Australian Government
National Health and Medical Research Council

NHMRC

NHMRC Information Paper: Evidence on the Effects of Lead on Human Health

May 2015

WORKING TO BUILD A HEALTHY AUSTRALIA

Publication Details

Publication title:	NHMRC Information Paper: Evidence on the Effects of Lead on Human Health
Published:	May 2015
Publisher:	National Health and Medical Research Council
NHMRC Publication reference:	EH58A
Online version:	www.nhmrc.gov.au/guidelines/publications/eh58
ISBN Online:	978-1-925129-36-6
Suggested citation:	National Health and Medical Research Council. *2015 NHMRC Information Paper: Evidence on the Effects of Lead on Human Health.* Canberra: National Health and Medical Research Council; 2015

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About NHMRC

The National Health and Medical Research Council (NHMRC) is Australia's peak body for supporting health and medical research. NHMRC is responsible for:

- funding the best research selected through a competitive peer review process
- developing health advice for the Australian community, health professionals and governments in the form of public health and clinical practice guidelines, public statements, information papers and evidence reviews
- providing advice on ethical behaviour in health care and in the conduct of health and medical research.

The work of NHMRC is directed by the *National Health and Medical Research Council (NHMRC) Act 1992* (Commonwealth) and guided by its strategic plan. The NHMRC Strategic Plan 2013–2015[1] has identified 'new and emerging health threats' (including infectious diseases, environmental hazards, and changes in the human environment) as one of the major health issues for consideration in this triennium.

This information paper is an example of how NHMRC fulfils its function to 'advise the community' under Section 7(1)(a) of the *NHMRC Act 1992.* It provides a summary of evidence on the health effects of lead and how they can be managed and is intended for the Australian community, health professionals and policy makers. It was produced by identifying, analysing and synthesising published research on this issue. It is intended that the information paper will be used to raise awareness of potential health risks, guide clinical practice and influence environmental health policy.

Executive summary

Summary of evidence

Background

Lead is a naturally occurring metal found in the earth's crust. It has a wide variety of uses in manufacturing due to its properties of being soft, malleable and corrosion resistant. Australia is one of the world's major lead-producing countries.

Exposure to lead is a possible health hazard. People are considered to be exposed to lead if there is lead in their immediate environment (e.g. home or workplace) which is likely to be absorbed into their body. People can absorb lead into their bodies by breathing air that contains very fine particles of lead, by swallowing contaminated dust, soil, water or food, or by mouthing objects such as toys that are contaminated with lead. In Australia, the standard test for exposure to lead is a blood test that measures the concentration of lead in the bloodstream.

Most people in Australia live in places where there are very small amounts of lead in food, drinking water, air, dust, soil and consumer products. However, peoples' exposure to lead has substantially reduced in recent decades due to national initiatives which have restricted the addition of lead to paint and petrol, and the use of lead in consumer goods (e.g. toys, cosmetics and cans). The average blood lead level among Australians is now estimated to be less than 5 micrograms per decilitre and it is uncommon for someone to have a blood lead level greater than 10 micrograms per decilitre. This level is likely to decrease further over time as the presence of lead in the environment continues to reduce.

A blood lead level greater than 5 micrograms per decilitre may indicate that a person has been, or continues to be, exposed to lead as a consequence of an activity they are doing or the presence of lead in their environment. People working in or living near lead smelters and lead mines can be exposed to higher levels of lead than are found in other areas. In Australia, state and territory governments manage programs to monitor and reduce lead exposure in these communities.

Effects of lead on human health

Health effects as a result of lead exposure differ substantially between individuals. Factors such as a person's age, the amount of lead, whether the exposure is over a short-term or a longer period, and the presence of other health conditions, will influence what symptoms or health effects are exhibited. Lead can be harmful to people of all ages, but the risk of health effects is highest for unborn babies, infants and children.

It is well established that blood lead levels greater than 10 micrograms per decilitre can have harmful effects on many organs and bodily functions. Effects such as increased blood pressure, abnormally low haemoglobin, abnormal kidney function, long-term kidney damage and abnormal brain function have been observed at blood lead levels between 10 micrograms and 60 micrograms per decilitre in adults and children.

Encephalopathy—which is characterised by irritability, agitation, poor attention span, headache, confusion, uncoordinated walking or movement, drowsiness, convulsions, seizures or coma—can occur at blood lead levels of 100–120 micrograms per decilitre in adults and 70–100 micrograms per decilitre in children. Death can occur at these blood lead levels in some cases.

The evidence for health effects occurring as a result of blood lead levels less than 10 micrograms per decilitre is less clear. NHMRC's comprehensive review of the health effects of lead found an association between reductions in Intelligence Quotient (IQ) and academic achievement in children at blood lead levels less than 10 micrograms per decilitre. There is weaker evidence that blood lead levels less than 5 micrograms per decilitre are associated with reductions in IQ or academic achievement.

For blood lead levels between 5 micrograms and 10 micrograms per decilitre, an association was observed between higher occurrence of behavioural problems (poor attention, impulsivity and hyperactivity) in children, increased blood pressure in adults (including pregnant women) and a delay in sexual maturation or puberty onset in adolescent girls and boys.

The relative contribution of lead to the above health effects is difficult to determine. The effects of blood lead levels less than 10 micrograms per decilitre on IQ, academic achievement and behavioural problems is likely to be small, with stronger influences being exerted by other factors such as socioeconomic status, education, parenting style, diet, or exposure to other substances.

Managing exposure to lead

In Australia, when an individual or group of people has an elevated blood lead level, finding and removing the source of lead is the most obvious strategy to reduce the risk of harm. NHMRC's systematic review assessed whether any particular intervention (e.g. action or treatment) for reducing lead exposure is more effective than other interventions or no intervention in children, adults, pregnant women and breastfeeding women.

Overall, the body of evidence for interventions to reduce lead exposure was small and of poor quality. Most studies were not appropriately designed or large enough to make accurate comparisons between participants receiving the intervention and those receiving no intervention or the usual care. Several studies did not report whether the source of lead exposure had been identified or confirmed whether it had been removed. The results of these studies may have been misleading if some participants were exposed to other sources of lead in addition to those targeted by the intervention strategy, or due to the release of lead that had previously been stored in bones.

The findings of studies cannot be applied to communities at high risk of exposure to lead from nearby lead mines, smelters or other lead industries. In these communities, lead management strategies are linked to community based screening, education and community wide engagement activities.

Conclusions

NHMRC's review of the health effects of lead found an association between blood lead levels less than 10 micrograms per decilitre and health effects in some population groups. However, there is insufficient evidence to support a causal association between blood lead levels less than 10 micrograms per decilitre and any of the health effects that were observed.

Reducing the amount of lead in the environment (e.g. in soil, dust, air and products) as much as possible will reduce the risk of harm from lead exposure, especially for young children and unborn babies. Health authorities in Australian states and territories should continue to focus on identifying people who have been exposed to more lead rather than the trace 'background' amounts typically found in the everyday environments of most communities.

If a person has a blood lead level greater than 5 micrograms per decilitre, their exposure to lead should be investigated and reduced. Identifying and controlling the source of lead exposure will reduce the risk of harm to the individual and to the community.

Introduction

Purpose

This information paper provides Australians with a summary of the evidence on the health effects of lead and how these health risks can be minimised. It is based on the findings of a comprehensive independent review of recent evidence,[2] which was commissioned by NHMRC.

This information paper replaces the 2009 NHMRC *Blood lead levels for Australians. An information paper for practitioners and policy makers.*[3]

Context

Research evidence available at the time of the 2009 NHMRC public statement on blood lead levels[4] indicated that all Australians should minimise exposure to lead as much as possible and that the source of exposure should be investigated where blood lead levels are found to be greater than 10 micrograms per decilitre, especially for children and pregnant women.

NHMRC has reviewed the latest published evidence on the health effects of lead to assess whether health effects occur at blood lead levels less than 10 micrograms per decilitre.

Scope

This information paper provides information about:

- how people can come into contact with lead i.e. how people are exposed to lead
- who should be tested for lead and how it is done
- the effects of lead exposure on the health of children and adults
- strategies to reduce or manage exposure to lead.

It does not contain information, policy or guidance about:

- which treatment, if any, a person should have if a blood test shows that they have a particular amount of lead in their blood
- how lead-contaminated sites should be managed
- how health risks due to lead should be managed in communities living near lead smelters or mines, or in people who work in industries that use lead
- how state, territory or federal governments should reduce lead in the environment or manage health risks due to lead across the whole population.

For people living in areas where there are higher amounts of lead in the environment, special management strategies are needed. Health authorities in each state and territory oversee these programs.

Why is lead a health issue?

Lead is a naturally occurring metal found in the earth's crust and has a wide variety of uses in manufacturing due to its properties of being soft, malleable and corrosion resistant. Unlike many other naturally found metals, lead and lead compounds are not beneficial or necessary for human health, and can be harmful to the human body. Reducing exposure to lead remains an important health issue in Australia because it is present in various sources throughout the environment.

The possibility of health effects from lead in the body is higher for children and babies (including unborn babies) than for adults, because their bodies are smaller and their brains are developing rapidly.

How lead enters the body

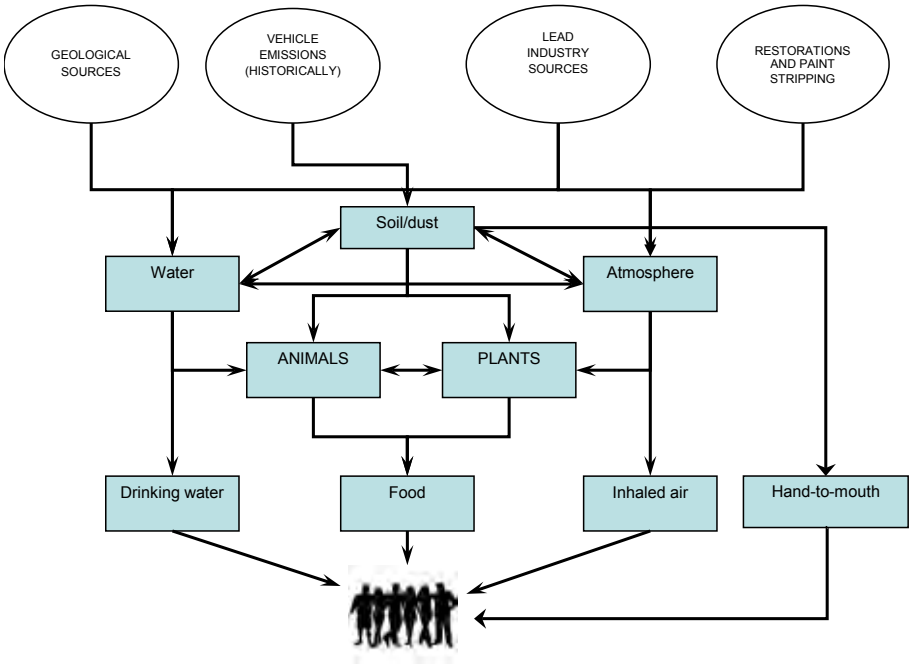
The main way people absorb lead into the body is by breathing lead-contaminated air or swallowing lead-contaminated particles. In pregnant women, lead in the bloodstream can cross the placenta into the foetus's blood. The proportion of lead that is absorbed depends on several factors including the solubility of the lead contaminant, the size of the lead particles and the person's age, sex, and diet.

Small children are also more likely than adults to swallow small amounts of lead, because they put things in their mouths, touch dusty surfaces indoors and outdoors, and touch their mouths more often. Children also absorb a higher proportion of lead than adults as their bodies are growing and changing constantly.[5]

Once in the lungs or gut, lead is absorbed into the bloodstream and is distributed to the liver, kidneys, lungs, brain, spleen, muscles, and heart, and can be stored in bones and teeth. Lead that has been stored in bones and teeth can be released many years after exposure. This tends to occur during times of calcium stress, which includes pregnancy, breastfeeding, menopause, growth spurts, prolonged bed rest or in osteoporosis.[6-9]

Over a number of years most of the lead in the blood is removed from the body by the kidneys in urine, and some is removed by the liver in faeces.

Figure 1: Principal pathway of lead from the environment to humans



Source: Environment Protection Agency (USA). Air Quality Criteria for Lead, Volume I (2006).[10]

Sources of lead in Australia

Most people in Australia live in places where there are very small amounts of lead in food, drinking water, air, dust, soil, and consumer products. Most of this lead is left over from when lead was widely used in the manufacture of industrial and household goods. Lead added to paint and petrol was previously the main source of lead exposure in the community. Prior to initiatives that limited the use of lead in manufacturing, most Australians handled, breathed and swallowed small amounts of lead every day.

The amount of lead in our homes and everyday surroundings has decreased substantially over recent years due to the following national initiatives:

- Lead has not been added to petrol in Australia since 2002.[11]
- The amount of lead in house paints was limited to 1% in 1965, 0.25% in 1992 and 0.1% in 1997.[12]
- Regulations now restrict or prevent the use of lead in consumer goods (e.g. toys, cosmetics, ceramics, water pipes), medicines and the importation of products that contain lead.[a]

Lead occurs in the environment as a wide variety of compounds and remains permanently in dust and soil until it is physically removed. In some communities with a history of high traffic flow, soil may still contain lead deposited from traffic fumes prior to the removal of lead from petrol. In some cases lead based paints in older residential areas are the source of lead in the environment.[13] When old houses and buildings are renovated, lead paint is often stripped or sanded which creates very fine particles of lead in dust that may be inhaled or consumed by people living or working inside or nearby the property.[14]

Although the use of lead in petrol and paints in Australia has been restricted, it may still be found in some fuels (aviation gasoline for piston engines and some racing fuels) and paints and finishes on some products (e.g. cars and boats). Lead is still used in lead-acid batteries and some ceramic glazes (Table 1).

Drinking water may contain small amounts of lead due to the existence of lead in the solder and fittings of older pipes.[15]

Blood lead levels in Australia

Most people in Australia will have some level of lead in their blood because of the small amounts of lead found throughout the Australian environment. Exposure to these small amounts of lead is considered to make up the 'background' level of exposure.

The average 'background' blood lead level among Australians today is not known, because few studies have measured levels in people who do not work in or live near lead mines, smelters, or workplaces that use lead.[13]

Based on the limited evidence from a number of small studies on Australian children[16,17] and studies in other developed countries[2], Australia's background lead level is estimated to be less than 5 micrograms per decilitre (0.24 micromoles per litre). This level is much lower than the level of exposure for previous generations as the presence of lead in the environment is slowly decreasing over time.[18]

a Information on current restrictions is available from the Australian Government Department of Health National Industrial Chemicals Notification and Assessment Scheme (http://www.nicnas.gov.au/).

In Australia, it is now uncommon for someone to have a blood lead level greater than 10 micrograms per decilitre. Occasionally, this level of lead exposure occurs due to workplace activities, soil contamination from industrial processes, building work and renovations, or household products (Table 1). Severe health effects due to high lead exposure, such as gastrointestinal pain, convulsions or death, are now extremely rare in Australia.

People working in or living near lead smelters and lead mines can be exposed to higher levels of lead than are found in other areas. These industries produce air pollution that contains lead which contaminates the local dust and soil. Exposure to lead has been documented in the communities of Port Pirie (South Australia), Mount Isa (Queensland), Broken Hill (New South Wales), Lake Macquarie (New South Wales), Goulburn (New South Wales) and Esperance (Western Australia).[19-24]

Table 1: Sources of lead exposure in Australia

In the home

- Food or drink containers made with lead (lead crystal, pewter, ceramic cookware), especially if it was improperly fired (e.g. imported tagines)
- Imported toys containing lead or coated with lead-based paints
- Imported 'traditional' medicines
- Imported jewellery
- Imported cosmetics
- Old iron enamelled bathtubs, old pipes, solder and plumbing fittings
- Soil contaminated with lead
- Dust contaminated with lead
- Fishing sinkers
- Curtain weights

Activities

- Restoring homes, boats, cars and furniture that are coated with lead-based paints
- Glazing and firing pottery
- Soldering (radiators, stained glass, electronics)
- Casting lead (e.g. to make ammunition, fishing sinkers)
- Burning of lead-stabilised plastics or materials coated with lead-based paints
- Recycling of objects containing or coated with lead products (e.g. motor vehicle bodies, batteries, electronic equipment)
- Eating animals hunted using lead shot
- Exposure to lead dust at shooting ranges
- Lead mining and smelting, other industries that use lead

The review process

The evidence review

NHMRC commissioned the Cochrane Public Health Group from the Melbourne School of Population and Global Health within the University of Melbourne (the reviewers) to conduct an independent review of the scientific evidence on lead and human health. The evidence review involved three components:

- **A background literature review** – finding and summarising the evidence on the health effects observed in individuals with a blood lead level 10 micrograms per decilitre and higher, available methods for testing for lead in individuals and how lead exposure is managed. This broad background literature review provided context for the two systematic reviews.
- **An overview of recent evidence on health effects of blood lead levels less than 10 micrograms per decilitre** (systematic review of systematic reviews) – finding, analysing and summarising existing reviews of evidence on the health effects associated with blood lead levels (i) less than 5 micrograms per decilitre and (ii) 5 micrograms to 10 micrograms per decilitre, in children and adults.
- **A review of recent evidence on managing exposure to lead** (systematic review) – finding, analysing and summarising the evidence on whether strategies for reducing blood lead levels in children and adults are effective.

The evidence review focused on recent (2004–2013) evidence from countries that belong to the Organisation for Economic Co-operation and Development (OECD), as their lead exposure patterns and policy are generally more comparable to those of Australia.

The research methods are described in Appendix A.

The full report of the evidence review (evidence report) is available at: www.nhmrc.gov.au/guidelines-publications/eh58

Oversight by the Lead Working Committee

Planning and processes of the evidence review were guided by the Lead Working Committee (Appendix B). The Lead Working Committee had expertise in public and environmental health, health risk management, toxicology, paediatric medicine, rural medicine and research methodology, and included a consumer representative. Its roles included:

- providing the reviewers with background information on lead, to help them develop the research questions
- providing scientific advice on the interpretation of the evidence
- guiding the development of the information paper
- identifying gaps in the evidence base.

Quality assurance processes

NHMRC uses rigorous quality assurance processes in the development of health advice. The processes used to ensure the quality of the independent review and the information paper are outlined in Appendix C.

Findings of the evidence review

Part A. Testing individuals for exposure to lead

Background

Exposure to lead can occur over a short period of time (acute exposure), or as repeated or continuous exposure over a longer period of time (chronic exposure).

Whether exposure to lead is acute or chronic will affect the amount of lead that is absorbed and stored in the body, especially in bone. The pattern of lead exposure, absorption and bone storage must be taken into account when interpreting blood lead tests (see *Interpretation of blood lead tests).*

Methods of testing for lead exposure

In Australia, doctors and toxicologists use the blood lead test as the standard, accepted and most accurate method for testing individuals and communities for recent exposure to lead. It involves collecting a blood sample from a vein (venous blood sample) or finger prick (capillary sample).

Venous blood is generally preferred because it is less prone to contamination from lead on the skin, although taking a capillary sample is less invasive and preferred in some screening programs.

Other methods of testing for lead include other types of blood tests (e.g. plasma lead test or erythrocyte protoporphyrin test) and tests of bone, teeth, sweat, nails or hair. These tests are sometimes used in research studies, but they are not recommended as standard tests to assess individuals by health professionals. These testing methods have not been standardised for medical use or been used in the same way blood lead levels have been used to measure associations between exposure to lead and health effects.

Testing of lead in sweat, nail and hair samples also tends to be inaccurate as they are prone to contamination by surface lead which affects the reliability of the result.

Accuracy of blood lead testing

The accuracy of blood lead tests (venous samples and capillary samples) are influenced by the timing of blood testing (relative to the exposure), the blood collection technique and the technique used to analyse the sample in the laboratory. Blood lead tests may not detect exposure to lead that occurred or stopped more than about 6 months before the sample was taken.

To avoid contamination with unabsorbed lead on the skin – resulting in a falsely high result – the blood sample must be collected from an area where the skin has been cleaned and is free of lead. Contamination of the sample in the laboratory must also be prevented.

As with any laboratory test, blood lead test results are not perfectly accurate, even when following strict protocols. It is more difficult to accurately measure samples in which the concentration of lead is less than 10 micrograms per decilitre. This means there is a small margin of error when interpreting results (e.g. if an individual's blood test result is 5 micrograms per decilitre, this would generally indicate that their actual blood level is somewhere between 4 micrograms and 6 micrograms per decilitre). There is also a slight variation in accuracy between different testing laboratories (e.g. if an

individual's actual blood lead level is 5 micrograms per decilitre, most laboratories would give a result somewhere between 3 micrograms and 7 micrograms per decilitre).[b]

This is also the case with capillary blood as the sample is very small so the test is harder to perform accurately. Combined with the risk of contamination discussed above, this means that capillary samples generally report higher concentrations of lead and have a greater margin of error than venous samples.

Interpretation of blood lead tests

A blood lead test generally detects lead that the person has breathed or swallowed within a few weeks or months.

If a person has been exposed to a steady, small amount of lead (rather than a larger amount from an unusual source), blood lead is a reliable indicator of their level of exposure, especially if several measurements are available. However, if a person is exposed to a large amount of lead, a blood lead test may not indicate the total amount of lead in a person's body. This is because the lead circulating in the body is excreted by the kidneys or liver (as urine and faeces) and the remainder is stored in bone. This stored lead may be released back into the blood during pregnancy, lactation, menopause, osteoporosis, periods of growth and periods of extended bed-rest.

If a person has a blood lead level greater than 5 micrograms per decilitre, there are several possible reasons:

- They may have recently been exposed to lead in a single incident such as accidently swallowing some lead dust or lead containing paint.
- They may have been exposed to higher-than-average amounts of lead over time such as from the continual inhalation of lead dust.
- Lead that had previously accumulated in their bones is being released into their bloodstream.

Who should be tested for lead?

Testing in individuals

Individuals should be tested for lead exposure if there is a reason to suspect they have swallowed or breathed lead from a particular source (more than the very small amounts in most people's everyday environments), or if they have unexplained health problems that could be due to lead.

The World Health Organization (WHO) recommends that a child should be tested for lead if:[25]

- they are known to have been exposed to lead, or there is a possibility they may have been exposed
- someone in their household has been exposed to lead
- they show severe health problems that could suggest exposure to lead (e.g. sudden severe abdominal pain, seizure or coma)
- they have other persistent, unexplained health problems (e.g. headache, muscle pain, tiredness, anaemia, constipation, joint pain, not eating, sleep disturbance or difficulty concentrating) **and** there is a reason to suspect they have been exposed to lead.

These recommendations also apply to pregnant women and other adults.

b Under the Australian Standard (AS 2411-1993), the acceptable reporting range for a blood lead level of 11 micrograms per decilitre is 7–14 micrograms per decilitre. However, many laboratories provide test results that are more accurate than this minimum standard, and some have a very high standard of accuracy.

Testing in higher-risk groups

In Australia, programs for testing for lead have been set up in whole communities or regions (screening programs) where there is a high risk of lead exposure due to lead smelting or lead mining industries such as in Mount Isa, Port Pirie and Broken Hill.

In many countries, including Australia, the regular monitoring of blood lead levels of workers likely to be exposed to lead is required by legislation. The legislation also requires that workers found to have blood lead levels above certain values should be protected from further exposure (for example, by being moved out of the workplace or away from contact with lead).

National screening

The WHO has a set of criteria that assess whether there is benefit in implementing national screening programs for health conditions.[26,27] Australia does not fulfil the criteria for implementing a national screening program for blood lead levels, for a number of reasons:

- The evidence from the small number of Australian studies is consistent with evidence from various OECD[c] countries indicating that, in the general community, the proportion of people exposed to additional sources of lead is very small.[2,16,17]
- There is no acceptable treatment for people exposed to lead who have no signs or symptoms of health problems caused by lead.
- The reduction in national blood lead levels that could be achieved by a screening program would be very small, compared with the substantial reduction that has been achieved in the population over the past 20–30 years.
- The cost of screening the whole population for elevated blood lead levels is difficult to justify when considered against the benefit of reducing the burden of disease in Australia.
- A 2002 expert report on health screening and surveillance in children[28] recommended against a national lead screening program for Australian children. The report's recommendation was based on evidence available at the time of publication,[28] when average blood lead levels among Australian children were higher than current blood lead levels.

Research and monitoring

At present, information about blood lead levels in Australia is predominantly available from high-risk areas where screening programs are implemented. There are limited data for low-risk areas which is confined to few research studies and data obtained through state and territory notification requirements. Reliable data would help Commonwealth, state and territory governments develop and revise policy for lead management.

Notification

Elevated blood lead levels are not notifiable conditions in the Australian Capital Territory, the Northern Territory or South Australia. However should a doctor refer someone with an elevated blood lead level, a public health practitioner or environmental health officer would follow up the case if warranted.

c Organisation for Economic Cooperation and Development

In other states and territories there is legislation that requires pathology laboratories (or medical practitioners) that conduct blood lead testing to notify public health authorities if a person's blood lead level is found to be above a specified level. As of January 2015, in New South Wales,[29] Queensland,[30] Tasmania[31] and Victoria,[32] pathology laboratories that conduct blood lead testing (and medical practitioners in Victoria) must notify public health authorities if a person's blood lead level is 10 micrograms per decilitre or higher.

In Western Australia,[33] medical practitioners must notify health authorities if they make a diagnosis of 'lead poisoning'.

Information on current requirements for notification is available from the department of health or equivalent in each state and territory.

Part B. Effects of lead on human health

Health effects associated with blood lead levels of 10 micrograms per decilitre and higher

Exposure to lead resulting in a blood lead level of 10 micrograms per decilitre and higher can have harmful effects on many organs and bodily functions (Figure 2). Very high exposure to lead can result in death.

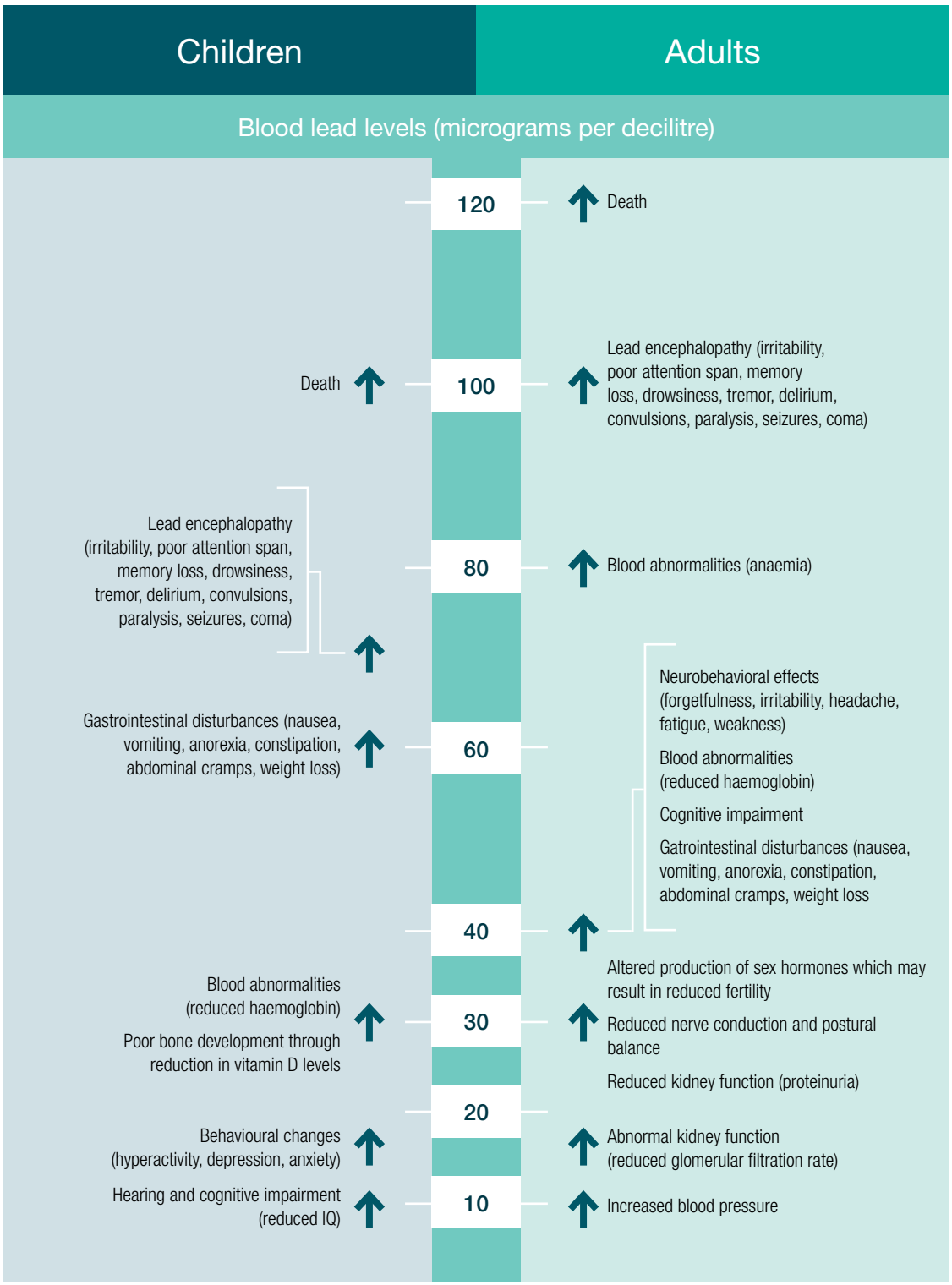
The health effects due to exposure to lead observed in an individual depends on a person's age, the amount of lead a person is exposed to and for how long, and if they have other health conditions. Lead can be harmful to people of all ages, but the risk is highest for unborn babies, infants and young children because their brain and nervous system is developing rapidly. For example, an adult exposed to lead in the workplace over several years may show different symptoms and health effects than a child exposed over a short period, even if both have the same blood lead level detected on a blood test. The following list summarises the health effects that have been reported in adults and children with blood lead levels of 10 micrograms per decilitre and higher:[2]

- **Effects on blood pressure** – Raised blood pressure (hypertension) has occurred after short-term exposure in adults with blood lead levels of approximately 50 micrograms per decilitre or more.
- **Effects on kidneys** – Abnormal kidney function has also occurred after repeated or long-term exposure in adults and children with blood lead levels between 10 micrograms and 20 micrograms per decilitre, with more severe effects at higher blood lead levels.

  Inflammation of the kidneys (acute interstitial nephritis) and abnormal kidney function (acute renal impairment) have occurred after short-term exposure in adults with blood lead levels of approximately 40 micrograms per decilitre or more.

  Long-term kidney damage (chronic nephropathy) severe enough to cause death has occurred after short-term exposure in adults and children with blood lead levels of approximately 60 micrograms per decilitre or more.
- **Effects on red blood cells** – Abnormally low levels of haemoglobin (the protein that carries oxygen around the body) have been measured after repeated or long-term exposure in adults and children with blood lead levels of approximately 40 micrograms per decilitre or more.
- **Effects on the brain and nerves** – Severely abnormal brain function (encephalopathy) has occurred in adults and children exposed to high amounts of lead resulting in blood lead levels of 100–120 micrograms per decilitre in adults and 70–100 micrograms per decilitre in children.[9] Signs and symptoms can include irritability, agitation, poor attention span, headache, confusion, uncoordinated walking or movement (ataxia), drowsiness, convulsions, seizures or coma. Other problems with brain and nerves have occurred after long-term exposure in adults and children with blood lead levels of approximately 40 micrograms per decilitre or more. These include problems with thinking, anxiety, mood changes, dizziness, fatigue, sleep disturbance, headache, irritability, lethargy, a general feeling of discomfort, slurred speech, convulsions, muscle weakness, sensation of burning, tingling or prickling in the skin, inability to control movement of the arms and legs, tremors and paralysis.

Figure 2: Health effects of blood lead levels 10 micrograms per decilitre and higher



Upward arrows indicate the lowest blood lead level at which the health effects were reported in individuals in various studies. Blood lead levels at which people exhibit symptoms vary greatly between individuals. It is possible for people with blood lead levels of 40 micrograms per decilitre or more not to exhibit noticeable health effects.

Sources: Agency for Toxic Substances and Disease Registry[USA]. *Toxicological profile for lead* (2007),[9] Health Protection Agency [UK]. HPA Compendium of Chemical Hazards Lead, version 4 (2012).[34]

Health effects associated with blood lead levels less than 10 micrograms per decilitre

Context

There is increasing scientific evidence that suggests blood lead levels less than 10 micrograms per decilitre may have subtle health effects that can only be detected when comparing large groups of people such as communities or regions (populations). However, blood lead levels less than 10 micrograms per decilitre do not cause noticeable health effects in individuals.

The NHMRC systematic review was designed to evaluate the recent evidence on the health effects in children and adults associated with blood lead levels less than 5 micrograms per decilitre and between 5 micrograms and 10 micrograms per decilitre.

The research methods are described in Appendix A.

Findings of the overview of recent evidence

Literature searches identified 112 eligible studies. Of these studies, 98 were included in two large systematic reviews on the effects of low-level exposure to lead:

- National Toxicology Program (NTP) monograph on health effects of low-level lead, US Department of Health and Human Services (2012).[35]
- Integrated Science Assessment for Lead by the US Environmental Protection Agency (EPA) (2013).[36]

Because both these systematic reviews were comprehensive and judged by the AMSTAR tool[37] to be of moderate quality, the NHMRC reviewers chose to systematically review these reviews (overview).[2] The overview process involved considering the findings of the included studies identified in the systematic reviews to form the body of evidence on health effects associated with blood lead levels less than 10 micrograms per decilitre. In drawing conclusions on this evidence, an evaluation of each study's design was required to judge its ability to answer the research question and to determine whether the methodology that was used was appropriate. This is because limitations in study design or in the way a study is conducted can affect the reliability of a study's results.

The reviewers also undertook a literature search, assessment of eligibility, quality assessment and consideration of results of studies other than systematic reviews. Recently published studies (not included in the NTP and EPA reviews) included two systematic reviews,[38,39] two prospective cohort studies[40,41] and ten cross-sectional studies.[42-51] These studies provided limited additional information to the evaluation of the evidence.

Based on the NTP and EPA reviews, the NHMRC reviewers summarised published evidence for associations between lead exposure and health effects as follows:

- Blood lead levels less than 5 micrograms per decilitre are associated with adverse cognitive effects in children (i.e. reduced academic achievement and reduced IQ), but the literature suggests that uncontrolled confounding had an important influence on the findings for IQ (i.e. factors that affect IQ, other than lead exposure, were not controlled in the studies).
- Blood lead levels less than 10 micrograms per decilitre are associated with the following health effects:
  - Adverse behavioural effects in children (i.e. effects on attention, impulsivity and hyperactivity).
  - Delay in sexual maturation or puberty onset in adolescent girls and boys.
  - Increased blood pressure and increased risk of hypertension among adults and pregnant women.

The reviewers identified that some of the individual studies included in the review were not of high quality or were not of an appropriate study design to answer the research question. In other instances the study design did not take into account potential errors in measurements or factors other than lead that may affect outcomes, such as IQ or blood pressure.

The Lead Working Committee took these points into consideration when considering the results of the overview. This is discussed in more detail below.

Interpreting evidence for health effects of lead exposure

In interpreting the overall body of evidence on the health effects of blood lead levels less than 10 micrograms per decilitre, the Lead Working Committee took the following into consideration:

- Whether the available evidence could be relied upon, based on the design and quality of the studies examined.
- The principles for assessing whether a particular risk factor *causes* a health effect in the community (Bradford Hill Criteria).
- How the evidence from community-wide studies applies to individuals.

1. What is the quality of the included studies and are there limitations in their design?

When considering a body of scientific evidence, it is important to identify the strengths and weaknesses of each study in order to assess the validity of the findings and their usefulness in addressing the issue under consideration.

In determining how much confidence could be placed on the results of the studies reported in the overview, the Lead Working Committee considered:

- If the individual study's design was appropriate for examining the research question.
- If there was adequate reporting on how the studies were conducted to determine whether the influence of chance and bias were minimised.
- Whether the study accounted for all plausible factors, other than lead, that may have influenced the health outcomes observed (i.e. confounding factors).
- If the method for measuring exposure and health outcomes were appropriate for determining the health effect being examined.
- The number of people studied, how they were selected and whether they were followed for a sufficient period of time.

The overview identified only a few studies that provided high quality evidence (i.e. studies that were well designed, well conducted and well reported) to assess the possible health effects of blood lead levels between 5 micrograms and 10 micrograms per decilitre, or less than 5 micrograms per decilitre.

The most reliable type of evidence that blood lead levels less than 10 micrograms per decilitre causes health effects would be from prospective cohort studies in which:

- investigators measured blood lead levels and compared the health of groups of people with different levels of exposure to lead over a period of time
- blood lead tests were performed by the same laboratory or used the same protocols for analysis
- the health measures were made by the same investigators, using well-defined standardised methods
- other risk factors for the health effects were identified and measured, and carefully taken into account when analysing the results.

However, few of the studies included in the overview had all these characteristics. This may be because it is difficult and expensive to design and conduct studies that reliably measure the effects of blood lead levels less than 10 micrograms per decilitre. Since all individuals in the community are, or have been, exposed to at least a small amount of lead, all studies on the health effects of lead compare groups with differing levels of lead exposure.

This is further complicated when combining evidence from studies conducted around the world, due to different methods of measuring blood lead levels and the varying accuracy of these tests. The error margin when measuring blood lead levels may be widened when comparing different studies and combining data (see *Testing individuals for exposure to lead).*

It is also difficult to characterise the health effects that occur in populations with low levels of lead present in their blood. For instance, the methods of measuring or estimating IQ varied between the studies included in the overview. IQ results are generally not precise or accurate enough to be confident that the small differences observed in a child's IQ are due to a particular factor and not simply due to natural variation or chance. It is also difficult to eliminate all the other plausible explanations for small differences in a child's IQ, such as socioeconomic status. Similarly, where an association was found between blood lead levels and blood pressure, the available studies often did not satisfactorily account for other factors such as smoking, eating and drinking habits, body weight and physical activity. In the studies where these factors were not carefully considered in the analysis and interpretation of results, it is very difficult to determine whether the observed health effects were due only to lead exposure, or to estimate the relative contribution of lead exposure in causing the observed health effects.

Almost all available evidence on the health effects of blood lead levels less than 10 micrograms per decilitre came from overseas studies, where patterns of exposure to lead (including the amounts of lead and the duration of exposure) and other health-related factors may differ from those in Australia.

2. Does the evidence demonstrate that blood lead levels less than 10 micrograms per decilitre cause health effects?

When the results of population studies show that there is an association between a risk factor in the environment (e.g. exposure to lead) and a measure of health (e.g. average blood pressure in a community), this does not prove that the risk factor directly caused the health condition. In order to make reliable conclusions about causation, the Lead Working Committee determined whether the overall body of evidence fulfilled the Bradford Hill criteria[52] for establishing causation, including that:

- there was a strong association between the risk factor and the health effect (given that there is more likely to be a causal association when a large difference is observed between effects on people with the risk factor and people without the risk factor)
- the same association has been consistently observed in several studies
- there are no other likely explanations for the association
- whether there is a plausible mechanism to explain how the exposure might result in health effects
- the effect can be demonstrated to have occurred after exposure to the risk factor, within a plausible period of time
- higher exposure to the risk factor was associated with a greater effect (dose–response relationship).

It is well established that blood lead levels greater than 10 micrograms per decilitre cause adverse health effects (i.e. harmful effects on kidneys, red blood cells, and on the brain and nerves) and that very high levels can cause death, because evidence accumulated over many years fulfils all these criteria.

The evidence from studies conducted in groups of people with blood lead levels less than 10 micrograms per decilitre does not fulfil all these criteria for the following reasons:

- Most of the reported associations did not show a large difference in health effects between the comparison groups and those people with blood lead levels between 5 micrograms and 10 micrograms per decilitre and with less than 5 micrograms per decilitre.
- While the same associations were consistently demonstrated in the studies assessing people with blood lead levels between 5 micrograms and 10 micrograms per decilitre, there were only a few studies that considered people with blood lead levels less than 5 micrograms per decilitre.
- Other explanations were not sufficiently ruled out, due to weaknesses of cross-sectional study designs, limitations in the methods used to measure blood-lead levels and health outcomes, and because other plausible explanations for the observed associations were not addressed in most of the studies.
- While a dose-response relationship was observed between health effects and blood lead levels between 5 micrograms and 10 micrograms per decilitre, there was insufficient data to determine whether a dose-response relationship was evident between health effects and blood lead levels less than 5 micrograms per decilitre.

Based on the current available evidence, it is not possible to conclude that lead was the direct cause of any of the reported health effects in individuals with blood lead levels less than 10 micrograms per decilitre. While the results from some studies indicate that blood lead levels less than 10 micrograms per decilitre may be associated with some health effects, the available cross-sectional studies do not provide the type of convincing evidence that would enable public health experts and statisticians to make confident conclusions about cause and effect.

3. Can the findings be applied to individuals?

The findings of the studies included in the overview reflect an association between average blood lead levels and health effects measured in groups of people, rather than directly showing an association between exposure and health in individual participants. For most measures of health, the studies reported only small average differences between groups with different average blood lead levels. The small differences in a group's average for a measure of health may not reflect health effects that can be tested or diagnosed by a doctor in an individual patient who has been exposed to lead. For example, it is not possible to conclude that if a person's blood lead level is slightly higher than the national average that this will lower their IQ.

Evidence on the health effects of blood lead levels less than 10 micrograms per decilitre

After considering the evidence and taking into account the quality and design of the studies, the Lead Working Committee made the following conclusions about the health effects on the population with blood lead levels less than 10 micrograms per decilitre:

- While the body of evidence indicates that there may be an *association* between blood lead levels and health effects in some population groups, there is not enough high-quality evidence (i.e. results of studies that were well-designed, well-conducted and well-reported) to conclude that a blood lead level less than 10 micrograms per decilitre was the *causing* factor for any health effects that were observed.
- The available evidence suggests that blood lead levels between 5 micrograms and 10 micrograms per decilitre are associated with reduced IQ and academic achievement in children. The relative contribution of lead in causing reduced IQ is unknown. Certain populations of children may be affected by other factors (e.g. socioeconomic status, education, parenting style, diet, or exposure to other substances) that put them at greater risk, making it difficult to know how much blood lead levels between 5 micrograms and 10 micrograms per decilitre may contribute to reduced IQ.

- There is weaker evidence of an association between blood lead levels of less than 5 micrograms per decilitre and reductions in IQ or academic achievement in children. Whilst these findings suggest that low-level exposure to lead may have a small effect on a child's brain function, the evidence strongly suggests that other factors in the groups of children studied have a much stronger influence on measured outcomes such as IQ and academic achievement.
- Blood lead levels between 5 micrograms and 10 micrograms per decilitre are associated with a higher occurrence of behavioural problems (poor attention, impulsivity and hyperactivity) in children. The relative contribution of lead exposure to these behavioural problems, compared with other factors (as described above), remains unclear.
- Blood lead levels between 5 micrograms and 10 micrograms per decilitre are associated with delays in sexual maturation and puberty onset in adolescent girls and boys. Although this finding provides evidence that lead exposure may have broader effects on the human body (additional to the effects observed on academic achievement and children's behaviour), it is uncertain whether the observed small effect on puberty onset across groups would have any important health effect on an individual or on the community.
- Blood lead levels between 5 micrograms and 10 micrograms per decilitre are associated with increased blood pressure in adults, including pregnant women. It has been estimated that each doubling of the average blood lead level is associated with an increase in the population's systolic blood pressure of 1 millimetre of mercury (mm Hg) (e.g. the average systolic blood pressure of a population with an average blood lead level of 10 micrograms per decilitre would be expected to be 1 mm Hg higher than for a similar group whose average blood lead level was 5 micrograms per decilitre). Small increases in the average blood pressure of a population can result in measurable adverse health effects in a community.

Part C. Managing exposure to lead

Background

National policies aim to reduce levels of lead in our everyday environments throughout Australia.

When an individual or group of people has been exposed to lead in Australia, finding and removing the source of lead is the most obvious strategy to prevent more harm.

Most state and territory health departments in Australia require doctors and/or laboratories to notify them if an individual's blood lead level exceeds a particular value (see *Notification).* Public health officers, environmental health officers or multidisciplinary teams with expertise in exposure risk management may be required to investigate the source. In addition to the blood test, consideration of other factors, such as the possible sources of lead exposure in the person's local environment, are taken into account when making recommendations on what actions should be taken.

Education is usually one part of a multifactorial approach to managing lead exposure. Where an individual's blood lead level is of concern, education on how to identify potential sources of lead exposure and strategies to minimise further exposure is usually provided to families and communities by medical practitioners and public health authorities.

Health professionals or public health authorities may also recommend medical treatment for individuals with a concerning level of lead in their bloodstream. Calcium supplementation is sometimes used as a preventive treatment for people who have been exposed to lead.

Chelation therapy is also available as a medical treatment for people with high blood lead levels. Lead chelation therapy involves the use of medicines that are designed to bind to lead so that it can be removed from the body via the kidneys. However, chelation does not remove lead that is in bones (the main place where lead is stored in the body).

Two types of chelation medicine are used in Australia:

- Intravenous chelation therapy (sodium calcium edetate)[d] is generally only used when a person has severe signs or symptoms of high exposure to lead such as encephalopathy.[53] The potential side effects of intravenous chelation therapy include problems with kidney function and deficiency of essential nutrients such as iron, zinc and copper.[53]
- Oral chelation therapy (succimer)[e] is normally used for people with high blood lead levels (e.g. 70 micrograms per decilitre or higher in adults, or 45 micrograms per decilitre in children) who do not have encephalopathy.[53] It is also used as follow-up treatment after receiving intravenous chelation therapy.[53] Side effects can include abdominal pain, skin rash, alteration in liver function (detected on a blood test) and a decrease in the proportion of neutrophils (a type of white blood cell) in blood.[53] The risks and benefits of the use of succimer in pregnancy should be discussed with a specialist clinician.

A specialist clinician should supervise the treatment of anyone who needs chelation therapy due to lead exposure.

The name 'chelation' is also sometimes used by practitioners of complementary and alternative medicine, to refer to other medicines intended to remove toxins. These medicines have not been tested in clinical trials with people exposed to lead. They should not be used in the treatment of children or adults exposed to lead.

d also called edetate calcium disodium (often abbreviated to calcium EDTA).

e also called dimercaptosuccinic acid (often abbreviated to DMSA).

Findings of the systematic review of recent evidence

The systematic review assessed whether any particular intervention (e.g. action or treatment) for reducing lead exposure is more effective than other interventions or no intervention in children, adults, pregnant women and breastfeeding women.

The reviewers searched for evidence published between January 2004 and mid-May 2013. The research methods used are described in Appendix A.

The literature searches identified 12 studies evaluating interventions to reduce lead in the participants' environment,[54-58] educational interventions designed to reduce exposure,[59] medical treatment[60-62] or combinations of these strategies.[63-65]

The majority of studies included children younger than 6 years old with elevated blood lead levels (between 5 micrograms and 45 micrograms per decilitre) or likely exposure to lead. The systematic review identified no recent studies conducted in older children aged up to 12 years, or in adults aged 60 years and over.

Two studies[60,64] assessed lead reduction interventions in pregnant women without confirmed lead exposure living in socioeconomically disadvantaged areas. The systematic review identified no studies conducted in breastfeeding women.

Recent studies assessing environmental interventions

Five studies assessed interventions designed to reduce lead in the participants' homes. Interventions included using bottled drinking water instead of tap water for young adults,[54] repairing children's homes[55] and moving houses for families with young children.[58]

The reviewers assessed this body of evidence to be very low quality for all the age groups for which data were available. None of the studies reported a reduction in blood lead levels that was large enough to be meaningful for a person's health and wellbeing.

Recent studies assessing educational interventions

One study evaluated the effectiveness of an education program targeting parents of newborn children in neighbourhoods with high risk for lead exposure.[59] There were no statistically significant differences in blood lead levels between children who received the program and those who received less education or usual care.

The reviewers assessed the body of evidence for children aged less than 1 year (one study only)[59] to be of low quality. No evidence was identified for other age groups or pregnant women.

Recent studies assessing medical treatments

Two studies assessed the effectiveness of calcium supplementation:

- A study[60] in pregnant women found that average blood lead levels were slightly lower (average reduction of less than 1 microgram per decilitre) among those who took calcium supplements compared with those who took placebo.
- A study[61] in children found that blood lead levels did not differ between those who took calcium supplements and those who took placebo.

One study assessed the effectiveness of up to three courses of chelation therapy (succimer) in infants aged 12–33 months with blood lead levels of 20–44 micrograms per decilitre.[62] This study was designed to evaluate chelation therapy as a preventive treatment in children with much lower lead exposure than patients who would normally receive this treatment in Australia (see *Overview of strategies used to manage lead exposure).* The study found that succimer treatment was effective in reducing blood lead levels during the first 6 months (by an average of 4.5 micrograms per decilitre, compared with placebo), but after 5 years there was no difference between blood lead levels in the succimer group and the placebo group.[62] The study did not permanently remove lead from the children's homes, so it is reasonable to assume that they continued to be exposed to lead after chelation was stopped.

The reviewers assessed the body of evidence for interventions in pregnant and breastfeeding women (one study)[60] to be of moderate quality. They assessed the body of evidence for interventions in children aged over 1 year and under 2 years (one study)[62] to be of moderate quality, and the body of evidence for interventions in children aged over 2 years and under 5 years to be of very low quality. There was no evidence for other age groups.

Recent studies assessing combination interventions

Three studies[63-65] assessed the effectiveness of combinations of interventions for reducing exposure to lead. Components included home visits, education and case management.

The reviewers assessed the body of evidence for interventions in children aged under 1 year, and the body of evidence for interventions in children aged over 1 year and under 2 years, to be of very low quality. Evidence for other groups was very low quality or absent.

Considerations in interpreting evidence for interventions to reduce lead exposure

The systematic review found very few studies that assessed the effectiveness of strategies to reduce lead exposure that occurs in people's homes (e.g. dust from lead paint).

Overall, the body of evidence was small and of poor quality. Most studies were not appropriately designed or large enough to make accurate comparisons between participants receiving the intervention and those receiving no intervention or the usual care. Several studies did not report whether the source of lead exposure had been identified or confirmed whether it had been removed. The results of these studies may have been misleading if some participants were exposed to other sources of lead in addition to those targeted by the intervention strategy, or due to release of lead that had previously been stored in bones.

The findings of these studies cannot be applied to communities at high risk of exposure to lead from nearby lead mines, smelters or other lead industries. In these communities, lead management strategies operate within a different context and are linked to community based screening, education and community wide engagement activities. Intervention strategies in these areas may require different approaches to those evaluated in this review.

Recommended approach to minimising the health effects of lead exposure

Managing lead exposure in communities

Based on the findings of the NHMRC's review of evidence on the health effects of lead, the following principles are proposed in developing health policy:

1. National policy should continue to aim to minimise communities' exposure to lead, including by minimising the amount of lead that is introduced into our living environments.
2. Health authorities in Australian states and territories should continue to focus on identifying people who have been exposed to more lead than the trace 'background' amounts typically found in the everyday environments of most communities.
3. A blood lead level greater than 5 micrograms per decilitre suggests that the person has been, or continues to be, exposed to lead at a level that is above what is considered the average 'background' exposure in Australia. Education is required to assist in identifying the additional source of lead exposure and further exposure prevented (see Recommendation 11).
4. In communities that are at risk of lead exposure due to industry (e.g. lead mining or smelting), health authorities should continue to run programs to monitor and reduce lead exposure.
5. In Australia, a nation-wide screening program is not warranted.
6. The only way to accurately establish the 'background' exposure to lead across the various regions of Australia would be to undertake coordinated research. This could assist the Commonwealth, state and territory governments to develop and revise their policies for lead management. Data for low-risk areas is limited to a few research studies and from state and territory notification requirements.

Managing lead exposure in individuals

Based on the findings of the NHMRC review of evidence on the health effects of lead, the advice to health professionals, individuals and families in Australia is that:

7. Everyone should avoid contact with lead in homes, communities and workplaces, by being aware of and taking care when performing activities that could expose them to lead.
8. In Australia the most effective method to identify if a person has been exposed to lead is by measuring the level of lead in their blood.
9. Doctors should arrange a blood lead test if there is a particular reason to suspect that a person has been exposed to lead, for example:
    - If they have been involved in activities that may result in them swallowing, breathing in (inhaling) or touching lead or a substance that is contaminated with lead. Examples of these activities include the sanding of surfaces covered in old paint and where children have eaten dirt that may be contaminated with lead.
    - If someone else in their household has had a blood test that showed a level exceeding 5 micrograms per decilitre.
    - If they have signs or symptoms that are consistent with exposure to lead.

10. If a blood test shows that a person's blood lead level is between zero and 5 micrograms per decilitre (0.24 micromoles per litre), no particular action or treatment is needed.
11. If a person has a blood lead level greater than 5 micrograms per decilitre, their exposure to lead should be investigated and reduced – particularly if the person is a child or pregnant woman:
    - They (or their carer if they are a child) should be provided with information on how to identify the possible sources of lead exposure and how it can be reduced.
    - Public health officers, environmental health officers or those with expertise in exposure risk management may be required to investigate how and where the person is being exposed to lead, and remove the source if possible, or prevent contact with it.
12. Chelation therapy is not recommended unless a person has high blood lead levels (e.g. 70 micrograms per decilitre or higher in adults, or 45 micrograms per decilitre in children), or severe signs or symptoms of high exposure to lead such as encephalopathy:
    - Chelation therapy should not be used as a preventive treatment when a person has moderately increased blood lead levels, because chelation does not deal with the problem of ongoing exposure. If the source of lead is still in the person's everyday environment, exposure to lead will continue or recur after chelation has stopped. Moderately elevated blood lead levels should be managed by finding and removing the source of lead or controlling the person's contact with lead.
    - Only specialist clinicians should prescribe and oversee chelation therapy in people who have been exposed to lead.

Conclusion

Minimising lead exposure remains a long-term goal for Australian governments, however, it is noted that exposure to lead in Australian homes and communities is decreasing.

Reducing the amount of lead in our environment (e.g. in soil, dust, air and products) as much as possible will reduce the risk of harm to future generations, especially for young children and unborn babies.

Appendix A. Research methods

Background literature review

The background literature review collected general information about how people can be exposed to lead in their environment, how lead harms the body, how various tests for exposure to lead should be used in individuals and communities, the accuracy of these tests, and strategies for reducing individuals' and communities' exposure to lead.

The methods and findings of the background literature review are described in the evidence report.[2]

Overview (i.e. systematic review of systematic reviews) of the health effects of blood lead levels less than 10 micrograms per decilitre

To assess the health effects of blood lead levels less than 10 micrograms per decilitre, the reviewers chose to conduct a systematic review of systematic reviews (also called an overview). An overview is an efficient method for summarising the findings of available evidence in a way that captures the output of work that has already been done and avoids duplicating research efforts.

The overview was designed to summarise existing systematic reviews of evidence for health effects associated with low-level exposure to lead (blood lead levels less than 5 micrograms per decilitre and blood lead levels between 5 micrograms and 10 micrograms per decilitre), including effects of exposure during pregnancy and breastfeeding, and any differences in effects between sexes and age groups. It was intended to provide information about people exposed to small amounts of lead in environments that were not known to have higher-than-average lead contamination.

The reviewers used a standard method for conducting an overview,[66] but also included some other types of evidence in addition to systematic reviews. The method involved searching for evidence using predefined strategies, assessing each piece of evidence identified using predefined eligibility criteria, assessing the quality of evidence using a standardised method, and considering its results.

The reviewers searched for evidence available from January 2004 to mid-May 2013. This period was selected to ensure that the search captured evidence published since the searches conducted for the previous NHMRC 2009 public statement on blood lead levels.[4] The search was conducted in a series of steps designed to identify the highest-quality evidence wherever possible:

- First, the reviewers identified high-quality systematic reviews of evidence (Level I evidence in the NHMRC hierarchy[f] of evidence).[67]
- Next, the reviewers identified recently published prospective cohort studies[g] (Level II evidence)[67] not already included in systematic reviews identified in the first step.

f Within the NHMRC hierarchy of evidence for making recommendations on health, the level of evidence reflects the quality or reliability of the type of evidence and is determined by study design and by the type of research. For research on the causes of disease (aetiological research questions), prospective cohort studies are considered the highest level of evidence (not including systematic reviews of multiple studies). Source: *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines.* NHMRC; 2009. Available from: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.

g Cohort studies measure health outcomes in a group of people over time.

- Finally, the reviewers identified lower-quality evidence only if there was no level I or level II evidence about a particular blood lead level or age group, or if the identified systematic reviews and prospective cohort studies did not provide clear evidence. In these circumstances, the reviewers identified recent retrospective cohort studies (level III-2), case-control studies (level III-3) and cross-sectional epidemiologic studies (level IV).

The overview only included evidence from:

- Appropriately designed studies (prospective cohort studies, cross-sectional studies, case control studies, or retrospective cohort studies, including systematic reviews of this type of evidence). The most useful evidence for effects of environmental lead comes from studies designed to select a group of people and then measure effects in the same group over time (prospective longitudinal studies), because these kind of studies can collect information about how much lead people are exposed to, how long they are exposed, when they are exposed and their age at the time of exposure.[67]
- Studies in humans – animal studies and laboratory studies were excluded.
- Studies that measured environmental exposure to lead using blood lead tests.
- Studies conducted in groups of people whose blood lead levels were within the two specified ranges (less than 5 micrograms per decilitre, and between 5 micrograms and 10 micrograms per decilitre).

The reviewers did not include evidence from:

- Studies of workers exposed to lead in industrial settings.
- Studies conducted in communities living in known lead-contaminated regions (e.g. lead mining towns).

Systematic reviews were included if they followed standard internationally accepted methods, which included stating the research question at the beginning of the process, collecting data from particular types of studies, clearly explaining how the searches were conducted, applying pre-specified criteria for including and excluding studies, extracting data from the selected studies for comparison, assessing the strength of evidence and results against pre-defined criteria, and making conclusions based on the results and presence or absence of supporting evidence. For existing systematic reviews, the reviewers assessed the quality of the systematic review process using a standardised, internationally accepted method (AMSTAR),[37] but did not extract or assess the individual studies included in the systematic review. For individual studies, the reviewers assessed quality and risk of bias using the NHMRC method,[67] and determined an overall quality rating.

The reviewers assessed the findings for effects on the nervous system, cardiovascular system, reproductive system, blood, immune system, kidney, bone, genes and cancer risk.

The systematic review of systematic reviews is described in more detail in the evidence report.[2]

Systematic review of intervention strategies to reduce blood lead in individuals

The systematic review was designed to assess whether any particular intervention for reducing lead exposure is more effective than other interventions or no intervention in children, adults, pregnant women and breastfeeding women.

The reviewers used a standard method for conducting a systematic review. The protocol for identifying and assessing the evidence was developed and agreed before beginning the search.

The reviewers searched for evidence available from January 2004 to mid-May 2013. This period was selected to ensure that the search captured evidence published since the searches conducted for the previous NHMRC 2009 public statement on blood lead levels.[4]

The overview only included evidence from:

- Appropriately designed studies (randomised controlled trials, quasi-randomised controlled trials, controlled before-and-after studies, or cohort studies). These types of studies can allow for trends in lead exposure over time. The best type of evidence for whether or not a treatment is effective comes from randomised controlled trials.
- Studies of interventions designed to reduce blood lead levels in individuals (not just in the general community).
- Studies that measured blood lead levels using whole blood samples.

The reviewers did not include evidence from:

- Studies with no comparison group. These types of studies may overestimate the effects of treatment because blood lead levels generally decrease over time as the body excretes lead.
- Studies assessing interventions that focus on reducing lead levels in soils or contaminated regions, such as lead mining towns.
- Studies comparing legislation between different jurisdictions.
- Non-OECD countries.

The reviewers assessed quality and risk of bias for each included study using a standardised method based on the Cochrane Collaboration's Risk of Bias Tool for randomised trials[68] and RTI International's item bank on risk of bias and precision of observational studies.[69]

Studies assessing similar interventions in each sub-population (i.e. age groups, pregnant women and breastfeeding women) were grouped together into a body of evidence. Each body of evidence was assessed for its overall quality using the GRADE method,[70] which takes into account the quality of all included studies.

The reviewers assessed the findings for each type of intervention and for each subpopulation, taking into account the quality of the evidence.

The systematic review is described in more detail in the evidence report.[2]

Appendix B. The Lead Working Committee

Membership

The members of the Lead Working Committee are listed in Table 2.

Table 2. Lead Working Committee

Name and qualifications	Job title and other relevant roles
Adjunct Associate Professor Sophie Dwyer PSM (Chair)	Executive Director, Health Protection, Chief Health Officer Branch, Queensland Health
Associate Professor Peter Baghurst	Discipline of Paediatrics and Reproductive Health, Faculty of Health Sciences, University of Adelaide
	Former Head, Public Health Research Unit, Women's and Children's Hospital, South Australia
Professor Brian Gulson	Emeritus Professor, Graduate School of the Environment, Macquarie University, NSW
	Honorary Research Fellow, Commonwealth Scientific and Industrial Research Organisation (CSIRO)
Ms Rosalind Harrison	Toxicologist, Public and Environmental Health Service, Department of Health and Human Services, Tasmania
Ms Vikki Lynch	Advisor, Health Risk Management, Environmental Health, Department of Health and Human Services, Victoria
Dr Martin Matisons	Principal Toxicologist, Environmental Health Directorate, Department of Health, Western Australia
Ms Stephanie Newell	Consumer Representative
Dr David Simon	Director, Scientific Services, Public Health Services, SA Health, Government of South Australia
Dr Simon Slota Kan	Senior Public Health Officer, Regulation, Health Protection & Emergency Management, Department of Health and Human Services, Victoria
	General Practitioner, Swinburne University Health Service
	Former Senior Rural Medical Practitioner, Northern Territory Department of Health
Professor Wayne Smith	Director, Environmental Health Branch, NSW Health
Dr Neil Wigg PSM	Retired. Former Associate Professor, Paediatrics and Child Health, University of Queensland, and former Senior Director, Community, Child and Youth Health, Children's Health Queensland

Former Member

Professor Michael Moore was a member of the Lead Working Committee from 1 December 2012 until his death in August 2014. Professor Moore was an Emeritus Professor of Toxicology at the University of Queensland and provided expert advice to the NHMRC in the development of the evidence review[2] and a consultation draft of the information paper.

Terms of reference

The roles of the 2012–2015 Lead Working Committee included the following:

- to advise on whether NHMRC's 2009 information paper[3] and public statement[4] on lead needed to be updated because of new evidence
- to advise on the development of information on managing individual exposure to lead in Australia (for GPs, paediatricians and public health/environmental health practitioners)
- to consider international reports on strategies to reduce blood lead levels
- to identify gaps in evidence-based public policy relating to management of high blood lead levels
- to advise on how to put into practice the findings from research on the best ways to manage high blood lead levels
- to advise on how NHMRC can best work with state and territory health departments, GPs and paediatricians.

The Committee reported to the Council of NHMRC, through the Prevention and Community Health Committee.

The Committee's full terms of reference are listed on the NHMRC's website (https://www.nhmrc.gov.au/your-health/lead-exposure-and-health-effects/nhmrc-lead-working-committee-2012-2014).

Appendix C. Quality assurance processes

The NHMRC evidence review[2] was reviewed by independent reviewers from the National Collaborating Centre for Environmental Health (NCCEH) in Canada. The NCCEH focuses on the health risks associated with the physical environment, and identifies evidence-based interventions to reduce those risks. The NCCEH examined the methodological quality of the systematic review report to ensure that the review followed the systematic and rigorous approach documented in the review protocol. The methodological review team completed a declaration of interest process before being appointed by NHMRC and no conflicts of interest were identified.

To ensure that all relevant evidence was considered and clearly interpreted by the Lead Working Committee, a draft information paper was released for public consultation from 16 July 2014 to 15 September 2014. During this period the information paper was reviewed by interested members of the public and invited stakeholders (including relevant health and environment departments of each state and territory). Seven public consultation submissions were received during the public consultation period.

To ensure that the evidence had been accurately represented in the information paper, a number of national and international experts in the fields of toxicology, environmental health, epidemiology and paediatrics were approached to review the draft information paper. Three international reviewers provided their comments on the draft information paper. The Lead Working Committee considered all public submissions and independent expert review reports, and revised the information paper as they considered appropriate.

Glossary

Blood lead level The concentration of lead in a person's blood, usually measured in micrograms per decilitre (µg/dL). The result can be converted from micrograms per decilitre to micromoles per litre by dividing by 20.7.

Blood pressure Blood pressure is measured using a sphygmomanometer. The unit of measurement for blood pressure is 'millimetres of mercury'. Systolic blood pressure is the pressure while the heart is contracting (the higher of the two numbers given in a blood pressure reading).

Chelation therapy A medical treatment that involves the use of medicines designed to bind to a metal (e.g. lead) so that it can be removed from the body via the kidneys.

Cohort study A type of research study that measures health outcomes in a group of people over time.

Controlled before-and-after study A type of research study that measures health outcomes in a group of people before and after a treatment.

Convulsions Convulsions are episodes of uncontrolled and involuntary contraction and relaxation of muscles, causing the person to shake.

Cross-sectional study A type of research study that measures health outcomes in a group of people at a particular point in time.

Encephalopathy Abnormal brain function. Signs and symptoms can include irritability, agitation, poor attention span, headache, confusion, ataxia (uncoordinated walking or movement), drowsiness, convulsions (episodes of uncontrolled and involuntary contraction and relaxation of muscles, causing the person to shake), seizures (episodes of abnormal physical movement or behaviour due to abnormal electrical activity in the brain, such as twitching, convulsions, falling down, drooling, unusual movements, sudden uncontrolled mood changes), or coma.

Exposure (to lead) Having traces of lead in the body (e.g. after swallowing or breathing it).

Overview (of evidence) See Systematic review of systematic reviews.

Placebo (in medical research studies) A sham treatment that is compared with the treatment being tested.

Population study A type of research study that collects information about members of a group (e.g. a community or country) to look for associations between a possible cause and a possible effect, but does not control people's exposure to various risk factors.

Prospective cohort study A cohort study in which the design and methods are planned and set out before the study begins.

Quasi-randomised controlled trial A type of research study in which the method of assigning participants to receive the treatment or a comparator was not truly random (e.g. alternation, date of appointment, date of birth).

Seizures Seizures are episodes of abnormal physical movement or behaviour due to abnormal electrical activity in the brain (e.g. twitching, convulsions, falling down, drooling, unusual movements, sudden uncontrolled mood changes).

Systematic review of systematic reviews (Also called a 'systematic overview of reviews' or 'overview') A research method that involves summarising existing systematic reviews of evidence to answer a research question (unlike a systematic review, which finds and summarises or synthesises original studies). A systematic overview of reviews involves assessing the limitations of included systematic reviews, but does not normally involve searching for original studies, assessing their eligibility for inclusion, or assessing risk of bias.[h]

Systematic review (of evidence) A research method that produces the highest level of evidence within the NHMRC hierarchy of research evidence. A systematic review tries to identify, select, synthesise and appraise all relevant high-quality research evidence to answer a particular, pre-specified question. The process involves collating all evidence that fits pre-specified eligibility criteria, and using explicit, systematic methods to minimise bias.[i]

h Source: The Cochrane Collaboration. Preparing a Cochrane Overview of reviews. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Revised March 2011]. The Cochrane Collaboration; 2011.

i Sources: NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. NHMRC; 2009.; Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: The Nuffield Provincial Hospitals Trust; 1972.; Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011.

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