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IN-DEPTH REVIEW

Lead toxicity

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Background	Since the last In-Depth Review of lead toxicity in 2004 there have been further developments with regard to safe exposure levels for lead workers.
Aims	To advise occupational health professionals of the latest research on the multi-system toxic effects of lead and the implications of this research for setting new safe and appropriate occupational suspension limits.
Methods	An extensive review of the current literature and an investigation of the database used by lead users to produce their submission under the REACH Regulations.
Results	Much of the published research on lead toxicity is on the effects of lead on the general population where blood lead levels are considerably lower than those seen in lead-exposed workers. It is always difficult to compare such studies with those undertaken on exposed workers as they may not be directly comparable and may not have taken into account all confounding variables and the well-acknowledged 'healthy worker' concept. However, it is clear that there is substantial evidence that potential health effects on lead workers may be seen at levels which were previously accepted as 'safe'.
Conclusions	There is undoubtedly a narrow margin of safety between current occupational blood lead suspension limits and subclinical effect. As a result, the lead users have produced a voluntary Code of Practice with suspension limits significantly below those seen in some national legislation, particularly the Control of Lead at Work Act 2002.
Key words	Inorganic lead; legislation; organic lead; toxicity.

Introduction

Inorganic lead is undoubtedly one of the oldest occupational toxins and evidence of cases of lead poisoning can be found dating back before the Christian era. As industrial lead production started at least 5000 years ago, it is likely that outbreaks of lead poisoning occurred from this time. Hippocrates (370 BC) described a severe attack of colic in a metal extractor and in the second century BC Nicander described the relationship of constipation, colic, pallor and paralysis to the action of lead on the body. Pliny (AD 23–79) stated that lead poisoning was known in his day and that lead workers tied up their faces in loose bags 'lest they should inhale the pernicious dust'. Dioscorides (AD 100) knew that ingestion of lead compounds caused colic, paralysis and delirium and later Ramazzini observed that for potters working with lead 'at first tremors appear in the hands, soon they are paralysed'. Vernatti (1678) probably made the earliest record of lead poisoning among white-lead workers in England. The general population could also be exposed to significant amounts of lead due to poorly glazed ceramic ware, the use of lead solder in the canning industry (this is postulated as a possible cause of death among members of the fated Franklin expedition to the Northwest Passage), high levels of lead in drinking water, the use of lead compounds in paint and cosmetics and by deposition on crops and dust from industrial and motor vehicle sources. Despite this, effective formal control of lead workers did not occur until the pioneering occupational health work of Ronald Lane in 1949 [1]. It is worth quoting from Lane's paper as little has changed in the 65 years since its publication. 'There is only one way to prevent lead poisoning and one way only, and that is to make the process safe.' In addition, he very wisely states 'The importance of education of the worker himself must be stressed. He must understand fully the dangers of his work. No attempt must be made to hide

it or to minimise it, but he must at the same time be shown his own responsibilities in any safety programme. This needs patience and hard work on the part of the doctor. Complete success will be impossible without the co-operation of the workman.'

In view of the long history of lead's toxicity and the extensive publications, one might assume that lead exposure is well controlled and lead poisoning should be of historical interest only. Unfortunately, this is not the case and there are still industries in this country (particularly, the demolition industry and industries involved in renovating structures that had previously contained lead, known as the remediation industry), where clinical lead poisoning occasionally occurs [2]. It is important to remember that significant exposure may occur in occupations that are not considered to be 'at risk' [3]. The aim of this paper is to review the latest evidence for the toxicity of lead and discuss present and future legislation for the protection of the lead worker in industry.

Inorganic lead

Reproductive toxicology

At very high blood lead levels, lead is a powerful abortifacient. At lower levels, it has been associated with miscarriages and low birth weight of infants [4]. In females, occupational exposure resulting in blood lead levels >10 µg/100 ml is associated with an increased risk of spontaneous abortion, premature delivery and low birth weight. In one study, the risk of spontaneous abortion doubled at maternal blood lead levels of 5–9 µg/100 ml [5]. Recent studies have shown that blood lead levels in men >40 µg/100 ml may be linked to low libido, low semen volume and sperm counts, increased abnormal sperm morphology and decreased sperm motility leading to impairment of reproductive function [6–13]. However, many studies have not taken into account potentially powerful confounders such as other occupational exposure (heat, solvents, etc.) or social factors such as smoking, alcohol consumption or the use of any medications. A study of lead workers in the UK, Belgium and Italy examined semen samples according to an agreed protocol. The results showed a 49% reduction in the median sperm concentration in men with blood lead levels >50 µg/100 ml with a likely threshold for effects of 44 µg/100 ml. In addition, there was some evidence of deterioration in sperm chromatin in men with the highest concentration of lead in spermatozoa. Biological monitoring data failed to show any long-term effects of lead on sperm quality or sperm chromatin [14]. Current thinking is that significant effects on reproductive capacity are unlikely below a blood lead concentration of around 50 µg/100 ml but blood lead concentrations >40 µg/100 ml may affect sperm morphology and function. It is clear that further studies are needed in male and female lead workers to give a clearer indication of the safe level of lead exposure.

Neurotoxicity

Acute encephalopathy can occur in children at blood lead concentrations of 80–100 µg/100 ml and in adults at blood lead concentrations of 100–120 µg/100 ml. The symptoms include irritability, agitation, headaches, confusion, ataxia, drowsiness, convulsions and coma [6,15,16]. Peripheral motor neuropathy is seen as a result of chronic high-level lead exposure and whilst there is some conflicting evidence, there is convincing evidence of a reduction in peripheral nerve conduction velocity at lower blood lead levels with a suggested threshold as low as 30 µg/100 ml although other studies have not seen effects below 70 µg/100 ml [17–20]. The clinical significance of any reduced nerve conduction velocity is uncertain. Neurobehavioural effects including disturbances in reaction time, visual motor performance, hand dexterity, IQ and cognitive performance, anxiety and mood have been observed in lead workers with blood lead concentrations >40 µg/100 ml [21–25]. Many of these studies have been well performed using well-matched controls but other variables such as alcohol consumption or the incidence of hypertension and cerebrovascular disease have not been adequately controlled. One interesting study by Baker *et al.* [26] showed a subjective improvement in tension, anger, depression, fatigue and confusion following a reduction in blood lead levels but no significant improvement was seen in the subtle neurophysiological test results. A meta-analysis by Goodman *et al.* [27] claimed to evaluate publication bias and concluded that none of the studies were adequate or conclusive in providing information on subclinical neurobehavioural effects of lead. It is notable that, as with many of the alleged effects of low-level lead exposure, an extensive search of the literature has failed to identify any significant recent studies. The generally accepted view is that clinically significant effects on workers are unlikely below blood lead levels of 40 µg/100 ml [28].

There is no doubt that children, and indeed foetuses, are more at risk from the toxic effects of lead. This is the main reason why the suspension limit for female workers of reproductive capacity is significantly lower than that for males. It has been argued that there is no safe level for exposure to lead in children and studies have suggested that for every 10 µg/100 ml increase in blood lead, there is a loss of 4–7 IQ points [29]. Some authorities conclude that it is not possible to identify a threshold for the association between lead exposure and decrements in IQ [30]. There is also some evidence that attention deficit hyperactivity disorder and hearing impairment in children increases with increasing blood lead levels and that lead exposure may affect balance and impair peripheral nerve function [31].

Carcinogenicity

The International Agency for Research on Cancer (IARC) has classified inorganic lead compounds as Group 2A carcinogens (likely to cause human cancer) [30,32]. The National Toxicity Programme in the USA states that lead is reasonably anticipated to be a human carcinogen based on limited human studies but sufficient animal laboratory data and the US Environmental Protection Agency states that lead is a probable human carcinogen [33]. Studies of lead-exposed workers have produced varying results with some having a small excess of lung cancers although there may well be strong confounders such as smoking and arsenic exposure. A recent study in Canada failed to show any association between lung cancer and exposure to inorganic or organic lead compounds [34,35]. Some analyses have also found an excess of stomach cancers where smoking and arsenic exposure are not thought to be confounders but there may well be other factors such as helicobacter pylori which have not been taken into consideration [33–36]. There is evidence to suggest an excess of renal cancers but the excesses have been very small and very close to expected levels and studies on cancers of the brain and central nervous system have failed to show any consistent results. Animal studies have shown good evidence of renal tumours, particularly with exposure to lead acetate. IARC has classified organic lead compounds as Group 3 (insufficient data) [37]. There must, however, be a degree of caution as organic lead compounds are metabolized in the body into a number of metabolites including inorganic lead prior to excretion in the urine.

Hypertension

In an occupational setting, the effect of lead exposure on blood pressure remains controversial and there have been no significant new studies to elucidate the issue. The studies are on considerably smaller populations than those used to consider the effects of low-level lead exposure on the general population. The main problem remains control of confounding issues such as alcohol intake, haemoglobin, obesity and smoking. Some studies have shown better correlation with bone lead levels. The studies show the difficulties of interpretation that are encountered in the statistical analysis of the small effect sizes suggested for lead when present in the midst of powerful confounding variables that have a much larger impact on blood pressure [38]. An investigation of 220 lead battery workers showed a stronger association between blood lead and hypertension in the 30% of the study population who possessed a particular version of the ATP1A2 gene [39]. The consensus remains that there is no clear evidence of an adverse impact of lead on workers with blood lead levels below 40 µg/100 ml. Population data are equally confusing. Pocock found no evidence of an association between blood lead concentrations and either systolic or diastolic pressure in a study of 7735 middle-aged men from 24 British towns [40]. A recent paper showed a correlation between blood lead and systolic blood pressure in black men and women but not Caucasian [41]. Also a study showed evidence of an elevation in blood pressure during pregnancy [42]. However, data from the National Health and Nutrition Examination Survey (NHANES III) may show population effects although authors disagree on the cut-off levels, the size of the effect and whether the impact is on all races [43].

Renal function

Exposure to high lead levels can produce renal tubular damage with glycosuria and aminoaciduria [44]. A number of studies, in particular a study in South African battery workers, have shown a linear correlation between blood lead and renal dysfunction at blood lead levels in the range <40 to >70 µg/100 ml but other studies including a large study in smelter workers failed to show any correlation between blood lead levels and sensitive indicators of tubular and glomerular damage [45–47]. The lowest level at which lead has an adverse effect on kidney function is hence unknown. Prominent inclusion bodies have been seen in the cells of the proximal tubules at blood lead levels in the range 40–60 µg/100 ml [48]. Lead accumulates in the mitochondria and causes structural and functional alterations thus impairing energy-dependent processes such as tubular transport. It may also have a direct effect on arterial smooth muscle. However, blood lead levels are a poor indicator of body lead burden and bone lead content may offer a better correlation although there are few studies to investigate this.

In children, the latent effects of lead exposure that occurred years earlier in childhood may cause chronic renal disease or a decrement in renal function. Population studies have shown the possibility of renal damage at lower blood lead levels. In the Normative Aging Study, a cross-sectional analysis showed that a 10 µg/100 ml increase in blood lead levels was associated with a 9% reduction in creatinine clearance and a longitudinal study showed that a 10-fold increase in blood lead levels predicted a 0.08 mg/100 ml increase in serum creatinine levels [49,50].

Immunology

Lead appears to reduce the resistance to infection and increase the mortality of experimental animals and a recent study showed a significant decrease in IgG levels in rats injected with lead acetate [51]. Lead apparently impairs antibody production and decreases immunoglobulin plaque-forming cells [52]. There is some evidence to suggest that workers with blood lead levels between 20 and 85 µg/100 ml may have an increased susceptibility to colds but a study of lead workers with blood lead levels <50 µg/100 ml showed no significant immunological changes [53,54]. An increased percentage and absolute count of B lymphocytes has been seen in workers with

blood lead levels >50 µg/100 ml [55]. A recent Chinese article appears to show that workers with blood lead levels >60 µg/100 ml have suppressed cellular immune function and abnormal T-cell subsets [56].

Endocrine effects

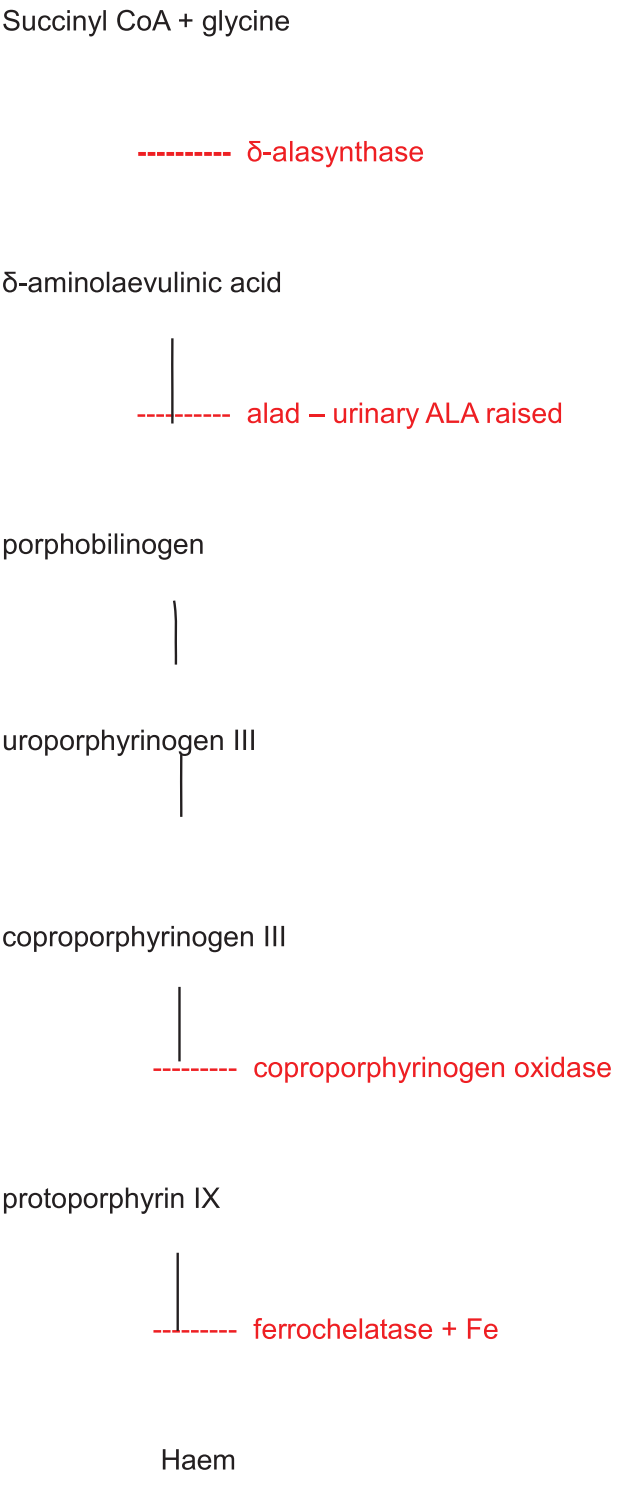
Children with chronically very high blood lead levels (>62 µg/100 ml) may show impeded conversion of vitamin D into its hormonal form, 1,25-dihydroxyvitamin D. This may impair cell growth, maturation and tooth and bone development. An early study, however, showed 1,25-dihydroxyvitamin D levels were reduced to levels seen in children with severe renal insufficiency at blood lead levels of 33–55 µg/100 ml [57,58]. Exposure of smelter workers to lead and cadmium together increased the concentration of 1α-dihydroxycholecalciferol [59]. This study also suggests that cadmium and lead interact with the renal mitochondrial hydroxylases of the vitamin D3 endocrine complex and may lead to the development of osteoporosis or osteomalacia. There are no data to show any effect of lead on other hormonal functions.

Developmental effects

Pre-natal exposure to relatively low blood lead levels (maternal blood lead levels of 14 µg/100 ml) may increase the risk of reduced birth weight and premature birth and may be associated with an increased risk of minor developmental abnormalities [60]. However, no association has been found between pre-natal lead exposure and major congenital abnormalities. A retrospective study showed a higher proportion of learning disabilities among school children with biological parents who were lead-poisoned as children 50 years previously [61].

Haematological effects

Lead is known to affect haem synthesis by poisoning enzymes at several stages in the haem synthesis pathway and this knowledge has led to methods used for biological effect monitoring. Raised urinary aminolaevulinic acid (ALA) levels and raised zinc protoporphyrin must be differentiated from acute porphyrias or sideroblastic anaemia [62]. Acute high-level lead exposure has been associated with haemolytic anaemia but the anaemia of chronic lead intoxication is hypochromic and normocytic or microcytic with a reticulocytosis. It has been estimated that the threshold blood lead level for a decrease in haemoglobin in occupationally exposed workers is 50 µg/100 ml but may be ≤40 for children. ALA may be inhibited at lower blood lead levels leading to a rise in urinary ALA but the meaning and possible sequelae of these biochemical and enzyme changes at these lower blood lead levels is uncertain.



Toxicokinetics

Studies have shown that genetic polymorphism has an impact on an individual's blood lead level. In a study of almost 800 lead workers and 135 controls, it was shown that subjects with the vitamin D BB or Bb allele had significantly higher blood lead levels than those with the bb allele [63]. In addition, individuals homozygous or

heterozygous for ALAD2 had higher blood lead levels than those with ALAD1 but showed no difference in tibial lead or chelatable lead concentrations compared with subjects lacking this allele. The authors believe that this study confirmed that ALAD and vitamin D receptor genes modify lead toxicokinetics [64]. A recent population study looking at data from NHANESIII suggests that the ALAD CG/CC genotype may be associated with decreased mortality from all causes and from cancer and this association does not seem to be affected by lead exposure [65].

Organic lead

The use of most of these chemicals is declining, particularly with the virtual demise in the worldwide use of lead alkyls in petrol. They were used extensively as octane enhancers and in the 1970's peak, worldwide production was of the order of 500 000 tonnes but now it is estimated that worldwide production of tetraethyl lead is ~4500 tonnes. Exposure is rarely seen during the production, transportation and blending of this substance into petrol and amongst workers involved in cleaning storage tanks which have contained leaded petrol although it is in this group that the highest potential morbidity and indeed mortality used to exist. Nonetheless, this will be an on-going concern for some years as tanks which have at some time in their lives been used to store leaded petrol will need to be cleaned or repaired and constant vigilance will be required. The toxicological profile of tetraethyl lead is different to that of inorganic lead and its compounds as it is essentially a central nervous system toxin which produces an acute toxic psychosis [66,67]. The early symptoms are subtle and non-specific and may be easily missed but in those with continuing exposure or where there has been a single massive exposure florid symptoms of a toxic psychosis or even coma and death may occur. IARC has classified tetraethyl lead as a category 3 carcinogen—i.e. insufficient evidence to enable classification but there is a single published paper suggesting an excess of rectal cancers among production workers [68]. Tetraethyl lead is metabolized in the liver to soluble alkyl lead chlorides and excreted in the urine. It is pathognomonic of organic lead poisoning that the blood lead level may only be moderately elevated whilst the urinary lead level may be extremely elevated with figures of several hundred micrograms of lead per gram of creatinine. Therefore, in suspicious cases, the urinary lead level must always be measured or the diagnosis may be missed. Unlike inorganic lead and its compounds, where chelating agents may be used in the case of poisoning, there is no specific antidote for organic lead poisoning—treatment consists of supportive treatment and adequate sedation.

Legislation

In the UK, lead workers are covered by the Control of Lead at Work Regulations (2002) (CLAW Regulations) [69]. These regulations outline the responsibilities of workers, employers and occupational physicians. Occupational physicians monitoring lead workers are either employees of the Health and Safety Executive (HSE) or doctors appointed under the regulations to act on their behalf. Duties include knowledge of the workplace, annual examination of lead workers and monitoring of their blood lead results and annual reporting of blood lead levels to the HSE. They must also be involved in the investigation of any worker whose blood lead level exceeds the suspension limit or who exhibits any signs or symptoms of lead toxicity. The appointed doctor must also notify the HSE if any worker is suspended from exposure to inorganic or organic lead and advise the employer to notify the HSE under the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations (RIDDOR) if it is believed that the worker is exhibiting signs or symptoms of lead poisoning [70]. The suspension level for male lead workers under the CLAW Regulations remains unchanged at 60 µg/100 ml and for female workers of reproductive capacity 30 µg/100 ml although it is possible that symptoms of lead poisoning could potentially occur at lower blood lead levels. The European Union Scientific Committee on Occupational Exposure Limits (SCOEL) recommended a suspension limit of 30 µg/100 ml for men but this has to be accompanied by an analysis of the socio-economic impact on industry before implementation of any new limit [71]. The author understands that SCOEL has been tasked by the European Commission to undertake a further review of the health effects of lead in the near future and to review their 2003 opinion that the health-based blood lead level

Table 1. Current international suspension limits

Country	PbB µg/dl	
	Males	Females
Germany	40	10
Finland	50	50
Denmark	20	20
Sweden	50	30
Italy	60	40
France	40	30
Belgium	70	70
Spain	70	70
Portugal	70	70
Netherlands	70	70
UK	60	30
Ireland	70	70
Switzerland	70	30
Hungary	50	30
Slovenia	40	30
Poland	50	50
Australia	30	10
Japan	40	40
China	40	
India	40	
South Africa	40	

should be set at 30 µg/100 ml. It is, of course, possible that SCOEL could review recent evidence and suggest an even lower limit. However, many European Union and other countries have legislated for lower suspension limits for male and female workers. In the absence of any action, the European Battery Association, the International Lead Association and the European Lead Sheet Association have all agreed a voluntary target that no employee's blood lead level should exceed 30 µg/100 ml by the end of 2016 for men and 10 µg/100 ml for women of reproductive capacity. This followed a formal risk assessment of the toxicity of lead as required under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulations (2006) [72]. One of the major publications influencing the outcome of the REACH assessment was the paper by Kosnett *et al.* [73] which was essentially a meta-analysis of published literature on the health effects of lead. These suspension limits have been taken up voluntarily by other lead users and indeed by some employers involved in other forms of lead exposure. There is now an interesting dichotomy that lead users have adopted industry agreed suspension limits derived under the REACH regulations while other workers exposed to lead but not technically lead users (e.g. demolition and remediation workers) remain controlled by the higher suspension limits seen in the CLAW Regulations. It is interesting that legislation is increasingly reflecting the long-held opinion within the lead industry that lead in air levels are not of particular significance and that the main factors determining an individual's blood lead level are personal hygiene and correct use of personal protective equipment. It is well known that cigarette smokers and nail biters have significantly higher blood lead levels than their fellow workers. As employers have an obligation under the CLAW Regulations to pay

Table 2. Blood lead levels and possible health impacts in adults

Blood lead level (µg)	Males	Females
<5	Nil	Nil
5–10	Possible hypertension and kidney dysfunction	Possible hypertension and kidney dysfunction Possible spontaneous abortion
11–20	Possible hypertension and kidney dysfunction Possible subclinical neurocognitive deficits	Possible hypertension and kidney dysfunction Possible subclinical neurocognitive deficits Reduced birth weight Possible postnatal developmental delay
21–29	Hypertension and kidney dysfunction Possible subclinical neurocognitive deficits	Hypertension and kidney dysfunction Possible subclinical neurocognitive deficits Possible spontaneous abortion Reduced birth weight Possible postnatal developmental delay
30–39	Hypertension and kidney dysfunction Possible neurocognitive deficits	Hypertension and kidney dysfunction Possible neurocognitive deficits Spontaneous abortion Reduced birth weight Possible postnatal developmental delay
40–79	Hypertension and kidney dysfunction Subclinical peripheral neuropathy Neurocognitive deficits Anaemia Sperm abnormalities Colic Possible gout	Hypertension and kidney dysfunction Subclinical peripheral neuropathy Neurocognitive deficits Anaemia Colic Possible gout Spontaneous abortion Reduced birth weight Possible postnatal developmental delay
80+	Hypertension Nephropathy Peripheral neuropathy Neurocognitive deficits Anaemia Sperm abnormalities Colic Gout Encephalopathy	Hypertension Nephropathy Peripheral neuropathy Neurocognitive deficits Anaemia Colic Gout Encephalopathy Spontaneous abortion Reduced birth weight Possible postnatal developmental delay

workers while they are suspended owing to high blood lead levels, the frequency with which workers will be monitored to ensure that their blood lead levels are not approaching the suspension limit will inevitably have to increase and approved analytical laboratories will have to respond with increasing accuracy and precision of results. It will be a particular challenge for the industry to ensure that females of reproductive capacity remain below the suspension limit of 10 µg/100 ml (Tables 1 and 2).

Conclusions

Although lead has been used for thousands of years and the toxic effects are well known, there remains considerable debate about the health effects of low-level lead exposure. There is no doubt that further quality research is needed but this is becoming increasingly difficult as the population of lead-exposed workers shrinks. There is undoubtedly a narrow margin of safety between current occupational blood lead suspension limits and subclinical effects. Pressure will therefore remain on industry to reduce occupational exposure. Experience from many industries employing 'best practice' has shown that it is possible to control the blood lead levels of the workforce within acceptable limits but constant vigilance is necessary to maintain this control [74]. There has been no major Cochrane review of lead toxicity and interestingly the last major overview of lead toxicity was carried out in 1989 by the International Programme on Chemical Safety (IPCS) [75]. All available data were also considered by the HSE working party producing the CLAW Regulations but, as mentioned above, UK legislation lags behind many other countries and it has been argued that the regulations are overdue a major review.

Key points

- Inorganic lead exposure produces damage to many organs and systems in the body.
- The effects of lead toxicity occur at levels below those currently allowed in UK legislation.
- The control of lead exposure has been understood for over 60 years but is not always implemented. As a result, cases of lead poisoning, both inorganic and organic, still occur.
- The primary aim is to avoid lead exposure as treatment of lead poisoning is not without risk.
- Availability of new evidence and the risk assessment carried out in the UK clearly indicate that the UK Control of Lead at Work Regulations needs urgent review.

Conflicts of interest

None declared.

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