Metallic lead

Evaluation of the effects on reproduction, recommendation for classification

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

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Mijnheer de staatssecretaris,

Bij brief van 3 december 1993, nr DGV/MBO/U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid om naast het afleiden van gezondheidskundige advieswaarden ook te adviseren over andere onderwerpen ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen. In 1995 heeft de Staatssecretaris van Sociale Zaken en Werkgelegenheid besloten tot het opstellen van een zogenaamde niet-limitatieve lijst van voor de voortplanting vergiftige stoffen. Op deze lijst komen stoffen die volgens de richtlijnen van de Europese Unie ingedeeld moeten worden in categorie 1, 2 en 3 wat betreft effecten op de voortplanting en stoffen die schadelijk kunnen zijn voor het nageslacht via de borstvoeding. De Gezondheidsraad is verzocht om voor stoffen een classificatie volgens de EU-criteria voor te stellen.

In dit kader bied ik u hierbij een advies aan over metallisch lood. Dit advies is opgesteld door de Commissie Reproductietoxische stoffen van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb deze publicatie heden ter kennisname aan de Minister van Volksgezondheid, Welzijn en Sport en aan de Minister van de Volkshuisvesting, Ruimtelijke Ordening en Milieu gestuurd.

Hoogachtend,

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Metallic lead

Evaluation of the effects on reproduction, recommendation for classification

Committee for compounds toxic to reproduction
A Committee of the Health Council of the Netherlands

to:

the Minister and State Secretary of Social Affairs and Employment

No. 2003/03OSH, The Hague, February 18, 2003

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues..." (Section 21, Health Act).

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Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid beoordeelt de Gezondheidsraad de effecten op de reproductie van stoffen waaraan mensen tijdens de beroepsuitoefening kunnen worden blootgesteld. De Commissie Reproductietoxische stoffen, een commissie van de Raad, adviseert een classificatie van reproductietoxische stoffen volgens Richtlijn 93/21/EEC van de Europese Unie. In het voorliggende rapport heeft de commissie metallisch lood onder de loep genomen.

De commissie is van mening dat metallisch lood overeenkomstig de anorganische lood verbindingen geclassificeerd moet worden (die reeds door de Europese Unie zijn geëvalueerd).

De aanbevelingen van de commissie zijn:

- Voor effecten op de fertiliteit adviseert de commissie metallisch lood te classificeren in categorie 3 (*stoffen die in verband met hun mogelijke voor de fertiliteit schadelijke effecten reden geven tot bezorgdheid voor de mens*) en met R62 (*mogelijk gevaarlijk voor de vruchtbaarheid*) te kenmerken.
- Voor effecten op de ontwikkeling adviseert de commissie metallisch lood in categorie 1 (*stoffen waarvan bekend is dat zij bij de mens ontwikkelingsstoornissen veroorzaken*) te classificeren en men R61 (*kan het ongeboren kind schaden*) te kenmerken.
- Voor effecten tijdens lactatie adviseert de commissie om metallisch lood met R64 (*kan schadelijk zijn via de borstvoeding*) te kenmerken.

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Executive summary

On request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the effects on the reproduction of substances at the workplace. The Health Council's Committee for Compounds Toxic to Reproduction recommends to classify compounds toxic to reproduction according to the Directive 93/21/EEC of the European Union. In the present report the committee has reviewed metallic lead.

The committee is of the opinion that metallic lead should be classified consistent with inorganic lead compounds (which have already been classified by the European Union).

The committee's recommendations are

- For effects on fertility, the committee recommends to classify metallic lead in category 3 (*substances which cause concern for human fertility*) and to label with R62 (*possible risk of impaired fertility*).
- For developmental toxicity, the committee recommends to classify metallic lead in category 1 (*substances known to cause developmental toxicity in humans*) and to label with R61 (*may cause harm to the unborn child*)
- For effects during lactation, the committee recommends that metallic lead should be labelled with R64 (*may cause harm to breastfed babies*).

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Chapter 1

Scope

1.1 Background

As a result of the Dutch regulation on registration of compounds toxic to reproduction that came into force on 1 April 1995, the Minister of Social Affairs and Employment requested the Health Council of the Netherlands to classify compounds toxic to reproduction. The classification is performed by the Health Council's Committee for Compounds Toxic to Reproduction according to the guidelines of the European Union (Directive 93/21/EEC). The committee's advice on the classification will be applied by the Ministry of Social Affairs and Employment to extend the existing list of compounds classified as toxic to reproduction (class 1, 2 or 3) or labelled as ‘may cause harm to breastfed babies’ (R64).

1.2 Committee and procedure

The present document contains the classification of metallic lead by the Health Council's Committee for Compounds Toxic to Reproduction. The members of the committee are listed in Annex A. The first draft of this report was prepared by dr ir MEM Kuilman and ir DH Waalkens-Berendsen at the Department of Target Organ Toxicology of TNO Nutrition and Food Research, Zeist, The Netherlands, by contract with the Ministry of Social Affairs and Employment. The classification is based on the evaluation of published human and animal studies concerning adverse effects with respect to fertility and development and lactation of the above mentioned compound.

Classification and labelling was performed according to the guidelines of the European Union listed in Annex C.

Classification for fertility and development	
Category 1	Substances known to impair fertility in humans (R60)
	Substances known to cause developmental toxicity in humans (R61)
Category 2	Substances which should be regarded as if they impair fertility in humans (R60)
	Substances which should be regarded as if they cause developmental toxicity in humans (R61)
Category 3	Substances which cause concern for human fertility (R62)
	Substances which cause concern for humans owing to possible developmental toxic effects (R63)
No classification for effects on fertility or development	
Labelling for lactation:	
	May cause harm to breastfed babies (R64)
	No labelling for lactation

In 2002, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft report are listed in Annex B. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Additional considerations

The classification of compounds toxic to reproduction on the basis of the Directive 93/21/EEC is ultimately dependent on an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity, and the dosages at which the various effects occur. The directive necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the directive, the committee has agreed upon a number of additional considerations.

- If there is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility or subsequent developmental toxic effects in the progeny, the compound will be classified in category 1, irrespective the general toxic effects (see Annex C, 4.2.3.1 category 1).
- Adverse effects in a reproductive or developmental study, in the absence of data on parental toxicity, occurring at dose levels which cause severe toxicity in other studies, need not necessarily lead to a category 2 classification.

- If, after prenatal exposure, small reversible changes in foetal growth and in skeletal development (e.g. wavy ribs, short rib XIII, incomplete ossification) in offspring occur at a higher incidence than in the control group in the absence of maternal effects, the substance will be classified in category 3 for developmental toxicity. If these effects occur in the presence of maternal toxicity, they will be considered as a consequence of this and therefore the substance will not be classified for developmental toxicity (see Annex C, 4.2.3.3 developmental toxicity final paragraph).
- Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.
- Effects on sex organs in a general toxicity study (e.g. in a subchronic or chronic toxicity study) may warrant classification for fertility.
- The committee not only uses guideline studies (studies performed according to OECD standard protocols*) for the classification of compounds, but non-guideline studies are taken into consideration as well.

1.4 Labelling for lactation

The recommendation for labelling substances for effects during lactation is also based on Directive 93/21/EEC. The Directive defines that substances which are absorbed by women and may interfere with lactation or which may be present (including metabolites) in breastmilk in amounts sufficient to cause concern for the health of a breastfed child, should be labelled with R64. Unlike the classification of substances for fertility and developmental effects, which is based on a hazard identification only (largely independent of the dosage), the labelling for effects during lactation is based on a risk characterisation and therefore also includes consideration of the level of exposure of the breastfed child.

Consequently, a substance should be labelled for effects during lactation when it is likely that the substance would be present in breast milk in potentially toxic levels. The committee considers a concentration of a compound as potentially toxic to the breastfed child when this concentration leads to exceedence of the exposure limit for the general population, eg the acceptable daily intake (ADI).

1.5 Data

Literature searches were conducted in the on-line databases Toxline and Medline, starting from 1966 up to 2000. Literature was selected primarily on the basis of the text

* Organisation for Economic Cooperation and Development

of the abstracts. Publications cited in the selected articles, but not selected during the primary search, were reviewed if considered appropriate. In addition, handbooks and a collection of most recent reviews were consulted as well as several websites regarding (publications on) toxicology and health. References are divided in literature cited and literature consulted but not cited.

The committee chose to describe human studies in the text, starting with review articles and, in addition, the studies are summarised in Annex D. Of each study the quality of the study design (performed according to internationally acknowledged guidelines) and the quality of documentation are considered.

Animal data are described in the text and summarised in Annex D.

1.6 Presentation of conclusions

The classification is given with key effects, species and references specified. In case a substance is not classified as toxic to reproduction, one of two reasons is given:

- Lack of appropriate data preclude assessment of the compound for reproductive toxicity.
- Sufficient data show that no classification for toxic to reproduction is indicated.

1.7 Final remark

The classification of compounds is based on hazard evaluation* only, which is one of a series of elements guiding the risk evaluation process. The committee emphasises that for derivation of health based occupational exposure limits these classifications should be placed in a wider context. For a comprehensive risk evaluation, hazard evaluation should be combined with dose-response assessment, human risk characterisation, human exposure assessment and recommendations of other organisations.

* for definitions see Tox95

Chapter 2

Metallic lead

2.1 Introduction

The aim of this report is to classify metallic lead for its possible effects on reproduction. Lead occurs in different forms, which can be categorised in soluble and insoluble lead salts, ionic lead, metallic lead and organic lead compounds (e.g. tetra ethyllead). However, in papers regarding exposure to lead or toxic effects of lead, the different lead compounds are usually not specified. The analytical methods for determining the lead exposure do no specify the different lead species. In general, only a distinction is made between organic and inorganic lead compounds (IPC95). Inorganic lead comprises metallic lead, its salts and oxides/sulfides (ATS97). Because metallic lead partly decomposes in air in several lead compounds (eg leadoxide), the committee is of the opinion that exposure to pure metallic lead is unlikely. The committee assumes that exposure to metallic lead is always accompanied by exposure to other inorganic lead compounds.

The group of lead compounds* has already been classified for effects on reproduction by the European Union. For effects on fertility, lead compounds have been classified in category 3 (*substances which cause concern for human fertility*) and labelled with R62 (*possible risk of impaired fertility*). Lead compounds have been classified for developmental toxicity in category 1 (*Substances known to cause*

* The ministry of Social Affairs and Employment assumed that metallic lead was not included in the group of inorganic lead compounds which is classified by the EU for effects on reproduction

developmental toxicity in humans) and labelled with R61 (*may cause harm to the unborn child*). For effects during lactation lead compounds have not been labelled.

2.2 Properties

Name	:	(metallic) lead
CAS-no	:	7439-92-1
Use	:	batteries, pigments, alloys
Mol weight	:	207.19
Chem formula	:	Pb
Conversion factor	:	1 ppm = 8.63 mg/m^3 (101 kPa, 25ºC) 1 mg/m^3 = 0.12 ppm 1% = 10000 ppm = 12000 mg/m^3

2.3 Human studies

Human studies are described in more detail in Tables 1, 2 and 3 (Annex D).

Fertility

Several studies regarding the effects of exposure to (unspecified) lead compounds on fertility in men were found.

Lancranjan *et al*. (Lan75) studied the reproductive ability of men occupationally exposed to unspecified lead compounds in a battery plant. Exposed men were divided into 1) lead poisoned men, men showing 2) moderately increased, 3) slightly increased or 4) physiological absorption of lead. Mean BLLs (blood (total) lead levels) of the groups were 230, 410, 530 and 750 µg/l. All groups showed effects on spermatogenesis (hypospermia and asthenospermia) and the group with BLLs higher than 410µg/l showed teratospermia.

Braunstein *et al*. (Bra78) found that the intercourse frequency and testosterone levels were significantly decreased in a small group of lead (unspecified) poisoned (BLL 387 µg/l) and (unspecified) lead exposed men (290 µg/l) working in a lead smelter compared to controls (161 µg/l). No significant differences occurred in sperm volume, motility and percentage of abnormal forms between the groups. Testicular biopsies of 2 lead poisoned men showed both increased peritubular connective tissue, decreased spermatogenesis and the presence of lipofuscin bodies. Moreover, the excretion of LH (luteinizing hormones) differed in the poisoned men compared to the other groups. Poisoned men quit working and were treated with Ca EDTA 3 months before the onset of the study.

Wildt *et al*. (Wil83) found no differences in sperm morphology, count, motility and biochemistry of men with high (unspecified) lead exposure (mean BLL 450 µg/l) compared to men with low exposure (220 µg/l) at a battery factory. However, the chromatin of the spermatozoa of the men with high (unspecified) lead exposure had a significantly lower stability than the chromatin of the lower exposed men and a decreased function of the accessory genital gland was found more frequently among higher exposed men.

Cullen (Cul84) described 7 men with several occupations who were intoxicated with (unspecified) lead compounds and underwent endocrine evaluation at the time of diagnosis (maximum BLLs 660-1390 µg/l). Defects in thyroid function were present in 3 patients, whereas 6 patients had subnormal glucocorticoid production and plasma cortisol responses. Although serum testosterone concentration was normal in 6 patients, 5 had defects in spermatogenesis, including 2 with oligospermia and 2 with azoospermia. Repeated examinations after chelation therapy showed only partial improvement.

Chowdhury *et al*. (Cho86) showed a small group of men who worked at a printing company with blood and semen (total) lead levels of 425 and 148 µg/l, respectively, to have less motile sperm, lower sperm counts and a higher amount of sperm with tail abnormalities than controls from the administrative staff (lead levels significantly lower, but unknown). Seminal plasma acid phosphatase, succinic dehydrogenase and fructose content were lower in exposed men, whereas sperm volume, pH, colour and viscosity did not differ between exposed and controls.

Wives of men working at a battery plant (mean BLL 640 µg/l) had a significantly ($p<0.01$) higher rate of spontaneous abortions compared to the controls with 2-3 times less lead (unspecified compounds) in their blood (AlH86).

Govoni *et al*. (Gov87) showed that the prolactin levels in men who were working in small pewter factories, were higher when blood lead (unspecified compounds) and ZPP (zinc protoporphyrin) levels were higher than 400 µg/l or when ZPP is higher than 400 µg/l. However, all prolactin levels were within the normal range).

Compared to cement workers, men working in a storage battery plant for 1 to 10 years showed significantly higher BLLs (610 versus 180 µg/l), semen lead (unspecified) and zinc protoporphyrin IX levels (Ass87). No differences were found in mean testosterone, prolactin, total neutral 17-ketosteroid, LH and FSH levels. However, the frequency distribution of sperm count was significantly lowered in unspecified lead exposed men.

Fischer-Fischbein *et al*. (Fis87) described the case of a firearms instructor who had not been able to conceive a child for 2 years. At the start of chelation therapy his BLL was 880 µg/l which sank within 6 months to 300 µg/l. After 2.5 years of therapy, the semen volume had decreased by a factor 2, whereas sperm density and total sperm count

had increased about 16 and 9 times, respectively. The motility of the sperm had remained equal whereas normal morphological appearance and head defects had slightly improved. After 1 year of therapy a healthy child was conceived.

Rodamilans *et al*. (Rod88) studied effects of exposure to (unspecified) lead compounds on several endocrine parameters of men working in a lead smelter for <1 year, 1-5 years or >5 years. BLLs and zinc protoporphyrin IX were significantly increased in all exposed groups (BLL ca. 700 µg/l) compared to the controls (170 µg/l). Serum testosterone was significantly decreased after more than 5 years of exposure and the free testosterone index after more than 1 year of exposure compared to controls. Steroid binding globulin was increased after exposure for more than 1 year and LH at all exposure durations. FSH concentration did not change.

Gustafson *et al*. (Gus89) studied hormone levels in men exposed to (unspecified) lead compounds in a secondary lead smelter (BLL 390 µg/l) and controls (50 µg/l). Only FSH levels were significantly decreased in the lead (unspecified) exposed men. When only workers aged younger than 40 years were taken into account (as correlations exist for several hormones and age), thyroxin levels were increased and FSH, LH and cortisol levels were decreased compared to controls.

Coste *et al*. (Cos91) showed that BLLs higher than 600 µg/l (overall mean 463 µg/l) in men working at a battery factory, are not associated with fertility (defined as the number of live births to a couple in one year).

Men exposed to (unspecified) lead compounds in three battery factories showed significantly higher blood lead (352 µg/l) and aminolevulinic acid dehydratase levels than controls (BLL 83 µg/l) (Ng91). Moreover, LH and FSH levels were significantly increased at the age of 40 years and younger, whereas testosterone was lower at the age of 40 years and older compared to controls. Prolactin levels did not differ. Both secondary hypogonadism and compensated primary hypogonadism were significantly elevated in the exposed group.

Lindbohm *et al*. (Lin91) concluded from a case-control study using a set of Finnish registries in which the association between paternal exposure to (unspecified) lead compounds and spontaneous abortions was studied, that the data only demonstrated a significant relationship between spontaneous abortion and BLLs higher than 311 µg/l at time of spermatogenesis.

Lerda *et al*. (Ler92) showed a significant decrease in sperm count, motility and death cells in men working at a battery factory with mean BLLs of 486-866 µg/l compared to controls working at the same factory (BLL 235 µg/l). In all exposed groups, the percentage of anomalies had increased significantly.

Hu *et al*. (Hu92) also reported decreased number of sperm and increased the incidence of teratospermia as well as a decreased level of lactate dehydrogenase-x in

sperm of men exposed to (unspecified) lead compounds in a printing house or battery factory (mean urine lead level 87.6 µg/l).

Gennart *et al*. (Gen92a) did not find evidence for significant differences in a variety of renal and endocrine blood parameters, total erythrocyte count and an autonomic nervous system parameter between men employed in a lead (unspecified lead compounds) acid battery factory for at least 1 year (mean BLL 510 µg/l) and comparable controls (209 µg/l).

Gennart *et al*. (Gen92b) studied the effects of exposure to (unspecified) lead compounds on male reproductive function in a battery plant. While the fertility, the probability of a live birth, of the lead-exposed workers (BLL 463 µg/l) was somewhat greater than that of the unexposed (104 µg/l) before the onset of exposure, a significant decrease in fertility was observed during the period of exposure to unspecified lead compounds.

Alexander *et al*. (Ale96) showed geometric mean sperm concentration and total sperm count to be inversely related to BLL (BLL <150 µg/l, 150-240 µg/l, 250-390 µg/l and >400 µg/l). Employees with BLLs higher than 400 µg/l had an increased risk of having low sperm concentration and low total sperm count according to WHO norms. Sperm concentration, total sperm count and total motile sperm count were inversely related to long term lead exposure. No relations were found between (unspecified) lead exposure and sperm motility and morphology and serum levels of reproductive hormones.

Lin *et al*. (Lin96) examined the relationship between exposure to (unspecified) lead compounds and fertility (actual versus expected number of births) for exposed men (BLLs 250-340 µg/l, 350-490 µg/l and >500 µg/l) with a group of bus drivers as a control. The overall standard fertility ratio was significantly lower for the exposed men, especially for men with heavy exposure (>500 µg/l and duration of exposure for 5 years) and long exposure (more than 5 years). BLLs of bus drivers were not measured.

Sallmén *et al*. (Sal00) studied the time to pregnancy of the wives of men occupationally exposed to (unspecified) lead compounds. Exposure categories were 104-186 µg/l, 207-290 µg/l, 311-373 µg/l and >394 µg/l; only for the 3rd category a significant relation was found between the adjusted fecundability density ratio for wives of exposed men and controls (BLLs <104 µg/l).

Sallmén *et al*. (1995) studied the fertility of women occupationally exposed to (unspecified) lead compounds with BLLs in three categories: 100 µg/l, 100<BLL>190 µg/l and BLL 190 µg/l. No relationships were found between BLL and time to pregnancy or decreased fecundability after adjustment for several confounders.

The committee emphasises that none of the above described fertility studies concerned exposure to *pure* metallic lead.

Development

In a retrospective case control study, Sallmén *et al*. (Sal92) showed an increased odds ratio for congenital malformations after paternal exposure to (unspecified) lead compounds for 80 days prior to conception (BLLs controls <186 µg/l, exposed between 207 µg/l and >394 µg/l). However, this increase was not significant. Moreover, all case children had a different type of malformation.

Kristensen *et al*. (Kri93) studied the effects of paternal exposure to (unspecified) lead compounds in members of three printers' unions in Oslo. The (unspecified) lead exposure did not appear to have substantial impact on preterm birth, birth weight and gestational age. However, exposure to unspecified lead compounds was associated with an increased risk of death in the perinatal period (combining late abortions, stillbirths and early neonatal deaths). Birth defects were generally not associated with lead exposure, although a significantly increased risk of cleft lip and/or palate was observed among the male offspring of fathers belonging after exposure to lead or to lead and solvents together.

Fahim *et al*. (Fah92) showed that preterm and term pregnancies with premature rupture of the membrane occured more in the area around a lead smelter than in an area without any mining activities. However, mean foetal and maternal BLL did not differ between the areas. For each area maternal and foetal BLLs for preterm and term with premature rupture were 2-4 times higher than for term pregnancies.

Several papers compared women living around a lead smelter in Port Pirie (Australia) to women living in the surrounding agricultural area. The mean prenatal and perinatal BLLs in the Port Pirie women (106 µg/l) were significantly higher than in the agricultural women (76 µg/l) (Mc86). Although more Port Pirie women had a spontaneous abortion than non-Port Pirie women, these were not related to BLL. The relative risk for a pre-term delivery was significantly increased at BLLs of >140 µg/l. Stillbirths were negatively associated with individual maternal BLL. BLLs were not related to birth weight, crown heel length, head circumference, premature rupture of membranes, congenital anomalies or difficulties in conceiving.

In the children born in the same Australian cohort, Wigg *et al*. (Wig88) studied neurological development at 24 months of age in relation to BLLs of the pregnant mother and of the child after birth. Bayley's Mental Development Index was only negatively correlated to the maternal BLL at 20 weeks of gestation, whereas Bayley's Psychomotor Development Index was not related to any BLL measured. At 4 years of age the children were assessed with the McCarthy Scales of Children's Abilities (Mc88). Although relations between antenatal BLLs and several parameters existed, they did not remain after adjustment for certain covariates.

A comparable cohort study was performed in Yugoslavia. BLLs were 160 and 52 µg/l for women living around the lead smelter and women from another town at the time of study (Mur90). After adjustment for cofactors no differences were found regarding town of residence and spontaneous abortion or stillbirths. In a different subgroup of this cohort, no relation between birth weight or length of gestation and town of residence or midpregnancy BLL (54 µg/l in the town versus 191 µg/l around the lead smelter) was observed (Fac91). In addition, it was shown that preterm delivery did not increase with BLL (neither with BLL at mid-pregnancy nor with cord or maternal BLL at delivery).

Mean gestational age, birth weight, height and head circumference were also not found to be related to BLLs of women working in a storage battery factory with maximal mean BLLs of 203.8 µg/l in comparison to control women (max. mean BLL 72.5 µg/l) (Wan96).

Finally, Rothenberg *et al*. (Rot92) described a case of a pregnant women whose BLL was ca. 100 µg/l until week 36 of pregnancy and rose, after starting using a glazed ceramic pitcher containing lead, to ca. 500 µg/l at delivery. The BLL of the baby amounted to ca. 1000 µg/l at delivery and decreased to 175 µg/l at 3 years of age. Psychometric and diagnostic testing yielded scores within normal limits out to 3 years. However, hypertonia, irritability, abnormal cry and other neurological soft signs at 2, 15 and 30 days were found. EEG sleep patterns were fragmented at 20 days and 3 months and abnormal respiratory patterns were noted to 6 months. Moreover, at every visit hyperactivity and distractibility were noted until finishing of the follow up at three years of age.

Again, the committee emphasises that none of the above described developmental toxicity studies concerned exposure to *pure* metallic lead.

Lactation

Several studies are summarised regarding lead (unspecified compounds) levels in milk. Two groups of studies are considered: exposure to chemically specified sources and non-specified sources. The latter studies are further subdivided according to geographic region because different lifestyle conditions may influence lead levels in breast milk.

The FAO/WHO (FAO93) recommended a PWTI (provisional tolerable weekly intake) for lead of 25 µg/kg body weight. From this, an acceptable lead level of 16 µg/l in human breast milk can be calculated (see Annex D).

Specified source

Three reports regarding concentrations of (unspecified) lead compounds in breast milk of women exposed specifically to lead were available. In the first 2 months of lactation, Ryu *et al*. (Ryu78) measured up to 63 µg/l in breast milk of a woman who had worked for 3 years at a producer of batteries until 7 weeks before delivery. Namihira *et al*. (Nam93) found a maximum of 350 µg/l (mean 24.7 µg/l) in breast milk given within 2 months after parturition by women living within 200 m of a lead smelter in Mexico City. Women around a lead smelter in Sweden gave, 6 weeks postpartum, milk with a mean of 0.9 µg Pb/l (Pal95).

Lead concentrations in breast milk of women not particularly exposed to lead also varied widely. The highest concentrations were reported by Noirfalise *et al*. (Noi67), who found up to 1500 µg/l in breast milk of women living in the province of Liège (Belgium). The mean lead content of the 76 samples amounted to 277 µg/l and 74 samples contained between 0 and 900 µg Pb/l. The analytical method used by Noirfalise *et al*. (Noi67) (polarography), however, differs widely from the ones used in other studies (atomic absorption spectrometry and anodic stripping voltametry).

Unspecified sources

Europe
Samples collected during four consecutive years in Germany (Niedersachsen) showed median breast milk lead (unspecified compounds) levels of <4, 43, 35 and 4 µg/l for 1987, 1988, 1989 and 1990, respectively (End92). Significant differences in breast milk lead levels between rural and urban areas were found in Croatia (4.7 versus 10.6 µg/l) (Frk97) and Germany (9.2 versus 13.2 µg/l) (Ste85). However, in studies in Austria (Tir 94) and Greece (Vav97) with mean breast milk lead levels of 3.4 µg/l (range 0-20.4 µg/l) and 90 µg/l (range 50-250 µg/l), these differences were not observed.

Lead content (unspecified compounds) of milk collected at various time points during the day did not differ (Ste85) nor did the lead content of milk collected 3 or 6 months post partum (mean 2 µg/l, range 0.5-9.0 µg/l) (Lar81). However, colostrum contained about 1.5-1.7 times more lead than mature milk (Ste85). Other European studies showed mean concentrations of lead in breast milk of 21 µg/l (Moo82), 4.1 µg/l (Kov84), 2.6 µg/l (Sch88), 16.8 µg/l (Par91) and 35.8 µg/l (Plo93) (overall range 0-70.3 µg/l). Milk samples were taken between 2 days and 8 weeks post partum.

North-America
Mean lead (unspecified) content in breast milk obtained from North-American women amounted to 20 µg/l (Lam73), 10.9 µg/l (Pin73), 26 µg/l (Dil74), 2.8 µg/l (Roc84), 17 µg/l (Rab 85) and 0.57 µg/l (Dab86) (overall range 0-72 µg/l). Samples were taken up to 16 months of lactation. Breast milk of mothers of full-term or premature infants did not differ in lead content (0-4 µg/l) (Fri99).

Oceania
Two studies in the area of Oceania were performed. Casey *et al*. (Cas77) did not found lead (unspecified) levels in milk above the detection limit (10 µg/l) in breast milk collected on day 4-10 of lactation of women in New-Zealand. Gulson *et al*. (Gul89) found a mean lead level as low as 0.73 µg/l (range 0.09-3.1 µg/l) in breast milk of Australian immigrant women.

Asia
Women living in heavily polluted areas of Bangkok produced breast milk containing 84.6 µg Pb/l (range 13.6-222.23 µg/l) (Cha78). Breast milk of Malaysian (Ong85), Phillippinian (Par91) and Indian (Tri99) women contained 47.7, 16.6 and 1.9 µg Pb/l (overall range 0-105.7 µg/l), respectively. The lead (unspecified) level in breast milk of rural and urban women in Malaysian differed significantly (21.1 versus 25.3 µg Pb/l) (Hua83). Parr *et al*. (Par91) did not find any differences in lead content of breast milk of women from different socio-economical classes in Malaysia.

Africa
Average concentrations of lead (unspecified) in breast milk of women in 20 urban and rural areas in Egypt amounted to 9.0-101.4 µg/l (individual range 0-158 µg/l) with highest concentration in urban areas (Sal96). Breast milk of women living in Nigeria and Zaire contained 4.9 and 5.0 µg Pb/l (Par91). No differences were found in milk samples obtained from women from different socio- economical classes.

South America
Only one report was available regarding lead (unspecified) levels in breast milk of women living on the South American continent. Parr *et al*. (Par91) found a mean lead level of 2.9 µg/l in breast milk of women from Guatemala. No differences were found in breast milk lead levels of women from different socio economical classes.

2.4 Animal studies

Quite a number of papers on the effects of lead exposure on reproduction are available. However, studies are performed with lead salts (predominantly lead acetate and lead nitrate) rather than with metallic lead. Moreover, in a number of papers, the exact entity of lead used for exposure is unclear.

Fertility studies

Animal studies regarding metallic lead exposure and fertility were not available.

Developmental toxicity

Sharma *et al*. (Sha76) dosed 12 Columbia-Rambouillet cross-bred ewes daily with 0.5 to 16 mg/kg (unspecified) lead in the diet to maintain a BLL of approximately 400 µg/l. Three days after starting the experiment a Dorset ram was turned into the group every morning and evening. The rate of abortions in exposed and unexposed animals was 27 and 0%, respectively. The rate of lambing in the exposed and unexposed sheep was 18 and 100%, respectively. Three animals in the exposed group either did not conceive or their foetuses were resorbed; two others were nongravid. One sheep contained a mummified fetus in the uterus on postmortem examination. Aborted and born foetuses/ lambs in the exposed group were all without apparent abnormalities.

Lactation

No publications were available.

2.5 Conclusion

In general, metallic lead is considered to belong to the group of inorganic lead compounds. Fertility effects found after male exposure to lead (unspecified compounds) included decreased intercourse frequency (Bra78, Cul84), reduced likelihood to have any children (Lin96), increased rate of spontaneous abortions (AlH86), slightly increased time to pregnancy (Sal00) and effects on sperm/spermatogenesis (Lan75, Bra78, Wil83, Cho86, Ass87, Ler92, Hu92, Ale96). On the hormonal level, effects were observed on testosterone (Bra78, Rod88, Ng91), LH (Cul84, Rod88, Gus89, Ng91), FSH (Cul84, Ass87, Rod88, Gus89, Ng91), prolactin, thyroxin and cortisol (Cul84, Gov87, Gus89), however, these results were not always consistent. In the only human

study regarding reproduction and female exposure to lead no effects on fertility and time to pregnancy were observed (Sal95).

Animal data concerning exposure to pure metallic lead and effects on fertility were not available.

The committee concludes that several effects on fertility were described in humans after exposure to (unspecified) lead compounds. However, these effects were not always consistent. In addition, the European Union has already classified the inorganic lead compounds in category 3. Because the committee assumes that exposure to metallic lead always involves exposure to other inorganic lead compounds, the committee recommends to classify metallic lead for effects on fertility in category 3 (substances which cause concern for human fertility).

Kristensen *et al*. (Kri93) found a significantly increased risk for male offspring with cleft lip and/or palate of fathers exposed to both lead and solvents. Lead exposure was also associated with an increased risk of death in the perinatal period. McMichael *et al*. (Mc86) found the relative risk for preterm delivery to be increased with maternal BLLs>140 µg/l. Fahim *et al*. (Fah76) showed maternal and foetal BLLs to be 2-4 times higher for preterm and term pregnancies with premature rupture compared to normal term pregnancies. However, this was unrelated to the presence or absence of a lead smelter in the area. Wigg *et al*. (Wig88) found Bayley's Mental Development Index at 24 months of age negatively correlated to maternal BLLs at 20 weeks of gestation.

A child with very high BLLs, described in a case report, performed within normal limits on the same psychometric tests. However, according to two behavioural scales, the child was hyperactive and easily distracted.

One animal study was available in which ewes received (unspecified) lead through the diet, resulting in an increased abortion rate and a decreased lambing rate (Sha76).

In conclusion, several effects on development were found in humans after exposure to (unspecified) lead. Moreover, the European Union has classified the inorganic lead compounds in category 1. Because the committee assumes that exposure to metallic lead always involves exposure to other inorganic lead compounds, the committee recommends to classify metallic lead for effects on development in category 1 (substances known to cause developmental toxicity in humans).

In several studies (Ryu78, Nam93, Pal95), mean (unspecified) lead levels in breast milk were determined after exposure to specified (known) sources. These lead levels in breast milk ranged up to 350 µg/l (Ryu78, Nam93, Pal95). These levels exceeded the calculated acceptable level of 16 µg/l breast milk. Because the committee assumes that exposure to metallic lead always involves exposure to other inorganic lead compounds,

the committee recommends to label metallic lead for effects during lactation with R64 (may cause harm to breastfed babies)*.

Proposed classification for fertility

Category 3

Proposed classification for developmental toxicity

Category 1

Proposed labelling for effect during lactation

R64

* The committee is of the opinion that all inorganic lead compounds should be labelled with R64.

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A The committee

B Comments on the public draft

C Directive (93/21/EEC) of the European Community

D Fertility and developmental toxicity studies

E Abbreviations

Annexes

Annex **A**

The committee

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Annex **B**

Comments on the public draft

A draft of the present report was released in 2002 for public review. The following persons and organisations have commented on the draft review:

- N van der Vliet, Uzimet BV, Rijswijk
- V Digernes, Federation of Norwegian Process Industries, Norway

Annex **C**

Directive (93/21/EEC) of the European Community

4.2.3 Substances toxic to reproduction

4.2.3.1 For the purposes of classification and labelling and having regard to the present state of knowledge, such substances are divided into 3 categories:

Category 1:

Substances known to impair fertility in humans

There is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility.

Substances known to cause developmental toxicity in humans

There is sufficient evidence to establish a causal relationship between human exposure to the substance and subsequent developmental toxic effects in the progeny.

Category 2:

Substances which should be regarded as if they impair fertility in humans:

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in impaired fertility on the basis of:

- Clear evidence in animal studies of impaired fertility in the absence of toxic effects, or, evidence of impaired fertility occurring at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of the other toxic effects.
- Other relevant information.

Substances which should be regarded as if they cause developmental toxicity to humans:

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in developmental toxicity, generally on the basis of:

- Clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects.
- Other relevant information.

Category 3:

Substances which cause concern for human fertility:

Generally on the basis of:

- Results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2.
- Other relevant information.

Substances which cause concern for humans owing to possible developmental toxic effects:

Generally on the basis of:

- Results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2.
- Other relevant information.

4.2.3.2 The following symbols and specific risk phrases apply:

Category 1:

For substances that impair fertility in humans:

T; R60: May impair fertility

For substances that cause developmental toxicity:

T; R61: May cause harm to the unborn child

Category 2:

For substances that should be regarded as if they impair fertility in humans:

T; R60: May impair fertility

For substances that should be regarded as if they cause developmental toxicity in humans:

T; R61: May cause harm to the unborn child.

Category 3:

For substances which cause concern for human fertility:

Xn; R62: Possible risk of impaired fertility

For substances which cause concern for humans owing to possible developmental toxic effects:

Xn; R63: Possible risk of harm to the unborn child.

4.2.3.3 Comments regarding the categorisation of substances toxic to reproduction

Reproductive toxicity includes impairment of male and female reproductive functions or capacity and the induction of non-inheritable harmful effects on the progeny. This may be classified under two main headings of 1) Effects on male or female fertility, 2) Developmental toxicity.

1 *Effects on male or female fertility*, includes adverse effects on libido, sexual behaviour, any aspect of spermatogenesis or oogenesis, or on hormonal activity or physiological response which would interfere

with the capacity to fertilise, fertilisation itself or the development of the fertilised ovum up to and including implantation.

2 *Developmental toxicity*, is taken in its widest sense to include any effect interfering with normal development, both before and after birth. It includes effects induced or manifested prenatally as well as those manifested postnatally. This includes embrytoxic/fetotoxic effects such as reduced body weight, growth and developmental retardation, organ toxicity, death, abortion, structural defects (teratogenic effects), functional defects, peripostnatal defects, and impaired postnatalmental or physical development up to and including normal pubertal development.

Classification of chemicals as toxic to reproduction is intended to be used for chemicals which have an intrinsic or specific property to produce such toxic effects. Chemicals should not be classified as toxic to reproduction where such effects are solely produced as a non-specific secondary consequence of other toxic effects. Chemicals of most concern are those which are toxic to reproduction at exposure levels which do not produce other signs of toxicity.

The placing of a compound in Category 1 for effects on Fertility and/or Developmental Toxicity is done on the basis of epidemiological data. Placing into Categories 2 or 3 is done primarily on the basis of animal data. Data from *in vitro* studies, or studies on avian eggs, are regarded as 'supportive evidence' and would only exceptionally lead to classification in the absence of *in vivo* data.

In common with most other types of toxic effect, substances demonstrating reproductive toxicity will be expected to have a threshold below which adverse effects would not be demonstrated. Even when clear effects have been demonstrated in animal studies the relevance for humans may be doubtful because of the doses administrated, for example, where effects have been demonstrated only at high doses, or where marked toxicokinetic differences exist, or the route of administration is inappropriate. For these or similar reasons it may be that classification in Category 3, or even no classification, will be warranted.

Annex V of the Directive specifies a limit test in the case of substances of low toxicity. If a dose level of at least 1000 mg/kg orally produces no evidence of effects toxic to reproduction, studies at other dose levels may not be considered necessary. If data are available from studies carried out with doses higher than the above limit dose, this data must be evaluated together with other relevant data. Under normal circumstances it is considered that effects seen only at doses in excess of the limit dose would not necessarily lead to classification as Toxic to Reproduction.

Effects on fertility

For the classification of a substance into Category 2 for impaired fertility, there should normally be clear evidence in one animal species, with supporting evidence on mechanism of action or site of action, or chemical relationship to other known antifertility agents or other information from humans which would lead to the conclusion that effects would be likely to be seen in humans. Where there are studies in only one species without other relevant supporting evidence then classification in Category 3 may be appropriate.

Since impaired fertility may occur as a non-specific accompaniment to severe generalised toxicity or where there is severe inanition, classification into Category 2 should only be made where there is evidence that there is some degree of specificity of toxicity for the reproductive system. If it was demonstrated that impaired fertility in animal studies was due to failure to mate, then for classification into Category 2, it would normally be necessary to have evidence on the mechanism of action in order to interpret whether any adverse effect such as alteration in pattern of hormonal release would be likely to occur in humans.

Developmental toxicity

For classification into Category 2 there should be clear evidence of adverse effects in well conducted studies in one or more species. Since adverse effects in pregnancy or postnatally may result as a secondary consequence of maternal toxicity, reduced food or water intake, maternal stress, lack of maternal care, specific dietary deficiencies, poor animal husbandry, intercurrent infections, and so on, it is important that the effects observed should occur in well conducted studies and at dose levels which are not associated with marked maternal toxicity. The route of exposue is also important. In particular, the injection of irritant material intraperitoneally may result in local damage to the uterus and its contents, and the results of such studies must be interpreted with caution and on their own would not normally lead to classification.

Classification into Category 3 is based on similar criteria as for Category 2 but may be used where the experimental design has deficiencies which make the conclusions less convincing, or where the possibility that the effects may have been due to non-specific influences such as generalised toxicity cannot be excluded.

In general, classification in category 3 or no category would be assigned on an ad hoc basis where the only effects recorded are small changes in the incidences of spontaneous defects, small changes in the proportions of common variants such as are observed in skeletal examinations, or small differences in postnatal developmental assessments.

Effects during Lactation

Substances which are classified as toxic to reproduction and which also cause concern due to their effects on lactation should in addition be labelled with R64 (see criteria in section 3.2.8).

For the purpose of classification, toxic effects on offspring resulting *only* from exposure via the breast milk, or toxic effects resulting from *direct* exposure of children will not be regarded as 'Toxic to Reproduction', unless such effects result in impaired development of the offspring.

Substances which are not classified as toxic to reproduction but which cause concern due to toxicity when transferred to the baby during the period of lactation should be labelled with R64 (see criteria in section 3.2.8). This R-phrase may also be appropriate for substances which affect the quantity or quality of the milk.

R64 would normally be assigned on the basis of:

a toxicokinetic studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk, and/or

b on the basis of results of one or two generation studies in animals which in- dicate the presence of adverse effects on the offspring due to transfer in the milk, and/or

c on the basis of evidence in humans indicating a risk to babies during the lactational period. Substances which are known to accumulate in the body and which subsequently may be released into milk during lactation may be labelled with R33 and R64.

Annex **D**

Fertility and developmental toxicity studies

Table 1.1 Human studies on effects of Pb on fertility

authors	subjects	exposure	design	effect/observations	remarks
occupationally exposed men					
Lancranjan *et al*. (1975)	exposed men (n=16-29) and a control group (n=50)	men working at a storage battery plant which were 1) Pb poisoned or showed 2) moderately increased, 3) slightly increased or 4) physiological absorption	physical and toxicological examination (Pb levels in blood and urine, analysis of coproporphyrine and d-ALA levels and total neutral 17-Ks elimination); semen analysis of semen collected after 3 days of abstinence	in all four exposed groups a significant increase in alterations in spermatogenesis (hypospermia and asthenospermia) was observed; in the three highest exposed groups teratospermia was found no relation was found between total neutral 17-Ks elimination and the level of Pb absorption (groups 1-4)	classification was based on clinical (group 1) and toxicological criteria: BLLs were 750, 530, 410 and 230 µg/l, urine Pb levels 390, 250, 100 and 92 µg/l, coproporphyrine levels 0.39, 0.30, 0.08 and 0.04 mg/l and δ-ALA levels 56.5, 22.4, 7.7 and 4.4 mg/l for group 1, 2, 3 and 4, respectively mean age of men was 38 years alcohol consumption was in all groups equally distributed 44% of the investigated men smoked BLLs in controls were unknown

Braunstein *et al*. (1978)	Pb poisoned men (n=6), Pb exposed men (n=4) and controls (n=9)	*Poisoned men* had a 2-11 year (mean 6 year) history of chronic exposure at a secondary Pb smelter. *Exposed men* worked at the same smelter for 1-23 years (mean 8.1 years), but had no clinical signs of poisoning, 3 of them had noted some decrease in libido and frequency of intercourse. *Controls* had no present or past history of excessive environmental Pb exposure	testicular biopsies were taken of two out of 6 poisoned men in all groups FSH, LH, TST, estradiol and prolactin were measured and semen samples were taken these parameters were also determined after administration of clomiphene or human chorionic gonadotropin or gonadotropin releasing hormone	frequency of intercourse had significantly decreased in both Pb exposed groups compared to controls. BLL at time of testing was 387 and 290 µg/l in the poisoned and exposed group compared to 161 µg/l in the controls. After administration of EDTA only the urine Pb level in the Pb poisoned group was significantly higher than the controls (999.3 vs. 224.6 µg/24°). No significant differences occurred in sperm volume, motility and % abnormal forms between the groups. The biopsies were similar and showed an increase in peritubular connective tissue, a decrease in spermatogenesis and the presence of lipofuscin bodies (degrading lysosomes) in the Sertoli cells. Differences in basal hormone levels were apparent for TST for both Pb exposed groups (lower TST levels in treated groups). Following administration of human chorionic gonadotropin, increment of TST was significantly increased in the Pb poisoned men, following administration of clomiphene the increment of estradiol in both Pb exposed groups was significantly decreased, in poisoned men increment of LH was also decreased; in poisoned men the peak response of LH had decreased after administration of gonadotropin releasing hormone	poisoned men suffered from peripheral neuropathy, saturine gout and encephalopathy and/or recurrent abdominal colicky pains controls were of similar socioeconomic background as the exposed groups mean age did not differ between groups (30-39 years) all poisoned men had been treated with Ca EDTA before the analyses were performed poisoned men were removed from this work for at least 3 months and had received one or more courses of chelation therapy

Table 1.2 Human studies on effects of Pb on fertility

authos	subjects	exposure	design	effects/observations	rem.
Wildt *et al*. (1983)	Group A: men exposed to Pb (n=31) and Group B: men not exposed to Pb (n=31)	all men worked in a battery factory in Sweden	31 men in group A were matched with 31 men in group B. Semen samples were obtained after 5 days of abstinence in September and April and quality was assessed	no difference was noted between the exposed and non-exposed men regarding sperm morphology, count, motility and biochemistry. Of group A, 28% had a low semen volume compared to 4% in group B. 43.5% of group A and 12.5% of group B showed a decreased function of the accesssory genital glands and the statistical analysis showed a significant difference only for zinc spermatozoa from exposed men had a significantly lower resistance against SDS treatment (chromatin stability) than those from the control group	men were matched for age and ethnic and social factors group A: BLL > 0.5 mg/l once in 6 months prior to the study (mean 450 µg/l); group B: BLL occasionally >0.3 mg/l and ZPP levels <0.3 mg/l (mean 220 µg/l) September was 3 months after the period with lowest exposure in the year and April 3 months after the period with highest exposure in the year
Cullen *et al*. (1984)	men diagnosed for Pb intoxication (n=7)	men were shake out man (1), furnace man (2), storage battery worker (3, 7), chemical operator (4) or painter (5, 6), exposure ranged from 5 weeks to 15 years	follow-up study patient were examined and patients 1, 3, 4, 5 and 7 were treated with Ca EDTA until BLL were <300 µg/l	*case 1* (11 y exp) was impotent and had chronic diffuse dermatitis and small testes with a BLL 550 µg/l and a free erythrocyte protoporphyrin of 533 units; sperm was not found in the ejaculate and LH and FSH levels were elevated; *case 2* (15 y exp) suffered from persistent back pain with BLL of 660 µg/l and a free erythrocyte protoporphyrin of 345 units; sperm count was $18x10^6$/ml with 40% motile sperm; *case 3* (6 mo exp) was impotent and had developed colic with a BLL of 830 µg/l and ZPP of 285 units; sperm count was $12x10^6$/ml with 11% motile sperm; *case 4* (2 mo exp) suffered from headaches, abdominal pain and paresthesias in his left arm with BLL 980 µg/l and ZPP 132 units; gonadal function was within the normal range; *case 5* (5 y exp) had decreased libido, insomnia, arhtralgia and depression with BLL of 700 µg/l and ZPP 222 units; sperm was 25% motile; *case 6* (5 wk exp) developed colic with a BLL of 900 µg/l and ZPP of 135 units (vasectomized); *case 7* (7 y exp) had developed diffuse arthralgias, intermittent abdominal pains and irritability with a BLL 390 µg/l; slightly small testes of normal texture with no sperm in ejaculate and elevated FSH; *cases 1, 2 and 7* had defects in thyroid function and except 6, all men had subnormal glucocorticoid production after treatment. case 1 had slightly improved thyroid and adrenal corticoid function, case 3 had slightly improved adrenal corticoid function and sperm count rise, case 4 had sperm count drop (due to re-exposure after treatment), case 5 had sperm count rise and case 7 had slightly improved adrenal corticoid function	cases men lived in Connecticut and were between 22 and 43 years of age (mean 35 year) normal free erythrocyte protoporphyrin <40; normal ZPP <28 units; normal sperm count >20 10^6/ml and % motile >50%

Table 1.3 Human studies on effects of Pb on fertility

authors	subjects	exposure	design	effect/observations	remarks
Chowdhury *et al*. (1986)	exposed men (n=10) and a control group (n=10)	exposed men were working at a newspaper printing press and were exposed 8 h/day for 10 years, controls were from the administrative staff of the same press	semen samples were colleted and physical characteristics of the semen were recorded	average Pb level in blood and semen of the exposed was 425 and 148 µg/l, respectively, and significantly higher than in the controls average sperm counts were significantly lower and sperm was less motile, seminal plasma acid phosphatase, succinic dehydrogenase and fructose content was decreased and tail abnormalities of sperm were of marked predominance compared to the controls; volume, pH, colour and viscosity of the semen were unaffected compared to the controls	mean age was 30 years and mean weight was 55 kg, controls were from the same age and body weight group no figures were given in the article, just descriptions of the effects Pb levels of the controls were not given
Al-Hakkak *et al*. (1986)	healthy exposed men (n=22) and a control group (n=22)	exposed men were working at a storage battery plant, controls were employees of the Scientific Research Council	questionnaire sheets on pregnancy outcome were distributed	the rate of spontaneous abortion (mean number of abortions per family) was significantly higher in the workers' family (1.04) compared to that in the controls (0.30) ($p<0.01$)	controls were matched for sex, age, work, years of service, social status and education BLLs were not measured, but in a paper regarding the same plant, dust samples contained 9725 µg/g and BLLs of exposed and unexposed men amounted to 380-960 µg/l (mean 640 µg/l) and 60-300 µg/l (mean 240 µg/l), respectively
Govoni *et al*. (1987)	Pb exposed men (n=76)	all men worked in small pewter factories	men were randomly selected from those regularly controlled by the NHS blood was taken and analysed for BLL, prolactin and ZPP men were divided into 4 groups	BLLs were 282, 603, 331 and 491 µg/l for group A, B, C and D, respectively ZPP levels were 244, 1310, 770 and 340 µg/l for group A, B, C and D, respectively prolactin levels were 34.4, 50.6, 53.4 and 33.1 µg/l for group A, B, C and D, respectively (all prolactin levels are within the normal range) ZPP and prolactin levels were significantly increased in group B and C compared to group A	men were divided into 4 groups: A BLL and ZPP <400 µg/l (n=22) B BLL and ZPP > 400 µg/l (n=33) C BLL <, ZPP >400 µg/l (n=13) D BLL >, ZPP <400 µg/l (n=8)

Table 1.4 Human studies on effects of Pb on fertility

authors	subjects	exposure	design	effects/observations	remarks
Assennato *et al*. (1987)	exposed men (n=18) and a control group (n=18)	exposed men worked at a storage battery plant (exposure 0.054-0.584 mg Pb/m^3) during 1-10 years control group were cement workers not particularly exposed to Pb	monitoring of exposure, questionnaire, physical examination, semen donation after 3-5 days of abstinence, collection of blood, urine and semen for analyses of Pb, ZPP, TST, prolactin, total neutral 17-ks, LH and FSH	blood Pb (610 vs.180 µg/l), urinary Pb (79 vs.18 µg/l), semen Pb (79 vs. 22 µg/l) and ZPP levels (2.1 vs. 0.24 mg/l) were significantly higher in battery workers than in cement workers; mean TST, prolactin, total neutral 17-ks, LH and FSH levels were not significantly different the cumulative frequency distribution of battery worker sperm counts was significantly shifted when compared to cement workers (38% lower median sperm count (45 vs. 73x10^6 cells/cc))	mean age of both groups was 40-41 year no differences between groups in wine and coffee consumption and smoking habits
Fischer-Fischbein *et al*. (1987)	reduced fertile man (n=1)	occupational exposure as firearms instructor and during cleaning and maintenance of the range	man was physically examined, blood Pb and ZPP levels were determined as well as semen quality; the man was hospitalized for chelation therapy	blood Pb level was 880 µg/l and blood ZPP level 3.6 mg/l, after chelating therapy for 6 months blood Pb level had sank to ca. 300 µg/l and blood ZPP level to 0.3 mg/l, both only slightly sank further during the course of the therapy 2.5 years after starting therapy semen volume had decreased from 1.3 to 0.7 ml, sperm density had increased from 9.6 to 158x10^6/ml and total sperm count had increased from 12.5 to 110x10^6/ ejaculate; motility had remained equal (50-60%) and the intensity of motility had changed from poor to good; normal morphological appearance of sperm cells had increased from 40 to 61% and head defects had decreased from 30 to 22% after 1 year of therapy a healthy child was conceived	case man was 41 years of age, having one child from a previous marriage and trying to have another child since 2 years man did not smoke and drank alcohol infrequently results of a physical examination were normal
Rodamilas *et al*. (1988)	exposed (n=23) and non-exposed (n=20) men	men worked in a Pb smelting works during 1) < 1 year 2) 1-5 years 3) >5 years	blood and serum were collected at 8 am and analysed for BLL, serum TST level, red blood cell, ZPP, SBG level and serum LH and FSH levels	BLL increased significantly from 170 µg/l in control men to ca. 700 µg/l in all exposed groups; ZPP had significantly increased in all exposed groups (2.5 vs. 0.19 mg/l); there were no differences between exposed groups for BLL and ZPP serum TST was only significantly lower in the longest exposed group (18.6 vs. 22.9 nmol/l) SBG had significantly increased in the two longest exposed groups to the same extend compared to the control group (34 vs. 25 nmol/l) the free TST index was decreased in the two longest exposed groups (71 and 55% vs. 93%) LH concentration was significantly increased in all exposed groups to the same extend (10 vs. 6 U/l) FSH concentration did not change significantly (5 U/l)	none of the men had clinical symptoms of Pb exposure 1) mean age 30 y (21-44, n=5) 2) mean age 33 y (21-46, n=8) 3) mean age 34 y (25-52, n=10) control men between 20-60 years of age

Table 1.5 Human studies on effects of Pb on fertility

authors	subjects	exposure	design	effects/observations	remarks
Gustafson *et al*. (1989)	healthy men exposed (n=25) and non-exposed to Pb (n=25)	exposed men worked at a secondary Pb smelter controls were engineering industry workers and post-office employees	matched study BLL was determined as well as LH, FSH, total TST and PRL in plasma and cortisol, TSH, T3, thyroxine and free TST in serum	BLLs differed significantly between exposed men and controls (390 vs. 50 µg/l) FSH level was significantly decreased in exposed men compared to controls (3.6 vs. 4.5 U/l) when persons who had taken selenium pills* were excluded from the study, the lower FSH in exposed workers was more pronounced, whereas a higher thyroxine level became significant. as correlations existed for age and TST, age and FSH and age and TSH, a subgroup of workers <40 years of age was selected: significant differences existed for thyroxine (exposed vs. control, 88 vs 73 nmol/l), FSH (2.9 vs. 4.1 U/l), LH (7.6 vs. 8.9 U/l) and cortisol (295 vs. 382 nmol/l)	average age was 36 and 36.8 years for exposed and control men none of the subjects had any known alcohol or drug problems general health was assessed by liver function and serum urate level men were matched for age and shiftsall values were within the normal range *Pb might influence selenium metabolism
Coste *et al*. (1991)	fertile men exposed (n=229) and non-exposed (n=125) to Pb (exposed 886 person-years, non-exposed 598 person-years)	men working at a battery factory divided in 4 groups: 1) workpost non-exposed 2) workpost with BLL <400 µg/l 3) workpost with 400 µg/l BLL 600 µg/l 4) workpost with BLL >600 µg/l	person-year-analysis taking confounders into account; infertility was defined by the non-occurrence of live birth during one observed year	Pb exposure did not appear to be associated with infertility, in contrast to age >40 years, French origin, primary school education level and having a child or children	men were aged 20-60 (mean 36.5) and had worked at least 1 year in the factory; average follow-up was 4.1 years and 63% of the subjects was observed for the entire duration of the study confounders taken into account were age, ethnic origin, education level, socio-economic status, no. of previous live births, alcohol consumption, smoking, exposure to heat, working hours and sulfuric acid exposure
Lindbohm *et al*. (1991)	men occupationally exposed to Pb and their pregnant wives having had a spontaneous abortion (n=213) or had given normal birth (n=300)	men were occupationally exposed to Pb and worked in numerous fields of industry	case-referent study questionnaire on job and pregnancies, data were obtained from medical registers and the Institute of Occupational Health BLLs were as much as possible obtained from the spermato-genesis period	Pb exposure in cases and referents did not differ significantly: ca. 25% of the men had BLL <207 µg/l and ca. 2.5% >394 µg/l BLLs were not found to be related significantly to the incidence of spontaneous abortion in general when only BLLs measured during or close to the time of spermatogenesis were taken into account, an increased risk on spontaneous abortion was detected for BLL >311 µg/l (OR 3.8, 95% CI 1.2-12)*	* model was adjusted for paternal exposure to Cd and Hg, maternal exposure to organic solvents, Hg and alcohol, parity, contraception, previous spontaneous abortion and the index of missing information

Table 1.6 Human studies on effects of Pb on fertility

authors	subjects	exposure	design	effects/observations	remarks
Ng *et al*. (1991)	men exposed (n=122) and non-exposed (n=49) to Pb	exposed men worked in three Pb battery factories (mean 18 mg Pb/m^3) controls were hospital engineering and maintenance workers or technicians	BLL and ALAD in erythrocytes analysis was carried out every 6 months starting January 1982 (mean 6.2 times) TST, LH, FSH and PRL levels were determined	average BLLs amounted to 352 and 83 µg/l for exposed and control men (p=0.0001) ALAD was 0.45 µM/h/ml RBC in exposed men and 1.25 µM/h/ml RBC in controls (p<0.0001); LH and FSH were significanlty increased in exposed men compared to controls (LH 4.59 vs. 3.24 IU/l and FSH 2.52 vs. 1.92 IU/l);TST and PRL did not differ significantly (TST ca. 7 ng/ml, PRL ca. 194 mIU/l); when the groups were divided in men younger than 40 years and 40 years and older, TST was significantly lower in the exposed group aged 40 years and above than in controls (p<0.01) and LH and FSH were significantly higher in exposed men younger than 40 years compared to controls (p<0.01); PRL did not show any age-specific differences reduced TST and normal LH levels (sec. hypogonadism) were noted in 13.9% of the exposed subjects and 4.1% of the non-exposed subjects (p=0.05); raised LH values with normal TST levels (compensated prim. hypogonadism) were found in 23.8% of the exposed and 6.1% of the non-exposed subjects (p<0.05)	none of the subjects had a history of liver, renal or other recent or chronic diseases or illnesses no significant differences in age, smoking and drinking habits existed between the two groups mean age was 34.4 and 32.6 years in non-exposed and exposed groups; mean years of exposure was 6.0
Lerda (1992)	healthy fertile men exposed (n=38) and non-exposed (n=30) to Pb	men working at a battery factory grouped according to Pb blood level A) 866 µg/l B) 659 µg/l C) 486 µg/l control 235 µg/l	blood and sperm samples were collected after 4 days of abstinencelevels of Pb and d-ALA in blood were analysed as well as several sperm parameters	mean δ-ALA levels in blood were 14.2, 19.4, 24.6 and 39.3 U/l for A, B, C and controls, respectivelysperm count (A vs. control, 69.2 vs. $101.5x10^6$/ml), motility (49.0 vs. 70.4%) and death (68.1 vs. 82.9%) had significantly decreased in all exposed groups compared to controls; the percentage of anomalies had increased significantly (72.5 vs. 33.4%) in all groups	average exposure time 11.7 years mean age 36 years (exposed) and 35 years (controls)
Hu *et al*. (1992)	men exposed (n=24) and non-exposed (n=24) to Pb	exposed men worked at small printing house or battery factory (concentration of Pb exceeded 0.03 mg/m^3 all year long), controls were building workers	questionnaire; analysis of urine Pb level and several semen parameters	mean Pb urine level differed significantly between exposed (87.6 µg/l) and controls (4.2 µg/l) sperm of exposed men contained significanlty less cells/ml ($56.9 vs. 76.7x10^8$/ml) and significantly more teratospermic cells (21.0 vs. 12.3%); sperm motility did not differ significantly between groups; a decreased level of lactate dehydrogenase-x was found in sperm of the exposed group	age, living conditions, smoking and drinking habits and exposure to other toxicants harmful to the reproductive system did not differ significantly between the groups

Table 1.7 Human studies on effects of Pb on fertility

authors	subjects	exposure	design	effects/observations	remarks
Gennart *et al*. (1992a)	men exposed (n=98) and non-exposed (n=85) to Pb	exposed men were employed in a Pb acid battery factory and were moderately exposed according to their BLL (mean 510 µg/l, range 400-750 µg/l) for at least 1 year, controls worked in factories in the area and had a mean BLL of 209 µg/l (range 44-390 µg/l)	questionnaire, determination of several parameters in blood and urine, and cardiac parasympathic function	no effect of Pb could be evidenced on the renal and endocrine parameters, total erythrocyte count or autonomic nervous system	no statistically significant difference in age, weight, height, smoking and drinking habits and urinary cadmium levels were observed between controls and exposed menblood parameters measured were ZPP, creatinine, β_2-microglobulin, triiodothyronine, thyroxine, triiodothyroine resin uptake, TSH, FSH, LH urine parameters measured were ALA, creatinine, retinol-binding protein, albumin, β_2-microglobulin, N-acetyl- b-D-glucosaminidas; parasympathic function was assessed by measuring interval variation between the consecutive R waves on the electrocardiogram
Lerda (1992)	healthy fertile men exposed (n=38) and non-exposed (n=30) to Pb	men working at a battery factory grouped according to Pb blood level A) 866 µg/l B) 659 µg/l C) 486 µg/l control 235 µg/l	blood and sperm samples were collected after 4 days of abstinencelevels of Pb and d-ALA in blood were analysed as well as several sperm parameters	mean d-ALA levels in blood were 14.2, 19.4, 24.6 and 39.3 U/l for A, B, C and controls, respectively sperm count (A vs. control, 69.2 vs. $101.5x10^6$/ml), motility (49.0 vs. 70.4%) and death (68.1 vs. 82.9%) had significantly decreased in all exposed groups compared to controls; the percentage of anomalies had increased significantly (72.5 vs. 33.4%) in all groups	average exposure time 11.7 years mean age 36 years (exposed) and 35 years (controls)

Table 1.8 Human studies on effects of Pb on fertility

authors	subjects	exposure	design	effects/observations	remarks
Alexander *et al*. (1996)	men (n=12-46)	men working at a Pb smelter were divided into 4 groups: 1) BLL <150 µg/l 2) BLL 150-240 µg/l 3) BLL 250-390 µg/l 4) BLL 400 µg/l	cross sectional study blood and semen samples were collected after 48h of abstinence and analysed for Pb level; semen was analysed for TST, FSH and LH level	mean blood Pb concentration was 224 µg/l (range 50-580 µg/l) geometric mean sperm concentration and total sperm count were inversely related to BLL; workers with BLL >400 µg/l had an increased risk of having a below WHO normal sperm concentration and total sperm count also after controlling for several effects* independent of current Pb exposure, sperm concentration, total sperm count and total motile sperm count were inversely related to measures of long term Pb exposure no association was found between Pb exposure and measures of sperm motility and morphology or serum concentrations of reproductive hormones	mean age of men 38.2-41.8 years mean years of service 15.7-19.8 *alcohol consumption, presence of other metals in blood, period of abstinence, history of reproduction difficulties, use of hot tubs and saunas and history of reproductive tract infection
Lin *et al*. (1996)	Pb exposed (n=4256) and non-exposed men (n=5148)	exposed men were reported to the New York State Heavy Metals Registry; controls were bus drivers licenced in the State of New York	retrospective cohort study Pb exposure was divided into high (500 µg/l), medium (350-490 µg/l) and low (250-340 µg/l) BLLs birth certificates were consulted	50.4% of the cases reported had low, 39.1% medium and 10.4% high BLLs Pb exposed workers had fewer births than expected (overall SFR 0.88, 95% CI 0.81-0.95) mean group BLLs were not associated with fertility, but workers with heavy exposure (>500 µg/l and duration of exposure >5 years) were significantly less likely to have any children compared to the control group (ratio 0.4 95% CI 0.2-0.7) as well as any worker with exposure time > 5 years (ratio 0.3, 95% CI 0.2-0.5) (after adjustment for confounders: ratio 0.38, 95% CI 0.23-0.61)	men were matched to age and residence BLLs of bus drivers were not measured no differences exist between groups for distribution of race, wife's age, parity of history of abortion men were registered when BLL 400 µg/l (1981-1986) or when BLL 250 µg/l (1986-1992) SFR = standard fertility ratio confounders were education, race and residence

Table 1.9 Human studies on effects of Pb on fertility

authors	subjects	exposure	design	effects/observations	remarks
Occupationally exposed women					
Sallmén *et al*. (2000)	wives of husband occupationally exposed to Pb (n=502)	exposed men were reported to the Finnish Institute of Occupational Health	retrospective study Pb exposure was assessed from blood Pb measurements and questionnaires completed by the men. data on wives was obtained from the central population register, TTP was calculated based on data obtained from the women themself	24.5% of the men in the study had BLL >207 µg/l and 4.6% had BLL >394 µg/l the fecundability density ratios, adjusted for potential confounders*, were 0.92 (95% CI 0.73-1.16), 0.89 (0.66-1.20), 0.58 (0.33-0.96) and 0.83 (0.50-1.32) for blood Pb categories 104-186 µg/l, 207-290 µg/l, 311-373 µg/l and >394 µg/l**	paternal exposure was assessed when possible about 80 days before the attempt at pregnancy began *age of wife, unplanned pregnancy, maternal and paternal life style, use of contraception, menstruational factors, age at menarche, previous pregnancies, year of pregnancy, frequency of intercourse, pregnancy outcome, maternal exposure to organic solvents or Pb, paternal exposure to organic solvents or other metals ** discontinuous categories arise from the translation of µmol/l in the paper to µg/l in this report
Sallmén *et al*. (1995)	women occupationally exposed to Pb (n=65) and non-exposed women (n=56)	women had been occupationally exposed to Pb and had been monitored at the Institute of Occupational Health (Finland); women from the two highest categories worked in the graphic industry, chemical industry and metal industry	based on biologically monitoring, work description and a self-report of exposure, women were divided in four exposure groups; time-to-pregnancy was related to exposure with the discrete proportional hazards regression	there were no systematic differences in the distribution of time to pregnancy between exposed and non-exposed women exposure to Pb was not significantly associated with decreased fecundability (measured as the incidence density ratio which estimates an average ratio of incidence densities of pregnancies for exposed women compared with the unexposed through menstrual cycle classes) after adjustment for exposure to carcinogens, age, parity, use of alcohol, use of coffee, older age at menarche, vaginitis and frequency of intercourse	exposure categories were: not exposed, BLL 100 µg/l, 100<BLL>190 µg/l, BLL 190 µg/l

ALA= -aminolevulinic acid; ALAD = aminolevulnic acid dehydratase; BLL= blood Pb level; FSH= follicle-stimulating hormone; ks= ketosteroid; LH=luteinizing hormone; PRL = prolactin; SHBG = sex hormone binding globulin; SBG = serum steroid binding globulin; T3 = triiodothyronine; TSH=thyroid-stimulating hormone; TST = testosterone; TTP = time to pregnancy; ZPP = zinc protoporphyrin IX

Table 2.1 Human studies on effects of Pb on development

authors	subjects	exposure	design	effects/observation	remarks
Exposed men					
Sallmén *et al*. (1992)	children with (n=27) or without (n=57) congenital malformations of Pb exposed and non-exposed men	men had been occupationally exposed to Pb and had been monitored at the Institute of Occupational Health (Finland)	retrospective case control study ata on exposure (1973-1983) women and pregnancies and pregnancy outcomes were collected all 18-40 year women with a malformed child were defined as cases and matched with 3 times as much age controls cases and controls were divided in 4 groups based on estimated BLLs during 80 d period before conception	80.7% of the controls had a BLL <186 µg/l and 19.3% had a BLL between 207-290 µg/l; for the cases 63% and 18.5% were in these first two groups, whereas 14.8% and 3.7% had BLL between 311-373 µg/l and >394 µg/l, respectively* the distribution of exposed cases by the type of malformation was heterogeneous and all the five case children of the men in the two highest Pb exposure categories had a different type of malformation the OR of congenital malformations for paternal Pb exposure was increased (OR 2.4, 95% CI 0.9-6.5) though not reaching statistical significance	BLLs used were obtained within 36 months of the spermatogenesis period prior to conception (80 d) occupations were repair of automobiles, electrical, painting and welding work and other iron and metal work *categories given in the paper are 0-0.9 µmol/l, 1.0-1.4 µmol/l, 1.5-1.8 µmol/l and 1.9 µmol/l
Kristensen *et al*. (1993)	men exposed to Pb only (n=1205) and all children born to printers (n=6251)	Pb exposed men were involved in several printing tasks (compositors, lithographers, bookbinders)	men were categorised as to their exposure to Pb and solvents, non-exposed employees served as controls; all births that occurred in Oslo during the same period served as an external reference records from the printers union and birth registration were linked	deaths occurring during the perinatal period (including late abortions, stillbirths, early neonatal deaths) were significantly increased for children of the Pb exposed men (adjusted OR 2.4, 95% CI 1.2-4.9) (early) preterm birth, length of gestational age, small for gestational age and low birth weight were not related to Pb exposure the standardized morbidity ratio for boys with fathers exposed to Pb or exposed to Pb and solvents (no distinction was made) was significantly increased for cleft lip (SMR 4.1, 95% CI 1.8-8.1)	

Table 2.2 Human studies on effects of Pb on development

authors	subjects	exposure	design	effects/observation	remarks
Exposed women					
Fahim *et al*. (1976)	pregnant women around delivery (n=249-253)	women living in the neighbourhood of a Pb smelter (Rolla, Missouri) were compared to women living in an area without any Pb mining activities (Colombia, Missouri)	Pb analyses in maternal and cord blood, placenta and membrane, recording of placenta weight and length and diameter of umbilical cord, morphological and histological examination of placenta, questionnaire regarding pregnancy and newborn	In the area around the smelter 70.0% of the women were term, 17.0% were term with PRM and 13.0% were preterm, in the control area these percentages were 96.4, 0.4 and 3% fetal and maternal BLLs did not differ significantly between the areas, however for both areas BLLs were significantly higher in term with PRM and preterm pregnancies compared to term pregnancies (maternal BLL 256-301 µg/l vs. 131-143 µg/l and fetal BLL 96-175 µg/l vs. 43-46 µg/l) no differences were observed for ceruloplasmin levels in both maternal and fetal blood except for premature pregnancies: fetal ceruloplasmin levels were significantly decreased for both the exposed and control group (98-105 mg/l vs. 175 mg/l) Pb levels in placenta and cord did not differ significantly (placenta 60-90 µg/kg, cord 90-120 µg/l) Pb levels in the membrane increased in both exposure groups significantly in preterm and term with PRM compared to term deliveries (ca. 250-400 µg/kg vs. 50-100 µg/kg)* no pathological findings in the cell structure were observed in histological sections taken from placenta, cord or membrane	women were between 20 and 25 years of age and living in the subsequent areas for at least 10 years definitions: premature: neonate born before 37 weeks of gestation and weighing less than 2500 g premature rupture of the membrane (PRM): spontaneous rupture of the membrane before the onset of labour and when labour does not begin within 12 hours *figures are obtained from a graph in the paper
McMichael *et al*. (1986)	pregnant mothers and their newborn babies (n=774-831)	women lived in the city of Port Pirie (78%), a Pb smelter community, or in the surrounding agricultural area (22%)	during 3 years women were enrolled for prospective study BLLs were determined at 14-20 weeks' gestation, around 32 weeks' gestation and at delivery (mother and umbilical cord), 31% enrolled much earlier and also then a blood samples was taken data on pregnancy outcome and socio-economic status was obtained	The mean prenatally and perinatally BLLs were in PP women significantly higher than in NP women, except between weeks 21-29 of gestation (106 µg/l vs. 76 µg/l) in NP women 1 woman had a spontaneous abortion, whereas in PP women 22; these were not related to BLL the relative risk for a pre-term delivery increased with maternal BLL and was significantly increased when BLL >140 µg/l (RR 4.4, 95% CI 1.2-16.8) and highest with BLL at delivery although more still births occurred in the PP women (17.5/1000 vs. 5.8/1000 live births), still births were negatively associated with individual maternal BLL BLLs were not significantly related to birth weight, crown heel length, head circumference, premature rupture of membranes, congenital anomalies or difficulties in conceiving	Port Pirie cohort study age distribution over Port Pirie (PP) and non-Port Pieri (NP) women were similar among PP women, 85% had lived there for at least 3 years, while 79% and 70% had lived there for at least 5 and 10 years, respectively pre-term delivery: birth before the 37th week, including stillbirths

Table 2.3 Human studies on effects of Pb on development

authors	subjects	exposure	design	effects/observation	remarks
Wigg *et al*. (1988)	pregnant mothers and their newborn babies (n=497-523)	all children were born in the city of Port Pirie, a Pb smelter community, or in the surrounding agricultural area	BLLs were determined at enrollment of the mothers (at 14-20 weeks of gestation), early in the third trimester, at delivery, from cord, and at postnatal age 6, 15 and 24 months of age and anually thereafter, at 24 months of age the developmental status of each child was assessed with the Bayley scales	mean BLL of umbilical blood amounted to 83 µg/l the mean MDI was 109.2 and the mean PDI 105.3 MDI was significantly negatively correlated with BLL after 20 weeks of gestation but not at delivery nor with cord BLL, PDI was not related with any of the BLLs measured prenatally or around birth	Port Pirie cohort study
McMichael *et al*. (1988)	pregnant mothers and their newborn babies (n=537-463)	all children were born in the city of Port Pirie, a Pb smelter community, or in the surrounding agricultural area	see previous study children were assessed with the McCarthy Scales of Children's Abilities at 4 years of age	mean maternal BLL varied from 91 µg/l at 16 weeks of gestation to 95 µg/l at delivery, mean BLL in the cord was 83 µg/l mean scores for verbal, perceptual performance, quantitative, GCI , memory and motor were 53.5, 56.9, 50.5, 107.1, 48.2 and 53.8 on a 100 (GCI) or 50 (all others) scale antenatal (average) BLL was significantly negatively correlated with GCI and memory scale, whereas BLL at delivery was significantly negatively related to GCI, perceptual-performance and memory scale, cord BLL was not related to any of the scales; after partial regression analyses incorporating covariates no associations remained	Port Pirie cohort study covariates included sex, residence, HOME score and aspects regarding parents and delivery

Table 2.4 Human studies on effects of Pb on development

authors	subjects	exposure	design	effects/observation	remarks
Murphy *et al*. (1990)	pregnant women (n=304-335)	women lived in Titova Mitrovica in the neighbourhood of a Pb smelter, refinery and battery plant controls were from Pristina both towns are in Yugoslavia	BLLs were determined and pregnancy outcome (first pregnancy) recorded	current BLLs were 160 and 52 µg/l for women from T. Mitrovica and Pristina, respectively erythrocyte protoporphyrin was higher in exposed women than in controls (0.71 vs. 0.5 µmol/l) haemoglobin was similar for both groups (123-125 g/l) as well as serum ferritin (10.8-12.5 µg/l) adjustment for maternal age at first pregnancy, current smoking, ethnic group, and maternal education, resulted in a small difference in the odds ratio regarding town of residence and spontaneous abortion (OR 1.1 (95% CI 0.9-1.4) or stillbirths (OR 1.0 (95% CI 0.6-1.5)	Kosovo study women were selected who had at least one previous pregnancy and had not moved since their first pregnancy mean maternal and paternal age was 21.7-22.1 and 25.6-26.0 years for both regions, respectively mean maternal and paternal education was 8.7 and 11.2-11.3 for both regions, respectively in T. Mitrovica 28.8% of the husbands were employed in Pb industry whereas in Pristina none of them was occupationally involved with Pb mean number of previous pregnancies, percentage current smokers and alcohol users and ethnic groups were equally distributed among both regions
Factor-Litvak *et al*. (1991)	pregnant women exposed (n=401) and non-exposed (n=506) to Pb and their newborn babies	women lived in Titova Mitrovica in the neighbourhood of a Pb smelter, refinery and battery plant controls were from Pristina both towns are in Yugoslavia	women were enrolled at mid-pregnancy and BLL were determined; at delivery birth weight and length of gestation were recorded as well as BLL in cord blood	BLLs at mid-pregnancy, delivery and in umbilical cord were 191, 234 and 222 µg/l for T. Mitrovica and 54, 68 and 56 µg/l for Pristina birth weight did not vary significantly between both towns or mid-pregnancy BLLs (TM 3308 g vs. P 3361 g) nor did length of gestation (TM 274 days vs. P 275 days) preterm delivery occurred in 16.8% of births in TM and 11.4% in P (unadjusted OR, using town as exposure variable = 1.6, 95% CI 1.3-1.9), however, when exposure was defined by BLL the odds of preterm delivery did not increase with BLL (neither mid-pregnancy nor cord or maternal BLL at delivery)	Kosovo study

Table 2.5 Human studies on effects of Pb on development

authors	subjects	exposure	design	effects/observation	remarks
Rothenberg *et al.* (1992)	pregnant women and her infant (n=1)	family lived in Mexico City	follow-up for 3 years BLLs of mother and child were determined child was regularly assessed for neurologic and general development	during pregnancy maternal BLL was ca. 100 µg/l until week 36, at delivery the BLL had risen to ca. 500 µg/l cord BLL amounted to ca. 700 µg/l, babies BLLs amounted to ca. 1000, 400, 350, 425, 325, 350 and 175 µg/l at 1.5, 6, 12, 15, 18, 24, 30 and 36 months of age, respectively NBAS and G/R showed hypertonia, irritability, abnormal cry and other neurological soft signs at 2, 15 and 30 days; brainstem auditory evoked responses and clinical EEG were essentially normal at 20 days, 3, 6 and 12 months; EEG sleep pattern was fragmented at 20 days and 3 months and abnormal respiratory patterns were noted at 6 months; psychometric and diagnostic testing yielded scores within normal limits up to 3 years; at every examination, testing protocols noted some combination of restlessness, agitation, distractibility, high energy level, lack of persistence, short attention span and poor fine motor control	case at week 36 a glazed ceramic pitcher was brought into the family woman complained of lumbar pain radiating to the abdomen, paresthesia in the lower extremities, nausea, occasional vomiting and hypertension child was nursed continuously until the age of 27 months psychometric testing included Bayley scales, Terman Merril and McCarthy scales diagnostic testing included Fagan test of infant intelligence
Wan *et al*. (1996)	pregnant mothers exposed (n=45) and non exposed (n=56) to Pb and their newborn infants	women worked in a storage battery, the concentration of air Pb in their work room ranged between 0.05-0.5 mg/m^3 depending on operational site controls worked in a electronics assembly plant	blood and urine was collected at the beginning of pregnancy and then every three months till delivery and analysed for Pb and ZPP (blood) and ALA and creatinine (urine) birth characteristics were recorded	BLLs in the first trimester, at delivery and in the cord amounted to 178.8, 203.8 and 185.6 µg/l for the exposed group and 54.1, 72.5 and 71.3 µg/l for the controls, respectively ZPP levels were 841.5, 936.2 and 692.4 µg/l for the exposed group and 319.8, 436.2 and 491.1 µg/l for the controls, respectively values for BLL and ZPP were significantly different between the exposed and control women mean gestational age in the exposed group was 274.6 days and birth weight, height and head circumference were 3352 g, 49.5 cm and 33.7 for the male babies and 3315 g, 49.7 cm and 33.6 cm for the female babies, no significant differences existed between the control and the exposed groups in the exposed group there were 2 still births and 4 pre-term births, whereas in the control group there were 3 pre-term births and no stillbirths	women had an average age of 25.5 y (23-34) and a mean exposure time of 3.5 years (0.6-6) pregnancies were diagnosed as normal and women had no chronic illnesses control women were selected with similar age distribution

δALA= δ-aminolevulinic acid; BLL = blood Pb level; CI = confidence interval; G/R = Graham/Rosenblith Behavioural Examination of the Neonate included General Maturation scale, Neurological Soft Sign Score and Muscle Tonus; HIAA = 5-hydroxy indoleacetic acid; HOME = Home Observation for Measurement of the Environment; MDI = mental development index (Bayley); NBAS = the Brazelton Neonatal Behavioural Assessment Scale; PDI = psychomotor development index (Bayley); ZPP = zinc protoporphyrin IX.

Mental Development Index is an age-corrected scale that assesses infants "sensory-perceptual acuities, discriminations, and the ability to respond to these; the early acquisition of 'object constancy', memory, learning, and problem solving ability: vocalizations and the beginnings of verbal communication; and early evidence of the ability to form generalizations and classifications, which is the basis of abstract thinking".
The McCarthy Scales of Children's Abilities can be subdivided in verbal, perceptual-performance and quantitative scales contributing to the general cognitive index and, partially overlapping the first three, in a memory and motor scale.
The items recorded for the G/R Soft Signs Scale included ratings of slight or moderate jitteriness, decreased strength of cry, high pitched cry, slight or definite indication of hypersensitivity to touch, to sound or to light, sharp state swings, and setting sun sign (one instance).

Table 3.1 Human studies on effects of Pb on lactation

authors	subjects	exposure	design	effects/observation	remarks
Ryu *et al*. (1978)	lactating woman	woman had worked 3 years (until 7 weeks before delivery) by a producer of electrical storage batteries and had been exposed during this occupation to considerable amounts of Pb dust	determination of Pb content in milk and blood of mother and child from 8 weeks before partition until day 245 of lactation	during exposure maternal blood Pb concentration ranged from 0.43-0.57 mg/l which decreased to 0.33 mg/l at delivery (mean Iowa women 0.1 mg/l (range 0.02 to 0.29)); during lactation Pb levels were higher with a peak after 6 months (0.63 mg/l) Pb concentration in cord blood amounted to 0.33 mg/l and in blood taken from the child aged 12 h, 6 days and 9 months 0.7, 0.51 and 0.2 mg/l, respectively. milk Pb concentrations were in the first three weeks of lactation 19-63 µg/l and the following month 36-62 µg/l, where after it decreased.; mean value 3rd month of lactation 24 µg/l, and month 4-7 of lactation 4-14 µg/l.	case woman was 25 years old first born daughter to the women and weight 2982 g, physical and neurologic examinations did not reveal any abnormality
Namihira *et al*. (1993)	healthy lactating women aged 15-39 (n=35)	living <200 m around a Pb smelter in 3 areas of Mexico City >1 year	Pb determination in blood and milk collected over a 2 months time	mean blood Pb level was 0.46 mg/l (range 0.15-0.99 mg/l) geometric mean milk level was 24.7 µg/l (range 9.2- 350 µg/l); 54% of samples was below detection level high correlation blood-milk Pb level (r=0.88) no correlations between parity, months of lactation, no. of children, years of residence and breast milk levels	women were 15-39 years of age and belonged to low socioeconomic class 51% of women had lived >10 years in this area 74% of the women had never smoked and the rest smoked <5 cigarettes/w 57% of the women had not nursed before mean duration of nursing 5.85 mo (range 1-27 mo)
Palminger Hallén *et al*. (1995)	healthy pregnant women (n=39)	women lived in Rönnskär or Holmsund in the neighbourhood of Rönnskär is a copper and Pb smelter situated	Pb analysis in maternal blood at delivery and 6 weeks postpartum and in milk 6 weeks postpartum	mean Pb concentration in blood from exposed mothers was 38.7 µg/l differed significantly from the control group, 32.3 µg/l at delivery (range 18-70 µg/l) 6w postpartum Pb concentration in the blood of exposed mothers had reduced to 31.7 µg/l, whereas the concentration in the control group remained stable Pb concentration in milk 6w postpartum differed significantly between the exposed and control group, 0,9 µg/l versus 0.5 µg/l (range 0.1-2.2 µg/l) 6w after delivery no correlation between Pb levels in blood and milk was observed, Pb levels in blood at delivery and in milk 6w postpartum were correlated as well as living area and milk Pb concentration	the mean age of both groups of women was 29 years 13 and 17 women in the exposed area and control group, respectively, were primaparous 8 and 4 children in the exposed and control group, respectively, received infant formula in addition to breast-feeding 6 weeks postpartum 16/35 and 37/39 samples of milk in exposed and control women respectively, were below the defined detection limit (1 µg/l)

Table 3.2 Human studies on effects of Pb on lactation

authors	subjects	exposure	design	effects/observation	remarks
Noirfalise *et al*. (1967)	lactating women (n=76)	no particular exposure, women lived in the province of Liège	Pb analyses in breast milk	milk contained on average 277 µg Pb/l (range 0-900 µg/l) two samples contained ca. 1200 and 1500 µg/l	women did not suffer from saturnism analytical method applied was a polarographic method
Lamm *et al*. (1973)	lactating women (n=7)	no particular exposure women lived in USA	determination of Pb content in milk	milk Pb concentrations amounted to 20 µg/l (range 0-70 µg/l)	
Pinkerton *et al*. (1973)	healthy lactating women aged 21-37 years (n=14)	no particular exposure women lived in Cincinnati, Ohio	determination of Pb content in milk samples collected between weeks 2 and 46 postpartum	Pb concentration in human and bovine milk ranged 6.0-20 µg/l (median 10.9 µg/l) and 9-154 µg/l (median 42.0 µg/l), respectively	women were 21-37 years of age women already had 1-6 children and nursed the present infant 2-46 weeks at sampling time 8 women smoked
Dillon *et al*. (1974)	lactating women (n=29)	no particular exposure women lived throughout the USA	determination of Pb content in milk samples	mean milk Pb concentration was 26 µg/l (range 6-58 µg/l)	women were white, urban, middle-class donors, aged 23-28
Casey (1977)	lactating women (n=25)	no particular exposure women lived in New Zealand	pooled milk sample taken 4-10 days after start of lactation	milk Pb content <10 µg/l	
Chatranon *et al*. (1978)	lactating women (n=164)	no particular exposure, women lived in heavily polluted areas of Bangkok	Pb analyses in breast milk collected from 1 day to more than 9 months post partum	mean milk Pb level was 84.6 µg/l (range 13.6-222.2 µg/l) no differences were observed between Pb levels in milks collected in different periods post partum	
Larsson *et al*. (1981)	healthy lactating women (n=41)	no particular exposure women lived in Uppsala (S)	measurement of Pb in breast milk 3 (18) and 6 (23) months post partum	mean Pb content in milk 2 µg/l (fresh weight) (range 0.5-9.0 µg/l) no differences in milk Pb content existed between the groups the calculated median weekly intake was 1.9 and 1.2 µg/kg bw for 3 and 6-month-old infants, respectively	
Moore *et al*. (1982)	healthy lactating women (n=93)	no particular exposure women lived in Glasgow	determination of Pb in milk and blood samples PN 6 w	geometric means for maternal and infant blood were 0.16 and 0.13 mg Pb/l, respectively, which were highly correlated median value for breast milk Pb concentration was 21 µg/l, which was correlated with maternal blood Pb concentration	none of the women (aged 17-37) had any known history of previous industrial Pb exposure all children showed normal mental and physical development
Huat *et al*. (1983)	lactating women (n=89-91)	three rural and three urban 3 areas in Malaysia	determination of Pb in milk at various times of lactation (<1->12 months)	mean milk Pb concentration significantly differed between urban (25.3 µg/l) and rural (21.1 µg/l) areas no specific pattern in Pb levels at different periods of lactation both among the urban and rural samples was observed	the estimated intake was for urban areas 15.5, 18.1 and 25.2 µg/day and for rural areas 12.9, 15.1 and 21.0 µg/day for infants at birth, and at the age of 6 and 12 months, respectively

Table 3.3 Human studies on effects of Pb on lactation

authors	subjects	exposure	design	effects/observation	remarks
Kovar *et al*. (1984)	healthy pregnant women (n=28) and their infants	no particular exposure women lived in London	measurement of Pb in blood of mother at delivery and PN day 5, in blood of child (cord) at delivery and in milk PN day 5	9 breast milk samples contained 4.1 µg Pb/l on average (range 0-8.9 µg/l), 19 samples contained amounts below the detection limit (1 µg/l) maternal blood contained 99.5 and 101.5 µg Pb/l at delivery and 5 days post partum, respectively and cord blood 87.0 µg Pb/l at delivery	mean age of women 29.2 medically uncomplicated pregnancies birth weight mean 3470 g all but one women took iron supplements during pregnancy and 9 took also multivitamins 6 women smoked during pregnancy and 2 until pregnancy was diagnosed
Rockway *et al*. (1984)	lactating women in rural and urban areas (in total 39 women)	no particular exposure women originated from rural and urban areas around Tucson, Arizona	measurement of Pb concentration in milk, hair and blood 1-16 months after partition	milk and blood contained 2.8 µg Pb/l and 119 µg Pb /l; hair contained 2002 µg Pb/kg no correlations were observed between the three parameters or between content in milk, month of lactation, concentration in other tissues and environmental concentration no differences between locations	women were 22-47 years of age
Ong *et al*. (1985)	pregnant/ lactating women and their babies (n=114)	no particular exposure, women lived in Malaysia	Pb analysis in maternal and cord blood collected at delivery and in milk collected PN day 3-5; 9 women continued to collect milk at PN days 3, 7, 10, 14, 20 and 30	on average maternal BLL was 151.3 µg/l (range 75.6-238.3), cord BLL was 114 µg/l (range 49.7-254.9) and breast milk contained 47.66 µg Pb/l (range 24.86-105.7 µg/l) BLL in maternal and cord blood were strongly relatedPb concentrations in breast milk did not vary significantly from three days to over a month postpartum	
Rabinowitz *et al*. (1985)	lactating women and their new borns (n=249)	no particular exposure; families lived within Greater Boston	Pb analysis in milk collected 1 and 6 months post partum, in cord blood and in capillary blood at 6 months of age	breast milk contained on average 17 µg Pb/l (range 0-72 µg/l) no differences were found in Pb level of breast milk collected 1 or 6 months post partum cord blood Pb (mean 0.072 mg/l, range 0-0.25) correlates poorly with breast milk Pb (mean 0.062 mg/l, range 0-0.49 mg/l) blood Pb at 6 months of age correlate very well with dietary Pb intake among children who were nursed	children were selected out of 11837 consecutive births and were drawn equally from the highest, lowest and centermost deciles of blood Pb children were free of serious medical conditions in general, the mothers were white (87%) and well educated (mean maternal schooling = 14.5 years), their mean age was 30 years

Table 3.4 human studies on effects of Pb on lactation

authors	subjects	exposure	design	effects/observation	remarks
Sternowsky and Wessolowski (1985)	lactating women (n=10)	no particular exposure women originate from rural (Soltau) and urban areas (Hamburg, D)	measurement of Pb in milk 0-90 days postpartum	colostrum and mature milk contained 15.5 and 9.1 µg/l and 12.5 and 8.0 µg/l in urban and rural areas, respectively from day 15 on mean concentrations were 13.2 and 9.1 µg/l, differing significantly from day 45 on (Hamburg increasing, Soltau decreasing) no differences in milk Pb content during day women >30 years excreted significantly more Pb into milk till day 5 than women <30 years calculated daily intake (840 ml milk, bw 5.5 kg) amounted to 0.9-1.3 and 1.5-2.3 µg/kg/day for rural and city infants, respectively	non-smoking females one rural women excreted very high levels of Pb into milk (cause unknown) and was excluded from study
Dabeka *et al*. (1986)	volunteers across Canada (n=210)	no particular exposure	determination of Pb content in milk samples	geometric mean milk level amounted to 0.57 µg/l (range <0.05- 15.8 µg/l) levels were highly correlated with age of house and traffic exposure ($p<0.012$)	
Schramel *et al*. (1988)	pregnant women (n=33) and their newborn babies	no particular exposure women lived in Munich (D)	measurement of Pb in maternal blood just before delivery, in cord blood after birth, in placenta and in milk	maternal blood and cord blood contained 39 and 30 µg/l, respectively placenta contained 18.7 µg/kg (fresh weight) milk contained 2.6 µg/l correlations exist between placenta and maternal blood (r=0.69), placenta and cord blood (r=0.67) and maternal and cord blood (r=0.90)	
Parr *et al*. (1991)	lactating women (n=2-74)	no particular exposure women belonged to A (well-to-do), B (urban poor) or C (living in rural environment) groups in Guatemala, Hungary, Nigeria, Philippines, Zaire (only A and C) and Sweden (one group)	Pb determination in milk collected at noon 2 months after start of lactation	median milk Pb levels were 2.9, 14.9, 4.9, 16.6, 16.8 and 5.0 µg/l in Guatemala, Hungary, Nigeria, Philippines, Sweden and Zaire, respectively no significant differences existed between the different socioeconomic classes	

Table 3.5 Human studies on effects of Pb on lactation

authors	subjects	exposure	design	effects/observation	remarks
Ende and Hille (1992)	lactating women (n=102-238) over the years 1987-1990	no particular exposure women lived in Niedersachsen, Germany	Pb-determination in milk	1987: milk Pb level <4-81 µg/l (median <4 µg/l) 1988: milk Pb level <2-124 µg/l (median 43 µg/l) 1989: milk Pb level <10-94 µg/l (median 35 µg/l) 1990: milk Pb level <3-50 µg/l (median 4 µg/l)	
Plöckinger *et al*. (1993)	women just after delivery (n=51)	no particular exposure women lived in Vienna (A)	measurement of Pb in maternal and cord blood immediately after delivery, in urine of mother and child on PN day 2, in milk from PN day 2 to PN day 4	maternal and cord blood contained 37.0 and 26.3 µg/l, respectively urine of mother and child contained 0.05 and 0.29 µg/l, respectively milk contained 35.8 µg/l (range 19-70.3 µg/l) a correlation was found between the Pb concentration in mother and child blood (r=0.66)	deliveries without problems at full term mean age of mothers 23.7 years 30 mother with first-child 10 women smoked cigarettes pregnancy 40.4 w birth weight 3354 g
Tiran *et al*. (1994)	lactating women (n=32)	no particular exposure, women lived in Graz, capital of Styria and the countryside of Styria (A)	Pb analyses in milk	the median milk Pb concentration was 3.4 µg/l (range 0-20.4 µg/l) there was no difference in Pb concentration between milk from urban mothers and from mothers from the countryside	mean age of women 29 years
Saleh *et al*. (1996)	lactating women from 20 different areas (n=6)	women living in 20 urban and rural areas in Egypt	determination of Pb content in breast milk	average district concentrations of Pb in breast milk ranged from 9.0-101.4 µg/l (individual range 0-158 µg/l) with highest concentrations in urbanic areas	women (aged 20-40) had been living in the same area for at least 10 years and had given birth to their 1st or 2nd child, which was healthy 85% of the women was a housewife none of the women smoked
Frkovic *et al*. (1997)	lactating women (n=29)	residence in urban or rural area (Croatia) (annual mean 0.054-0.151 vs. 0.013-0.026 µg Pb/m^3)	determination of Pb concentration in milk PN days 2 and 12	Pb content of milk averaged 7.3 µg/l (range 0.3-44 µg/l) significant differences in milk Pb concentration exist due to residence (urban 10.6 vs region 4.7 µg/l) no differences due to age, parity or smoking habits	women were 17-45 years of age and had normal pregnancy parity 1-7, weight gain 7-22 kg, gestation 36-41 w newborns weight 2200-4400 g, length 46-53 cm, Apgar score (1/5 min) 5-10/7-10
Vavilis *et al*. (1997)	healthy lactating women (n=40-51)	rural and urban (Thessaloniki) areas in Greece	determination of Pb concentration in milk from PN days 4-5 (colostrum)	mean milk Pb concentrations were 90 µg/l (range 50- 250 µg/l) and 84 µg/l (range 50-140 µg/l) for urban and rural areas, respectively (non-significant difference)	women were aged 18-41 and had gestation periods of 37-41 weeks the pregnancies, deliveries and infants were normal air Pb concentrations in the two year prior to study ranged from 0.54-0.67 µg/m3 in the city; in rural areas they were 15 times lower

Table 3.6 Human studies on effects of Pb on lactation

authors	subjects	exposure	design	effects/observation	remarks
Gulson *et al*. (1998)	healthy lactating women (n=15)	women belonged to Australian immigrants or to the 2nd generation Australian women	determination of Pb content by isotope ratio measurement in venous blood PN day 60, and breast milk collected monthly	Pb content in maternal blood (all subjects) was <0.5 mg/l, in cord blood of immigrants 9.1-36.1 µg/l (mean 20.2 µg/l) and of Australians 9.6-36.7 µg/l (mean 25.1 µg/l) Pb concentration milk averaged 0.73 µg/l (range 0.09-3.1 µg/l) (all subjects, no difference in groups)	women were 18-35 years of age
Friel *et al*. (1999)	healthy lactating women, who delivered premature (wk 29.4) (n=24) and full-term (wk 39.8) (n=29) infants	no particular exposure women lived in Newfoundland, Canada	determination of Pb in milk collected PN days 2 to 56 weekly with one final sample taken PN day 84	Pb concentration in milk from women with a premature child varied from 0-1 µg/l and in milk from women with a full-term child from 0-4 µg/l	none of the women (aged 20-35) was vegetarian ca. 95% of the women was of European origin and no aboriginal women participated birth weight was 1312 and 3672 g for premature and full-term infants, respectively
Tripathi *et al*. (1999)	lactating women (n=30)	no particular exposure Mumbai area (India)	determination of Pb content in milk samples	geometric mean milk level amounted to 1.9 µg/l and 1.7 µg/l for human and cow milk, respectivelydaily intake for a 6-12 month old infant from human milk was estimated to be 1.3 µg, from formulae up to 9.4 µg	

PN = postnatal; BLL = blood Pb level

Annex **E**

Calculation safe levels of lead in (human) breast milk

Assumptions

- body weight woman: 60 kg
- body weight infant: 4.5 kg (4-5 kg)
- Intake breast milk: 900 ml (800-1000 ml)
- An infant is as sensitive for the effects of lead as an adult

Calculation safe levals of lead in (human) breast milk

The FAO/WHO (FAO93) recommends a PWTI (provisional tolerable weekly intake) of 25 µg/kg body weight. This corresponds to:

- a tolerable intake level of 3.6 µg/kg body weight per day.
- a safe intake level per infant of 14 µg/ infant /day
- a safe level of lead in breast milk of 16 µg/l

In conclusion, the committee consideres 16 µg lead/ liter breast milk as a safe level.

Annex **F**

Abbreviations

Abbreviations used:

bw	body weight
CI	confidence interval
CNS	central nervous system
d	day
F	female(s)
GD	gestation day
i.p.	intraperitoneal
IRPC	increased renal pelvic cavitation
i.v.	intravenous
M	male(s)
n	number
NOAEL	no adverse effect level
OECD	Organisation for Economic Cooperation and Development
OR	Odds ratio
OT	Operating theatre
PN	postnatal
RR	relative risk