



Protecting and improving the nation's health

Evaluation of whether to lower the public health intervention concentration for lead exposure in children

A report by the lead intervention concentration working group

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Executive summary

Lead exposure is especially harmful in young children and the developing fetus. Blood lead concentration (BLC) is measured to determine recent exposure and alongside clinical evaluation, helps to guide clinical and public health actions.

A BLC of $\geq 10\mu\text{g/dL}$ ($0.48\mu\text{mol/L}$) is the current threshold ('public health intervention concentration') for public health case management in England as well as the existing case definition for surveillance purposes for children under 16 years old, however, this intervention concentration has not been reviewed in the last few years.

Choosing a BLC to use as an intervention concentration requires balancing sensitivity and specificity to reliably detect higher risk cases.

A Public Health England (PHE) led multi-agency 'lead intervention working group' ('the working group'), used rapid systematic and overview review methods to assemble, synthesise and appraise relevant evidence regarding the toxic effects of lead in children even at low BLCs. Given there has been no recent representative BLC estimates in children in England, the group trends in estimated BLCs in other high-income populations have been used to infer how BLCs may have changed in the UK since the 1990s, and therefore where a potential BLC range for children in the UK population may now lie.

Lead is a non-threshold contaminant and therefore may cause adverse health effects when someone is exposed to any concentration. There was strong evidence for adverse effects on cognitive function at BLC $< 5\mu\text{g/dL}$ ($< 0.24\mu\text{mol/L}$), and occurrence of externalising behaviours, and delay in sexual maturation or puberty onset in adolescence at BLC $< 10\mu\text{g/dL}$ ($< 0.48\mu\text{mol/L}$).

The working group did not review the evidence regarding population distribution of BLCs in pregnancy for high-income settings within this report due to it being outside the initial scope. However, there was some evidence from human epidemiological studies of adverse health effects of in utero lead exposure at a maternal BLC $< 10\mu\text{g/dL}$ ($< 0.48\mu\text{mol/L}$). These findings were less consistent, and therefore less certain than for postnatal lead exposure. There is also evidence that lead crosses the placental barrier from maternal exposure. Animal data supported neurotoxic and growth impairment effects. There is human toxicological evidence that in utero exposures to lead contribute to BLCs once the child is born (and potentially to the child experiencing a wide range of adverse health effects). A precautionary approach to minimise in utero exposures would be most consistent with these findings.

On the basis of this review, PHE recommends that the public health intervention concentration and surveillance case definition for children under 16 years old and pregnant women should be lowered from $\geq 10\mu\text{g/dL}$ ($0.48\mu\text{mol/L}$) to $\geq 5\mu\text{g/dL}$ ($\geq 0.24\mu\text{mol/L}$).

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In general, children with the highest BLCs $\geq 5\mu\text{g/dL}$ ($\geq 0.24\mu\text{mol/L}$) are more likely to be exposed to defined, high-concentration sources of lead or to have other health problems that result in increased lead ingestion. Investigation and management of these cases can be complex. Therefore, these children are likely to benefit from multi-disciplinary case investigation and public health management.

For children with BLCs $< 5\mu\text{g/dL}$ ($< 0.24\mu\text{mol/L}$) comprehensive primary prevention measures taken at a population level will instead be required to lower lead concentrations in food, water, soil, industrial emissions and housing.

Although the new public health intervention concentration for children under 16 years old and pregnant women will be $\geq 5\mu\text{g/dL}$ ($\geq 0.24\mu\text{mol/L}$), it is important to note that a BLC of less than $5\mu\text{g/dL}$ ($0.24\mu\text{mol/L}$) is still associated with adverse health effects. The BLC which triggers local public health action of other adults remains as $10\mu\text{g/dL}$ ($0.48\mu\text{mol/L}$). Therefore clinicians, clinical biochemists and environmental health officers (EHOs) may still contact PHE for advice on minimising sources of lead exposure when a BLC is $< 5\mu\text{g/dL}$ ($< 0.24\mu\text{mol/L}$) and should still notify PHE of cases if they are concerned there is a wider public health risk.

Introduction

Background

Lead is a naturally occurring element in the Earth’s crust. However, the widespread occurrence of lead in the environment (air, land and water) is mainly as a result of anthropogenic activities (1). The implementation of legislation and regulations (see Table 1) aimed at reducing exposure to lead has resulted in a substantial reduction in lead in the environment over the past few decades (2).

However, there are still sources of lead in the environment including:

- food is an important source of exposure to lead for the general population. Lead may be found in food as a result of environmental contamination, processing, handling and packaging (2). For further information on lead in food, please refer to the Food Standards Agency (FSA)
- flaking or chipped lead paint and lead paint dust are the main sources of lead exposure in children with elevated blood lead concentrations. Lead paint may be present in properties built before the 1960s (3)
- imported cookware and lead-glazed ceramics can result in the contamination of food (4)
- contaminated soil may be ingested by infants and young children (2)
- drinking water where historic lead piping, soldering or fittings are present in the home or at service connections. Lead is rarely present in tap water as a result of its dissolution from natural sources (5)
- antique toys and imported modern toys may be coated with lead-containing paint
- imported spices, some traditional medicines and cosmetics (4)

Table 1: Legislation and regulations aimed at reducing exposure to lead (6 to 17)

Source of Exposure	Legislation
Drinking water	The use of lead water pipes was phased out by the end of the 1960s and the use of lead solders by the late 1980s. The Water Supply (Water Fittings) Regulations 1999 - lead pipe, fittings and solder are prohibited for use in new installations. The Water Supply (Water Quality) Regulations 2016 (for public supplies) and The Private Water Supplies (England) Regulations 2016 – regulatory limit of 10 µg/L for lead in drinking water.
Air	National air quality objective – 0.25µg/m ³ (annual mean) Directive 2008/50/EC of 21 May 2008, on Ambient Air Quality and Cleaner Air for Europe - EU limit value 0.5µg/m ³

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Land or Soil	<p>Town and Country Planning Act 1990 - the developer is responsible for ensuring that a development is safe and that the land is suitable for the intended use.</p> <p>Part 2A of the Environmental Protection Act 1990 - risk-based approach to the identification and remediation of land where contamination poses an unacceptable risk to human health or the environment.</p> <p>There are no UK regulatory limits for contaminants in soil. Screening levels that can be used to assess land contamination are set to be protective of health.</p> <p>Category 4 Screening Levels - provided for lead for generic land use (residential, commercial, allotments and public open space), based on toxicological review and exposure modelling, as part of the technical guidance to support Part 2A.</p>
Toys	<p>The Toy (Safety) Regulations 2011 and the Toy Safety Directive 2009/48 EC - lead may not be intentionally used in parts of toys that are accessible to children and includes migration limits (how much toy material a child may intake per day and how it may leak into the body) for lead from toys.</p>
Jewellery	<p>Entry 63 of Annex XVII Regulation (EC) No 1907/2006 - lead and its compounds shall not be placed on the market or used in any individual part of jewellery if the concentration of lead is $\geq 0.05\%$ by weight. This regulation includes bracelets, necklaces, rings, piercing jewellery, watches, brooches and cufflinks.</p>
Paint	<p>The Environmental Protection (Controls on Injurious Substances) Regulations 1992 and Entry 16 and 17 of Annex XVII Regulation (EC) No 1907/2006 (REACH regulation) - prohibits the supply and use of certain lead paint other than its supply and use, under certain conditions, for the restoration or maintenance of certain historic buildings or of fine or decorative works of art.</p>
Food	<p>Regulation (EC) No 2006/1881 – includes maximum concentrations for lead in certain foods.</p>

Health effects

Lead exposure is especially harmful to young children and the developing fetus (18). Blood lead concentration (BLC) is measured to determine recent exposure, and alongside clinical evaluation, helps to guide clinical and public health actions. A BLC of $\geq 0.48 \mu\text{mol/L}$ ($\geq 10 \mu\text{g/dL}$) is the current threshold ('public health intervention concentration') for public health case management in England (19).

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Lead is absorbed following ingestion, inhalation and to a much lesser extent via dermal contact. The absorption of lead can be influenced by various factors including a person's age, physiological status, nutritional status and genetic factors.

Lead is generally described as a classic chronic toxin. However, high level acute or short-term exposure can cause colic, (abdominal pain, constipation, vomiting and anorexia) renal and hepatic dysfunction. Very high level exposure can result in encephalopathy (headache, confusion, drowsiness, convulsions and coma (20)) which is more commonly seen in children.

Long-term exposure to lead can cause a range of adverse health effects including anaemia, neurological effects, nephrotoxicity, cardiovascular toxicity (high blood pressure) and effects on male and female reproductive function. Young children and the unborn fetus are particularly vulnerable to neurotoxic effects of lead, as it can adversely affect the development of the brain and the central nervous system (1).

Rationale

BLC is measured to determine recent exposure, and alongside clinical evaluation, helps to guide clinical and public health actions. Lower intervention concentration limits (in the range of 3.5 to 5µg/dL (0.17 to 0.24µmol/L)) have been implemented in several high-income countries following increased awareness of the harmful health effects of lead at even low BLCs. Germany was the first to lower their action level, in 2010 (21), followed by the USA Centers for Disease Control (CDC) in 2012 (22). In addition to lowering their action levels, both nations also adopted new terminology, the 'reference value', because no lower threshold for the adverse effects of lead exposure have been demonstrated. Recognising that any exposure to lead may be harmful, the reference values were instead set to determine unusually high lead exposure in the population, which may be more likely to occur from a specific source.

As such, the reference value, and hence level for public health action, was also lowered in other high-income countries as population lead exposure declined. France and Australia also used extremes of population exposure to set new action levels (23, 24). As there have been no recent population surveys in Australia, the National Health and Medical Research Council of Australia (NHMRC) inferred from previous surveys and data from other high-income settings that 'Australia's background [population] lead level is estimated to be less than 5µg/dL' (24). Wales took a similar approach in 2017 (25).

As the evolving evidence has particularly focused on the harm to children and pregnant women with low BLCs, a multi-agency working group (Public Health England (PHE), National Poisons Information Service (NPIS), University of Bristol and NHS) was formed to review and support the implementation of lowering the lead intervention concentration for children and pregnant women in England. As part of this the working group also considered some of the

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wider contexts of lead exposure such as socioeconomic and health inequalities but these are not discussed within this report.

Methods

Population surveys are a more reliable method to estimate the population's exposure to lead. However, there are no recent survey data estimating the number of children in England exposed to lead (the last survey took place in the 1990s) (26, 27). Therefore, systematic reviews conducted on other high-income countries considering the lead exposure concentrations and health effects were reviewed.

The last review of the health effects of lead exposure was published in 2015 by the NHMRC in Australia; this review took a systematic approach to identifying and appraising literature (28). This review reported an overview of recent systematic reviews, and also an update of primary research literature published, up to May 2013 to summarise the association between low BLCs and adverse health effects in children.

The working group elected to update the NHMRC review by searching for systematic reviews published since 2013. The working group adopted rapid methods to systematically identify and appraise reviews for potential inclusion that is, to perform an overview of reviews). Reviews of potential interest were screened against pre-defined inclusion criteria, and then quality scored using the AMSTAR 2 tool (29). If the AMSTAR 2 score indicated a critically low confidence in the review findings then the working group did not continue to extract information on strength of evidence for association with health outcomes. An example search strategy and screening flow diagram are reported in Appendix A. However, due to the critically low confidence in these studies' findings they were not included in this report and the working group elected to base the conclusions on the results of the NHMRC 2015 overview (28).

A rapid systematic search for surveys or population-based studies estimating BLC in the UK population (national, regional, or sub-regional level) was conducted. The working group also systematically searched for surveys or population-based studies that estimated BLCs in the UK and other high-income countries since 1980, at national, regional, or sub-regional level. Trends in estimated BLCs in other high-income populations allowed the working group to infer how BLCs have changed in the UK, and where a potential BLC range for children in the UK population may now lie.

Results and summary

Overview of systematic reviews and primary research

The NHMRC 2015 overview (28) identified 2 systematic reviews, namely the US National Toxicology Program (NTP) Monograph on Health Effects of Low-Level Lead, 2012 and US Environmental Protection Agency (EPA) Integrated Science Assessment (ISA), 2013, which investigated the adverse health effects of exposure to lead in children (including in utero) at BLCs $<10\mu\text{g/dL}$ ($<0.48\mu\text{mol/L}$) as seen in Table 2 (30, 31).

Both reviews considered human epidemiological evidence when drawing conclusions regarding the health effects of lead exposure. However, they also used toxicokinetic evidence from animal and in vitro studies in addition to epidemiological data to support their conclusions.

For the purpose of the NHMRC review, evidence of association was deemed to occur when the NTP review concluded there was sufficient evidence and the EPA ISA review concluded a causal relationship (see Appendix B), which occurred for the following (taking the highest common BLC):

- child cognitive function decrement at BLC $<5\mu\text{g/dL}$ ($<0.24\mu\text{mol/L}$)
- child externalising behaviours: attention, impulsivity and hyperactivity at BLC $<10\mu\text{g/dL}$ ($<0.48\mu\text{mol/L}$)
- delay in sexual maturation or puberty onset in adolescent girls and boys at BLC $<10\mu\text{g/dL}$ ($<0.48\mu\text{mol/L}$)

The NHMRC review concluded that:

- BLCs $<5\mu\text{g/dL}$ ($<0.24\mu\text{mol/L}$) are associated with adverse cognitive (academic achievement and IQ decrements) effects in children
- BLCs $<10\mu\text{g/dL}$ ($<0.48\mu\text{mol/L}$) are associated with the following health effects:
 - adverse behavioural (attention, impulsivity and hyperactivity) effects amongst children
 - delay in sexual maturation or puberty onset in adolescent girls and boys (15)

Child outcomes

For the cognitive effects, behavioural effects, and sexual maturation or puberty onset health outcomes, the NTP monograph and EPA ISA concluded that they were associated with lead exposure, at low BLCs, even after considering other explanations (30, 31).

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For IQ, one study observed a decline in IQ points of 6.2 (95%CI: 3.8,8.6) with increases in blood lead levels from $<1\mu\text{g/dL}$ to $10\mu\text{g/dL}$ (<0.05 to $0.48\mu\text{mol/L}$) with greater associations at lower levels (32). Therefore, harm may occur at any exposure, but greater exposure results in greater deficit, with proportionally greater harm incurred by initial lower level exposures than subsequent higher exposures. There is more limited evidence on the durability of cognitive function effects into later life, but the evidence available suggests poor reversibility leading to reduced educational attainment (30, 31). The absolute cognitive deficits at low BLCs are relatively small. However, cognitive deficits may have a greater impact in the context of existing potential socioeconomic and health inequalities of lead exposure, and affected individuals may have fewer resources to manage the effects.

Prenatal exposure and birth outcomes

For auditory function decrements, atopy, and birth outcomes the NTP and EPA ISA reports came to differing conclusions (30, 31). Motor impairment, conduct disorder and haematological outcomes (the latter based heavily on animal data) were only included in the EPA ISA (31). For these outcomes there is therefore some evidence, but less certainty, of a potentially causal association with lead exposure.

Birth outcomes are of particular interest as these relate to in utero exposures that would require public health interventions for the pregnant mother. Of these outcomes the largest body of evidence exists for impaired fetal growth. The NTP report found sufficient evidence among women for reduced fetal growth and lower birth weight at BLCs $<5\mu\text{g/dL}$ ($<0.24\mu\text{mol/L}$), but the EPA ISA noted inconsistencies in the observational study findings with decreased certainty of a true association, grading the evidence as being 'suggestive of a causal relationship' (30, 31). For effects on academic performance, the NTP report concluded there was inadequate evidence of an association with prenatal low level lead exposure due to the sparseness of studies (30). They also concluded there was limited evidence of an association with cognitive outcomes due to contradictory study findings. The EPA report deliberately did not make this distinction between prenatal and postnatal exposure (31).

Table 2. Conclusions of the systematic reviews included in the NHMRC 2015 report (relevant to children or in utero exposure) (28, 30 to 31)

SYSTEM	HEALTH EFFECT	NTP MONOGRAPH	EPA ISA
Neurological	Child cognitive function decrement	Sufficient evidence for achievement and IQ, <5µg/dL (<0.24µmol/L)	Causal relationship, <5µmol/L (<0.24µmol/L) (Full Scale IQ, academic performance, and executive function)
	Child externalising behaviours: attention, impulsivity and hyperactivity	Sufficient evidence for attention and behaviour problems, <5µg/dL (<0.24µmol/L)	Causal relationship, <10µg/dL (<0.48µmol/L)
	Child and young adult externalising behaviours: conduct disorder	Not reported	Likely causal relationship
	Child internalising behaviour	Inadequate evidence (unclear, some data >10µg/dL (<0.48µmol/L))	Likely causal relationship
	Child auditory function decrements	Sufficient evidence, <10µg/dL (<0.48µmol/L)	Likely causal relationship
	Child visual function decrements	Inadequate evidence	Inadequate to infer causal relationship
	Child motor function decrements	Not reported	Likely causal relationship

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SYSTEM	HEALTH EFFECT	NTP MONOGRAPH	EPA ISA
Immune	Atopic and inflammatory response	Limited evidence for increased antibody immunoglobulin E (IgE) in children and increased hypersensitivity and allergy for prenatal and children	Likely causal relationship
	Autoimmunity	Inadequate evidence	Inadequate to infer causal relationship
Renal	Reduced kidney function	Limited evidence for children >12 years	Suggestive of causal relationship
Reproductive and developmental	Delay in sexual maturation or puberty onset in adolescent girls and boys	Sufficient evidence, <10 µg/dL (<0.48µmol/L); Limited evidence for blood lead levels <5µg/dL (<0.24µmol/L)	Causal relationship, <5µg/dL (<0.24µmol/L)
	Birth outcomes: low birth weight, spontaneous abortions	Sufficient evidence among women for reduced foetal growth and lower birth weight, <5µg/dL (<0.24µmol/L); Limited evidence for spontaneous abortion and preterm birth and gestation age	Suggestive of causal relationship

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SYSTEM	HEALTH EFFECT	NTP MONOGRAPH	EPA ISA
Haematological	Decreased red blood cell function and survival	Not reported	Causal relationship, <5µg/dL (<0.24µmol/L), animal data
	Altered haem synthesis	Not reported	Causal relationship, <10µg/dL (0.48µmol/L), animal data

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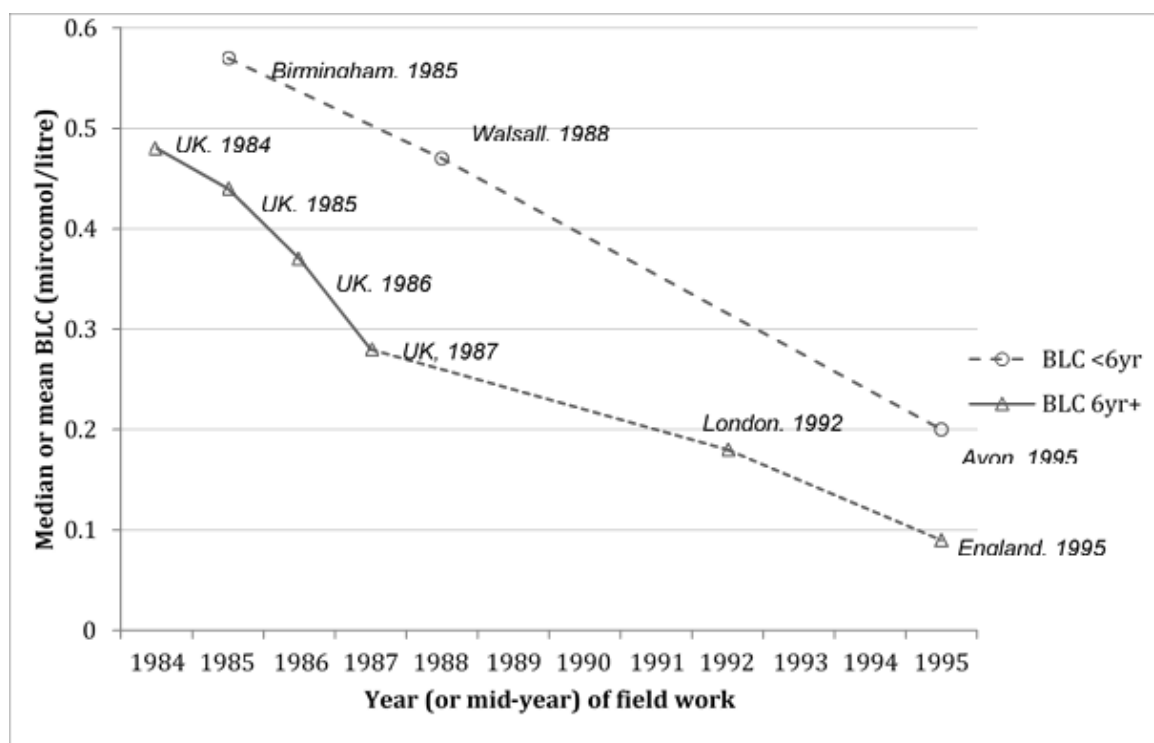
Despite non-consensus between the 2 major reviews, regarding adverse effects of low level lead exposure on birth outcomes and the effect of prenatal lead exposure on neurodevelopment, these judgements are often based on relatively scant data. The findings also have to be considered alongside evidence that lead crosses the placental barrier from maternal exposure, animal data supporting neurotoxicity and growth impairment effects, and that in utero exposures contribute to BLCs once born (31) (and hence conceivably to a wide range of adverse health effects once born). A precautionary approach to minimise in utero exposures would be most consistent with these findings.

Estimates of population BLCs

UK Studies

Estimates of BLCs for children under 5 years old and children 6 years and older are summarised in figure 1 below. The BLCs demonstrate a substantial decline since the mid-1980s (11.80µg/dL (0.57µmol/L)), showing by 1995 a 65% reduction in BLCs for children less than 6 years old and a 83% reduction in BLCs in those aged 6 and older (8.28µg/dL (0.40µmol/L)).

Figure 1. Blood lead concentration (µmol/L) estimates by year, stratified by age group, for included studies in the United Kingdom 1984 to 1995



Solid lines indicate trends between cross-sectional surveys repeated using the same sampling design, broken lines indicate trends between separate single cross-sectional studies. Includes data extracted from Singal 1988, Davies 1990, Chandramouli 2009, Department for the Environment 1984 to 1987, O'Donohoe 1998, and Health Survey for England 1995 (33 to 38)

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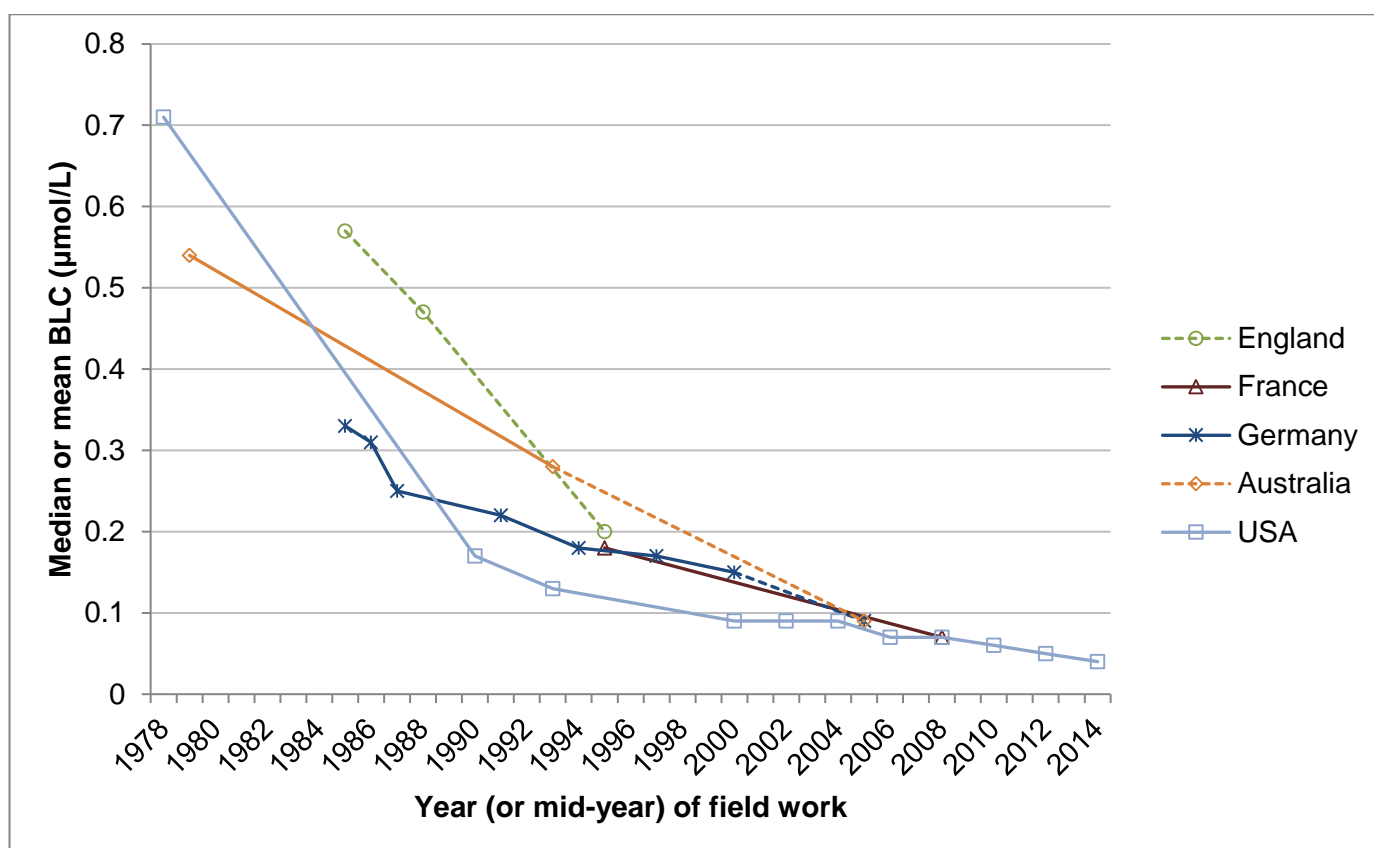
Other high-income countries

Children under 6 years old

Figure 2 summarises BLC estimates for children under 6 years old including available data from USA, Australia, France and Germany. For all 4 countries with estimates from both the 1970s, 80s and 1990s, there was a large decrease in BLCs over this period.

Contemporaneous BLC estimates were generally lowest in US children, whereas BLCs in UK children were similar to their French and German counterparts in 1993 to 1995.

Figure 2. Blood lead concentration ($\mu\text{mol/L}$) estimates in children less than 6 years old, by year, stratified by country, for included studies in high-income countries, 1978 to 2014



Solid lines indicate trends between cross-sectional surveys repeated using the same sampling design, broken lines indicate trends between separate single cross-sectional studies

Includes data extracted from (England) Singal 1988, Davies 1990, Chandramouli 2009; (France) Réseau National de Santé, Publique, 1997 and Etchevers 2014; (Germany) Wilhelm 2007, Schulz 2009; (Australia) Taylor 1995, Guttinger 2008; (USA) Pirkle 1994, Iqbal 1008, Jones 2009, Jain 2016, Tsoi 2016 (data from Tsoi 2016 is for males only for year 2014) (27, 33 to 35, 39 to 47)

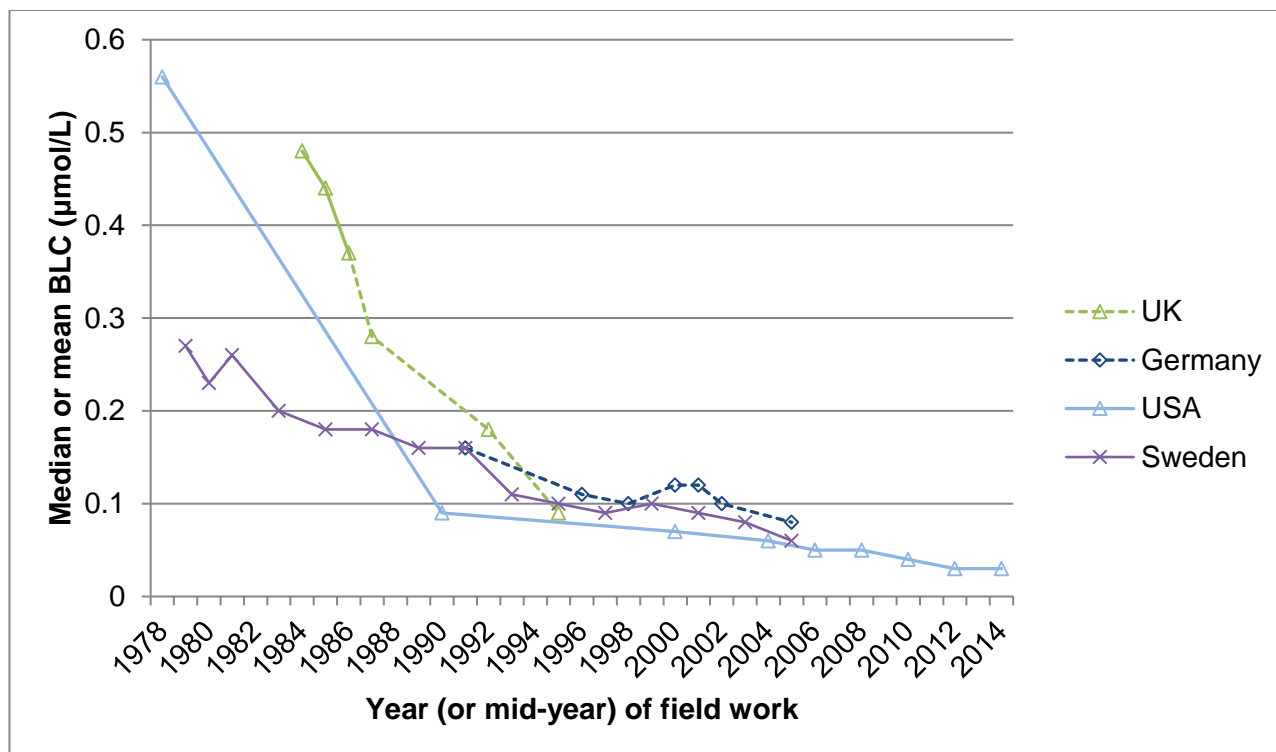
Children at least 6 years old

Figure 3 summarises BLC estimates for children at least 6 years old (for Germany children were 3 to 17 years old), including data from 1978 for the USA and 1979 for Sweden for completeness. For the USA and UK, there was a large decrease in BLCs from the 1980s to 1990s for children at least 6 years old. Similarly for children less than 6 years old, BLCs have

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continued to fall since the early to mid-1990s in Sweden, Germany and the USA, but at a slower rate compared to the changes from the 1980s to 1990s.

Figure 3. Blood lead concentration ($\mu\text{mol/L}$) estimates in children at least 6 years old, by year, stratified by country, for included studies in high-income countries, 1978 to 2014



Solid lines indicate trends between cross-sectional surveys repeated using the same sampling design, broken lines indicate trends between separate single cross-sectional studies

Includes data extracted from (UK or England) Department for the Environment 1984 to 1987, O'Donohoe 1998, and Health Survey for England 1995; (Germany) Wilhelm 2006, Link 2007, Siefert 2000, Schulz 2009; (USA) Pirkle 1994, Iqbal 2008, Jain 2016, Tsoi 2016 (data from Tsoi 2016 is for males only for 2014); (Sweden) Stromberg 2008 (27, 36 to 38, 41, 42, 45 to 46, 48, 49 to 51)

The rapid decline in BLCs seen during the 1980s has been widely attributed to falling lead concentrations in the atmosphere, mostly from reduction in the use of leaded petrol (39). The data also demonstrates that BLCs have continued to fall, albeit more slowly, in the USA, Sweden, France, Germany and Australia even since the complete phase out of lead from fuel in these countries. Similar findings have also been reported in Canada, where BLCs reached a low of $0.62\mu\text{g/dL}$ ($0.03\mu\text{mol/L}$) in 3 to 11 year olds in 2014 to 2015 (52). From the dataset extracted from numerous cross-sectional surveys, population estimates $<1.04\mu\text{g/dL}$ ($<0.05\mu\text{mol/L}$) have not yet been reported from European child populations but appear likely to be recorded in future surveys.

The working group did not review the evidence regarding population distribution of BLCs during pregnancy in high-income settings in this report. However, recently published data from The USA National Health and Nutrition Examination Surveys (NHANES) biomonitoring study

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estimated a mean BLC of 0.41µg/dL (0.02µmol/L) in pregnant women, and 0% to have a BLC ≥5µg/dL (≥0.24µmol/L) in 2013/14 (27).

Conclusion

There is strong evidence for adverse effects on cognitive function at BLC <5µg/dL (<0.24µmol/L), externalising behaviours and delay in sexual maturation or puberty onset in adolescence at BLC <10µg/dL (<0.48µmol/L). There was some evidence that the neurodevelopmental effects are not reversible. There was evidence of a supra-linear dose response with deficits in measures of intelligence such as IQ, without an identifiable lower threshold below which exposure to lead does not result in adverse effects. Therefore, harm may occur from any exposure to lead. However, greater exposure to lead results in greater IQ deficit, with proportionally greater harm incurred by initial lower level exposures than subsequent higher exposures. The health effects at BLCs <5µg/dL (<0.24µmol/L) are likely to be sub-clinical and may have a relatively modest impact on an individual however, the cumulative impact on health and wellbeing of potentially multiple adverse effects (for example, separately on IQ, and on externalising behaviour) in the longer term are likely to be more severe, particularly in the context of the socioeconomic and health inequalities of lead exposure.

There was some evidence from human epidemiological studies of adverse health effects of in utero lead exposure at a maternal BLC <10µg/dL (<0.48µmol/L), however the findings were less consistent, and therefore less certain than for postnatal lead exposure. There was also evidence that lead from maternal exposure crosses the placental barrier. Animal data supports neurotoxic and growth impairment effects. There is human toxicological evidence that in utero exposures to lead contribute to a child's BLC once born and potentially to a wide range of adverse health effects. Therefore, a precautionary approach to minimise maternal exposures would be beneficial to public health.

Taken as a whole, the evidence implies that only (primary) prevention of any exposure will prevent any harm and it is therefore vital to reduce lead exposure to the general population. For children who are exposed to lead (including in utero), the source of the lead needs to be identified and if possible removed to prevent ongoing exposure and escalating adverse health effects.

Therefore the working group recommend that the public health intervention concentration and the surveillance case definition should be lowered from ≥10µg/dL (≥0.48µmol/L) to ≥5µg/dL (≥0.24µmol/L for children aged under 16 years old and pregnant women. The BLC which triggers local public health action of other adults should remain as 10µg/dL (0.48µmol/L).

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Appendices

Appendix A

Specific Objectives

1. Provide context to the report by briefly describing current and historic sources of lead exposure in children in England and high-income countries
2. Describe the rationale used by other public health agencies to select a reference value for public health action
3. Review existing evidence or provide new evidence to consider the following questions to assist decision makers in deciding whether or not to lower the intervention concentration, and what intervention concentration to choose:
4. In what range is the mean BLC in children aged 0 to 15 years in England likely to lie?
5. What proportion of children in England aged 0 to 15 years are likely to have a BLC $\geq 10\mu\text{g/dL}$, $\geq 5\mu\text{g/dL}$, and $\geq 2.5\mu\text{g/dL}$ ($\geq 0.48\mu\text{mol/L}$, $\geq 0.24\mu\text{mol/L}$, and $\geq 0.12\mu\text{mol/L}$)?
6. Is there an association between low BLC ($< 10\mu\text{g/dL}$ ($< 0.48\mu\text{mol/L}$), and $< 5\mu\text{g/dL}$ ($< 0.24\mu\text{mol/L}$)) and adverse health outcomes in children?
7. Is the association likely causal?

Search Strategy

Sources/search method: Major medical databases; grey literature as per background literature review; references from identified studies.

Search terms and limits: librarian to assist based on:

- population – children < 16 years of age
- exposure – elevated BLC (baseline or concomitant) from any cause in childhood
- outcomes – nervous system effects; cardiovascular effects; renal effects; immune system effects; haematologic effects; reproductive effects; developmental effects and cancer. Must include an estimation of the association between outcome and exposure for BLCs $< 10\mu\text{g/dL}$ ($< 0.48\mu\text{mol/L}$) in humans. Exclude occupational studies, solely animal studies or in vitro studies
- timing – to update NHMRC review search which ended May 2013, that is, 1 May 2013 to 2018

Inclusion or exclusion criteria: Based on criteria above. Exclude studies that are not systematic reviews (that is, take a systematic approach to study identification, eligibility,

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data extraction and grading quality). Exclude occupational exposures. English language studies only.

Study retrieval: All potential studies identified from the literature search will be downloaded into Endnote reference management software and de-duplicated. The working group will screen titles and abstracts (by one investigator) for inclusion according to the eligibility criteria above. If there is a title that cannot be rejected with certainty from the title and abstract, the full text paper will be retrieved and reviewed for eligibility. Only the latest and/or most completely reported version of each study will be included.

Data and/or information for extraction: To support AMSTAR 2 criteria to assess systematic review study quality (29). If AMSTAR 2 score indicates a critically low confidence in the review findings then we will not continue to extract information on strength of evidence for association with health outcomes.

Review of sources of study bias: as above (29)

Synthesis of findings: Reported as per Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) recommendations (53). Narrative; tabulated individual studies; tabulated narrative summaries of the strength of evidence for an association from the included reviews by health outcome and BLC category (BLC <5µg/dL, ≥5 to <10µg/dL, ≥10µg/dL (<0.24µmol/L, ≥0.24 to <0.48µmol/L, ≥0.48µmol/L)) if applicable.

Decision on certainty of findings: Narrative (see Appendix B)

Example Medline search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Daily and Versions(R) <1946 to November 9, 2018>

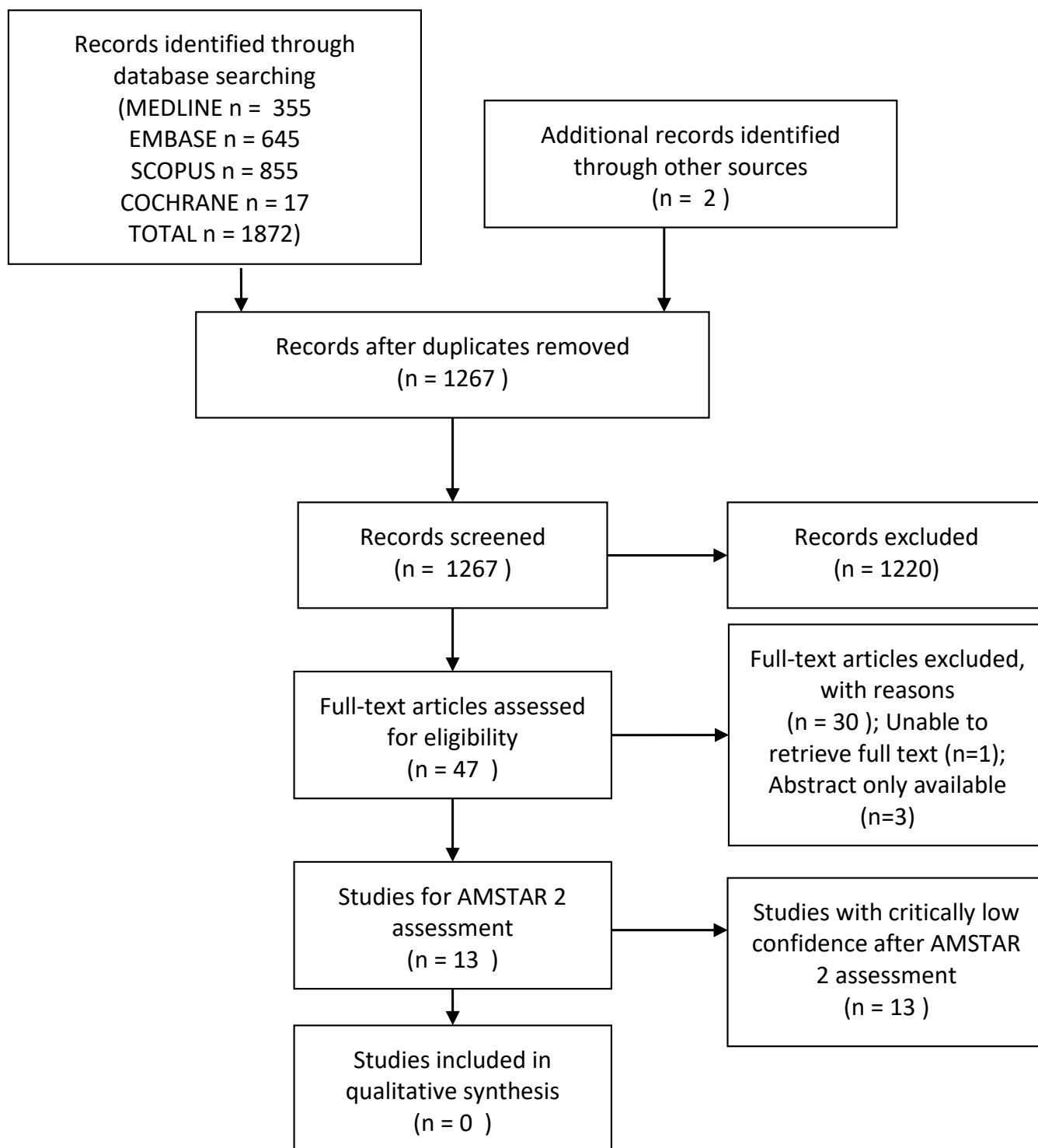
Search Strategy: 12 November 2018

1. (("blood lead" adj2 (concentration or level*)) or (lead adj2 (toxicity or poison* or exposure or exposed))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (19638)
2. exp Lead Poisoning/ (11581)
3. 1 or 2 (19638)
4. (review* or meta-analys* or "meta analy*" or metanaly* or synthes*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (4336178)
5. exp Meta-Analysis/ (94057)

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6. 4 or 5 (4336178)
7. 3 and 6 (2342)
8. (2013 05* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019*).dt. (5763077)
9. 7 and 8 (355)

Figure 4. Rapid overview of reviews serch results (PRISMA flow diagram)



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Figure 4 above demonstrates:

After initial database searching a total of 1872 records were identified (MEDLINE=355; EMBASE=645; SCOPUS=855 and CHOCHRANE=17) with two further records identified through other sources.

Deduplication left a total of 1267 records for screening.

At the initial screening phase 1220 records were removed leaving 47 articles to be assessed for eligibility.

At the full-text screening stage 30 were excluded for not meeting the criteria, one full-text was not able to be retrieved and three records were abstract only.

This left 13 studies which were assessed using the AMSTAR 2 tool.

After AMSTAR 2 assessment all 13 studies were judged as critically low confidence and excluded.

Therefore zero studies were included for qualitative synthesis.

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Appendix B

Table 3. Grading of certainty of association considered to be broadly equivalent between the reviews for the purpose of National Health and Medical Research Council (Australia) evaluation (28, 30 to 31)

United States National Toxicology Programme Monograph	United States Environmental Protection Agency Integrated Science Assessment
Sufficient evidence of an association	Causal relationship
No equivalent to EPA ISA	Likely to be a causal relationship
Limited evidence of an association	Suggestive of a causal relationship
Inadequate evidence of an association	Inadequate to infer a causal relationship
Evidence of no association	Not likely to be a causal relationship

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