Australian Government
National Health and Medical Research Council

NHMRC

Expert review — summary of key issues

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

May 2015

WORKING TO BUILD A HEALTHY AUSTRALIA

Publication Details

Publication title:	Expert review — summary of key issues NHMRC Draft Information Paper: Evidence on the Effects of Lead on Human Health
Published:	May 2015
Publisher:	National Health and Medical Research Council
NHMRC Publication reference:	EH58C
Online version:	www.nhmrc.gov.au/guidelines/publications/eh58
ISBN Online:	978-1-925129-38-0
Suggested citation:	National Health and Medical Research Council. *2015 Expert review — summary of key issues NHMRC Draft Information Paper: Evidence on the Effects of Lead on Human Health.* Canberra: National Health and Medical Research Council; 2015

Contact us

To obtain information regarding NHMRC publications or submit a copyright request, contact:

E: nhmrc.publications@nhmrc.gov.au

P: 13 000 NHMRC (13 000 64672) or call (02) 6217 9000

Expert review

During public consultation on the draft National Health and Medical Research Council (NHMRC) Information Paper: *Evidence on the Effects of Lead on Human Health* 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 reviewers (all from the United States of America) accepted NHMRC's invitation to review the draft Information Paper and completed NHMRC's Disclosure of Interest form.

The reviewers were asked to consider whether the draft Information Paper clearly explained how the NHMRC Evidence Review was undertaken, whether the Lead Working Committee accurately and clearly translated the evidence and whether the overall findings of the draft Information Paper aligned with their understanding of the latest evidence on the health effects of lead.

Lead Working Committee's consideration and revisions to the Information Paper

The Lead Working Committee gave due regard to expert review comments and, over several meetings, carefully considered issues that were raised. Key issues and the Lead Working Committee's responses are summarised in the table below.

Issue	Lead Working Committee Response
The Information Paper does not adequately describe how the NHMRC Evidence Review came to differing conclusions to that of the United States *National Toxicology Program Monograph on Health Effects of Low-Level Lead (NTP) and Environmental Protection Agency, Integrated Science Assessment for Lead* (EPA) reviews regarding the strength of evidence for health effects less than 10 micrograms per decilitre.	The Cochrane Public Health Group at the University of Melbourne (authors of the NHMRC Evidence Review) utilised established methodologies to develop specific study inclusion and evaluation criteria to form the basis of the NHMRC Evidence Review. The NHMRC Evidence Review utilised the AMSTAR tool to assess the NTP and EPA reviews, which were found to be of moderate quality. Although the NTP and EPA reviews were done well, some of the individual studies included within these reviews were not of high quality. Factors that effected study quality included: • The study was not confined to blood lead levels less than 10 micrograms per decilitre; • The study did not adequately control for confounding factors (such as socioeconomic status, nutrition and education); and • The study was not designed to take into account potential errors in measurements (such as variations in Intelligence Quotient (IQ) testing). In addition, although the NTP and EPA reviews describe the potential for bias and confounding in reaching their conclusions, a formal rating tool was not provided, making it difficult to determine how the reviewers accounted for these factors in arriving at their overall conclusions. Also, The NTP and EPA reviews considered other forms of evidence, such as assessment of toxicological data obtained through animal models (see consideration of animal studies below) and studies conducted outside of OECD[1] countries. These factors limited the NHMRC Evidence Review in drawing definitive conclusions from the literature. Although the NHMRC Evidence Review found a weaker relationship between health effects and blood lead levels less than 10 micrograms per decilitre than the NTP and EPA reviews, the Committee came to the conclusion that lead and lead compounds are not beneficial or necessary for human health and can be harmful to the human body. In light of the expert review comments, the Committee amended the Information Paper to include further detail around the evaluation methodology used in the NHMRC Evidence Review.

1 Organisation for Economic Co-operation and Development

Issue	Lead Working Committee Response
Given the findings of the NHMRC Evidence Review, further clarification is required regarding how the Committee came to its advice for Australians and the lowering of the trigger for investigation to 5 micrograms per decilitre.	In developing its advice for Australians, the Committee considered the findings of the NHMRC Evidence Review with regard to the overall body of evidence relating to the health effects of lead. This included consideration of the plausibility, toxicokinetics and consistency of effect across the scientific literature. NHMRC's review on 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. The Committee noted that whilst low-level exposure (blood lead levels less than 10 micrograms per decilitre) may have an effect, the evidence strongly suggests that other factors (e.g. socioeconomic status, education, parenting style, diet, or exposure to other substances) in the groups of children studied also have a strong influence on measured outcomes such as IQ or school performance. In providing advice to the Australian community the Committee recognised that although the NHMRC Evidence Review suggests that confounding plays an important influence in the findings on the effects of lead on human health, lead and lead compounds are not beneficial or necessary for human health and can be harmful to the human body. The Information Paper reflects that a blood lead level greater than 5 micrograms per decilitre is the level of lead that is considered to be above the 'average' background level of exposure in the Australian environment. The purpose of setting the investigation level to 5 micrograms per decilitre is to identify those people who have been exposed to an additional source of lead (greater than the small amounts found in the everyday environments of most Australians) to reduce the risk of harm to the community. In clarifying how the Committee developed its advice, the structure of the Information Paper was amended to more clearly differentiate between i) the findings of the NHMRC Evidence Review; ii) the Committee's interpretation of the NHMRC Evidence Review; iii) factors that were considered when interpreting the NHMRC Evidence Review; and iv) the Committee's advice to Australians.

Issue	Lead Working Committee Response
The Information Paper does not adequately present the strength of evidence for health effects less than 5 micrograms per decilitre.	In considering this issue the Committee acknowledged that there are differing views internationally around the toxicokinetics of low level lead exposure, with some experts describing the inverse relationship between lead exposure and IQ in children being at its greatest at the lower blood lead levels. This relationship was noted in the NTP review. The Committee noted that the body of evidence relating to the health effects of blood lead levels less than 5 micrograms per decilitre is relatively small and subject to a high level of bias and confounding, making it difficult to draw any meaningful conclusions from the literature. The Committee noted that it was supportive of the findings of the NHMRC Evidence Review, which found that 'uncontrolled confounding had an important influence' on the findings of an association between IQ decrements and blood lead levels less than 5 micrograms per decilitre. In particular, the Committee was concerned that a study undertaken by *Canfield et al* of very disadvantaged children may have significantly skewed the size of effect reported within the literature in this area. The Committee felt nevertheless that caution should be applied when interpreting the findings of population studies showing subtle health outcomes, as the shift in IQ distribution curve may be different for a population of children experiencing high exposure compared with another population experiencing lower exposure. The Committee noted the importance of accurately presenting the scientific evidence on the health effects of blood lead levels less than 5 micrograms per decilitre, and the need to contextualise this information to support evidence based policy decisions. For example, if the health effects of lead were found to be more detrimental at the lower blood lead levels, more stringent lead management strategies would be required. The Committee agreed that evidence to support such a policy response does not exist at this time. Greater detail on the strength of evidence, confounding factors and the relative significance of lead in influencing children's IQ was added into Part B of the Information Paper.
The Information Paper does not adequately present the strength of evidence regarding health effects between 5 micrograms and 10 micrograms per decilitre.	The Committee agreed that there is a greater body of evidence relating to the health effects of blood lead levels between 5 micrograms and 10 micrograms per decilitre, relative to blood lead levels less than 5 micrograms per decilitre. The Committee agreed that there is demonstrated evidence that a dose response relationship between intellectual development and lead exposure occurs at blood lead levels greater than 10 micrograms per decilitre. The Committee noted that the plausibility of this relationship continuing down into the 5 micrograms to 10 micrograms per decilitre range at a population level is supported by a consistency of effect within the literature. The Committee was supportive of the findings of the NHMRC Evidence Review which asserts that caution be applied when interpreting the association between health effects and blood lead levels between 5 micrograms and 10 micrograms per decilitre. In clarifying the Committee's position, greater detail on the strength of evidence, confounding factors and the relative significance of lead in influencing children's IQ was added into the Committee's interpretation of the NHMRC Evidence Review in the Information Paper.

Issue	Lead Working Committee Response
The Information Paper does not adequately describe why a blood lead screening program is not warranted in Australia.	The Committee's advice regarding population screening and monitoring is based on the scientific evidence around health effects of lead exposure, with regard to a number of other factors that are specific to Australia. These factors include estimations of population lead exposure, potential sources of exposure in Australia and likely patterns of exposure in the future. These factors were considered by the Committee against the World Health Organization's criteria for screening. This consideration found that screening in non-endemic areas in Australia is not warranted. In clarifying how the Committee determined its overall conclusions, supporting text around screening and monitoring was taken out of the recommendations section and moved into the body of the Information Paper. The Committee noted the comments of one of the expert reviewers, which stated that 'The history of lead shows that if one doesn't systematically look, people with elevated lead exposure won't be identified. It would be more helpful to enumerate factors that would produce an increase in the index of suspicion that someone is potentially exposed and therefore should be tested'. The Committee agreed that there is a need to better understand patterns of exposure to lead, outside lead-endemic areas in Australia. This information would provide a better picture of average 'background' exposures in various regions with different levels of risk. In providing guidance on the testing of individuals, the Committee agreed that often individuals are not aware of sources of lead to which they could be exposed. The Information Paper makes reference to *Table 1* (sources of lead in Australia), when advising Australians to avoid unnecessary contact with lead.
Further explanation is required to discuss why studies conducted overseas should be interpreted with caution when generalising the findings to the Australian community.	The Committee noted that the majority of the evidence relating to health effects of blood lead levels less than 10 micrograms per decilitre comes from studies conducted overseas. The Committee agreed that this has implications is for the generalisability of these findings to the Australian setting. It was noted that even among groups of people with the same blood lead level the consistency, duration and nature of lead exposure will have an effect on the relative health outcome between each group. Many of the sources of lead in Australia are known, and patterns of exposure in Australia differ to that of other countries. For example, large numbers of people of low socioeconomic status living in aged high density housing (where lead based paint is present) is unlikely in Australia. The Committee responded to the comments of the expert reviewers by providing more supportive text around its position on the generalisability of the findings of the NHMRC Evidence Review to the Australian environment.
The Information Paper could better distinguish between the health effects of lead in adults and children at blood lead levels greater than 10 micrograms per decilitre.	The Committee acknowledged that although the health effects of lead greater than 10 micrograms per decilitre is not the focus of the Information Paper, further detail could be included to differentiate between the health effects of lead in adults and children at blood lead levels greater than 10 micrograms per decilitre. Several amendments to the Information Paper were incorporated within this section of the document. The Committee also included further information regarding why children are more sensitive to the effects of lead. Information relating to factors that influence individual variation in the manifestation of health effects was also included.

Issue	Lead Working Committee Response
The Information Paper should consider the results of animal and Magnetic Resonance Imaging (MRI) studies regarding health effects of lead less than 10 micrograms per decilitre.	The Committee discussed the suggestion from one of the expert reviewers to include a summary of the findings relating to animal and MRI studies within the Information Paper. These studies were considered by the NTP and EPA reviews, however by definition are excluded from the Cochrane methodology used for the NHMRC Evidence Review. It was noted that the 2007 ATSDR toxicological profile for lead states that 'many of the behavioural deficits observed in children exposed to lead have been reproduced in similar studies in animals, particularly monkeys and at similar blood lead levels'. The Committee noted that many of these animal studies were dated, lacked detail and relied on outdated protocols. In particular, it was noted that lead dosing within these studies was variable, with blood lead levels spiking significantly above 10 micrograms per decilitre from birth and remaining elevated for a period of months to years. The Committee noted there is significant uncertainty around predicting health outcomes (behavioural and learning effects) through interpretation of MRI results. The Committee noted that although the findings of these studies provide evidence of a direction of effect, the study design and type of evidence is not of a sufficient quality to warrant summarising these findings within the Information Paper. No amendments to the Information Paper were made regarding this matter.
Conclusions relating to the variability of IQ testing in the Information Paper are not justified.	The Committee considered the expert reviewers' comments around the precision of IQ testing presented in the Information Paper, and the supposition that repeated IQ testing can be measured reliably between population groups. The Committee confirmed its position that IQ results are generally not precise or accurate enough to be confident that small differences in children's IQ are due to a particular factor and not simply due to natural variation and chance. The Committee also noted that Methods of measuring or estimating IQ varied between studies which may lead to errors when comparing different studies and combining data. No change to the Information Paper was made with regard to this comment.