: a scenario for potential diagnostic confusion. *Br J Ind Med* 1993;50:1119-1121.

Egeland GM, Burkhart GA, Schnorr TM, Hornung RW, Fajen JM, Lee ST. Effects of exposure to carbon disulfide and low density lipoprotein cholesterol concentration and diastolic blood pressure. *Brit J Ind Med* 1992;49:287-293.

Ehle AL, MvKee DC. Neuropsychological effect of lead in occupationally exposed workers: A critical review. *Crit Rev Toxicol* 1990;20:237-255.

Ehrlich R, Robins T, Jordaan E, Miller S, Mbuli S, Selby P, Wynchanl S, Cantrell A, De Broe M, D'Haese P, Todd A, Landrigan P. Lead absorption and renal dysfunction in a South African battery factory. *Occup Environ Med* 1998;55:453-460.

Elhelu MA, Caldwell DT, Hirpassa WD. Lead in inner-city soil and its possible contribution to children´s blood lead. *Arch Environ Health* 1995;50:165-169.

Elinder CG. Orsakar bly njurskador? Resultat i ansedd tidskrift förvånar. *Läkartidniongen* 2003;100:1736.

Elinder CG, Alvestrand A. Letter to the Editor. *N Engl J Med* 2003;348:1811.

Emmerson BT. Lead stores in patients with renal insufficiency. *Nephron* 1991;58:233-234.

Emory E, Ansari Z, Pattillo R, Archibold E, Chevalier J. Maternal blood lead effects on infant intelligence at age 7 months. *Am J Obstet Gynecol* 2003;188:S26-S32.

Endo G, Konishi Y, Kiyota A, Horiguchi S. Urinary α_1-microglobulin in lead workers. *Bull Environ Contam Toxicol* 1993;50:744-749.

Englyst V, Lundstrom NG, Gerhardsson L, Rylander L, Nordberg G. Lung cancer risks among lead smelter workers also exposed to arsenic. *Sci Total Environ* 2001;273:77-82.

Erfurth EM, Gerhardsson L, Nilsson A, Rylander L, Schütz A, Skerfving S, Börjesson J. Effects of lead on the endocrine system in lead smelter workers. *Arch Environ Health* 2001;56:449-455.

Erkkilä J, Armstrong R, Riihimäki V, Chettle DR, Paakari A, Scott M, Somervaille L, Starck J, Kock B, Aitio A. In vivo measurements of lead in bone at four anatomical sites: Long-term occupational and consequent endogenous exposure. *Brit J Ind Med* 1992;49:631-644.

Ettinger AS, Téllez-Rojo MM, Amarasiriwardena C, González-Cossio T, Peterson KE, Aro A, Hu H, Hernández-Avila M. Levels of lead in breast milk and their relation to maternal blood and bone lead levels at one month post partum. *Environ Health Perspect* 2004a;112:926-931.

Ettinger AS, Téllez-Rojo MM, Amarasiriwardena C, Bellinger D, Peterson K, Schwartz J, Hu H, Hernández-Avila M. Effect of breast milk lead on infant blood lead levels at 1 month of age. *Environ Health Perspect* 2004b;112:1381-1385.

EU. Protection of the health and safety of workers against risks associated with chemical agents in the worklife. Commission of the European Communities, Directive 98/24/EC, 7 April 1998. 1998. *Off J Eur Comm L* 131/11, 5.5.1998a.

EU. Council directive 98/83/EG on the quality of water for human consumption. *Off J Eur Comm L* 330/32, 5 December 1998b.

EU. Air quality guidelines. Commission of the European Communities, 1999. Council Directive 1999/30/EC, 22 April 1999. *Off J Eur Comm L* 163, 29.6.1999.

EU SCOEL. Recommendation from Scientific Committee on Occupational Exposure Limits for lead and its inorganic compounds. In press.

Ewers U, Krause C, Schulz C, Wilhelm M. Reference values and human biological monitoring values for environmental toxins. Report on the work and recommendations of the Commission on Human Biological Montoring of German Federal Environmental Agency. *Int Arch Occup Environ Health* 1999;72:255-260.

Factor-Litvak P, Kline JK, Popovac D, Hadzialjevic S, Lekic V, Preteni-Rexhepi E, Capuni-Paracka S, Slavokovich V, Graziano J. Blood lead and blood pressure in young children. *Epidemiology* 1996;7:633-637.

Factor-Litvak P, Wasserman G, Kline JK, Graziano J. The Yugoslavia Prospective Study of environmental lead exposure. *Environ Health Perspect* 1999;107:9-15.

Fagher U, Laudanski T, Schütz A, Sipowicz M, Åkerlund M. The relationship between cadmium and lead burdens and preterm labor. *Int J Gynecol Obstet* 1993;40:109-114.

Far HS, Pin NT, Kong CY, Fong KS, Kian CW, Yan CK. An evaluation of the significance of mouth and hand contamination for lead absorption in lead-battery workers. *Int Arch Occup Environ Health* 1993;64:439-443.

Farago ME, Thornton I, White ND, Tell I, Mårtensson M-B. Environmental impacts of a secondary lead smelter in Landskrona, southern Sweden. *Environ Geochem Health* 1999;21:67-82.

Fels LM, Wünsch M, Baranowski J, Norska-Borówka I, Price RG, Taylor Sa, Patel S, De Broe M, Elsevier MM, Lauwerys R, Roels H, Bernard A, Mutti A, Gelpi E, Joan Roselló, Stolte H. Adverse effects of chronic low level lead exposure on kidney function – a risk group study in children. *Nephrol Dial Transplant* 1998;13:2248-2256.

Fergusson DM, Horwood J, Lynskey MT. Early dentine lead levels and subsequent cognitive and behavioural development. *J Child Psychol Psychiat* 1993;34:215-227.

Fertmann R, Hentschell S, Dengler D, Janssen U, Lommel A. Lead exposure by drinking water: an epidemiological study in Hamburg, Germany. *Int J Hyg Environ Health* 2004;207:235-244.

Fewtrell LJ, Prüss-Ustün A, Landrigan P, Ayuso-Mateos JL. Estimating the global burden of disease of mild mental retardation and cardiovascular disease from environmental lead exposure. *Environ Res* 2004;94:120-133.

Figà-Talamanca I, Dondero F, Gandini L, Lenzi A, Lombardo F, Osborn J. Male infertility and occupational exposures: A case-control study. *J Occup Med Toxicol* 1992;1:255-264.

Finnish Social Welfare and Health Mininstry. *HTTP-värden 2002*. Social- och hälsoministeriet, Tammerfors, 2002.

Fischer AB, Georgieva R, Halkova J, Bainova A, Hristev Penkov D, Alandjiisk D. Health risk for children from lead and cadmium near a non-lead smelter in Bulgaria. *Int J Hyg Environ Health* 2003;206:25-38.

Fischbein A, Tsang P, Luo JC, Bekesi JG. The immune system as target for subclinical lead related toxicity. *Brit J Ind Med* 1993a;50:185-186.

Fischbein A, Tsang P, Luo JC, Roboz JP, Jiang JD, Bekesi JG. Phenotypic aberrations of CD3+ and CD4+ cells and functional impairment of lymphocytes at low-level occupational exposure to lead. *Clin Immunol Immunopathol* 1993b;66:163-168.

Fleming DE, Boulay D, Richard NS, Robin JP, Gordon CL, Webber CE, Chettle DR. Accumulated body burden and endogenous release of lead in employees of a lead smelter. *Environ Health Perspect* 1997;105:224-233.

Fleming DE, Chettle DR, Wetmur JG, Desnick RJ, Robin JP, Boulay D, Richard NS, Gordon CL, Webber CE. Effect of the delta-aminolevulinate dehydratase polymorphism on the accumulation of lead in bone and blood in lead smelter workers. *Environ Res* 1998;77:49-61.

Fleming DE, Chettle DR, Webber CE, O'Flaherty EJ. The O'Flaherty model of lead kinetics: an evaluation using data from a lead smelter population. *Toxicol Appl Pharmacol* 1999;161:100-109.

Foo SC, Khoo NY, Heng A, Chua LH, Chia SE, Ong NG, Ngim CH, Jeyaratnam J. Metals in hair as biological indices for exposure. *Int Arch Occup Environ Health* 1993;65:S83-S86.

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

Fujimura Y, Araki S, Murata K, Sakai T. Assessment of peripheral, central and autonomic nervous system functions in two lead smelters with high blood lead concentrations: A follow-up study. *J Occup Health* 1998;40:9-15.

Fukui Y, Miki M, Ukai H, Okamoto S, Takada S, Higashikawa K, Ikeda M. Urinary lead as a possible surrogate of blood lead among workers occupationally exposed to lead. *Int Arch Occup Environ Health* 1999;72;516-520.

Gamblin C, Gordon CL, Muir DC, Chettle DR, Webber CE. In vivo measurements of bone lead content in residents of southern Ontario. *Appl Radiat Isot* 1994;45:1035-1038.

Gao W, Li Z, Kaufman RB, Jones RL, Wang Z, Chen ZC, Zao X, Wang N. Blood lead levels among children aged 1 to 5 years in Wuxi City , China. *Environ Res* 2001;87:11-19.

Gemmel A, Tavares M, Alperin S, Soncini J, Daniel D, Dunn J, Crawford S, Braveman N, Clarkson TW, McKinlay S, Bellinger DC. Blood lead level and dental caries in school-age children. *Environ Health Perspect* 2002;110:625-630.

Gennart JP, Bernard A, Lauwerys R. Assessment of thyroid, testes, kidney and autonomic nervous system function in lead-exposed workers. *Int Arch Occup Environ Health* 1992a;64:49-57.

Gennart JP, Buchet JP, Roels H, Ghyselen P, Ceulemans E, Lauwerys R. Fertility of male workers exposed to cadmium, lead or manganese. *Am J Epidemiol* 1992b;135:1208-1219.

Gerhardsson L, Nordberg GF. Lung cancer in smelter workers - interactions of metals as indicated by tissue levels. *Scand J Work Environ Health* 1993;19 Suppl 1:90-94.

Gerhardsson L, Chettle DR, Englyst V, Nordberg GF, Nyhlin H, Scott MC, Todd AC, Vesterberg O. Kidney effects in long term exposed lead smelter workers. *Br J Ind Med* 1992;49:186-192.

Gerhardsson L, Attewell R, Chettle DR, Englyst V, Lundström N-G, Nordberg GF, Nyhlin H, Scott MC, Todd AC. In-vivo measurements of lead in bone in long-term exposed lead smelter workers. *Arch Environ Health* 1993;48:147-156.

Gerhardsson L, Englyst V, Lundström NG, Nordberg G, Sandberg S, Steinvall F. Lead in tissues of deceased lead smelter workers. *J Trace Elem Med Biol* 1995a;9:136-143.

Gerhardsson L, Hagmar L, Rylander L, Skerfving S. Mortality and cancer incidence among secondary lead smelter workers. *Occup Environ Med* 1995b;52:667-672.

Gerhardsson L, Kazantzis G, Schütz A. Evaluation of selected publications on reference values for leas in blood. *Scand J Work Environ Health* 1996;22:325-331.

Gerhardsson L, Skerfving S, Oskarsson A. Effects of acid precipitation on the environment and on human health. In: PN Cheremisinoff, ed. *Health and toxicology. Advances in environmental control technology series*, 1997a, Chapter 15, pp. 355. ISBN 0-87201-238-7.

Gerhardsson L, Skerfving S, Schütz A. Heavy metal exposure in and around smelters. In: D Brune, G Gerhardsson, GW Crockford, D D'Auria, eds. *The workplace. Volume 1: Fundamentals of health, safety and welfare*. International Occupational Safety and Health Information Centre (CIS), International Labour Office, Geneva and Scandinavian Science Publisher As, Oslo 1997b, pp. 484-500. ISBN 82-91833-00-1.

Gerhardsson L, Börjesson J, Grubb A, Hultberg B, Mattsson S, Schütz A, Skerfving S. *In vivo* XRF as a means to evaluate the risk of kidney effects in lead and cadmium exposed smelter workers. *Appl Radiat Isot* 1998;49:711-712.

Gerhardsson L, Börjesson J, Mattsson S, Schütz A, Skerfving S. Chelated lead in relation to lead in bone and ALAD genotype. *Environ Res* 1999;80:389-398.

Gerhardsson L, Schütz A. Blyhalter i blod, jord och dricksvatten i ett blyexponerat område i Kosovo. Svenska Läkaresällskapets Riksstämma 28-30 november 2001. *Svenska Läkaresällskapets handlingar Hygiea* 2001;110:142. Abstract.

Gerhardsson L, Dahlin L, Knebel R, Schütz A. Blood lead concentration after a shotgun accident. *Environ Health Perspect* 2002;110:115-117.

Glenn BS, Stewart WF, Schwartz BS, Bressler J. Relation of alleles of the sodium-potassium adonisine triphosphatase alpha 2 gene with blood pressure and lead exposure. *Am J Epidemiol* 2001;153:537-545.

Glenn BS, Stewart WF, Links JM, Todd AC. Schwartz BS. The longitudinal association of lead with blood pressure. *Epidemiology* 2003;14:30-36.

Goldman RH, White R, Kales SN, Hu H. Lead poisoning from mobilization of bone stores during thyrotoxicosis. *Am J Ind Med* 1994;25:417-424.

Gomaa A, Hu H, Bellinger D, Schwartz J, Tsaih SW, Gonzalez-Cossio T, Schnaas L, Peterson K, Aro A, Hernandez-Avila M. Maternal bone lead as an independent risk factor for fetal neurotoxicity: A prospective study. *Pediatrics* 2002;110:110-118.

Gonzalez-Cossio T, Peterson KE, Sanin LH, Fishbein E, Palazuelos E, Aro A, Hernandez-Avila M, Hu H. Decrease in birth weight in relation to maternal bone-lead burden. *Pediatrics* 1997;100:856-862.

Goodman M, LaVerda N, Mandel J. Commentary on "A meta-analysis for neurobehavioural results due to occupational lead exposure with blood lead concentrations <70 μg/100 ml" by M. Meyer-Baron and A. Seeber. *Arch Toxicol* 2001;75:439-440.

Goodman M, LaVerda N, Clarke C, Foster ED, Iannuzzi J, Mandel J. Neurobehavioural testing in workers occupationally exposed to lead: systematic review and meta-analysis of publications. *Occup Environ Med* 2002;59:217-223.

Goodman M, LaVerda N, Clarke C, Foster ED, Iannuzzi J, Mandel J. Neurobehavioural testing in workers occupationally exposed to lead. Author´s reply. *Occup Environ Med* 2003;145:145-146.

Goodrum PE, Diamond GL, Hassett JM, Johnson DL. Monte Carlo modeling of childhood lead exposure: development of a probabilistic methodology for use with the USEPA IEUBK model for lead in children. *Hum Ecol Risk Assess* 1996;2:681-708.

Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, Richardson RJ. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. *Neurotoxicology* 1999;20:239-248.

Goyer RA. Toxic effets of metals. In: Klasse C, ed. *Casarett & Doull´s Ttoxicology: The basic science of poisons*. New Yrok: McGraw-Hill, 1996, pp 691-737.

Grandjean P. Effects on reserve capacity: significance for exposure limits. *Sci Total Environ* 1991;101:25-32.

Grandjean P, Nielsen GD, Jørgensen PJ, Hørder M. Reference intervals for trace elements in blood: significance of risk factors. *Scand J Clin Lab Invest* 1992;52:321-337.

Griffin S, Marcus A, Schulz T, Walker S. Calculating the interindividual geometric standard deviation for use in the integrated exposure uptake biokinetic model for lead in children. *Environ Health Perspect* 1999;107:481-487.

Gulson BL, Gillings BR. Lead exchange in teeth and bone—a pilot study using stable lead isotopes. *Environ Health Perspect* 1997;105:820-824.

Gulson BL, Mahaffey KR, Mizon KJ, Korsch MJ, Cameron MA, Vimpani G. Contribution of tissue lead to blood lead in adult female subjects based on stable lead isotope methods. *J Lab Clin Med* 1995;125:703-712.

Gulson BL, Mahaffey KR, Vidal M, Jameson CW, Law AJ, Mizon KJ, Smith AJ, Korsch MJ. Dietary lead intakes for mother/child pairs and relevance to pharmacokinetic models. *Environ Health Perspect* 1997a;105:1334-1342.

Gulson BL, Jameson CW, Mahaffey KR, Mizon KJ, Korsch MJ, Vimpani G. Pregnancy increases mobilization of lead from maternal skeleton. *J Lab Clin Med* 1997b;130:51-62.

Gulson L, Cameron MA, Smith AJ, Mizon KJ, Korsch MJ, Vimpani G, McMichael AJ, Pisaniello D, Jameson CW, Mahaffey KR. Blood lead-urine lead relationships in adults and children. *Environ Res* 1998a;78:152-160.

Gulson BL, Jameson CW, Mahaffey KR, Mizon KJ, Patison N, Law AJ, Korsch MJ, Salter MA. Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother. *Environ Health Perspect* 1998b;106:667-674.

Gulson BL, Mahaffey KR, Jameson CW, Patison N, Law AJ, Mizon KJ, Korsch MJ, Pederson D. Impact of diet on lead in blood and urine in female adults and relevance to mobilization of lead from bone stores. *Environ Health Perspect* 1999;107:257-263.

Gulson BL, Mizon KJ, Korsch MJ, Mahaffey KR, Pederson D. Limited seasonality effects on blood lead for a small cohort of female adults and children. *Sci Total Environ* 2000a;253:119-126.

Gulson BL, Mizon KJ, Palmer JM, Korsch MJ, Patison N, Jameson CW, Donelly JB. Urinary lead isotopes during pregnancy and postpartum indicate no preferential partitioning of endogenous lead into plasma. *J Lab Clin Med* 2000b;136:236-242.

Gulson BL, Mizon KJ, Korsch MJ, Mahaffey KR, Taylor AJ. Dietary intakes of selected elements from longitudinal 6-day duplicate diets for pregnant and nonpregnant subjects and elemental concentrations of breast milk and infant formula. *Environ Res* 2001;87:160-174.

Gulson BL, Mizon KJ, Korsch MJ, Palmer JM, Donnely JB. Mobilization of lead from human bone tissue during pregnancy and lactation—a summary of long-term research. *Sci Total Environ* 2003;303:79-104.

Gustavsson P, Plato N, Hallqvist J, Hogstedt C, Lewne M, Reuterwall C, Scheele P. A population-based case-referent study of myocardial infarction and occupational exposure to motor exhaust, other combustion products, organic solvents, lead, and dynamite. Stockholm Heart Epidemiology Program (SHEEP) Study Group. *Epidemiology* 2001;12:222-228.

Hagmar L, Bonassi S, Strömberg U, Mikoczy Z, Lando C, Hansteen I-L, Montagud AH, Knudsen L, Norppa H, Reuterwall C, Tinnerberg H, Brogger A, Forni A, Hogstedt B, Lambert B, Mitelman F, Nordenson I, Saomaa S, Skerfving S. Cancer predictive value of cytogenetic markers used in occupational health surveillance programs: a report from an ongoing study by the European Study Group on Cytogenetic Biomarkers and Health. *Mutat Res* 1998;405:171-178.

Hakim RB, Stewart WF, Canner JK, Tielsch JM. Occupationa lead exposure and strabismus in offspring: A case-control study. *Am J Epidemiol* 1991;133:351-356.

Hallén IP, Jorhem I, Lagerkvist BJ, Oskarsson A. Lead and cadmium levels human milk and blood. *Sci Total Environ* 1995;166:149-155.

Hanninen H, Aitio A, Kovala T, Luukkonen R, Matikainen E, Mannelin T, Erkkila J, Riihimaki V. Occupational exposure to lead and neuropsychological dysfunction. *Occup Environ Med* 1998;55:202-209.

Hartwig A. Role of DNA repair inhibition in lead- and cadmium-induced genotoxicity: A review. *Environ Health Perspect* 1994;102 Suppl 3:45-50.

Haynes EN, Kalkwarf HJ, Hornung R, Wenstrup R, Dietrich K, Lanphear BP. Vitamin D receptor Fok1 polymorphism and blood lead concentration in children. *Environ Health Perspec* 2003;111:1665-1669.

Hedmer M, Bergdahl I, Björk J, Gerhardsson L, Schütz A, Skerfving S, Strömberg U. Bly i plasma och helblod hos blyexponerade arbetare. Svenska Läkaresällskapets Riksstämma 28-30 november 2001. *Svenska Läkaresällskapets handlingar Hygiea* 2001;110:145. Abstract.

Hengstler JG, Bolm-Audorff U, Faldum A, Janssen K, Reifenrath M, Gotte W, Jung D, Mayer-Popken O, Fuchs J, Gebhard S, Bienfait HG, Schlink K, Dietrich C, Faust D, Epe B, Oesch F. Occupational exposure to heavy metals: DNA damage induction and DNA repair inhibition prove co-exposures to cadmium, cobalt and lead as more dangerous than hitherto expected. *Carcinogenesis* 2003;24:63-73.

Hense HW, Filipiak B, Keil U. The association of blood lead and blood pressure in population surveys. *Epidemiology* 1993;4:173-179.

Herber RFM. Review of trace elements concentrations in biological specimens according to the TRACY protocol. *Int Arch Occup Environ Health* 1999;72:279-283.

Hernandez-Avila M, Gonzalez-Cossio T, Palazuelos E, Romieu I, Aro A, Fischbein E, Peterson KE, Hu H. Dietary and environmental determinant of blood and bone lead levels in lactating postpartum women living in Mexico City. *Environ Health Perspect* 1996;104:1076-1082.

Hernandez-Avila M, Smith D, Meneses F, Sanin LH, Hu H. The influence of bone and blood lead on plasma lead levels in environmentally exposed adults. *Environ Health Perspect* 1998;106:473-477.

Hernandez-Avila M, Villalpando CG, Palazuelos E, Hu H, Villalpando ME, Martinez DR. Determinants of blood lead levels across the menopausal transition. *Arch Environ Health* 2000;55:355-360.

Hernandez-Avila M, Peterson KE, Gonzalez-Cossio T, Sanin LH, Aro A, Schnaas L, Hu H. Effect of maternal bone lead on length and head circumference of newborns and 1-month-old infants. *Arch Environ Health* 2002;57:482-488.

Hernandez-Avila M, Gonzalez-Cossio T, Hernandez-Avila JE, Romieu I, Peterson KE, Aro A, Palazuelos E, Hu H. Dietary Ca supplements to lower blood lead levels in lactating women: a randomized placebo-controlled trial. *Epidemiology* 2003;14:206-212.

Hertz-Picciotto I. The evidence that lead increases the risk for spontaneous abortion. *Am J Ind Med* 2000;38:300-309.

Hertz-Picciotto I, Croft J. Review of the relation between blood lead and blood pressure. *Epidemiol Rev* 1993;15:352-373.

Higashikawa K, Zhang ZW, Shimbo S, Moon CS, Watanabe T, Nakatsuka H, Matsuda-Inoguchi N, Ikeda M. Correlation between concentration in urine and in blood of cadmium and lead among women in Asia. *Sci Tot Environ* 2000;246:97-107.

Hirata M, Kosaka H. Effects of lead exposure on neurophysiological parameters. *Environ Res* 1993;63:60-69.

Hirata M, Yoshida T, Miyajima K, Kosaka H, Tabuchi T. Correlation between lead in plasma and other indicators of lead exposure among lead-exposed workers. *Int Arch Occup Environ Health* 1995;68:58-63.

Hodgkins DG, Robins TG, Hinkamp DL, Schork MA, Krebs WH. A longitudinal study of the relation of lead in blood to lead in air concentrations among battery workers. *Brit J Ind Med* 1992;49:241-248.

Hoppin JA, Aro AC, Williams PL, Hu H, Ryan PB. Validation of K-XRF bone lead measurement in young adults. *Environ Health Perspect* 1995;103:78-83.

Hoppin JA, Aro A, Hu H, Ryan PB. In vivo bone lead measurement in suburban teenagers. *Pediatrics* 1997;100:365-370.

Hoppin JA, Aro A, Hu H, Ryan PB. Measurement variability associated with KXRF bone lead measurement in young adults. *Environ Health Perspect* 2000;108:239-242.

Horiguchi S, Kiyota I, Endo G, Teramoto K, Shinagawa K, Wakitani F, Konishi Y, Kiyota A, Ota A, Tanaka H. Serum immunoglobulin and complement C3 levels in workers exposed to lead. *Osaka City Med J* 1992a;38:139-143.

Horiguchi S, Endo G, Kiyota I, Teramoto K, Shinagawa K, Wakitani F, Tanaka H, Konishi Y, Kiyota A, Ota A. Frequency of cold infections in workers at a lead refinery. *Osaka City Med J* 1992b;38:79-81.

Hovatta O, Venäläinen ER, Kuusimäki L, Heikkilä J, Hirvi T, Reima I. Aluminium, lead and cadmium concentration in seminal plasma and spermatozoa, and semen quality in Finnish men. *Human Reprod* 1998;13:115-119.

Hsieh LL, Liou SH, Chen YH, Tsai LC, Yang T, Wu TN. Association between aminolevulinate dehydrogenase genotype and blood lead levels in Taiwan. *J Occup Environ Med* 2000;42:151-155.

Hu H. A 50-year follow-up of childhood plumbism. Hypertension renal function, and haemoglobin levels among survivors. *Am J Dis Child* 1991a;145:681-687.

Hu H. Knowledge of diagnosis and reproductive history among survivors of childhood plumbism. *Am J Public Health* 1991b;81:1070-1072.

Hu H, Hernandez-Avil M. Invited commentary: lead, bones, women, and pregnancy – the poison within. *Am J Epidemiol* 2002;156:1088-1091.

Hu H, Pepper L, Goldman R. Effect of repeated occupational exposure to lead, cessation of exposure, and chelation on levels of lead in bone. *Am J Ind Med* 1991;20:723-735.

Hu H, Watanabe H, Payton M, Korrick S, Rotnizky A. The relationship between bone lead and haemoglobin *JAMA* 1994;272:1512-1517.

Hu H, Aro A, Payton M, Korrick S, Sparrow D, Weiss ST, Rotnitzky A. The relationship of bone and blood lead to hypertension. The Normative Aging Study. *JAMA* 1996a;17:1171-1176.

Hu H, Payton M, Korrick S, Aro A, Sparrow D, Weiss ST, Rotnizky A. Determinants of bone and blood lead levels among community-exposed middle-aged to elderly men. The normative aging study. *Am J Epidemiol* 1996b;144:749-759.

Hu H, Hashimoto D, Besser M. Levels of lead in blood and bone of women giving birth in a Boston hospital. *Arch Environ Health* 1996c;51:52-58.

Hu H, Rabinowitz M, Smith D. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. *Environ Health Perspect* 1998;106:1-8.

Hu H, Wu MT, Cheng Y, Sparrow D, Weiss S, Kelsey K. The delta-aminolevulinic acid dehydratase (ALAD) polymorphism and bone and blood lead levels in community-exposed men: the Normative Aging Study. *Environ Health Perspect* 2001;109:827-832.

Hunaiti AA, Soud M. Effect of lead concentration on the level of glutathione, glutathione S-transferase, reductase and peroxidase in human blood. *Sci Total Environ* 2000;248:45-50.

Hwang KY, Schwartz BS, Lee BK, Strickland PT, Todd AC, Bressler JP. Associations of lead exposure and dose measures with erythrocyte protein kinase C activity in 212 current Korean lead workers. *Toxicol Sci* 2001;62:280-288.

Hwang KY, Lee BK, Bressler JP, Bolla KI, Stewart WF, Schwartz BS. Protein kinase C activity and the relations between blood lead and neurobehavioral function in lead workers. *Environ Health Perspect* 2002;110:133-138.

IARC. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Suppl. 7*. Lyon: International Agency for Research on Cancer 1987;Suppl. 7:230-232.

IARC. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. *IARC Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans, Vol 58*. Lyon: International Agency for Research on Cancer 1993;58.

Ichiba M, Tomokuni K, Mori K. Erythrocyte nucleotides in lead workers. *Int Arch Occup Environ Health* 1992;63:419-421.

ICRP. International Commission on Radiological Protection. *Age-dependent doses to members of the public from intake of radionucleides*. Oxford: Pergamon Press 1993, ICPR Publication 56, Part 2.

Ikeda M, Zhang ZW, Shimbo S, Watanabe T, Nakatsuka H, Moon CS, Matsuda-Inoguchi N, Higashikawa K. Exposure of women in general populations to lead via food and air in east and southeast Asia. *Am J Ind Med* 2000a;38:271-280.

Ikeda M, Zhang ZW, Shimbo S, Watanabe T, Nakatsuka H, Moon CS, Matsuda-Inoguchi N, Higashikawa K. Urban population exposure to lead and cadmium in east and southeast Asia. *Sci Tot Environ* 2000b;249:373-384.

Irgens A, Kruger K, Skorve AH, Irgens LM. Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. *Am J Ind Med* 1998;34:431-437.

Jaffe EK, Bagla S, Michini PA. Reevaluation of a sensitive indicator of early lead exposure. Measurement of porphobilinigen synthase in blood. *Biol Trace Elem Res* 1991;28:222-231.

Jaffe EK, Volin M, Bronson-Mullins CR, Dunbrack RL Jr, Kervinen J, Martins J, Quinlan JF, Sazinsky MH, Steinhouse EM, Yeung AT. An artificial gene for human prophobilinogen synthesase allows comparison of an allelic variation implicated in susceptibility to lead poisoning. *J Biol Chem* 2000;275:2619-2626.

Jaffe EK, Martins J, Li J, Kervinen J, Dunbrack RL Jr. The molecular mechanism of lead inhibition of human porphobilogene synthesase. *J Biol Chem* 2001;276:1531-1537.

Japan Society for Occupational Health. Recommended occupational exposure limits (2002-2003). *J Occup Health* 2002;44:267-282.

Jarosinska D, Rogan WJ. Preventing lead poisoning in children: can the US experience inform other countries? The case of Poland. *Centr Eur J Publ Health* 2003;11:192-197.

Järvholm B (ed). *Arbetsliv och hälsa – en kartläggning*. Arbetarskyddsstyrelsen. Arbetslivs-institutet. Rådet för Arbetslivsforskning. AB Boktryck, Helsingborg, 1996, p 29. ISBN 91-7045-366-7.

JEFCA. Joint FAO/WHO Expert Committee on Food Additives. *Lead*. Report TRS 896-JEFCA 53/81, 1999. www.inchem.org/documents/jefca.

Kaiser R, Henderson AK, Daley WR, Naughton M, Khan MH, Rahman M, Kieszak S, Rubin CH. Blood lead levels of primary school children in Dhaka, Bangladesh. *Environ Health Perspect* 2001;109:563-566.

Kajiyama K, Doi R, Sawada J, Hashimoto K, Hazama T, Nakata S, Hirata M, Yoshida T, Miyajama K. Significance of subclinical entrapment of nerves in lead neuropathy. *Environ Res* 1993;60:248-253.

Kamel F, Umbach DM, Munsat TL, Shefner JM, Howard H, Sandler DP. Lead exposure and amyotrophic lateral sclerosis. *Epidemiology* 2002;13:311-319.

Kamel F, Umbach DM, Lehman TA, Park LP, Munsat TL, Shefner JM, Sandler DP, Hu H, Taylor JA. Amyotrophic lateral sclerosis, lead and genetic susceptibility: Polymorphism in the delta-aminolevulinic acid dehydratase and vitamin D receptor genes. *Environ Health Perspect* 2003;111:1335-1339.

Kaufmann RB, Clouse TL, Olson DR, Matte TD. Elevated blood lead levels and blood lead screening among US children aged one to five years: 1988-94. *Pediatrics* 2000;106:E79.

Kaufmann RB, Staes CJ, Matte TD. Deaths related to lead poisoning in the United States 1979-98. *Environ Res* 2003;91:78-84.

Kelada SN, Shelton E, Kaufman RB, Khoury MJ. Delta-aminolevulinic acid dehydratase genotype and lead toxicity: A HuGE Review. *Am J Epidemiol* 2001;154:1-13.

KemI. *KIFS 1994:12 and 2001:3 om klassificering och märkning av kemiska produkter. Annex 5*. National Swedish Chemical Inspectorate, Solna, 2001. Eupean Council Directive 67/548/EEG (Annex I).

Kentner M, Fisher T. Lead exposure in starter battery production: investigation of the correlation between air lead and blood lead levels. *Int Arch Occup Environ Health* 1994;66:223-228.

Khalil-Manesh F, Gonick HC, Cohen AH, Alinovi R, Bergmaschi E, Mutti A, Rosen VJ. Experimental model of lead nephropathy. I. Continuous high-dose lead administration. *Kidney Int* 1992a;41:1192-1203.

Khalil-Manesh F, Gonick HC, Cohen AH, Bergmaschi E, Mutti A. Experimental model of lead nephropathy. II. Effect of removal from lead exposure and chelation treatment with dimethylsuccinic acid (DMSA). *Environ Res* 1992b;58:35-54.

Kim Y, Harada K, Ohmori S, Lee B-K, Miura H, Uedad A. Evaluation of lead exposure in workers at a lead-acid battery factory in Korea: with focus on activity of erythrocyte pyrimidine 5´-nucleotidase (P5N). *Occup Environ Med* 1995a;52:484-488.

Kim R, Hu H, Rotnitzky A, Bellinger D, Needleman H. A longitudinal study of chronic lead exposure and physical growth in Boston children. *Environ Health Perspect* 1995b;103:952-957.

Kim R, Hu H, Rotnizky A, Bellinger D, Needleman H. Longitudinal relationship between dentin lead levels in childhood and bone lead levels in young adulthood. *Arch Environ Health* 1996a;51:375-382.

Kim R, Rotnizky A, Sparrow D, Weiss ST, Wager C, Hu H. A longitudinal study of low-level lead exposure and impairment of renal function. The Normative Aginge Study. *JAMA* 1996b;275:1177-1181.

Kim R, Landrigan C, Landrigan C, Mossman P, Sparrow D, Hu H. Age and secular trends in bone lead levels in middle-aged and elderly men: three-year longitudinal follow-up in the Normative Aging Study. *Am J Epidemio*l 1997;145:586-591.

Koh D, Ng V, Chua LH, Yang Y, Ong HY, Chia SE. Can salivary lead be used for biological monitoring of lead exposed individuals? *Occup Environ Med* 2003;60:696-698.

Koller K, Brown T, Spurgeon A, Levy L. Recent developments in low-level lead exposure and intellectual impairment in children. *Environ Health Perspec* 2004;112:987-994.

Korrick SA, Hunter DJ, Rotnizky A, Hu H, Speizer FE. Lead and hypertension in a sample of middle-aged women. *Am J Public Health* 1999;89:330-335.

Korrick SA, Schwartz J, Tsaih SW, Hunter DJ, Aro A, Rosner B, Speizer FE. Correlates of bone and blood lead levels among middle-aged and elderly women. *Am J Epidemiol* 2002;156:335-343.

Kosnett MJ, Becker CE, Osterloh JD, Kelly TJ, Pasta DJ. Factors influencing bone lead concentration in a suburban community assessed by noninvasive K x-ray fluorescence. *JAMA* 1994;271:197-203

Kovala T, Matiainen E, Mannelin T, Erkikila J, Riihimäki V, Hänninen H, Aitio A. Effect of low level exposure to lead and neurophysiological functions among lead battery workers. *Occup Environ Med* 1997;54:487-493.

Kristensen P, Andersen A. A cohort study on cancer incidence in offspring of male printing workers. *Epidemiology* 1992;3:6-10.

Kristensen P, Irgens LM, Daltveit AK, Andersen A. Perinatal outcome among children of men exposed to lead and organic solvents in the printing industry. *Am J Epidemiol* 1993;137:134-144.

Kumar BD, Krishnanaswamy K. Detection of occupational lead nephropathy using early renal markers. *J Toxicol Clin Toxicol* 1995;33:331-335.

Kuo HW, Wang CS, Lai JS. Semen quality in workers with long-term lead exposure: a preliminary study in Taiwan. *Sci Tot Environ* 1997;204:289-292.

Lagerkvist BJ, Söderberg HA, Nordberg GF, Eksrydh S, Englyst V. Biological monitoring of arsenic, lead and cadmium in occupationally and environmentally exposed pregnant women. *Scand J Work Environ Health* 1993;19 Suppl 1:50-53.

Lagerkvist BJ, Ekesrydh S, Englyst V, Nordberg GF, Söderberg HA, Wiklund DE. Increased blood lead and decreased calcium levels during pregnancy: a prospective study of Swedish women living near a smelter. *Am J Public Health* 1996;86:1247-1252.

Lai JS, Wu TN, Liou SH, Shen CY, Guu CF, Ko KN, Chi HY, Chang PY. A study of the relationships between ambient lead and blood lead among lead battery workers. *Int Arch Occup Environ Health* 1997;69:295-300.

Landrigan PJ, Boffetta P, Apostoli P. The reproductive toxicity and carcinogenicity of lead: a critical review. *Am J Ind Med* 2000;38:231-243.

Lanphear BP, Dietrich KN, Auinger P, Cox C. Cognitive deficits associated with blood lead concentrations <10 microg/dL in US children and adolescents. *Publ Health Rep* 2000;115:521-529.

Latorre FG, Hernandez-Avila M, Orozco JT, Medicina CA, Aro A, Palazuelos E, Hu H. Relationship of blood and bone lead to menopause and bone mineral density among middle-age women in Mexico City. *Environ Health Perspect* 2003;111:631-636.

Laudanski T, Sipowicz M, Modzelewski P, Bolinski J, Szamatowicz J, Razniewska G, Akerlund M. Influence of high lead and cadmium soil content on human reproductive outcome. *Int J Gynaecol Obstet* 1991;36:309-315.

Lee BK, Schwartz BS, Stewart W, Ahn KD. Provocative chelation with DMSA and EDTA: evidence for differential access to lead storage sites. *Occup Environ Med* 1995;52:13-19.

Lee BK, Ahn KD, Lee SS, Lee GS, Kom YB, Schwartz BS. A comparison of different lead biomarkers in their associations with lead-related symptoms. *Int Arch Occup Environ Health* 2000;73:298-304.

Lee BK, Lee GS, Stewart WF, Ahn KD, Simon D, Kelsey KT, Todd AC, Schwartz BS. Associations of blood pressure and hypertension with lead dose measures and polymorphisms in the vitamin D receptor and delta-aminolevulinic acid dehydratase genes. *Environ Health Perspect* 2001a;109:383-389.

Lee SS, Lee BK, Lee GS, Stewart WF, Simon D, Kelsey K, Todd AC, Schwartz BS. Associations of lead biomarkers and delta-aminolevulinic acid dehydratase and vitamin D receptor genotypes with hematopoietic outcomes in Korean lead workers. *Scand J Work Environ Health* 2001b;27:402-411.

Leggett RW. An age-specific kinetic model of lead metabolism in humans. *Environ Health Perspect* 1993;7 Suppl 101:598-616.

Lerda D. Study of sperm characteristics in persons occupationally exposed to lead. *Am J Ind Med* 1992;22:567-571.

Li PJ, Sheng YZ, Wang QY, Gu LY, Wang YL. Transfer of lead via placenta and breast milk in human. *Biomed Environ Sci* 2000;13:85-89.

Lidsky TI, Schneider JS. Lead neurotoxicity in children: basic mechanisms and clinical correlates. *Brain* 2003;126:5-19.

Lin JL, Yeh KH, Tseng HC, Chen WY, Lai HH, Lin YC and the Green Cross Health Service Associaiton Study Group. Urinary N-acetyl-glucosaminidase excretion and environmental lead exposure. *Am J Nephrol* 1993;13:442-447.

Lin JL, Lim PS. Does lead play a role in the development of renal insufficiency in some patients with essential hypertension. *J Human Hypertension* 1994;8:495-500.

Lin JL, Huang PT. Body lead stores and urate excretion in men with chronic renal disease. *J Rheumatol* 1994;21:705-709.

Lin S, Hwang SA, Marshall EG, Stone R, Chen J. Fertility rates among lead workers and professional bus drivers. *Ann Epidemiol* 1996;6:201-208.

Lin JL, Ho HH, Yu CC. Chelation therapy for patients with elevated body lead burden and progressive renal insufficiency. *Ann Intern Med* 1999;130:7-13.

Lin JL, Yu CC, Lin-Tan DT, Ho HH. Lead chelation therapy and urate excretion in patients with chronic renal disease and gout. *Kidney International* 2001a;60:266-271.

Lin JL, Tan DT, Hsu KH, Yu CC. Environmental lead exposure and progressive renal insufficiency. *Arch Intern Med* 2001b;161:264-271.

Lin JL, Lin-Tan DT, Hsu KH, Yu CC. Environmental lead exposure and progression of chronic renal diseases in patient without diabetes. *N Engl J Med* 2003;348:277-286.

Lin C, Kim R, Tsaih SW, Sparrow D, Hu H. Determinants of bone and blood lead levels among minorities living in the Boston area. *Environ Health Perspec* 2004;112:1147-1151.

Lindgren KN, Masten VL, Ford DP, Bleeker ML. Relation of cumulative exposure to inorganic lead and neuropsychological performance. *Occup Environ Med* 1996;53:472-477.

Links JM, Schwartz BS, Simon D, Bandeen-Roche K, Stewart WF. Characterization of toxicokinetics and toxicodynamics with linear systems theory: Application to lead-associated cognitive decline. *Environ Health Perspect* 2001;109:361-368.

Linz DH, Barrett ET Jr, Pfaumer JE, Keith RE. Neuropsychologic and postural sway improvement after Ca++-EDTA chelation for mild lead intoxication. *J Occup Med* 1992;34:638-641.

Liu X, Dietrich KN, Radcliffe J, Ragan NB, Rhoads GG, Rogan WJ. Do children with falling blood lead levels have improved cognition? *Pediatrics* 2002;110:787-791.

Loghman-Adham M. Renal effects of environmental and occupational lead exposure. *Environ Health Perspect* 1997;105:928-938.

Lucchini R, Albini E, Cortesi I, Placidi D, Bergamaschi E, Traversa F, Alessio L. Assessment of neurobehavioral performance as a function of current and cumulative occupational lead exposure. *Neurotoxicology* 2000;21:805-812.

Lundh T, Bergdahl I, Hallmans G, Jansson J-H, Stegmayr B, Wennberg M, Skerfving S. *Spårelement i blodkroppar från väster- och norrbottningar 1990-99. Slutrapport för projekt 215 0105 inom Nationella Miljöövervakningen*. Rapport 021209 från Yrkes- och miljömedicin, Universitetssjukhuset i Lund, 2002.

Lundström NG, Nordberg G, Englyst V, Gerhardsson L, Hagmar L, Jin T, Rylander L, Walla S. Cumulative lead exposure in relation to mortality and lung cancer morbiditiy in a cohort of primary smelter workers. *Scand J Work Environ Health* 1997;23:24-30.

Lustberg M, Silbergeld E. Blood lead levels and mortality. *Arch Intern Med* 2002;162:2443-2448.

Lutz E, Lind B, Herin P, Krakau I, Bui TH, Vahter M. Conctrations of mercury, cadmium and lead in brain and kidney of second trimester fetuses and infants. *J Trace Elem Med Biol* 1996;10:61-67.

Maheswaren R, Gill JS, Beevers DG. Blood pressure and industrial lead exposure. *Am J Epidemiol* 1993;137:645-653.

Maizlish NA, Parra G, Feo O. Neurobehavioural evaluation of Venezuelan workers exposed to inorganic lead. *Occup Environ Med* 1995;52:408-414.

Manton WI, Angle CR, Stanek KL, Reese YR, Kuehnemann TJ. Acquisition and retention of lead by young children. *Environ Res* 2000;82:60-80.

Manzo L, Artigas F, Martinez E, Mutti A, Bergamaschi E, Nicotera P, Tonini M, Candura SM, Ray DE, Costa LG. Biochemical markers of neurotoxicity. A review of mechanistic studies and applications. *Hum Exp Toxicol* 1996;15 Suppl 1:S20-35.

Markowitz SB, Nunez CM, Klitzman S, Munshi AA, Kim WS, Eisinger J, Landrigan PJ. Lead poisoning due to Hai Ge Fen. The porphyrin content of individual erythrocytes. *JAMA* 1994;271:932-934.

Masci O, Carelli G, Vinci F, Castellino N. Blood lead concentration and biological effects in workers exposed to very low lead levels. *JOEM* 1998;40:886-894.

Mathee A, von Schirnding YER, Levin J, Ismail A, Huntley R, Cantrell A. A survey of blood lead levels among young Johannesburg school children. *Environ Res* 2002;90:181-184.

Mattsson S, Ahlgren L, Christoffersson JO, Nilsson U, Börjesson J. *In vivo* measurements of elemental lead and cadmium in occupational and environmental studies. In: Skerfving S, ed. *Toxicology of metals. A symposium in memory of Andrejs Schütz,* 2002.

McCabe MJ. Mechanisms and consequences of immunomodulation by lead. In: Dean JH, Luster MI, Munson AE, Kimber I eds. *Immunotoxicity and immunopharmacology*, 2nd ed. New York: Raven Press 1994, pp 143-162.

McDonald JA, Potter NU. Lead´s legacy. Early and late mortality of 454 lead-poisoned children. *Arch Environ Health* 1996;51:116-121.

Meyer PA, Hoelscher B, Frye C, Becker K, Wichmann HE, Heinrich J. Temporal changes in blood lead levels of children in east Germany. *Int J Hyg Environ Health* 2003a;206:181-192.

Meyer PA, McGeehin MA, Falk H. A global approach to childhood lead poisoning prevention. *Int J Hyg Envrion Health* 2003b;206:363-369.

Meyer-Baron M, Seeber A. A meta-analysis for neurobehavioural test results due to occupational lead exposure with blood lead concentrations <70 µg/100 ml. *Arch Toxicol* 2000;73:510-518.

Micciolo R, Canal L, Maranelli G, Apostoli P. Non-occupational lead exposure and hypertension in northern Italy. *Int J Epidemiol* 1994;23:312-320.

Michaels D, Zolroth S, Stern F. Does low-level lead exposure increase risk of death? *Int J Epidemiol* 1991;20:978-983.

Mielke HW, Reagan PL. Soil is an important pathway of human lead exposure. *Environ Health Perspect* 1998;106, Suppl 1:217-229.

Min YI, Correra-Villasenor A, Stewart PA. Parental occupational lead exposure and low birth weight. *Am J Ind Med* 1996;30:569-578.

Ministry of the Environment. *Förordning om miljökvalitetsnormer för utomhusluft*. SFS 2001:527. Stockholm, 2001.

Mitchell CS, Shear MS, Bolla KI, Schwartz BS. Clinical evaluation of 58 organolead manufacturing workers. *JOEM* 1996;38:372-378.

Moel DI, Sachs HK. Renal function 17 to 23 years after chelation therapy for childhood plumbism. *Kidney Int* 1992;42:1226-1231.

Morita Y, Araki S, Sakai T, Araki T, Masuyama Y. Determination of delta-aminolevulinic acid in plasma using high-performance liquid chromatography: a sensitive indicator of lead effects. *Ind Health* 1994;32:85-96.

Morita Y, Sakai T, Araki S, Araki T, Masuyama Y. Nicotinamide adenine dinucleotide synthetase activity in erythrocytes as a toll for the biological monitoring of lead exposure. *Int Arch Occup Environ Health* 1997;70:195-198.

Moss ME, Lanphear BP, Auinger P. Association of dental caries and blood lead levels. *JAMA* 1999;281:2294-2298.

Mulrow PJ. *Hypertension - A worldwide epidemic*. American Heart Association, Council of High Blood Pressure Research, Dallas, TEX, 1999.

Muntner P, He J, Vupputuri S, Coresh J, Batuman V. Blood lead and chronic kidney disease in the general United States population: Results form NHANES III. *Kidney International* 2003;63:1044-1050.

Murata K, Araki S. Autonomic nervous system dysfunction in workers exposed to lead, zinc, and copper in relation to peripheral nerve conduction: A study of R-R interval variability. *Am J Ind Med* 1991;20:663-671.

Murata K, Araki S, Yokoyama K, Uchida E, Fujimura Y. Assessment of central, peripheral, and autonomic nervous system functions in lead workers: neurophysiological studies. *Environ Res* 1993;61:323-336.

Murata K, Araki S, Yokoyama K, Nomiyama K, Nomiyama H, Tao YX, Liu SJ. Autonomic and central nervous system effects of lead in female glass workers. *Am J Ind Med* 1995;28:233-244.

Murata K, Sakai T, Morita Y, Iwata T, Dakeishi M. Critical dose of lead affecting delta-aminolevulinic acid levels. *J Occup Health* 2003;45:209-214.

Murphy MJ, Graziano JH, Popovac D, Kline JK, Mehmeti A, Factor-Litvak P, Ahmedi G, Shrout P, Rajovic B, Nenezic DU. Past pregnancy outcomes among women living in the vicinity of a lead smelter in Kosovo, Yugoslavia. *Am J Public Health* 1990;80:33-35.

Møller L, Kristensen TS. Blood lead as a cardiovascular risk factor. *Am J Epidemiol* 1992;136:1091-1100.

Namihira D, Saldivar L, Pustilnik N, Carreón GJ, Salinas ME. Lead in human blood and milk from nursing women living near a smelter in Mexico City. *J Toxicol Environ Health* 1993;38:225-232.

Nash D, Magder L, Lustberg M, Sherwin RW, Rubin RJ, Kaufmann RB, Silbergeld EK. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. *JAMA* 2003;289:1523-1532.

National Swedish Food Agency. *Livsmedelsverkets föreskrifter om drickvatten*. SLVFS 2001:30. Uppsala, 2001.

Nawrot TS, Thijs L, Den Hond EM, Roels HA, Staessen JA. An epidemiological re-appraisal of the association between blood pressure and blood lead: a meta-analysis. *J Hum Hypertens* 2002;16:123-131.

Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. *JAMA* 1996;7:363-369.

Needleman HL, McFarland C, Ness RB, Feinberg SE, Tobin MJ. Bone lead levels in adjudicated delinquents. A case control study. *Neurotoxicol Teratol* 2002;24:211-217.

Ng TP, Goh HH, Ng YL, Ong HY, Ong CN, Chia KS, Chia SE, Jayaratnam J. Male endocrine functions in workers with moderate exposure to lead. *Brit J Ind Med* 1991;48:485-491.

Nielsen JB, Grandjean P, Jorgensen PJ. Predictors of blood lead concentrations in the lead-free gasoline era. *Scand J Work Environ Health* 1998;24:153-156.

Nielsen U, Kamp JJ, Grandjean P, White RF. Environmental lead exposure and neuro-developmental outcome in Danish preschool children (Commntary). *Neurotoxicology* 2000;21:896-897.

Nilsson K. *Blyexponering från helkristall (Lead exposure from crystal). Valfritt moment - vetenskapligt arbete avseende T10*. Department of Occupational and Environmental Medicine, University Hospital, Lund, Sweden, 2002. In Swedish.

Nilsson T. *Bestämning av trafikrelaterade PM10-bidrag i urban miljö (Determination of traffic-related PM10 contributions in urban environment)*. Department of Nuclear Physics, Lund University. LUTFD2(TFKF-5048)/1-44 (2003). In Swedish.

Nilsson U, Skerfving S. In vivo X-ray fluorescence measurements of cadmium and lead. *Scand J Work Environ Health* 1993;19 Suppl 1:54-58.

Nilsson U, Attewell R, Christoffersson J-O, Schütz A, Ahlgren L, Skerfving S, Mattsson S. Kinetics of lead in bone and blood after end of occupational exposure. *Pharmacol Toxicol* 1991;68:477-484.

Nolan CV, Shaikh ZA. Lead nephrotoxicity and associated disorders: biochemical mechanisms. *Toxicology* 1992;73:593-596.

Nordberg M, Winblad B, Fratiglioni L, Basun H. Lead concentrations in elderly urban people related to blood pressure and mental performance: Results from a population-based study. *Am J Ind Med* 2000;38:290-294.

Norwegian Directorate for the Labour Inspectorate. *Administrative normer for forurensning i arbeidsatmosfaere, 2003*. Veiledning. Oslo, 2003.

Nuyts GD, Daelemans RA, Jorens PG, Elseviers MM, Van de Vyver FL, De Broe ME. Does lead play a role in the development of chronic renal disease. *Nephrol Dial Tranplant* 1991;6:307-315.

Odland JO, Nieboer E, Romanova N, Thomassen Y, Lund E. Blood lead and cadmium and birth weight among sub-arctic and arctic populations of Norway and Russia. *Acta Obstet Gynecol Scand* 1999;78:852-860.

O´Flaherty EJ. Physiologically based models for bone-seeking elements. IV: Kinetics of lead disposition in humans. *Toxicol Appl Pharmacol* 1993;118:16-29.

O´Flaherty EJ. Physiologically based models for bone-seeking elements. V. Lead absorption and disposition in childhood. *Toxicol Appl Pharmacol* 1995;131:297-308.

O'Flaherty EJ. A physiologically based kinetic model for lead in children and adults. *Environ Health Perspect Suppl* 1998;106:1495-1503.

Ojajärvi IA, Partanen TJ, Ahlbom A, Boffetta P, Haukulinen T, Jourenkova N, Kauppinen TP, Kogevinas M, Porta M, Vainio HU, Weiderpass E, Wesseling CH. Occupational exposures and pancreatic cancer: a meta-analysis. *Occup Environ Med* 2000;57:316-324.

Olivieria S, Aro A, Sparrow D, Hu H. Season modifies the relationship between bone and blood lead levels: the Normative Aging Study. *Arch Environ Health* 2002;57:466-472.

Olshan AF, Teschke K, Baird P. Birth defects among offspring of firemen. *Am J Epidemiol* 1990;131:312-321.

Olsson M, Gerhardsson L, Jensen A, Börjesson J, Schütz A, Mattsson S, Skerfving S. Lead accumulation in highly exposed smelter workers. *Ann N Y Acad Sci* 2000;904:280-283.

Omokhidion FO, Crockford GW. Lead in sweat and its relationship to salivary and urinary lead levels. *Sci Tot Environ* 1991;103:113-122.

Ong CN, Chia SE, Foo SC, Ong HY, Tsakok M, Liouw P. Concentrations of heavy metal in maternal and umbilical cord blood. *Biometals* 1993;6:61-66.

Oskarsson A, Palminger Hallén I, Sundberg J. Exposure to toxic elements *via* breast milk. *Analyst* 1995;120:765-770.

Osman K, Zejda JE, Schütz A, Mielzynska D, Elinder CG, Vahter M. Exposure to lead and other metals in children from Katowice district, Poland. *Int Arch Occup Environ Health* 1998a;71:180-186.

Osman K, Schütz A, Åkesson B, Maciag A, Vahter M. Interactions between essential and toxic elements in lead exposed children in Katowice, Poland. *Clin Biochem* 1998b;31:657-665.

Osman K, Pawlas K, Schütz A, Gazdzik M, Sokal JA, Vahter M. Lead exposure and hearing effects in children in Katowice, Poland. *Environ Res* 1999a;80:1-8.

Osman K, Elinder G, Schütz A, Grubb A. Biomarkers of nephrotoxicity in children environmentally exposed to lead in Poland. *J Environ Med* 1999b;1:33-38.

Osman K, Åkesson A, Berglund M, Bremme K, Schütz A, Ask K, Vahter M. Toxic and essential elements in placentas of Swedish women. *Clin Biochem* 2000;33:131-138.

Osterloh JD, Clark OH. Effects of hyperparathyroidism on blood lead concentrations in man. *Environ Res* 1993;62:1-6.

Osterloh JD, Kelly TJ. Study of the effect of lactational bone loss on blood lead concentrations in humans. *Environ Health Perspect* 1999;107:187-194.

Otto DA, Fox DA. Auditory and visual dysfunction following lead exposure. *Neurotoxicology* 1993;14:191-207.

Österberg K, Börjesson J, Gerhardsson L, Schütz A, Skerfving S. A neurobehavioural study of long-term occupational inorganic lead exposure. *Sci Tot Environ* 1997;201:39-51.

Pashal DC, Ting BG, Morrow JC, Pirkle JL, Jackson RJ, Sampson EJ, Miller DT, Caldwell KL. Trace metals in urine of United States residents: Reference range concentrations. *Environ Res* 1998;76:53-59.

Payton M, Hu H, Sparrow D, Young JB, Landsberg L, Weiss ST. Relation between blood lead and urinary biogenic amines in community-exposed men. *Am J Epidemiol* 1993;138:815-825.

Payton M, Hu H, Sparrow D, Weiss ST. Low-level lead exposure and renal function in the normative aging study. *Am J Epidemiol* 1994;140:821-828.

Payton M, Riggs KM , Spiro A, Weiss ST, Hu H. Relation of bone and blood lead to cognitive function: the VA Normative Aging Study. *Neurotoxicol Teratol* 1998;20:19-27.

Perneger TV, Nieto FJ, Wheltoin PK, Klag MJ, Comstock GW, Szklo M. A prospective study of blood pressure and serum creatinine. *JAMA* 1993;269:488-493.

Pfister E, Böckelmann I, Brosz M, Ferl T, Winter CG. Ermittlung neurotoxischer Effekte infolge langjähriger Bleiexposition in der Kufpferindustrie Sachsen-Anhalts anhand psychometrischer Leistungsdaten. *Zbl Arbeitsmed* 1994;44:422-432.

Pfister E, Böckelmann I, Darius S, Wurthmann C. Einbeziehung psychopathologischer Verfahren zur Objektivierung von neurotoxischen Früeffekten durch Blei und Lösemittelgemische. *Fortschr Neurol Psychiatr* 1999;67:435-440.

Pierre F, Vallayer C, Baruthio F, Peltier A, Pale S, Rouyer J, Goutet P, Aubrège B, Lecossois C, Guillemin C, Elcabache J-M, Verelle B, Fabries J-F. Specific relationship between blood lead and air lead in the crystal industry. *Int Arch Occup Environ Health* 2002;75:217-223.

PIMs. Poison information monographs. *Lead, inorganic*. 1994. www.inchem.org/documents.

Pinkerton LE, Biagnini RE, Ward EM, Hull R, Deddens JA, Boeniger MF, Schnorr TM, MacKenzie BA, Luster MI. Immunologic findings among lead-exposed workers. *Am J Ind Med* 1998;33:400-408.

Pires JB, Bezerra FF, Laboissiere FP, Miekeley N, Donangelo CM. Lead levels in erythrocytes and biomarkers of bone turnover in pregnant and lactating women with marginal calcium intakes. *Nutr Res* 2001;21:831-841.

Pirkle JL, Kaufmann RB, Brody DJ, Hickman T, Gunter EW, Paschal DC. Exposure of the U.S. population to lead, 1991-94. *Environ Health Perspect* 1998;106:745-750.

Potula V, Serrano J, Sparrow D, Hu H. Relationship of lead in drinking water to bone lead levels twenty years later in Boston men: the Normative Aging Study. *JOEM* 1999;41:349-355.

Proctor SP, Rotnizky A, Sparrow D, Weiss ST, Hu H. The relationship of blood lead and dietary calcium to blood pressure in the normative aging study. *Int J Epidemiol* 1996;25:528-536.

Prpic-Majíc D, Bobíc J, Simíc D, House DE, Otto DA, Jurasovíc J, Pizent A. Lead absorption and psychological function in Zagreb (Croatia) school children. *Neurotoxicol Teratol* 2000;22:347-356.

Queiroz MLS, Almeida M, Gallao MI, Höer NF. Defective neutrophil function in workers occupationally exposed to lead. *Pharmacol Toxicol* 1993;72:73-77.

Queiroz ML, Perlingeiro RC, Bincoletto C, Almeida M, Cardoso MP, Dantas DC. Immunoglobulin levels and cellular immune function in lead exposed workers. *Immunopharmacol Immunotoxicol* 1994;16:115-128.

Quintanilla-Vega B, Hoover D, Bal W, Silbergeld EK, Waalkes MP, Anderson LD. Lead effects on protamine-DNA binding. *Am J Ind Med* 2000;38:324-329.

Rabito FA, Shorter C, White LE. Lead levels in children who live in public housing. *Epidemiology* 2003;14:263-268.

Rahman A, Maqbool E, Zuberi HS. Lead-associated deficits in stature, mental ability and behaviour in children in Karachi. *Ann Trop Paeditr* 2002;22:301-311.

Reckonor JC, Reigart JR, Darden PM, Goyer RA, Olden K, Richardson MC. Prenatal care and infant lead exposure. *J Pediatr* 1997;130:123-127.

Rice D, Silbergeld EK. Lead neurotoxicity: concordance of human and animal research. In: Chang LW, ed. *Toxicology of metals*. Boca Ration: CRC Press, 1996, p 659-676.

Robins TG, Bornman MS, Ehrlich RI, Cantrell AC, Pienaar E, Vallabh J, Miller S. Semen quality and fertility of men employed in a South African lead acid battery plant. *Am J Ind Med* 1997;32:257-263.

Roels H, Lauwerys R, Konings J, Buchet JP, Bernard A, Green S, Bradeley D, Morgan W, Chettle D. Renal function and hyperfiltration capacity in lead smelter workers with high bone lead. *Occup Environ Med* 1994;51:505-512.

Rogan WJ, Dietrich KN, Ware JH, Dockery DW, Salganik M, Radcliffe J, Jones RL, Ragan NB, Chisolm JJ, Rhoads GG. Treatment of Lead-Exposed Children Trial Group. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N Engl J Med* 2001;344:1421-1426

Rosborg I, Nihlgård B, Gerhardsson L. Inorganic constituents of well water in one acid and one alkaline area of south Sweden. *Water, Air and Soil Pollution* 2003a;142:261-277.

Rosborg I, Nihlgård B, Gerhardsson L. Hair element concentrations in females in one acid and one alkaline area in south Sweden. *Ambio* 2003b;32:440-446.

Rothenberg S, Karchemer S, Schnaas L, Perroni E, Zea F, Fernandez Alba J. Changes in blood lead levels during pregnancy. *Environ Health Perspect* 1994;102:876-880.

Rothenberg SJ, Manalo M, Jiang J, Cuellar R, Reyes S, Sanchez M, Diaz M, Khan F, Aguilar A, Reynoso B, Juaregui M, Acosta S, Johnson C. Blood lead level and blood pressure during pregnancy in South Central Los Angeles. *Arch Environ Health* 1999a;54:382-389.

Rothenberg SJ, Schnaas L, Perroni E, Hernández RM, Martínez S, Hernández C. Pre- and postnatal lead effect on head circumference: A case for critical periods. *Neurotoxicol Teratology* 1999b;21:1-11.

Rothenberg SJ, Kahn F, Manalo M, Jiang J, Cuellar R, Reyes S, Acosta S, Jauregui M, Diaz M, Sanchez M, Todd AC, Johnson C. Maternal bone lead contribution to blood lead during and after pregnancy. *Environ Res* 2000;82:81-90.

Rothenberg SJ, Kondrashov V, Manalo M, Jiang J, Cuellar R, Garcia M, Reynoso B, Reyes S, Diaz M, Todd AC. Increases in hypertension and blood pressure during pregnancy with increased bone lead levels. *Am J Epidemiol* 2002;156:1079-1087.

Roy MM, Gordon CL, Beaumont LF, Chettle DR, Webber CE. Further experience with bone lead content measurements in residents of southern Ontario. *Appl Radiat Isot* 1997:48:391-396.

RTECS. Registry of Toxic Effects of Toxic Substances. *Lead*. 2003.

Rubens O, Logina I, Kravale I, Eglite M, Donaghy M. Peripheral neuropathy in chronic occupational inorganic lead exposure: a clinical and electrophysiological study. *J Neurol Neurosurg Psychiatry* 2001;71:200-204.

Ruff HA, Bijur PE, Markowitz M, Ma YC, Rosen JF. Declining blood lead levels and cognitive changes in moderately lead-poisoned children. *JAMA* 1993;269:1641-1646.

Ruff HA, Markowitz ME, Bijur PE, Rosen JF. Relationships among blood lead levels, iron deficiency, and cognitive development in two-year-old children. *Environ Health Perspect* 1996;104:180-185.

Sakai T. Biomarkers of lead exposure. *Ind Health* 2000;38:127-142.

Sakai T, Morita Y. delta-Aminolevulinic acid in plasma or whole blood as a sensitive indicator of lead effects, and its relation to the other heme-related parameters. *Int Arch Occup Environ Health* 1996;68:126-132.

Sakai T, Ushio K, Ikeya Y. Mobilized plasma lead as an index of lead body burden and its relation to the heme-related indices. *Ind Health* 1998;36:240-246.

Sakai T, Morita Y, Araki T, Kano M, Yoshida T. Relationship between delta-aminolevulinic acid dehydratase genotypes and heme precursurs in lead workers. *Am J Ind Med* 2000;38:355-360.

Saleh MA, Ragab AA, Kamel A, Jones J, El-Sabae AK. Regional distribution of lead in human milk from Egypt. *Chemosphere* 1996;32:1859-1867.

Sallmén M, Lindbohm ML, Anntila A, Taskinen H, Hemminki K. Paternal occupational lead exposure and congenital malformations. *J Epidemiol Community Health* 1992;46.519-522.

Sallmén M, Anttila A, Lindbohm ML, Kyyronen P, Taskinen H, Hemminki K. Time to pregnancy among women occupationally exposed to lead. *J Occup Environ Med* 1995;37:931-934.

Sallmén M, Lindbohm ML, Anttila A, Taskinen H, Hemminki K. Time to pregnancy among the wives of men occupationally exposed to lead. *Epidemiology* 2000;11:141-147.

Sánches-Fructuoso AI, Torralbo A, Arroyo M, Luque M, Ruilope LM, Santos JL, Cruceyra A, Barrientos A. Occult lead intoxication as a cause of hypertension and renal failure. *Nephrol Dial Transplant* 1996;11:1775-1780.

Sanin LH, Gonzalez-Cossio T, Romieu I, Peterson KE, Ruiz S, Palazuelos E, Hernandez-Avila M, Hu H. Effect of maternal lead burden on infant weight and weight gain at one month of age among breastfed infants. *Pediatrics* 2001;107:1016-1023.

Santos AC, Colacciopo S, Dal Bo CMR, Guinaim dos Santos NA. Occupational exposure to lead, kidney function tests, and blood pressure. *Am J Ind Med* 1994;26:635-643.

Sata F, Araki S. Adjustment of creatinine-adjusted value to urine flow rate in lead workers. *Arch Environ Health* 1996;51:329-333.

Sata F, Araki S, Murata K, Fujimura Y, Uchida E. Are faster or slower large myelinated nerve fibers more sensitive to chronic lead exposure? A study of the distribution of conduction velocities. *Environ Res* 1993;62:333-338.

Sata F, Araki S, Yokoyama K, Murata K. Adjustment of creatinine-adjusted values in urine to urinary flow rate: a study of eleven heavy metals and organic substances. *Int Arch Occup Environ Health* 1995;68:64-68.

Sata F, Araki S, Tanigawa T, Morita Y, Sakurai S, Katsumo N. Changes in natural killer cell subpopulations in lead workers. *Int Arch Occup Environ Health* 1997;69:306-310.

Schell LM, Czerwinski S, Stark AD, Parsons PJ, Gomez M, Samelson R. Variation in blood lead and hematocrit levels during pregnancy in a socioeconomically disadvantaged population. *Arch Environ Health* 2000;55:134-140.

Schnaas L, Rothenberg SJ, Perroni E, Martinez S, Hernández C, Hernández RM. Temporal pattern in the effect of postnatal blood lead level on intellectual development of young children. *Neurotoxicol Teratol* 2000;22:805-810.

Schütz A. Analytical aspects of trace elements in biological samples. In: Abdulla M, Vohora SB, Athar M, eds. *Trace and toxic elements in nutrition and health. Proceedings of the fourth International Conference on Health and Desease: Effects of Essential and Toxic Trace Elements*. New Delhi, February 8-12, 1993, pp. 453-459, Wiley Eastern Ltd, New Delhi, 1995. ISBN: 81-224-0724-2.

Schütz A, Bergdahl IA, Ekholm A, Skerfving S. Measurement by ICP-MS of lead in plasma and whole blood of lead workers and controls. *Occup Environ Med* 1996;53:736-740.

Schütz A, Barregård L, Sällsten G, Wilske J, Manay N, Pereira L, Cousillas A. Blood lead in Uruguayan children and possible sources of exposure. *Environ Res* 1997;74:17-23.

Schütz A, Olsson M, Jensen A, Gerhardsson L, Börjesson J, Mattsson S, Skerfving S. Lead in finger-bone, whole-blood, plasma and urine in lead smelter workers – extended exposure range. Submitted 011106 to *Int Arch Occup Environ Health*.

Schwartz J. Low-level lead exposure and children´s IQ: a meta-analysis and search for a threshold. *Environ Res* 1994;65:42-55.

Schwartz J. Lead, blood pressure, and cardiovascular disease in men. *Arch Environ Health* 1995;50:31-37.

Schwartz BS, Stewart WF. Different associations of blood lead, meso 2,3-dimercaptosuccinic acid (DMSA)-chelatable lead, and tibial lead levels with blood pressure in 543 former organolead manufacturing workers. *Arch Environ Health* 2000;55:85-92.

Schwartz BS, Bolla KI, Stewart W, Ford DP, Agnew J, Frumkin H. Decrements in neurobehavioral performance associated with mixed exposure to organic and inorganic lead. *Am J Epidemiol* 1993;137:1006-1021.

Schwartz BS, McGrail MP, Stewart W, Pluth T. Comparison of measures of lead exposure, dose, and chelatable lead burden after provocative chelation in organolead workers. *Occup Environ Med* 1994;51:669-673.

Schwartz BS, Lee BK, Stewart W, Ahn KD, Springer K, Kelsey K. Associations of delta-aminolevulinic acid dehydratase genotype with plant, exposure duration, and blood lead and zinc protoporphyrin levels in Korean lead workers. *Am J Epidemiol* 1995;142:738-745.

Schwartz BS, Lee BK, Stewart W, Ahn KD, Kelsey K, Bressler J. Associations of subtypes of hemoglobin with delta-aminolevulinic acid dehydratase genotype and dimercaptosuccinic acid-chelatable lead levels. *Arch Environ Health* 1997a;52:97-103.

Schwartz BS, Lee BK, Stewart W, Sithisarankul P, Strickland PT, Ahn KD, Kelsey K. Delta-aminolevulinic acid dehydratase genotype modifies four hour urinary lead excretion after oral administration of dimercaptosuccinic acid. *Occup Environ Med* 1997b;54:241-246.

Schwartz BS, Stewart WF, Todd AC, Links JM. Predictors of dimercaptosuccinic acid chelatable lead and tibial lead in former organolead manufacturing workers. *Occup Environ Med* 1999;56:22-29.

Schwartz BS, Stewart WF, Bolla KI, Dimon D, Bandeen-Roche K, Gordon B, Links JM, Todd AC. Past adult lead exposure is associated with longitudinal decline in cognitive function. *Neurology* 2000a;55:1144-1150.

Schwartz BS, Lee BK, Lee GS, Stewart WF, Simon D, Kelsey SD, Todd AC. Associations of blood lead, dimpercaptosuccinic acid-chelatable lead, and tibia lead with polymorphisms in the vitamin D receptor and [delta]-aminolevulinic acid dehydratase genes. *Environ Health Perspect* 2000b;108:949-954.

Schwartz BS, Stewart WF, Kelsey KT, Simon D, Park S, Links JM, Todd AC. Associations of tibial lead levels with BsmI polymorphisms in the vitamin D receptor in former organolead manufacturing workers. *Environ Health Perspect* 2000c;108:199-203.

Schwartz BS, Lee BK, Lee GS, Stewart WF, Lee SS, Hwang KY, Ahn KD, Kim YB, Bolla KI, Simon D, Parsons PJ, Todd AC. Associations of blood, dimercaptosuccinic acid-chelatable lead, and tibia lead with neurobehavioral test scores in South Korean lead workers. *Am J Epidemiol* 2001;153:453-464.

Schwartz BS, Stewart W, Hu H. Neurobehavioural testing in workers occupationally exposed to lead. *Occup Environ Med* 2002;59:648-650.

Seeber A, Meyer-Baron A. Neurobehavioural testing in workers occupationally exposed to lead. *Occup Environ Med* 2003;60:145-146

Seeber A, Meyer-Baron M, Schäper M. A summary of two meta-analyses on neurobehavioural effects due to occupational lead exposure. *Arch Toxicol* 2002;76:137-145.

Shadick NA, Kim R, Weiss S, Liang MH, Sparrow D, Hu H. Effect of low level lead exposure on hyperuricemia and gout among middle aged and elderly men: the normative aging study. *J Rheumatol* 2000;27:1708-1712.

Shen XM, Yan CH, Guo D, Wu SM, Li RQ, Huang H, Ao LM, Zhou JD, Hong ZY, Xu JD, Jin XM, Tang JM. Low-level prenatal lead exposure and neurobehavioral development of children in the first year of life: a prospective study in Shanghai. *Environ Res* 1998;79:1-8.

Shi L, Chia SE. A review of studies on maternal occupational exposures and birth defects, and the limitations associated with these studies. *Occup Med* 2001;51:230-244.

Shimbo S, Zhang ZW, Moon CS, Watanabe T, Nakatsuka H, Matsuda-Inoguchi N, Higakashawa K, Ikeda M. Correlation between urine and blood concentrations, and dietary intake of cadmium and lead among women in the general population of Japan. *Int Arch Occup Environ Health* 2000;73:163-170.

Silbergeld EK, Waalkes M, Rice JR. Lead as a carcinogen: Experimental evidence and mechanisms of action. *Am J Ind Med* 2000;38:316-323.

Simons T. Lead transport and binding by human erythrocytes in vitro. *Pflügers Arch* 1993;423:307-313.

Simons TJ. The affinity of human erythrocyte porphobilinogen synthase for Zn2+ and Pb2+. *Eur J Biochem* 1995;234:178-183.

Sithisarankul P, Schwartz BS, Lee BK, Kelsey KT, Strickland PT. Aminolevulinic acid dehydratase genotype mediates plasma levels of the neurotoxin, 5-aminolevulinic acid, in lead-exposed workers. *Am J Ind Med* 1997;32:15-20.

Skerfving S. *Nordiska Expertgruppen för Gränsvärdesdokumentation. 104. Oorganiskt bly (Inorganic lead)*. Arbete och Hälsa 1992;43:1-111. Arbetsmiljöinstitutet, Solna. (In Swedish)

Skerfving S. *Criteria dokuments from the nordic expert group 1992*. Inorganic lead. Arbete och hälsa 1993;1:125-238. National Institute of Occupational Health, Solna.

Skerfving S, Nilsson U. Assessment of accumulated body burden of metals. *Toxicol Lett* 1992;64/65:17-24.

Skerfving S, Nilsson U, Schütz A, Gerhardsson L. Biological monitoring of inorganic lead. *Scand J Work Environ Health* 1993;19 Suppl 1:59-64.

Skerfving S, Gerhardsson L, Schütz A, Svensson B-G. Toxicity of detrimental metal ions. Lead. In: Handbook of Metal-Ligand Interactions in Biological Fluids. *Bioinorganic Medicine* 1995;2:755-765. ISBN: 0-8247-9638-1.

Skerfving S, Gerhardsson L, Schütz A, Strömberg U. Lead - biological monitoring of exposure and effects. *J Trace Elem Exp Med* 1998;11:289-301.

Skerfving S, Bencko V, Vahter M, Schütz A, Gerhardsson L. Environmental health in the Baltic region – toxic metals. *Scand J Work Environ Health* 1999;25 Suppl 3:40-64.

Smith CM, Wang X, Hu H, Kelsey KT. A polymorphism in the delta-aminolevulinic acid dehydratase gene may modify the pharmacokinetics and toxicity of lead. *Environ Health Perspect* 1995a;103:248-253.

Smith CM, Hu H, Wang X, Kelsey KT. ALA-D genotype is not associated with Ht or Hb levels among workers exposed to low levels of lead. *Med Lav* 1995b;86:229-235.

Smith DR, Osterloh JD, Flegal AR. Use of endogenous, stable lead isotopes to determine release of lead from the skeleton. *Environ Health Perspect* 1996;104:60-66.

Smith DR, Illustre RP, Osterloh JD. Methodological considerations for the accurate determination of lead in human plasma and serum. *Am J Ind Med* 1998;33:430-438.

Smith D, Hernandez-Avila M, Telez-Rojo MM, Mercado A, Hu H. The relationship between lead in plasma and whole blood in women. *Environ Health Perspect* 2002;110:263-268.

Soldin OP, Hanak B, Soldin SJ. Blood lead concentrations in children: new ranges. *Clin Chim Acta* 2003;327:109-113.

Solliway BM, Schaffer A, Pratt H, Yannai S. A multidisciplinary study of lead-exposed subjects. I. Delayed target detection P-300 latency, and electrophysiological parameter, correlates with urinary delta-ALA. *Environ Res* 1994;67:168-182.

Solliway BM, Schaffer A, Erez A, Mittelman N, Pratt H, Yannai S. The effect of lead exposure on target detection and memory scanning differs. *J Neurol Sci* 1995a;134:171-177.

Solliway BM, Schaffer A, Erez A, Mittelman N, Pratt H, Yannai S. Visual evoked potential N75 and P100 latencies correlate with urinary delta-aminolevulinic acid, suggesting gamma-aminobutyric acid involvement in their generation. *J Neurol Sci* 1995b;134:89-94.

Solliway BM, Schaffer A, Pratt H, Yannai S. Effect of exposure to lead on selected biochemical and haematological variables. *Pharmacol Toxicol* 1996;78:18-22.

Soweres MR, Scholl T, Hall G, Jannausch ML, Kemp FW, Li X, Bogden JD. Lead in breast milk and maternal bone turnover. *Am J Ostet Gyn* 2002;187:770-776.

Spurgeon A. Occupational lead exposure. Do current exposure standards protect workers from harm? A review of neurobehaviuoral findings since 1978. *Indoor Environ* 1994;3:112-118.

Staes C, Matte T, Parrish RG, Staehling N, Rosenblum L, Binder S. Lead poisoning deaths in the United States, 1979 through 1988 (letter). *JAMA* 1995; 273:847-848.

Staessen JA, Lauwerys RR, Buchet JP, Bulpitt CJ, Rondia D, Vanrenterghem Y, Amery A, and the Cadmibel Study Group. Impairment of renal function with increasing blood lead concentrations in the general population. *N Engl J Med* 1992;327:151-156.

Staessen JA, Bulpitt CJ, Fagard R, Lauwerys RR, Roels H, Thijs L, Amery A. Hypertension caused by low-level lead exposure: myth or fact? *J Cardiovasc Risk* 1994;1:87-97.

Staessen JA, Roels H, Lauwerys RR, Amery A. Low-level lead exposure and blood pressure. *J Hum Hypertens* 1995;9:303-328.

Staessen JA, Buchet JP, Ginucchio G, Lauwerys RR, Lijnen P, Roels H, Fagard R. Public health implications of environmental exposure to cadmium and lead: an overview of epidemiological studies in Belgium. Working Groups. *J Cardiovasc Risk* 1996;3:26-41.

Stauber JL, Florence TM, Gulson BL, Dale LS. Percutaneous absorption of inorganic lead compounds. *Sci Total Environ* 1994;2:55-70.

Steenland K, Selevan S, Landrigan P. The mortality of lead smelter workers: An update. *Am J Public Health* 1992;82;1641-1644.

Stewart WF, Schwartz BS, Simon D, Bolla KI, Todd AC, Links J. Neurobehavioral function and tibial and chelatable lead levels in 543 former organolead workers. *Neurology* 1999;52:1610-1617.

Stokes L, Letz R, Gerr R, Kolczak M, McNeill FE, Chettle DR, Kaye WE. Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience. *Occup Environ Med* 1998;55:507-516.

Stollery BT, Broadbent DE, Banks HA, Lee WR. Short term prospective study of cognitive functioning in lead workers. *Brit J Ind Med* 1991;48:739-749.

Stretesky PB, Lynch MJ. The relationship between lead exposure and homicide. *Arch Pediatr Adolesc Med* 2001;155:579-582.

Strömberg U, Schütz A, Skerfving S. Substantial decrease of blood lead in Swedish children 1978-94, associated with petrol lead. *Occup Environ Med* 1995;52:764-769.

Strömberg U, Lundh T, Schütz A, Skerfving S. Yearly measurements of blood lead in Swedish children since 1978: an update focusing on the petrol lead free period 1995-2001. *Occup Environ Med* 2003;60:370-372.

Süzen HS, Duydu Y, Aydin A, Isimer A, Vural N. Influnce of the delta-aminolevulinic acid dehydratase (ALAD) polymorphism on biomarkers of lead exposure in Turkish storage battery manufacturing workers. *Am J Ind Med* 2003;43:165-171.

Svensson B, Schütz A, Nilsson A, Skerfving S. Lead exposure in indoor firing ranges. *Int Arch Occup Environ Health* 1992;64:219-221.

Swedish NBOSH (National Board of Occupational Safety and Health). Bly. *Arbetarskydds-styrelsens kungörelse med föreskrifter om bly samt allmänna råd om tillämpning av föreskrifterna*. Arbetarskyddstyrelsen, Solna, 1992;17: 25 pp.

Swedish NBOSH (National Board of Occupational Safety and Health). *Årsredovisning 1992/93*, sid 39. Arbetarskyddsstyrelsen, Solna, 1993.

Swedish NBOSH (National Board of Occupational Safety and Health). *Hygieniska gränsvärden och åtgärder mot luftföroreningar*. Arbetarskyddsstyrelsen, Stockholm 2000:3.

Symanski E, Hertz-Picciotto I. Blood lead levels in relation to menopause, smoking, and pregnancy history. *Am J Epidemiol* 1995;141:1047-1058.

Tabacova S, Balabaeva L. Environmental pollutants in relation to complications of pregnancy. *Environ Health Perspect* 1993;101 Suppl 2:27-31.

Tas S, Lauwerys R, Lison D. Occupational hazards for the male reproductive system. *Crit Rev Toxicol* 1996;26:261-307.

Tassler PL, Schwartz BS, Coresh J, Stewart WF, Todd AC. Associations of tibia lead, DMSA-chelatable lead, and blood lead with measures of peripheral nervous system function in former organolead manufacturing workers. *Am J Ind Med* 2001;39:254-261.

Telisman S, Cvitkovic P, Jurasovic J, Pizent A, Gavella M, Rocic B. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. *Environ Health Perspect* 2000;108:45-53.

Telisman S, Jurasovic J, Pizent A, Cvitkovic P. Blood pressure in relation to biomarkers of lead, cadmium, copper, zinc, and selenium in men without occupational exposure to metals. *Environ Res* 2001;87:57-68.

Tell I, Somervaille LJ, Nilsson U, Bensryd I, Schütz A, Chettle DR, Scott MC, Skerfving S. Chelated lead and bone lead. *Scand J Work Environ Health* 1992;18:113-119.

Tell I, Bensryd I, Chettle DR, Gerhardsson L, Nilsson U, Schütz A, Skerfving S. Njurfunktionsmarkörer hos blyarbetare. Svenska Läkaresällskapets Riksstämma 24 - 26 november 1998. *Svenska Läkaresällskapets handlingar Hygiea* 1998;107:139. Abstract.

Téllez-Rojo MM, Hernández-Avila M, Gonzales-Cossio T, Romieu I, Aro A, Palazuelos E, Schwartz J, Hu H. Impact of breastfeeding on the mobilization of lead from bone. *Am J Epidemiol* 2002;155:420-428.

Téllez-Rojo MM, Hernández-Avila M, Lamadrid-Figueroa H, Smith D, Hernández-Cadena L, Mercado A, Aro A, Schwartz J, Hu H. Impact of bone lead and bone resorption on plasma and whole blood lead levels during pregancey. *Am J Epidemiol* 2004;160:668-678.

Teruya K, Sakurai H, Omac K, Higashi T, Muto T, Kaneko Y. Effects of lead on cardiac parasympathetic function. *Int Arch Occup Environ Health* 1991;62:549-553.

Thomas VM, Socolow RH, Fanelli JJ, Spiro TG. Effects of reducing lead in gasoline: and analysis of the international experience. *Environmental Science & Technology* 1999;33:3942-3954.

Tiran B, Rossipal E, Tiran A, Karpf E, Lorenz O. Burden of cadmium and lead content in human milk and milk formulas in Styria, Austria. *Trace Elements Electrolytes* 1994;11:42-45.

Todd AC, Chettle DR. In vivo X-ray fluorescence of lead in bone: review and current issues. *Environ Health Perspect* 1994;102:172-177.

Todd AC, Lee BK, Lee GS, Ahn KD, Moshier EL, Schwartz BS. Predictors of DMSA chelatabel lead, tibial lead, and blood lead in 802 Korean lead workers. *Occup Environ Med* 2001;58:73-80.

Tong S, Baghurst P, McMichael A, Sawyer M, Mudge J. Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study. *BMJ* 1996;312:1569-1575.

Tong S, Baghurst PA, Sawyer MG, Burns J, McMichael AJ. Declining blood lead levels and changes in cognitive function during childhood. *JAMA* 1998;280:1915-1919.

Tong S, McMichael AJ, Baghurst PA. Interaction between environmental lead exposure and sociodemographic factors on cognitive development. *Arch Envirn Health* 2000;55:330-335.

Tsaih SW, Schwartz J, Lee Ml, Amarasiriwardena C, Aro A, Sparrow D, Hu H. The independent contribution of bone and erythrocyte lead to urinary lead among middle-aged and elderly men: the normative aging study. *Environ Health Perspect* 1999;107:391-396.

Tsaih SW, Korrick S, Schwartz J, Lee ML, Amarasiriwardena C, Aro A, Sparrow D, Hu H. Influence of bone resorption on the mobilization of lead from bone among middle-aged and elderly men: the Normative Aging Study. *Environ Health Perspect* 2001;109:995-999.

Tsaih SW, Korrick S, Schwartz J, Amarasiriwardena C, Aro A, Sparrow D, Hu H. Lead, diabetes, hypertension, and renal function: The normative aging study. *Environ Health Perspec* 2004;112:1178-1182.

UK Health and Safety Executive. *Occupational Exposure Limits 2002*. Health and safety Executive, London, 2002.

Ulenbelt P, Lumens M, Geron H, Herber R, Broersen S, Zielhuis R. Work hygien behaviour as modifier of the lead-air-lead blood relation. *Int Arch Occup Environ Health* 1990;62:203-207.

Undeger U, Basaran N, Canpinar H, Kansu E. Immune alterations in lead-exposed workers. *Toxicology* 1996;109:167-172.

US ATSDR. Agency for Toxic Substances and Disease Registry. *Toxicological profile for lead (update)*. US Department of Health and Human Services, Atlanta, GA, 1999, 640 pp. http:/www.atsdr.cdc.gov/toxprofiles.

US CDC. Centers for Disease Control and Prevention. *Preventing lead poisoning in young children*. Atalanta, GA, 1991.

US CDC. National Center for Environmental Health. *Screening young children for lead poisoning: Guidance for state and local public health Officials*. Centers for Disease Control and Prevention (CDC). Nov 1997.

US CDC. Centers for Disease Control and Prevention. *Managing elevated blood lead levels among young children: recommendations from the Advisory Committee on Childhood lead Poisoning Prevention*. Atlanta, GA, 2002.

US CDC. Centers for Disease Control and Prevention. *Second national report on human exposure to environmental chemicals*. US Department of Health and Human Services, NCEH Publication No. 02-0716, 2003. http://www.cdc.gov/exposurereport/pdf/SecondNER.pdf

US CDC. Centers for Disease Control and Prevention. *A review of the evidence of health effects of blood lead levels <10 μg/dL in children*. Reported by a Work Group of the Advisory Committee on Childhood lead Poisoning prevention to Centers for Disease Control and Prevention. Final for review, February 23, 2004.

US EPA. Environmental Protection Agency. *Technical review workgroup for lead. Integrated exposure uptake Biokinetic model for lead in children (IEUBK)*. Version 0.99d. NTIS No. PB94-505117. US Environmental Protection Agency, Washington DC,1994.

US EPA. Environmental Protection Agency. *National air quality and emissions trend report, 1999*. US Environmental Protection Agency, 1999.

US EPA. Environmental Protection Agency. User's Guide for the integrated exposure uptake biokinetic model for lead in children. (IEUBK). May 2002. http:/www.epa.gov/air/aqtrnd99/index.html.

US EPA. Environmental Protection Agency. *National ambient air quality standards (NAAQS)*. 2003. http:/www.epa.gov/reg3artd/airquality/NAAQS.htm.

US OSHA. Occupational Safety and Health Administration. *Code of Federal Regulations. Part 1910*. Occupational Safety and Health Standards. Section 29.1910.1025 Lead. 1998.

Vagenlov A, Carbonell E, Marcos R. Biomonitoring of workers exposed to lead. Genotoxic effects, its modulation by polyvitamin treatment and evaluation of the induced radioresistance. *Mut Res* 1998;418:79-92.

Vaglenov A, Creus A, Laltchev S, Petkova V, Pavlova S, Marcos R. Occupational exposure to lead and induction of genetic damage. *Environ Health Perspect* 2001;109:295-298.

Vahter M, Johansson G, Akesson A, Rahnster B. Faecal elimination of lead and cadmium in subjects on a mixed and a lactovegetarian diet. *Food Chem Toxicol* 1992;30:281-287.

Vahter M, Counter SA, Laurell G, Buchanan LH, Ortega F, Schütz A, Skerfving S. Extensive lead exposure in children living in an area with production of lead-glazed tiles in the Ecuadorian Andes. *Int Arch Occup Environ Health* 1997;70:282-286.

Vahter M, Berglund M, Ask K, Åkesson A. Disposition of toxic metals during pregnancy and lactation. In: Skerfving S, ed. *Toxicology of metals. A symposium in memory of Andrejs Schütz*. 2002.

Vainio H. Lead and cancer – association or causation? *Scand J Work Environ Health* 1997;23:1-3.

Valentiono M, Governa M, Marchiseppe I, Visona I. Effects of lead on polymorphonuclear leukocyte (PMN) funtions in occupationally exposed workers. *Arch Toxicol* 1991;65:685-688.

Verberk MM, Willems TE, Verplanke AJ, De Wolff FA. Environmental lead and renal effects in children. *Arch Environ Health* 1996;51:83-87.

Vesterberg O, Nordberg G, Gerhardsson L, Brune D. A database for easy retrieval of normal concentration ranges of toxic metals in blood and urine. *Metal Compounds in Environment and Life* 1992;4: pp 63-70.

Viskum S, Rabjerg L, Jorgensen PJ, Grandjean P. Improvement in semen quality associated with decreasing occupational lead exposure. *Am J Ind Med* 1999;35:257-263.

Vupputuri S, He J, Muntner P, Bazzano LA, Whelton PK, Batuman V. Blood lead level is associated with elevated blood pressure in blacks. *Hypertension* 2003;41:463-468.

Walkowiak J, Altmann L, Krämer U, Sveinsson K, Turfeld M, Weishoff-Houben M, Winneke G. Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: Adjustment for intelligence and contrast sensitivity in computerized testing. *Neurotoxicol tertaol* 1998;20:511-521.

Wang CL, Chuang HY, Ho CK, Yang CH, Tsai JL, Wu TS, Wu TN. Relationship between blood lead concentrations and learning achievements among primary school children in Taiwan. *Environ Res* 2002;89;12-18.

Ward NI, Durrant S, Sankey RJ, Bound JP, Bryce-Smith D. Elemental factors in human fetal development. *J Nutr Med* 1990;1:19-27.

Waring WS, Webb DJ, Maxwell SRJ. Systematic uric acid administration increases serum antioxidant capacity in healthy volunteers. *J Cardiovasc Pharmacol* 2001;38:365-371.

Wasserman GA, Liu X, Popovac D, Factor-Litvak P, Kline J, Waternaux C, LoIacono N, Graziano JH. The Yugoslavia Prospective Lead Study: contributions of prenatal and postnatal lead exposure to early intelligence. *Neurotoxicol Teratol* 2000;22:811-818.

Wasserman GA, Factor-Litvak P, Liu X, Todd AC, Kline JK, Slavkovich V, Popovac D, Graziano JH. The relationship between blood lead, bone lead and child intelligence. *Child Neuropsychol* 2003;9:22-34.

Watanabe H, Hu H, Rotnitzky A. Correlates of bone and blood lead levels in carpenters. *An J Ind Med* 1994;26:255-264.

Weaver VM, Lee BK, Ahn KD, Lee GS, Todd AC, Stewart WF, Wen J, Simon DJ, Parsons PJ, Schwartz BS. Associations of lead biomarkers with renal function in Korean lead workers. *Occup Environ Med* 2003;60:551-562.

Webber CE, Chettle DR, Bowins RJ, Beaumont LF, Gordon CL, Song X, Blake JM, McNutt RH. Hormone replacement therapy may reduce the return of endogenous lead from bone to the circulation. *Environ Health Perspect* 1995;103:1150-1153.

Wennberg M, Lundh T, Bergdahl IA, Hallmans G, Jansson JH, Stegmay B, Custodio HM, Skerfving S. Time trends in burdens of cadmium, lead and mercury in the population of Northern Sweden. Submitted.

Wesseling C, Pukkala E, Neuvonen K, Kauppinen T, Boffetta P, Partanen T. Cancer of the brain and nervous system and occupational exposures in Finnish women. *J Occup Environ Med* 2002;44:663-668.

West WL, Knight EM, Edwards CH, Manning M, Spulock B, James H, Johnson AA, Oyemade UJ, Cole JO, Westney OE, Laryea H, Jones S, Westney LS. Maternal low level lead and pregnancy outcome. *J Nutr* 1994;124:981S-986S.

Wetmur JG. Influence of the common human delta-aminolevulinate dehydratase polymorphism on lead body. *Environ Health Perspect* 1994;102 Suppl 3:215-219.

Wetmur JG, Lehnert G, Desnick RJ. The delta-aminolevulinate dehydratase polymorphism: higher blood lead levels in lead workers and environmentally exposed children with the 1-2 and 2-2 isozymes. *Environ Res* 1991;56:109-119.

White RF, Diamond R, Proctor S, Morey C, Hu H. Residual cognitive deficits 50 years after lead poisoning during childhood. *Brit J Ind Med* 1993;50:613-622.

White PD, Van Leuwen P, Davis BD, Maddaloni M, Hogan KA, Marcus AH, Elias RW. The conceptual structure of the integrated exposure uptake biokinetic model for lead in children. *Environ Health Perspect* 1998;106 Suppl 6:1513-1530.

WHO. *Biological monitoring of chemical exposure in workplace*. Vol 1, Chapter 3. Selected metals. 3.3 Lead. World Health Organization, Geneva, 1996, pp 112-131.

WHO. *Guidelines for air quality*. World Health Organization, Geneva, 2000a, 185 pp. ISBN 93 890 1358 3. www.who.int/peh/.

WHO. International Programme on Chemical Safety. *Safety evaluation of certain food additives and contaminants*. Fifty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JEFCA). Lead. WHO Food Additives Series: 44. World Health Organization, Geneva, 2000b. http://www.inchem.org/documents/jefca/jecmono/v44jec.html.

WHO. *Guidelines for drinking-water quality*. Second edition. Volume 1. Recommendations. World Health Organisation, Geneva, 2003. www.who.int/water_sanitation_health/GDWQ.

WHO/ICPS. International Programme on Chemical Safety. *Environmental Health Criteria 165*. Inorganic lead. World Health Organization, Geneva, 1995. ISBN 9241571659.

Willers S, Attewell R, Bensryd I, Schütz A, Skarping G, Vahter M. Exposure to environmental tobacco smoke in the household and urinary cotinine excretion, heavy metals retention, and lung function. *Arch Environ Health* 1992;47:357-363.

Willers S, Hein HO, Schütz A, Suadicani P, Gyntelberg F. Cadmium and lead levels in house dust from smokers and non-smokers homes related to nicotine levels. *Indoor Environ* 1993;2:14-18.

Wingren G, Axelson O. Epidemiologic studies of occupational cancer as related to complex mixtures of trace elements in the art glass industry. *Scand J Work Environ Health* 1993;19 Suppl 1:95-100.

Wolf C, Wallnofer A, Waldhor T, Vutuc C, Meisinger V, Rudiger HW. Effect of lead on blood pressure in occupationally non-exposed men. *Am J Ind Med* 1995;27:897-903.

Wong O, Harris F. Cancer mortality study of employees at a lead battery plant and lead smelters, 1947-1995. *Am J Ind Med* 2000;38:255-270.

Wright RO, Shannon MW, Wright RO, Shannon MW, Wright RJ, Hu H. Association between iron deficiency and low-level lead poisoning in an urban primary care clinic. *Am J Public Health* 1999;89:1049-1053.

Wright RO, Tsaih SW, Schwartz J, Wright RJ, Hu H. Association between iron deficiency and blood lead level in a longitudinal analysis of children followed in an urban primary care clinic. *J Pediatr* 2003;142:9-14.

Wu FY, Chang PW, Wu CC, Kuo HW. Correlations of blood lead with DNA-protein cross-links and sister chromatid exchanges in lead workers. *Cancer Epid Biomarkers Prevention* 2002;11:287-290.

Wu MT, Kelsey K, Schwartz J, Sparrow D, Weiss S, Hu H. A delta-aminolevulinic acid dehydratase (ALAD) polymorphism may modify the relationship of low-level lead exposure to uricemia and renal function: the normative aging study. *Environ Health Perspect* 2003a;111:335-341.

Wu T, Buck GM, Mendola P. Blood lead levels and sexual maturation in U.S. girls: The Third National Health and Nutrition Examination Survey, 1988-94. *Environ Health Perspect* 2003b;111:737-741.

Xu B, Chia SE, Tsakok M, Ong CN. Trace elements in blood and seminal plasma and their relationship to semen quality. *Reprod Toxicol* 1993;7:613-618.

Xu B, Chia SE, Ong CN. Concentrations of cadmium. lead, selenium, and zinc in human blood and seminal plasma. *Biol Trace Elem Res* 1994;40:49-57.

Xu DX, Shen HM, Zhu QX, Chua L, Wang QN, Chia SE, Ong CN. The associations among semen quality, oxidative DNA damage, in human spermatozoa and concentrations of cadmium, lead and selenium in seminal plasma. *Mut Res* 2003;534:155-163.

Yeh JH, Chang YC, Wang JD. Combined electroneurographic and electromyographic studies in lead workers. *Occup Environ Med* 1995;52:415-419.

Yokoyama K, Araki S, Aono H. Reversibility of psychological performance in subclinical lead absorption. *Neurotoxicology* 1988;9:405-410.

Yokoyama K, Araki S, Murata K, Morita Y, Katsuno N, Tanigawa T, Mori N, Yokota J, Ito A, Sakata E. Subclinical vestibulo-cerebellar, anterior cerebellar lobe and spinocerebellar effects in lead workers in relation to concurrent and past exposure. *Neurotoxicology* 1997;18:371-380.

Yokoyama K, Araki S, Aono H, Murata K. Calcium disodium ethylenediaminetetraacetate-chelated lead as a predictor for subclinical lead neurotoxicity: a follow-up study on gun-metal foundry workers. *Int Arch Occup Environ Health* 1998;71:459-464.

Yokoyamna K, Araki S, Sato H, Aono H. Circadian rhythms of seven heavy metals in plasma, erythrocytes an urine in men: Observations in metal workers. *Ind Health* 2000;38:205-212.

Yokoyama K, Araki S, Yamashita K, Murata K, Nomiyama K, Nomiyama H, Tao Y-X, Liu S-J. Subclinical cerebellar anterior lobe, vestibulocerebellar and spinocerebellar afferent effects in young female lead workers in China: Computerized posturography with sway frequency analysis and brainstem auditory evoked potentials. *Ind Health* 2002a;4:245-253.

Yokoyama K, Araki S, Nishikitani M, Sato H. Computerized posturography with sway frequency analysis: application in occupational and environmental health. *Ind Health* 2002b;40:14-22.

Zhang J, Ichiba M, Wang Y, Yukitake S, Tomokuni K. Relation between polymorphism of δ-aminolevulinic acid dehydratase and some parameters in lead workers. *J Occup Health* 1998;40:77-78.

Submitted for publication April, 2005.