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IN-DEPTH REVIEW

Lead toxicity

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Lead is one of the oldest known and most widely studied occupational and environmental toxins. Despite intensive study, there is still vigorous debate about the toxic effects of lead, both from low-level exposure in the general population owing to environmental pollution and historic use of lead in paint and plumbing and from exposure in the occupational setting. The majority of industries historically associated with high lead exposure have made dramatic advances in their control of occupational exposure. However, cases of unacceptably high exposure and even of frank lead poisoning are still seen, predominantly in the demolition and tank cleaning industries. Nevertheless, in most industries blood lead levels have declined below levels at which signs or symptoms are seen and the current focus of attention is on the subclinical effects of exposure. The significance of some of these effects for the overt health of the workers is often the subject of debate. Inevitably there is pressure to reduce lead exposure in the general population and in working environments, but any legislation must be based on a genuine scientific evaluation of the available evidence.

Key words Inorganic lead; legislation; organic lead; toxicity.

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Introduction

Inorganic lead is undoubtedly one of the oldest occupational toxins and evidence of lead poisoning can be found dating back to Roman times. As industrial lead production started at least 5000 years ago, it is likely that outbreaks of lead poisoning occurred from this time. These episodes of poisoning were not limited to lead workers. The general population could be significantly exposed owing to poorly glazed ceramic ware, the use of lead solder in the food canning industry, 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. It was an important cause of morbidity and mortality during the Industrial Revolution and effective formal control of lead workers did not occur until the pioneering occupational health work of Ronald Lane in 1949 [1]. In view of the long history of lead's toxicity and the extensive publications (it is probably the most widely studied occupational toxin) one would think that lead exposure is controlled and lead poisoning was merely a historical entity. Unfortunately, this is not the case. Lead exposure is generally well controlled in the major lead-using industries such as smelting and battery manufacture. However, there are still industries in this country (particularly the demolition industry) where clinical lead poisoning occasionally still occurs [2]. A recent paper by Sen *et al.* [3] has also shown that significant exposure can occur in occupations that are not normally considered to be at risk. In this paper, significant blood lead levels were seen in scaffolders involved in erecting and dismantling access structures during the renovation of previously lead-painted structures [3]. In addition, although the production of lead alkyls (now only tetra-ethyl lead) is rapidly declining with the increasing world usage of lead-free petrol, organic lead poisoning is still occasionally seen in tank cleaners who clean petrol storage tanks that have contained leaded petrol. In this paper I will discuss the latest evidence for the toxicity of lead and discuss present and future legislation for the protection of the lead worker in industry.

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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 weights of infants [4]. Predominantly to protect the developing fetus, legislation for lead workers often includes lower exposure criteria for women of 'reproductive capacity'.

The reproductive toxicity of lead on male lead workers has been studied but, to date, the results have been inconsistent [5–9]. Some studies have shown reduced sperm count and motility, but there are few data showing an effect on reproductive capability. In addition, many of the studies have not taken into account potentially powerful confounding factors such as other occupational exposures (e.g. heat and solvents) or social factors such as alcohol consumption, smoking or the use of any medications. A recent study of 503 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 level for effects of 44 μg/100 ml. In addition, there was some evidence of deterioration of 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 quantity or sperm chromatin [10]. Current thinking is that significant effects on reproductive capacity are not seen below a blood lead level of ≥50 μg/100 ml, but blood lead concentrations of >40 μg/100 ml may affect sperm morphology and function [11].

Neurotoxicity

Much debate surrounds the potential effects of low-level lead exposure on young children. There is no doubt that subtle effects on child neuropsychological development can be seen at blood lead levels above ~20 μg/100 ml. Moreover, one recent US study has produced data suggesting effects below 10 μg/100 ml with no discernible no-effect level [12]. It is beyond the scope of this article to discuss the extensive and controversial data that abound on subtle effects on children's intelligence quotients and neuropsychological development. However, it is one important component, which has been taken into account in setting suitable occupational exposure limits for women of 'reproductive capacity' in the lead industry.

Studies have shown a slowing of sensory motor reaction time in male lead workers and some disturbance of cognitive function in workers with blood lead levels >40 μg/100 ml. Peripheral motor neuropathy is seen as a result of chronic high-level lead exposure, but there is conflicting, although on the whole convincing, evidence of a reduction in peripheral nerve conduction velocity at lower blood lead levels. The threshold has been suggested to be as low as 30 μg/100 ml, although other studies have not seen effects below a blood lead level of 70 μg/100 ml [13–15]. The clinical significance of reduced nerve conduction velocity is uncertain [16].

Subtle changes in neuropsychological function have been seen in inorganic lead workers. These effects are seen in visual/motor performance, memory, attention and verbal comprehension [17–20]. These effects can be detected in workers with blood lead levels of >50 μg/100 ml, but it is claimed that sensory motor function is more sensitive than cognitive function and effects may be observed at blood lead levels as low as 40 μg/100 ml [21]. Many of these tests have been well performed and used non-exposed controls who had been well-matched for educational achievement. However, there are other variables that have not been adequately controlled, e.g. alcohol consumption or the incidence of hypertension and cerebrovascular disease. One interesting study has shown a subjective improvement in levels of tension, anger, depression, fatigue and confusion following a significant improvement in occupational exposure and reduction in blood lead levels, but no significant improvement in the subtle neuropsychological test results [22].

A recent meta-analysis of occupational studies has been published, which claims to evaluate publication bias. The paper concludes that none of the individual studies is adequate or conclusive in providing information on the subclinical neurobehavioural effects of lead exposure. The authors claimed that studies do not provide adequate data for drawing firm conclusions about the biological effects of current levels of exposure [23]. However, the findings of this paper are challenged by others who claim that there are consistent associations of blood lead levels with test scores in executive abilities, manual dexterity and peripheral motor strength at blood lead levels as low as 18 μg/100 ml [24].

Carcinogenicity

The International Agency for Research on Cancer has concluded that the evidence for the carcinogenicity of lead and inorganic lead compounds in humans is inadequate [25]. Several large epidemiological studies of lead workers have found inconclusive evidence of an association between lead exposure and the incidence of cancer [26,27]. In many of the studies there has been no attempt to deal with confounding factors such as smoking and exposure to other potential carcinogens. A major study of a cohort of >4500 battery plant workers and 2300 lead smelter workers for the period 1947–1995 showed a significantly increased mortality from stomach cancer. However, based on closer analysis the increase did not appear to be related to lead exposure. There was

also a small but significant increase in the incidence of lung cancer, but this could have been the result of confounding from cigarette smoking or concurrent arsenic exposure [28]. A recent study from Sweden has suggested a slight excess of lung cancer in certain lead workers in a foundry but, to date, has not been able to determine whether this was due to the confounding effect of arsenic, which is a potent inducer of lung cancer [29]. There are therefore at present insufficient data for suggesting that lead compounds are carcinogenic in humans [30]. However, the International Agency for Research on Cancer is revisiting the issue of the carcinogenicity of lead and its compounds in February 2004.

Hypertension

There have been interesting studies carried out in animals and in humans. It would appear that, in animals exposed to lead in drinking water, lead exposure affects the renin–angiotensin system, inducing sympathetic hyperactivity and increasing sensitivity to stimulation of cardiac and vascular β receptors and dopaminergic receptors [31,32]. There is some evidence in humans that there is an association between low-level lead exposure and blood pressure, but the results are inconsistent. The authors of a recent meta-analysis concluded that such a relationship may not be causal and is unlikely to entail any public health implications regarding hypertension [33]. There are inconsistent data for workers exposed to higher lead levels: a study of battery workers with blood lead levels of 40 ± 13 μg/100 ml showed a small but non-significant association between blood lead levels and blood pressure [34]. It is suggested that the failure to demonstrate increased blood pressure levels in some studies with high-level lead exposure may be due to a biphasic effect of lead on blood pressure. However, as in many other areas, it is possible that other confounders of raised blood pressure, e.g. obesity, cigarette smoking and alcohol consumption, might not have been properly considered in at least some of the studies. It is also obviously important that measurements of blood pressure are properly carried out using equipment that is properly calibrated and manned by appropriately qualified and experienced observers. Issues such as observer number preference and the impact of the actual measurement on the individual (white coat syndrome) must also be quantified. Two recently published studies have provided new information. It is possible that bone lead as opposed to blood lead is a better predictor of the risk of hypertension. An association between patellar lead levels was found in 833 Boston volunteers, although there was no association with blood lead levels [35]. Another study among 220 lead industry workers showed a much stronger association between blood lead and hypertension in the 30% of the population who possessed a particular variant of the ATP1A2 gene [36].

Renal function

Exposure to high lead levels can produce renal tubular damage with glycosuria and aminoaciduria (saturnine gout). Some studies have shown a linear correlation between serum creatinine levels and blood lead levels above 40 μg/100 ml while others have shown no effect below 60 μg/100 ml [37–39]. Other studies have found increased levels of *N*-acetyl-β-D-glucosaminidase and β2 microglobulin in the urine of lead workers, whereas other studies have not found such changes [40,41]. Whether these are of any clinical significance, whether they represent minor cellular modifications rather than significant functional changes or irreversible renal damage or, interestingly, whether pre-existing renal impairment may lead to higher blood lead levels are still open to discussion. There are certainly no definitive data to suggest that current lead exposure levels lead to clinically significant renal damage. It has been suggested that these changes may be related to the cumulative lead dosage rather than the blood lead level and that measures of lead accumulation such as bone lead levels may give a closer correlation.

Immunology

Lead appears to reduce the resistance and increase the mortality of experimental animals [42]. It apparently impairs antibody production and decreases immunoglobulin plaque-forming cells. There is some evidence for suggesting that workers with blood lead levels between 20 and 85 μg/100 ml may have an increased susceptibility to colds [43], but a study of lead workers with blood lead levels of <50 μg/100 ml showed no significant immunological changes [44]. An increased percentage and increased absolute count of B lymphocytes may be seen in workers with blood lead levels of >50 μg/100 ml [45].

Toxicokinetics

Although it is widely accepted that personal hygiene is the most important determinant of an individual's blood lead level, recent interesting information has shown that genetic polymorphism may also have an impact. In a study of almost 800 lead workers and 135 controls, it was shown that subjects with the vitamin D receptor B allele had significantly higher levels of lead in the blood and tibia than did those with the vitamin D receptor bb allele. In addition, subjects with the ALAD2 allele showed higher concentrations of lead in the blood but no differences in tibial lead or chelatable lead concentrations compared with subjects lacking this allele. The authors

believed that this study confirmed that the ALAD and the vitamin D receptor genes modify lead toxicokinetics [46].

Organic lead

The use of most of these chemicals is declining with the gradual demise of the use of lead in petrol, but lead naphthenates and stearates are still used in stabilizers for plastics and as lead 'soaps'. In fact, the only compound now produced for petrol usage is tetra-ethyl lead. Exposure is only seen during the production, transportation and blending of this substance into petrol and in workers involved in cleaning storage tanks that have contained leaded petrol. It is in this final group, the tank cleaners, where the highest potential morbidity and mortality may be seen.

It is important to remember that the toxicological profile of tetra-ethyl lead is totally different to that of inorganic lead and its compounds [47,48]. It is essentially a central nervous system toxin that produces an acute toxic psychosis. The early signs and symptoms are subtle and non-specific and may be easily missed, but in those with continuing exposure or after a massive single exposure, florid symptoms of a toxic psychosis or even coma and death may occur. It is not recognized by the International Agency for Research on Cancer as a potential human carcinogen, but there is a published paper suggesting an excess of rectal cancers among production workers [49].

Tetra-ethyl 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 be only moderately elevated whilst the urinary lead level may be extremely elevated with figures of several hundred micrograms of lead per gram of creatinine [50]. 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 other than supportive treatment and sedation.

Legislation

In the UK lead workers are covered by *The Control of Lead at Work Regulations (2000)* [51]. These regulations outline the responsibilities of occupational physicians examining lead workers, either employment medical advisers or appointed doctors appointed by the Health & Safety Executive under the regulations. The blood lead suspension level for inorganic lead workers has been lowered to 60 μg/100 ml, with suggested maximum intervals between blood lead tests for workers with lower blood lead levels. There are specific guidelines for women 'of reproductive capacity'. It was expected that the regulations would be reviewed 3 years after publication in order to determine whether new data were available that might lead to the imposition of stricter suspension levels. However, as mentioned above, the European Union (EU) is reviewing data on carcinogenicity, reproductive toxicity and neuropsychological changes and it is expected that new suspension levels may be imposed in the near future. The EU Scientific Committee on Occupational Exposure Limits has recommended a suspension limit of 30 μg/100 ml but this has to be accompanied by an analysis of the socio-economic impact on the industry. This is yet to be carried out and the time-scale on any changes in legislation is therefore uncertain, but it is unlikely that any changes to the suspension levels will be proposed before 2005. Following any new proposals there will presumably be a reasonable time-scale for the introduction of the new limits. An educated 'guess' is that a suspension level of between 40 and 50 μg/100 ml will be agreed. This may be accompanied by a further reduction in the allowable air lead concentration. However, a precedent may have been set by Germany imposing a blood lead suspension limit of 40 μg/100 ml.

Lead industries in the USA introduced a voluntary programme for reducing blood lead levels to <40 μg/100 ml. This has been extremely successful and the initiative has been followed by some European lead industries. It is particularly interesting that legislation is increasingly reflecting the long-held opinion within the industry that lead in air levels is not of particular significance and that the major factor determining an individual's blood lead levels is personal hygiene. It is well known that cigarette smokers and nail biters have significantly higher blood lead levels than their fellow workers [52].

As employers have an obligation under the regulations to pay 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 level is bound to increase and approved laboratories will have to respond with increasing accuracy and precision of results.

Conclusions

Despite the wealth of scientific studies carried out over the years on the toxic effects of lead, there are still considerable gaps in our knowledge and uncertainties over the health effects of low-level lead exposure. There is no doubt that there is a narrow margin of safety between current occupational blood lead suspension limits and evidence of subclinical effects and pressure on industry will therefore continue in order to reduce occupational exposure. Experience from industries employing 'best practice' has shown that it is possible to control the blood lead levels of the workforce within acceptable limits.

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