Evaluation of evidence related to exposure to lead

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- Addition of Golub 2010 to Table 8, to reflect that it is included in Appendix 10: Evidence tables from studies recently published and not included in existing systematic reviews.

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Conflicts of interest

We advise that the author team has no conflicts of interest to declare.

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Executive Summary

Lead is a naturally occurring metal with properties that make it useful for a wide range of applications, such as the production of solder, batteries, x-ray shielding, and ammunition. Some applications of lead compounds have been reduced or eliminated in much of the developed world due to evidence of adverse health effects, but it remains ubiquitous in the environment.

NHMRC commissioned this independent evaluation of the evidence relating to individual level lead exposure in Australia. The major aims of this evaluation of evidence were to provide a synthesis of available evidence of (1) the health effects associated with low blood lead levels <5 µg/dL and 5 to 10 µg/dL in children and adults, and (2) the effectiveness of intervention strategies aimed at reducing blood lead levels at an individual level, in children and adults.

The overview of evidence of health effects associated with low blood lead levels <5 µg/dL and 5 to 10 µg/dL in children and adults, presented in Section 2 of this report, summarises the evidence from two moderate-quality systematic reviews. Findings of the systematic reviews should be interpreted with caution, due predominantly to methodological limitations of studies included in the reviews, such as uncontrolled confounding (for example, many studies do not take into account the potential impact of socioeconomic status) and measurement error. The overview of evidence, based on a summary of findings of the two systematic reviews, suggests the following:

- blood lead levels <5 µg/dL are associated with adverse cognitive (academic achievement and IQ decrements) effects in children (although literature suggests uncontrolled confounding may play an important role in the findings regarding IQ);
- blood lead levels <10 µg/dL are associated with the following health effects:
    - adverse behavioural (attention, impulsivity and hyperactivity) effects among *children*;
    - delay in sexual maturation or puberty onset in *adolescent girls and boys*; and

- increased blood pressure and increased risk of hypertension among *adults* and *pregnant women* (although there is uncertainty regarding the clinical significance of the findings regarding an increase in blood pressure).

It is known that removal of the source of lead exposure reduces blood lead levels in exposed individuals. The systematic review of the effectiveness of intervention strategies aimed at reducing blood lead levels at an individual level, in children and adults (presented in Section 3 of this report), found very little relevant evidence and many of the included studies were problematic in that the source of lead exposure being addressed by an intervention was not clearly identified, nor its removal confirmed. Also, the majority of included studies were conducted with children or families from disadvantaged areas with blood lead levels greater than 10μg/dL; therefore, it is uncertain to what degree the body of evidence included in the systematic review applies to the Australian context. Furthermore, the available evidence was generally of very low quality due to issues concerning risk of bias (for example, lack of allocation concealment, large loss to follow up and concerns about confounding) as well as issues with imprecision (wide confidence intervals).

Introduction

Lead is a naturally occurring metal with properties that make it useful for a wide range of applications, such as the production of solder, batteries, x-ray shielding, and ammunition. Some applications of lead compounds have been reduced or eliminated in much of the developed world due to evidence of adverse health effects, but it remains ubiquitous in the environment.

Historically, public health regulatory efforts have attempted to identify a "threshold" of lead toxicity in order to set limits of exposure (as measured by blood lead level) below this putative threshold. Now it appears that no threshold can be identified for developmental neurotoxicity, vascular toxicity and other systemic effects, and the emphasis has shifted to understanding the impacts of a gradation of lower blood lead levels.

The major aim of this evaluation of evidence is to provide a synthesis of available evidence of (1) the health effects associated with low blood lead levels <5 µg/dL and 5 to 10 µg/dL in children and adults, and (2) the effectiveness of intervention strategies aimed at reducing blood lead levels at an individual level, in children and adults. This report also aims to provide relevant background information in order that the findings from the syntheses of evidence can be considered in the real-world context.

The NHMRC has commissioned this independent evaluation of the evidence relating to individual lead exposure in Australia in order to inform a revision of the NHMRC 2009 Public Statement (NHMRC 2009c) and Information Paper (NHMRC 2009a) (if required) and the development of a guideline on the management of individual exposure to lead in Australia for health practitioners.

This report focuses on evidence from countries that belong to the Organisation for Economic Co-operation and Development (OECD), since their policy frameworks are more closely aligned with that of Australia compared to non-OECD countries. Also, occupationally exposed populations and lead-endemic communities are not the focus of this report, since such populations are the focus of specific, targeted guidelines and

intervention strategies. This report has been developed to address evidence in non lead-endemic areas where exposure is considered to be episodic.

Professor Elizabeth Waters from the University of Melbourne was approached by NHMRC to lead this report. As leader of the Cochrane Public Health Group (The Cochrane Collaboration 2013a) she is an international expert in the development of best evidence on the effectiveness of health interventions. The work presented in this report was conducted by Elizabeth and her colleagues between March 2013 and February 2014.

This report is presented in three sections. Section 1 is a background literature review which provides context for the remainder of the report, with regard to health effects, testing and management of blood lead levels in individuals. Section 2 presents an overview of evidence of the health effects associated with blood lead levels <5 and 5 to 10 µg/dL in children and adults. Section 3 presents the methodology and findings of a systematic review of the effectiveness of intervention strategies aimed at reducing blood lead levels at an individual level, in children and adults. Finally, the report culminates with conclusions arising from this body of work.

An explanation of the purpose and methodology of a systematic review

A systematic review is a high-level overview of primary research on a particular research question that tries to identify, select, synthesize and appraise all high quality research evidence relevant to that question in order to answer it (AL Cochrane 1972). Systematic reviews seek to collate all evidence that fits pre-specified eligibility criteria in order to address a specific research question, and aim to minimise bias by using explicit, systematic methods (JPT Higgins & S Green 2011). In comparison, traditional reviews, such as that presented in Section 1 of this report, describe previous work but do not systematically identify, assess for quality or synthesise (NHMRC 1999).

The systematic review methodology is viewed as producing a higher level of research evidence than any other research design (NHMRC 2009b).

A systematic review generally requires considerably more effort than a traditional review (NHMRC 1999). The process is similar to primary scientific research and involves the careful and systematic collection, measurement, and synthesis of data (the 'data' in this instance being research papers). It may be appropriate to provide a quantitative synthesis of the data but this is neither necessary nor sufficient to make a review 'systematic'. A systematic review involves a number of discrete steps (JPT Higgins & S Green 2011; NHMRC 1999):

- question formulation;
- finding studies;
- appraisal and selection of studies;
- summary and synthesis of relevant studies; and
- determining the applicability of results.

Before starting a systematic review, a protocol outlining the question to be answered and the proposed methods is drafted (NHMRC 1999).

An explanation of the purpose and methodology of an overview of evidence

Section 2 was conducted as an overview of evidence. The methodology for this section was based on that of Cochrane Overviews (The Cochrane Collaboration 2013b), which summarise existing systematic reviews rather than find and summarise or synthesise original studies. As described by Cochrane, Cochrane Overviews do not aim to repeat the searches, assessment of eligibility, and assessment of risk of bias or meta-analyses from the included systematic reviews. They do include assessment of limitations of included systematic reviews, and may include meta-analyses across reviews to provide indirect comparisons of the effects of different interventions on a given outcome. The overview presented in Section 2 extends the Cochrane methodology by including a search, assessment of eligibility, quality assessment and consideration of results of studies other than systematic reviews.

Section 1: Literature review of health effects, testing and management of lead exposure

Background

The objective of this literature review is to appraise recent and relevant publications on lead exposure testing methods and accuracy, adverse health effects of lead exposure on major human physiologic systems, and intervention strategies for reducing blood lead levels. The review provides background information for the overview of evidence and systematic review, which are presented later in this report (in Sections 2 and 3, respectively).

The following questions are considered in this review, as agreed with NHMRC.

Health effects:

- What are the sources and routes of human exposure to lead?
- What are the mechanisms of lead toxicity and their clinical correlates?

Testing:

- What are the clinical indicators for testing for recent exposure to lead, for different subgroups of age/pregnancy and lactation?
- What are the population indicators for testing for recent exposure to lead?
- What biomarkers can be used to test for recent lead exposure and for cumulative body burden?
- What is the availability of lead exposure tests?
- What is the diagnostic accuracy of available lead exposure tests, particularly at low levels of exposure to lead? How do they compare to each other?
- What factors influence the accuracy of the available lead exposure tests?

Intervention:

- What intervention strategies can be implemented (at an individual, community or policy level) to reduce or treat exposure to lead?

This background literature review provides broad contextual information for the subsequent reviews and thus includes within its scope high as well as low level lead exposure contexts, including occupationally exposed populations, and communities in which lead is endemic (although these are not the primary interests of the body of work presented in this report). The literature search included relevant academic databases and government websites, as guided by the NHMRC Lead Working Committee. Policy documents, commentaries, historic descriptions, annual reports from health authorities, reviews and editorials, textbooks, and, where applicable, research studies, were included in the review.

Health Effects

What are the sources and routes of human exposure to lead?

Sources

There is a background level of exposure to lead that is unavoidable in Australia and many developed countries. The extent of background exposure in Australia is not well understood, since few studies have measured levels in populations not affected by industrial lead sources. The authors of a recent review of potential lead exposure in Australian inner cities suggest children in Sydney may have similar blood lead levels to children in two comparable US cities, Milwaukee and New Orleans (MAS Laidlaw & MP Taylor 2011). In these cities, between 5 to 10% of children have a blood lead level >10 µg/dL, and 94% of children have a blood lead level >2 µg/dL. The most recent studies with Australian pre-school children show lower mean blood lead levels: a geometric mean[1] of 2.1 µg/dL in Sydney up to 2006 (B Gulson et al. 2008) and 1.83 µg/dL in

[1] The geometric mean is a type of mean or average, which indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean which uses their sum). The geometric mean is defined as the nth root (where n is the count of numbers) of the product of the numbers.

Fremantle in 2005 (R Guttinger et al. 2008). However these studies may be too small (n = 113 and n = 100, respectively) to reliably predict blood lead level in Australian children more broadly (MAS Laidlaw & MP Taylor 2011). Numerous interventions have been implemented worldwide to eradicate sources of lead exposure (this will be discussed later in this section of the report). Despite this, several sources of lead remain, including deteriorating paint and dust in older homes, contaminated soil and water, acid batteries and lead in certain ceramics, cosmetics, children's toys, or traditional medicines (ATSDR 2007; CDC 2005b; US EPA 2013).

Homes may be the source of lead exposure through domestic paint. Historically, lead paint was used on the inside and outside of homes in Australia, exposing inhabitants (particularly young children, who spend a significant amount of time at home) to high levels of lead. In the 1960s lead paint began to be phased out, and currently the recommended amount of lead in Australian domestic paint is 0.1% (Australian Government Department of Environment 2012). Despite this, exposure to lead paint remains a problem in old homes and buildings, where children and pets can ingest flecks of paint as it chips or peels from walls. Renovations of older homes and buildings are a particular concern in terms of lead exposure both to those in close proximity to the renovation and to others who are exposed as the dust moves into the wider environment (BL Gulson, JJ Davis & J Bawden-Smith 1995).

Petrol was an important source of lead exposure in Australia until 2002, when lead was phased out nationally following interventions in Western Australia and Queensland in 2000 and 2001 respectively (Australian Government Department of Environment 2001).

Evidence suggests soil contamination may be an important source of lead exposure in urban Australia. For example, analysis of 41 residential housing soil samples from an inner-Sydney suburb found that 68% exceeded the National Environmental Protection Council 300 mg/kg residential soil lead guideline (National Environment Protection Council 2013; Royal Prince Alfred Hospital and Central and Southern Sydney Area Health Service 1988). A recent review of existing evidence concluded that previous use of lead in petrol and paint has contaminated urban soils in the older inner suburbs of large Australian cities, and that the risks to human health remain poorly understood

due in part to a lack of knowledge of the distribution of soil lead concentrations across Australia (MAS Laidlaw & MP Taylor 2011).

With the decline in atmospheric lead since the introduction of fuel-related interventions, water is now the largest controllable source of lead exposure in the USA (R Levin, MR Schock & AH Marcus 1989; WHO 2011b) and a source of concern in other countries (MJ Quinn & JC Sherlock 1990; JC Sherlock & MJ Quinn 1986). The Australian Drinking Water Guidelines state that the concentration of lead in drinking water should not exceed 0.01 mg/L (NHMRC 2011), and the guideline document reports that for major reticulated water supplies in Australia total lead concentrations can reach 0.01 mg/L; typical concentrations are less than 0.005 mg/L (NHMRC 2011).

In older Australian homes lead can be present in drinking water as a result of dissolution from household plumbing (for example, pipes, solder and fittings). The amount of lead dissolved depends on a number of factors, including pH, temperature, water hardness, and standing time (NHMRC, 2011).

Food can also be a major source of exposure to lead (ATSDR, 2007), although the average Australian dietary intake of <0.01 mg/day (Food Standards Australia New Zealand 2011) is below the level considered by the Joint FAO/WHO Expert Committee on Food Additives to have a low risk of reducing the population IQ for children or increasing the systolic blood pressure in adults (WHO 2011c).

Plants grown for consumption either at the household or commercial level can be a source of lead exposure if contaminated water, soil or airborne dust remains on the plant at the time of ingestion (ATSDR 2007).

Products imported into Australia are a potential source of exposure. The Australian Government National Industrial Chemicals Notification and Assessment Scheme ensures that imported products have appropriate concentrations of lead (Australian Government Department of Health 2013).

Individuals are also affected by larger-scale sources of lead exposure such as smelting and mining endeavours (Health Canada 2013). Adults who work in these industries are exposed to lead, as are individuals and families living near these activities. In Australia,

communities in Port Pirie, Mt Isa, Broken Hill, Lake Macquarie and Goulburn in the Southern Tablelands of NSW have been exposed in this way, amongst others (PA Baghurst et al. 1992; M Chiaradia, G B.L. & K MacDonald 1997; AK Mackay et al. 2013; A Willmore et al. 2006).

Sources of lead exposure vary between children and adults (ATSDR 2007; US EPA 2013). For example, children's and adult's diets often differ substantially. Lifestyle and behavioural factors also explain potential differences in sources of exposure. For example, children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors.

Routes

Lead enters the human body primarily through ingestion and inhalation. Lead is then absorbed, distributed, and excreted (ATSDR 2007). The rate of absorption through the lungs is much more efficient than absorption through the gastrointestinal tract, resulting in higher uptake of lead by inhalation (ATSDR 2007).

Once lead is absorbed into the body, it is widely distributed to blood, soft tissue (liver, kidneys, lungs, brain, spleen, muscles, and heart), and mineralising tissues (bones and teeth). Lead travels in the blood to soft tissues and organs and is later stored in bones and teeth after several weeks. Some lead may be released back into the blood stream during times of calcium stress; for example, pregnancy, lactation, menopause, osteoporosis (ATSDR 2007), periods of growth and periods of extended bed-rest.

Lead that is not distributed in the body's organs or stored in the bones is excreted through the urine, with the half-life of lead in blood being around 30 days. Thus the kidney is the principal route for lead excretion (ATSDR 2007).

Maternal lead crosses the placenta to the fetus (B Gulson et al. 2003) with the maternal/fetal blood lead concentration ratio, indicated from cord blood lead levels, being approximately 0.9 (RA Goyer 1990). Thus, factors that increase maternal blood lead levels will have the additional effect of increasing fetal blood lead levels.

Various factors influence the rate of lead uptake, including age, gender, nutritional status, and size of lead-containing particles entering the body (ATSDR 2007; FJ Barbosa

et al. 2005). Ageing adults are considered to be a vulnerable population in terms of effects of lead exposure (Health Canada 2013).

Studies show that children absorb a significantly higher proportion of lead compared to adults; for example, children can absorb 40- 50% of an oral dose of water-soluble lead compared to 3-10% for adults (ATSDR 2007). The increased susceptibility of young children to the harmful effects of lead is thought to be derived from factors such as the continual growth of young children, which contributes to a state in which lead stored in bone is continually released back into the blood compartment, a process that has been described as "endogenous contamination" (BL Gulson et al. 1996).

Popovic et al. found different long-term lead kinetics between men and women (M Popovic et al. 2005). Compared to men and postmenopausal women, premenopausal women appear to retain lead more readily (or release lead more slowly).

Regarding nutritional status, low iron levels, calcium deficiency, and fasting increase the rates of lead absorption into the body (ATSDR 2007).

The absorption of inhaled lead is influenced by particle size and solubility. During the inhalation of inorganic lead, larger particles (>2.5 μm) that are deposited in the ciliated airways (nasopharyngeal and tracheobronchial regions) can be transferred by mucociliary transport into the oesophagus and swallowed (ATSDR 2007). Smaller particles (<1 μm), which can be deposited in the alveolar region, can be absorbed after extracellular dissolution or ingestion by phagocytic cells. With regard to ingestion of lead, it has been found that the solubility of lead sulphide in gastric acid in vitro is much lower for particles of 100 μm compared with 30 μm in diameter (MA Healy et al. 1982).

What are the mechanisms of lead toxicity and their clinical correlates?

Much of the information presented in this section is drawn from the Health Protection Agency (HPA) Compendium of Chemical Hazards Lead (S Bull 2007). It is important to recognise that, as stated in the document, the information reflects an evaluation of the scientific evidence available at the time of publication of the document; however a systematic review process was not undertaken to arrive at the findings presented. The reader is referred to Section 2 of this report for an overview of health effects associated with blood lead levels <5 μg/dL and 5 to 10 μg/dL in children and adults.

The table below provides an overview of threshold toxicity values for lead, in adults and children, based on a review of scientific literature conducted by The Health Protection Agency (S Bull 2007). The methodology used in the review process is not presented in the review. The table below does not provide details of health effects of blood lead levels <10 µg/dL; this topic will be considered in detail in Section 2 of this report.

Table 1. Threshold toxicity values for lead in adults and children (S Bull 2007)

Blood lead conc. ($\mu g\ dl^{-1}$)	SIGNS AND SYMPTOMS	
	ADULTS	CHILDREN
10		Hearing impairment
10-15		Cognitive impairment
30	Decreased nerve conduction velocity	Reduced haemoglobin levels
40 - 60	GI disturbances: nausea, vomiting, anorexia, constipation, abdominal cramps, weight loss, reduced haemoglobin levels, cognition impairment	
40 - 120	Malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libdo, dizziness, weakness and paraesthesia	
60 - 100		GI disturbances: abdominal pain, constipation, nausea, vomiting, anorexia, weight loss, frank anaemia
80	Frank anaemia	Signs and symptoms of lead encephalopathy: irritability, poor attention span, headache, memory loss, tremor, ataxia, convulsions, drowsiness, malaise, coma, seizures, death
100-120	Signs and symptoms of lead encephalopathy: irritability, poor attention span, headache, memory loss, tremor, ataxia, convulsions, drowsiness, malaise, coma, seizures, death	

The remainder of this section considers specific haematological, endocrine, cardiovascular, neurological and renal effects of exposure to lead, and highlights the effects of acute compared to chronic exposure.

Haematological Effects

The effects of chronic or repeated lead exposure on the haematopoietic system include increased urinary porphyrins, coproporphyrins, δ-aminolaevulinic acid, erythrocyte protoporphyrin and zinc protoporphyrin (ATSDR 2007). Lead alters the activity of three enzymes that are important in haem biosynthesis: ALAS (which is stimulated by lead),

ALAD (inhibited by lead) and ferrochelatase (inhibited by lead). Evidence suggests ALAD may be inhibited at 3 -34 µg/dL, with no threshold yet apparent (S Bull 2007).

The interference to haem synthesis from lead results in the body's inability to make haemoglobin (ATSDR 2007). Reduced haemoglobin synthesis has occurred at 50 µg/dL in adults and 40 µg/dL in children (S Bull 2007). A reduction of haemoglobin in the blood results in a hypochromic, normocytic anaemia (ATSDR 2007); that is, anaemia in which the red blood cells are paler than normal.

Endocrine Disruption

High levels of exposure to lead have been associated with changes to thyroid, pituitary, and testicular hormones in occupational studies (ATSDR 2007). It appears that changes in circulating levels of thyroid hormones occur with mean blood lead levels of ≥40–60 µg/dL (A Gustafson, P Hedner & A Schutz 1989; CM Lopez, AE Pineiro & N Nunez 2000 ; B Singh, V Chandran & HK Bandhu 2000) compared with altered serum levels of reproductive hormones, which have been observed at levels of ≥30– 40 µg/dL (N Dursun & A Tutus 1999 ; A Gustafson, P Hedner & A Schutz 1989). It has been suggested that effects of lead on pituitary function may precede these changes in thyroid and reproductive hormones (ATSDR 2007).

Cardiovascular Effects

Acute exposure to lead has been associated with hypertension at blood lead levels of 48 – 120µg/dL (S Bull 2007). A summary of the HPA review is presented in full below (note that no information was provided regarding the methodology of their review).[2]

Meta-analyses of epidemiological data have found a persistent trend in the data that supports a significant, albeit weak, association between PbB [blood lead level] and blood pressure. The association amounts to an increase in systolic blood pressure of approximately 1 mmHg with each doubling of PbB, without any identifiable threshold [2,

[2] References for this section are provided in Appendix 1.

5]. The lead contribution to elevated blood pressure appears to be more pronounced in middle age than at younger ages [2].

JECFA concluded that it was not possible to establish a threshold for cardiovascular effects in adults (critical endpoint being increase in systolic blood pressure). The Committee carried out dose response analysis and reported that a lead exposure level of 3.0 µg kg^{-1} bw day^{-1} would be expected to cause a population increase of approximately 2 mmHg in systolic blood pressure[3]. An increase on this scale has been associated with moderate increases in risk of ischaemic heart disease and cerebrovascular stroke. The Committee considered this to be of some concern, but less so than the neurodevelopmental effects observed in children [14].

The EFSA CONTAM Panel concluded that there is no evidence for a threshold for lead induced cardiovascular effects in adults. The Panel reported that an estimated lead intake of 1.50 µg kg^{-1} bw day^{-1} was associated with a 1% change in systolic blood pressure, which corresponds to a 1.2mm Hg from the baseline value of 120mmHg in a normotensive adult. The panel concluded that such a change could have significant consequences for human health on a population basis [5].

A range of mechanisms have been suggested to contribute to the phenomenon of increased blood pressure due to exposure to lead, including depletion of nitric oxide, which plays a role in regulating blood pressure; disturbance of cell-signalling mechanisms in endothelial cells; activation of the renin-angiotensin-aldosterone system; alterations in the production of renal prostaglandins; and constriction of the vascular smooth muscle associated with increased intracellular calcium levels (ATSDR 2007).

[3] The unit µg kg^{-1}bw day^{-1} refers to the amount of lead ingested per kilogram of body weight per day. The unit µg/dL (used throughout this report) refers to micrograms of lead per deciliter of blood, and is the unit used to measure blood lead level.

Neurological Effects

The most frequent neurological effect of acute lead exposure is encephalopathy, which can occur at blood lead levels of 80 – 100µg/dL in children and 100 - 120µg/dL in adults (S Bull 2007). Symptoms include irritability, agitation, poor attention span, headache, confusion, ataxia, drowsiness, convulsions and coma (S Bull 2007).

A summary of the HPA review is presented in full below (note that no information was provided regarding the methodology of their review).[4]

Chronic lead exposure may lead to dizziness, fatigue, sleep disturbance, headache, irritability, lethargy, malaise, slurred speech and convulsions at PbB concentrations of 40 –120µg/dL [2]. Muscle weakness, paraesthesia, ataxia, tremors and paralysis may also occur [2, 7].

Neurobehavioral effects may be observed in lead workers with PbB concentrations of 40 - 80 µg/dL, including disturbances in reaction time, visual motor performances, hand dexterity, IQ and cognitive performance, anxiety and mood [2, 11].

Several studies have been carried out to investigate the correlation between behaviour and intelligence and lead exposure in children. Overall, most studies reported an inverse association between PbB and IQ in children. Exposures that correspond to a PbB as low as 2µg/dL have been reported to cause developmental lead neurotoxicity [5].

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that it was not possible identify a threshold for the association between lead exposure and decrements in IQ [13].

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) also concluded that it was not possible to establish a threshold for the neurological effects of lead in children. The Committee carried out a dose response analysis and reported that a lead exposure level of 0.3 µg kg^{-1} bw day^{-1} was calculated to be associated with a population decrease of

[4] References for this section are provided in Appendix 1.

0.5 IQ points. A lead exposure level of 1.9 µg kg^{-1} bw day^{-1} was calculated to be associated with a population decrease of 3 IQ points, the Committee deemed this to be of concern [14].

The European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM) also concluded that there is no evidence for a threshold for lead-induced developmental neurotoxicity in young children. The Panel reported that an estimated intake of 0.5 µg kg^{-1} bw day^{-1} was associated with decrease in IQ of 1 point on the full scale IQ score. The panel concluded that such a change could have significant consequences for human health on a population basis [5].

Renal Effects

As discussed by HPA, acute lead exposure can cause proximal renal tubular dysfunction, with proteinuria, aminoaciduria, glycosuria, renal tubular acidosis and cellular casts (S Bull 2007). It has been found that most of these effects are generally reversible (S Bull 2007). A form of acute renal impairment involving prominent inclusion bodies that are visible in the cells of proximal tubules can occur at blood lead levels of 40 – 80µg/dL; this, too, is generally reversible. Acute interstitial nephritis has also been reported at 40 – 80µg/dL (S Bull 2007).

HPA summarises their findings on the effects of chronic or repeated lead exposure and renal toxicity, as follows (S Bull 2007)[5]:

Chronic exposure to lead may cause lead nephrotoxicity characterised by glomerular sclerosis, interstitial fibrosis and proximal tubular nephropathy [2]. Depressed glomerular filtration rate has been observed in association with exposures resulting in average PbB levels <20 µg/dL [2, 5]. Enzymuria and proteinuria are generally observed at PbB >30 µg/dL and severe deficits in renal function and pathological changes are associated with PbBs >50 µg/dL [2]. Mortality following chronic nephropathy may occur at PbB concentrations exceeding 60 µg/dL [11].

[5] References for this section are provided in Appendix 1.

The EFSA CONTAM Panel concluded that there is no evidence for a threshold for lead induced nephrotoxicity in adults. The Panel reported that an estimated lead intake of 0.63 µg kg^{-1} bw day^{-1} was associated with a 10% change in prevalence of chronic kidney disease and concluded that that such a change could have significant consequences for human health on a population basis [5].

Testing

What are the clinical indicators for testing for recent exposure to lead, for different subgroups of age/pregnancy and lactation?

Clinical indicators for testing for lead exposure include the suspected or identified presence of a risk factor for exposure (such as known ingestion of lead-based paint), physical signs or symptoms, or the presence of a household member with known exposure to lead (WHO 2010a).

When symptoms from lead exposure occur, they are generally nonspecific. Symptoms include constipation, abdominal pain, anaemia, headache, fatigue, myalgia and arthralgia, anorexia, sleep disturbance and difficulty concentrating (US EPA 2013; WHO 2010a). The reader is directed to Section 2 of this report for more detail on the symptoms of lead exposure. Measurement of lead levels should also be considered for acutely ill children presenting with severe colic, seizure or coma.

Pregnant and lactating women may present with severe abdominal colic, seizure, coma, persistent headache, or fatigue (ATSDR 2007; CDC 2010). Lead exposure has been associated with increased risk for gestational hypertension (M Rabinowitz et al. 1987; M Vigeh et al. 2004) but the magnitude of the effect, the exposure level at which risk begins to increase, and whether risk is most associated with acute or cumulative exposure are not known (CDC 2010). Screening tools are available to assess risk factors for exposure to lead in pregnant and lactating women; see, for example, the work of Stefanak and colleagues (MA Stefanak, CC Bourguet & T Benzies-Styka 1996). While these tools are not validated they may be useful to create a dialogue between women and their health practitioners (CDC 2010).

What are the population indicators for testing for recent exposure to lead?

There are various scenarios under which testing of lead levels may be warranted in entire communities or in subgroups of a population.

Suspected intoxication

A group of people may be tested in cases of large-scale suspected intoxication such as that caused by environmental contamination from processing lead-rich ore or transport of lead-rich ore (Education and Health Standing Committee 2007), or large-scale suspected intoxication caused by outbreaks arising from use of contaminated Ayurvedic medicines (CDC 2011-2012; RS Tsutsui, J Van Schalkwyk & D Spriggs 2013), food products (M Villalobos et al. 2009) or spices (WHO 2011a).

Exposure assessment

Populations at risk of lead exposure may undergo health risk assessments, including estimation of lead exposure (WHO 2011a). People living near a lead-processing factory are one such example. In a health risk assessment, steps are taken to estimate or measure magnitude, frequency and duration of exposure to lead, along with the number and demographic characteristics of the population exposed.

Screening

Since lead-exposed individuals are often asymptomatic, screening for lead exposure is often carried out for individuals suspected to be exposed in a population at risk or in the general population (WHO 2011a). Screening programmes usually cover relatively large populations.

In 1997, the US Centers for Disease Control and Prevention (CDC) issued new guidance on screening children for lead exposure that recommended a systematic approach to the development of appropriate lead screening in states and communities (CDC 1997). The objective of the revised guidelines was maximum screening of high-risk children and reduced screening of low-risk children, as contrasted with previous guidelines (CDC 1991) which recommended universal screening. It was recommended that the following children should be screened: children aged one, two three and six years who have not previously been screened, and who meet at least one of a number of criteria (CDC

1997). The criteria relate to assessing the extent of lead hazards in the home, based on age and location, along with criteria related to the child's risk of exposure.

Similarly, in Australia a universal lead screening program for children is not recommended or undertaken. Instead, surveys every five years of representative samples of children in high and low lead exposure areas have been recommended; however, these surveys have not been implemented (Centre for Community Child Health 2002).

Occupational health

The measurement of blood lead levels is often part of the routine occupational health monitoring of workers active in the lead industry or other work involving lead (WHO 2011a). In many countries, including Australia, the regular monitoring of blood lead levels of such workers is required by legislation, which also provides for the suspension or removal from further exposure of those with blood lead levels above certain values.

Options for Testing

The following questions were considered:

- What biomarkers can be used to test for recent lead exposure?
- What is the availability of lead exposure tests?
- What is the diagnostic accuracy of available lead exposure tests, particularly at low levels of exposure to lead? How do they compare to each other?
- What factors influence the accuracy of the available lead exposure tests?

Biomarkers are defined as indicators signalling events in biological systems or samples. Lead concentrations can be measured in various biological materials such as blood, bone, erythrocyte protoporphyrin, plasma, sweat, teeth, nails and hair (ATSDR 2007). Blood lead level is the most widely used and well-established biomarker of exposure to lead and for this reason will be discussed in most detail in this section.

Blood

Description & Indications

Lead measured in whole blood samples is the most commonly used biomarker of exposure to lead in clinical, population surveillance and epidemiological research settings (Health Canada 2013). Blood comprises less than 2% of the total lead body burden, but it is the initial receptacle of absorbed lead and is responsible for distributing lead throughout the body to other tissues. Since the mean life of blood lead is about 1 month (MB Rabinowitz 1991) it is best used to determine recent lead exposure (exposure occurring in the preceding 6 weeks) (Health Canada 2013).

Available tests

Blood lead level testing is a simple and inexpensive. There are two types of blood tests available: venous blood testing and capillary blood testing (ATSDR 2007).

Venous blood testing: The method of collection for venous blood involves the direct puncture of veins in the arm or the top of the hand by venepuncture using a vascular access device. Venous blood samples contain deoxygenated blood that flows from small blood vessels into larger veins. Venous blood testing is the preferred method for most routine laboratory tests due to its higher sensitivity and specificity compared with capillary blood testing (ATSDR 2007).

Capillary blood testing: The method of collection for capillary blood involves dermal puncture of the fingertip, which is also referred to as the finger-stick method. Blood samples from capillary blood testing contain a mixture of arterial and venous blood along with interstitial and intracellular fluids. Capillary blood testing is often the preferred method for infants, very young children, elderly patients with fragile veins, and severely burned patients as it is less invasive (MK Anderson et al. 2007).

Notification levels

Blood lead, levels >10 µg/dL, has been used as a level to notify public health authorities to manage risks to community health. There is some variability in Australian State and Territory legislation for blood lead notification, as seen in Table 2, with four states having a notifiable rate of either greater than, or equal to or greater than, 10 µg/dL.

Table 2. Australian State and Territory legislation for blood lead notification (current as at January 2014)

State/territory	Level	Who	Notifier	Legislation	Details
ACT	Not notifiable at any level				
NSW	Notifiable – venous sample ≥10 µg/dL (>0.72 µmol/L)	Regional public health unit by routine mail	Laboratories on diagnosis	*Public Health Act 1991*	Notification results from pathology service to be sent to the Regional Public Health Unit Regional Public Health Unit receives and responds to notificationshttp://www.health.nsw.gov.au/PublicHealth/Infectious/phus.asp
Northern Territory	Not notifiable at any level				
Queensland	Notifiable ≥10 µg/dL (≥0.48 µmol/L)	Local public health unit within 48 hrs	Medical practitioners on diagnosis	Public Health Regulations 2005	http://www.health.qld.gov.au/ph/documents/cdb/notif_conditions_rpt.pdf Nearest Public Health Unit receives and responds to notifications
South Australia	Not notifiable at any level				
Tasmania	Notifiable >10 µg/dL (>0.48 µmol/L)	Department of Health and Human Services	Laboratories	*Public Health Act 1997*	http://www.dhhs.tas.gov.au/__data/assets/pdf_file/0003/53319/Notifiable_Diseases_+_Guideline_FINAL_Feb_2010.pdf
Victoria	Notifiable >10 µg/dL (>0.48 µmol/L)	Department of Health	Laboratories and medical practitioners on diagnosis	Public Health and Wellbeing Act 2008	http://docs.health.vic.gov.au/docs/doc/Notifiable-Conditions-Form Reg 72, Section 128
Western Australia	A person who is or may be suffering from lead poisoning		Medical practitioners after diagnosis of lead poisoning	Health Act 1911 Health (Notification of Lead Poisoning) Regulations 1985	http://www.public.health.wa.gov.au/3/507/2/lead_poisoning_notifications.pm

Accuracy

Measuring the level of lead in blood is the most accurate type of testing available in Australia for detecting recent lead exposure. A recent review of the clinical interpretation and management of blood lead levels <10 µg/dL conducted by the CDC Advisory Committee on Childhood Lead Poisoning Prevention (H Binns, C Campbell & M Brown 2007) discussed two studies that highlight the relatively high accuracy of blood lead level testing (both of which focus on venous blood testing). One study of duplicate testing of identical blood samples (all with mean blood lead levels of < 10 µg/dL) at 8 laboratories found results of < 10 µg/dL and within 3 µg/dL of the overall mean for that specimen value (NK Johanputra et al. 1998). The other study indicated that the majority of laboratories performing blood lead level testing can achieve routine performance of +/- 2 µg/dL at levels of ≤10 µg/dL without difficulty (PJ Parsons, C Geraghty & MF Verostek 2001). Results of these studies should be considered alongside the fact that US Federal regulations allow laboratories that perform blood lead level testing to operate with a total allowable error of +/- 4 µg/dL or +/- 10%, whichever is greater (H Binns, C Campbell & M Brown 2007). Readers should refer to relevant documents from Standards Australia for comparable Australian information (Standards Australia 1993).

Compared with venous lead testing, capillary tests carry a considerable risk of surface contamination from the finger and result in a higher rate of false positive results (ATSDR 2007). Thus, capillary tests are not recommended for diagnostic purposes (MK Anderson et al. 2007; Minnesota Department of Health 2008).

Irrespective of whether venous or capillary testing is used, the accuracy of the test is influenced by the timing of blood testing, the blood collection technique, and the analytical measures used.

Timing of blood testing: As was noted previously, lead is initially absorbed in the blood before distribution to other tissues. Because of this, blood lead levels are best used to determine lead exposure in the preceding six weeks and cannot detect a higher exposure that occurred (or ended) several months earlier (ATSDR 2007; Health Canada 2013). The timing of testing should be linked to risk, such as that of potential exposure to lead (Contra Costa Health Services 2005).

Blood collection techniques: When collecting blood samples, it is necessary to cleanse the site of injection; this is particularly important for capillary samples due to their susceptibility to environmental contamination. A clean, "lead-free" location should be set up prior to sample collection in the field (PJ Parsons & JJ Chisolm, Jr. 1997; WHO 2011a).

Sample handling within the laboratory also involves risk of contamination. Laboratories should be as close to lead free as possible, and staff should be trained to prevent sample contamination. Sample preparation should be performed in a clean environment with minimal air particulates, ideally in an International Organisation for Standardisation class 5 setting (i.e. having no more than 10^5 particles per m^3) or better, in a laminar flow biological safety cabinet (WHO 2011a).

Analytical measures: Analytical methods for measuring lead in blood include flame atomic absorption spectrometry (AAS), graphite furnace atomic absorption spectrometry (GFAAS), anode stripping voltammetry (ASV), inductively coupled plasma atomic emission spectroscopy (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS) and, rarely, the "gold" standard of isotope dilution thermal ionization mass spectrometry (WI Manton & JD Cook 1984). The methods vary in terms of accuracy, precision, reportable range, and analytical detection limit. Table 3 shows the strengths and limitations of each analytical method (WHO 2011a). Avoiding lead contamination at the analysis stage is extremely important; refer, for example, to the paper by Settle and Pattison which describes lead contamination in canned tuna that went undetected for decades due to sampling and analytical errors (DM Settle & CC Patterson 1980).

Risks

Serious adverse events linked with drawing blood are rare, but may include loss of consciousness with tonic clonic seizures (WHO 2010b). Less severe events include pain at the site of venepuncture, anxiety and fainting. Perhaps the most likely source of potential harm to the patient is the risk of emotional distress, and training in procedures to minimise such distress is integral for those involved in taking blood (WHO 2010b). The World Health Organization (WHO) Guidelines On Drawing Blood

provide detailed risk management procedures for drawing venous and capillary blood, including specific advice for testing children (WHO 2010b).

Table 3. Overview of analytical methods for blood lead level measurement (WHO 2011a)

Method	Strengths	Limitations
Flame atomic absorption spectrometry (FAAS)	Requires only basic laboratory expertise Rapid analysis Small sample size using Delves cup (50–100 µl) Low purchase and running costs Relatively few interferences Robust interface	Relatively high detection limit (~10 µg/dL) Time needed for sample digestion/preconcentration if not using Delves cup Large sample size needed for nebulization methods
Graphite furnace atomic absorption spectrometry (GFAAS)	Good detection limit (<1–2 µg/dL) Small sample size Moderate purchase and running costs Some multielement capacity Relatively few interferences (although more than with FAAS) Widely used, available from multiple vendors	Longer analysis time Requires some laboratory expertise (more than FAAS) Greater potential spectral interference than with FAAS
Laboratory anodic stripping voltammetry (ASV)	Good detection limit (2-3 µg/dL) Low purchase and running costs Rapid Small sample size (~100 µl) Relative simplicity of equipment	Requires some laboratory expertise (similar to GFAAS) Sample pretreatment needed Some factors might affect measurement (e.g. presence of copper) Becoming less available
Portable ASV	Portable; measurement at point of care possible Simple to use; does not require skilled laboratory personnel Very low purchase and running costs Reasonably good detection limit for a portable device (3.3 µg/dL) Rapid	Not as accurate as other methods Can determine levels only up to 65 µg/dL Levels above 8 µg/dL should be confirmed by a laboratory method

Method	Strengths	Limitations
Inductively coupled plasma mass spectrometry (ICP-MS)	Excellent method detection limit (~0.1 µg/dL) Rapid Small sample size (50–100 µl) Relatively few, well-understood, spectral interferences Isotopic measurements possible Economic if very large number of samples Multielement capability	High purchase and running costs Highly skilled laboratory operator required

Bone

In contrast to blood lead level, bone lead level, because of its extremely long half-life (10 to 30 years) is an indicator of chronic lead exposure (ATSDR 2007; Health Canada 2013). Chronic exposure is arguably a more useful indicator than recent exposure, however in practice blood lead level measurement is preferred due to the limited availability of the equipment required for non-invasive bone assessment (Health Canada 2013).

Bone lead level measurements are based on non-invasive in vivo X-ray fluorescence methods which use fluorescing photons to remove an inner-shell electron from a lead atom, leaving it in an excited state (FJ Barbosa et al. 2005). The result is emission of X-ray photons that are characteristic of lead. There are four types of X-ray fluorescence: two involve fluorescence of the K-shell electrons of lead and the other two involve fluorescence of the L-shell electrons (AC Todd et al. 2002). A definitive upper range for normal lead concentration as measured in bone was not identified in this process of conducting this literature review. Since test results are highly dependent on bone site and type as well as age of patient, these factors should be taken into account in the interpretation of test results.

X-ray fluorescence displays a certain amount of imprecision, estimated (using a goodness-of-fit statistic from the curve fitting of the background) to range from 3 to 30 µg lead/g of bone mineral (TM Ambrose, M Al-Lozi & MG Scott 2000). Thus, measurement of low-level lead exposures, such as in young children or non-exposed

populations, is problematic. Further information on variance in bone lead measurement can be found in the work of Todd (AC Todd 2000; AC Todd et al. 2001).

Several groups, mainly in the US, have reported the development of in vivo measurement systems; the majority have adopted K-X-ray fluorescence rather than the L-X-ray approach because it has a better detection limit and a lower effective (radiation) dose (AC Todd & DR Chettle 1994). No such equipment is available in Australia.

Lead is not distributed uniformly in bone. Lead accumulates in regions of bone undergoing the most active calcification at the time of exposure. Following from this, lead accumulation during childhood predominantly occurs in trabecular bone (e.g. the patella, calcaneus and sternum) whilst in adulthood it predominates at sites of remodelling in cortical (e.g. the mid-tibia, phalanx and ulna) as well as trabecular bone (ATSDR 2007). Therefore test results depend on bone site under analysis.

As has been mentioned, bone lead testing captures cumulative lead exposure, so it follows that bone lead levels and age are positively correlated (H Hu, D Hashimoto & M Besser 1996; MJ Kosnett et al. 1994; MM Roy et al. 1997). It is thought that this positive association is stronger after adolescence (JA Hoppin et al. 1997).

Bone lead measurements use radiation. The dose delivered by all bone lead measurement methods is small and a review of relevant literature concluded that the radiation dose is not a limiting factor in using these techniques with humans (AC Todd & DR Chettle 1994).

Erythrocyte Protoporphyrin

Exposure to lead can also be evaluated by measuring erythrocyte protoporphyrin (EP) in blood samples. EP is a part of red blood cells that is known to increase when the amount of lead in the blood is high. However, the EP level is not as sensitive as blood lead levels in identifying levels ≤20 µg/dL and should only be used to identify elevated blood levels above 20 µg/dL (ATSDR 2007). The US CDC Advisory Committee recommends that the upper limit of normal for an EP test result is 30 µg/dL of whole blood (PJ Parsons & JJ Chisolm, Jr. 1997). Results of numerous studies have shown poor diagnostic sensitivity of EP for detecting blood lead levels at 10 µg/dL, and even at 25

µg/dL, coupled with an equally poor specificity (MD McElvaine et al. 1991; PJ Parsons, AA Reilly & A Hussain 1990). In 1991 the US CDC recommended EP no longer be used as a screening test to detect lead-exposed children (CDC 1991). EP is still seen as a valuable test in the medical management and follow-up care of children with confirmed elevated blood lead levels (ATSDR 2007). The risks for testing EP lead levels entail any risk associated with drawing blood (see previous information provided on this topic).

Other

Lead concentration can be gauged from a range of other body components in addition to blood, bone and erythrocyte protoporphyrin. Plasma lead measures the portion of blood lead that is available to cross cell membranes and enter specific tissues, but this is technically difficult to measure and requires specialized equipment. Lead has also been measured in hair, urine and other materials, but typically levels in these materials fluctuate considerably and are less useful measures compared to blood and bone. In studies investigating reproductive effects of exposure, lead level in other tissues and fluids (e.g. semen, placenta, ovarian follicles) has been measured, but these analyses are not as easily interpretable as those arising from blood or bone lead measurement (PJ Parsons & JJ Chisolm, Jr. 1997).

Sources for more information on measurement of lead level at the individual level include Binns et al (2007), Health Canada (2013a) and ATSDR (2007).

Interventions

What intervention strategies can be implemented (at an individual, community or policy level) to reduce or treat exposure to lead?

At the level of individuals, chelation therapy involves the provision of chelating (binding) agents to remove heavy metals from the body. It has been suggested that adults with blood lead levels ≥ 100 µg/dL almost always warrant chelation, those with blood lead levels 80–99 µg/dL (with or without symptoms) should be considered for chelation, as should symptomatic adults with blood lead levels 50–79 µg/dL (MJ Kosnett et al. 2007).

Lead education programs aimed at individuals, households and/or communities have been widely conducted across the globe, as have environmental clean-up programs

aimed at households within particular localities. Refer to the systematic review in Section 3 of this report for a review of the evidence supporting the efficacy of environmental, educational, pharmacological and combination interventions that are targeted at individuals.

At the community level, screening and surveillance of lead exposure is a mainstay of many international lead reduction programs. In Australia, it has been recommended that samples of children aged four and under who live in high lead exposure areas should be regularly screened for lead exposure and that universal lead screening for children is not necessary (Centre for Community Child Health 2002).

Policy-level lead interventions in Australia include those focused on the removal of lead from paint and petrol, as has been mentioned. In Australia lead paint was first prohibited in Queensland in 1922, to halt the use of "lead paint on veranda railings and outside surfaces within reach of children's fingers." (R Rabin 1989). It was not until the mid-1960s that lead in domestic paint was phased out across the country, resulting in a drop in the recommended amount of lead in Australian domestic paint from 50% before 1965, to 1% in 1965 and 0.1% in 1997 (Australian Government Department of Environment 2012). Lead paint remains a problem in old buildings; thus, guidelines and factsheets regarding safety during renovations and when repainting old buildings have been produced (CDC 2005a; Commonwealth of Australia 2009). Soil and dust contamination from home renovations and deteriorating lead paint remains a possible source of lead exposure.

The removal of lead compounds from petrol has been a central focus of international efforts to reduce lead exposure. As has been discussed, petrol was an important source of lead exposure in Australia until 2002, when it was phased out nationally (Australian Government Department of Environment 2001). (Western Australia and Queensland phased it out slightly earlier, in 2000 and 2001 respectively.) The success of strategies aiming to eradicate lead based petrol in terms of decreasing lead exposure has been documented in many countries (E De Miguel et al. 1997; F Monna et al. 1997; VM Thomas et al. 1999).

Australia, like many nations, has regulatory frameworks in place to protect consumers from lead in products such as children's toys and cosmetics. See, for example, the

'Regulation Impact Statement: Proposed mandatory standard for limits on lead and certain elements in children's toys' (Australian Competition & Consumer Commission Product Safety Policy Section 2008). Many public health authorities around Australia provide practical advice for minimising lead exposure, covering home renovations, living with contaminated soil and dust, hygiene and nutrition, hobbies, and exposure of children. Other policy level interventions include enforcement of occupational and environmental health standards, water treatment and removing lead solder from food cans (Australian Government 2003; WHO 2013).

Summary

There is a background level of exposure to lead that is unavoidable in Australia, with recent studies of pre-school children showing blood lead levels of 2.6 µg/dL in Sydney (B Gulson et al. 2006) and 1.83 µg/dL in Fremantle (R Guttinger et al. 2008). With major sources of lead such as petrol and paint having been removed, remaining sources include deteriorating paint and dust in older homes, contaminated soil and water, and lead in certain ceramics, cosmetics, children's toys, and traditional medicines.

Lead enters the human body through ingestion or inhalation and once absorbed is distributed to blood and soft tissues, and is later stored in bones and teeth or excreted through urination. The mechanisms for lead toxicity differ between key human physiological systems, and this review has summarised the mechanisms for the haematologic, endocrine, cardiovascular, neurologic and renal systems.

Many factors influence the rate of lead uptake, including age, gender, nutritional status, and size of lead-containing particles entering the body (ATSDR 2007; FJ Barbosa et al. 2005; FY Scinicariello 2011). Maternal lead crosses the placenta to the fetus (B Gulson et al. 2003); thus, factors that increase maternal blood lead levels will have the additional effect of increasing fetal lead levels.

Testing for exposure to lead at an individual level is indicated when the presence of a risk factor for exposure has been identified or is suspected, a household member with known exposure has been identified, or there are physical signs or symptoms (WHO 2010a). Testing at a population level may be warranted in instances of suspected

intoxication, as part of a health risk or health monitoring assessment, or as a screening tool for exposed individuals (WHO 2011a).

Blood lead testing is the most common method of gauging lead exposure, and determines recent exposure. The test is simple, inexpensive, relatively accurate and widely available. Bone lead is an indicator of chronic lead exposure but bone lead testing is less available due to the specialist equipment required. Lead has also been measured in hair, urine and other materials, but typically levels in these materials fluctuate considerably and are less useful measures compared to blood and bone.

There is worldwide interest in minimising lead exposure and many types of interventions have been implemented with this aim, including the banning of leaded petrol and paint, environmental standards, occupational health standards, water treatment, surveillance and screening of potentially exposed populations, and chelation therapy for individuals who have been exposed.

This literature review provides background information for Section 2, a systematic review of the evidence of the health effects of lead associated with low blood lead levels, and Section 3, a systematic review of intervention strategies for reducing blood lead levels at an individual level in children and adults.

Section 2: Overview of evidence of health effects associated with blood lead levels <5 µg/dL and 5 to 10 µg/dL in children and adults

Methods

Objective and scope of the overview of evidence

The objective of this overview of evidence is to summarise recent (2004 forward) and best evidence on the associated health effects of low blood lead levels and characterize lead biomarker-response relationships in children and adults.

Questions considered are:

1. What are the health effects associated with lead exposure as measured by blood lead levels <5 µg/dL and blood lead levels between 5 to 10 µg/dL?
2. How do health effects vary between age subgroups (0-<1 year, 1-<2 years, 2-<5 years, 5-<12 years, 12-<60 years and ≥60 years) and by gender?
3. What health effects result from lead exposure during pregnancy and lactation?

The methodology for this overview of evidence was based on that of Cochrane Overviews (The Cochrane Collaboration 2013b), which summarise existing systematic reviews rather than find and summarise or synthesise original studies. As described by Cochrane, Cochrane Overviews do not aim to repeat the searches, assessment of eligibility, and assessment of risk of bias or meta-analyses from the included systematic reviews. They do include assessment of limitations of included systematic reviews, and may include meta-analyses across reviews to provide indirect comparisons of the effects of different interventions on a given outcome. The overview presented in this section extends the Cochrane methodology by including a search, assessment of eligibility, quality assessment and consideration of results of studies other than systematic reviews.

The scope of the overview with respect to populations, exposures, and outcomes is as follows. Epidemiological studies of humans (prospective cohort, cross-sectional, case control, retrospective cohort studies) of all age groups that investigate the effects of low blood lead levels were included. Animal studies and in vitro studies were excluded. Environmental exposure was assessed by blood lead levels <5 µg/dL and 5 to 10 µg/dL.

The following population subgroups were of interest. The subgroups differ according to sources of lead exposure and by vulnerability to health effects of lead exposure (as discussed in Section 1 of this report).

- Children 0-<1 year (crawling)
- Children 1-<2 years (some on ground, some walking)
- Children 2-<5 years (walking at home)
- Children 5-<12 years (walking at school)
- Adults 12-<60 years
- Old age ≥ 60 years
- Pregnant and lactating women (all ages)

However it was not feasible in this overview to consider findings by these subgroups. This is because one of the included systematic reviews collated and presented evidence collectively for children aged <18 years (NTP 2012b)

Subjects with occupational exposure to lead and populations living in geographic areas of known high contamination (e.g. mining operations) were excluded, since the focus of this report is on populations in non-endemic areas for whom exposure is considered to be episodic.

The lowest level at which adverse health effects occur when blood lead levels are 10 µg/dL or less was examined. The absence of adverse health effects on particular organs or systems at blood lead levels of 10 µg/dL or less was also considered. The outcome measures in the overview were health effects involving the following systems: neurological, cardiovascular, reproductive, hematopoietic, immune, renal, and bone; as well as genotoxicity and carcinogenicity health outcomes.

Criteria for the inclusion and exclusion of studies

The overview includes studies conducted in OECD countries due to their lead-related policy frameworks being more closely aligned with those of Australia, compared with frameworks in non-OECD countries. Studies conducted with people living in non-OECD countries were excluded. Thus, studies conducted in the following countries were included: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, and United States.

Studies of subjects with occupational exposure to lead and populations living in geographic areas of known high contamination (e.g. mining operations) were excluded.

Publications in all languages were included.

To ensure a focus on new and emerging research, studies available from January 2004 through mid-May 2013 were included in the literature search process. The start date of January 2004 was specified by NHMRC, and ensures that this overview of evidence builds on the evidence base presented in the NHMRC public statement released in 2009 (NHMRC 2009c). In instances where draft reports were included in this overview and subsequently published between mid-May 2013 and the submission of this overview, the final version of the report is referenced.

Since the aim was to examine the relationship between blood lead levels and health effects, prospective longitudinal study designs were considered to be the most informative data as they allow assessment of the magnitude, duration, and timing of exposure as well as the life stage at which the outcome is assessed (NHMRC 2009b).

This overview of evidence uses a tiered approach to summarise the evidence on human health effects of low blood lead levels.

- Tier 1 is comprised of extant high-quality systematic reviews of the scientific evidence. This aligns with Level I evidence in the NHMRC hierarchy of evidence for recommendations for developers of guidelines(NHMRC 2009b).

- Tier 2 consists of recently published prospective cohort studies found in literature searches; studies that are not already included in existing high-quality reviews. This aligns with Level II evidence for aetiological research (NHMRC 2009b).
- Where systematic reviews and prospective cohort studies are absent or yield equivocal findings, recent retrospective cohort studies, case-control studies, and cross-sectional epidemiologic studies that were found in literature searches are summarised to provide supplemental evidence. These align with evidence levels III-2, III-3, and IV, respectively, for aetiological research questions (NHMRC 2009b).

Systematic reviews were included in this review in their entirety. The alternative, reevaluating each study included in these reviews, would require abstracting study content, coding outcomes, assessing risk of bias, and conducting statistical analyses. It was decided that this duplication of effort, when considered alongside its likely cost, was not warranted.

It was acknowledged at the outset of this overview of evidence that there may be differences in scope between this overview and included systematic reviews; for example, in terms of search strategies used and exclusion criteria applied. This was a possibility because NHMRC was not involved in the conduct of existing systematic reviews. Such instances are highlighted in the methods section of this report.

Search strategy

Academic research, government studies and grey literature were included with no language restrictions. The electronic databases searched included EMBASE. MEDLINE and MEDLINE In Process, CINAHL, LILACS, Science Citation Index, Scopus, TOXLINE, and OpenGreysearches. All search strategies are available in Appendix 2; they were purposely broad to ensure that as many studies as possible were assessed as to their relevance to the overview. The search was not restricted to specific health conditions or outcomes. Articles that were obviously unsuitable (e.g. animal studies, in vitro studies, non-OEDC countries, occupational exposure studies) were excluded on the basis of abstracts and titles presented in electronic catalogues, whilst the decision to exclude or include other potentially relevant articles was based on full text review. Citations found in included studies were reviewed. Websites were searched for relevant reports, including the Australian Office of Health Protection, the OECD iLibrary, the European

Environment Agency (EEA), the European Centre for Disease Prevention and Control, the Health Protection Agency, National Health Service (NHS) Evidence, Health Canada, the US Centers for Disease Control and Prevention (CDC), and the US Environmental Protection Agency.

Study retrieval, screening, and data extraction

All potential studies identified from the literature search were downloaded into Endnote reference management software and duplicates were removed. The titles and abstracts were screened by one investigator for inclusion according to the eligibility criteria (see Criteria for the inclusion and exclusion of studies). Where a title could not be rejected with certainty from the title and abstract, the full text paper was retrieved and reviewed for eligibility. Multiple reports originating from the same study population were linked together so that the unit of inclusion was the study.

Where relevant systematic reviews were found, the summarised data were extracted and the authors' interpretation of findings were compiled. As has been mentioned, data were not extracted from individual studies included in the systematic reviews. In extant systematic reviews, references to studies that met the inclusion criteria for this overview (as outlined previously) were compared to the set of studies screened as eligible in the systematic review in order to identify new and distinct individual studies. Data from newly identified studies were then extracted and coded by one investigator. The ACCESS-based study coding form captured information on the study objectives, study design, period of data collection, sample size, recruitment and retention of study subjects, demographic characteristics, blood lead level ascertainment methods, laboratory quality control procedures, health effects and methods of outcome ascertainment, validity and reliability of diagnostic tests or instruments, data analysis methods, and potential confounders and methods of adjustment.

Assessment of quality and risk of bias

The quality of a systematic review was assessed using the 11-item AMSTAR tool that is available in Appendix 3 (B Shea et al. 2007). Systematic reviews were considered of high quality if all assessment criteria were met. Otherwise they were assessed as moderate quality (8 criteria met) and low quality (<8 criteria met).

For individual studies, quality and risk of bias was assessed using the NHMRC guidance on conducting evidence reviews of studies of aetiology and risk factors (Appendix 4) (NHMRC 2009b). For individual studies, statements supporting judgments for each criterion were coded to ensure decisions were transparent. Then each study was given an overall summary of quality (high, moderate, low) by considering 1) the study design, where prospective cohort studies were considered strongest, retrospective cohort and case-control studies of moderate strength, and cross-sectional studies of the least strength; and 2) by considering the NHMRC criteria for assessing bias in aetiology studies (NHMRC 1999). Table 1 provides a description of the study rating method.

Table 1. Individual study summary quality rating

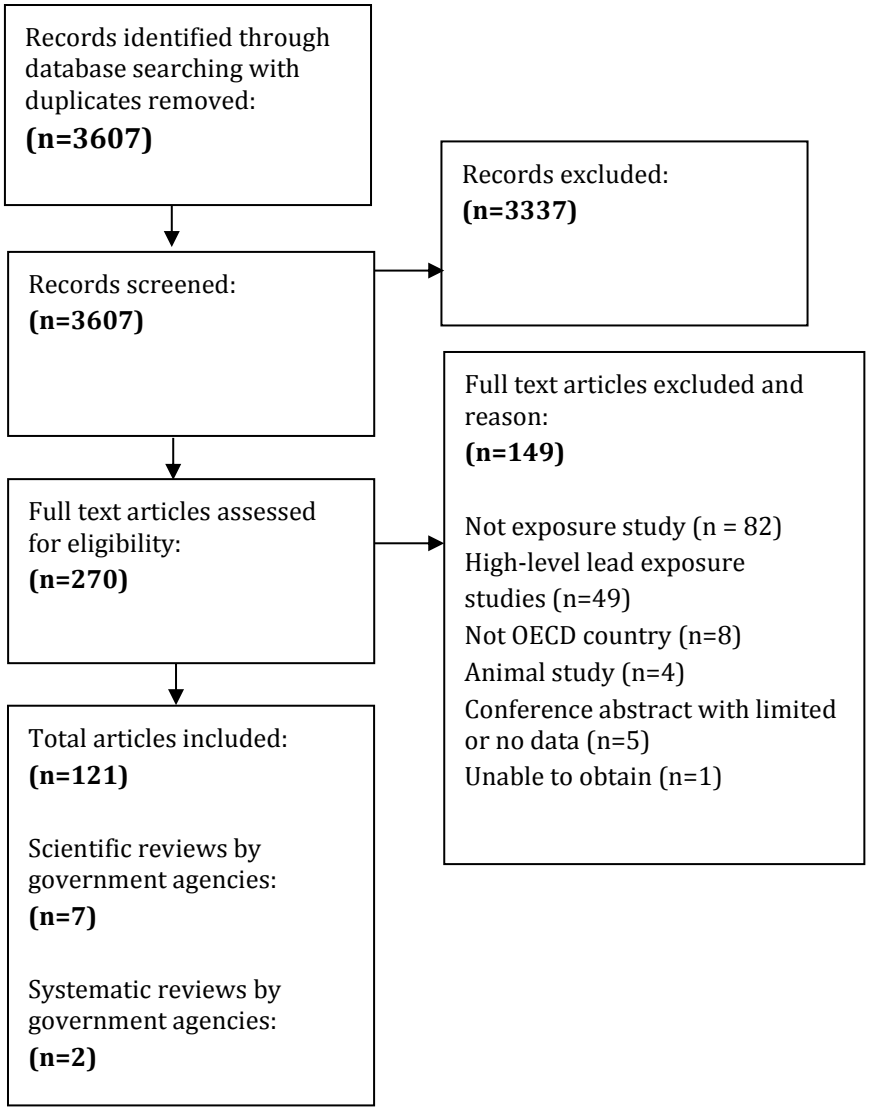
	Criteria for study design	*Criteria for Aetiology studies s* (NHMRC 2009b)
High quality	Prospective cohort	All criteria rated as low risk of bias
Moderate quality	Prospective cohort	At least four criteria rated as low risk of bias
	Retrospective cohort Case-control study	All criteria rated as low risk of bias
Low quality	Prospective cohort	Less than four criteria rated as low risk of bias
	Retrospective cohort Case-control study	Not all criteria rated as low risk of bias
	Cross-sectional study	Cross-sectional design considered lower quality

Results

Literature search results and screening results

All searches were completed by 28 May 2013. Electronic searches yielded 3607 unique titles and abstracts following removal of duplicates. Figure 1 describes the results of searching the literature for low-level lead health effects studies, screening titles and abstracts for potentially relevant studies, and retrieving and screening full-text papers of potentially relevant studies to identify eligible studies.

Figure 1. Flowchart for literature search on health effects associated with low blood lead levels



Titles and abstracts (n=3607) were screened for potential eligibility based on the inclusion criteria, i.e. lead exposure study, human subjects, OECD country, not high risk population due to occupational or lead contaminated setting, and publication date of 2004 or later. Full-text copies of 270 potentially eligible papers were retrieved and assessed against the inclusion criteria. A total of 121 papers met the inclusion criteria (see Appendix 5). Studies were excluded when they were not studies of lead-response relationships in humans (e.g. conceptual papers, toxicokinetic in-vitro or animal studies, biomarker methodology studies), studies of high-level lead exposure (e.g. occupational exposure studies), or non-OECD populations (Appendix 6). Five of the reports excluded

were paragraph abstracts from conference proceedings with incomplete or no data reported and no full publication located in Pub Med.

Two systematic reviews were identified and included in this overview. These reviews were considered as systematic reviews as they met standard methodological criteria (National Library of Medicine 2002). That is, they went beyond an examination of the literature to include the following design characteristics:

- specific research questions were posed at the start of the review;
- study data collected were limited to particular study designs;
- sources (e.g., databases) of literature and search strategies were reported;
- criteria used to include or exclude studies were defined;
- data extracted from the selected studies were presented for comparison;
- strength of evidence was assessed against pre-defined criteria and used to evaluate results;
- conclusions were based on the results and/or the presence or absence of supporting evidence.

These characteristics reduce the chance of bias by employing transparent decision rules for how evidence was collected and how final conclusions were drawn.

The two systematic reviews were,

1. the National Toxicology Program (NTP) Monograph on Health Effects of Low-Level Lead published by the US Department of Health and Human Services in June 2012 (NTP 2012b);
2. the US Environmental Protection Agency, Integrated Science Assessment for Lead (EPA/ISA) published in July 2013 (US EPA 2013).

This overview of evidence is the result of a rapid evidence review that was conducted in a 3 month period. It is not in the scope of this overview to discuss in-depth the individual studies cited in the two large systematic reviews that have been identified. The National Toxicology Program (NTP) Monograph, for example, cites 157 articles on neurologic effects, 79 articles on immunologic effects, 89 articles on cardiovascular effects, 51 articles on renal effects, and 188 articles on reproductive and developmental

effects, for a total of over 560 articles on human health effects. The EPA Integrated Science Assessment, a voluminous review, included health effects in human and animal studies as well as lead toxicokinetics. Chapter 4 on health effects alone cites 1,630 articles. Both reports are a resource for the closer examination of individual studies that have been published recently or are considered seminal research on the topic. A comprehensive set of individual study evidence tables on human health effects studies from the NTP report is provided at Appendix 7 as they focused only on studies of subjects with low blood lead levels. This overview of evidence synthesises and summarises the main conclusions of the NTP and EPA/ISA systematic reviews and relates them to the research questions being addressed in this overview. An international lead expert (M.J. Brown, U.S. CDC) was consulted to ensure that the literature cited in this overview was current and inclusive.

Synthesis of recent and best evidence of health effects of low blood lead levels

The two systematic reviews that were identified were published quite recently and are discussed in the sections that follow. For each of these reviews the methodology used to conduct the review, the criteria for assessing study quality and relevance, the health effects evaluated and the conclusions drawn based on the evidence provided are described. An overall rating of the quality of each review is provided based on AMSTAR criteria for evaluating systematic reviews (B Shea et al. 2007).

The second research question guiding this overview of evidence stipulates an interest in health effects for various age subgroups (0-<1 year, 1-<2 years, 2-<5 years, 5-<12 years, ≥ 12 years); however it was not feasible in this overview to consider findings for these subgroups. This is because one of the included systematic reviews collated and presented evidence collectively for children aged <18 years (NTP 2012b). Since systematic reviews were considered in their entirety (as has been discussed), the present review presents findings for children (<18 years) and adults (≥18 years).

Systematic reviews

U.S. National Toxicology Program, U.S. Department of Health and Human Services, NTP Monograph on Health Effects of Low-Level Lead, June 2012 (NTP 2012b)

Methods

The National Toxicology Program (NTP) at the U.S. National Institutes of Health recently conducted a review of the health effects of low blood lead levels based on evaluation of data from epidemiological studies that focused on blood lead levels <10 µg/dL. As the basis for the review, NTP considered recent government evaluations as authoritative sources, specifically, the EPA-ISA for Lead; the ATSDR Toxicological Profile for Lead; and the CDC 2005 report from the Advisory Committee on Childhood Lead Poisoning Prevention on health effects in children with blood lead levels <10 µg/dL.

The NTP review included studies on health effects in humans. However, when drawing conclusions on health effects they also considered the body of animal studies examining lead effects and in their report they refer readers to the EPA-ISA report and the ATSDR Toxicological Profile for review of the animal data.

The key questions in the NTP review were:

- What is the evidence that adverse health effects are associated with blood lead levels <10 µg/dL?
- What reproductive, developmental, neurological, immune, cardiovascular, and renal health effects are associated with blood levels <10 µg/dL?
- What is the blood lead level associated with a given health effect (i.e., <10 µg/dL or <5 µg/dL)?
- At which life stages (childhood or adulthood) is the effect identified?
- Are there data to evaluate the association between bone lead and the health effect, and how does the association to this biomarker of lead exposure compare to the association with blood lead level?

Literature search strategy

The EPA-ISA (2012 draft) and the ATSDR Toxicological Profile were screened for citations on health effects in humans with blood lead levels <10 µg/dL and up to 15 µg/dL. In addition, primary literature searches were conducted in MEDLINE, Web of

Science, Scopus, Embase, and TOXNET through mid-September 2011 to capture studies published subsequent to the above cited reports. The number of new studies identified in primary literature searches was not reported.

Study assessment criteria

The NTP review states that the quality of individual studies was considered in reaching health effects conclusions, including consideration of known confounders, appropriateness of the method of diagnosis, strength of the study design, and the sample size. General strengths and limitations of study designs were considered when developing conclusions, with prospective studies providing stronger evidence than cross-sectional or case-control studies. Consistency of effects across the body of evidence and other factors such as the number of studies, exposure levels, biological plausibility, and support from the animal literature were assessed when developing the NTP conclusions. Summary evidence tables provided in the report (Appendix 7) indicate the study designs, but do not provide an overall assessment of study quality and risk of bias in the individual studies or across the body of evidence.

Health effects evaluated

Each included study was evaluated for evidence that low-level lead is associated with neurological, immunological, cardiovascular, renal, and/or reproductive and developmental effects. These health effects areas were selected because there is a large database of human studies in each area. Characteristics of studies reported include study design and geographic location; population sample size, description, years of study, percent male, age (mean age and standard deviation); blood lead level µg/dL (mean and standard deviations); health effects assessed; statistical methods used and cofactors included in analyses; summary of results and conclusion (effect/no effect/equivocal) and description. Potential overlap of subjects in multiple publications from the same epidemiological study was also noted and these studies were not considered as independent findings.

The NTP considered four possible conclusions for health effects within each area as shown in Table 2.

Table 2. National Toxicology Program - weight of evidence for health effects of low-level lead exposure (NTP 2012b)

Sufficient Evidence of an Association: An association is observed between the exposure and health outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence.
Limited Evidence of an Association: An association is observed between the exposure and health outcome in studies in which chance, bias, and confounding could not be ruled out with reasonable confidence.
Inadequate Evidence of an Association: The available studies are insufficient in quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between exposure and health outcome, or no data in humans are available.
Evidence of No Association: Several adequate studies covering the full range of levels of exposure that humans are known to encounter (in this case limited to blood Lead levels <10 µg/dL) are mutually consistent in not showing an association between exposure to the agent and any studied endpoint.

NTP monograph on health effects of low-level lead: weight of evidence and conclusions

The overarching conclusion of the NTP review was that there was sufficient evidence of an association for adverse health effects in children and adults at blood lead levels <10 µg/dL and <5 µg/dL. Table 3 provides a summary of findings in relation to the NHMRC key research questions. Table 4 provides conclusions by physiologic system and principal health effect observed. Appendix 8 provides more extensive conclusions and shows papers included in the NTP report.

The NTP states the epidemiological studies provide data to support health effects at lower and lower blood lead levels, particularly in children. More recent prospective studies in children address the lower limits of blood lead levels associated with health effects because they focus on children whose blood lead levels remain <10 µg/dL or <5 µg/dL during their lifetime. Studies of health effects in adults cannot eliminate the potential effects of early-life lead exposure on health effects observed as adults because older adults were likely to have had blood lead levels >10 µg/dL as children.

In relation to the NHMRC key research questions, the NTP report provides the following contributing evidence.

Table 3. NHMRC research question and NTP contributing evidence on low-level lead health effects

NHMRC research questions	NTP contributing evidence			
What are the health effects of lead exposure as measured by blood lead levels <5 µg/dL and 5 to 10 µg/dL?	Children	<5 µg/dL	Sufficient evidence of an association	Decrements in academic achievement, IQ, cognitive measures; increased attention disorders and behaviour disorders
			Limited evidence of an association	Delayed puberty and decreased kidney function at ≥ 12 years
		<10 µg/dL	Sufficient evidence of an association	Delayed puberty, reduced postnatal growth, decreased IQ, decreased hearing
			Limited evidence of an association	Increased sensitivity to allergens and increased IgE
	Adults	<5 µg/dL	Sufficient evidence of an association	Decreased glomerular filtration rate; Maternal blood lead and reduced fetal growth
			Limited evidence of an association	Increased essential tremor
		<10 µg/dL	Sufficient evidence of an association	Increased blood pressure, risk of hypertension, and essential tremor
			Limited evidence of an association	Psychological effects, decreased cognitive function, decreased hearing, increased incidence of ALS, increased cardiovascular mortality; maternal blood lead and increased spontaneous abortion and preterm birth
How do health effects vary by subgroups (0-5 years, 6-13 years, 14 and older, and by gender?	Children ≥ 12 years	<5 µg/dL	Limited evidence of an association	Decreased glomerular filtration rate
	Adults	<5 µg/dL	Sufficient evidence of an association	Decreased glomerular filtration rate
What health effects result from exposure during	Pregnancy	<5 µg/dL	Sufficient evidence of an association	Reduced fetal growth

NHMRC research questions	NTP contributing evidence			
pregnancy and lactation?			Limited	Increased spontaneous abortion and preterm birth

Rating the quality and relevancy of the NTP Lead Monograph

The focus of the NTP Lead Monograph was low blood lead levels so it is of greater relevance to the questions addressed in this overview. The NTP monograph did not provide details on how individual studies were assessed for quality. They did consider prospective cohort studies as the strongest design. They describe the potential for bias and confounding in studies that were considered when reaching conclusions about the strength of the evidence on health effects, but a formal rating tool was not provided. Duplicate study selection and data extraction was not reported and the likelihood of publication bias was not assessed. When applying AMSTAR criteria to grade the quality of this scientific review, it is considered of moderate quality. Overall the NTP review was thorough, well-written, and directly applicable to the key questions guiding this overview of evidence.

Systematic reviews can provide the information needed to replicate the review findings. The NTP review is thorough and transparent and provides sufficient information to replicate the *body of evidence* underpinning the conclusions; however it is not possible to precisely reconstruct the *scientific reasoning* underlying each conclusion as this was based on a complex set of data and judgments by experts in weighting that data, and there is no exact algorithm (e.g. number of human studies, quality of those studies, estimated effect sizes, etc.) to directly replicate each conclusion.

Although considered to be of moderate quality, considerable caution should be applied when considering the evidence-based findings from the NTP review. This is because the review synthesises evidence from observational studies. Such study designs are limited by issues such as uncontrolled confounding, precluding understanding of the true contribution of lead to the health effects being investigated.

Table 4. NTP conclusions on health effects of low-level lead by major health effect areas (NTP 2012b)

Health Area	Population or Exposure Window		NTP Conclusion	Principal Health Effects	Blood Pb Evidence	Bone Pb Evidence
Neurological	Prenatal		*Limited*	Decrease in measures of cognitive function	Yes, <5 µg/dL	No data
			Limited	Decreased IQ, increased incidence of attention-related and problem behaviors, decreased hearing	Yes, <10 µg/dL	No data
	Children		*Sufficient*	Decreased academic achievement, IQ, and specific cognitive measures; increased incidence of attention-related and problem behaviors	Yes, <5 µg/dL	Tibia and dentin Pb are associated with attention, behavior, and cognition.
			Sufficient	Decreased hearing	Yes, <10 µg/dL	No data
	Adults		*Sufficient*	Increased incidence of essential tremor	Yes, <10 µg/dL	No data
			Limited	Psychiatric effects, decreased hearing, decreased cognitive function, increased incidence of ALS	Yes, <10 µg/dL	The association between bone Pb and cognitive decline is more consistent than blood.
			Limited	Increased incidence of essential tremor	Yes, <5 µg/dL	
Immune	Children		*Limited*	Increased hypersensitivity/allergy by skin prick test to common allergens and IgE* (not a health outcome)	Yes, <10 µg/dL	No data
			Inadequate	Asthma, eczema	Unclear	No data
	Adults		*Inadequate*	—	Unclear	No data
Cardiovascular	Children		*Inadequate*	—	Unclear	No data
	Adults		*Sufficient*	Increased blood pressure and increased risk of hypertension	Yes, <10 µg/dL	The association between bone Pb and cardiovascular effects is more consistent than blood.
			Limited	Increased cardiovascular-related mortality and ECG abnormalities	Yes, <10 µg/dL	
Renal	Children <12 years old		*Inadequate*	—	Unclear	No data
	Children ≥12 years old		*Limited*	Decreased glomerular filtration rate	Yes, <5 µg/dL	No data
	Adults		*Sufficient*	Decreased glomerular filtration rate	Yes, <5 µg/dL	Yes, one study
Reproductive and Developmental	Prenatal		*Limited*	Reduced postnatal growth	Yes, <10 µg/dL	No data
	Children		*Sufficient*	Delayed puberty, reduced postnatal growth	Yes, <10 µg/dL	One study does not support effects of bone Pb on growth.
			Limited	Delayed puberty	Yes, <5 µg/dL	
	Adults	Women	*Sufficient*	Reduced fetal growth	Yes, <5 µg/dL	Maternal tibia Pb is associated
			Limited	Increase in spontaneous abortion and preterm birth	Yes, <10 µg/dL	No data
		Men	*Sufficient*	Adverse changes in sperm parameters and increased time to pregnancy	Yes, ≥15-20 µg/dL	No data
			Limited	Decreased fertility	Yes, ≥10 µg/dL	No data
			Limited	Increased spontaneous abortion	Yes, >31 µg/dL	No data
		Adults	*Inadequate*	Stillbirth, endocrine effects, birth defects	Unclear	No data

Abbreviations: ALS, amyotrophic lateral sclerosis; ECG, electrocardiography; IgE, immunoglobulin E; IQ, intelligence quotient.

*Increased serum IgE is associated with hypersensitivity; however increased IgE does not equate to disease.

U.S. Environmental Protection Agency (EPA), Integrated Science Assessment for Lead (ISA) June 2013

(US EPA 2013)

Methods

The EPA-ISA provides a review, synthesis, and evaluation of the available science on the effects of lead exposure to provide a scientific foundation for the regulatory National Ambient Air Quality Standards. In addition to health effects, the comprehensive report considers ecological effects, atmospheric science (source, concentration, and fate and transport), exposure, and toxicokinetics of lead. The EPA-ISA has been updated regularly, since the initial 1977 Air Quality Criteria for Lead was released, and this assessment updates the 2006 review with new studies published since then. Each iteration builds upon the conclusion of previous assessments, as well as consideration of the current population levels of environmental lead exposure.

The process for developing the EPA-ISA includes literature searches, study selection, evaluation and integration of the evidence, development of scientific conclusions and causal judgments, scientific review, and public comment. Studies that have undergone scientific peer review and have been published or accepted for publication, and reports that have undergone scientific review, are considered for inclusion. The bibliographic repository for references used in the EPA-ISA for Lead, as well as other EPA risk assessments on the health and environmental effects of pollutants and chemicals, is the Health and Environmental Research Online (HERO) database available at http://hero.epa.gov/index.cfm.

The chapter on health effects in the EPA-ISA provides an in-depth discussion of the relationships between various modes of action by which lead exposure exerts its health effects and physiologic system effects in human and animal studies. A summary of findings in the EPA-ISA relevant to this overview is provided. It is beyond the scope of this overview to provide detail on the individual studies reporting health effects cited in the report; however the study citations and study designs that underpin the summary of causal

determinations for the relationship between blood lead levels and health effects are reported in Table 6.

Study assessment criteria

Study assessment and evaluation criteria for the EPA-ISA for lead included:

- Are the study populations or subjects adequately selected and are they sufficiently well-defined to allow for meaningful comparisons between study or exposure groups?
- Are the statistical analyses appropriate, properly performed, and properly interpreted?
- Are likely covariates adequately controlled or taken into account in the study design and statistical analysis?
- Are the exposure or dose metrics of adequate quality and sufficiently representative of information regarding ambient conditions?
- Are the health effect measurements meaningful, valid and reliable?
- Do the analytical methods provide adequate sensitivity and precision to support conclusions?

Health effects evaluated

The EPA-ISA report on the health effects of lead exposure is extensive and provides information on health effects from epidemiological studies of human populations as well as in-vitro and animal studies. The EPA-ISA report is not confined to low blood lead levels; however emphasis is placed on studies that examine effects associated with blood lead levels relevant to the current population and exposures. Older studies can remain the primary focus in some health effects areas where these studies remain the definitive works available in the literature.

The EPA-ISA integrates data across outcomes beyond the physiological systems that are the focus of this overview (i.e. neurological, cardiovascular, reproductive, haematopoietic, immunological, renal, and bone, and genotoxic and carcinogenic effects) and includes evidence on the modes of action by which lead exerts its health effects (i.e. altered ion status, protein binding, oxidative stress, inflammation, endocrine disruption, cell death and genotoxicity). Here, the epidemiologic evidence and conclusions relevant to the questions

guiding this overview and physiologic systems of interest are reported. The presentation of evidence is limited to human health effects studies; however the EPA-ISA conclusions draw upon the results of all studies determined to meet their criteria including animal, toxicokinetic, and ecological outcomes.

EPA-ISA for lead: weight of evidence and conclusions

Conclusions in the EPA-ISA report are based on EPA's evaluation of the quantitative evidence regarding lead concentration-response relationships, exposure duration, exposure conditions and patterns at which effects are observed, and populations and life stages differentially affected.

The weight of evidence in support of causation is characterised by the strength of causal classification. Criteria used in the EPA-ISA to judge causality are provided in Appendix 9. Table 5 provides the five-level hierarchy used to determine the strength of evidence for causal determinations.

Table 5. Weight of evidence for causal determination of health effects (US EPA 2013)

Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (i.e., doses or exposures generally within one to two orders of magnitude of current levels). That is, the pollutant has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: a) controlled human exposure studies that demonstrate consistent effects; or b) observational studies that cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes multiple high-quality studies
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures, but important uncertainties remain. That is, the pollutant has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence but potential issues remain. For example: a) observational studies show an association, but co-pollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or b) animal toxicological evidence from multiple studies from different laboratories that demonstrate effects, but limited or no human data are available. Evidence generally includes multiple high-quality studies.
Suggestive of a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures, but is limited. For example, (a) at least one high-quality epidemiologic study shows an association with a given health outcome but the results of other studies are inconsistent; or (b) a well-conducted toxicological study, such as those conducted in the National Toxicology Program (NTP), shows effects in animal species.

Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence is suggestive of no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations, are mutually consistent in not showing an effect at any level of exposure.

The EPA-ISA report uses the term "causation" in their assessments of blood lead levels and adverse health effects, while the NTP report discusses the strength of the "association". Epidemiologic or observational studies examine the association between an exposure and an outcome, but since other exposures may be occurring simultaneously that can never be completely accounted for, they can only provide evidence of some relationship between exposure and outcome. Thus association is arguably a more appropriate term for discussion of epidemiological study results. However, when directly reproducing findings from the EPA-ISA review in this report, the language utilized within the review is used.

The EPA-ISA review conclusions are shown in Table 6. These conclusions are based on epidemiological studies of human populations as well as toxicokinetic and animal studies. Health effects are grouped by systems, age groups and gender (where applicable), and include neurological, cardiovascular, renal, immunological, hematologic, reproductive and developmental. The table concludes with evidence of carcinogenic effects.

It is beyond the scope of this overview to include details from individual studies, however, citations to epidemiologic studies underlying the causal determinations are provided in Table 6. Access to the full evidence tables for each study is available in the EPA/ISA report at http://www.epa.gov/ncea/isa/lead.htm (see Chapter 4 Health Effects). In addition, many of the evidence tables in the NTP review overlap those cited in the EPA/ISA review and are included in this report (in Appendix 7).

Where EPA-ISA causal conclusions were drawn based on animal studies (with limited or no epidemiologic in humans) this is noted in the Table 6. The greater part of the epidemiologic evidence considered in this overview of evidence is from recent studies published since the 2006 EPA-ISA report that typically investigate low blood lead levels, however, some of the included studies are of blood lead levels >10 μg/dL .

Table 6. EPA-ISA Summary of causal determinations for the relationship between blood lead levels and health effects* (US EPA 2013)

I. Nervous System Effects
Child Cognitive Function Decrements (Causal Relationship) Clear evidence of cognitive function decrements (as measured by Full Scale IQ, academic performance, and executive function) in young children (4 to 11 years old) with mean or group blood lead levels measured at various life stages and time periods between 2 and 8 µg/dL. Epidemiologic evidence base: Prospective cohort studies: (D Bellinger et al. 1994; D Bellinger et al. 1987; D Bellinger et al. 1991; RL Canfield, MH Gendle & DA Cory-Slechta 2004; RL Canfield, CR Henderson, et al. 2003; K Chandramouli et al. 2009a; B Claus Henn et al. 2012; G Cooney, A Bell & C Stavrou 1991; KN Dietrich et al. 1993; KN Dietrich et al. 1991; CB Ernhart et al. 1987; CB Ernhart, M Morrow-Tlucak & AW Wolf 1988; DM Fergusson, LJ Horwood & MT Lynskey 1997; A Gomaa et al. 2002; T Greene, CB Ernhart & TA Boyd 1992; H Hu et al. 2006; W Jedrychowski et al. 2009b; TA Jusko et al. 2008; K Kordas et al. 2011; BP Lanphear et al. 2005b; A Leviton et al. 1993; M Mazumdar et al. 2011; MYO Min et al. 2009b; ML Miranda et al. 2009; HL Needleman & CA Gatsonis 1990; JR Pilsner et al. 2010; MD Ris et al. 2004; L Schnaas et al. 2006a; KM Stiles & DC Bellinger 1993; S Tong, P Baghurst, A McMichael, M Sawyer & J Mudge 1996; USEPA 2006; GV Vimpani et al. 1985; G Wasserman et al. 1992; GA Wasserman et al. 1997) Cross-sectional studies: (RK Canfield, DA; Cornwell, C; Henderson, CR, Jr. 2003; LM Chiodo et al. 2007; LM Chiodo, SW Jacobson & JL Jacobson 2004; SK Cho, BN; Hong, YC; Shin, MS; Yoo, HJ; Kim, JW; Bhang, SY; Cho, IH; Kim, HW. 2010; TE Froehlich et al. 2007; M Fulton et al. 1987; Y Kim et al. 2009; K Kordas et al. 2006; EF Krieg et al. 2010; BP Lanphear et al. 2000; A Roy et al. 2011; O Solon et al. 2008; PJ Surkan et al. 2008; PJ Surkan et al. 2007; MM Téllez-Rojo et al. 2006)
Child Externalizing Behaviours: Attention, Impulsivity and Hyperactivity (Causal Relationship) Clear evidence of attention decrements, impulsivity and hyperactivity (assessed using objective neuropsychological tests and parent and teacher ratings) in children 7-17 years and young adults ages 19-20 years. The strongest evidence for blood Lead-associated increases in these behaviours was found in prospective studies examining prenatal (maternal or cord), age 3-60 months, age 6 years, or lifetime average (to age 11-13 years) mean blood lead levels of 7 to 14 µg/dL and groups with early childhood (age 30 months) blood lead levels >10 µg/dL. Epidemiologic evidence base: *Prospective cohort studies:* (D Bellinger et al. 1994; JB Burns, PA; Sawyer, MG; McMichael, AJ; Tong, SL. 1999 ; K Chandramouli et al. 2009; PS Chen & AY Tan 2007; DM Fergusson, LJ Horwood & MT Lynskey 1993; A Leviton et al. 1993; MD Ris et al. 2004; GF-L Wasserman, P. 2001) *Case-control studies:* (J Nigg et al. 2008) *Cross-sectional studies:* (RK Canfield, DA; Cornwell, C; Henderson, CR, Jr. 2003; LM Chiodo et al. 2007; LM Chiodo, SW Jacobson & JL Jacobson 2004; SK Cho, BN; Hong, YC; Shin, MS; Yoo, HJ; Kim, JW; Bhang, SY; Cho, IH; Kim, HW. 2010; TE Froehlich et al. 2009; K Kordas et al. 2007 ; HL Needleman et al. 1979; R Nicolescu et al. 2010; P Plusquellec et al. 2010; MB Rabinowitz, JD Wang & WT Soong 1992; A Roy et al. 2009; PA Silva et al. 1988)
Child and Young Adult Externalizing Behaviours: Conduct Disorders (Likely Causal Relationship) Prospective epidemiologic studies find that early childhood (age 30 months, 6 years) or lifetime average (to age 11-13 years) blood lead levels or tooth lead

levels (from ages 6-8 years) are associated with criminal offenses in young adults ages 19-24 years and with higher parent and teacher ratings of behaviours related to conduct disorders in children ages 8-17 years. Lead-associated increases in conduct disorders were found in populations with mean blood lead levels 7 to14 µg/dL; associations with lower blood lead levels as observed in cross-sectional studies were likely to be influenced by higher earlier lead exposures. There is coherence in epidemiologic findings among related measures of conduct disorders.

Epidemiologic evidence base:

Prospective cohort studies: (D Bellinger et al. 1994 ; JB Burns, PA; Sawyer, MG; McMichael, AJ; Tong, SL. 1999 ; K Chandramouli et al. 2009; PS Chen & AY Tan 2007; KN Dietrich et al. 2001; DM Fergusson, JM Boden & LJ Horwood 2008; GF-L Wasserman, P. 2001 ; JP Wright et al. 2008)

Case-control studies: (HL Needleman et al. 2002; HL Needleman et al. 1996; J Nigg et al. 2008)

Cross-sectional studies: (JM Braun et al. 2008 ; LM Chiodo et al. 2007; WG Sciarillo, G Alexander & KP Farrell 1992)

Child Internalizing Behaviours (Likely Causal Relationship)

Prospective epidemiologic studies find associations of higher lifetime average blood (mean: ~14 µg/dL) or childhood tooth (from ages 6-8 years) Lead levels with higher parent and teacher ratings of internalizing behaviours such as symptoms of depression or anxiety, and withdrawn behaviour in children ages 8-13 years. Consideration of potential confounding by parental care-giving was not consistent and findings from cross-sectional studies in populations ages 5 and 7 years with mean blood lead levels of 5 µg/dL were mixed.

Child Auditory Function Decrements (Likely Causal Relationship)

A prospective epidemiologic study and large cross-sectional studies indicate associations between blood lead levels and increased hearing thresholds at ages 4-19 years. Across studies, associations were found with blood lead levels measured at various time periods, including prenatal maternal, neonatal (10 day, mean 4.8 µg/dL), lifetime average, and concurrent (ages 4-19 years) blood Pb levels (median 8 µg/dL).

Child Visual Function Decrements (Inadequate to Infer a Causal Relationship)

The available epidemiologic and toxicological evidence is of insufficient, quantity, quality and consistency.

Child Motor Function Decrements (Likely Causal Relationship)

Prospective epidemiologic studies provide evidence of associations of fine and gross motor function decrements in children ages 4-17 years with lifetime average blood lead levels and with blood lead levels measured at various time periods with means generally ranging from 4.8 to 12 µg/dL. Results were inconsistent in cross sectional studies with concurrent blood lead level means 2-5 µg/dL.

Adult Cognitive Function Decrements: (Likely Causal Relationship)

Prospective studies indicate associations of higher baseline bone lead levels with declines in cognitive function (executive function, visual-spatial skills, learning and memory) in adults (>age 50 years) over 2- to 4-year periods. Cross-sectional studies provide additional support. Uncertainties remain regarding the timing, frequency, duration and level of the lead exposures contributing to the effects observed and residual confounding by age.

Epidemiologic evidence base:

Prospective cohort studies: (K Bandeen-Roche et al. 2009; FT Wang et al. 2007 ; MG Weisskopf et al. 2007)

Cross-sectional studies: (S Gao et al. 2008; TA Glass et al. 2009; EF Krieg & MA Butler 2009 ; EF Krieg et al. 2009 ; EF Krieg et al. 2010; P Rajan et al. 2008; RA Shih et al. 2006; E van Wijngaarden, JR Campbell & DA Cory-Slechta 2009 ; J Weuve et al. 2006; J Weuve et al. 2009)

Adult Psychopathological Effects: (Likely Causal Relationship)

Cross-sectional studies in a few populations demonstrate associations of higher concurrent blood or tibia lead levels with self-reported symptoms of depression and anxiety in adults. Uncertainties remain regarding the timing, frequency, duration and level of lead exposures contributing to the observed associations and residual confounding by age.

Adult Auditory Function Decrements: (Suggestive of a Causal Relationship)

A high-quality prospective epidemiologic study finds associations of higher tibia lead level with a greater rate of elevations in hearing threshold over 20 years.

Adult Visual Function Decrements: (Inadequate to Infer a Causal Relationship)

The available epidemiologic and toxicological evidence is of insufficient, quantity, quality and consistency.

Adult Neurodegenerative Diseases: (Inadequate to Infer a Causal Relationship)

The available epidemiologic and toxicological evidence is of insufficient, quantity, quality and consistency.

II. Cardiovascular Effects

Hypertension: (Causal Relationship)

Prospective epidemiologic studies with adjustment for multiple potential confounders consistently find associations of blood and bone lead levels with hypertension incidence and increased blood pressure (BP) in adults. Cross-sectional studies provide supporting evidence. Meta-analyses underscore the consistency and reproducibility of the lead associated increase in blood pressure and hypertension (a doubling of concurrent blood lead level (between 1 and 40 µg/dL) is associated with a 1 mmHg increase in systolic BP); however, uncertainties remain regarding the timing, frequency, duration and level of lead exposures contributing to the effects observed in epidemiologic studies.

Epidemiologic evidence base:

Prospective cohort studies: (Y Cheng et al. 2001; BS Glenn et al. 2006; JL Peters et al. 2007)

*Cross-sectional studies: (*D Martin, TA Glass, K Bandeen-Roche, AC Todd, W Shi, et al. 2006; SK Park, B Mukherjee, et al. 2009a; F Scinicariello, H Abadin & HE Murray 2010)

Subclinical Atherosclerosis: (Suggestive of a Causal Relationship)

Cross-sectional analyses of NHANES data find associations of blood lead level with peripheral artery disease (PAD) in adults.

Epidemiologic evidence base:

Prospective cohort studies: (BS Glenn et al. 2006; A Navas-Acien et al. 2008; JL Peters et al. 2007)

Cross-sectional studies: (SF Elmarsafawy et al. 2006; D Martin et al. 2006; P Muntner et al. 2005; A Navas-Acien et al. 2008; SK Park, B Mukherjee, et al. 2009; T Perlstein et al. 2007; JL Peters et al. 2007; F Scinicariello et al. 2010; VM Weaver et al. 2008; C Yazbeck et al. 2009; A Zhang et al. 2010)

Coronary Heart Disease: (Causal Relationship)

Prospective epidemiologic studies consistently find associations of lead biomarkers with cardiovascular mortality and morbidity, specifically myocardial infarction (MI), ischemic heart disease (IHD), or HRV; however, uncertainties remain regarding the timing, frequency, duration and level of lead exposures contributing to the effects observed in epidemiologic studies.

Epidemiologic evidence base:

Prospective cohort studies: (K-D Eum et al. 2011; NP Jain, V; Schwartz, J; Vokonas, PS; Sparrow, D; Wright, RO; Nie, H; Hu, H. 2007)

Cross-sectional studies: (P Muntner et al. 2005; A Navas-Acien et al. 2005; SK Park, H Hu, et al. 2009; SK Park et al. 2006)

Cerebrovascular Disease: (Inadequate to Infer a Causal Relationship)

The available epidemiologic and toxicological evidence is of insufficient, quantity, quality, and/or consistency. Plausible MOAs, which are shared with hypertension and atherosclerosis, are demonstrated.

III. Renal Effects

Reduced Kidney Function: (Suggestive of a Causal Relationship)

Multiple high quality epidemiologic studies provide evidence that lead exposure is associated with reduced kidney function; however, uncertainty remains regarding the potential for reverse causality to explain findings in humans. Further, inconsistencies and limitations in occupational studies, epidemiologic studies of children and clinical trials of chelation of CKD patient preclude strong inferences to be drawn based on their results. Although longitudinal studies found lead-associated decrements in renal function in populations with mean blood lead levels of 7 and 9 µg/dL, the contributions of higher past lead exposures cannot be excluded.

Epidemiologic evidence base:

Prospective cohort studies: (R Kim et al. 1996; SW Tsaih et al. 2004; CC Yu, JL Lin & DT Lin-Tan 2004)

Cross-sectional studies: (A Akesson et al. 2005; R Kim et al. 1996; P Muntner et al. 2003; A Navas-Acien et al. 2009; M Payton et al. 1994; JA Staessen et al. 1992; SW Tsaih et al. 2004)

IV. Immune System Effects

Atopic and Inflammatory Responses: (Likely Causal Relationship)

Prospective studies of children ages 1-5 years indicate associations of prenatal cord and childhood blood lead levels with asthma and allergy. This evidence is supported by cross-sectional associations between higher concurrent blood lead levels (>10 µg/dL) in children and higher IgE.

Epidemiologic evidence base:

Prospective cohort studies: (W Jedrychowski et al. 2011; CLM Joseph et al. 2005; MB Rabinowitz et al. 1990)

Cross-sectional studies: (KL Hon et al. 2009; KLE Hon et al. 2010; P Pugh Smith & JO Nriagu 2011)

Autoimmunity: (Inadequate to Infer a Causal Relationship)

The available toxicological and epidemiologic studies do not sufficiently inform lead-induced generation of auto-antibodies with relevant lead exposures.

V. Hematologic Effects

Decreased Red Blood Cell (RBC) Survival and Function: (Causal Relationship)

A limited body of epidemiologic studies provides support to numerous animal toxicological studies in blood lead levels relevant to humans (2-7 µg/dL) that demonstrate altered haematological parameters (Haemoglobin [Hb], Haematocrit [Hct], and mean corpuscular volume [MCV]), increase measures of oxidative stress and increase cytotoxicity in red blood cell (RBC) precursor cells.

Altered Haem Synthesis: (Causal Relationship)

A limited body of epidemiologic studies provides support to consistent findings in experimental adult animal studies with relevant exposures (e.g. blood lead levels of 6.5 µg/dL) caused decreased ALAD and ferrochelatase activities. Support from a larger body of ecotoxicological studies demonstrate

decreased ALAD activity across a wide range of species.

VI. Reproductive and Developmental Effects

Development: (Causal Relationship)

Multiple cross-sectional epidemiologic studies report associations between concurrent blood lead levels and delayed pubertal onset for girls (6-18 years) and boys (8-15 years). These associations are consistently observed in populations with concurrent blood lead levels 1.2-9.5 µg/dL. Few studies consider confounding by nutrition. Uncertainties remain regarding the timing, frequency, duration and level of lead exposures contributing to the effects observed in epidemiologic studies of older children.

Epidemiologic evidence base:

Prospective cohort studies: (N Naicker et al. 2010; PL Williams et al. 2010)

Cross-sectional studies: (E Den Hond et al. 2011; M Denham et al. 2005; AL Gollenberg et al. 2010; R Hauser et al. 2008; N Naicker et al. 2010; SG Selevan et al. 2003; HY Tomoum et al. 2010; J Wolf & AJ Daley 2007; MS Wolff et al. 2008; T Wu, GM Buck & P Mendola 2003)

Birth Outcomes e.g., low birth weight, spontaneous abortion: (Suggestive of Causal Relationship)

Some well-conducted epidemiologic studies report associations of maternal lead biomarkers or cord blood lead with preterm birth and low birth weight/foetal growth; however, the epidemiologic evidence is inconsistent overall.

Epidemiologic evidence base:

Prospective cohort studies: (Z Berkowitz et al. 2006; D Cantonwine et al. 2010; PC Chen, IJ Pan & JD Wang 2006; C Gundacker et al. 2010; LL Jelliffe-Pawlowski et al. 2006; MR Lamb et al. 2008; E Örün et al. 2011; LM Schell et al. 2009; M Vigeh et al. 2010; M Vigeh et al. 2011; BL Williams et al. 2007)

Case-control studies: (Y Yin et al. 2008)

Retrospective cohort studies: (M Zhu et al. 2010)

Cross-sectional studies: (M Afeiche et al. 2011; I Al-Saleh, N Shinwari, et al. 2008; ME Atabek et al. 2007; D Cantonwine et al. 2010 ; R Hauser et al. 2008; Z Ignasiak et al. 2006; R Iranpour et al. 2007; NZ Janjua et al. 2009; EA Jones et al. 2010; K Kordas et al. 2009; H Lamadrid-Figueroa et al. 2007; B Little, B. et al. 2009; J Liu et al. 2011; MN Llanos & AM Ronco 2009; M Mahram et al. 2007; KB Min et al. 2008; J Olivero-Verbel et al. 2007; AB Patel & AS Prabhu 2009; E Sanna & E Vallascas 2011; HY Tomoum et al. 2010; E Wells et al. 2011; H Zailina et al. 2008; LE Zentner, PH Rondó & SS Mastroeni 2006)

Male Reproductive Function: (Causal Relationship)

Consistent associations in studies of occupational populations with concurrent blood lead levels of 25 µg/dL and greater, report detrimental effects of lead on sperm; however, uncertainties remain regarding the timing, frequency, duration and level of lead exposures contributing to the effects observed in epidemiologic studies. However key evidence is provided by studies in rodents, non-human primates, and rabbits showing detrimental effects on semen quality, sperm and fecundity/fertility toxicological studies with relevant lead exposure routes leading to blood lead levels ranging from 5-43 µg/dL reported effects on sperm quality and sperm production rate, sperm DNA damage, and histological or ultra-structural damage to the male reproductive organs.

Epidemiologic evidence base:

Prospective cohort studies: (SJ Hsieh et al. 2009; N Naha & AR Chowdhury 2006; N Naha & B Manna 2007)

Case-control studies: (J Mendiola et al. 2011)

Cross-sectional studies: (PC Hsu et al. 2009; A Kasperczyk et al. 2008; JD Meeker et al. 2008; JD Meeker et al. 2010; J Slivkova et al. 2009; S Telisman et al.

2007)
Female Reproductive Function: (Suggestive of Causal Relationship) Although findings are mixed overall, the body of evidence includes some high-quality epidemiologic and toxicological studies, suggesting that lead may affect some aspects of female reproductive function (hormone level, placental pathology). Epidemiologic evidence base: *Prospective cohort studies:* (I Al-Saleh, S Coskun, et al. 2008; MS Bloom, GM Louis, et al. 2011 ; MS Bloom, PJ Parsons, et al. 2011 ; MS Bloom et al. 2010 ; LW Jackson et al. 2011; AZ Pollack et al. 2011; T Silberstein et al. 2006) *Case-control studies:* (SH Chang et al. 2006) *Cross-sectional studies:* (EF Krieg, Jr. 2007)
VII. Cancer
Cancer: (Likely Causal Relationship) Findings from epidemiologic studies were inconsistent, however animal toxicological literature provides the strong evidence for long-term exposure (i.e., 18 months or 2 years) to high levels of lead (> 2,600 ppm) inducing tumour development. Epidemiologic evidence base: *Prospective cohort studies:* (SR Jones et al. 2007; N Khalil et al. 2009; A Menke et al. 2006; SE Schober et al. 2006; E van Wijngaarden & M Dosemeci 2006 ; MG Weisskopf et al. 2009) *Case-control studies:* (P Bhatti et al. 2009; NG Lundstrom et al. 2006; SY Pan et al. 2011; P Rajaraman et al. 2006; MC Rousseau et al. 2007; M Santibanez et al. 2008) *Cross-sectional studies:* (A Mendy, J Gasana & ER Vieira 2012; J Obhodas et al. 2007)

*Note that in addition to epidemiologic studies of human populations, conclusions in the integrated science assessment for lead also include additional animal toxicological studies, in vitro studies supporting possible mechanisms of action, and ecological studies.

Rating the quality and relevancy of the EPA-ISA

The EPA-ISA is quite comprehensive with respect to the populations, exposure levels, and health outcomes reported. Prospective cohort studies were considered the strongest design, and other study designs (case-control, cross-sectional studies) provided supplemental evidence to support decisions. When applying AMSTAR criteria to grade the quality of this scientific review, it is considered of moderate quality because duplicate study selection and data extraction were not reported and the likelihood of publication bias was not assessed. However, it is likely the most comprehensive evaluation of the health effects of lead exposure available and the HERO database of scientific studies (http://hero.epa.gov) on lead and other toxic exposures is a useful resource as it is continually updated.

As was mentioned with regard to the NTP review, considerable caution should be applied when considering the findings from the EPA-ISA review due to the likelihood of uncontrolled confounding factors influencing the results of studies included in the review.

Areas of agreement or disagreement in the systematic reviews conducted by NPT and EPA/ISA

Conclusions of the two systematic reviews discussed above are shown in Table 7. Instances where sufficient evidence (NTP review) or a causal relationship (EPA-ISA review) was found are demarcated in bold text and the blood lead level associated with the finding is noted in the table in accord with NHMRC's interests (that is, <5µg/dL or <10µg/dL). The NTP review presents its findings according to these blood lead level categories, but as seen in Table 6, the EPA-ISA report does not. For the latter report, the blood lead level category noted in Table 7 represents the lowest relevant category. For example, the EPA-ISA reported a causal relationship between child cognitive function decrements and blood lead levels 2-8 µg/dL (as seen in Table 6); in Table 7 this is noted as evidence of association at blood lead level <5µg/dL. Scenarios where the conclusion of sufficient evidence/causal relationship was based significantly on animal data are noted in Table 7.

Table 7. Comparison of the NTP and the EPA-ISA conclusions on lead health effects

System	Health effect	NTP	EPA-ISA	Similar?
Neurological	Child cognitive function decrements	**Sufficient evidence for achievement and IQ, <5 µg/dL**	**Causal relationship, <5 µg/dL**	yes
	Child externalizing behaviours: attention, impulsivity & hyperactivity	**Sufficient evidence for attention and behaviour problems, <5 µg/dL**	**Causal relationship, <10 µg/dL**	yes
	Child and young adult externalizing behaviours: conduct disorder	Not reported	Likely causal relationship	n/a
	Child internalizing behaviour	Inadequate evidence (unclear, some data >10 µg/dL)	Likely causal relationship	no
	Child auditory function decrements	**Sufficient evidence, <10 µg/dL**	Likely causal relationship	yes
	Child visual function decrements	Inadequate evidence	Inadequate to infer causal relationship	yes
	Child motor function decrements	Not reported	Likely causal relationship	n/a
	Adult cognitive function decrements	Limited evidence	Likely causal relationship	yes
	Adult psychopathological associations	Limited evidence	Likely causal relationship	yes
	Adult auditory function decrements	Limited evidence	Suggestive of causal relationship	yes
	Adult visual function decrements	Inadequate evidence	Inadequate to infer causal relationship	yes
	Adult neurodegenerative diseases	**Sufficient evidence for essential tremor, <10 µg/dL;** Limited evidence for ALS; Inadequate evidence for Alzheimer's and Parkinson	Inadequate to infer causal relationship	no/mixed

	Health effect	**NTP**	**EPA-ISA**	
Cardiovascular	Hypertension	**Sufficient evidence for risk of hypertension, adults and pregnant women, <10 µg/dL**	**Causal relationship for increased blood pressure**[1]	yes
	Subclinical atherosclerosis	Not reported	Suggestive of causal relationship	n/a
	Coronary heart disease	Limited evidence for general CVD and CVD mortality	**Causal relationship**[2]	no
	Cerebrovascular disease	Not reported	Inadequate to infer causal relationship	n/a
	Health effect	**NTP**	**EPA-ISA**	
Renal	Reduced kidney function	**Sufficient evidence for adults <5 µg/dL;** Limited evidence for children ≥ 12 years	Suggestive of causal relationship	no/mixed
	Health effect	**NTP**	**EPA-ISA**	
Immune	Atopic and inflammatory response	Limited evidence for increased IgE in children and increased hypersensitivity and allergy for prenatal and children	Likely causal relationship	yes
	Autoimmunity	Inadequate evidence	Inadequate to infer causal relationship	yes
	Health effect	**NTP**	**EPA-ISA**	
Haematological	Decreased red blood cell function and survival	Not reported	**Causal relationship, <5 µg/dL, animal**	n/a
	Altered haem synthesis	Not reported	**Causal relationship, <10 µg/dL, animal**	n/a
	Health effect	**NTP**	**EPA-ISA**	
Reproductive and	Development	**Sufficient evidence for blood lead**	**Causal relationship, <5 µg/dL**	

Developmental		**levels <10 µg/dL;** Limited evidence for blood lead levels <5 µg/dL		yes <10 µg/dL
	Birth outcomes: low birth weight, spontaneous abortions	**Sufficient evidence among women for reduced foetal growth and lower birth weight, <5 µg/dL;** Limited evidence for spontaneous abortion and preterm birth and gestation age	Suggestive of causal relationship	mixed
	Male reproductive function	**Sufficient evidence for sperm parameters and time to conception, ≥15-20 µg/dL** Limited evidence for fertility	**Causal relationship, ≥25 µg/dL for adults, < 10 µg/dL for animals**	mixed
	Female reproductive function	Inadequate evidence	Suggestive of causal relationship	no
	Health effect	**NTP**	**EPA-ISA**	
Cancer	Cancer	Not reported	Likely causal relationship	n/a

1: As in Table 6, a doubling of concurrent blood lead level (between 1 and 40 µg/dL) is associated with a 1 mmHg increase in systolic BP; however, uncertainties remain regarding the timing, frequency, duration and level of lead exposures contributing to the effects observed in epidemiologic studies (US EPA 2013).

2: As in Table 6, uncertainties remain regarding the timing, frequency, duration and level of lead exposures contributing to the effects observed in epidemiologic studies (US EPA 2013).

While mostly consistent, there are some differences in conclusions between the two systematic reviews. The differences may be due to the fact that the EPA-ISA review included studies of blood lead levels >10 µg/dL, while the NTP review did not.

In summarising results from the two systematic reviews for the purposes of this overview, evidence of association is deemed to occur when the NTP review concluded there was sufficient evidence *and* the EPA-ISA review concluded a causal relationship. As seen in Table 7, this occurred in five areas:

- Among children, adverse cognitive (academic achievement and IQ decrements) effects were evident at blood lead levels <5 µg/dL.
- Among children, adverse behavioural (attention, impulsivity and hyperactivity) effects were evident at blood lead levels <10 µg/dL.
- Among adults and pregnant women, increased blood pressure and increased risk of hypertension were evident at blood lead levels <10 µg/dL.
- Delay in sexual maturation or puberty onset in adolescent girls and boys was evident at blood lead levels <10 µg/dL.
- Adult male reproductive function (sperm parameters and time to conception) was adversely affected at blood lead levels ≥25 µg/dL in humans, and <10 µg/dL in animals (the latter finding is from the EPA-ISA report).

(Where one review concluded there is an association at a higher blood lead level than the other, this overview presents the evidence as occurring at the higher blood lead level.)

New studies not identified in existing reviews

The literature searches conducted for this overview of evidence of health effects associated with low blood lead levels yielded 112 eligible studies published between 2004 and 2013 (see Appendix 5 Included Studies). Of these, 98 were included in the extant scientific reviews discussed above. Two new systematic reviews and twelve recently published studies were not included in the existing scientific reviews and are characterized in Table

8. The studies are presented in order of strength of study design, authors and year, and health effect examined. The systematic reviews and prospective cohort studies are discussed below. Evidence tables are provided for all the studies in Appendix 10.

Table 8. Studies not included in the EPA-ISA and NTP systematic reviews

Study Design	Author & Year	Health Effect
Systematic Review & meta-analysis	Kennedy 2012(DA Kennedy et al. 2012)	Hypertension and preeclampsia in pregnant women
	Goodlad 2013(JK Goodlad, DK Marcus & JJ Fulton 2013)	Attention deficit disorder
Prospective cohort study	Eum 2012(K-D Eum et al. 2012)	Depression and anxiety in middle-to-older age women
	Zhang 2012(A Zhang et al. 2012)	Prenatal exposure and blood pressure in children
Cross-sectional studies	Cave 2010(M Cave et al. 2010)	PCBs, lead and mercury and liver disease (NHANES)
	Choi 2012(YH Choi et al. 2012)	Cadmium, lead and hearing loss (NHANES)
	Golub 2010(Golub et al., 2010)	Depression
	Hicken 2012(M Hicken et al. 2013)	Black-white difference in blood pressure (NHANES)
	Martin 2007(MD Martin et al. 2007)	Dental caries in children adjusted for IQ
	Mendola 2012(P Mendola et al. 2013)	Menopause (NHANES)
	Shargorodsky 2011(J Shargorodsky et al. 2011)	Adolescent hearing loss (NHANES)
	Van Bemmel 2011(DM Van Bemmel et al. 2011)	ALAD gene polymorphism and mortality (NHANES)
	Van Wijngaarden 2011(E van Wijngaarden, PC Winters & DA Cory-Slechta 2011)	Cognitive function in older adults (NHANES)
	Zhang 2013(N Zhang et al. 2013)	Child academic achievement

Study Design	Author & Year	Health Effect

New systematic reviews identified in literature searches

A recent systematic review by Kennedy et al. investigated whether maternal blood lead levels were associated with the development of gestational hypertension or pre-eclampsia (DA Kennedy et al. 2012). The review included dissimilar populations (high and low income countries) with a wide range of blood lead levels. They provide no assessment of individual study quality and potential risk of bias. Interpretation of results was based on counting the number of studies that found significant results (i.e. vote counting), without consideration for study quality. Thus it is considered of low quality based on AMSTAR assessment of systematic reviews, and provides limited additional scientific evidence.

The systematic review and meta-analysis by Goodlad et al. aimed to estimate the strength of the associations between lead burden with inattention symptoms and lead burden and hyperactivity/impulsivity symptoms (JK Goodlad, DK Marcus & JJ Fulton 2013). Lead measurements included blood, tooth, urine, hair, and bone measurements and combined these metrics with no consideration of validity/reliability of lead burden measures. Furthermore, outcomes were assessed (inattention or hyperactivity symptoms) without consideration of validity or reliability of psychometric instruments used. Blood lead levels spanned a large range (0.03 to 36 μg/dL). Significant heterogeneity among effects was reported. Based on AMSTAR criteria the review is considered low quality and offers limited new evidence.

New prospective cohort studies identified in literature searches

A long-standing Mexico City prospective birth cohort was examined by Zhang et al. (A Zhang et al. 2012) to investigate the relationship of prenatal lead exposure, assessed by both maternal bone and umbilical cord lead, with blood pressure (BP) in 7 to 15-year-old children. The study was considered of moderate quality, primarily due to high attrition and thus being at risk of selection bias. Otherwise it was a well-conducted study that found maternal tibia lead levels were significantly associated with increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in girls but not in boys. Among girls, an

interquartile range increase in tibia lead (13 μg/g) was associated with 2.11-mm Hg [95%(CI): 0.69, 3.52] and 1.60-mmHg (95% CI: 0.28, 2.91) increases in SBP and DBP, respectively. This provides some evidence of possible gender difference in lead toxicokinetics. Neither patella nor cord lead was associated with child BP.

Eum and colleagues (K-D Eum et al. 2012) explored the association between lead in bone and mental health among middle-age and elderly women, specifically symptoms of depression and anxiety, using data from the Nurses' Health Study. No consistent association between bone lead and depression and anxiety symptoms were found. They did find statistically significant results in a post-hoc analysis using a subset of 142 women (of the original sample of 617) who were premenopausal women and postmenopausal women consistently on HRT. When compared with the lowest tertile of tibia lead, those in the highest tertile scored worse on the Mental Health Index. This finding came from a subset (n=142) of the full study (n=617) and it should be noted that there is a higher risk of selection bias. The women in this subset came from an earlier case-control study of hypertension and lead exposure. Therefore, while the study quality rating for Eum et al. was considered high for the analysis of the full study sample, it was considered only of moderate quality for the subset analysis that yielded the significant findings on the Mental Health Index reported above.

Discussion and conclusions

There is a very extensive literature on the health effects of lead exposure and a growing body of evidence on the effects of low blood lead levels. This overview of evidence identified two moderate-quality systematic reviews which considered the same or very similar questions as those addressed in the present overview, the NTP and EPA-ISA reviews (NTP 2012a; US EPA 2013). Little new evidence was found to advance understanding of the health effects of low blood lead levels beyond that found in these reviews. Findings were generally consistent between the two systematic reviews.

What are the health effects of lead exposure as measured by blood lead levels <5 µg/dL and 5 to 10 µg/dL? & How do health effects vary by subgroups (0-5 years, 6-13 years, 14 and older, and by gender)?

In this overview of evidence it was not possible to consider the evidence according to the age subgroups stipulated in the research question, as has been discussed. Instead, evidence was considered separately for children (<18 years old) and adults.

This overview of evidence of health effects associated with low blood lead levels <5 µg/dL and 5 to 10 µg/dL in children and adults, summarises the evidence from two moderate-quality systematic reviews. Findings of the systematic reviews should be interpreted with caution, due predominantly to methodological limitations of studies included in the reviews, such as uncontrolled confounding (for example, many studies do not take into account the potential impact of socioeconomic status) and measurement error. The overview of evidence, based on a summary of findings of the two systematic reviews, suggests the following:

- blood lead levels <5 µg/dL are associated with adverse cognitive (academic achievement and IQ decrements) effects in children (although literature suggests uncontrolled confounding may play an important role in the findings regarding IQ) (AS Kaufman 2001).
- blood lead levels <10 µg/dL are associated with the following health effects:

- adverse behavioural (attention, impulsivity and hyperactivity) effects among *children*;
- delay in sexual maturation or puberty onset in *adolescent girls and boys*; and
- increased blood pressure and increased risk of hypertension among *adults* and *pregnant women* (although there is uncertainty regarding the clinical significance of the findings regarding an increase in blood pressure).

Of interest, this overview found that blood lead levels <10 µg/dL are associated with adverse effects to reproductive function in *male animals* (sperm parameters and time to conception). This was noted in the EPA-ISA review. However, in humans such effects are only evident at blood lead levels ≥25 µg/dL. Therefore this overview concludes that there is no evidence of effects to reproductive function in human males at low blood lead levels.

What health effects result from exposure during pregnancy and lactation?

As stated previously, this overview found evidence of increased blood pressure and risk of hypertension for pregnant women at blood lead levels <10 µg/dL. No evidence was found for other health outcomes for pregnant women or any health outcomes for offspring as a result of low blood lead levels during pregnancy or lactation.

Interpretation of overview findings

The clinical significance of the finding regarding increased blood pressure and increased risk of hypertension among adults and pregnant women may be minimal. As has been stated, one of the included systematic reviews concluded that there was evidence of a causal relationship between blood lead level and increased blood pressure in adults. However, when considered in further detail, the systematic review conclusion was that a doubling of concurrent blood lead level (between 1 and 40 µg/dL) is associated with only a 1 mmHg increase in systolic blood pressure (US EPA 2013).

Considerable caution should be applied when considering the evidence-based findings from this overview. The two moderate-quality systematic reviews included in the overview

are based on results of observational studies. As has been mentioned, such study designs are limited in that unaccounted-for factors that are related to the exposure and outcome under investigation may influence study results. In the context of this overview, studies of health effects of low (and high) blood lead levels commonly fail to control for important potential confounders such as socioeconomic status and parenting style; see, for example, a discussion of this issue in a literature review of the association between blood lead levels and IQ decrements (AS Kaufman 2001). The issue of uncontrolled confounding precludes understanding of the true contribution of lead to the health effects being investigated. Thus, findings of the included systematic reviews, and in turn the present overview, should be considered in this light and interpreted as suggestive rather than definitive.

In addition to the issue of uncontrolled confounding, other methodological limitations contribute to the need to apply caution when considering the evidence base for health impacts of lead exposure. For some health effects considered in the two systematic reviews, a sizeable proportion of included studies are cross-sectional in design. For example in the NTP review, seven of the 16 papers addressing the relationship between low level lead (<10 μg/dL) and standardized IQ measures in children, are cross-sectional in design. Since cross-sectional studies cannot necessarily establish the temporal relationship between the exposure and onset of outcome in a reliable manner, evidence provided by cross-sectional studies is considered to be of low quality. Measurement error is a further reason for the need for cautionary interpretation of the conclusions of the systematic reviews and the current overview; see, for example, a discussion of measurement error in the literature regarding effects of lead on children's IQ (AS Kaufman 2001). Although conclusions of both the NTP and EPA-ISA systematic reviews were informed by quality assessments of included studies (either formal or informal), it is not possible to understand the precise manner with which the assessments influenced final conclusions. This should be taken into consideration when interpreting the findings of this overview.

The findings of this overview are based on statistically significant research findings. The clinical significance of findings also requires examination in the process of considering the relevance of overview results. In particular, the finding of increased blood pressure and

increased risk of hypertension among adults at blood lead levels <10 μg/dL draws heavily from the conclusion of the EPA-ISA review that a doubling of concurrent blood lead level (between 1 and 40 μg/dL) is associated with a 1mmHg increase in systolic blood pressure. As highlighted in the EPA-ISA report, this may translate to a clinically significant increase in blood pressure in the population subgroup with the highest blood pressure. Authors of the report suggest that a relatively small effect size in a moderately-sized population thus has important health consequences for the risk of sequelae of increased blood pressure, such as stroke, myocardial infarction, and sudden death.

When interpreting the conclusions of systematic reviews, the quality of the reviews should be considered. Both included reviews are of moderate quality according to the AMSTAR criteria (B Shea et al. 2007). The methodological limitations of each review should be kept in mind when interpreting conclusions; for example, the NTP review did not formally rate the quality of included studies and the EPA-ISA review did not assess publication bias and does not appear to have utilised duplicate study selection and data extraction.

This overview has concentrated on conclusions shared by the two included systematic reviews. Each of the reviews additionally made conclusions based on sufficient evidence (NTP review) or a causal relationship (EPA-ISA review) that did not match findings of the other review. This discrepancy may be due to a difference in the body of literature reviewed, or another methodological difference between the two systematic reviews.

The two systematic reviews differed in scope from the current overview in four areas. First, the EPA-ISA report was not limited to studies of low blood lead levels. However, for this overview it has been possible to identify from the report instances in which EPA-ISA concluded that blood lead levels of <5 μg/dL and <10 μg/dL were associated with detrimental health outcomes.

Second, while the focus of this overview was human health, the conclusions reached in both the EPA-ISA and the NTP reviews are based on a complex set of human, animal and toxicological data (and ecological data in the EPA-ISA), which, within the resources allocated to this overview, could not be disaggregated in order to determine conclusions

based solely on human data. This is not a major issue in interpretation of the key findings of this overview because there is a relatively extensive literature based on human data supporting these findings.

Third, the protocol for this overview specified exclusion of studies from non-OECD countries, whereas both the NTP and EPA-ISA reviews included such studies. Since the two systematic reviews were included in this review in their entirety, evidence from non-OECD countries contributes to this overview's findings. It is not possible to determine the influence that this evidence may have had on the findings of the present overview.

Fourth, the protocol for this overview specified inclusion of documents published over the period 2004-May 2013. However, the NTP included older studies, since the initial search strategy involved screening studies included in the 2006 EPA AQCD for Lead (U.S. EPA 2006) and the 2007 ATSDR Toxicological Profile for Lead (ATSDR 2007). Further, the NTP review did not include studies published between September 2011 and May 2013. The EPA-ISA report was an update of a previous version and predominantly included studies published over the period 2006-2011, although older studies remained a primary focus in the health effects areas where these studies remained the definitive works available in the literature at the time of publication. Differences in the publication date ranges between the two systematic reviews may at least partially explain the areas of discrepant findings between the reviews. It is difficult to determine whether this difference, or the differences in date range between the two systematic reviews and the protocol for the current overview, might bias the results of this overview.

The four areas of difference in the scope of this overview and the included systematic reviews highlight the challenges of synthesizing evidence from existing systematic reviews. Such challenges are the focus of an area of active methodological development for health researchers around the world.

Standard best practices for reviews that are conducted in an expedient and efficient manner were utilised. Thus, study screening, data extraction, assessments of quality and risk of bias assessments were undertaken by one reviewer. To mitigate potential for error,

these processes were checked for accuracy and internal consistency in two ways: through regular team meetings to approve planned processes with another team member, and having a second reviewer double check a small proportion (~5%) of work at each stage (i.e. study selection, and data extraction).

Section 3: Systematic review of intervention strategies for reducing blood lead levels at an individual level in children and adults

Methods

Review question

In children (0-<1 year, 1-<2 years, 2-<5 years, 5-<12 years), adults (12-<60 years, ≥ 60 years) and pregnant and lactating women, are there any interventions that are more effective than standard interventions or no interventions in reducing lead exposure as measured by blood lead levels?

Criteria for considering studies in this review

Types of studies

The following study designs were included: randomised controlled trials, quasi-randomised controlled trials (where a method of assignment has been used that is not truly random, e.g. alternation, date of appointment, date of birth), controlled before and after studies, and cohort studies. Such study designs can allow for secular trends in blood lead level. For study designs that involved allocation to an intervention, this may have been carried out at an individual level or a cluster level. Study designs without a comparison group were not included due to the downward trend over time in blood lead level, particularly in children. Such studies may overestimate the effectiveness of interventions.

Types of participants

The following population subgroups were considered. The subgroups differ according to sources of lead exposure and by vulnerability to health effects of lead exposure (as discussed in Section 1 of this report).

- Children 0-<1 year (crawling)
- Children 1-<2 years (some on ground, some walking)
- Children 2-<5 years (walking at home)
- Children 5-<12 years (walking at school)
- Adults 12-<60 years
- Old age ≥ 60 years
- Pregnant and lactating women (all ages)

Studies conducted with people living in non-OECD countries were excluded, as specified by NHMRC. OECD countries were selected due to their lead-related policy frameworks being more closely aligned with those of Australia.

Types of interventions

Interventions that aimed to reduce blood lead levels at an individual level were included. Eligible interventions were categorised as environmental household, educational, and pharmacological. Environmental household interventions included activities such as cleaning, maintenance and/or monitoring to detect and reduce potential sources of lead exposure both within and outside a residential dwelling. The review also included environmental interventions that took place in public places. Educational interventions included increasing awareness of the sources of lead exposure and preventive measures. Examples of pharmacological interventions include calcium supplementation for women during lactation and for people with osteoporosis. Interventions provided as part of population programs that were delivered at an individual level (for example, state-based lead hazard control programs), were also included, and were categorized as educational, environmental, pharmacological or combination, as appropriate. The review included treatment interventions (in addition

to prevention activities) as the focus was on intervention strategies for a range of levels of exposure to lead.

Interventions that focussed on remediation of diffuse sources of lead, such as soils, and interventions conducted in environments where lead is 'endemic' (for example, in towns where lead is mined or smelted) were excluded. This is because such communities have targeted strategies to address sources of exposure. This systematic review focuses on non lead-endemic areas where exposure is considered to be episodic.

Population-based screening interventions (that did not include a subsequent intervention to manage lead exposure) and studies comparing legislative frameworks within and between jurisdictions were also excluded.

Types of comparisons

Any type of comparison or control intervention was acceptable for the purposes of this systematic review; for example, no intervention, a standard intervention in regular use, or a different type of intervention (other than that under direct investigation).

Types of outcome measures

The primary outcome measure in this review was blood lead level, measured in whole blood samples. Blood lead level serves as a time-integrated indication of the dose of lead from both current environmental exposure and previous exposures evident in internal body burden. Measures of current blood lead level were examined separately from historic blood lead level or average levels over time. If outcomes were measured at more than one time point post interventions, data from all time points were extracted.

Search methods for identification of studies

Electronic database searches

The following electronic databases were searched from January 2004 to May 2013 to identify relevant evidence/studies in all languages:

- MEDLINE and MEDLINE In Process
- Cochrane Library

- Cochrane Public Health Specialized register
- EMBASE
- Science Citation Index (including conference proceedings)
- Scopus
- CINAHL
- LILACS
- TOXLINE

Both published and unpublished literature that is publicly available was considered. The primary search strategy, developed for Medline (See Appendix 11) was adapted for use in the other databases. Searches were completed in May 2013. The start date of January 2004 was specified by NHMRC, and ensures that this systematic review builds on the evidence base presented in the NHMRC public statement released in 2009 (NHMRC 2009c).

Grey literature

OpenGrey was searched from 2004 to May 2013. Searches of the government agency websites listed below, as well as conference proceedings, helped ensure all relevant literature was identified.

Web sites

Government agency web sites:

- WHOLIS (http://www.who.int/library/databases/en/)
- OECD iLibrary (http://www.oecd-ilibrary.org/)
- Australian Office of Health Protection (OHP) (http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-about.htm)
- The European Environment Agency (EEA) (http://www.eea.europa.eu/)
- European Centre for Disease Prevention and Control (www.ecdc.europa.eu/ý)
- Health Protection Agency (UK) (http://www.hpa.org.uk/)
- NHS Evidence (UK) (www.evidence.nhs.uk/ý)
- Public Health Agency of Canada (http://www.phac-aspc.gc.ca/index-eng.php)

- Centers for Disease Control and Prevention (US) (http://www.cdc.gov/)
- US Environmental Protection Agency (http://www.epa.gov/)
- Health Evidence (Canada) (http://www.healthevidence.org)

Additional study identification strategies

Further strategies were employed to identify additional studies, including:

- Contacting the first author of all included studies to request information on unpublished work or research in progress
- Checking the reference lists of included studies and relevant systematic reviews
- Searching for unpublished or ongoing studies using the International Clinical Trials Registry Platform (ICTRP) (which includes Clinicaltrials.gov and the Australian New Zealand Clinical Trials Registry).

Finally, members of the Lead Working Committee were consulted to identify further unpublished or ongoing studies.

Data collection and analysis

Selection of studies

All potential studies identified in the searching process were downloaded into the Endnote reference management software (Thomson Reuters 2009). After duplicates were removed, all titles were screened for inclusion. Full text copies of all eligible papers were retrieved. Where a title was not able to be rejected with certainty from the title and the abstract, the full text paper was used to determine eligibility. Titles were not screened in duplicate; however pilot testing, using two reviewers, was undertaken of the eligibility criteria on 20 studies at the full text stage (including ones that were thought to be definitely eligible, definitely not eligible and doubtful). There was 100% consistency between reviewers in eligibility decisions made. This was used to clarify the interpretation of eligibility criteria and make any necessary alterations prior to screening the titles (at full text stage) for this review. When there was any doubt about

the eligibility of a title, a second reviewer was consulted. Multiple reports originating from the same study were linked together so that the unit of inclusion is the study.

Data extraction and management

Data were extracted for each study once, using a data extraction form developed for the purposes of this review. Where available, the study characteristics extracted included:

- Study Design/ level of evidence
- Location
- Setting
- Sample size at baseline and follow up
- Recruitment details
- Population description
- Intervention type
- Duration of intervention
- Duration of follow-up
- Outcomes
- Potential confounders/moderators of outcomes and methods of adjustment used
- Resource/cost requirements of the intervention

Where key information was missing; such as incomplete outcome data, length of follow-up and factors relating to confounding, study authors were contacted.

Assessment of risk of bias in included studies

Risk of bias was assessed according to the criteria specified below for each study design (Table 1). Since the studies eligible for inclusion in this review include randomised controlled trials, controlled before and after studies and cohort studies, these risk of bias questions are based on a combination of the Cochrane Collaboration's Risk of Bias Tool for randomised trials (JPT Higgins et al. 2011) and the RTI Item Bank on Risk of Bias and Precision for Observational Studies (M Viswanathan & ND Berkman 2011). For each study, the relevant criteria were rated as low, medium, or high risk of bias and

supporting statements for judgements were recorded. The ratings for each risk of bias criterion were used to make an overall determination about the risk of bias of each individual study. A consistent rating scheme (Table 2) was applied.

Study authors were contacted when key risk of bias information was missing, such as randomisation and allocation concealment (randomised controlled trials and quasi-randomised controlled trials) and factors related to confounding (cohort and controlled before and after studies). All authors were contacted, with the majority providing further information as able.

Table 1. Risk of bias criteria according to study design

Origin of question*	Risk of bias question	Applicable designs		
		RCT/ QRCT	CBA	cohort
RTI	Do the inclusion/exclusion criteria vary across the comparison groups of the study?		x	x
RTI	Does the strategy for recruiting/allocating participants differ across groups?		x	x
Cochrane	Was the allocation sequence adequately generated?	x		
Cochrane	Was the allocation adequately concealed?	x		
RTI	Does the study account for important variations in the execution of the study from the proposed protocol? [Consider intensity, duration, frequency, route, setting, and timing of intervention/exposures. Also consider possibility of contamination.]	x	x	x
Cochrane	Were participants blinded to their intervention or exposure status?	x	x	
Cochrane	Were investigators blinded to the intervention or exposure status of participants?	x	x	
RTI; Cochrane	Were outcome assessors blinded to the intervention or exposure status of participants?	x	x	x
RTI	Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding	x	x	x
RTI	Was the length of follow-up different across study groups? [If different lengths of follow-up were adjusted by statistical techniques, (e.g., survival analysis), risk of bias is low. Studies in which differences in follow-up were ignored should be answered high risk of bias.]			x
Cochrane; [additional questions from RTI]	Were incomplete outcome data adequately addressed? [Consider completeness of data for each outcome, including attritions/exclusions from analysis. Were reasons for attrition/exclusions reported? In cases of high loss to follow-up (or differential loss to follow-up), was the impact assessed (e.g., through sensitivity analysis or other adjustment method)?]	x	x	x

Origin of question*	Risk of bias question	Applicable designs		
		RCT/ QRCT	CBA	cohort
Cochrane; [additional questions from RTI]	Was the study free from selective outcome reporting? [Are any important primary outcomes missing from the results? Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results?]	x	x	x
RTI	Were the important confounding and effect modifying variables taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment)?	x	x	x
Cochrane	Was the study free from other risks of bias?	x	x	x
*Indicates risk of bias tool that the question was derived from RTI: RTI Item Bank in Risk of Bias and Precision of Observational Studies (M Viswanathan & ND Berkman 2011) or Cochrane: Cochrane Collaboration Risk of Bias Tool for randomised trials (JPT Higgins et al. 2011) Abbreviations: RCT (randomised controlled trial), QRCT (quasi-randomised controlled trial), CBA (controlled before and after study)				

Table 2. Determining overall risk of bias ratings for individual studies

Individual study risk of bias rating	Criteria for randomised controlled trials, and quasi-randomised controlled trials	Criteria for controlled before and after studies, and cohort studies
Very Low	Rated 'Low' risk of bias for randomisation and allocation concealment + no other major concerns about risk of bias	Not applicable ('Very Low' risk of bias rating not applied to non-randomised study designs)
Low	Rated 'Unclear'/'High' risk of bias for one or both of randomisation and allocation concealment and/or some other concerns about risk of bias	Rated 'Low' risk of bias for factors related to confounding + no other major concerns about risk of bias
Moderate	Rated 'High' risk of bias for both randomisation and allocation concealment + other major concerns about risk of bias	Rated 'Unclear'/'High' risk of bias for factors related to confounding and/or some other concerns about risk of bias
High	N/A	Rated 'High' risk of bias for factors related to confounding + other major concerns about risk of bias

Measures of intervention effect

The primary outcome as specified above was used to assess intervention effectiveness. Where available, continuous outcomes are presented as post-intervention means (M) and standard deviations (SD). The treatment effects are presented as mean difference (MD) between groups, with 95% confidence intervals (95% CI). For dichotomous outcomes, the number of events and total number of participants were reported presenting the treatment effect as risk ratios (RR) with 95% CI.

If data were not reported in this way, study authors were contacted for more information. Where these data remained missing, study data were imputed where able (for example, calculating a standard deviation or confidence interval from a p-value) using the formulas available in the Cochrane Handbook (JPT Higgins & S Green 2011). In the instances where this was not possible data reported by the authors were used.

Many authors presented multiple measures to report on a single outcome (for example using mean blood lead level and number of children with blood lead level ≥10 μg/dL), at multiple time-points and in some cases, presented many measures within this (i.e. adjusted and unadjusted scores, or multiple control groups). All relevant outcome measures were extracted at all time-points and the most appropriate available data are reported (i.e. adjusted scores, or the best matched control group, etc.).

Assessment of heterogeneity

To assess heterogeneity, the meaningful variation in participants, interventions and outcomes in included studies (clinical heterogeneity) and variation in study designs (methodological heterogeneity) were considered. As meta-analysis was not warranted, forest plots were not visually examined for heterogeneity, nor was the I^2 statistic considered. (The I^2 statistic quantifies the level of statistical heterogeneity, which may be a consequence of clinical or methodological heterogeneity or both.)

Assessment of publication bias

A qualitative assessment of publication bias was conducted by considering the direction and strength of the treatment effect of large compared with small studies. Since > 10

studies did not report the same outcome, publication bias was not explored using funnel plots to assess the relationship between effect size and study precision.

Data synthesis

To synthesise the results, studies were grouped according to intervention type (environmental, educational, medical, combination) and then population subgroup. The following subgroups were used, based on the rationale presented in Section 1 of this report:

- Children 0-<1 year (crawling)
- Children 1-<2 years (some on ground, some walking)
- Children 2-<5 years (walking at home)
- Children 5-<12 years (walking at school)
- Adults 12-<60 years
- Old age ≥ 60 years
- Pregnant and lactating women (all ages)

Within each category of intervention and population subgroup, where studies reported similar outcomes, insufficient studies (that were clinically and methodologically homogenous) were available to pool using meta-analysis. As such, results are presented narratively and where possible, graphically, using RevMan 5.1 (Review Manager 2012).

Where the age range of participants in the studies did not match exactly with the pre-determined sub-groups the mean age of participants was used to determine the best fit. In the instances that studies presented data in more than one age group, data are presented twice, under the relevant age categories.

A second synthesis of data was conducted after excluding the cohort studies; that is, including only randomised controlled trials, quasi-randomised controlled trials and controlled before and after studies.

Assessment of evidence quality

Once the studies were grouped according to intervention and population sub-group the quality of the evidence was assessed for each outcome, using GRADE (G Guyatt et al. 2011). The GRADE approach considers five criteria that affect evidence quality; risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each criterion is assessed (and graded up or down accordingly) to come up with an overall rating of evidence quality. Using this approach, the evidence for each outcome can be rated as High, Moderate, Low or Very Low. These ratings refer to what degree further research is likely to change the result and what level of confidence can be placed in the results (see Table 3).

Table 3. GRADE criteria for rating the quality of evidence (G Guyatt et al. 2011)

Criteria	Rating (circle as appropriate)		Quality of the evidence	Interpretation
Risk of Bias	No serious (-1) very serious (-2)		High (no downgrade)	Further research is very unlikely to change our confidence in the estimate of effect or accuracy.
Inconsistency	No serious (-1) very serious (-2)		Moderate (-1 downgrade)	Further research is likely to have an important impact on our confidence in the estimate of effect or accuracy and may change the estimate.
Indirectness	No serious (-1) very serious (-2)			
Imprecision	No serious (-1) very serious (-2)		Low (-2 downgrade)	Further research is very likely to have an important impact on our confidence in the estimate of effect or accuracy and is likely to change the estimate.
Publication Bias	Undetected Strongly suspected (-1)			
Other (upgrading factors)	Large effect (+1 or +2) Dose response (+1 or +2) No plausible confounding (+1 or +2)		Very Low (-3 downgrade or more)	Any estimate of effect or accuracy is very uncertain.

It is important to note that evidence quality is not the same as risk of bias. Risk of bias considers the limitations of individual studies, whereas GRADE considers the quality of evidence from all relevant studies included in an outcome. Risk of bias is just one of the factors that is considered in GRADE.

A number of additional synthesis methods were proposed, had there been sufficient studies to pool using meta-analysis. These are outlined below for transparency, and could be used in future updates.

If there were sufficient studies to pool results using meta-analysis, a pooled estimate would have been generated using RevMan 5.1 (Review Manager 2012) with a random-effects model as the default mode. Controlled before and after studies and cohort studies would be synthesised separately from randomised controlled trials and quasi-randomised controlled trials, with the results presented graphically. Had there been sufficient data, conducted subgroup analyses would have been conducted according to gender and socio-economic status to test for significant differences between the subgroups, not for significance of their main effects.

Sensitivity analyses

Sensitivity analyses were planned, to compare the findings from studies with adequate randomisation compared with those without adequate randomisation. This was not undertaken as there were insufficient randomised controlled trials and quasi-randomised controlled trials included.

Results

Results of the search

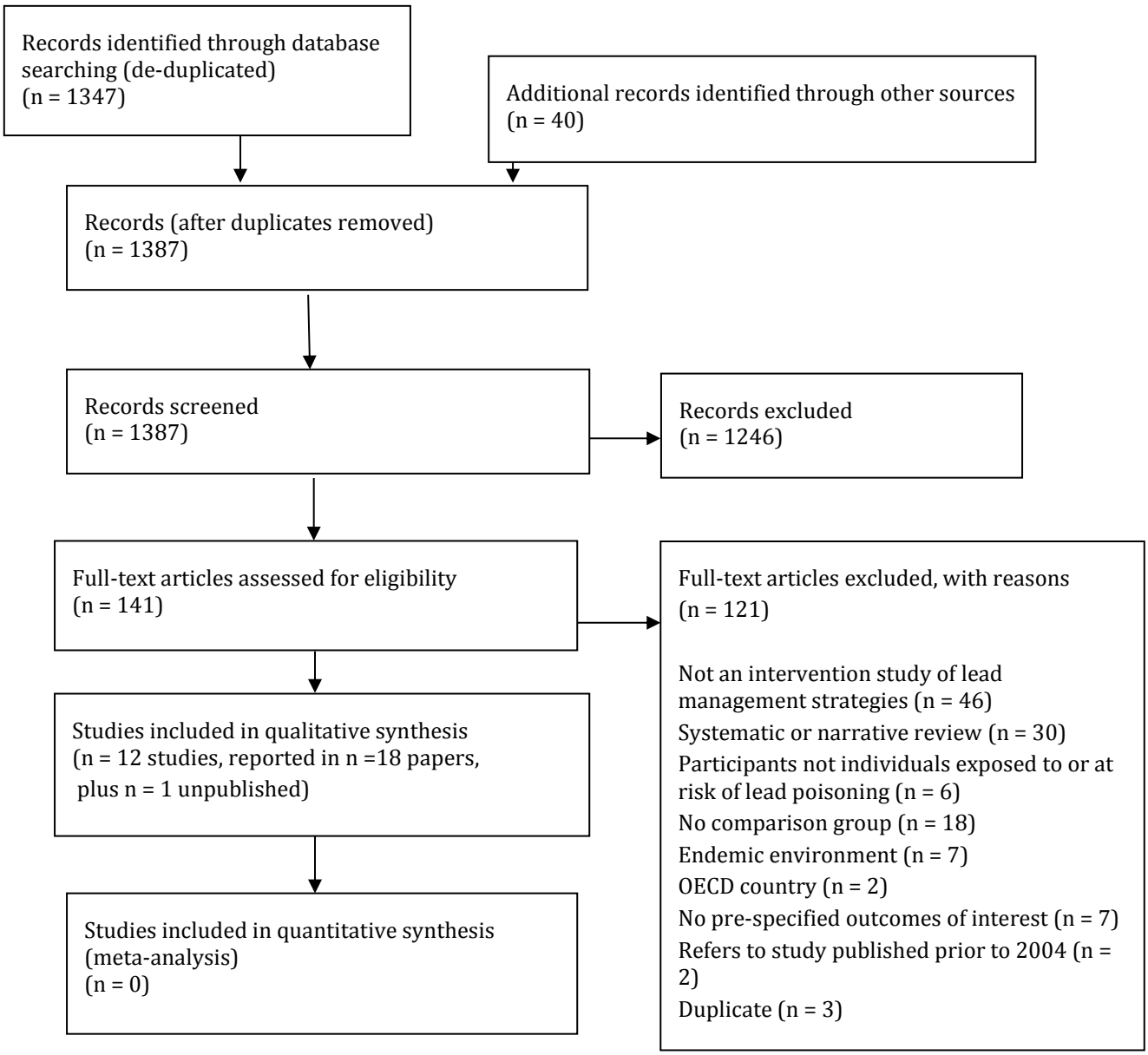
The search identified 1,347 de-duplicated records from electronic database searching and 40 records from other sources (See Figure 1. Study selection flow chart). Screening of 1,387 records on title and abstract was undertaken, excluding 1,246 of these. Full text records of 141 papers were obtained, of which 121 were subsequently excluded (see Figure 1 and Appendix 12). Twelve studies were included, reported in 18 papers. One

further study was unable to be assessed (BP Lanphear n.d.), as the work is unpublished and the author did not provide any further detail.

Included studies

Twelve studies, reported in 18 papers were included, measuring the effect of interventions to reduce blood lead levels in 7,329 participants. Table 4 provides an overview of included studies, Appendix 13 provides details of each study, and Appendix 14 lists the 12 studies together with the additional relevant papers.

Figure 1. Study selection flow chart



The majority of studies were conducted in the United States (n = 10), with one each conducted in Germany (R Fertmann et al. 2004) and Mexico (AS Ettinger et al. 2009). Of the 12 studies, five were randomised controlled trials (MJ Brown et al. 2006; KN Dietrich et al. 2004; K Dugbatey et al. 2005; AS Ettinger et al. 2009; R Fertmann et al. 2004), five were cohort studies (ME Markowitz, M Sinnett & JF Rosen 2004; P McLaine et al. 2006; K Rappazzo et al. 2007; W Strauss et al. 2005; NS Whitehead & R Leiker 2007) and two were controlled before and after studies (DR Berg et al. 2012; C Campbell et al. 2012). All studies took place in the community, with many conducted in the home. No study report declared a conflict of interest and all funders listed in published papers and reports were government departments or philanthropic organisations.

For some studies, sources of lead exposure were identified prior to the intervention, and included deteriorated paint or lead dust on floor, sills, soil and play areas (DR Berg et al. 2012), and water pipes (R Fertmann et al. 2004). The principal source of lead was not clear in six of the studies reviewed (K Dugbatey et al. 2005; AS Ettinger et al. 2009; ME Markowitz, M Sinnett & JF Rosen 2004; K Rappazzo et al. 2007; W Strauss et al. 2005; NS Whitehead & R Leiker 2007), creating difficulty in contextualising results of the studies and understanding implications for the Australian community. Details pertaining to each study can be found in Appendix 14.

There was considerable heterogeneity in terms of the interventions assessed and populations included. Most studies assessed the effect of environmental interventions (i.e. home remediation or cleaning) (DR Berg et al. 2012; R Fertmann et al. 2004; P McLaine et al. 2006; K Rappazzo et al. 2007; W Strauss et al. 2005), but all intervention categories (environmental, educational, pharmacological and combination) were included across the 12 studies.

The majority of studies included children less than six years, with elevated blood lead levels (MJ Brown et al. 2006; KN Dietrich et al. 2004; ME Markowitz, M Sinnett & JF Rosen 2004; P McLaine et al. 2006; K Rappazzo et al. 2007; W Strauss et al. 2005), or

likely lead exposure (DR Berg et al. 2012; C Campbell et al. 2012; NS Whitehead & R Leiker 2007). One study (R Fertmann et al. 2004) recruited non-pregnant women with likely lead exposure and two studies recruited pregnant women living in disadvantaged areas with no confirmed lead exposure (K Dugbatey et al. 2005). No study investigated the effect of a lead intervention in lactating women.

Studies measured blood lead level, as either a continuous (mean blood lead level, µg/dL), and/or dichotomous (i.e., number of children with blood lead level ≥ 10 µg/dL) variable. Half the studies in this review completed their last outcome assessment before or at 12 months post-intervention (MJ Brown et al. 2006; AS Ettinger et al. 2009; R Fertmann et al. 2004; ME Markowitz, M Sinnett & JF Rosen 2004; P McLaine et al. 2006; NS Whitehead & R Leiker 2007).

A number of studies collected process outcomes, such as dust lead levels in the home (MJ Brown et al. 2006; C Campbell et al. 2012; ME Markowitz, M Sinnett & JF Rosen 2004; P McLaine et al. 2006), and adherence/compliance with the intervention (KN Dietrich et al. 2004; AS Ettinger et al. 2009; R Fertmann et al. 2004; ME Markowitz, M Sinnett & JF Rosen 2004).

Assessment of risk of bias

There was considerable variability between studies in the potential risks of bias identified. Overall ratings ranged between very low (optimal) to high risk of bias (see Table 4 overleaf, and Appendix 13). Due to the inherent potential for confounders in non-randomised study designs, these studies tended to be rated as being at higher risk of bias. Despite this, most non-randomised study designs made attempts to control for confounding through matching and adjusted analyses. Loss to follow up was experienced in several studies. In three studies loss to follow up was greater than 50% (K Dugbatey et al. 2005; P McLaine et al. 2006; W Strauss et al. 2005), and was a likely source of measurement bias.

Assessment of publication bias

Publication bias seems unlikely in this review because most studies did not find compelling evidence of a treatment effect.

Table 4. Summary of included studies

Study ID	Type of Study (level)[β]	Intervention Comparison	Population; age	N =	Risk of bias[π]	Follow up	Results
Environmental Interventions							
Berg 2012	CBA (Level III-2)	Home remediation (paint stabilisation, window replacement and cleaning as needed) Matched controls with no home remediation	Newborn children[‡], living in homes with lead hazards	180	High	Mean age 18 months (range 0.8 to 2.7 years)	MD -0.93 (95% CI -1.70 to -0.16, *p* = 0.019). Mean (µg/dL) blood lead level at follow-up RR 0.59 (95% CI 0.29 to 1.22, P=0.143). No. of children with blood lead level ≥ 5 µg/dL RR 0.18 (95% CI 0.01 to 3.21, *P*=0.128).) No. of children with blood lead level ≥ 10 µg/dL
Fertmann 2004	RCT (Level II)	Replacement of tap water with bottled water for drinking and cooking (excluding) Flyer about minimising lead contamination from tap water (minimising)	Young women; 20 to 30 years	52	Moderate	Post-intervention (likely 10 weeks post-baseline)	Authors report that the mean change between groups was not statistically significant (p=0.17)
McLaine 2006	Cohort (Level III-2)	Housing relocation with direct practical and financial assistance Housing relocation with indirect assistance and education No housing relocation No home lead hazard control work	Children* with blood lead level > 19 µg/dL; < 6 years	87[ϕ]	High	12 months post-baseline	MD 0.40 (95% CI -3.56 to 4.36) Mean blood lead level (µg/dL) post-intervention (Intervention A vs B) MD -2.86 (95% CI -6.38 to 0.66 Mean blood lead level (µg/dL) post-intervention (Intervention A + B vs control)

Study ID	Type of Study (level)[β]	Intervention Comparison	Population; age	N =	Risk of bias[π]	Follow up	Results
Rappazzo 2007	Cohort (Level III-2)	Compliance with housing standards (post-remediation) No compliance with housing standards (post-remediation)	Children* with blood lead level ≥ 10 µg/dL ; < 6 years (and sub-set < 2 years)	959 (<6 yrs), 747 (<2 yrs)	Moderate	Between 1 and >3 years	MD -0.22 (95% CI -1.36 to 0.92, p > .2). Mean change in blood lead level (µg/dL), 0 to 6 year olds, all time points MD 0.35 (95% CI -1.09 to 1.79, p > .2). Mean change in blood lead level (µg/dL), 0 to 2 year olds, all time points
Strauss 2005	Cohort (Level III-2)	Interior and exterior home lead hazard control interventions	Children** with blood lead level > 5 µg/dL ; < 3 years	1,138	High	Between 12 to 36 months post-baseline	Authors report there was no difference between groups at all time-points
Educational Interventions							
Campbell 2012	CBA (Level III-2)	3 x home visits with standard education, additional education, cleaning supplies (Maintenance education group) 2 x home visits with standard education (Standard education group Matched controls from community who received usual care	Newborn children* living in high risk neighbourhoods (for lead)	942	High	12 and 24 months of age (approx.)	MD 0.10 (95% CI -0.38 to 0.58, p ≥0.1) Mean blood lead level (µg/dL) at 12 months (intervention A vs B) MD -0.10 (95% CI - 0.38 to 0.18, p ≥0.1) Mean blood lead level (µg/dL) at 12 months (intervention A + B versus B) MD 0.20 (95% CI -0.16 to 0.56, p ≥0.1) Mean blood lead level (µg/dL) at 24 months (intervention A + B vs control)

Pharmacological Interventions							
Dietrich 2004	RCT (Level II)	Chelation therapy (up to 3 x 26 day courses of succimer) + house cleaned prior to chelation Placebo chelation therapy + house cleaned prior to chelation	Children with blood lead level 20 to 44 µg/dL ; 12 to 33 months	780	Very Low	7 years of age[◊]	MD -4.5 (95% CI -3.7 to -5.3) Mean blood lead level over first 6 months MD -2.7 (95% CI -1.9 to -3.5) Mean blood lead level (µg/dL) at 12 months MD 0.0 (95% CI -0.62 to 0.62) Mean blood lead level (µg/dL) at 7 years of age RR 0.92 (95% CI 0.71 to 1.20) No. of children blood lead level ≥10 µg/dL at 7 yrs MD 0.40 (95% CI -1.65 to 2.45) Cognition (full scale IQ) at 7 years of age MD -1.17 (95% CI -0.41 to -1.93) Height (cm) at 7 years of age MD -0.12 (95% CI 0.10 to -0.35) Weight (kg) at 7 years of age
Ettinger 2009	RCT (Level II)	Calcium supplementation for 8 months (1200mg daily) and lead pottery advice Placebo and lead pottery advice	Pregnant women; < 14 weeks gestation at recruitment	670	Moderate	Third trimester (8 months pregnant)	MD -11% (95% CI -17.8% to -3.7%, (p = 0.004). Percentage mean difference in blood lead level (µg/dL), using log transformed data

Study ID	Type of Study (level)[β]	Intervention Comparison	Population; age	N =	Risk of bias[π]	Follow up	Results
Markowitz 2004	RCT (Level II)	Calcium supplementation for 3 months (to reach 1800mg daily) and education Placebo calcium supplementation and education	Children with blood lead level 10 to 45 µg/dL ; 1 to 6 years	88	Moderate	3 and 6 months after baseline	MD -1.50 (95% CI -4.75 to 1.75, p> 0.1) Mean blood lead level (µg/dL) 3 months after baseline MD -0.40 (95% CI -4.04 to 3.24, p> 0.1) Mean blood lead level (µg/dL) 6 months after baseline
Combined Interventions							
Brown 2006	RCT (Level II)	5 x home visits with lead hazard testing and tailored education (Comprehensive home visits) 2 x home visits with standard education (Standard home visits)	Children* with blood lead level 15 to 19 µg/dL; < 28 months	173	Very Low	3, 6 and 12 months post-baseline	RR 1.00 (95% CI 0.74 to 1.34) No. of children whose last available blood lead level ≥ 10 µg/dL RR 0.71 (95% CI 0.28 to 1.82) No. of children with any blood lead level ≥ 20 µg/dL
Dugbatey 2005	RCT (Level II)	Full case management (tailored education sessions, print materials, home inspection, counselling) Partial case management (lead assessment with written report, monthly newsletter, quarterly visits but no counselling Standard lead education	Newborn children‡ living in disadvantaged neighbourhoods	151	Low	Likely to be 6, 12, 18 and 24 months of age (not explicitly stated)	MD -2.17 (95% CI -8.48 to 4.14, p>0.1) Mean blood lead level (µg/dL) at fourth time point (intervention A vs B) MD 0.68 (95% CI -8.34 to 9.70, p>0.1) Mean blood lead level (µg/dL) at fourth time point (intervention A+ B vs control)

Study ID	Type of Study (level)[β]	Intervention Comparison	Population; age	N =	Risk of bias[π]	Follow up	Results
Whitehead 2007	Cohort (Level III-2)	Various lead hazard control interventions were compared with each other, by method of contact (mail, telephone or home visit) and by the type of service delivered (education or lead investigation).	Children* with blood lead level 10 to 19 ug/dL; < 2 years	2,109	High	Between 3 to 12 months post-baseline	The authors concluded that "home visit protocols were associated with a larger decline in blood lead levels than mail or telephone contact protocols, regardless of a child's initial blood lead level" (p<0.001)

[β]Type of study (level), taken from NHMRC Levels of Evidence, i.e. Level I = Systematic review of RCTs, Level II = RCT, Level III-1 = QRCT, Level III-2 = Cohort Study/CBA, (NHMRC 1999)
[π]Risk of bias: for interpretation of overall risk of bias rating see Table2
*Outcomes collected in children but intervention provided to the families of these children
‡Outcomes collected in infants but the intervention was provided to women who were recruited in pregnancy
[Ω]Neurobehavioural outcomes (multiple outcomes measured, see Appendix 13 for full list)
◊ Only longest follow up data presented (see results section and tables in Appendix 13 for full description/presentation of data)
[Φ]N = 87 families (n = 112 children) but only one child per family was included in the blood lead level data
Abbreviations: RCT (randomised controlled trial), QRCT (quasi-randomised controlled trial), CBA (controlled before and after study), 95% CI (95% confidence interval), RR = relative risk, MD = mean difference

Assessment of evidence quality

Findings of the GRADE assessments are presented in detail in Appendix 15. In summary, of the ten intervention/population subgroups, all but three were assessed as providing very low quality of evidence (DR Berg et al. 2012; MJ Brown et al. 2006; K Dugbatey et al. 2005; R Fertmann et al. 2004; ME Markowitz, M Sinnett & JF Rosen 2004; P McLaine et al. 2006; K Rappazzo et al. 2007; W Strauss et al. 2005; NS Whitehead & R Leiker 2007). The single study investigating educational interventions for children aged 0-<1 year provides a low quality of evidence (C Campbell et al. 2012), and moderate-quality evidence is available for pharmacological interventions for children aged 1-<2 years (KN Dietrich et al. 2004) and for pregnant and lactating women (AS Ettinger et al. 2009), from a single study in both cases.

Effects of interventions

This section presents the effects of interventions according to each intervention/population subgroup of interest for which studies were identified for inclusion in this review. A summary of the GRADE assessment finding and its implications are included for each subgroup in order to assist interpretation of the research findings presented.

As mentioned in the methods section, where the age range of participants in the studies did not match exactly with the pre-determined subgroup categories the mean age of participants was used to determine the best age category within which to present the findings. In instances that studies presented data in more than one age group, the study data are presented twice, under the relevant age categories.

Environmental interventions

Children 0-<1 year (crawling)

According to GRADE assessment, the quality of the evidence about environmental interventions for children aged 0-<1 is very low (see Appendix 15 for details). This means that any estimate of effect or accuracy is very uncertain.

One controlled before and after study (DR Berg et al. 2012) assessed the effect of an environmental intervention provided to pregnant women, on their newborn children's blood lead levels (n =180). Berg (2012) compared the effect of home lead remediation provided by a certified contractor (paint stabilization, window replacement and cleaning as needed), with matched controls who did not receive home remediation (see Appendix 15 for details of the intervention).

The authors measured blood lead level in three different ways, finding that home remediation reduced mean blood lead level by nearly 1 µg/dL in children at 1.5 years of age (MD -0.93, 95% CI -1.70 to -0.16, p = 0.019) (see Figure 2). However, as discussed in Section 1 of this report, evidence suggests the majority of laboratories performing blood lead level testing achieve routine performance of +/- 2 µg/dL at blood lead levels ≤10 µg/dL (PJ Parsons, C Geraghty & MF Verostek 2001), so the impact of this intervention does not exceed the routine laboratory error margin for blood lead level testing. Berg et al. found no difference between groups when the number of children with blood lead level ≥ 5 µg/dL (RR 0.59, 95% CI 0.29 to 1.22, p =0.143) or ≥10 µg/dL (RR 0.18, 95% CI 0.01 to 3.21, P=0.128) were considered (see Figure 3).

Results of these studies should be considered alongside the fact that US Federal regulations allow laboratories that perform blood lead level testing to operate with a total allowable error of +/- 4 µg/dL or +/- 10%, whichever is greater (H Binns, C Campbell & M Brown 2007).

Figure 2. Environmental interventions, children aged 0-<1 year, mean blood lead level (µg/dL) at 1.5 years of age

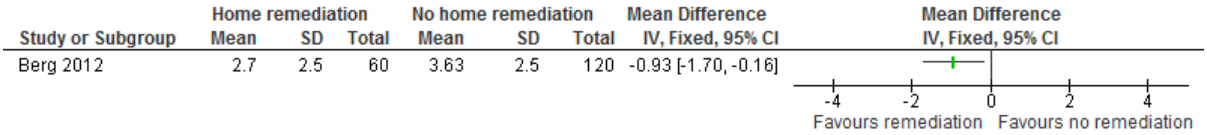
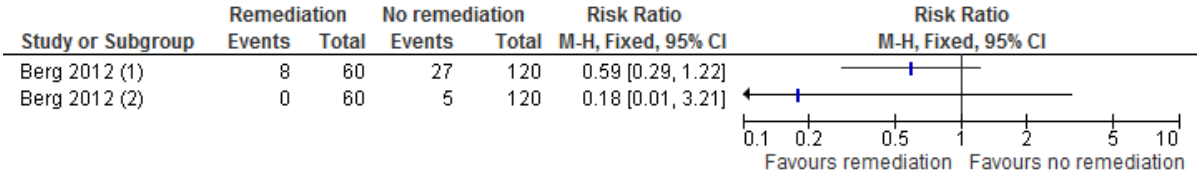


Figure 3. Environmental interventions, children aged 0-<1 year, number of children with blood lead level ≥ 5, and ≥ 10 µg/dL



(1) Number of children with BLLs >= 5ug/dL
(2) number of children with BLLs >= 10ug/dL

Children 1-<2 years (some on ground, some walking)

According to GRADE assessment, the quality of the evidence about environmental interventions for children aged 1-<2 years is very low (see Appendix 15 for details). This means that any estimate of effect or accuracy is very uncertain.

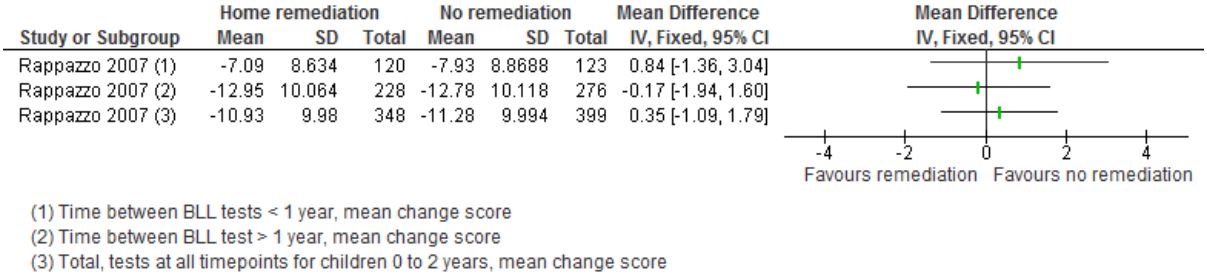
Two cohort studies (K Rappazzo et al. 2007; W Strauss et al. 2005) assessed the effect of an environmental intervention on blood lead level in children aged 1-<2 years (n = 1,437). Strauss (2005) compared home lead hazard control work (e.g. paint stabilisation, window cleaning etc.) with no home remediation in children < 3 years, with blood lead level >5 µg/dL. Rappazzo (2007) compared compliance with US housing standards (involving remediation work to achieve), with non-compliance with these standards in children aged 0-2 years, with blood lead level ≥10 µg/dL. Due to the differing interventions, results of studies were not pooled.

Neither study found their environmental intervention was effective in reducing blood lead level in children aged 1-<2 years. Strauss (2005) reported that there was no difference in mean blood lead level between children living in homes that had remediation work versus

children living in homes without remediation work at one, two and three years' post-intervention (MD not calculable, p >0.05; all time points) (no forest plot available) (see included studies table).

Rappazzo (2007) found no difference between the mean blood lead level change scores in children living in homes that were compliant with US housing standards and those living in homes that were non-compliant (MD 0.35, 95% CI -1.09 to 1.79, p > .2 all time-points; greater than and less than 1 year) (see Figure 4).

Figure 4. Environmental interventions, children aged 1-<2 years, mean change blood lead level (µg/dL) scores at different ages and time-points



(1) Time between BLL tests < 1 year, mean change score
(2) Time between BLL test > 1 year, mean change score
(3) Total, tests at all timepoints for children 0 to 2 years, mean change score

Children 2-<5 years (walking at home)

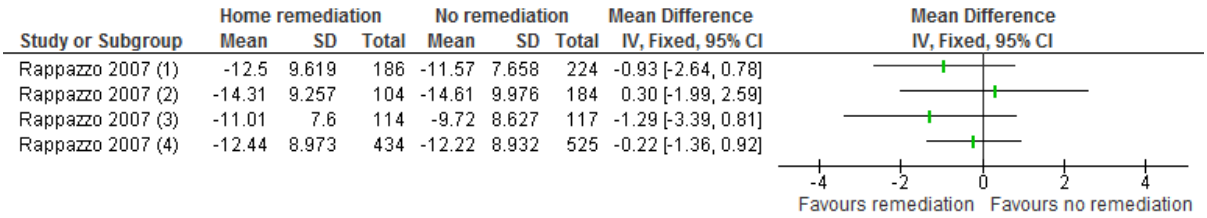
According to GRADE assessment, the quality of the evidence about environmental interventions for children aged 2-<5 years is very low (see Appendix 15 for details). This means that any estimate of effect or accuracy is very uncertain.

Two cohort studies (P McLaine et al. 2006; K Rappazzo et al. 2007) assessed the effect of environmental interventions on blood lead level in children aged 2-<5 years (n = 1,046). Rappazzo considered the effect of compliance with US housing standards in children aged 0-6 years with blood lead level >10 µg/dL (see previous section, children 1-<2 years) (K Rappazzo et al. 2007). McLaine (2006) considered the effect of home relocation, with direct assistance (case management and financial support) or indirect assistance (education and support) compared with no relocation in children aged 0-6 years (mean age 36 months) with blood lead level > 19 µg/dL. Because the families who did not relocate also received

some program assistance (but subsequently elected not to relocate), the two comparisons in this study were considered to be relocation (irrespective of assistance provided) versus no relocation and relocation with direct assistance versus relocation with indirect assistance. Due to the differing interventions, study results were not pooled.

Rappazzo (2007) found no difference between the mean blood lead level change scores of children living in homes compliant with US housing standards and those living in homes that were non-compliant (MD -0.22, 95% CI -1.36 to 0.92, p >0.2); all time-points; 1 to greater than 3 years post-intervention) (see Figure 5).

Figure 5. Environmental interventions, children aged 2-<5 years, mean blood lead level (µg/dL), various time points



(1) Time between BLL test 2 to 3 years, mean change score
(2) Time between BLL tests > 3 years, mean change score
(3) Time between BLL tests 1.5 to 2 years, mean change score
(4) Total, tests all timepoints for children 0 to 6 years, mean change score

At 12 months post-intervention, McLaine (2006) found no difference in blood lead level in children of families who relocated versus those who did not relocate (MD -2.86, 95% CI -6.38 to 0.66, P>0.05), with the type of assistance received (direct or indirect) having little effect on blood lead level (MD 0.40, 95% CI -3.56 to 4.36, P>0.05) (see Figures 6 and 7).

Figure 6. Environmental interventions, children aged 2-<5 years, mean blood lead level (µg/dL) at 12 months post-intervention

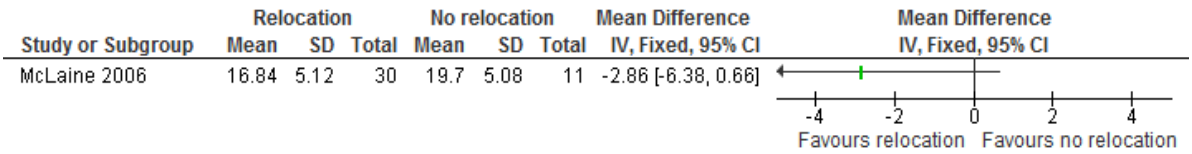
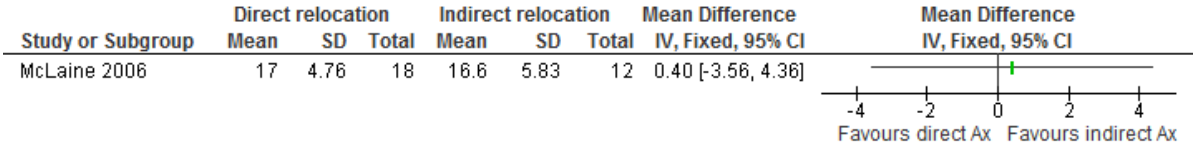


Figure 7. Environmental interventions (intervention A versus B), children aged 2-<5 years, mean blood lead level (µg/dL) at 12 months post-intervention



Adults 12-<60 years

The quality of the evidence about environmental interventions in adults aged 12-<60 years is very low (see Appendix 15 for details). This means that any estimate of effect or accuracy is very uncertain.

One controlled before and after study (R Fertmann et al. 2004) assessed the effect of an environmental intervention in young women living in houses with confirmed lead in the water pipes (n = 52). The authors compared the effect of replacing some women's tap water with bottled water for 10 weeks (excluding) with an educative leaflet encouraging tap water lead minimisation practices (minimizing). Since the mean life of blood lead is about 1 month (MB Rabinowitz 1991) the 10 week duration should be sufficient to gauge a change in blood lead level.

Fertmann (2004) provided the mean blood lead level in the excluding and minimising group (2.1 µg/dL; 3.0 µg/dL) but not the standard deviation or p-value, so the mean difference was not calculated. However, authors reported that the mean change in blood lead level between groups was not statistically significant (p = 0.17) (no forest plot available, see Table 4 Summary of included studies).

Educational interventions

Children 0-<1 year (crawling)

The quality of the evidence about educational interventions for children aged 0-<1 year is low (see Appendix 15 for details). This means that further research is very likely to have an important impact on confidence in the estimate, and is likely to change this estimate.

Campbell (2012) conducted a controlled before and after study, investigating the effect of education provided to families on the blood lead level of their newborn children (n = 942). Intervention participants were provided with extensive home-based education regarding lead poisoning prevention and given cleaning materials ("maintenance"), or generic home-based lead poisoning prevention education ("standard"). Matched control participants received lead poisoning prevention information as normally provided during their clinical visits with health professionals (usual care).

The authors compared the effect of "maintenance" versus "standard" education on children's blood lead level at one year of age, finding no difference between groups (MD 0.10, 95% CI -0.38 to 0.58, p ≥0.1) (see Figure 8). To compare the effect of education versus usual care, the authors pooled the results of "maintenance" and "standard" education groups, again finding very little difference in blood lead level between groups at one year of age (MD -0.10, 95% CI -0.38 to 0.18, p ≥0.1); and two years of age (MD 0.20, 95% CI -0.16 to 0.56, p ≥0.1) (see Figure 9).

Figure 8. Educational interventions (intervention A versus B), children aged 0-<1 year, mean blood lead level (µg/dL) at 1 year of age

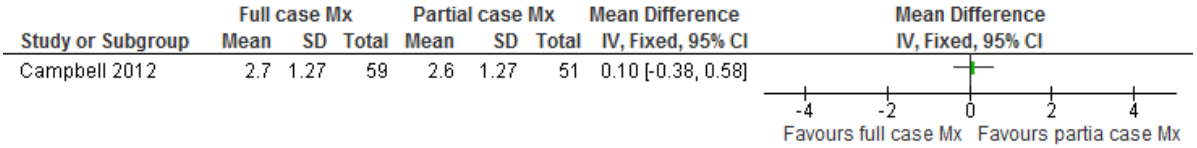
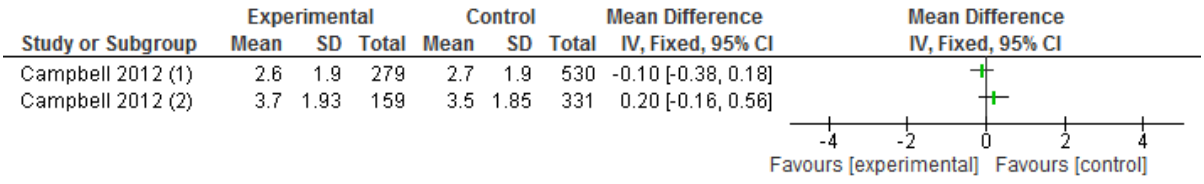


Figure 9. Educational interventions, children aged 0-<1 year, mean blood lead level (µg/dL) at 1 year of age



(1) BLLs at approximately 12 months old
(2) BLLs at approximately 24 months old

Pharmacological interventions

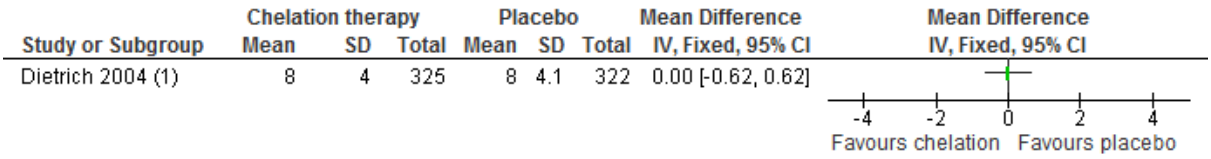
Children 1-<2 years (some on ground, some walking)

The quality of the evidence for pharmacological interventions (chelation) on blood lead level in children aged 1-<2 years is moderate (see Appendix 15 for details). This means that further research is likely to have an important impact on confidence in the estimate of effect or accuracy, and may change the estimate.

One randomised controlled trial (KN Dietrich et al. 2004) investigated the effect of a pharmacological intervention on blood lead level, height, cognition and neurobehavioural outcomes in children aged 12 to 33 months; n = 780. (Note that the mean age of control and treatment groups was 25 months.) They compared the effect of up to three, 26-day courses of chelation therapy (succimer) with placebo in children with blood lead levels between 20 to 44 µg/dL. The authors measured the effect at multiple time points, concluding when children were seven years of age (five years post-intervention).

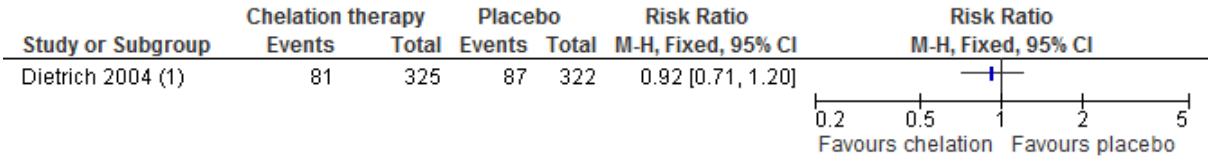
Dietrich (2004) described reductions in blood lead level with chelation therapy over the first 6 months post-treatment (average MD -4.5, 95% CI -3.7 to -5.3) and at 12 months post-treatment (MD -2.7, 95% CI -1.9 to -3.5). However these reductions were not sustained at 7 years of age when measured as mean blood lead level (MD 0.00, 95% CI -0.62 to 0.62, P>0.05) or the number of children with blood lead level > 10 µg/dL (RR 0.92, 95% CI 0.71 to 1.20, P>0.05) (see Figures 10 and 11) (p values not reported by authors).

Figure 10. Pharmacological interventions, children 1-<2 years, mean blood lead level (µg/dL) at 7 years of age.



(1) BLLs at 7 years of age (no earlier data available)

Figure 11. Pharmacological interventions, children 1-<2 years, number of children with blood lead level ≥ 10 µg/dL at 7 years of age



(1) Number of children with BLL >= 10ug/dL at 7 years of age

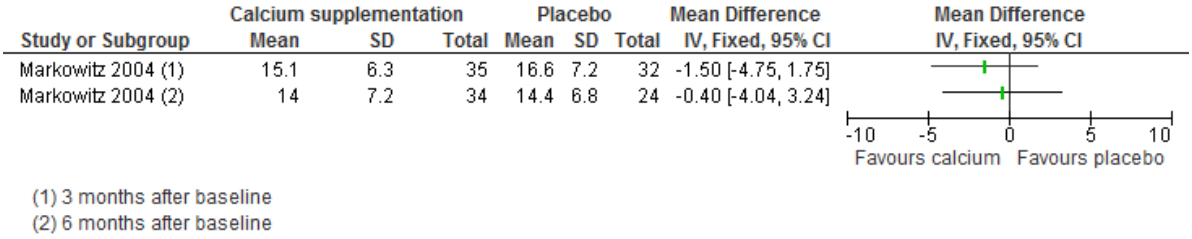
Children 2-<5 years (walking at home)

The quality of the evidence regarding pharmacological interventions for children aged 2-<5 years was very low (see Appendix 15 for details). This means that any estimate of effect or accuracy is very uncertain.

One randomised controlled trial (ME Markowitz, M Sinnett & JF Rosen 2004) investigated the effect of a pharmacological intervention on children aged 2-<5 years (n = 87). Markowitz (2004) compared the effect of calcium supplementation (to reach 1800mg daily, taking into account daily dietary calcium intake) for three months, with placebo, in children aged 0-6 years (mean age 3.6 years) with blood lead level between 10 and 45 µg/dL. Families of children in both groups also received standard clinic education about managing lead exposure.

The authors found no difference in blood lead level in children who received calcium supplementation at 3 months (MD -1.50, 95%CI -4.75 to 1.75, p> 0.1) or 6 months after baseline (MD -0.40, 95% CI -4.04 to 3.24, p> 0.1) (see figure 12).

Figure 12. Pharmacological interventions, children aged 2-<5 years, Mean blood lead level at 3 and 6 months after baseline



(1) 3 months after baseline
(2) 6 months after baseline

Pregnant and lactating women (all ages)

The quality of the evidence about pharmacological interventions in pregnant women is moderate (see Appendix 15 for details), meaning that further research is likely to have an important impact on confidence in the estimate of effect or accuracy, and may change the effect.

One randomised controlled trial (AS Ettinger et al. 2009) investigated the effect of a pharmacological intervention in pregnant women (n = 670). Ettinger (AS Ettinger et al. 2009) compared the effect of an 8-month course of calcium supplementation (1200mg daily), with placebo, on blood lead level of women living in low income areas, who were less than 14 weeks pregnant at recruitment (AS Ettinger et al. 2009).

The authors did not present raw data, but provided a log transformed score, showing an average reduction in blood lead level of 11% among participants who received calcium supplementation, compared to placebo (MD -11%, 95% CI -17.8% to -3.7%, p = 0.004). This analysis was adjusted for a number of factors including baseline blood lead level and dietary calcium intake. In addition, Ettinger (AS Ettinger et al. 2009) stratified the results by compliance with medication. When they considered the effects in those who were compliant (>75% pills taken) there was a statistically significant reduction in blood lead level between groups in both the second and third trimesters of pregnancy (p < 0.01).

Combination interventions

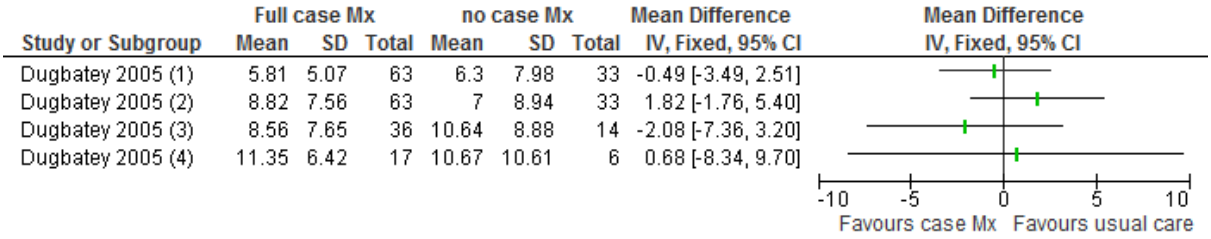
Children 0-<1 year (crawling)

The quality of the evidence about combination interventions in children aged 0 -<1 year is very low (see Appendix 15 for details), meaning that any estimate of effect or accuracy is very uncertain.

One study investigated the effect of combination interventions provided to pregnant women on blood lead level in their infant children (n = 151) (K Dugbatey et al. 2005). They compared the effect of full case management (tailored education, home lead inspection and counselling at quarterly visits) with partial case management (written report of home lead inspection, newsletter and quarterly visits) and with standard lead education (usual care, delivered by health professionals). They measured these effects at four time-points: 6, 12, 18 and 24 months after baseline.

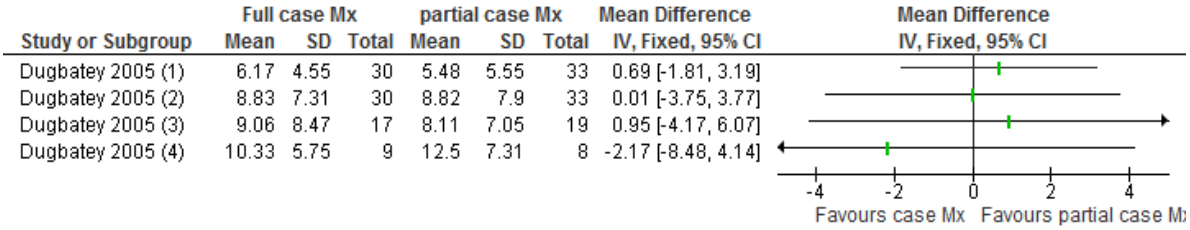
Dugbatey (2005) reported the mean blood lead levels in each of the three groups at each time point, concluding that, "there were no statistically significant differences between study groups for any of the follow up blood lead level measures". For the analysis in this review, results of the two case management groups were pooled and compared with the usual care group, finding no difference between groups, with the direction of effect varying at different time points (e.g. MD 0.68, 95% CI -8.34 to 9.70, p>0.1, time-point four) (see Figure 13). This same pattern of non-significant effects was seen when comparing the effects of full versus partial case management (e.g. MD -2.17, 95% CI -8.84 to 4.14, p>0.1, time-point four) (see Figure 14).

Figure 13. Combination interventions, Children 0-<1 year, case management (full + partial) versus usual care, mean blood lead level (µg/dL) at four time points



(1) Mean BLL at time-point 1 (likely 6 months after baseline)
(2) Mean BLL at time-point 2 (likely 12 months after baseline)
(3) Mean BLL at time-point 3 (likely 18 months after baseline)
(4) Mean BLL at time-point 4 (likely 24 months after baseline)

Figure 14. Combination interventions, Children aged 0-<1 year, full case management versus partial case management, mean blood lead level (µg/dL) at four time points



(1) Mean BLL at time-point 1 (likely 6 months after baseline)
(2) Mean BLL at time-point 2 (likely 12 months after baseline)
(3) Mean BLL at time-point 3 (likely 18 months after baseline)
(4) Mean BLL at time-point 4 (likely 24 months after baseline)

Children 1-<2 years (some on ground, some walking)

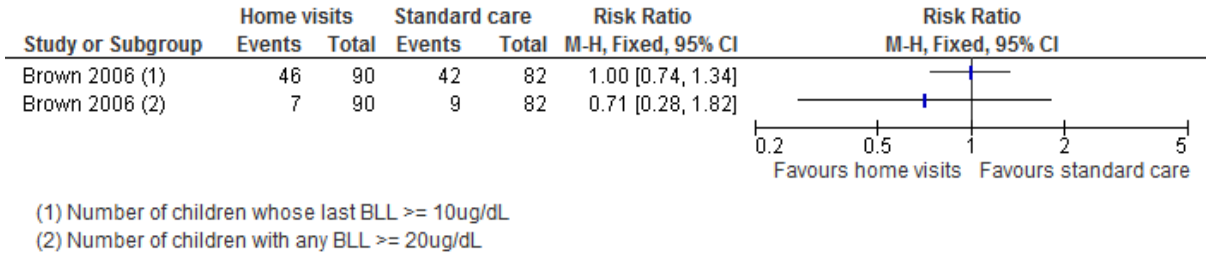
The quality of the evidence about combination interventions in children aged 1-<2 years is very low (see Appendix 15 for details), meaning that any estimate of effect or accuracy is very uncertain.

Two studies, a randomised controlled trial (n = 175) (MJ Brown et al. 2006) and a cohort study (n = 2,109) (NS Whitehead & R Leiker 2007) investigated the effect of combination interventions on blood lead level in children aged 1-<2 years. Brown (2006) compared the effect of a comprehensive home visit program delivered by a nurse, providing lead hazard

identification and support to mitigate exposure, with a standard home visit program with an outreach worker, providing lead education only, in children aged < 28 months (mean age ~ 18 months), with blood lead level between 15 to 19 µg/dL. Whitehead and Leiker (2007) compared the relative effectiveness of different components of state-based lead poisoning prevention case management programs, in children aged < 2 years with blood lead level between 10 to 19 µg/dL. Specifically, they compared the method of contact (mail, telephone, home visit) and the type of service delivered (educational materials, lead source investigation) between programs. Study results were not pooled due to differences in study designs and interventions.

Brown (2006) reported that there was no difference between the comprehensive and standard home visit programs, in terms of the number of children whose last blood lead level reading was ≥ 10 µg/dL (RR 1.0, 95% CI 0.74 to 1.34). There was no difference in the number of children with blood lead level ≥ 20 µg/dL, however the confidence interval includes a wide range of possible effects (RR 0.71, 95% CI 0.28 to 1.82) (see Figure 15). The authors do not present mean blood lead level numerically, but report that mean blood lead level "did not differ significantly at 3, 6 or 12 months after baseline."

Figure 15. Combination interventions, children 1-<2 years, number of children whose last blood lead level was ≥10, and ≥20 µg/dL



(1) Number of children whose last BLL >= 10ug/dL
(2) Number of children with any BLL >= 20ug/dL

Whitehead (2007) presented the adjusted and unadjusted mean blood lead level change scores (and standard error) between groups for all children (blood lead level between 10 to 19 µg/dL) and stratified by lead level (children with blood lead level between 10 to 14 µg/dL and blood lead level between 15 to 19 µg/dL). As the results are consistent across

population groups, results for all children are reported. The mean blood lead level change scores (and standard error) (µg/dL, unadjusted) for the each comparison group in method of contact were; -1.96 (0.4) (home visits), -0.72 (0.02) (telephone), 1.18 (0.2) (mail) and for type of service provided were 0.36 (0.2) (education) and -0.92 (0.5) (investigation). The authors report that there was a statistically significant difference between the adjusted blood lead level change scores of participants who received their intervention by mail, compared with by home visit and telephone, with blood lead levels changing less for the mail group. There was no statistically significant difference between the adjusted blood lead level change scores between those who received education versus a lead inspection.

Effects of interventions, excluding cohort studies

Three of the five included environmental studies were cohort studies (P McLaine et al. 2006; K Rappazzo et al. 2007; W Strauss et al. 2005). After excluding these studies, the review no longer includes any study of environmental interventions for children aged 1-<2 years or 2-<5 years. There is no change to the evidence base for children aged 0-<1 year or adults aged 12-<60 years.

All educational and pharmacological interventions included in this review were evaluated within a controlled study design (C Campbell et al. 2012; KN Dietrich et al. 2004; AS Ettinger et al. 2009; ME Markowitz, M Sinnett & JF Rosen 2004).

One of the two combined studies that investigated blood lead levels in children aged 1-<2 years old was a cohort study and thus was excluded for the second narrative analysis (NS Whitehead & R Leiker 2007). The remaining study in children aged 1-<2 years old found no effect of the intervention (MJ Brown et al. 2006).

Adverse events

Only one study (ME Markowitz, M Sinnett & JF Rosen 2004) explicitly considered adverse events or harms, finding no “serious” adverse events with calcium supplementation, but infrequent abdominal pain in both groups. It is not unreasonable to consider an increase in

blood lead level in the intervention group compared with the control group as a harmful event. As most studies reported non-significant differences in blood lead level there is no clear evidence of harm. Whilst not described as a harm, Dietrich (2004) found that children who received chelation (succimer) were on average 1cm shorter than children who received placebo at seven years of age.

Process outcomes

In addition to the pre-specified outcome of interest to this review, most studies measured the effect of their intervention on additional outcomes (see Appendix 15). Some of these outcomes, such as home lead levels, and adherence, could be considered important process or contextual outcomes, to consider in light of the effect the interventions on blood lead level.

Four studies assessed the effect of a range of intervention types on home lead levels, as measured by dust samples on surfaces like floors and window sills (MJ Brown et al. 2006; C Campbell et al. 2012; ME Markowitz, M Sinnett & JF Rosen 2004; P McLaine et al. 2006). Markowitz (2004) and Campbell (2012) found no difference in dust lead levels between groups post-intervention (Campbell only assessed between intervention groups). This compares to Brown (2006)and McLaine (2006) who found significant differences or reductions in blood lead level between groups, favouring the intervention groups. In both these studies, these reductions did not translate into reductions in blood lead level of participants.

The three studies that assessed pharmacological interventions all measured treatment adherence (KN Dietrich et al. 2004; AS Ettinger et al. 2009; ME Markowitz, M Sinnett & JF Rosen 2004). Compliance was better in studies by Dietrich et al. (2004) and Markowitz et al. (2004) with all study groups taking approximately 80% of the intended medications in both studies. Compliance was poorer in the study by Ettinger et al. (2009) with only 36% of participants taking more than ¾ of prescribed pills. Ettinger et al. (2009) report a dose-response effect when the results were stratified by treatment compliance, with greater

reductions in blood lead level as compliance increased. Fertmann (2004) also assessed compliance with the tap water reductions was different between groups (68% in the 'minimising' group versus 91% in the 'excluding' group).

Discussion and conclusions

This systematic review was conducted to respond to the following question, 'In children (0-<1 year, 1-<2 years, 2-<5 years, 5-<12 years), adults (12-<60 years, ≥ 60 years) and pregnant and lactating women, are there any interventions that are more effective than standard interventions or no interventions in reducing lead exposure as measured by blood lead levels?'. Twelve studies were included in the review, with a maximum of two studies in each analysis intervention/population subgroup. None of the studies considered the effectiveness of any intervention on blood lead levels for children aged 5-<12 years old or adults ≥ 60 years old, and only one study focused on pregnant women. This review found the following:

<u>Children 0-<1 year</u>

- One controlled before and after study (DR Berg et al. 2012) (high risk of bias, very low quality evidence), found that an environmental intervention (home remediation, consisting of paint stabilization, window replacement and cleaning as needed) versus no intervention was associated with a reduced mean blood lead level of nearly 1 µg/dL (MD -0.93, 95% CI -1.70 to -0.16, p = 0.019). However, the impact of this intervention does not exceed the routine laboratory error margin for blood lead level testing. The study found no difference between groups when only children with blood lead level ≥ 5 µg/dL (RR 0.59, 95% CI 0.29 to 1.22) or ≥10 µg/dL (RR 0.18, 95% CI 0.01 to 3.21, P=0.128) were considered.
- No effect of an educational intervention in reducing blood lead levels of children 0-<1 year old (one before and after study, low quality of evidence) (C Campbell et al. 2012).

- No effect of a combination intervention consisting of full case management versus partial case management and standard lead education delivered to pregnant women on blood lead levels of children 0-<1 year (one randomised controlled trial, low risk of bias) (K Dugbatey et al. 2005).

Children 1-<2 year

- One randomized controlled trial (very low risk of bias, moderate quality evidence) found that chelation therapy was associated with reduced blood lead levels for children aged 1-<2 years at 6 (average MD -4.5, 95% CI -3.7 to -5.3) and 12 months post treatment (MD -2.7, 95% CI -1.9 to -3.5), but that these reductions were not sustained (~ 5 years post treatment MD 0.00, 95% CI -0.62 to 0.62) (KN Dietrich et al. 2004).
- One cohort study (categorized as a combination study, high risk of bias) showed that home and telephone contact interventions versus mail contact only interventions were associated with reduced blood lead levels (NS Whitehead & R Leiker 2007). (One other combined study was considered for this age group and found no effect, but since the intervention was very different the discrepant findings need not be compared.)
- No effect of environmental interventions in reducing blood lead levels of children 1-<2 years old (two cohort studies, very low quality evidence) (K Rappazzo et al. 2007; W Strauss et al. 2005).
- No effect of a combination intervention consisting of a comprehensive home visit program delivered by a nurse versus a standard home visit program for reducing blood levels in children aged 1-<2 years (one randomised controlled trial, very low quality evidence) (MJ Brown et al. 2006).

Children 2-<5 years

- No effect of environmental interventions in reducing blood lead levels of children 2-<5 years old (two cohort studies, very low quality evidence) (P McLaine et al. 2006; K Rappazzo et al. 2007).
- No effect of a pharmacological intervention in reducing blood lead levels of children 2-<5 years old (one randomised controlled trial, very low quality evidence) (ME Markowitz, M Sinnett & JF Rosen 2004).

Adults 12-<60 years

- No effect of an environmental intervention in reducing blood lead levels of adults 12-<60 years old (one controlled before and after study, very low quality evidence) (R Fertmann et al. 2004).

Pregnant and lactating women

- For pregnant women, one randomized controlled trial (moderate risk of bias, moderate quality evidence), found that calcium supplementation may reduce blood lead levels (MD -11%, 95% CI -17.8% to -3.7%, p = 0.004) (AS Ettinger et al. 2009).

In summary, there is very little evidence available regarding the effectiveness of interventions in reducing blood lead levels across the population subgroups of interest, and the evidence that is available is generally of very low quality due to issues concerning risk of bias (for example, lack of allocation concealment, large loss to follow up and concerns about confounding) as well as issues with imprecision (wide confidence intervals). Furthermore, caution should be applied in the application of available evidence to population subgroups since in most cases it is based on findings of only one study. Other issues concerning the evidence include the fact that, in many included studies, the source of lead exposure was not clearly identified, nor its removal confirmed. Also, the majority of included studies were conducted with children or families from disadvantaged areas with

blood levels greater than 10µg/dL; therefore, it is uncertain to what degree the body of evidence included in this systematic review applies to the Australian context.

Interpretation of review findings

The findings of this systematic review were broadly consistent with that of another systematic review that considered the effect of interventions to reduce blood lead levels in individuals. Yeoh and colleagues published a Cochrane Review of household interventions to prevent domestic lead exposure in children (B Yeoh et al. 2008). Their differing inclusion criteria and search dates meant only one of the 12 studies included in this review was included in the review by Yeoh et al. Yeoh et al report no evidence for effectiveness of environmental and educational measures (i.e. dust control in the home) on blood lead levels, and insufficient evidence for an effect of combination interventions.

In this review, across most intervention types (i.e. environmental, educational and combination) the quality of the evidence is low to very low, due in part to a small number of studies and small sample sizes, and imprecise and inconsistent effect estimates, rather than the studies having inherent methodological limitations (i.e. high risk of bias). The quality of evidence supporting pharmacological interventions was higher, due in part to the studies being relatively well conducted randomised controlled trials, with some more compelling effect estimates. Overall, this means that the conclusions of this review could or are, very likely to change in light of evidence from future studies. It is important to note that the quality of evidence was considered for each outcome, within each population subgroup for each intervention. As such, the evidence within each outcome was drawn from no more than two studies. Reducing the number of population sub-groups (or including a greater number of studies) would increase the number of studies within each outcome, which could increase the quality of evidence.

One study included in this systematic review suggests that calcium supplementation in pregnant women may reduce blood lead levels (AS Ettinger et al. 2009). An earlier study (B Gulson et al. 2004), not included in this review due to the very small comparison group

(n=2), supports this finding. Of interest, the study by Gulson and colleagues also considered the role of calcium supplementation during lactation, with the findings suggesting supplementation is ineffective in reducing maternal blood lead levels. However both findings from this study should be approached with caution due to the lack of control group.

It is notable that the majority of studies in this review included children with blood lead levels ≥ 10 μg/dL (MJ Brown et al. 2006; KN Dietrich et al. 2004; AS Ettinger et al. 2009; R Fertmann et al. 2004; ME Markowitz, M Sinnett & JF Rosen 2004; P McLaine et al. 2006; K Rappazzo et al. 2007; NS Whitehead & R Leiker 2007). How well these interventions may work with children with lower blood lead levels or those at risk of lead exposure is unclear. This is important as the literature describing blood lead levels in Australian children, while scant, suggests that average levels in Australia may be lower, as was noted in Section 1 of this report (B Gulson et al. 2008; R Guttinger et al. 2008).

The majority of studies reviewed did not show statistically significant findings. A range of factors may have contributed to this. One possible reason for this is inadequate length of follow up. As has been noted, half of the studies in this review completed their last outcome assessment before or at 12 months post-intervention (MJ Brown et al. 2006; AS Ettinger et al. 2009; R Fertmann et al. 2004; ME Markowitz, M Sinnett & JF Rosen 2004; P McLaine et al. 2006; NS Whitehead & R Leiker 2007). In addition, in no study was it clear how long participants had been exposed to lead prior to study enrolment. For children with blood lead levels > 10 μg/dL, it can take months to years for blood lead levels to decline, depending on the duration and level of exposure (H Binns, C Campbell & M Brown 2007). In one study the mean length of time to achieve a reduction in blood lead level, from 10 to 14 μg/dL at baseline to < 10 μg/dL post-intervention, was 11.6 months (NS Whitehead & R Leiker 2007). However, for children with blood lead level < 10 μg/dL, the time needed for a decline in blood lead level in response to an intervention is unknown (H Binns, C Campbell & M Brown 2007).

The comparison group in the included studies usually received some kind of partial intervention, or at the very least, usual care as provided by health professionals. This would reduce any potential differences in blood lead levels between groups post-intervention. Additionally, some of the smaller studies are likely to be underpowered (unable to detect a statistically significant effect even if such an effect exists), while the larger studies are mostly evaluations of state-wide programs in which there is uncertainty about whether all participants received the intended interventions.

In three of the five environmental studies, the lead contaminant was either not removed (P McLaine et al. 2006) or it is unclear as to whether or not its removal occurred (R Fertmann et al. 2004; W Strauss et al. 2005), pointing to issues of adherence to intervention or to flaws in the study design. The study by McLaine and colleagues provided housing relocation that aimed to remove the source of lead contamination for families (P McLaine et al. 2006). However, at the time of relocation 35% of homes identified by the Kennedy Krieger Institute Lead Poisoning Prevention and Treatment Program for relocation had lead level loadings above the 1995 HUD clearance standards which were in effect at the time (United States Department of Housing and Urban Development 1995), and less than half (47%) met the current Federal (US EPA 2001) standards. Thus, further research should be conducted on the benefits of environmental lead reduction interventions on blood lead levels, ensuring that the intervention includes removal of the source of lead contamination and that this is reported in research and evaluation findings.

The results of the study by Dietrich and colleagues point to the difficulty in preventing re-exposure to lead after its initial removal (KN Dietrich et al. 2004; B Yeoh et al. 2008). After house cleaning and treating children with chelation, mean blood lead levels in the treatment were 4.5 μg/dL less over the first six months, but this decrease was not sustained at 5 years post-intervention.

Regarding the apparent lack of success of the educational intervention included in this review (C Campbell et al. 2012), some specific factors should be taken into account. First,

the intervention does not appear to have a prominent theoretical basis, a factor that is regarded as important in the design of health education interventions (K Glanz, BK Rimer & K Viswanath 2008; T Pettman et al. 2013). Second, the city of Philadelphia, where the study was conducted, has a relatively active lead exposure prevention program and control families may have received lead interventions from other sources (C Campbell et al. 2012). This would have biased the blood lead comparison toward a null finding. Last, the study participants were largely from low socio-economic backgrounds; therefore, study findings may not be generalizable to other socio-economic groups.

The issue of potential confounding is problematic in the body of literature included in this review. Many included studies did not take into account known confounders such as socioeconomic status or race, and it is likely that other as yet unknown confounding factors play a role in influencing study results.

This review focused on interventions that could be used to reduce blood lead levels at an individual level. These are the kind of interventions that can be implemented by clinicians and public health professionals in response to individual cases of lead exposure. As such, it does not take into account population-level strategies, such as the removal of lead in water, paint and petrol, that have been credited with the global decline in blood lead levels in Australia and elsewhere (R Guttinger et al. 2008; US EPA 2013). While blood lead levels continue to decline at a population level, there remain a number of potential lead hazards in the Australian urban environment (MAS Laidlaw & MP Taylor 2011).

This review sought to summarise the evidence that is most applicable to Australians who are not living or working in environments where lead is endemic. Studies conducted with people living in non-OECD countries were excluded, as well as studies of populations living or working in environments where lead is endemic due to, for example, lead mining and smelting. While this increases the relevance of review findings to the Australian context, it does mean that several otherwise eligible studies were excluded. It is important to note that the management of lead exposure in endemic environments may require different

approaches, such as soil remediation (US EPA 2013). As such, the results of this review are not directly applicable to Australians exposed to lead via endemic sources, or in the workplace.

This review only includes studies published since 2004. While the inclusion of earlier studies would have expanded and perhaps strengthened the body of evidence, the results may have been less relevant for Australian children and adults recently exposed to lead. It is likely that the blood lead levels of participants in those studies excluded would have been higher than more recent observations, due to the trend in recent decades of blood lead level reductions (R Guttinger et al. 2008; US EPA 2013). Nevertheless, the results of this review should be considered along with the results of earlier primary studies and reviews.

The strength of this review is that best practices in systematic review methods were followed; including a comprehensive search of published and unpublished literature, following a pre-approved protocol and using systematic and transparent methods (JPT Higgins & S Green 2011; B Shea et al. 2007). Tools and software to assess and integrate evidence quality and study results were employed, such as GRADE (GRADE Working Group 2004) and the meta-analytic software RevMan 5.1 (Review Manager 2012).

Standard best practices for reviews that are conducted in an expedient and efficient manner were employed, whilst including processes that increase rigour. Study screening, data extraction, and risk of bias assessment were undertaken by one reviewer. To mitigate potential for error, these processes were checked for accuracy and internal consistency in two ways; by regular meetings to approve planned processes with another team member, and having a second reviewer double check a small proportion of work at each stage (i.e. study selection, and data extraction).

A limitation of this review is that the included studies analysed results using age categories that did not necessarily match the age categories of interest in this review. As mentioned in

the methods section, where the age range of participants in a study did not match exactly with the review categories, the mean age of participants was used to determine the best age category within which to consider study findings. If this review is repeated in the future a greater number of studies per intervention type/population subgroup may be available, warranting a meta-analysis. At such a time, standardised age categories should be used to consider the data across the available studies.

Report conclusions

The overview of evidence of health effects associated with blood lead levels <5 µg/dL and 5 to 10 µg/dL in children and adults (presented in Section 2 of this report), suggests, based on evidence from two moderate-quality systematic reviews, that blood lead levels <5 µg/dL may be associated with adverse cognitive effects in children, and that blood lead levels <10 µg/dL may be associated with adverse behavioural effects in children, delays in sexual maturation or puberty onset in adolescent girls and boys, and increased blood pressure and risk of hypertension among adults and pregnant women. However it is important that this evidence be interpreted with caution, due predominantly to methodological limitations such as uncontrolled confounding and measurement error within studies included in the systematic reviews, as well as uncertainties regarding the clinical significance of findings regarding increased blood pressure.

The systematic review of effectiveness of interventions in reducing blood lead levels in specific population subgroups (presented in Section 3 of this report) found very little relevant evidence. Much of the evidence was problematic in that the source of lead exposure being addressed by an intervention was not clearly identified, nor its removal confirmed. Also, the majority of included studies were conducted with children or families from disadvantaged areas with blood lead levels greater than 10µg/dL; therefore, it is uncertain to what degree the body of evidence included in the systematic review applies to the Australian context. Furthermore, the available evidence was generally of very low quality due to issues concerning risk of bias (for example, lack of allocation concealment, large loss to follow up and concerns about confounding) as well as issues with imprecision (wide confidence intervals).

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Appendices

Appendix 1. References from Health Protection Agency Compendium of Chemical Hazards Lead (S Bull 2007)

The following references are relevant to Section 1 of this report, sub-section 'What are the mechanisms of lead toxicity and their clinical correlates?'. The numbers below correspond to the numbers provided in the main body of this report.

Cardiovascular Effects

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Renal Effects

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Appendix 2. Search strategies and databases.

Database	Date	No. of hits
MEDLINE	28/05/2013	1061
MEDLINE In Process	28/05/2013	83
EMBASE	28/05/2013	1754
CINAHL	28/05/2013	1362
Science Citation Index (including conference proceedings)	28/05/2013	875
Scopus	23/05/2013	677
LILACS	23/05/13	111
TOXLINE	28/05/13	296
OPENGREY	22/05/13	0
Total (de-duped)	3607	

MEDLINE

Database: **Ovid MEDLINE(R)** <1946 to May Week 3 2013>
Search Strategy:
1 Lead/ and (expos* or poison* or toxic*).tw. (10256)
2 exp Environmental Exposure/ and lead.mp. (11745)
3 exp Environmental Pollutants/ and lead.mp. (12801)
4 (lead adj3 (expos* or poison* or toxic*)).tw. (12552)
5 exp Lead Poisoning/ (10337)
6 (plumbism or colica pictonum or saturnism or devon colic or painter's colic).tw. (389)
7 or/1-6 (32438)
8 exp Blood/ (914991)
9 (blood adj3 (concentration* or level* or measurement* or amount* or quantit*)).tw. (140279)
10 8 or 9 (1042208)
11 7 and 10 (5682)
12 exp animals/ not humans.sh. (3849536)
13 11 not 12 (4630)
14 (Algeria$ or Egypt$ or Liby$ or Morocc$ or Tunisia$ or Western Sahara$ or Angola$ or Benin$ or Botswana$ or Burkina Faso or Burundi$ or Cameroon or Cape Verde or Central African Republic or Chad$ or Comoros or Congo or Djibouti or Eritrea$ or Ethiopia$ or Gabon$ or Gambia$ or Ghana$ or Guinea or Keny$ or Lesotho or Liberia$ or Madagasca$ or Malawi$ or Mali or Mauritania or Mauritius or Mayotte or Mozambiq$ or Namibia$ or Niger or Nigeria$ or Reunion or Rwand$ or Saint Helena or Senegal$ or Seychelles or Sierra Leone or Somalia$ or Somali or South Africa$ or Sudan$ or Swaziland or Tanzania$ or Togo or Ugand$ or Zambia$ or Zimbabw$ or China or Chinese or Hong Kong or Macao or

Mongolia$ or Taiwan$ or Tibet$ or Belarus or Moldov$ or Russia$ or Ukrain$ or Afghanistan or Afghani or Armenia$ or Azerbaijan$ or Bahrain$ or Cyprus or Cypriot or Georgia$ or Iran$ or Iraq$ or Jordan$ or Kazakhstan$ or Kuwait$ or Kyrgyzstan or Leban$ or Oman or Pakistan$ or Palestin$ or Qatar or Saudi Arabia$ or Syria$ or Tajikistan or Turkmenistan or United Arab Emirates or Uzbekistan or Yemen or Bangladesh$ or Bhutan$ or British Indian Ocean Territory or Brunei Darussalam or Cambodia$ or India$ or Indonesia$ or Lao or People's Democratic Republic or Malaysia$ or Maldives or Myanmar or Nepal$ or Philippin$ or Singapore$ or Sri Lanka$ or Thai$ or Timor Leste or Vietnam$ or Albania$ or Andorra or Bosnia$ or Herzegovina$ or Bulgaria$ or Croatia$ or Faroe Islands or Greenland or Liechtenstein or Lithuani$ or Macedonia or Malta or Maltese or Romania$ or Serbia$ or Montenegr$ or Svalbard or Argentina$ or Belize or Bolivia$ or Brazil$ or Colombia$ or Costa Rica$ or Cuba$ or Ecuador$ or El Salvador$ or French Guiana$ or Guatemala$ or Guyana or Haiti$ or Honduras or Honduran or Jamaica$ or Nicaragua$ or Panama$ or Paraguay$ or Peru$ or Puerto Ric$ or Suriname or Uruguay$ or Venezuela$ or developing countr$).ti,sh. (802296)
15 13 not 14 (3979)
16 limit 15 to yr="2004 -Current" (1061)

MEDLINE In-Process

Database: Ovid **MEDLINE(R) In-Process** & Other Non-Indexed Citations <May 24, 2013>
Search Strategy:
1 Lead/ and (expos* or poison* or toxic*).tw. (0)
2 exp Environmental Exposure/ and lead.mp. (0)
3 exp Environmental Pollutants/ and lead.mp. (0)
4 (lead adj3 (expos* or poison* or toxic*)).tw. (582)
5 exp Lead Poisoning/ (0)
6 (plumbism or colica pictonum or saturnism or devon colic or painter's colic).tw. (17)
7 or/1-6 (598)
8 exp Blood/ (1)
9 (blood adj3 (concentration* or level* or measurement* or amount* or quantit*)).tw. (5961)
10 8 or 9 (5962)
11 7 and 10 (110)
12 exp animals/ not humans.sh. (3)
13 11 not 12 (110)
14 (Algeria$ or Egypt$ or Liby$ or Morocc$ or Tunisia$ or Western Sahara$ or Angola$ or Benin$ or Botswana$ or Burkina Faso or Burundi$ or Cameroon or Cape Verde or Central African Republic or Chad$ or Comoros or Congo or Djibouti or Eritrea$ or Ethiopia$ or Gabon$ or Gambia$ or Ghana$ or Guinea or Keny$ or Lesotho or Liberia$ or Madagasca$ or Malawi$ or Mali or Mauritania or Mauritius or Mayotte or Mozambiq$ or Namibia$ or Niger or Nigeria$ or Reunion or Rwand$ or Saint Helena or Senegal$ or Seychelles or Sierra

Leone or Somalia$ or Somali or South Africa$ or Sudan$ or Swaziland or Tanzania$ or Togo or Ugand$ or Zambia$ or Zimbabw$ or China or Chinese or Hong Kong or Macao or Mongolia$ or Taiwan$ or Tibet$ or Belarus or Moldov$ or Russia$ or Ukrain$ or Afghanistan or Afghani or Armenia$ or Azerbaijan$ or Bahrain$ or Cyprus or Cypriot or Georgia$ or Iran$ or Iraq$ or Jordan$ or Kazakhstan$ or Kuwait$ or Kyrgyzstan or Leban$ or Oman or Pakistan$ or Palestin$ or Qatar or Saudi Arabia$ or Syria$ or Tajikistan or Turkmenistan or United Arab Emirates or Uzbekistan or Yemen or Bangladesh$ or Bhutan$ or British Indian Ocean Territory or Brunei Darussalam or Cambodia$ or India$ or Indonesia$ or Lao or People's Democratic Republic or Malaysia$ or Maldives or Myanmar or Nepal$ or Philippin$ or Singapore$ or Sri Lanka$ or Thai$ or Timor Leste or Vietnam$ or Albania$ or Andorra or Bosnia$ or Herzegovina$ or Bulgaria$ or Croatia$ or Faroe Islands or Greenland or Liechtenstein or Lithuani$ or Macedonia or Malta or Maltese or Romania$ or Serbia$ or Montenegr$ or Svalbard or Argentina$ or Belize or Bolivia$ or Brazil$ or Colombia$ or Costa Rica$ or Cuba$ or Ecuador$ or El Salvador$ or French Guiana$ or Guatemala$ or Guyana or Haiti$ or Honduras or Honduran or Jamaica$ or Nicaragua$ or Panama$ or Paraguay$ or Peru$ or Puerto Ric$ or Suriname or Uruguay$ or Venezuela$ or developing countr$).ti,sh. (35500)
15 13 not 14 (94)
16 limit 15 to yr="2004 -Current" (83)

EMBASE

Database: **EMBASE** <1947-Present>
Search Strategy:
---
1 Lead/ and (expos* or poison* or toxic*).tw. (18601)
2 exp Environmental Exposure/ and lead.mp. (6816)
3 exp Pollutant/ and lead.mp. (13411)
4 (lead adj3 (expos* or poison* or toxic*)).tw. (17655)
5 exp Lead Poisoning/ (13334)
6 (plumbism or colica pictonum or saturnism or devon colic or painter's colic).tw. (594)
7 or/1-6 (44519)
8 exp Blood/ (1982129)
9 (blood adj3 (concentration* or level* or measurement* or amount* or quantit*)).tw. (210798)
10 8 or 9 (2128832)
11 7 and 10 (9022)
12 exp animal/ not human.sh. (4787592)
13 11 not 12 (7234)
14 (Algeria$ or Egypt$ or Liby$ or Morocc$ or Tunisia$ or Western Sahara$ or Angola$ or Benin$ or Botswana$ or Burkina Faso or Burundi$ or Cameroon or Cape Verde or

Central African Republic or Chad$ or Comoros or Congo or Djibouti or Eritrea$ or Ethiopia$ or Gabon$ or Gambia$ or Ghana$ or Guinea or Keny$ or Lesotho or Liberia$ or Madagasca$ or Malawi$ or Mali or Mauritania or Mauritius or Mayotte or Mozambiq$ or Namibia$ or Niger or Nigeria$ or Reunion or Rwand$ or Saint Helena or Senegal$ or Seychelles or Sierra Leone or Somalia$ or Somali or South Africa$ or Sudan$ or Swaziland or Tanzania$ or Togo or Ugand$ or Zambia$ or Zimbabw$ or China or Chinese or Hong Kong or Macao or Mongolia$ or Taiwan$ or Tibet$ or Belarus or Moldov$ or Russia$ or Ukrain$ or Afghanistan or Afghani or Armenia$ or Azerbaijan$ or Bahrain$ or Cyprus or Cypriot or Georgia$ or Iran$ or Iraq$ or Jordan$ or Kazakhstan$ or Kuwait$ or Kyrgyzstan or Leban$ or Oman or Pakistan$ or Palestin$ or Qatar or Saudi Arabia$ or Syria$ or Tajikistan or Turkmenistan or United Arab Emirates or Uzbekistan or Yemen or Bangladesh$ or Bhutan$ or British Indian Ocean Territory or Brunei Darussalam or Cambodia$ or India$ or Indonesia$ or Lao or People's Democratic Republic or Malaysia$ or Maldives or Myanmar or Nepal$ or Philippin$ or Singapore$ or Sri Lanka$ or Thai$ or Timor Leste or Vietnam$ or Albania$ or Andorra or Bosnia$ or Herzegovina$ or Bulgaria$ or Croatia$ or Faroe Islands or Greenland or Liechtenstein or Lithuani$ or Macedonia or Malta or Maltese or Romania$ or Serbia$ or Montenegr$ or Svalbard or Argentina$ or Belize or Bolivia$ or Brazil$ or Colombia$ or Costa Rica$ or Cuba$ or Ecuador$ or El Salvador$ or French Guiana$ or Guatemala$ or Guyana or Haiti$ or Honduras or Honduran or Jamaica$ or Nicaragua$ or Panama$ or Paraguay$ or Peru$ or Puerto Ric$ or Suriname or Uruguay$ or Venezuela$ or developing countr$).ti,sh. (1105927)
15 13 not 14 (6421)
16 limit 15 to yr="2004 -Current" (1754)

CINAHL

Database: EBSCO **CINAHL**: 28 May 13

MM "Lead" AND TX (expos* or poison* or toxic*)	727
MH "Environmental Exposure+" AND TX lead	3086
MH "Environmental Pollutants+" AND TX Lead	749
TX (expos* or poison* or toxic*) N3 lead	4914
MM "Lead Poisoning"	1025
TX plumbism OR TX colica pictonum OR TX saturnism OR TX devon colic OR TX painter's colic 37	
S1 OR S2 OR S3 OR S4 OR S5 OR S6	7001
MH "Blood+"	27310
TX (concentration* or level* or measurement* or amount* or quatit*) N3 Blood	39537
S8 OR S9	65773
S7 AND S10	1924
MH "Animals+" NOT MH Humans	50472
S11 NOT S12	1877

TI (Algeria$ or Egypt$ or Liby$ or Morocc$ or Tunisia$ or Western Sahara$ or Angola$ or Benin$ or Botswana$ or Burkina Faso or Burundi$ or Cameroon or Cape Verde or Central

African Republic or Chad$ or Comoros or Congo or Djibouti or Eritrea$ or Ethiopia$ or Gabon$ or Gambia$ or Ghana$ or Guinea or Keny$ or Lesotho or Liberia$ or Madagasca$ or Malawi$ or Mali or Mauritania or Mauritius or Mayotte or Mozambiq$ or Namibia$ or Niger or Nigeria$ or Reunion or Rwand$ or Saint Helena or Senegal$ or Seychelles or Sierra Leone or Somalia$ or Somali or South Africa$ or Sudan$ or Swaziland or Tanzania$ or Togo or Ugand$ or Zambia$ or Zimbabw$ or China or Chinese or Hong Kong or Macao or Mongolia$ or Taiwan$ or Tibet$ or Belarus or Moldov$ or Russia$ or Ukrain$ or Afghanistan or Afghani or Armenia$ or Azerbaijan$ or Bahrain$ or Cyprus or Cypriot or Georgia$ or Iran$ or Iraq$ or Jordan$ or Kazakhstan$ or Kuwait$ or Kyrgyzstan or Leban$ or Oman or Pakistan$ or Palestin$ or Qatar or Saudi Arabia$ or Syria$ or Tajikistan or Turkmenistan or United Arab Emirates or Uzbekistan or Yemen or Bangladesh$ or Bhutan$ or British Indian Ocean Territory or Brunei Darussalam or Cambodia$ or India$ or Indonesia$ or Lao or People's Democratic Republic or Malaysia$ or Maldives or Myanmar or Nepal$ or Philippin$ or Singapore$ or Sri Lanka$ or Thai$ or Timor Leste or Vietnam$ or Albania$ or Andorra or Bosnia$ or Herzegovina$ or Bulgaria$ or Croatia$ or Faroe Islands or Greenland or Liechtenstein or Lithuani$ or Macedonia or Malta or Maltese or Romania$ or Serbia$ or Montenegr$ or Svalbard or Argentina$ or Belize or Bolivia$ or Brazil$ or Colombia$ or Costa Rica$ or Cuba$ or Ecuador$ or El Salvador$ or French Guiana$ or Guatemala$ or Guyana or Haiti$ or Honduras or Honduran or Jamaica$ or Nicaragua$ or Panama$ or Paraguay$ or Peru$ or Puerto Ric$ or Suriname or Uruguay$ or Venezuela$ or developing countr$) 66044

S13 NOT S14	1809
S15 AND DT 2004 – 2013	1362

OPENGREY

Searched for: lead AND (exposure OR expose OR poison OR poisoning OR toxic OR remediation)
Manual screen as no export feature and no results >2004

LILACS

Searched for: lead AND (exposure OR toxic OR poison) AND blood then manually selected >2004
Results = 111

Science Citation Index & Conference Proceedings

8 **875** #6 NOT #7
Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC
Timespan=2004-2013

7 **876,535** TS=(rat OR rats OR mice OR mouse)
Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC

Timespan=2004-2013

6 **1,054** #5 AND #4
Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC
Timespan=2004-2013

5 **60,109** TS=((blood) NEAR/3 (concentration* or level* or measurement* or amount* or quantit*))
Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC
Timespan=2004-2013

4 **5,219** #3 OR #2 OR #1
Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC
Timespan=2004-2013

3 **183** TS=((lead) NEAR/1 (environmental) NEAR/2 (exposure))
Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC
Timespan=2004-2013

2 **44** TS=(plumbism or colica pictonum or saturnism or devon colic or painter's colic)
Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC
Timespan=2004-2013

1 **5,179** TS=((lead) NEAR/1 (expos* OR poison* OR toxic))
Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC
Timespan=2004-2013

Scopus

((((ABS("Lead expos*" OR "lead poison*" OR "lead toxic*") AND PUBYEAR > 2003) OR (ABS("Environmental Exposure" W/3 lead) AND PUBYEAR > 2003) OR (ABS("environmental pollutant*" W/3 lead) AND PUBYEAR > 2003) OR (ABS(plumbism OR colica pictonum OR saturnism OR devon colic OR painter's colic) AND PUBYEAR > 2003))) AND (((TITLE-ABS-KEY(blood W/3 concentration* OR level* OR measurement* OR amount* OR quantit*) AND PUBYEAR > 2003) OR (TITLE-ABS-KEY(blood) AND PUBYEAR > 2003)))) AND (EXCLUDE(EXACTKEYWORD, "Nonhuman") OR EXCLUDE(EXACTKEYWORD, "Animals") OR EXCLUDE(EXACTKEYWORD, "Rat") OR EXCLUDE(EXACTKEYWORD, "Animal tissue") OR EXCLUDE(EXACTKEYWORD, "Rats")) AND (EXCLUDE(AFFILCOUNTRY, "India") OR EXCLUDE(AFFILCOUNTRY, "China") OR EXCLUDE(AFFILCOUNTRY, "Brazil") OR EXCLUDE(AFFILCOUNTRY, "Taiwan") OR EXCLUDE(AFFILCOUNTRY, "Iran") OR EXCLUDE(AFFILCOUNTRY, "South Korea") OR EXCLUDE(AFFILCOUNTRY, "Egypt") OR EXCLUDE(AFFILCOUNTRY, "Thailand") OR EXCLUDE(AFFILCOUNTRY, "Nigeria") OR EXCLUDE(AFFILCOUNTRY, "South Africa") OR EXCLUDE(AFFILCOUNTRY, "Pakistan") OR EXCLUDE(AFFILCOUNTRY, "Saudi Arabia") OR EXCLUDE(AFFILCOUNTRY, "Slovakia") OR EXCLUDE(AFFILCOUNTRY, "Bangladesh") OR EXCLUDE(AFFILCOUNTRY, "Peru") OR EXCLUDE(AFFILCOUNTRY, "Croatia") OR

EXCLUDE(AFFILCOUNTRY, "Iraq")) AND (EXCLUDE(SUBJAREA, "VETE") OR EXCLUDE(SUBJAREA, "BUSI") OR EXCLUDE(SUBJAREA, "MATE") OR EXCLUDE(SUBJAREA, "ARTS") OR EXCLUDE(SUBJAREA, "COMP") OR EXCLUDE(SUBJAREA, "ECON") OR EXCLUDE(SUBJAREA, "MATH") OR EXCLUDE(SUBJAREA, "PHYS") OR EXCLUDE(SUBJAREA, "Undefined"))

TOXLINE

lead AND (exposure OR poison OR toxic) AND (blood) AND (health) AND (association OR cause OR predictor OR relationship)
In all fields, 2004-2013, with 'not pubmed records' selected

WEBSITES

General

WHOLIS (http://dosei.who.int/uhtbin/cgisirsi/Thu+Jul++5+16:26:22+MEST+2012/0/49)

Search in all libraries:
subject "lead blood" OR subject "lead adverse associations" OR subject "lead toxicity" OR subject "lead poisoning" OR words or phrase "lead poisoning" OR words or phrase "lead exposure" OR words or phrase "lead AND blood"
Resulted in 54 titles saved as word document

OECD iLibrary (http://www.oecd-ilibrary.org/)

lead' AND Full Text containing 'blood' AND All Fields containing 'expos* OR poison* OR contamin* OR pollut*' Including Multilingual Summaries Published Between 1900 and 2013 = 7 hits
lead exposure in ALL fields = 11 hits
Lead poisoning = 6 hits
Combined together = 20 hits saved as word document

Australia

Australian Office of Health Protection (OHP)
(**http://www.health.gov.au/internet/main/publishing.nsf/Content/ohp-about.htm**)
Browsed publications and also 'research reports' within the 'environmental health' section in Publications, statistics and research section (1 relevant paper)
Also keyword searched the whole site for plumbism (0 hits) colica pictonum (0 hits), "lead poisoning" (16 hits – only one new paper relevant) and "lead exposure" (18 hits only one new paper relevant). Total hits saved = 3.

Europe

The European Environment Agency (EEA) (http://www.eea.europa.eu/)

Within publications, and with categories 'environmental health' and 'chemicals' sections – searched for the keyword 'lead' 2 hits. Neither appeared to be a research study. See below. General browsing of the website also did not identify research articles.

European Centre for Disease Prevention and Control (http://www.ecdc.europa.eu/en/Pages/home.aspx)
Searched whole site for Blood AND lead AND any of the words (expos, poison) 186 hits, 0 relevant.
Checked health topics by list – none were relevant.
8 hits

Health Protection Agency (http://www.hpa.org.uk/)

Phrase searches for 'all words', restricted to publications (exclude press releases and webpages): Lead poisoning – 5 hits (see below)
Browsed publications Within Chemical Research Reports (4 hits)
Also downloaded excel sheet of chemical incident reports – and keyword searched over 700 records for 'lead'. Of those 17 appeared to be relevant to topic
26 hits total – see word doc 'european websites'

NHS Evidence (www.evidence.nhs.uk/ý)

Searched for ("Lead Poisoning" OR "lead exposure") AND blood AND (health effect OR health outcome OR adverse OR reduc* OR prevent*)
With following types of information: Evidence Summaries(27), Grey Literature(5) , Primary Research(5) , Systematic Reviews(4)
Total 40 hits (see word doc 'European websites'

North America

Health Canada

11 hits. In addition to browsing (0 relevant found), ran two separate searches as 'exact phrases'
"Lead poisoning" 5 hits
"Lead exposure" 6 hits
Total = 11 hits

US Centers for Disease Control

Within topic – environmental health, browsed ADSDR publication pages – none relevant.
Also checked publications for Childhood Lead Poisoning Publications. 57 records on topic were saved into word document 'north america'

US Environmental Protection Agency (http://www.epa.gov/)

Browsed EPA Home >Research & Development>Exposure Research>Products>Publications 31 records not relevant. Searched: intitle:lead poisoning AND intitle:research OR study OR evidence within all areas of the EPA. 429 records. Scanned these, appear relevant.

Appendix 3. AMSTAR Quality Rating Criteria for Systematic Reviews.

(B Shea et al. 2007)

Assessment Criteria	Yes	No	Unclear	N/A
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□	□	□	□
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□	□	□	□
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□	□	□	□
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□	□	□	□
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□	□	□	□
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□	□	□	□
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□	□	□	□
8. Was the scientific quality of the included studies used appropriately in formulating	□	□	□	□

conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I2). If heterogeneity exists a random associations model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ □ □ □
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ □ □ □
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ □ □ □

Appendix 4. NHMRC Assessment of individual study quality: Aetiology studies.

(NHMRC 1999)

Assessment	Risk of Bias Rating	Explanation for Rating
1. Study participant inclusion and exclusion criteria are well defined in terms of time, place, and personal characteristics? (Selection bias)	High ☐ Low ☐ Unclear ☐	
2. A low percentage of individuals or clusters refused to participate? (Selection bias)	High ☐ Low ☐ Unclear ☐	
3. Exposure or outcomes are measured in a standard, valid and reliable way? (Measurement bias)	High ☐ Low ☐ Unclear ☐	
4. Risk factors and outcomes are measured independently (blind) of each other? (Measurement bias)	High ☐ Low ☐ Unclear ☐	
5. All important risk factors are included in the analysis? (Bias due to confounding)	High ☐ Low ☐ Unclear ☐	
6. A high percentage of participants recruited into the study are included in the analysis? (Bias due to missing data)	High ☐ Low ☐ Unclear ☐	
7. Other risk of study bias (explain)?	High ☐ Low ☐ Unclear ☐	

Appendix 5. List of Included Studies.

1. Afeiche, M., K. E. Peterson, B. N. Sanchez, L. Schnaas, D. Cantonwine, A. S. Ettinger, M. Solano-Gonzalez, M. Hernandez-Avila, H. Hu and M. M. Tellez-Rojo (2012). "Windows of lead exposure sensitivity, attained height, and body mass index at 48 months." Journal of Pediatrics 160(6): 1044-1049.
2. Arora, M., J. Weuve, M. G. Weisskopf, D. Sparrow, H. Nie, R. I. Garcia and H. Hu (2009). "Cumulative lead exposure and tooth loss in men: The normative aging study." Environmental Health Perspectives 117(10): 1531-1534.
3. Bhattacharya, A., R. Shukla, K. N. Dietrich and R. L. Bornschein (2006). "Effect of early lead exposure on the maturation of children's postural balance: A longitudinal study." Neurotoxicology and Teratology 28(3): 376-385.
4. Bouchard, M. F., D. C. Bellinger, J. Weuve, J. Matthews-Bellinger, S. E. Gilman, R. O. Wright, J. Schwartz and M. G. Weisskopf (2009). "Blood lead levels and major depressive disorder, panic disorder, and generalized anxiety disorder in US young adults." Archives of General Psychiatry 66(12): 1313-1319.
5. Braun, J. M., T. E. Froehlich, J. L. Daniels, K. N. Dietrich, R. Hornung, P. Auinger and B. P. Lanphear (2008). "Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001-2004." Environmental Health Perspectives 116(7): 956-962.
6. Braun, J. M., R. S. Kahn, T. Froehlich, P. Auinger and B. P. Lanphear (2006). "Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children." Environmental Health Perspectives 114(12): 1904-1909.
7. Budtz, J., D. Bellinger, B. Lanphear, P. Grandjean, B. P. Lanphear, R. Hornung, J. Khoury, K. Yolton, P. Baghurst, D. C. Bellinger, R. L. Canfield, K. N. Dietrich, R. Bornschein, T. Greene, S. J. Rothenberg, H. L. Needleman, L. Schnaas, G. Wasserman, J. Graziano and R. Roberts (2013). "An international pooled analysis for obtaining a benchmark dose for environmental lead exposure in children." Risk Analysis 33(3): 450-461.
8. Campbell, J. R. and P. Auinger (2007). "The association between blood lead levels and osteoporosis among adults - Results from the third National Health and Nutrition Examination Survey (NHANES III)." Environmental Health Perspectives 115(7): 1018-1022.
9. Canfield, R. L., M. H. Gendle and D. A. Cory-Slechta (2004). "Impaired neuropsychological functioning in lead-exposed children." Developmental Neuropsychology 26(1): 513-540.
10. Cantonwine, D., H. Hu, B. N. Sanchez, H. Lamadrid-Figueroa, D. Smith, A. S. Ettinger, A. Mercado-Garcia, M. Hernandez-Avila, R. O. Wright and M. M. Tellez-Rojo (2010). "Critical windows of fetal lead exposure: Adverse impacts on length of gestation and risk of premature delivery." Journal of Occupational and Environmental Medicine 52(11): 1106-1111.
11. Cave, M., S. Appana, M. Patel, K. Falkner, C. McClain and G. Brock (2010). "Polychlorinated biphenyls, lead, and mercury are associated with liver disease in american adults: NHANES 2003--2004." Environmental Health Perspectives 118(12): 1735-1742.
12. Chandramouli, K., C. D. Steer, M. Ellis and A. M. Emond (2009). "Associations of early childhood lead exposure on academic performance and behaviour of school age children." Archives of Disease in Childhood 94(11): 844-848.
13. Chiodo, L. M., C. Covington, R. J. Sokol, J. H. Hannigan, J. Jannise, J. Ager, M. Greenwald and V. Delaney-Black (2007). "Blood lead levels and specific attention associations in young children." Neurotoxicology and Teratology 29(5): 538-546.
14. Chiodo, L. M., S. W. Jacobson and J. L. Jacobson (2004). "Neurodevelopmental associations of postnatal lead exposure at very low levels." Neurotoxicology and Teratology 26(3): 359-371.
15. Choi, Y. H., H. Hu, B. Mukherjee, J. Miller and S. K. Park (2012). "Environmental cadmium and lead exposures and hearing loss in U.S. adults: The National Health and Nutrition Examination Survey, 1999 to 2004." Environmental Health Perspectives 120(11): 1544-1550.
16. Claus, H. B., L. Schnaas, A. S. Ettinger, J. Schwartz, H. Lamadrid-Figueroa, M. Hernandez-Avila, C. Amarasiriwardena, H. Hu, D. C. Bellinger, R. O. Wright, M. M. Tellez-Rojo, B. Claus Henn, L. Schnaas, A.

S. Ettinger, J. Schwartz, H. Lamadrid-Figueroa, M. Hernandez-Avila, C. Amarasiriwardena, H. Hu, D. C. Bellinger, R. O. Wright and M. M. Tellez-Rojo (2012). "Associations of early childhood manganese and lead coexposure with neurodevelopment." Environmental Health Perspectives 120(1): 126-131.
17. Fang, F., L. C. Kwee, K. D. Allen, D. M. Umbach, W. Ye, M. Watson, J. Keller, E. Z. Oddone, D. P. Sandler, S. Schmidt and F. Kamel (2010). "Association between blood lead and the risk of amyotrophic lateral sclerosis." American Journal of Epidemiology 171(10): 1126-1133.
18. Fraser, S., G. Muckle and C. Despres (2006). "The relationship between lead exposure, motor function and behaviour in Inuit preschool children." Neurotoxicology and Teratology 28(1): 18-27.
19. Froehlich, T. E., B. P. Lanphear, P. Auinger, R. Hornung, J. N. Epstein, J. Braun and R. S. Kahn (2009). "Association of tobacco and lead exposures with attention-deficit/ hyperactivity disorder." Pediatrics 124(6): e1054-e1063.
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Appendix 6. List of Excluded Studies and Reason for Exclusion.

Not an exposure study **e.g. concept or discussion paper, toxicokinetic in-vitro studies, biomarker methodology**
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High-risk population

e.g. occupational exposure, study subjects with blood lead >10 µg/dL

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Appendix 7. NTP Evidence Tables.

Note for NHMRC: Appendix 6 (NTP Evidence Tables) is attached as a separate document as it is only available in PDF form+

Appendix 8. National Toxicology Program Conclusions and References

1. NTP Conclusions on neurological associations of low level lead

Health Effect		Population or Exposure Window	NTP Conclusion	Blood Pb Evidence	Bone Pb Evidence
Cognitive Function	Academic achievement	Prenatal	*Inadequate*	No studies located	Not studied
		Children	*Sufficient*	Yes, <5 µg/dL	Yes, tooth dentin Pb
	IQ	Prenatal	*Limited*	Yes, <10 µg/dL	Not studied
		Children	*Sufficient*	Yes, <5 µg/dL	Yes, tibia and tooth dentin Pb
	Other general and specific measures	Prenatal	*Limited*	Yes, <5 µg/dL	Not studied
		Children	*Sufficient*	Yes, <5 µg/dL	Yes, tibia and tooth dentin Pb
		Older adults	*Limited*	Yes, <10 µg/dL	Yes, tibia and patella Pb
Behavior	Attention-related behaviors	Prenatal	*Limited*	Yes, <10 µg/dL	Not studied
		Children	*Sufficient*	Yes, <5 µg/dL	Yes, tibia and tooth dentin Pb
		Adults	*Inadequate*	No studies located	Not studied
	Behavioral problems	Prenatal	*Limited*	Yes, <10 µg/dL	Not studied
		Children	*Sufficient*	Yes, <5 µg/dL	Yes, tooth dentin Pb, bone, hair
		Adults	*Inadequate*	No studies located	Not studied
Psychological Effects	Depression, anxiety, other	Prenatal	*Inadequate*	No studies located	Not studied
		Children	*Inadequate*	Unclear, some data >10 µg/dL	Not studied
		Adults	*Limited*	Yes, <10 µg/dL	Tibia and patella Pb
Neuro-degeneration	ALS	Adults	*Limited*	Yes, <10 µg/dL	Yes, tibia and patella
	Alzheimer's disease	Adults	*Inadequate*	No studies <10 µg/dL located	Not studied
	Essential tremor	Adults	*Sufficient*	Yes, <10 µg/dL	Not studied
			Limited	Yes, <5 µg/dL	Not studied
	Parkinson's disease	Adults	*Inadequate*	No studies <10 µg/dL located	Yes, tibia and PBPK (cumulative)
Sensory Function	Auditory	Prenatal	*Limited*	Yes, <10 µg/dL	Not studied
		Children	*Sufficient*	Yes, <10 µg/dL	Not studied
		Adults	*Limited*	Yes, <10 µg/dL	Yes, tibia and patella
	Visual	Prenatal	*Inadequate*	Yes, <10 µg/dL	Not studied
		Children	*Inadequate*	Yes, <10 µg/dL	Not studied
		Adults	*Inadequate*	No studies <10 µg/dL located	Not studied

Abbreviation: ALS, amyotrophic lateral sclerosis; PBPK, physiologically based pharmacokinetic.

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2. NTP Conclusions on immunological associations of low level lead

Health Effect	Population or Exposure Window	NTP Conclusion	Blood Pb Evidence	Bone Pb Evidence
Increased serum immunoglobulin E (IgE)	Prenatal	*Inadequate*	Unclear	Hair Pb data
	Children	*Limited*	Yes, <10 µg/dL	No data
	Adults	*Inadequate*	Unclear	No data
Increased hypersensitivity and allergy (e.g., positive skin prick test)	Prenatal	*Limited*	Maternal and umbilical cord <10 µg/dL	No data
	Children	*Limited*	Yes, <10 µg/dL	No data
	Adults	*Inadequate*	Unclear	No data
Asthma, eczema, etc.	Prenatal	*Inadequate*	Unclear	No data
	Children	*Inadequate*	Unclear	No data
	Adults	*Inadequate*	Unclear	No data
Altered serum IgG, IgM	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	Unclear	No data
	Adults	*Inadequate*	Unclear	No data
Altered antibody response	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	No data	No data
	Adults	*Inadequate*	No data	No data
Immunophenotyping (e.g., T-cells, B-cells)	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	Unclear	No data
	Adults	*Inadequate*	Unclear; >15 µg/dL data suggest changes in T-cells or T-cell subpopulations	No data
Monocyte/macrophage function	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	Unclear (one study)	No data
	Adults	*Inadequate*	No data	No data
Neutrophil function	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	No data	No data
	Adults	*Inadequate*	Unclear; >30 µg/dL data suggest changes in chemotaxis and lytic activity	No data
Delayed-type hypersensitivity (DTH) response	Prenatal	*Inadequate*	No data	No data
	Children	*Inadequate*	No data	No data
	Adults	*Inadequate*	No data	No data

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3. NTP Conclusions on cardiovascular associations of low level lead

Health Effect	Population	Conclusion	Blood Pb Evidence	Bone Pb Evidence
Blood pressure and hypertension	Adults	*Sufficient*	Yes, <10 µg/dL	Yes
	Children	*Inadequate*	Unclear	Yes (one study)
	Pregnant women	*Sufficient*	Yes, <10 µg/dL	Not studied
	Menopausal women	*Inadequate*	Unclear	Not studied
Heart rate variability	Adults	*Inadequate*	Unclear	Yes (one study)
Electrocardiogram abnormalities	Men	*Limited*	No	Yes (one study)
	Children	*Limited*	Yes, <5 µg/dL (one study)	Not studied
Clinical cardiovascular disease (general)	Adults	*Limited*	Yes, <5 µg/dL	Yes (one study)
Clinical cardiovascular disease (specific)	Adults	*Inadequate*	Unclear	Yes (one study)
Cardiovascular mortality	Adults	*Limited*	Yes, <10 µg/dL	Yes (one study)

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4. NTP Conclusions on renal associations of low level lead

Health Effect	Population	NTP Conclusions	Blood Pb Evidence	Bone Pb Evidence
Increased chronic kidney disease (CKD) and decreased glomerular filtration rate (GFR)	Adults	*Sufficient*	Yes, <5 µg/dL	Not studied
	Children ≥12 years old	*Limited*	Yes, <5 µg/dL	Not studied
	Children <12 years old	*Inadequate*	Unclear	Not studied

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5. NTP Conclusions on reproductive and developmental associations of low level lead

Health Effect	Population or Exposure Window	NTP Conclusion	Blood Pb Evidence	Bone Pb Evidence
Delayed puberty	Prenatal	*Inadequate*	No data	No data
	Children	*Sufficient*	Yes, <10 µg/dL	No data
		Limited	Yes, <5 µg/dL	
Postnatal growth	Prenatal	*Limited*	Yes, <10 µg/dL	One study
	Children	*Sufficient*	Yes, <10 µg/dL	One study available, no evidence of an association
Sperm parameters	Children	*Inadequate*	No data	No data
	Men	*Sufficient*	Yes, ≥15 µg/dL	No data
Fertility / delayed conception time	Men: time to conception	*Sufficient*	Yes, ≥20 µg/dL	No data
	Men: fertility	*Limited*	Yes, ≥10 µg/dL (one study)	No data
	Women	*Inadequate*	Unclear	No data
Spontaneous abortion	Men	*Limited*	Yes, >31 µg/dL	No data
	Women	*Limited*	Yes, <10 µg/dL	No data
Stillbirth	Adults	*Inadequate*	Unclear	No data
Reduced fetal growth and lower birth weight	Men	*Inadequate*	Unclear	No data
	Women	*Sufficient*	Yes, <5 µg/dL	Yes, tibia
Preterm birth and gestational age	Men	*Inadequate*	Unclear	No data
	Women	*Limited*	Yes, <10 µg/dL	No data
Endocrine effects	Adults	*Inadequate*	Unclear	One study
Birth defects	Adults	*Inadequate*	Unclear	No data

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Appendix 9. Environmental Protection Agency, Integrated Science Assessment for Lead.

Aspects used to aid in judging causality

Consistency of the observed association	An inference of causality is strengthened when a pattern of elevated risks is observed across several independent studies. The reproducibility of findings constitutes one of the strongest arguments for causality. If there are discordant results among investigations, possible reasons such as differences in exposure, confounding factors, and the power of the study are considered.
Coherence	An inference of causality from one line of evidence (e.g., epidemiologic, clinical, or animal studies) may be strengthened by other lines of evidence that support a cause-and-effect interpretation of the association. Evidence on ecological or welfare associations may be drawn from a variety of experimental approaches (e.g., greenhouse, laboratory, and field) and sub-disciplines of ecology (e.g., community ecology, biogeochemistry, and paleontological/historical reconstructions). The coherence of evidence from various fields greatly adds to the strength of an inference of causality. In addition, there may be coherence in demonstrating associations across multiple study designs or related health endpoints within one scientific line of evidence.
Biological plausibility	An inference of causality tends to be strengthened by consistency with data from experimental studies or other sources demonstrating plausible biological mechanisms. A proposed mechanistic linking between an effect and exposure to the agent is an important source of support for causality, especially when data establishing the existence and functioning of those mechanistic links are available.
Biological gradient (exposure-response relationship)	A well-characterized exposure-response relationship (e.g., increasing associations associated with greater exposure) strongly suggests cause and effect, especially when such relationships are also observed for duration of exposure (e.g., increasing associations observed following longer exposure times).
Strength of the observed association	The finding of large, precise risks increases confidence that the association is not likely due to chance, bias, or other factors. However, it is noted that a small magnitude in an effect estimate may represent a substantial effect in a population.
Experimental evidence	Strong evidence for causality can be provided through "natural experiments" when a change in exposure is found to result in a change in occurrence or frequency of health or welfare associations.
Temporal relationship of the observed association	Evidence of a temporal sequence between the introduction of an agent, and appearance of the effect, constitutes another argument in favor of causality.
Specificity of the observed association	Evidence linking a specific outcome to an exposure can provide a strong argument for causation. However, it must be recognized that rarely, if ever, does exposure to a pollutant invariably predict the occurrence of an outcome, and that a given outcome may have multiple causes.
Analogy	Structure activity relationships and information on the agent's structural

	analogs can provide insight into whether an association is causal. Similarly, information on mode of action for a chemical, as one of many structural analogs, can inform decisions regarding likely causality.

Appendix 10. Evidence tables from studies recently published and not included in existing systematic reviews

Study Citation and Quality Appraisal	Systematic Review Scope	Review Characteristics
Short citation: Kennedy 2012 *AMSTAR Appraisal of systematic review quality (✓ indicates this was done):* ✓Was an 'a priori' design provided? □ Was there duplicate study selection and data extraction? □ Was a comprehensive literature search performed? □ Was the status of publication (i.e. grey literature) used as an inclusion criterion? □ Was a list of studies (included and excluded) provided? ✓Were the characteristics of the included studies provided? □ Was the scientific quality of the included studies assessed and documented? □ Was the scientific quality of the included studies used appropriately in formulating conclusions? □ Were the methods used to combine the findings of studies appropriate? □ Was the likelihood of publication bias assessed? ✓Was the conflict of interest stated? AMSTAR Quality rating: LOW	Review Objective: To investigate whether maternal blood lead concentrations may be associated with the development of gestational hypertension or pre-eclampsia. Literature search: MEDLINE, Embase and Web of Science were searched from inception to August 2011 using the terms: blood lead levels, pregnancy, pregnancy induced hypertension, gestational hypertension and pre-eclampsia. Study inclusion: limited to human studies, no language restrictions or country, had to report the results of a laboratory assessment of blood lead concentrations in pregnancy and the association with hypertension or pre-eclampsia. Studies that only investigated lead concentrations in other body matrices (amniotic fluid, cord blood, bone) were excluded. Number of studies in review (total population n): 9 papers (n=3402) evaluated (a) BLL and gestational hypertension (n=4), (b) BLL and incidence of pre-eclampsia (n=4), and (c) (3) BLL and both conditions. Study publication period: 2000 - 2011 Study Design: Cohort (5), case-control(2), cross-sectional(2) Outcomes measure: Gestational hypertension was defined as systolic BP >140 mmHg and/or a diastolic BP >90 mmHg. Definition of preeclampsia not provided.	Geographic region included: US(3),Iran(2) Malta, France, Nigeria, India Population density: Assessment of study quality: no evaluation of individual study quality and potential risk of bias. Consideration of key confounders was not discussed. Analysis: authors provide a narrative description of studies and table with study characteristics. No pooled analysis provided. Interpretation of results based on counting the number of studies that found significant results, without consideration for study quality. Blood lead levels: were high in 3 (e.g. Nigeria range 8.6 to 51 µg/dL; India mean 18.4, U.S. range 04 to 30; US range 35 to 37. No description of occupational/environmental exposure of study populations.
Review Conclusion: Based on counting the number of studies that found a significant association between BLL and either gestational hypertension or pre-eclampsia, the authors state the results as: "Positive associations between lead and gestational hypertension or pre-eclampsia were found in six studies."		

Review Citation and Quality Appraisal	Systematic Review Scope	Review Characteristics
Short citation: Goodlad (2013) *AMSTAR Appraisal of systematic review quality (✓indicates this was done):* ✓Was an 'a priori' design provided? □ Was there duplicate study selection and data extraction? ✓ Was a comprehensive literature search performed? □ Was the status of publication (i.e. grey literature) used as an inclusion criterion? □ Was a list of studies (included and excluded) provided? ✓Were the characteristics of the included studies provided? □ Was the scientific quality of the included studies assessed and documented? □ Was the scientific quality of the included studies used appropriately in formulating conclusions? ✓ Were the methods used to combine the findings of studies appropriate? □ Was the likelihood of publication bias assessed? ✓Was the conflict of interest stated? AMSTAR Quality rating: LOW	Review Objective: to estimate the size of the associations between lead burden with inattention symptoms and lead burden and hyperactivity/impulsivity symptoms. Literature search: searches of PsycINFO and Medline, Study inclusion: English language only; reporting inattention or hyperactivity symptoms using rating scales or a continuous performance test, or studies that included a diagnosis of ADHD; published in a peer-reviewed source. Excluded studies of adults and animal studies. The types of study designs that were eligible for the review were not reported. Number of studies in review (total population n) 33 studies (N=10,232) total. 17 assessed both inattention and hyperactivity/impulsivity symptoms; 10 assessed inattention symptoms; and 6 measured hyperactivity/impulsivity alone. Study publication period: 1972 to 2010 Study Design: a description of eligible study designs was not provided Lead measurement: included blood, tooth, urine, hair, and bone measurements and combined these effects with no discussion of measurement validity/reliability. Outcomes measure: any measure reporting inattention or hyperactivity symptoms using rating scales or a continuous performance test, or studies that included a diagnosis of ADHD. Validity or reliability of instruments was not assessed. Where studies included multiple measures of inattention or hyperactivity/impulsivity, the effects pooled and an average effect size computed.	Geographic region included: North American (n=19), Europe (n=7), Australia and New Zealand (n=4), India (n=2), Korea (n=1). Populations: The average age 8.7 years (SD=3.3). Seven studies assessed preschool children, 18 studies assessed primary school children, one study examined adolescents Assessment of study quality: No assessment of individual study quality or risk of bias was presented. No description of eligible study designs was provided, or hierarchy of evidence for conclusions. Analysis: random effects meta-analysis; high heterogeneity across studies reported. Blood lead levels: ranged from .03 to 36 µg/dL across studies.
Review Conclusion: The association between inattention symptoms and lead exposure (n=27 studies) was reported as r=0.16, p< 0.001. The association between hyperactivity/impulsivity and lead exposure (n=23 studies) was reported as r=0.13, p< 0.001. There was significant heterogeneity among effects for both analyses. Also, there was overlap of studies in these two meta-analyses. Studies using hair lead measurement reported larger effects. When these were excluded from the meta-analyses the results were r=0.14, p<0.001 for inattention, and r=0.12, p< 0.001 for hyperactivity.		
Study Citation and Quality Appraisal	**Study Characteristics**	**Population Characteristics**

Short citation: Eum 2012 *NHMRC Appraisal of study quality:* *(✓indicates this was done):* ✓ Study participants well-defined in terms of time, place, and personal characteristics. ✓ Low % of individuals or clusters refused to participate ✓ Exposure or outcomes are measured in a standard, valid and reliable way. ✓ Risk factors and outcomes are measured independently (blind) of each other ✓ All important risk factors are included in the analysis ✓ High % of participants recruited in study are included in analysis Other risk of bias: potential selection bias in sample selected from earlier case-control study of hypertension and lead exposure. Study quality rating: HIGH (for analysis of full study sample)	Study Objective: the primary study objective was to explore the association between lead in bone and mental health among middle-age and elderly women Study type/design: analysis of data from the Nurses' Health Study Sampling method: a cohort of 121,700 registered nurses recruited in 1976 when they were between 30 and 55 years of age, and followed via biennial mailed questionnaires. This analysis uses a sub-sample of women with lead level measures from 2 previous studies: a 1990 to 1994 subset recruited for the lead and hypertension study, and those recruited from 2001 to 2004 for a lead and osteoporosis study. Sample size: 617 Low attrition. Lead measurement: K-shell X-ray fluorescence measurements of mid-tibial shaft and patella. Data collection period: 1990 to 1994 and 2001 to 2004 for bone lead measures. All biennial measures of psychological symptoms (pre and post periods of bone measurement) available (21 women with one, 91 with two, and 488 with three). Psychological symptoms ascertained by the Mental Health Index (MHI-5) and Crown-Crisp Index (CCI). Health outcome classification: Neurological effects Health outcome diagnostic test validity and reliability: validated measures.	Geographic region: Boston MA Population density: urban Ethnicity: not reported Socioeconomic status: not reported Population description: Mean ± SD (range) age of women was 60.9 ± 6.0 (46–74) years at time of lead measurement. The mean ± SD levels of tibia lead and patella lead were 10.3 ± 9.5 μg/g and 12.5 ± 11.2 μg/g, respectively. Potential confounders: analyses controlled for age at psychological symptom measurement, education (registered nurse, bachelor's degree, master's or doctorate degree), alcohol consumption, smoking, husband's education and employment status at time of symptom measurement.
Reported Health Effects/Outcomes: No consistent association between bone lead and depression and anxiety symptoms were found. Compared with the lowest tertile of tibia lead, women in the middle tertile scored 1.70 MHI-5 points worse (95% CI: −3.75, 0.34), and those in the highest tertile scored 1.1 points worse (95% CI: −3.1, 0.94). In a post-hoc analysis of a subset (N=142 premenopausal women and postmenopausal women consistently on HRT) of the study sample, compared with women in the lowest tertile of tibia lead, those in the highest scored 7.78 points worse [95% confidence interval (CI): −11.73, −3.83] on the MHI-5, *p* trend =0.0001)		

Study Citation and Quality Appraisal	Study Characteristics	Population Characteristics
Short citation: Zhang 2012 *NHMRC Appraisal of study quality:* *(✓indicates this was done):* ✓Study participants well-defined in terms of time, place, and personal characteristics. □ Low % of individuals or clusters refused to participate ✓ Exposure or outcomes are measured in a standard, valid and reliable way. ✓ Risk factors and outcomes are measured independently (blind) of each other ✓ All important risk factors are included in the analysis □ High % of participants recruited in study are included in analysis Study quality rating: MODERATE	Study Objective: to examine the relationship of prenatal lead exposure, assessed by both maternal bone and umbilical cord lead, with BP in 7- to 15-year-old children. Study type/design: A longitudinal birth cohort study in Mexico City that comprises the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project to investigate the long-term consequences of prenatal exposure on child development Sampling method: mother–child pairs from three of the four longitudinal birth cohort studies in Mexico City Sample size: original sample 1,272, follow-up sample 457 High attrition: approximately 40% of original sample were included in this analysis. Data collection period: Subjects were originally recruited between 1994 and 2003, follow-up between 2008 and 2010 when the children were 7–15 years of age. Lead measurement: 1-month postpartum maternal tibia and patella bone lead; umbilical cord blood lead; and concurrent blood lead levels. Health outcome classification: Cardiovascular Health outcome diagnostic test validity and reliability: validated measures.	Geographic region: Mexico City Population density: urban Ethnicity: Mexican Socioeconomic status: not reported Population description: mothers mean (± SD) age of 25.6 ± 5.4 years (range, 19–31 years) at the time of the index child's birth Lead level measurements: 1-month postpartum maternal tibia and patella bone lead had median [interquartile range (IQR)] values of 9.3 (3.3–16.1) and 11.6 (4.5–19.9) μg/g, respectively. Umbilical cord blood lead had a mean of 5.51 ± 3.45 μg/ dL. Concurrent blood lead level was 2.96 ± 1.72 μg/dL. Potential confounders: In linear regression analyses of non-lead covariates, children's age, height, and BMI were significantly associated with SBP and DPB in boy and girls.
Reported Health Effects/Outcomes: Maternal tibia lead was significantly associated with increases in systolic BP (SBP) and diastolic BP (DBP) in girls but not in boys (p-interaction with sex = 0.025 and 0.007 for SBP and DBP, respectively). Among girls, an interquartile range increase in tibia lead (13 μg/g) was associated with 2.11-mmHg [95%(CI): 0.69, 3.52] and 1.60-mmHg (95% CI: 0.28, 2.91) increases in SBP and DBP, respectively. Neither patella nor cord lead was associated with child BP.		

Study Citation and Quality Appraisal	Study Characteristics	Population Characteristics
Short citation: Cave 2010 Quality rating: Low (cross-sectional)	Study Objective: The primary objective was to explore the association between environmental pollutants and elevation of serum alanine aminotransferase (ALT) activity and suspected nonalcoholic fatty liver disease (NAFLD) in U.S. adults. Study type/design: Cross-sectional analyses of NHANES survey data (2003-04) Sampling Method: Adults age 18 or older participating in NHANES (2003-04) without viral hepatitis, hemochromatosis, or alcoholic liver disease. Sample size: 4,582 Lead measurement: Blood lead levels (µg/dL) Data collection period: 2003-2004 Health outcome classification: Elevated ALT and suspected NAFLD Health outcome diagnostic test validity and reliability: Valid lab analyses for ALT levels	Geographic region: US Population density: Not reported Ethnicity: Non-Hispanic White (72.3%), Non-Hispanic Black (10.8%), Hispanic (11.7%), Other (5.1%) Socioeconomic status: Not reported Population description: 52.2% female, mean age (SD) 47.2 (±21.2), age range 18-85 Potential confounders: Analyses adjusted for age, sex, race, PIR, HOMA-IR and BMI
Reported Health Effects/Outcomes		
An association was found between blood lead levels and unexplained elevation of ALT. ORs for elevated ALT across blood lead level quartiles were calculated and adjusted for age, sex, race, PIR, HOMA-IR and BMI. Results were significant (p trend = 0.014)		

Study Citation and Quality Appraisal	Study Characteristics	Population Characteristics
Short citation: Choi 2012 Quality rating: Low (cross-sectional)	Study Objective: The primary objective was to explore the association between blood lead levels and hearing loss. Study type/design: Cross-sectional analyses of NHANES survey data (1999-2004) auditory examination component participants. Sampling Method: Of the NHANES (1999-2004) auditory examination component participants, 5,742 were excluded for unilateral hearing loss, missing lead or cadmium measurements, and occupational, recreational or firearm noise exposure. Sample size: 3,622 Lead measurement: Blood lead levels (µg/dL) Data collection period: 1999-2004 Health outcome classification: Neurological (hearing loss)	Geographic region: US Population density: Not reported Ethnicity: Non-Hispanic White (72.5%), Non-Hispanic Black (10.5%), Mexican-American (6.6%), Other (10.4%) Socioeconomic status: Not reported Population description: 51.4% female, mean age = 42.06 years (SE ± .28 years), 11.9% with hearing loss Potential confounders: Analyses adjusted for age, sex, race, education, BMI, ototoxic medication, pack-years of smoking,

	Health outcome diagnostic test validity and reliability: Valid auditory examination	hypertension, diabetes, and recreational noise, and firearm noise exposure.
Reported Health Effects/Outcomes		
Associations of blood lead levels and hearing loss were significant before but not after adjusting for noise exposure across blood lead level quintiles (p trend = 0.041).		
Study Citation and Quality Appraisal	**Study Characteristics**	**Population Characteristics**
Short citation: Martin 2007 Quality rating: Low (cross-sectional)	Study Objective: The primary objective was to examine the relationship between lead exposure and dental caries in a population or normatively healthy children. Study type/design: Cross-sectional Sampling Method: Children (ages 8-12 years) participating in a clinical trial of dental materials Sample size: 507 Lead measurement: Blood lead levels (µg/dL) Data collection period: Not reported Health outcome classification: Dental Health outcome diagnostic test validity and reliability: Valid clinical examination	Geographic region: Lisbon, Portugal Population density: Urban Ethnicity: White (70.8%), Black (28.2%), Other (1.0%) Socioeconomic status: Not Reported Population description: Children attending 7 schools in Lisbon. Average age: 10.1 (0.9) years. 55% male Potential confounders: Analyses adjusted for age, sex, race, and neurobehavioral status (IQ, attention, memory, visuomotor)
Reported Health Effects/Outcomes		
A gender specific association (males only) between lead exposure and dental caries in primary teeth (p = 0.03) but for dental caries in permanent teeth.		
Study Citation and Quality Appraisal	**Study Characteristics**	**Population Characteristics**
Short citation: Golub 2010 Quality rating: Low (cross-sectional)	Study Objective: Evaluate the relationship between blood lead levels and depression Study type/design: Cross-sectional analyses Sampling Method: Adults 20 years or older participating in the NHANES survey (2005-06) with blood lead level measurements Sample size: 4,159 Lead measurement: Blood lead levels (µg/dL) Data collection period: 2005-2006 Health outcome classification: Neurological (depression) Health outcome diagnostic test validity and reliability: Patient Health Questionnaire (PHQ-9) valid for screen for depression in	Geographic region: US Population density: Not Reported Ethnicity: Non-Hispanic White (73.27%), Non-Hispanic Black (10.85%), Mexican-American (7.76%), Other Hispanic (3.24%), Other (4.88%) Socioeconomic status: Not Reported Population description: Average age 46.5 (0.73) years, 51.59% female, education level less than high school (16.98%), average PIR 3.13 (0.07) Potential confounders: Analyses adjusted for

	primary care settings	age, race, sex, education level, PIR
Reported Health Effects/Outcomes		
No clear association between blood lead levels and depression. Increase in ORs across blood lead levels non-significant.		
Study Citation and Quality Appraisal	**Study Characteristics**	**Population Characteristics**
Short citation: Hicken 2013 Quality rating: Low (cross-sectional)	Study Objective: Explore the association between blood lead levels and blood pressure for blacks and whites and the role that depression may play Study type/design: Cross-sectional Sampling Method: Black and white participants of NHANES (2005-08) age 20 years or more and excluding those with missing data and pregnant females. Sample size: 4,470 (1,218 Blacks, 3,252 Whites) Lead measurement: Blood lead levels (µg/dL) Data collection period: 2005-2008 Health outcome classification: Cardiovascular Health outcome diagnostic test validity and reliability: valid blood pressure measurements	Geographic region: US Population density: Not Reported Ethnicity: Black (27.24%), White (72.75%) Socioeconomic status: C Population description: Average age 47.1 (± 10.8) years, 51% female Potential confounders: Analyses adjusted for age, sex, education level, PIR, haematocrit, BMI, heavy alcohol use, smoking, diabetes, depressive symptoms
Reported Health Effects/Outcomes		
Blacks but not Whites show a positive association between blood lead levels and systolic blood pressure. This disparity between Blacks and Whites is found in high depressive groups but is not significant in low depressive groups.		
Study Citation and Quality Appraisal	**Study Characteristics**	**Population Characteristics**
Short citation: Mendola 2013 Quality rating: Low (cross-sectional)	Study Objective: Explore the association between blood lead levels and menopause Study type/design: Cross-sectional Sampling Method: Females ages 45-55 participating in 6 cycles of the NHANES survey (1999-2010) excluding those who report no menstrual period due to medical, surgical or other reasons. Sample size: 1,782 Lead measurement: Blood lead levels (µg/dL) Data collection period: 1999-2010 Health outcome classification: Reproductive	Geographic region: US Population density: Not Reported Ethnicity: Non-Hispanic White (73.3%), Non-Hispanic Black (9.6%), Mexican-American (6.2%), Other (10.9%) Socioeconomic status: Not Reported Population description: Average age 49.5 (0.1) years, blood lead levels 1.38 (0.03) µg/dL Potential confounders: Analyses adjusted for age, race/ethnicity, current hormone

	Health outcome diagnostic test validity and reliability: Self-report	replacement therapy, smoking, poverty, bone alkaline phosphatase, femoral neck bone density
Reported Health Effects/Outcomes		
Blood lead levels higher among menopausal women (geometric means: 1.71 (0.04) vs. 1.23 (0.02)). Increases in ORs were found across quartiles of blood lead levels with adjustments.		
Study Citation and Quality Appraisal	Study Characteristics	Population Characteristics
Short citation: Shargorodsky 2011 Quality rating: Low (cross-sectional)	Study Objective: Explore the association between heavy metal exposure and hearing loss among US adolescents. Study type/design: Cross-sectional Sampling Method: Participants of NHANES (2005-08) ages 12 – 19 excluding those with incomplete auditory examination and missing blood lead level measurements. Sample size: 2,535 Lead measurement: Blood lead levels (µg/dL) Data collection period: 2005-08 Health outcome classification: Neurological (hearing loss) Health outcome diagnostic test validity and reliability: Valid auditory examination	Geographic region: US Population density: Not Reported Ethnicity: Not Reported Socioeconomic status: Not Reported Population description: Not Reported Potential confounders: Analyses were stratified by age, sex, race, PIR, loud noise exposure, history of ear infections, smoking
Reported Health Effects/Outcomes		
A blood lead level greater than or equal to 2 µg/dL compared to blood levels less than 1 µg/dL was associated with increased odds of high-frequency hearing loss (OR, 2.22; 95% CI, 1,02-9.25). No significant associations were found across quartiles of blood lead levels and no significant interactions were found with sex, PIR, noise exposure, and smoking history.		
Study Citation and Quality Appraisal	Study Characteristics	Population Characteristics
Short citation: van Bemmel 2011 Quality rating: Low (cross-sectional)	Study Objective: Explore the effects of 5-aminolevulinic acid dehydrase (ALAD) G177C single nucleotide polymorphism (SNP) on the relationship between lead exposure and mortality Study type/design: Cross-sectional with follow-up Sampling Method: Genotyped participants of NHANES III (1991-1994) excluding those less than age 40 years at interview and those with missing data Sample size: 3,223	Geographic region: US Population density: Not Reported Ethnicity: Non-Hispanic White (81%), Non-Hispanic Black (8%), Mexican-American (4%), Other (7%) Socioeconomic status: Not Reported Population description: *Demographics for low lead (<5 µg/dL) vs. high lead (≥5 µg/dL)*

	Lead measurement: Blood lead levels (μg/dL) Data collection period: 1991-2000; Baseline: 1991-1994; Follow-up: until 12/31/2000. Health outcome classification: Mortality (All-cause, Cardiovascular, Cancer) Health outcome diagnostic test validity and reliability: Death Records	*groups:* (a) median age at baseline (57 vs. 61); (b) % male (41% vs. 68%); (c) average blood lead levels (2.6 μg/dL vs. 7.5 μg/dL); (d) mean follow-up time (7.8 vs. 7.5 years); (e) education level less than high school (22% vs. 39%); (f) income less than $20,000 (26% vs. 40%) Potential confounders: Analyses adjusted for age, education, sex, smoking status, race/ethnicity, ALAD. Analyses not adjusted for type of Cancer mortality
Reported Health Effects/Outcomes		
High blood lead levels (≥5 μg/dL) were associated with a suggestive increase risk of Cancer mortality (1.48 (0.92-2.38)) but not associated with risk of all-cause or cardiovascular mortality. No significant interactions between lead and gene were found.		
Study Citation and Quality Appraisal	Study Characteristics	Population Characteristics
Short citation: van Wijngaarden 2011 Quality rating: Low (cross-sectional)	Study Objective: Explore the relationship between blood lead levels and cognitive functioning in older US adults. Study type/design: Cross-sectional Sampling Method: Adults age 60 or older participating NHANES 1999-2008 excluding those with incomplete data Sample size: 9,576 Lead measurement: Blood lead levels (μg/dL) Data collection period: 1999-2008 for participants self-reporting confusion and memory. 1999-2002 for participant with Digit Symbol Substitution Test (DSST) scores Health outcome classification: Neurological (cognitive functioning) Health outcome diagnostic test validity and reliability: Self-reported memory problems and valid cognitive functioning test (DSST)	Geographic region: US Population density: Not Reported Ethnicity: Not Reported Socioeconomic status: Not Reported Population description: Average age was 72; average blood lead level was 2.46 μg/dL (range: 0.18-54.0); 12.43% reported memory problems; the average DSST score was 46.35 (range: 0-117) Potential confounders: Analyses were adjusted for age, sex, educational level, ethnicity, PIR, self-reported health status
Reported Health Effects/Outcomes		
Blood lead levels were not associated with either self-reported cognitive status or performance on the DSST. Non-significant ORs across quartiles of blood lead level measurements.		
Study Citation and Quality Appraisal	Study Characteristics	Population Characteristics

Short citation: Zhang 2013 Quality rating: Low (cross-sectional)	Study Objective: Asses the long term effects of lead exposure on academic achievement in mathematics, science and reading of elementary and junior high school children. Study type/design: Cross-sectional Sampling Method: Detroit public school children taking state achievement tests in grades 3, 5 or 8 across 3 years (2007-08, 2008-09, 2009-10) matched with lead surveillance data collected prior to age 6 Sample size: 21,281 Lead measurement: Blood lead levels (µg/dL) Data collection period: 2007-2010 with blood lead level measurements collected prior to age 6 Health outcome classification: Neurological (cognitive functioning: academic achievement) Health outcome diagnostic test validity and reliability: Valid achievement tests	Geographic region: Detroit, Michigan Population density: Urban Ethnicity: 90.6% Black Socioeconomic status: High poverty (79.6% free school lunch participants) Population description: Predominantly black, high poverty, urban elementary and junior high school children. 44.5% female The mean highest blood lead level prior to age 6 was 7.12 (7.26) µg/dL measured at a mean age of 3.10 (1.32) years. 77% of students' mothers did not receive education beyond high school Potential confounders: Analyses adjusted grade level, gender, race, language, maternal education, SES (school free lunch status)
Reported Health Effects/Outcomes		
High blood lead levels before age 6 were strongly associated with poor academic achievement in grades 3, 5, & 8. Students with blood lead levels greater than 10 µg/dL were more than twice as likely to score "not proficient" ($p < .05$) as students with blood levels $\leq$ 1 µg/dL (OR (95% CI): Mathematics 2.40 (2.07, 2.77); Science 2.26 (1.84, 2.78); Reading 2.69 (2.31, 3.12). F statistics from multivariate analyses were statistically significant ($p < .001$) for blood lead levels and mathematics, science and reading proficiency scores.		

Appendix 11. OVID Medline search strategy.

Database(s): **Ovid MEDLINE(R)** 1946 to May Week 2 2013

Search Strategy:

#	Searches	Results
1	(lead adj3 remediat*).tw.	71
2	exp Environmental Remediation/ and (Lead adj3 (strateg* or intervention* or policy or policies or scheme*)).tw.	10
3	(lead adj3 (expos* or poison* or toxic*) adj3 (reduc* or lower or limit or decreas* or lessen* or diminish or prevent* or treat* or therap*)).tw.	1280
4	Lead/ and ((reduc* or lower or limit or decreas* or lessen* or diminish* or prevent* or treat* or therap*) adj3 (expos* or poison* or toxic*)).tw.	1033
5	Lead/ and ((strateg* or intervention* or policy or policies or scheme*) adj3 (expos* or poison* or toxic*)).tw.	53
6	(lead adj3 (expos* or poison* or toxic*) adj3 (strateg* or intervention* or policy or policies or scheme*)).tw.	75
7	exp Environmental Exposure/ and (Lead adj3 (strateg* or intervention* or policy or policies or scheme*)).tw.	99
8	exp Lead Poisoning/dt, pc, th [Drug Therapy, Prevention & Control, Therapy]	2599
9	exp Environmental Pollutants/ and (Lead adj3 (strateg* or intervention* or policy or policies or scheme*)).tw.	62
10	exp Health Policy/ and lead/	39
11	or/1-10	3906
12	exp animals/ not humans.sh.	3847813
13	11 not 12	3241
14	(Algeria$ or Egypt$ or Liby$ or Morocc$ or Tunisia$ or Western Sahara$ or Angola$ or Benin$ or Botswana$ or Burkina Faso or Burundi$ or Cameroon or Cape Verde or Central African Republic or Chad$ or Comoros or Congo or Djibouti or Eritrea$ or Ethiopia$ or Gabon$ or Gambia$ or Ghana$ or Guinea or Keny$ or Lesotho or Liberia$ or Madagasca$ or Malawi$ or Mali or Mauritania or Mauritius or Mayotte or Mozambiq$ or Namibia$ or Niger or Nigeria$ or Reunion or Rwand$ or Saint Helena or Senegal$ or Seychelles or Sierra Leone or Somalia$ or Somali or South Africa$ or Sudan$ or Swaziland or Tanzania$ or Togo or Ugand$ or Zambia$ or Zimbabw$ or China or Chinese or Hong Kong or Macao or Mongolia$ or Taiwan$ or Tibet$ or Belarus or Moldov$ or Russia$ or Ukrain$ or Afghanistan or Afghani or Armenia$ or Azerbaijan$ or Bahrain$ or Cyprus or Cypriot or Georgia$ or Iran$ or Iraq$ or Jordan$ or Kazakhstan$ or Kuwait$ or Kyrgyzstan or Leban$ or Oman or Pakistan$ or Palestin$ or Qatar or Saudi Arabia$ or Syria$ or Tajikistan or Turkmenistan or United Arab Emirates or Uzbekistan or Yemen or Bangladesh$ or Bhutan$ or British Indian Ocean Territory or Brunei Darussalam or Cambodia$ or India$ or Indonesia$ or Lao or People's Democratic Republic or Malaysia$ or Maldives or Myanmar or Nepal$ or Philippin$ or Singapore$ or Sri Lanka$ or Thai$ or Timor Leste or Vietnam$ or Albania$ or Andorra or Bosnia$ or Herzegovina$ or Bulgaria$ or Croatia$ or Faroe Islands or Greenland or Liechtenstein or Lithuani$ or Macedonia or Malta or Maltese or Romania$ or Serbia$ or Montenegr$ or Svalbard or Argentina$ or Belize or Bolivia$ or Brazil$ or Colombia$ or Costa Rica$ or Cuba$ or Ecuador$ or El Salvador$ or French Guiana$ or Guatemala$ or Guyana or Haiti$ or Honduras or Honduran or Jamaica$ or Nicaragua$ or Panama$ or Paraguay$ or Peru$ or Puerto Ric$ or Suriname or Uruguay$ or Venezuela$ or developing countr$).ti,sh.	801455

15	13 not 14	3004
16	limit 15 to yr="2004 -Current"	754

Appendix 12. Excluded studies, with reasons.

Not an intervention study (n = 46)

Apostoli, P, Neri, G, Alessio, L, Carta, P, C., F, Alinovi, R, De Palma, G, Mutti, A, Murgia, N, Muzi, G, Abbritti, G, Soleo, L & Cassano, F 2005, 'Proceedings of the National Conference: Environmental and occupational exposure to inorganic lead: assessment of toxic effects of current doses and related preventive measures', *G Ital Med Lav Erg* vol. 27, no. 1, pp. 6-14.

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Appendix 13. Characteristics of included studies tables.

Berg, DR, Eckstein, ET, Steiner, MS, Gavard, JA & Gross, GA 2012, 'Childhood lead poisoning prevention through prenatal housing inspection and remediation in St. Louis, MO', American Journal of Obstetrics & Gynecology, vol. 206, no. 3, pp. 199-4.

Affiliation/source of funds	Affiliation: City of St. Louis, Source of funds: not reported
Study Design	Controlled Before and After Study
Location/Setting	St. Louis, Missouri, United States; community-based intervention
Population	Newborn children living in homes with identified screening hazards (outcomes collected in children but the intervention was delivered to mothers who were recruited during pregnancy); n = 180. The women were identified as being part of a "high risk population" by virtue of geography, race and income. Blood lead levels of women at time of recruitment was not reported.
Source of lead	Lead source confirmed (defined as deteriorated paint, or lead dust on floor, sills, soil and play areas)
Removal of lead source	All homes that underwent remediation passed inspection dust wipes (meaning lead should have been removed)
Intervention	Home remediation performed by a certified contractor, including paint stabilization, window replacement and cleaning as needed
Comparison	Matched controls with no home remediation (matched by census tract)
Length of follow up	Mean follow up was at 1.5 years of age (range 0.8 to 2.7 years)
Outcomes	Mean blood lead levels (μg/dL) and number of children with blood lead levels ≥ 5 μg/dL and ≥ 10 μg/dL
Comments	Some children had multiple blood lead levels measured. In this instance, the authors used the highest blood lead level recorded. Children in the intervention group were living in homes identified during screening as having lead hazards. Children in the control groups were not necessarily living in homes with lead hazards.
RISK OF BIAS	

Bias Domain	Judgement	Support for judgement
Do inclusion/exclusion criteria vary across comparison groups?	Unclear	Inclusion criterion for intervention participants was being identified in screening as having lead control hazards in their home. Control participants did not necessarily have lead hazards. Intervention and control participants were both excluded from the study if they had had previous lead control work in their homes.
Does the strategy for recruiting/allocating participants vary across groups?	Unclear	Intervention participants were recruited for a screening program from outpatient hospital that served people likely to be high risk for lead exposure. Control participants were selected from

		records in a database (matched on infant age and census tract). They were matched according to census tract and age of newborn. However by selecting people from a hospital they may have been more likely to include participants who were more likely to follow best practice in pregnancy/more likely to have been more active around lead prevention. However, I note that authors state there were no significant differences in terms of race, sex or age at time of testing.
Does the study account for important variations in the execution of the study from the proposed protocol?	Unclear	No protocol mentioned. Intervention subjects received at least one reminder call from study staff urging them to have their blood lead levels checked by their health practitioner (this was not provided to control subjects) and may have acted as a co-intervention, favouring a treatment effect.
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Participants blood lead levels were not assessed as part of the study (investigators obtained blood lead levels from state records). It is doubtful that those taking and measuring blood lead levels would have been aware that the children were part of a study
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Low	Consistent and reliable inclusion criteria applied across groups. Inclusion criteria were assessed via census tracts, blood lead levels and standardised home inspections, all objective and/or reliable measures. The outcome was blood lead level which is likely to be reliable. Other demographic factors collected (race, age, gender, time of lead testing) are unlikely to be inaccurate.
Were incomplete outcome data adequately addressed?	Low	Only one participant's data was excluded due to lack of remediation occurring in their new home. But an ITT analysis did not change the findings
Was the study free from selective outcome reporting?	Low	blood lead level was primary outcome. Unlikely to be others that were not reported (no protocol available)
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	High	Matching - controls were matched on age and census tract but NOT on blood lead level. The baseline blood lead level of participants is not reported, so we are unable to determine whether the differences at follow-up could be due to baseline imbalances. The analysis was not adjusted for any possible confounders.
Was the study free from other risks of bias?	Unclear	Note that n = 60 (over 60%) of initially screened participants were lost to follow up, with n = 29 parents not taking their children for a blood lead level check. May favour a treatment effect. Note that all pregnant women in Missouri were screened for lead hazards, therefore women in the control group (who had not received a lead hazard intervention) must have also been screened by the state and not found to have high blood lead levels. Favours a treatment effect.
Overall risk of bias rating (Optimal result: “very low”, meaning the study is at very low risk of bias)	HIGH	controlled before and after study; rated as high risk of bias for factors relating to confounding, some loss to follow up
RESULTS		

Outcome	Home remediation		No remediation		Measure of effect/effect size
	M (SD) or n =	N =	M (SD) or n =	N =	MD or RR, 95% Confidence Interval
Mean blood lead levels at 1.5 years of age (µg/dL)	2.7 (2.5)	60	3.65 (2.5)	120	**MD -0.93** (95% CI -1.70 to -0.16)
No. of children with blood lead levels ≥ 5 µg/dL	8	60	27	120	**RR 0.59** (95% CI 0.29 to 1.22)
No. of children with blood lead levels ≥ 10 µg/dL	0	60	5	120	**RR 0.18** (95% CI 0.01 to 3.21)

Brown, MJ, McLaine, P, Dixon, S & Simon, P 2006, 'A randomized, community-based trial of home visiting to reduce blood lead levels in children', Pediatrics, vol. 117, no. 1, pp. 147-53.

Affiliation*/source of funds	Affiliation: Centers for Disease Control and Prevention, Source of funds: Centers for Disease Control and Prevention and Maternal and Child Health Bureau
Study Design	Randomised controlled trial
Location/Setting	Rhode Island, United States; community-based intervention
Population	Children aged < 28 months (mean age approx. 18 months) with blood lead levels 15 to 19 µg/dL (outcomes collected in children but the intervention was delivered to families); n = 173. Families were minority groups and lived in urban, low income areas with a lot of old, deteriorated homes.
Source of lead	Possible sources of lead identified by a detailed questionnaire as part of the intervention.
Removal of lead source	Lead was not removed but changed housekeeping practices reduced dust lead level post-intervention.
Intervention	Five home visits by a nurse over a one-year period, involved identification and testing of potential lead hazards in the home and individualized nursing care plans directed at parent teaching and other services (Comprehensive home visit program)
Comparison	Two home visits with an outreach worker, providing standard lead education (Standard home visit program)
Length of follow up	3, 6 and 12 months after baseline, during the 12-month intervention
Outcomes	Number of children whose last available blood lead level was ≥ 10 µg/dL, number of children with any blood lead level ≥ 20 µg/dL

	(data for mean blood lead levels at 3, 6 and 12-months not fully reported, authors refer to statistical significance only)				
Comments	The control participants still received education and home visits, that may have enhanced the retention of educational messages. The authors also conducted environmental lead analysis (interior dust and soil samples) and assessed the parent-child interaction and reported housekeeping practices.				
RISK OF BIAS					

Bias Domain	Judgement	Support for judgement
Was the allocation sequence adequately generated?	Low	random numbers table used to assign cases to either intervention or comparison, sequentially by study coordinator
Was the allocation adequately concealed?	Low	Group assignments sealed in envelopes and unknown to either study personnel or families until after parental consent was obtained.
Does the study account for important variations in the execution of the study from the proposed protocol?	Low	Did not seem to be major deviations from intervention described.
Were participants blinded to their intervention or exposure status?	Unclear	Families were told that the intervention group would get five visits and the comparison group would get 2 visits. So they could have worked out which group they were in. Knowing about the intervention may have caused parents to change their behaviour in response to the intervention more than they normally would.
Were investigators blinded to the intervention or exposure status of participants?	Low	Nurses providing follow up for comparison group were blinded. Nurses providing care to intervention group were not blinded. Differential blinding is unusual. This is probably more of an issue for outcome assessment so has been captured there.
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Not reported. blood lead levels conducted in 1 laboratory. Would have been easy to blind analysts since they weren't involved in other aspects of the study. Since blood lead level is objective, less of an issue. For other outcomes recorded by nurses, this would be considered a risk of bias (as intervention nurses not blinded) and may have been more likely to rate them as improved as a result of their intervention.
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Low	Inclusion assessed consistently across groups (based on blood lead level through routine blood testing). Outcomes assessed consistently across groups. Characteristics of study population described for each group.
Were incomplete outcome data adequately addressed?	Unclear	Lost 20 out of 173 children during follow up (12%). Reasons provided. Numbers in each group not given, however odds of not completing the study did not differ significantly between comparison and intervention. Impact of attrition not assessed.
Was the study free from selective outcome reporting?	Low	blood lead level was primary outcome as expected. Other outcomes related to lead levels

		in home. No reason to suspect there would have been other outcomes not reported, particularly with null findings.
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	Low	Randomised controlled trial. Intervention and comparison children did not differ on factors known to affect risk for elevated blood lead levels.
Was the study free from other risks of bias?	Low	No further risks of bias noted
Overall risk of bias rating (Optimal result: "very low", meaning the study is at very low risk of bias)	VERY LOW	Randomised controlled trial; rated as low risk of bias for randomisation and allocation concealment, no other major concerns about risk of bias

RESULTS					
Outcome	Comprehensive home visits		Standard home visits		Measure of effect/effect size
	(n/N)		(n/N)		RR (95% Confidence Interval)
No. of children whose last available blood lead level ≥ 10µg/dL	46	90	42	82	**RR 1.0** (95% CI 0.74 to 1.34)
No. of children with any blood lead level ≥ 20µg/dL	7	90	9	82	**RR 0.71** (95% CI 0.28 to 1.82)
Mean blood lead levels (µg/dL)	Data presented graphically, but actual values not reported. The authors state that blood lead level "did not differ significantly at 3, 6 or 12 months after baseline."				
Comments					

Campbell, C, Tran, M, Gracely, E, Starkey, N, Kersten, H, Palermo, P, Rothman, N, Line, L & Hansen-Turton, T 2011, 'Primary prevention of lead exposure: The Philadelphia Lead Safe Homes Study', Public Health Reports, vol. 126, pp. 76-88.

Affiliation/source of funds	Affiliation: The Children's Hospital of Philadelphia and Drexel University School of Public Health, Source of funds: US Department of Housing and Urban Development
Study Design	Controlled before and after study (the two intervention groups were randomised but the control group was not. As the two intervention groups were merged for the main analysis of blood lead levels versus control, we classified this trial as a controlled

	before and after).
Location/Setting	Philadelphia, United States; community-based intervention
Population	Newborn children living in neighbourhoods where the prevalence of elevated blood lead levels is higher than average (outcomes collected in children but the intervention was delivered to families); n = 942. Participants lived in urban, low income neighbourhoods.
Source of lead	97% of homes had identified lead hazards (visual inspection). 90% of homes were referred for home remediation.
Removal of lead source	Only 50% of remediated homes passed a subsequent lead inspection.
Intervention	Intervention A: Three home visits over one year with an outreach worker who provided standard lead poisoning prevention education, extensive education regarding maintenance practices and cleaning materials/supplies. The outreach worker reinforced the additional education messages at each visit (Maintenance education group) Intervention B: Three home visits over one year with an outreach worker who provided standard lead poisoning prevention education (standard education group). In addition, remediation work was carried out in the homes of families in either of the intervention groups, should this have been required (more families in the Maintenance education group were referred for home remediation work at baseline (93% versus 86%) however this difference had disappeared by the one-year follow up.
Comparison	Matched controls who received the standard program in the community, i.e. such as information provided by the child's health professional during clinical visits. Controls were matched by age, census tract, racial/ethnic background and gender), 2:1 ratio of controls: intervention groups
Length of follow up	Approximately one and two years of age
Outcomes	Geometric mean blood lead levels (µg/dL)
Comments	The type or intensity of lead interventions that control participants may have received in the community is unknown (may favour the null hypothesis). Timing of outcome assessment was not exact as this was undertaken by program staff and passed onto the study team. A number of additional outcomes were measured relating to measuring lead hazards (i.e. home lead dust levels) and assessing possible exposure from other sources (i.e. occupational history of parents)

RISK OF BIAS					
Bias Domain	Judgement	Support for judgement			
Do inclusion/exclusion criteria vary across comparison groups?	High	Inclusion criteria differed between intervention and control groups. Intervention participants: English or Spanish speaking, no previous elevated blood lead levels, had a home judged to be in a suitable condition for remediation. Excluded people who had participated in the Lead Safe Program or received services from the State Dept for lead exposure for another child. These criteria did not apply to control participants, who were selected from a database and matched on age, census tract, race and gender. No further details were known about control participants.			

Does the strategy for recruiting/allocating participants vary across groups?	High	Children for two intervention arms recruited from urban outpatient practices (Children's Hospital of Philadelphia, St. Christopher's Hospital for Children and several nurse-managed health centers) located in low-income neighbourhoods of Philadelphia, then randomised to one of two arms. Comparison group (not randomised) was identified from The Children's Hospital of Philadelphia clinical database (controls matched by age, census tract, race, and gender).
Does the study account for important variations in the execution of the study from the proposed protocol?	Unclear	blood lead levels were measured at different ages since this was left up to healthcare providers, so 1 year and 2 year estimates were conducted over a very broad range. One analysis adjusted for actual age at which blood was drawn. Comparison children may have received lead exposure prevention from other sources - would bias towards the null.
Were participants blinded to their intervention or exposure status?	Unclear	Participants in the 2 intervention groups were blinded to their intervention status. Control participants were matched from a database.
Were investigators blinded to the intervention or exposure status of participants?	High	The research team were aware of the intervention status of the two intervention groups due to the didactic nature of the materials
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Not reported, however blood lead level samples drawn by regular physicians and results reported to study team so unlikely that laboratory staff were aware of the study.
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Low	Difficult to assess for inclusion/exclusion since groups were recruited differently. For blood lead level and confounders (those that were measured), valid and reliable measures were used. Lack of information about comparison group (this was inconsistent compared with intervention group), however this is assessed under confounding.
Were incomplete outcome data adequately addressed?	High	110 of 314 intervention participants completed the study (only 35%).
Was the study free from selective outcome reporting?	Low	No reason to suspect selective outcome reporting (blood lead level was the only outcome) but no protocol reported.
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	High	The comparison group was matched on age, census tract, race, gender, however it seems likely that there were other potential confounders that were not taken into account with this design. Regression analyses were conducted adjusted for age when 2 year blood lead level was drawn (this varied a lot) and type of health insurance (proxy for SES). This was not done for the 1 year blood lead level. Authors acknowledge a limitation was lack of detailed knowledge about comparison group children.
Was the study free from other risks of bias?	Low	No further risks of bias noted
Overall risk of bias rating (Optimal result: “very low”, meaning the study is at very	HIGH	controlled before and after study; rated as high risk of bias for factors relating to confounding, some loss to follow up

low risk of bias)							
RESULTS							
Outcome	Maintenance Education		Standard Education		Usual care		Measure of effect/effect size
	M (SD)	N =	M (SD)	N =	M (SD)	N =	MD, 95% Confidence Interval
Mean blood lead level (µg/dL) at 1 year of age (Intervention A vs B)	2.7 (1.27)	59	2.6 (1.27)	51	N/A		**MD 0.10** (95% CI -0.38 to 0.58)
Mean blood lead level (µg/dL) at 1 year of age (Intervention A + B vs control)	2.6 (1.90) N = 279				2.7 (1.90)	530	**MD -0.10** (95% CI - 0.38 to 0.18)
Mean blood lead level (µg/dL) at 2 years of age (Intervention A + B vs control)	3.7 (1.93) N = 159				3.5 (1.85)	331	**MD 0.20** (95% CI -0.16 to 0.56)
Comments							

Dietrich, KN, Ware, JH, Salganik, M, Radcliffe, J, Rogan, WJ, Rhoads, GG, Fay, ME, Davoli, CT, Denckla, MB, Bornschein, RL, Schwarz, D, Dockery, DW, Adubato, S, Jones, RL & Treatment of Lead-Exposed Children Clinical Trial, G 2004, 'Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry', Pediatrics, vol. 114, no. 1, pp. 19-26.

Affiliation*/source of funds	Affiliation: University of Cincinnati College of Medicine, Source of funds: National Institute of Environmental Health Science and National Institutes of Health and the Centers for Disease Control and Prevention
Study Design	Randomised controlled trial
Location/Setting	Various cities (Philadelphia, Newark, Cincinnati and Baltimore), United States; outpatient clinics
Population	Children aged between 12 to 33 months with blood lead levels between 20 to 44 µg/dL; n = 780. Participants were predominantly low-income, African-American and received public assistance.

Source of lead	The source of lead was identified prior to inclusion in the study (only those homes that were considered 'cleanable' were included in the study). Cleaning consisted of vacuuming, mopping and wiping with specialised lead-removal equipment, and paint stabilisation and minor carpentry, as necessary.
Removal of lead source	No information provided on the success of home cleaning.
Intervention	Chelation therapy, delivered as up to three, 26-day courses of succimer (100mg, taken as capsules), aiming for 1050mg/m2 per day for the first seven days and then 700mg/m2 per day thereafter. The majority of children finished within 6 months, with the last child finishing 13 months after commencing treatment. Capsules were administered at the clinic but delivered by caregivers at home.
Comparison	Placebo chelation therapy; up to three courses; capsules were identical in look and smell (succimer has a strong odour)
Length of follow up	Approximately five years (children were tested at 7 years of age). Earlier tests were conducted (at 6, 12 and 34 months after baseline) but these results were not reported in full (mean difference only)
Outcomes	Mean blood lead level (μg/dL) and number of children with blood lead levels > 10μg/dL at seven years; Height (cm); Weight (kg), Cognition (measured by WISC-II = Weschler Intelligence Scales for Children-III (full scale IQ), Attention/Executive Functions (measured by Developmental Neuropsychological Assessment (Attention and Executive functions subscale = NSPSY-A and Connors Continuous Performance test, d Prime) Verbal learning and Memory (measured by California Verbal Learning Test for Children (List A memory and Learning Scope), Reading (measured by WLPB-R = Woodcock Language Proficiency Battery-revised,), Behavioural conduct (measured by the behavioural assessment system for children-parent rating scale (externalising problems), behavioural and academic conduct (measured by the behavioural assessment system for children-teacher rating scale (adaptive skills, externalising problems, school problems), neurological outcomes (measured by neurological examination for subtle signs (rapid sequential movements times) and Motor speed (measured by Connors' continues Performance Test)(hit reaction time)
Comments	All children had their house cleaned prior to receiving the course of treatment. Adherence was measured by parental report (> 90% of doses given) and pill count (approx. 76% of capsules gone). Difficulty administering the capsules was self-reported by parents and differed between groups (40% in the intervention group and 20% in the control group).

RISK OF BIAS		
Bias Domain	Judgement	Support for judgement
Was the allocation sequence adequately generated?	Low	Treatment assignments were blocked by centre, 6 categories of body surface area, 2 strata of blood lead level at 2nd clinic visit, and (at Newark site), English or Spanish language.
Was the allocation adequately concealed?	Low	clinics obtained treatment assignments from data-coordinating centre by phone, usually the day before the scheduled visit at which the succimer or placebo would be dispensed. Data-coordinating centre assigned a study number corresponding to blinded bottle stored at the clinical site containing the appropriate # of capsules for child's body surface area.

Does the study account for important variations in the execution of the study from the proposed protocol?	Low	compliance assessed. Protocol seemed to be adhered to fairly well over the course of follow-up. Detailed protocol provided in 1998 paper.
Were participants blinded to their intervention or exposure status?	Low	Participants were blinded to group assignment
Were investigators blinded to the intervention or exposure status of participants?	Low	Those administering the drug and physicians and nurses monitoring health of patients were blinded to group assignment as well as blood lead levels (during treatment)
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	physicians and nurses monitoring health of patients, and psychometricians administering neuropsychological assessment were blinded to group assignment
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Low	inclusion based on blood lead levels, intervention compliance measured, many outcomes including blood lead level, growth, cognitive and behavioural measures assessed according to standardised scales
Were incomplete outcome data adequately addressed?	Low	Final proportion analysed was a little low, but similar between groups (approximately 82%).Possible reasons for discontinuing treatment were provided but not quantified by reason. A total of 128 lost to follow up. Children who discontinued treatment and participated in the study through 7 years were included in intent-to-treat analysis. Succimer and placebo groups that discontinued treatment did not differ with respect to mean blood lead level at baseline or at 7 years.
Was the study free from selective outcome reporting?	Low	Study design/ methods paper available. Expected outcomes were reported
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	Low	Randomised controlled trial. Two treatment groups balanced with respect to baseline characteristics. Adjusted for clinical center, baseline blood lead level, use of Spanish in home, race, gender, baseline age, caregiver's IQ, child's baseline score on Bayley Scales of Infant Development-II Mental Development Index.
Was the study free from other risks of bias?	Low	No further risks of bias noted
Overall risk of bias rating (Optimal result: “very low”, meaning the study is at very low risk of bias)	VERY LOW	RANDOMISED CONTROLLED TRIAL; rated as low risk of bias for randomisation and allocation concealment, no other major concerns about risk of bias

RESULTS					
Outcome	Chelation therapy		Placebo		Measure of effect/effect size
	Mean (SD) or n =	N =	Mean (SD) or n =	N =	MD or RR, 95% Confidence Interval
Mean blood lead level (µg/dL)					

	Average over first 6 months post-treatment	Not reported		Not reported		**MD -4.5** (95% CI -3.7 to -5.3)
	At 12 months post-treatment	Not reported		Not reported		**MD -2.7** (95% CI -1.9 to -3.5)
	At 7 years of age (5 years post-treatment)	8.0 (4.0)	325	8.1 (4.1)	322	**MD 0.00** (95% CI -0.62 to 0.62)
	No. of children with blood lead levels > 10 µg/dL at 7 years of age	81	325	87	322	**RR 0.92** (95% CI 0.71 to 1.20)
Height (cm) at 7 years of age (for earlier time points see comments)		Not reported		Not reported		**MD -1.17** (95% CI -0.41 to -1.93) (adjusted, see comments)
Weight (kg) at 7 years of age (for earlier time points see comments)		Not reported		Not reported		**MD -0.12** (95% CI 0.10 to -0.35) (adjusted, see comments)
Neurobehavioural outcomes; at 7 years (higher scores optimal, see comments for exceptions; all scores unadjusted)						
	Cognition (WISC-III, NEPSY, WLPB-R)					
	-Full scale IQ	86.9 (13.2)	323	86.5 (13.4)	321	**MD 0.40** (95% CI -1.65 to 2.45)
	-Attention/executive functions	86.3 (16.5)	300	88.1 (17.6)	293	**MD -1.80** (95% CI -4.5 to 1.0)** (see comments)
	-Reading	94.8 (18.4)	302	93.9 (18.5)	298	**MD 0.90** (95% CI -2.05 to 3.85)
	Behaviour (BASC)					
	-Adaptive skills (teacher reported)	46.6 (9.7)	259	46 (9.2)	272	**MD 0.60** (95% CI -1.01 to 2.21)
	-Externalising problems (teacher reported)*	55.2 (13.9)	266	55.3 (12.1)	274	**MD -0.10** (95% CI -2.30 to 2.10)
	-School Problems (teacher reported)*	55.9 (12.4)	267	56.5 (12.1)	275	**MD -0.60** (95% CI -2.66 to 1.46)
	-Externalising problems (parent reported)*	58.8 (16.5)	325	57.2 (14.1)	323	**MD 1.60** (95% CI -0.76 to 3.96)
	Learning and Memory (CVLT-C)					
	-List A Memory	43.4 (11.3)	325	43.9 (11.8)	320	**MD -0.50** (95% CI -2.28 to 1.28)
	-List A leaning Slope	-0.4 (1.1)	325	-0.4 (1.2)	320	**MD 0.00** (95% CI -0.18 to 0.18)
	Attention (CPT)					
	-d Prime*	55.2 (9.8)	287	56.3 (9.9)	285	**MD -1.10** (95% CI -2.71 to 0.51)
	Neuromotor (CPT, NESS)					
	-Hit Reaction Time	42.7 (13.1)	287	42.6 (12.8)	285	**MD 0.10** (95% CI -2.02 to 2.22)

	-Sequential Movements Time*	1 (1.3)	286	0.9 (1.3)	279	**MD 0.10** (95% CI -0.11 to 0.31)
	Postural balance					
	-Dynamic postural sway test (BC) response	Mean dynamic postural sway score was 6.6% lower (p = 0.04) in the succimer group compared to placebo				
	-Five other static and semi-dynamic tests	No statistically significant differences between groups				
	Functional locomotor					
	-Medio-lateral postural sway	Mean medio-lateral postural sway score was 19% lower (p = 0.001) in the succimer group compared to placebo				
	-Normal walking test	Four out of eight dependent variables showed statistically significant differences between succimer and placebo groups				
	BOMPT performance					
	-Eight sub-tests	No statistically significant differences between groups				
Comments		Height: measured at multiple time points after treatment (6, 9, 12, 18, 24 and 34 months, plus 7 years of age). At all time-points children provided with chelation therapy were slightly shorter (by less than 0.5cm, confidence interval did not cross 1) than children provided with placebo. Analysis adjusted for age, gender, ethnicity, clinical centre, and gender-specific z-scores at baseline. Weight: Measured at multiple time points (as per height). There was no difference in weight between groups at all time-points. Adjusted analysis as per height. *Denotes lower scores optimal for these outcome measures **Adjusted analysis reached statistical significance (p = 0.045) favouring the placebo group				

Dugbatey, K, Croskey, V, Evans, RG, Narayan, G & Osamudiamen, OE 2005, 'Lessons from a primary-prevention program for lead poisoning among inner-city children', Journal of Environmental Health, vol. 68, no. 5, pp. 15-20.

Affiliation/source of funds	Affiliation: Saint Louis School of Public Health, Source of funds: Centers for Disease Control
Study Design	Randomised controlled trial
Location/Setting	St Louis, Missouri, USA; community-based intervention
Population	Newborn children, from disadvantaged area but no specific lead exposure (outcomes collected in children but the intervention was delivered to women, recruited when pregnant); n = 151. Participants were described as ‘poor’, including a range of ethnic

	backgrounds.
Source of lead	Source of lead not confirmed. All had a home lead inspection but the results are not reported.
Removal of lead source	It is unclear whether a final home inspection was completed to determine if lead source was removed.
Intervention	Intervention A: Tailored lead exposure prevention education (including personal and environmental hygiene, nutrition, and print information on lead exposures sources), environmental assessment of lead-containing paint in home interior and counselling at quarterly visits, provided by case management team (full case management). Intervention B: Written report of environmental inspection of lead-containing paint in home interior, monthly lead poisoning prevention newsletter, quarterly visits by case management team, with no individual counselling or guidance (partial case management)
Comparison	Standard lead education materials routinely distributed by health departments and clinics (standard lead education)
Length of follow up	Not explicitly reported (likely to be two years: data was reported at four time points and study visits occurred every six months)
Outcomes	Mean blood lead levels (µg/dL) at four time points
Comments	The control group still received some education (favours the null hypothesis). The authors conducted a qualitative assessment of the barriers to implementation. They found that lead exposure prevention was not a priority for many participants; they had other significant challenges due to living in poverty. Study attrition was high as many participants lived in rental properties and feared eviction.
RISK OF BIAS	

Bias Domain	Judgement	Support for judgement
Was the allocation sequence adequately generated?	Unclear	The authors report that study allocation was randomly assigned. No further information provided.
Was the allocation adequately concealed?	Unclear	Not reported
Does the study account for important variations in the execution of the study from the proposed protocol?	Unclear	very little detail provided about what actually occurred in terms of intervention, although the extensive follow up issues are likely to be the main problem with implementing the intervention.
Were participants blinded to their intervention or exposure status?	Unclear	Not reported
Were investigators blinded to the intervention or exposure status of participants?	Unclear	Not reported
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Not reported. blood lead level is an objective outcome, so probably not an issue.
Were valid and reliable measures, implemented consistently across all study participants used to assess	Unclear	Not reported. No detail given on outcome measures. Inclusion/exclusion criteria not

inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?		clear.
Were incomplete outcome data adequately addressed?	High	Very high attrition. A detailed description of the reasons for this and the challenges in implementing the study are given which is useful, but the results are likely to suffer from this bias.
Was the study free from selective outcome reporting?	Low	Little detail provided, however it seems clear that the aim was to examine blood lead level. That is the only outcome reported.
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	Unclear	Very little detailed provided to assess this.
Was the study free from other risks of bias?	Unclear	Insufficient information in the publication to assess the study.
Overall risk of bias rating (Optimal result: "very low", meaning the study is at very low risk of bias)	LOW	Randomised controlled trial; unclear ratings for randomisation and allocation concealment and very high attrition

RESULTS					
Outcome	Full case management		Partial case management		Measure of effect/effect size
Intervention A vs B	Mean (SD)	N =	(Mean, SD)	N =	MD, 95% Confidence Interval
Mean blood lead level (µg/dL) at time 1	6.17 (4.55)	30	5.48 (5.55)	33	**MD 0.69** (95% CI -1.81 to 3.19)
Mean blood lead level (µg/dL) at time 2	8.83 (7.31)	30	8.82 (7.9)	33	**MD 0.01** (95% CI -3.75 to 3.77)
Mean blood lead level (µg/dL) at time 3	9.06 (8.47)	17	8.11 (7.05)	19	**MD 0.95** (95% CI -4.17 to 6.07)
Mean blood lead level (µg/dL) at time 4	10.33 (5.75)	9	12.5 (7.31)	8	**MD -2.17** (95% CI -8.48 to 4.14)

	Case Management (full + partial)		Standard lead education		Measure of effect/effect size
Interventions (A+B) vs control	Mean (SD)	N =	Mean, SD)	N =	MD, 95% Confidence Interval
Mean blood lead level (µg/dL) at time 1	5.81 (5.07)	63	6.3 (7.98)	33	**MD -0.49** (95% CI -3.49 to 2.51)

	Mean blood lead level (µg/dL) at time 2	8.83 (7.56)	63	7 (8.4)	33	**MD 1.82** (95% CI -1.76 to 5.40)
	Mean blood lead level (µg/dL) at time 3	8.56 (7.65)	36	10.64 (8.88)	14	**MD -2.08** (95% CI -7.36 to 3.20)
	Mean blood lead level (µg/dL) at time 4	11.35 (6.41)	17	10.67 (10.61)	6	**MD 0.68** (95% CI -8.34 to 9.70)
Comments	The authors report a loss to follow up at each time point. Rather than conducting an intention-to-treat analysis, they provide the data at each four time-points based on the number of participants included at each time point, and just for the participants who were there at the final time-point. We elected to take the most complete data set at each time point.					

Ettinger, AS, Lamadrid-Figueroa, H, Téllez-Rojo, MM, Mercado-García, A, Peterson, KE, Schwartz, J, Hu, H & Hernández-Avila, M 2009, 'Effect of calcium supplementation on blood lead levels in pregnancy: a randomized placebo-controlled trial', Environmental Health Perspectives, vol. 117, no. 1, pp. 26-31.

Affiliation/source of funds	Affiliation: Harvard School of Public Health, Source of funds: US National Institute of Environmental Health Sciences, Consejo Nacional de Ciencia Y Technologia and Consejo de Estudios para Restauracion y Valoracion Ambiental.
Study Design	Randomised controlled trial
Location/Setting	Mexico City, Mexico; outpatient clinics
Population	Pregnant women (recruited at < 14 weeks gestation) from low to moderate income areas; n = 670. Baseline blood lead levels were between 3.8 and 4.1 ìg/dL between groups.
Source of lead	Unclear. Women did not necessarily have increased blood lead levels to join the study but many reported use of lead-glaed ceramic pottery.
Removal of lead source	No information provided on the source of lead or its removal.
Intervention	8-month course of calcium supplementation (1200mg daily; 2 x 600mg tablets at bedtime). Participants were also provided advice about avoiding lead-glazed ceramic pottery. Participants received the tablets at the clinic but administered them at home.
Comparison	Placebo calcium supplementation and advice about avoiding lead-glazed pottery
Length of follow up	Participants followed until their third trimester (8 months)
Outcomes	blood lead levels (µg/dL) (only adjusted data, taking into account baseline blood lead levels, maternal age, dietary calcium intake,

	daily energy intake and trimester, is provided by the authors)				
Comments	Adherence was measured at each visit using a pill count. Only n = 241 (36%) of participants consumed more than 75% of their pills. The authors saw a dose-response effect when they stratified participants into groups according to their level of compliance.				
RISK OF BIAS					

Bias Domain	Judgement	Support for judgement
Was the allocation sequence adequately generated?	Unclear	Not reported
Was the allocation adequately concealed?	Unclear	Not reported
Does the study account for important variations in the execution of the study from the proposed protocol?	Low	Compliance with medication was assessed. Conducted analysis according to differing levels of compliance to examine the impact on the main outcome.
Were participants blinded to their intervention or exposure status?	Unclear	Not reported. Only mention is calling the study a double-blind study, so they may have been blinded but not specifically mentioned.
Were investigators blinded to the intervention or exposure status of participants?	Unclear	Not reported. Only mention is calling the study a double-blind study, so they may have been blinded but not specifically mentioned.
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Not reported. Only mention is calling the study a double-blind study, so they may have been blinded but not specifically mentioned. blood lead level is objective so less of an issue.
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Low	Consistent inclusion criteria across groups. Main outcome blood lead level (reliable measure) measured consistently across groups. Important confounder (dietary calcium intake) was assessed consistently across groups and included in analyses.
Were incomplete outcome data adequately addressed?	Low	84% completed follow up. Detailed participant flow provided. Intervention group lost 46 (14%); placebo group lost 59 (18%). Compared group who completed with those lost to FU and found no sig differences by treatment group assignment. Those remaining in the study reported higher daily energy intake and higher use of LGC - no differences by treatment group
Was the study free from selective outcome reporting?	Low	No protocol available but no reason to suspect selective outcome reporting.
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	Low	Randomised controlled trial. blood lead levels were slightly higher at baseline in placebo group (4.1 vs 3.8 p=0.05). Baseline blood lead level was included in models. Maternal age differed by 1 year, however age was included in models. Dietary calcium intake (important confounder) included in analyses.
Was the study free from other risks of bias?	Low	No further risks of bias noted

Overall risk of bias rating (Optimal result: "very low", meaning the study is at very low risk of bias)	MODERATE	Randomised controlled trial; unclear randomisation and allocation concealment, but not other concerns about risk of bias			
RESULTS					
Outcome	Calcium supplementation		Placebo		Measure of effect/effect size
	Mean (SD)	N =	Mean (SD)	N =	MD (95% Confidence Interval)
Mean blood lead level (µg/dL) at 7 to 8 months pregnant	Not provided	283	Not provided	274	MD -11% (95% CI -17.8% to -3.7%) (log transformed, adjusted data, see comments)
Mean blood lead level (µg/dL), all time-points (high compliance group)	The authors stratified the results by compliance with medication. When considering the effects in those who were compliant (>75% pills taken) there was a statistically significant reduction in blood lead level between groups in both the second and third trimesters of pregnancy ($p < 0.01$)				
Comments	The authors adjusted the analysis for or baseline blood lead level, maternal age, dietary calcium intake at baseline, daily energy intake at baseline, treatment group, and trimester of pregnancy. They did not provide the unadjusted means and standard deviations as they advised that the adjusted scores represented a more accurate estimate of the treatment effect.				

Fertmann, R, Hentschel, S, Dengler, D, Janssen, U & Lommel, A 2004, 'Lead exposure by drinking water: an epidemiologial study in Hamburg, Germany', International Journal of Hygiene & Environmental Health, vol. 207, no. 3, pp. 235-44.

Affiliation/source of funds	Affiliation: Department of Environment and Health and Institute for Medical Biometry and Epidemiology, Source of funds: Not reported
Study Design	Randomised controlled trial
Location/Setting	Hamburg, Germany; Community-based intervention
Population	Young women aged 20-30 living in an old area of Hamburg, with mains water that had been tested and shown to have a lead concentration ≥ 10 µg/L; n = 52. No further information on demographics provided. Baseline mean blood lead levels were 35ìg/dL.
Source of lead	Participants had confirmed exposure through their water pipes but could have had other sources of lead in the home too.
Removal of lead source	Unable to objectively measure. Removal of lead depended on the adherence to minimising or excluding the use of their mains water.

Intervention	Participants were supplied with bottled water and encouraged to use this for cooking and drinking over a 10-week period (Excluding)
Comparison	Participants were provided with an “official” flyer from public health services, suggesting participants minimise exposure to lead by flushing water prior to consumption (Minimizing)
Length of follow up	Unclear, likely to be immediately post-intervention (after 10 weeks)
Outcomes	Mean blood lead levels (µg/dL) (Standard deviation not provided and not calculable)
Comments	Likely to be underpowered
RISK OF BIAS	

Bias Domain	Judgement	Support for judgement
Do inclusion/exclusion criteria vary across comparison groups?	Unclear	Participants were allocated to groups "by chance" but no further detail reported to confirm it was truly randomised.
Does the strategy for recruiting/allocating participants vary across groups?	Unclear	Not reported
Does the study account for important variations in the execution of the study from the proposed protocol?	Low	Interventions were very simple and proportion of participants who were able to follow instructions was captured. This was different between groups due to differences in the intervention (much less variability likely in the excluding group - provided with bottled water), however this was part of what was being compared.
Were participants blinded to their intervention or exposure status?	Low	Participants weren't blinded but both groups were aware they were implementing a measure to reduce lead exposure, given the cross sectional study conducted beforehand. Given the simplicity of the interventions and the objective outcome (blood lead level), it seems unlikely to be an issue.
Were investigators blinded to the intervention or exposure status of participants?	Unclear	Not reported
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Not reported. blood lead level is an objective outcome, so probably not an issue.
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Unclear	Inclusion criteria applied consistently based on lead levels in water. Outcome blood lead level is reliable and was assessed consistently across groups although the time span of intervention was inconsistent (more heterogeneous for the minimising group compared with excluding group). Some information about confounders (water consumption) was given for cross-sectional sample but not for the intervention sample.
Were incomplete outcome data adequately addressed?	Unclear	Authors state that 113 women were invited, and that 52 of initially 54 women completed the intervention program. So perhaps only 2 dropped out partway through - but it's not

		entirely clear.
Was the study free from selective outcome reporting?	Low	No protocol available. blood lead level was primary outcome as expected, so no real reason to expect selective outcome reporting
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	High	Participants were allocated to intervention by chance (not clear that they were randomised). Either way, the participant numbers are so small that it's very likely that confounders were not balanced between groups. Little information provided about these factors. No adjustments mentioned in analysis.
Was the study free from other risks of bias?	Low	No further risks of bias noted
Overall risk of bias rating (Optimal result: "very low", meaning the study is at very low risk of bias)	MODERATE	Randomised controlled trial; unclear risk of bias for randomisation and allocation concealment, likely to be confounding present due to small sample size.

RESULTS					
Outcome	Excluding		Minimising		Measure of effect/effect size
	Mean (SD)	N =	Mean (SD)	N =	MD, 95% Confidence Interval
Mean blood lead levels post-intervention (µg/dL)	2.1 (no SD)	33	3.0 (no SD)	19	Authors report that the mean change between groups was not statistically significant (p=0.17)
Comments	The authors report blood lead level in µg/L, which we converted into µg/dL to be consistent with the unit of measurement in the other studies.				

Markowitz, ME, Sinnett, M & Rosen, JF 2004, 'A randomized trial of calcium supplementation for childhood lead poisoning', Pediatrics, vol. 113, no. 1 Pt 1, pp. e34-9.

Affiliation/source of funds	Affiliation: Children's Hospital at Montefiore Bronx, New York Source of funds: National Institute of Environmental Health Sciences
Study Design	Randomised controlled trial
Location/Setting	Bronx, New York, United States; medical centre
Population	Children aged 1 to 6 years (mean age 3.6 years) with blood lead levels between 10 to 45 (µg/dL); n = 88. No demographic of related information provided.
Source of lead	Not reported but all children received an inspection and removal of lead source by a government agency prior to the intervention

	taking place.
Removal of lead source	Home lead levels were assessed by the study group and lead levels decreased by 70% from pre- to post-intervention, suggesting most of the lead was removed.
Intervention	Calcium supplementation (1800mg per day of Calcium, obtained through diet and supplementation) for three months. Calcium dosage adjusted bi-weekly on the basis of 24-hour dietary recall questionnaire administered bi-weekly. Dose divided into 3 portions, dispensed by parents (provided by clinic) taken before meals. Families of all children were provided with standard clinic-based lead education through. Additionally, three home visits (at baseline, 3 and 6 months) were undertaken to collect process outcomes (i.e. dust lead levels) but no further intervention was provided at this time.
Comparison	Placebo calcium supplementation (with additional components as described above).
Length of follow up	Three and six months after baseline
Outcomes	Mean blood lead level (μg/dL)
Comments	Diet diary kept to determine the amount of calcium required to reach 1800mg. Likely to be underpowered
RISK OF BIAS	

Bias Domain	Judgement	Support for judgement
Was the allocation sequence adequately generated?	Low	Children stratified by age into two groups and randomisation list prepared, generated from a computer program.
Was the allocation adequately concealed?	Low	restricted randomisation list prepared before trial and used by pharmacist to assign enrollees into groups (investigators were blinded)
Does the study account for important variations in the execution of the study from the proposed protocol?	Low	Compliance assessed based on quantity remaining in bottle at each visit and was comparable between groups.
Were participants blinded to their intervention or exposure status?	Low	parents blinded to assignment group
Were investigators blinded to the intervention or exposure status of participants?	Low	investigators blinded to assignment group
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Videotapes of child behaviour coded by blinded evaluator. Seems likely that lab staff analysing blood lead levels could easily have been blinded. Also blood lead level is an objective outcome, so less of an issue.
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Low	Consistent inclusion criteria across groups based on blood lead level (reliable measure). Main outcome blood lead level (reliable measure) measured consistently across groups. Important confounder (dietary Ca intake) was assessed consistently across groups.

Were incomplete outcome data adequately addressed?			High		high % attrition. Higher in placebo group. The impact of attrition was not assessed. It may be that the higher attrition tended to attenuate any differences. Those missing may have had higher blood lead levels as they may also have been less likely to participate in behaviour change strategies to reduce lead.
Was the study free from selective outcome reporting?			Low		No protocol available. blood lead level was primary outcome as expected. Other outcomes were related to lead levels in home. Not obvious that there would have been other outcomes measured and not reported given the aim of the study (and the finding of no effect when they expected to find one).
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?			Low		Randomised controlled trial. Baseline blood lead level similar between groups. Baseline characteristics similar between groups (age, measures of home exposure, hand/object-to-mouth behaviour. Adjusted analyses conducted to take into account important confounders (e.g. dietary calcium intake).
Was the study free from other risks of bias?			Low		No further risks of bias noted
Overall risk of bias rating (Optimal result: "very low", meaning the study is at very low risk of bias)			MODERATE		Randomised controlled trial; rated as low risk of bias for randomisation and allocation concealment but high attrition (and higher in placebo group).
RESULTS					
Outcome	Calcium supplementation (mean, SD)		Placebo calcium supplementation (mean, SD)		Measure of effect/effect size (95% Confidence Interval
Mean blood lead level (µg/dL) at 3 months post-baseline	15.1 (6.3)	35	16.6 (7.2)	32	**MD -1.50** (-4.75 to 1.75)
Mean blood lead level (µg/dL) at 6 months post-baseline	14.0 (7.2)	34	14.4 (6.8)	24	**MD -0.40** (-4.04 to 3.24)
Comments					

McLaine, P, Shields, W, Farfel, M, Chisolm, JJ, Jr. & Dixon, S 2006, 'A coordinated relocation strategy for enhancing case management of lead poisoned children: outcomes and costs', Journal of Urban Health, vol. 83, no. 1, pp. 111-28.

Affiliation/source of funds	Affiliation: National Center for Healthy Housing; Source of funds: National Center for Healthy Housing, Fannie Mae Foundation, J.C. Penney Foundation and the US Department of Housing and Urban Development
Study Design	Cohort
Location/Setting	Baltimore, Maryland, United States; community-based intervention
Population	Children <6 years of age with blood lead levels >19 μg/dL (outcomes collected in children but the intervention was delivered to families); n = 87 (n = 112 children included but only one child per family included in the analysis). Participants included mainly low-income families (96% received public assistance).
Source of lead	86% of children lived in homes that had identified lead hazards pre-intervention.
Removal of lead source	At follow-up, 53% of children lived in homes that did not meet lead standards.
Intervention	Intervention A: Housing relocation assistance, including: liaison with prospective landlords by a social worker, visual inspection of prospective homes to check for lead, provision of transport to view prospective homes, small financial assistance (e.g. security deposits and rental application fees (Direct assistance) Intervention B: In-home and clinic-based education, visual inspection of child's home to check for lead with thorough explanation of any identified program hazards, in-home cleaning demonstration, access to a social worker and provided with a lead of potential new homes (Indirect assistance) Both indirect and direct assistance provided by social workers, housing assessor and program coordinators.
Comparison	No housing relocation
Length of follow up	12-months post-baseline, or until the end of the evaluation period
Outcomes	Mean blood lead level (μg/dL)
Comments	Some families relocated without any assistance from program staff; these families were included in one of the intervention groups (not clear which one). All families were enrolled in the relocation program; therefore those who did not relocate still received either the direct or indirect assistance program. Children who needed chelation therapy were identified as part of the program and provided with free chelation therapy (regardless of group assignment). The authors also compared program costs, time taken to move and dust lead levels. Program costs per child were approximately $1,500 (whether they relocated or not because all children were enrolled in the program) and mean time to move was 5 months in both the relocation groups. At the time of relocation, 65% of dwellings in the direct assistance group had dust lead levels below minimum standards, compared with 33% in the indirect assistance group and 26% in the no relocation group.
RISK OF BIAS	

Bias Domain	Judgement	Support for judgement
Do inclusion/exclusion criteria vary across comparison groups?	Low	Inclusion/inclusion did not vary across groups
Does the strategy for recruiting/allocating	High	All families were invited to receive the intervention but families made the decision to relocate

participants vary across groups?		or not, effectively self-selecting which group they entered into
Does the study account for important variations in the execution of the study from the proposed protocol?	Unclear	Some families moved homes without any direct or indirect program assistance; they were counted in one of the relocation groups. Some families did not move homes but received relocation assistance. In addition, some families moved multiple times during the study period. Some children received chelation therapy as part of the program (but these children were excluded from the blood lead level analysis between groups).
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Not reported but as the outcomes were assessed in the context of an evaluation this is unlikely. blood lead level is an objective outcome, so less of an issue
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Low	Inclusion/exclusion criteria - consistently implemented, but reliability and validity are unclear (although not applicable for most inclusion criteria).
Was the length of follow-up different across study groups?	Unclear	The length of follow up was 12 months or until the end of the evaluation period. It is not reported how many participants were not followed up for 12 months
Were incomplete outcome data adequately addressed?	High	blood lead levels were not assessed in a number of children at the 12 months follow up (unclear reasons). In addition a number of children were excluded from the analysis. In total 41/112 children's blood lead levels were tested. They were not accounted for in the analysis.
Was the study free from selective outcome reporting?	Low	No published protocol but unlikely to have been selective outcome reporting (with blood lead level being the most relevant outcome)
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	High	Demographic details (rental versus owner occupied, income, number of children, marital status of parents) not reported by comparison group. Additional details (i.e., education, knowledge of lead hazards) not reported. Therefore unable to assess important differences between groups at baseline. The intervention groups were self-selected so it is possible that some of these variables may have acted as confounders.
Was the study free from other risks of bias?	Low	No other risks of bias noted
Overall risk of bias rating (Optimal result: "very low", meaning the study is at very low risk of bias)	HIGH	Cohort study; Rated as high risk of bias for items related to confounding and very high loss to follow up

RESULTS				
Outcome	Home relocation (Direct assistance)	Home relocation (Indirect assistance)	No home relocation (mean, SD)	Measure of effect/effect size

	M (SD)	N =	M (SD)	N =	M (SD)	N =	(MD, 95% Confidence Interval)
Mean blood lead levels (µg/dL) post-intervention (Intervention A vs B)	17.0 (4.76)	18	16.6 (5.83)	12	N/A		**MD 0.40** (95% CI -3.56 to 4.36)
	M (SD)		N =		M (SD)	N =	
Mean blood lead levels (µg/dL) post-intervention (Intervention A + B vs control)	16.84 (5.12)		30		19.7 (5.08)	11	**MD -2.86** (95% CI -6.38 to 0.66)

Rappazzo, K, Cummings, CE, Himmelsbach, RM & Tobin, R 2007, 'The effect of housing compliance status on children's blood lead levels', Archives of Environmental & Occupational Health, vol. 62, no. 2, pp. 81-5.

Affiliation/source of funds	Affiliation: US Environmental Protection Agency; Source of funds: US Environmental Protection Agency
Study Design	Cohort
Location/Setting	Philadelphia, PA, United States; community-based intervention
Population	Children* with blood lead levels ≥ 10ug/dL; < 6 years (and sub-set < 2 years) (outcomes collected in children but the intervention was delivered to families); n = 959 (<6 yrs), n = 747 (<2 yrs). The authors report they were provided with no demographic information.
Source of lead	Source of lead not reported.
Removal of lead source	Removal of lead hazards confirmed by a visual and environmental home assessment. Children included in the compliance group lived in homes that had passed these inspections.
Intervention	Compliance with US lead housing standards (the owners of homes in Philadelphia with children with blood lead levels >= 10ug/dL living in them were required by law to remediate their houses. Remediation could have been by city contractors or home owners). Compliance meant the house passed a visual inspection (i.e. no chipping or peeling paint) and environmental inspection, in that dust lead levels were less than current standards on floors, window sills, soil in children's play area and soil in the rest of the yard. Inspections were conducted by home inspectors.
Comparison	Non-compliance with US lead housing standards
Length of follow up	Between 1.5 years to greater than three years (results stratified by timing of blood lead test; 1.5 to 2 years, 2 to 3 years and > 3

	years)				
Outcomes	Mean change in blood lead level (μg/dL) (results stratified by age groups; 0 to 6 years and 0 to 2 years)				
Comments					
RISK OF BIAS					

Bias Domain	Judgement	Support for judgement
Do inclusion/exclusion criteria vary across comparison groups?	Low	No. All children who with blood lead levels greater than 10ug/dL were invited to participate. Some exclusions applied in the analysis that differed between time points but these were applied across both the intervention and control groups
Does the strategy for recruiting/allocating participants vary across groups?	Low	No. All children were "recruited" from the Childhood Lead Poisoning Prevention of Philadelphia database.
Does the study account for important variations in the execution of the study from the proposed protocol?	Unclear	Houses could be remediated by city contractors or by homeowners. Despite the fact that they had to pass a lead inspection, the authors note that the homeowner remediated houses may not have been as well remediated as the contractor remediated homes. The time between blood tests was variable (between 1.5 to 3 years) - program guidelines recommended that children be tested at least yearly. More children in the non-compliant group (63%) had a three-year blood lead level test than the non-compliant group (36%). The drop outs in the compliant group could've been different to those that stayed.
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Only outcome measure was blood lead levels. As blood lead levels were measured by lab staff as part of the statewide program (not part of the study) they would likely have been unaware of the compliance status of participants, nor the fact that their data would be used in a future evaluation.
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Low	blood lead levels - as an inclusion criteria and outcome measure were consistently implemented and are reliable. Determination of compliance with housing standards was done via an inspection. It is not clear how consistent the assessments were between houses. No other confounders - i.e. demographics were assessed
Was the length of follow-up different across study groups?	Unclear	Yes. The authors stratified the results by time between pre and post-intervention blood test and provided this between groups. While approximately 50% of children aged between 0 to 6 years had two follow up tests before the age of three, the percentage of intervention and control participants who had a third test was very different (63% versus 36%). For children aged between 0 to 2, the percentages of children who had a test before and after the age of 1 are no different between groups.
Were incomplete outcome data adequately addressed?	Low	Only children with complete blood lead level results were included in the analysis. There

		was no missing data.
Was the study free from selective outcome reporting?	Low	blood lead level was the main outcome and this data was reported. Unlikely to have been other outcomes that were not reported.
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	High	Important confounders such as socio-economic status, seasonality, age at testing and others were not taken into account in the analysis - thus a number of potential confounders exist.
Was the study free from other risks of bias?	Low	No further risks of bias noted
Overall risk of bias rating (Optimal result: "very low", meaning the study is at very low risk of bias)	moderate	Cohort; rated as high on some aspects of confounding, no other study issues

RESULTS					
Outcome	Compliant with housing standards		Non-compliant with housing standards Mean, SD)		Measure of effect
	Mean *change* (SD)	N =	Mean *change* (SD)	N =	Mean change difference (MD), 95% CI
Children aged 0 to 2 years (n = 747)					
Mean change (pre- to post-intervention) blood lead level (µg/dL), children tested at < 1 years	-7.09 (8.634)	120	-7.93 (8.868)	123	**MD 0.84** (95% CI -1.36 to 3.04)
Mean change (pre- to post-intervention) blood lead level (µg/dL), children tested at > 1 years	-12.95 (10.064)	228	-12.78 (10.118)	276	**MD -0.17** (95% CI -1.94 to 1.60)
Mean change (pre- to post-intervention) blood lead level (µg/dL),TOTAL, all timepoints	-10.93 (9.98)	348	-11.28 (9.994)	399	**MD 0.35** (95% CI -1.09 to 1.79)
Children aged 0 to 6 years (n = 959)					
Mean change (pre- to post-intervention) blood lead level (µg/dL), children tested at 1.5 to 2 years	-11.01 (7.6)	114	-9.72 (8.627)	117	**MD -1.29** (95% CI -3.39 to 0.81)
Mean change (pre- to post-intervention) blood lead level (µg/dL), children tested at 2 to 3 years	-12.5 (9.619)	186	-11.57 (7.658)	224	**MD -0.93** (95% CI -2.64 to 0.78)
Mean change (pre- to post-intervention) blood lead level (µg/dL), children tested at > 3 years	-14.31 (9.257)	104	-14.61 (9.976)	184	**MD 0.30** (95% CI -1.99 to 2.59)

	Mean change (pre- to post-intervention) blood lead level (µg/dL), TOTAL, all timepoints	-12.44 (8.973)	434	-12.22 (8.932)	525	**MD -0.22** (95% CI -1.36 to 0.92)
Comments						

Strauss, W, Pivetz, T, Ashley, P, Menkedick, J, Slone, E & Cameron, S 2005, 'Evaluation of lead hazard control treatments in four Massachusetts communities through analysis of blood-lead surveillance data', Environmental Research, vol. 99, no. 2, pp. 214-23.

Affiliation/source of funds	Affiliation: Batelle Memorial Institute, Source of funds: not reported
Study Design	Cohort
Location/Setting	Massachusetts (various cities), United States; community-based intervention
Population	Children < 3 years with blood lead levels > 5µg/dL (outcomes collected in children but the intervention was delivered to families); n = 690 (post-intervention data only, n = 1,138 in pre-intervention data). Baseline blood lead levels were 5.76ìg/dL (intervention) and 7.07ìg/dL (control). No demographic information provided.
Source of lead	Home owners who have children with increased blood lead levels living in their home are required by law to do lead remediation or abatement work. Whether the exact source of lead was identified before the lead control work began is unclear.
Removal of lead source	Whether the lead control work was sufficient to remove any lead hazards is unclear.
Intervention	Interior and exterior home lead hazard control interventions. The type and intensity of interventions varied between communities, but all included removing and/or stabilising interior and exterior lead-based (two of the four cities included interior cleaning, floor treatment, window replacement and wall enclosure/encapsulation). The providers of the intervention were not explicitly stated but it is implied they were Massachusetts lead program staff.
Comparison	No home lead hazard control work (control participants were matched on housing and blood lead level from a pool of children < 3 years of age with at least one pre-intervention blood lead level > 0µg/dL).
Length of follow up	Between one to three years post-intervention (results of all blood lead tests included in the single post-intervention analysis. Additionally, approximately 45% of children had repeated blood lead level measures (20% had two tests, 11% had three tests and 14% had four or more tests).
Outcomes	Mean blood lead level (µg/dL). Note that the authors also reported the percentage of blood lead level tests ≥ 10ug/dL. As this was the number of tests, not the number of children we do not report this outcome.
Comments	The authors selected three different control groups; matched on housing only; housing and blood lead level and blood lead level only. We selected blood lead level only as it controlled for two potential confounders. Additionally, the authors presented the

	arithmetic and geometric blood lead levels. We selected geometric blood lead levels as this provides a more accurate estimate of longitudinal change data. Across the communities, the average cost of the interior treatments ranged from about $4500 to $8500 per unit while average exterior treatment costs ranged from about $2000 to $8000 per unit.				
RISK OF BIAS					
Bias Domain		Judgement	Support for judgement		
Do inclusion/exclusion criteria vary across comparison groups?		Unclear	Inclusion criteria for intervention and control groups was based on the same data obtained from three different sources. Intervention group was chosen from participants within this database that received a lead hazard control intervention and had a blood lead level ≥ 5 ug/dL. The tax status and physical location of each house was recorded. Three different matched controls were created (only one used for the purposes of this review - Housing-blood lead level: matched on housing and blood lead levels).		
Does the strategy for recruiting/allocating participants vary across groups?		High	Intervention participants were allocated based on their exposure to the intervention. Potential for bias as the reasons that the intervention participants received the intervention and the control participants did not.		
Does the study account for important variations in the execution of the study from the proposed protocol?		High	The interventions differed across the four communities in which it was delivered (in terms of components and intensity) but the authors provide little detail about the differences. They report that participants in Boston and Cambridge received cleaning, window replacement and floor cleaning. This was not included in participants in Springfield and Malden. It is unclear how consistently they were delivered. In addition, the authors report that they cannot be sure that all participants included in the control group definitely did NOT receive a lead hazard control intervention as they were reliant on the accuracy of the databases that they used		
Were outcome assessors blinded to the intervention or exposure status of participants?		Low	Unknown. While each child in each state "received" an intervention, the children's blood lead levels were assessed retrospectively. It is highly unlikely that the staff who tested blood lead levels would've been aware that this data would be later formally compared with other communities in MA.		
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?		Low	Consistent inclusion criteria (government databases and tax status) across groups, outcome blood lead level (reliable), demographic factors not measured		
Was the length of follow-up different across study groups?		Unclear	Length of follow up unclear. Approximately 45% had repeated blood lead measures (two, three or four or more)		
Were incomplete outcome data adequately addressed?		High	There was a large loss to follow-up in terms of the children included in the pre- and post-		

			intervention tests (between 35% to 45% in intervention and control groups). This does not seem to have been accounted for in the analysis.		
Was the study free from selective outcome reporting?		Low	No published protocol but unlikely when blood lead level data is the most important outcome and was reported		
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?		Low	Participants were matched on tax income and location. Pre- and post-intervention change data was adjusted for time, seasonality, age and gender.		
Was the study free from other risks of bias?		Low	No further risks of bias noted		
Overall risk of bias rating (Optimal result: "very low", meaning the study is at very low risk of bias)		HIGH	Cohort; some concerns re confounding, the interventions differed across states and there was a large loss to follow up.		
RESULTS					
Outcome	Home lead hazard control		No home lead hazard control		Measure of effect/effect size
	Mean (SD)	N =	Mean (SD)	N =	MD, 95% Confidence Interval
Mean blood lead level (µg/dL)	3.57 (no SD)	392	3.96 (no SD)	298	MD not calculable, but authors report there was no difference between groups at all time-points (see comments)
EXTERNAL VALIDITY					
Generalisability	We note that home remediation work was not uniform across the different US states in which it was implemented, thus it is unclear whether certain remediation elements were more effective than others.				
Applicability	It is likely that the home remediation described in this study would be reproducible in the Australian context as it consisted of standardised remediation work, such as paint stabilisation and window cleaning.				
Comments	Note that pre-intervention mean geometric blood lead levels were different between groups (7.07µg/dL in the intervention group versus 5.76µg/dL in the control group, however, the authors also calculated the difference in mean blood lead level changes from pre- to post-intervention between groups using a model adjusted for time, seasonality, age and gender, finding no difference at one year (p=0.566), two years (p = 0.256) and three years (p = 0.116). When they compared the difference in the percentage of blood tests ≥10µg/dL (not number of children) there was a statistically significant difference between groups at two years (p = 0.006) and 3 years (p = 0.001) but not at one year post-intervention (p = 0.067)				

Whitehead, NS & Leiker, R 2007, 'Case management protocol and declining blood lead concentrations among children', Preventing Chronic Disease [serial online], vol. 4, no. 1, < http://www.cdc.gov/pcd/issues/2007/jan/06_0023.htm>.

Affiliation/source of funds	Affiliation: Research Triangle Institute International; Source of funds: Not reported				
Study Design	Cohort				
Location/Setting	Six states, United States; community-based intervention				
Population	Children < 2 years at enrolment with blood lead levels between 10 - 19 ug/dL (outcomes collected in children but the intervention was delivered to families); n = 2,109. Participants came from a range of racial backgrounds but nil further demographic information provided.				
Source of lead	Source of lead is not reported.				
Removal of lead source	Whether or not the lead source was removed is not reported.				
Intervention	All children received case management by their local lead poisoning prevention program, but the specific programs differed between (and sometimes within) each state				
Comparison	There was no control group; rather the relative effectiveness of intervention-type was compared with each other. Interventions were classified by their method of contact (three categories: mail, telephone or home visit) and by the type of service delivered (two categories: educational materials on lead exposure prevention or lead source investigation). All interventions were included in both classifications (i.e. method of contact and type of service delivered).				
Length of follow up	Between 3 to 12 months (many children had at two or more tests during this period, all available test results were included)				
Outcomes	Mean change in blood lead level (ug/dL)				
Comments	The authors did not know the exact nature of interventions provided in each state and did not do a comparison of results between states.				
RISK OF BIAS					
Bias Domain	Judgement	Support for judgement			
Do inclusion/exclusion criteria vary across comparison groups?	Low	Inclusion criteria into the study (aged <2 years at initial testing) and follow up blood lead level taken between 3 to 12 months later do not vary across groups.			
Does the strategy for recruiting/allocating participants vary across groups?	High	Criteria for entry into each of the State-based case management programs are not stated beyond being under 6 years of age with 10-19 µg/dL blood lead level. It is likely that process differed for screening/finding children with lead exposure. In addition, data was collected in 1994 and 1995. In 1996, targeted screening for lead exposure replaced universal screening - which resulted in changed inclusion criteria. Depending on the "evenness" of recruitment between states, this could have changed the demographics and blood lead levels of children who received the intervention in 1996.			

Does the study account for important variations in the execution of the study from the proposed protocol?	High	There was some variation in the timing of the follow up assessment - 3 to 12 months, based on the recommended timing within each state-based program. The authors note that they assume each child in the study received the interventions as provided in their home state, but it is possible that some children did not receive any intervention - favours the null. In addition, very little information was known by the authors about the components of state-based case management protocols beyond what is provided in the report, i.e. intensity, duration, length
Were outcome assessors blinded to the intervention or exposure status of participants?	Low	Unknown. While each child in each state "received" an intervention, the children's blood lead levels were assessed retrospectively. It is highly unlikely that the staff who tested blood lead levels would've been aware that this data would be later formally compared with other states.
Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure, outcomes, participant health benefits and harms, and confounding?	Low	Inclusion based on blood lead level (reliable measure). Outcome measure blood lead level (reliable measure). Only age (reliable measure) was assessed as a confounder. Other demographic details (i.e. SES, race and ethnicity), State of residence, and the presence of additional lead exposure prevention interventions were not assessed.
Was the length of follow-up different across study groups?	Unclear	Yes. Length of follow up differed between different case management protocols. The authors mitigated this somewhat by only including participants who had at least one follow up assessments taken between 3 and 12 months. The authors estimate that most children had 1-2 follow up tests and this usually happened 3 to 4 months after the first follow up test. The authors controlled for length of follow up time in the analysis though, mitigating this effect somewhat.
Were incomplete outcome data adequately addressed?	High	Only participants with follow up blood lead levels were included (no incomplete blood lead level data). However the demographic data was incomplete (23% complete). When this data was assessed to look at the impact of race and payment source they found that telephone contact was no longer showed a statistically significant impact on blood lead levels. In addition, the number of follow up tests participants had was determined by their case management protocol. Those that had more tests would've had more time to show a reduction in blood lead levels. As change scores were used, this is a potential confounder
Was the study free from selective outcome reporting?	Low	No protocol mentioned however blood lead level is the most relevant outcome so selective outcome reporting unlikely
Were the important confounding and effect modifying variables taken into account in the design and/or analysis?	High	No matching undertaken in design. Results were stratified by method of contact and type of case management service and adjusted and unadjusted blood lead levels were provide. Adjusted scores took into account child's age (score 1) and child's age at initial and follow up test (score 2), which effectively controlled for the variable follow up time. Demographic factors (SES/parental education level, race, ethnicity) were not reported/not collected sufficiently to include as confounders in the analysis. In addition, the minimal information provided about the case management protocols means that differences in the

		intensity/components of the intervention could confound the differences seen in method of contact and type of service.
Was the study free from other risks of bias?	Unclear	Approximately half the participants were from Wisconsin. The relative effect in Wisconsin versus other states was not reported
Overall risk of bias rating (Optimal result: "very low", meaning the study is at very low risk of bias)	HIGH	Cohort; concerns re confounding, follow up differed markedly, and no matching undertaken in design or analysis

RESULTS							
Outcome	Mail		Telephone		Home visit		Measure of effect/effect size
	(Mean, SE)	N =	(Mean, SE)	N =	(Mean, SE)	N =	Mean difference, 95% Confidence Interval
Mean change in blood lead level (µg/dL) ALL children, pre- to post (by method of contact)	1.18 (0.2)	1383	–0.72 (0.02)	262	–1.96 (0.4)	464	The authors concluded, "we found that home visit protocols were associated with a larger decline in blood lead concentrations than mail or telephone contact protocols, regardless of a child's initial blood lead concentration. Mailed educational materials alone were not associated with lower blood lead concentrations."
	Education			Investigation			
	(Mean, SE)	N =		(Mean, SE)		N =	
Mean change in blood lead level (µg/dL) ALL children, pre- to post (by type of service delivered)	0.36 (0.2)	1939		-0.92 (0.5)		170	
Comments	The authors compared the effects within two populations sub groups (children with initial blood lead level between 10 to 14µg/dL and children with blood lead level between 15 to 19 µg/dL)						

Appendix 14. Included studies, and additional related papers.

Berg 2012

Berg, D. R., E. T. Eckstein, et al. (2012). "Childhood lead poisoning prevention through prenatal housing inspection and remediation in St. Louis, MO." American Journal of Obstetrics & Gynecology 206(3): 199-194.

Brown 2006

Brown, M. J., P. McLaine, et al. (2006). "A randomized, community-based trial of home visiting to reduce blood lead levels in children." Pediatrics 117(1): 147-153.

Campbell 2012

Campbell, C., E. Gracely, et al. (2012). "Primary prevention of lead exposure--blood lead results at age two years 16." International Journal of Environmental Research and Public Health 9(4): 1216-1226.

Campbell, C., M. Tran, et al. (2011). "Primary Prevention of Lead Exposure: The Philadelphia Lead Safe Homes Study." Public Health Reports 126: 76-88.

Dietrich 2004

Chen, A., G. G. Rhoads, et al. (2006). "The Effect of Chelation on Blood Pressure in Lead-Exposed Children: A Randomized Study." Environmental Health Perspectives 114(4).

Dietrich, K. N., J. H. Ware, et al. (2004). "Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry." Pediatrics 114(1): 19-26.

Bhattacharya, A., R. Shukla, et al. (2007). "Effect of succimer chelation therapy on postural balance and gait outcomes in children with early exposure to environmental lead." Neurotoxicology 28(3): 686-695.

Peterson, K. E., M. Salganik, et al. (2004). "Effect of succimer on growth of preschool children with moderate blood lead levels." Environmental Health Perspectives 112(2): 233-237.

Treatment of Lead-exposed Children Trial, G. (1998). "The Treatment of Lead-exposed Children (TLC) trial: design and recruitment for a study of the effect of oral chelation on growth and development in toddlers." Paediatric and Perinatal Epidemiology 12(3): 313-333.

Dugbatey 2005

Dugbatey, K., V. Croskey, et al. (2005). "Lessons from a primary-prevention program for lead poisoning among inner-city children 371." Journal of Environmental Health 68(5): 15-20.

Ettinger 2009

Ettinger, A. S., H. Lamadrid-Figueroa, et al. (2009). "Effect of calcium supplementation on blood lead levels in pregnancy: a randomized placebo-controlled trial." Environmental Health Perspectives 117(1): 26-31.

Téllez-Rojo, M., H. Lamadrid-Figueroa, et al. (2006). "A Randomized Controlled Trial of Calcium Supplementation to Reduce Blood Lead Levels (and Fetal Lead Exposure) in Pregnant Women." Epidemiology 17(6): S123.

Fertmann 2004

Fertmann, R., S. Hentschel, et al. (2004). "Lead exposure by drinking water: an epidemiologial study in Hamburg, Germany." International Journal of Hygiene & Environmental Health 207(3): 235-244.

Markowitz 2004

Markowitz, M. E., M. Sinnett, et al. (2004). "A randomized trial of calcium supplementation for childhood lead poisoning." Pediatrics 113: e34.

McLaine 2006

McLaine, P., W. Shields, et al. (2006). "A coordinated relocation strategy for enhancing case management of lead poisoned children: outcomes and costs." Journal of Urban Health 83(1): 111-128.

Rappazzo 2007

Rappazzo, K., C. E. Cummings, et al. (2007). "The effect of housing compliance status on children's blood lead levels 287." Archives of Environmental & Occupational Health 62(2): 81-85.

Strauss 2005

Strauss, W., T. Pivetz, et al. (2005). "Evaluation of lead hazard control treatments in four Massachusetts communities through analysis of blood-lead surveillance data." Environmental Research 99(2): 214-223.

Whitehead 2007

Whitehead, N. S. and R. Leiker (2007). "Case management protocol and declining blood lead concentrations among children." Preventing Chronic Disease 4(1): Serial online.

Appendix 15. Results of GRADE Assessments for the systematic review of management strategies for reducing lead exposure at an individual level in children and adults

Studies	GRADE rating	Comments
Environmental interventions, children aged 0-<1 year		
Berg 2012	Very low	Very serious issues with risk of bias (lack of allocation concealment, large loss to follow up and concerns about confounding) and serious issues with imprecision (wide confidence intervals, indicating possible harm or benefit). This means that any estimate of effect or accuracy is very uncertain.
Environmental interventions, children aged 1-<2 years		
Rappazzo 2007 Strauss 2005	Very low	Very serious issues with risk of bias (lack of allocation concealment, large loss to follow up in one study and concerns about confounding) and serious issues with imprecision (wide confidence intervals, indicating possible harm or benefit). This means that any estimate of effect or accuracy is very uncertain.
Environmental interventions, children aged 2-<5 years		
McLaine 2006 Rappazzo 2007	Very low	Very serious issues with risk of bias (lack of allocation concealment, large loss to follow up in one study and concerns about confounding), serious issues with inconsistency (inconsistent direction of effect between and within studies) and serious issues with imprecision (wide confidence intervals, indicating possible harm or benefit). This means that any estimate of effect or accuracy is very uncertain.
Environmental interventions, adults aged 12-<60 years		
Fertmann 2004	Very low	Serious issues with risk of bias (uncertainty about allocation concealment and loss to follow up) and very serious issues with precision (confidence interval likely to be wide, very small sample size). This means that any estimate of effect or accuracy is very uncertain.
Educational interventions, children aged 0-<1 year		
Campbell 2012	Low	Very serious issues with risk of bias (lack of allocation concealment, large loss to follow up). This means that further research is very likely to have an important impact on our confidence in the estimate, and is likely to change this estimate.
Pharmacological interventions, children aged 1-<2 years		
Dietrich 2004	Moderate	Serious issues with imprecision (moderately wide confidence intervals), but no further issues. This means that further research is likely to

Studies	GRADE rating	Comments
		have an important impact on our confidence on the estimate of effect or accuracy, and may change the estimate.
Pharmacological interventions, children aged 2-<5 years		
Markowitz 2004	Very low	Serious issues with risk of bias (moderate loss to follow up) and very serious issues with imprecision (wide confidence intervals suggesting possible harm or benefit, small sample size). This means that any estimate of effect or accuracy is very uncertain.
Pharmacological interventions, pregnant and lactating women		
Ettinger 2009	Moderate	Serious issues with risk of bias (uncertainty about allocation concealment). This means that further research is likely to have an important impact on our confidence in the estimate of effect or accuracy, and may change the effect.
Combination interventions, 0-<1 year		
Dugbatey 2005	Very low	Very serious issues with risk of bias (uncertainty about allocation concealment, high attrition) and very serious issues with imprecision (wide confidence intervals suggesting possible harm or benefit, small sample size). This means that any estimate of effect or accuracy is very uncertain.
Combination interventions, 1-<2 year		
Whitehead 2007 Brown 2006	Very low	Serious issues with risk of bias (lack of allocation concealment in one study), serious issues with inconsistency (differences in interventions) and imprecision (wide confidence intervals, indicating possible harm or benefit). This means that any estimate of effect or accuracy is very uncertain.