Emerging aspects of assessing lead poisoning in childhood

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This review covers the epidemiology of lead poisoning in children on a global scale. Newer sources of lead poisoning are identified. The methods that are used to assess a population of children exposed to lead are discussed, together with the ways of undertaking an exposure risk assessment; this includes assessing the time course and identifying sources of lead exposure. Human assessment measures for lead toxicity, such as blood lead concentrations, deciduous tooth lead, and use of zinc protoporphyrin estimations are evaluated. The role of isotopic fingerprinting techniques for identifying environmental sources of exposure is discussed. Among emerging data on the cognitive and behavioral effects of lead on children, the review considers the growing evidence of neurocognitive dysfunction with blood lead concentrations even below 10 μg/dl. The challenge of assessing and explaining the risk that applies to an individual as opposed to a population is discussed. Intervention strategies to mitigate risk from lead are examined together with the limited role for and limitations of chelation therapy for lead. Lessons learned from managing a population lead-dust exposure event in Esperance, Western Australia in 2007 are discussed throughout the review.

Introduction

Lead exposure remains a major environmental issue around the world, as the poverty of measures to deal effectively with the problem in both developing and developed countries has led to significant ongoing exposure. The annual cost of the health effects of lead exposure in the United States alone was estimated at US$43.5 billion in 1997—much higher than that associated with any other environmental toxin.1 Few doubt that lead exposure has significant health consequences at levels below those considered medically acceptable decades ago, but there is still debate over what levels of lead exposure in the modern world, if any, can be considered of minimal harm.

This review focuses on lead poisoning in children because of the high prevalence of lead in the environment, and because the impact of lead exposure on children's neurocognitive development, in particular, is substantial.1 Emerging data suggest a health impact on neurocognitive function at much lower blood concentrations of lead than thought earlier.2-5 Children are particularly sensitive and susceptible to lead toxicity and as such are a subpopulation6 at which prevention strategies need to be targeted. Childhood lead remains a major public health problem for certain groups of children, specifically African-American children in the USA,1,7 children living in areas of low socioeconomic status,8 children living in rural mining communities, and children in developing countries such as India and the Philippines.9,10 This paper also presents a case study of the assessment of children exposed to lead in Esperance, Western Australia, to illustrate the principles of managing such events from a public health perspective, as well as the scientific rationale for this approach.

Ethical background

To illustrate the issues of children's lead exposure and management, a case example of environmental exposure in Esperance, Western Australia, is frequently referred to in this review. All human data in this paper were obtained for clinical or public health prevention purposes, and thus a formal research ethics application was not submitted or required to undertake this review. However, the blood sampling conformed to Western Australian Health department guidelines and ethical principles. This paper uses publicly available data on the Esperance lead-contamination incident.
Lessons from managing the lead exposure incident in Esperance

Esperance is a town on the Southern Coast of Western Australia, 721 km from Perth, which enjoys a reputation of a ‘pristine environment,’ with ‘snow white beaches,’ clear ‘aqua blue waters,’ and an ‘abundance of wildlife.’ In December 2006, Esperance community members reported that birds were ‘actually falling from the sky,’ and by the end of March 2007 local government agencies had estimated that the total number of bird deaths in the area was 4500. The detection of elevated lead concentrations in the liver of these birds prompted an environmental investigation that identified significant lead-dust contamination in the town. The point source was found to be the Port of Esperance, which had begun storing and shipping lead carbonate (ore) in 2005. Dust from the port had contaminated rooves; therefore, drinking water from rainwater tanks was a significant source of lead exposure for the population. This newer source contrasts in duration of exposure with the lead mining and smelters found in areas of Australia such as Broken Hill and Port Pirie. The difference is seen in the magnitude of clinical effects but also in terms of appropriate remediation strategies and health surveillance. Sadly, much disproportionate fear has been invoked in the population of Esperance from stories of lead-smelting areas in Australia.

Concern was expressed by the local population about the potential for lead poisoning among children, and those with blood lead concentrations ≥5 μg/dl entered a blood test surveillance programme, where testing occurred at three-month intervals. The aim of such a programme was to evaluate if ongoing exposure and lead accumulation was occurring after environmental remediation had taken place. The level of 5 μg/dl was chosen to give a margin of safety (being significantly lower than the intervention level of 10 μg/dl set by the US Centers for Disease Control and Prevention, CDC, discussed below), and to ensure a sufficient sample size across the town for meaningful data collection. Isotopic lead estimation (described below) was also used, and data collected with this technique revealed that several children had significant blood lead levels associated with exposures from sources other than the primary point source (i.e., the Port).

Active measures were taken to control the population’s lead exposure through dust. These measures included advice against drinking water from rainwater tanks (contaminated by dust), wet mopping of dust, cleaning with other methods, and hand washing. As a consequence, average blood lead concentrations in children five years of age or younger fell rapidly at three and six months after these measures were instituted.

The role of the toxicologist in risk communication is important and conventional concepts in risk communication, such as consistency of messaging and explaining relative risks, were applied in Esperance. Risk messages about the absence of serious toxicity risk were communicated while urging the residents not to be complacent.

This message was both simple and wholly reliable. It was important that the toxicologist involved in the response to the Esperance incident had no connection with government agencies. The role was to keep an active communications channel with concerned members of the public and professionals alike, and to problem-solve where communications had slipped. To ensure that the message had reached the entire community, toxicologists and public health physicians personally saw parents, general practitioners, and community leaders such as aboriginal communities, pediatricians, and activist groups. It was important to be prepared to explain the detailed science and medicine behind decisions to those who sought to understand them. For example, explaining the risks to an individual versus the whole population for lead’s effect on IQ, and explaining some of the confounding factors considered in interpreting existing studies.

It was also helpful to give people choice in how they responded to the situation, for example, by offering a variety of intervention strategies (see below) to reduce ongoing exposure. These included hand washing, availability of high-efficiency particulate air (HEPA) vacuums, personal house cleaning, and professional house cleaning.

It was important to acknowledge the fear provoked by the event. Key to managing this incident was to understand that the community had chosen to live in Esperance because it was a pristine environment. It was also important to understand concerns about the impact of pollution on that image and the prospects of loss of income from tourism.

Potential sources of lead exposure

Longstanding and ongoing sources of external exposure to environmental lead include lead-smelter areas, melted lead batteries, lead in drinking water, the glazing industry, and lead paint. Moreover, exposure can occur in work environments and through the transfer of lead from mother to fetus, which occurs with a placental transmission ratio of 0.6. The transfer of lead from mothers to nursing infants through breast milk occurs in much lower amounts by comparison, with the mammary gland being a barrier that effectively maintains a low milk:plasma ratio for lead. Despite a documented wide range of lead concentrations in human milk, there have been no reports of toxicity caused by breast feeding. For children in non-lead polluting industrial areas, paint provides the most common source of exposure to lead.

In many developed countries, a reduction in the use of leaded petrol over the last decade has diminished lead poisoning; this has led to complacency. The ban of leaded petrol in Australia, in effect since 2002, has resulted in declining blood lead levels—though interestingly, even today some dust from road sides still contains significant concentrations of lead. The most recent Australian National blood lead survey, conducted in 1996 by the Australian Institute of Health and Welfare (AIHW), found a mean blood lead level
of 5.8 μg/dl in a random sample of children, where 92.7% of lead levels recorded were below 10 μg/dl. The US National Health and Nutrition Examination Survey (NHANES) of 1976–1980, 1991–1994, and 1999–2002 has documented a steady decline in the number of children aged one to five years in the USA with blood levels > 10 μg/dl, from 77.8% to 4.4% and to 1.6%, respectively. The average blood lead level for Swedish children aged 7–11 years whose residence was not near industrial sources of the chemical was 2.1 μg/dl between 1995 and 2001.

However, pockets of ongoing population exposure to lead still occur in developed countries. For example, the Guys and St. Thomas Medical Toxicology Clinic in the UK saw many tens of patients with significant lead poisoning requiring chelation therapy in South London from 1998–2006. Lead paint from Victorian houses remains a source of lead poisoning when it chips and flakes before and during restoration. This is also a source of exposure in the USA, where the economically disadvantaged, recent migrants, and children with developmental delays are at a higher risk of lead exposure than the general population. Mean blood lead concentrations in these higher risk populations have declined over time, but remain elevated in some locations and among some populations.

More recently identified sources of lead exposure for children include industrial environmental sources, such as the shipping of lead in the case of Esperance. Newly identified sources of lead poisoning over the last 10 years also include fishing weights, otherwise known as sinkers, snooker chalk, and lead paint found on products including children’s toys and barbeques. Increasing globalization has a marked impact on risk as, for example, in the case of lead paint on toys made in China appearing in shops in the USA and Australia. As a result, there is an increasing need for public health authorities to be vigilant for both domestic and imported lead hazards and to put surveillance systems in place for early identification of such hazards. The most recent US death associated with lead toxicity was in a child who swallowed metal jewelry. This ‘imported risk’ may affect certain ethnic groups more than others. For example, significant amounts of lead are found as a contaminant in some herbs and ethnic remedies including ayurvedic herbal products, imported spices, or Hispanic folk remedies such as ‘litargirio’. However, toys made with lead paint are distributed more widely than these remedies.

What effect does lead have on children?

General principles

Lead is neurotoxic. It interferes with signal transmission at the synapse and interferes with cellular adhesion molecules, causing disruption in cellular migration during critical times of nervous system development. Disruption of subunit expression of the N-methyl-D-aspartate receptor (NMDAR) and NMDAR-mediated calcium signaling in glutamatergic synapses is considered the main mechanism of lead-induced deficits in synaptic plasticity, and in learning and memory deficits documented with animal models of lead toxicity. At fairly substantial levels of exposure, lead inhibits the enzymes ferrochelatase and delta amino levulinic acid dehydratase, resulting in microcytic hypochromic anemia.

There is no single clinical neurological set of effects that make up a ‘signature’ injury associated with lead exposure. Deficits have been reported in verbal IQ, performance IQ, academic skills such as reading and maths, visuo-spatial skills, problem solving, fine and motor skills, memory and language skills. As methods of measuring both lead exposure and cognitive development become more sensitive, subtle adverse impacts of very low blood lead levels become more quantifiable. One of the greatest challenges facing clinicians dealing with lead issues today is determining what this means for individual patients and populations, and mitigating these risks.

Emerging literature on health effects of blood lead concentrations > 10 μg/dl

Several older meta-analyses of observational epidemiological studies indicate that a child’s IQ scores decline 2–3 points per 10 μg/dl increase in blood lead level between 10 and 30 μg/dl. Below 10 μg/dl, a pooled analysis using a log-linear model shows that the function that best describes the data predicts a 9.2 point decline in IQ over the range of <1 to 30 μg/dl; with two thirds of the decline predicted to occur in the range of <1 to 9.9 μg/dl. A plausible explanatory hypothesis for such findings is a lead-sensitive effect that is rapidly saturated at blood levels <10 μg/dl. Some long-running prospective studies suggest that lead-associated neurodevelopmental deficits induced by postnatal exposure resolve over several years. But other studies, such as those involving the Port Pirie data, do not indicate this. Moreover, brain functional imaging studies show differences between those people with and without past exposure to the metal. At higher doses, the impacts of lead include damage to the nervous, hemopoeitic, endocrine, and renal systems. Data indicate that lead contributes to nephrotoxicity even at blood lead levels below 5 μg/dl, especially in susceptible population groups such as those with hypertension, diabetes mellitus, or chronic renal disease.

Emerging literature on health effects of blood lead concentrations <10 μg/dl

Recent studies suggest that there is no concentration threshold for injury from absorbed lead in children, and blood lead levels under 10 μg/dl have been correlated with declining IQ scores. Lanphear et al found that for every 1 μg/dl increase in lead concentration there was a 0.5 point decrease in average scores of arithmetic and reading for children whose blood lead concentrations were <5 μg/dl. Individual studies associating blood lead levels below 10 μg/dl with adverse cognitive impacts must be interpreted carefully, in light of what is known about timing of exposure.
Factors that make children most susceptible to lead toxicity

It is only recently that the concept of considering children as a sensitive subpopulation in health risk terms has gained acceptance in environmental toxicology. Children are more susceptible to the adverse effects of lead than adults for several reasons. Lead exposure around 28 weeks of gestation coincides with a time of critical neurological development, leading potentially to permanent effects even at low levels. As infants and toddlers, their behavior is marked by a high frequency of hand-to-mouth activities, and hence they tend to ingest more dust. The fraction of ingested lead absorbed by young children is higher than that absorbed by adults and the developing nervous system is more susceptible to toxins. In addition, some children have an urge to repetitively consume non-food products such as lead paint flakes—this is called pica.

Assessing a population that may have been exposed to lead

When assessing a population that may have been exposed to lead, the following factors need to be taken into consideration:

- Time course and sources of exposure
- Type of lead compound involved and its physical form, for example dust, pellets, paints, dissolved lead in solution
- The age distribution of the children exposed

Children’s risk of lead poisoning correlates positively with their ability to walk and their hand-to-mouth behavior. Typically, peak blood lead levels occur by 18–30 months of age and then decline gradually through the rest of toddler and school years. Children who have persistent pica are at high risk for continued lead exposure well into their school-aged years; this includes those children with developmental delays. Most young children are exposed by poisoned by the ingestion of lead-containing dust as a result of hand-to-mouth behaviors. In a poisoning incident, inquiry into the possible lead contamination of all the environments in which the child spends significant amounts of time needs to be undertaken. What is the age of the house? Have any renovations taken place recently? Are there bite marks on windows or furniture? Other potential sources of lead also need to be considered (Table 1). What source of water does the family use for drinking? The family's dust control and hand-washing behaviors need to be known. A full physical examination with an emphasis on neurological function is required as part of the assessment. Parents may describe irritability, insomnia, aggressiveness, lack of focus and attention, poor appetite, and speech delays. But these features are, of course, also found in non-lead exposed children, and most children with blood lead levels considered elevated will be asymptomatic, showing no physical signs of poisoning. A developmental evaluation should be considered and appropriate developmental monitoring should be established.

Table 1  A checklist of sources of lead poisoning

| Home | Occupational sources that can bring lead dust into the home |
|------|---------------------------------------------------------|
| Toys, crayons, cribs, furniture | Car repair |
| Contaminated foods, e.g., flour | Mining |
| Surma (kohl) cosmetics | Smelting |
| Ceramic bowls, glazes | Demolition |
| Drinking water from lead pipes | Battery manufacture |
| Dust | Construction |
| Traditional remedies | Pipe fitting |
| Soldered pots, kettles | Plumbing |
| Paint, plaster, putty | Shipbuilding |
| Metallic jewelry | Bridge reconstruction |
| Soil | Glazing, pottery |
| Snooker chalk | |
| Lead fishing weights/sinkers | |
| Renovations | |
Diagnostic modalities for assessing lead poisoning in children

The best way to assess the degree of lead poisoning in children is by taking venous blood for lead estimation. Heel or finger prick testing is prone to significant error because of environmental skin contamination. However, with prior thorough cleaning of the skin, it has been used by many to collect biomonitoring samples. Recently, in undertaking health surveillance after the lead-dust exposure scenario in Esperance, venous blood testing was performed on children under five years of age without the anticipated difficulties of difficult venous access. Retesting was carried out at three monthly intervals in children with lead concentrations >5 µg/dl, and showed significant expected falls (with the estimated elimination half-life of lead from blood being 30 days). This showed that bioaccumulation from ongoing environmental exposure was not occurring, since a rapid fall in concentration indicates long-term exposure. Roberts et al. found that the average time for blood lead to decline was linearly related to the peak concentration of blood lead, but the time for 50% of the blood lead to decline to <10 µg/dl was not linear and varied with peak lead levels. Venous blood lead estimation is a short-term measure of lead exposure (half-life of 30 days) that reflects exposure from current exogenous sources and the release of lead from bone.

The US CDC has, for screening purposes, defined a blood lead level of 10 µg/dl as the threshold level of concern, a value never intended as a definition of what is safe or ‘normal’. The CDC recommends that state and local health departments develop appropriate screening strategies for their areas. In the USA, some states have adopted universal annual screening of preschool children 1–5 years old for lead in blood. An elevated ZPP in a child shown to be iron-sufficient indicates a longer duration of exposure to lead, with a body burden (i.e., more lead deposition in bone) that will require more extensive chelation therapy. In cases where the timing and location of exposure is known, it carries little value. Potentially, it can also be used as a screening tool as a surrogate marker for blood lead. The best screening tool and marker of lead exposure in children remains blood lead and should not be replaced by ZPP. ZPP measurements are fraught with difficulty because there is a poor correlation between ZPP and blood lead at lower blood lead concentrations. Moreover, there are other conditions (e.g., iron deficiency) that can increase ZPP and there is significant inter-individual variation in values. Thus, in the case of lead-dust exposure in Esperance, its use was rejected because of expected relatively low sensitivity and specificity. There is better correlation between ZPP and blood lead at higher concentrations (>20 and particularly >40 µg/dl).

Speciation of lead by isotoping is a newly developed research application of a technique that is very helpful in identifying the source of lead exposure. By comparing the isotopic profiles (isotope ratio) of lead among samples, it is possible to identify or exclude source(s) that contribute to cases of pediatric lead poisoning. In cases of environmental exposure, it can confirm the source of exposure and also help to identify individuals who have not been exposed by this point source.

An abdominal X-ray may reveal recently ingested lead paint chips, sinkers, or plaster—sources of exposure that require removal with polyethylene glycol to prevent further lead absorption. Long bone X-rays can show ‘lead lines’ (which represent growth arrest), but do not alter the way a case of child poisoning should be managed. Routine screening of populations with iron deficiency for lead is also of very limited value because of the low detection rate.

Other risk factors for lead poisoning include concurrent iron deficiency, and it is important that pale or anemic-looking children are screened for this. Both conditions cause anemia and produce a more severe form when combined. The explanation for this is that lead is somehow taken up by the iron transport system in the gut, which is up-regulated in iron-deficient states. It follows that treatment of iron deficiency limits uptake of lead and helps with hematopoiesis, and thus the prevention of iron deficiency may represent a public health intervention for reducing lead exposure in humans. However, iron supplementation has not been shown to benefit iron-replete children with pre-existing lead poisoning and may reduce lead excretion.

be used as a biomarker of lead exposure. It is unsuitable as a measure of acute recent exposures.

The use of zinc protoporphyrins (ZPP) can be helpful in individuals with moderate-to-high blood lead concentrations, where the objective is to determine the chronicity of exposure. An elevated ZPP indicates circulating lead in the preceding 90 days. In cases where the timing and location of exposure is known, it carries little value. Potentially, it can also be used as a screening tool as a surrogate marker for blood lead.

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Current and future intervention strategies to mitigate risk from lead

The US CDC and the World Health Organization define a blood lead level of 10 μg/dl as the threshold level of concern, at which point active management of exposure to lead should be initiated.\(^7\) In addition to strategies discussed above, other lead-reduction strategies include changes in industrial working practices and litigation.\(^7,22\) Childhood lead-prevention programmes should concentrate on home visits and lead source investigations.\(^5,4,7,6\) Five randomized trials examined the effectiveness of intervention strategies, professional house cleaning, vacuuming with HEPA air filters, provision of an individualized healthcare plan, and parental teaching on lead exposure prevention.\(^7,6\) Only repeated professional house cleaning reduced the blood lead concentration significantly. However, because of ethical constraints, in four trials, the control group also had information about lead poisoning prevention, which is a confounding factor to the effects of the study intervention alone.\(^7,6\) Individual lead exposure-reduction strategies such as hand washing and wet mopping of dust reduce the lead burden attributed to dust, and allow an individual to regain a sense of control.\(^7,22\) In explaining the measures taken to reduce lead risk in a population, it is important to give people control over their own risk.

There is a very limited role for chelation therapy, using meso-2,3-dimercatosuccinic acid (DMSA), in cases where levels of lead in the body are elevated as a result of environmental exposure. In a randomized, double-blind, placebo-controlled trial conducted between September 1994 and June 2003 in the USA, 1854 children from 12–33 months with referral blood lead levels between 20 and 44 μg/dl (0.96–2.12 μmol/l) received chelation therapy with DMSA. This lowered their average blood lead concentrations for approximately six months, but resulted in no benefit in cognitive, behavioral, or neuromotor end points.\(^7,7\) There was no relationship between falling blood lead levels and improved cognition in the group treated with active drug.\(^7,7,7\) Although DMSA lowers blood lead in moderately poisoned children, it has no beneficial effect on growth and may have adverse effects.\(^7,7\) Even with higher blood lead concentrations, the problem in essence arises from ongoing exposure situations where continuing lead mining operations, such as Broken Hill in New South Wales, Australia, result in bone deposition of lead. When this happens, the reservoir of lead in bone is in equilibrium with blood. DMSA removes lead from blood, but probably only 1% of the total body burden.\(^8,0–8,2\) Re-equilibration then takes place and blood levels rise again. This can happen particularly sharply if ongoing exposure takes place.\(^8,0,8,1\) Thus, repeated chelation therapy is required to remove the lead.\(^8,0,8,1\) This may cause mild and reversible elevation of liver enzymes. In one study, there were no reported differences in liver function tests between participants treated with DMSA and placebo groups.\(^8,4\) Prevention of exposure is thus unquestionably a much more effective intervention strategy than post-exposure chelation therapy. However, it takes enormous efforts to reduce the time required to make a home ‘lead safe’.\(^8,2\)

Prevention of lead exposure is key to averting risk, so engineering solutions, dust monitoring of industrial sites, and lowering environmental pollution all show promise in this regard. As the evidence accumulates that lead toxicity is significant at lower doses than recognized earlier, there will be more pressure to reduce exposure from known lead sources. In meeting these needs, emerging technologies will need to be developed further to give early warning of the potential for exposure to take place. One such early warning technology is lead-dust monitoring of the air around ports and smelter stacks.

Conclusions

Many countries in the world have a public health burden from lead. In many developed regions, there is complacency because leaded petrol has been phased out, yet certain subpopulations remain exposed to the toxic metal. In the developing world, lead exposure is ongoing and comes from multiple sources. None of us can afford to be ignorant of the risks associated with lead. We need to know how to approach the issue of preventing exposure where possible, and how to apply appropriate health screening and surveillance approaches if exposure has occurred. Measuring blood lead concentrations remains the cornerstone of testing for degree of lead poisoning. Dealing with the population’s fear of unemployment versus a fear of risks to children and tolerance of environmental toxins is a key issue in the modern world. Nowhere is there a better example of that than in cases of lead exposure. Toxicologists have a duty of care to present risks in a balanced way to allow communities to take informed decisions about prevention of exposure, and to recognize the likely health consequences of exposure to lead. People quite rightly expect their clinicians to be better informed and demonstrate excellence in risk communication.

Conflicts of interest

The author has no competing interests.

Provenance and peer review

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