

REVIEW OF HAZARDS AND HEALTH EFFECTS  
OF INORGANIC LEAD – IMPLICATIONS FOR  
WHS REGULATORY POLICY

**CAUTION**

**LEAD  
HAZARD**

**DO NOT ENTER WORK AREA  
UNLESS AUTHORIZED**



July 2014

### **Acknowledgements**

This research report was undertaken by ToxConsult Pty Ltd under commission from Safe Work Australia. This report is authored by Dr Roger Drew, PhD, DABT and Ms Tarah Hagen, MSc.

The authors would like to thank Dr Stephen Leonard from the United States National Institute for Occupational Safety and Health for his review of the report.

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### **Suggested citation**

Safe Work Australia. (2014). Review of hazards and health effects of inorganic lead – implications for WHS regulatory policy. Canberra: Safe Work Australia.

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ISBN 978-1-74361-719-9 [PDF]

ISBN 978-1-74361-720-5 [DOCX]

## Foreword

Safe Work Australia is currently (2014) reviewing workplace blood lead removal levels, i.e. the levels at which a worker must be removed from lead risk work, and the associated workplace exposure standard for lead and has commissioned this report to examine the health effects of exposure to lead and based on the analysis, advise on appropriate blood lead removal levels and a workplace exposure standard for lead.

This report covers the following areas:

- documentation and assessment of international regulatory standards including airborne exposure standards, biological exposure standards and blood lead removal levels
- information on alternative biomonitoring methods for lead
- identification and review of key epidemiological and toxicological studies relevant to workplace exposure and the setting of revised blood lead removal levels and workplace exposure standard
- the relationship between air lead levels and expected blood lead levels
- advice about the risks to worker health at a range of air lead exposures and the health benefits of lowering blood lead levels, and
- consideration of sensitive workers and advice as to the protection afforded to them by reduced blood lead removal levels and workplace exposure standard.

This report and subsequent business consultation will inform a consultation Regulation Impact Statement on proposed changes to the workplace blood lead removal levels and workplace exposure standard for lead.

For further information visit [www.safeworkaustralia.gov.au](http://www.safeworkaustralia.gov.au)

## Executive Summary

### *Overview*

The health effects of lead are directly related to the concentration of lead in the affected organ systems. This in turn is directly proportional to whole blood concentrations. Blood lead (PbB) concentrations have been the traditional measurement of internal exposures to lead and indicators for management actions for persons overexposed to lead in the workplace. This report examines the dose-response of lead to inform selection of Blood Lead Removal Levels (BLRL) and a target PbB that will be protective of nearly all workers in lead related jobs. These Blood Lead Removal Levels (BLRL) are used by duty holders under the model Work Health and Safety (WHS) Regulations and medical staff to manage the health of workers in lead industries. The relationship between PbB and concentrations of PbAir provides information for selection of WESs.

The BLRLs are different for different worker populations in industry. For ease of reading, this summary primarily refers to men and women of non-reproductive capacity. For information on women of reproductive capacity and pregnant/breast feeding women the reader is encouraged to consult the text of this report.

The BLRLs are reported as micrograms of lead per 100 mL of blood, these units are simplified to  $\mu\text{g}/\text{dL}$ . The WESs are concentrations of PbAir reported as milligrams of lead per cubic metre of air; simplified to  $\text{mg}/\text{m}^3$ .

### *International benchmarking*

A review of current BLRLs and WESs established by international authorities or recommended by committees of scientific/medical experts indicates a trend for decreased values as knowledge of the health effects of lead has been acquired over the last two decades. Nevertheless many of the BLRLs and WESs currently on the regulatory statutes of various countries were established a long time ago and are not well documented. The deliberations of the American Conference of Government Industrial Hygienists (ACGIH) in 1995 have been influential since many jurisdictions appear to have 'picked up' the ACGIH recommendations.

WESs set by national and international authorities in the early 1990s were  $0.15 \text{ mg}/\text{m}^3$ . This is still the current WES in Australia. More recent WESs have been set at 0.1 or  $0.05 \text{ mg}/\text{m}^3$ , although California in 2013 has recently proposed  $0.0005 \text{ mg}/\text{m}^3$ .

The early regulatory BLRLs set by international authorities for men were 50 µg/dL, or higher, and as mentioned above not many have been reviewed in recent years. The current BLRL in Australia for men is 50 µg/dL. Contemporary BLRLs are mostly set at 20 – 30 µg/dL.

### *Biomonitoring*

PbB is by far the most common and arguably most convenient exposure metric used by regulatory authorities, industry and researchers. This may however have arisen as a result of historical use. A number of alternatives have been suggested by the scientific community but have not found their way into the regulatory arena. These include lead measurements in a range of accessible biological fluids and tissues. Of these the procedure with the most promise for supplementing PbB information is measurement of bone lead by non-invasive X-Ray Fluorescence (XRF) techniques. It provides a good, perhaps better indication, of chronic past exposures and total body burden. Unfortunately since bone lead reflects chronic exposures it arguably may not be an ideal method in the workplace to identify 'at risk' persons (i.e. persons currently assimilating unacceptable levels of Pb from workplace exposures). Whether the technique has been adequately developed and validated as a routine monitoring tool is also arguable.

Biochemical measurements of blood enzymes that are sensitive to inhibition by lead have been proposed by researchers. A major issue with the use of biomarkers is the lack of relevant information linking the concentrations of lead with changes in biomarker and demonstrable health impacts.

Because of its historical use, the database and available knowledge on the relationships of exposure, PbB and health effects is large. PbB therefore remains the preferred metric for determining critical lead exposures.

### *Toxicology, health effects and BLRL*

In humans and animals, lead has a wide range of biological effects. Many organ systems can be affected depending upon the level and duration of exposure. It is noted that effects in adult males in the general community have been reported at lower PbB concentrations than for workers. This may be because there is a greater physiological diversity in the wider public which translates to more variability in effect sensitivity. It is also apparent that some subtle endpoints pursued in general population epidemiology studies have not been examined as thoroughly in the occupational setting. We consider the information on worker cohorts to be more germane for informing decisions regarding standards for workplace exposure than the general public information.

Most health endpoints (effects on the nervous system, increased blood pressure, heart rate variability, kidney dysfunction, changes in immune system markers, reduced sperm quality, haematological effects) for which there is sufficient information for them to be reasonably linked with lead exposure at work have been associated with occupational cohort mean PbB levels of >20 µg/dL. The majority of studies report health effect associations starting at worker population mean PbB levels of 25 - 30 µg/dL. At mean PbB concentrations >30 µg/dL the associations become more robust and reliable. Hence in the workplace, for females not of reproductive capacity and for males it is suggested a BLRL of 20 – 30 µg/dL is appropriate.

Of this range, 20 µg/dL is a pragmatic No Observed Adverse Effect Level (NOAEL) and can be rationally argued as an appropriate precautionary BLRL for the protection of nearly all workers, particularly since it relates to a central rather than a lower bound estimate for populations of lead exposed workers. Nevertheless there is uncertainty regarding the lead dose – response relationship at low worker exposure, not all occupational investigations report health effects at similar low PbB levels, and the effects are not necessarily clinically important for the individual. In addition some workplaces may initially struggle to comply with a BLRL of 20 µg/dL. It is therefore suggested a target PbB of 20 µg/dL and a BLRL of 30 µg/dL could also be considered.

In this report deliberations on the potential beneficial effects of lowering the BLRL and determining an attending WES consider either 20 or 30 µg/dL as the possible BLRL.

A recent study was published by the Monash Centre for Occupational and Environmental Health of workers currently in 'scheduled' lead related jobs (i.e. lead exposed jobs). Of workers for whom PbB results were available, approximately 30% have had at least one PbB measurement greater than 30 µg/dL.

The effects of most concern are carcinogenicity (lead compounds have recently been reclassified by the International Agency for Research on Cancer from possible to probable human carcinogens), nervous system effects manifested as subtle behavioural changes, changed risks for cardiovascular disease resulting from small lead associated increases in blood pressure, and changes in sperm quality that may be important for men with a natural tendency towards having low sperm count (i.e. men who may be oligospermic or bordering on being oligospermic).

#### *Health implications of reducing the BLRL*

For some of the health effects associated with workplace exposure to lead it is not possible to quantify the health gains that may be realised by lowering the BLRL. However lowering the BLRL for males from 50 µg/dL to 20 or 30 µg/dL is expected to be associated with:

- Reduction in cardiovascular disease associated with ameliorating lead induced increased blood pressure (Section 4.4.2). Although the reductions in blood pressure are only small or modest for an individual, the prevalence of cardiovascular disease and cost of medication prevention is such that there could be marked gains for the overall lead exposed workforce.
- Gains in sperm quality for potentially oligospermic men (Section 4.4.3).
- A decreased risk of cancer for a large proportion of men who work in 'scheduled' lead jobs and currently have PbB > 30 µg/dL. Assuming that the PbB results for 2612 workers in 'scheduled' lead jobs in Victoria and NSW combined are representative of the full cohort (4114 workers), approximately 1200 persons will have had at least one blood lead level above 30 µg/dL at some time (Section 4.4.4). Of the epidemiological studies investigating associations with cancer in which PbB concentrations have been reported, mean PbB concentrations were 28-80 µg/dL, with many above 50 µg/dL.

For women of reproductive capacity, lowering the BLRL from 15 or 20 to 10 µg/dL is likely to be associated with:

- Lowered body burden and hence lower risk of detrimental intellectual development of their as yet conceived and unborn children.
- Decreased risk of spontaneous abortion (Section 4.4.3).

#### *PbAir and PbB*

In addition to good occupational hygiene practice another way to manage lead exposure in the workplace and judge the effectiveness of engineering controls is to measure PbAir. However to use air measurements as a routine method for judging whether exposures are likely, or not, to compromise worker health, the WES should be at a concentration such that absorption of lead will result in PbB levels less than the BLRL for nearly all workers. *Prima facie* this is contingent on incidental ingestion in the workplace not being a significant contributor to PbB levels. Nevertheless deliberations in this document have incorporated non-inhalation exposures when determining WESs compatible with the BLRLs.

The relationship of PbAir and PbB is called the air slope factor (ASF). The ASF reflects the incremental increase in PbB for each unit increase in PbAir concentration and has the units (µg/dL)(µg/m<sup>3</sup>)<sup>-1</sup>. The relationship is not linear; the relative contribution of PbAir to PbB is greater at low air concentrations compared to high concentrations. Given the non-linear nature of the association of PbAir with PbB, and PbB with health effects, a single ASF to describe the relationship of PbB (and health effects) with different air concentrations will be misleading. ASFs in this report have therefore been determined from the literature for three nominated PbAir concentrations. These

are 0.15 mg/m<sup>3</sup> (the current WES), 0.1 and 0.05 mg/m<sup>3</sup> (the alternative WESs being explored by Safe Work Australia).

While the ASFs in this document account for background non-occupational exposures, they purposefully do not separate PbB arising from incidental ingestion of lead dusts (e.g. by hand-to-mouth action) from that due to PbAir. Firstly it is difficult to undertake such analysis using the available literature information and secondly it was considered unnecessary for the purposes of determining a WES compatible with the nominated BLRLs. It has been reasoned, that due to lead particulate fallout, the fraction of PbB attributable to workplace non-inhalation exposure is likely to be proportional to the WES. Consequently calculations for a WES should account for the associated non-inhalation exposure rather than assuming good hygiene practice is in place and will totally eliminate such exposures. This was achieved by developing, from the literature for a range of lead industries, ASFs that inherently incorporated non-inhalation exposure. Thus the ASFs herein do not represent the 'pure' relationship between PbAir and PbB. It is recognised there is uncertainty in the estimated ASFs and they could overestimate PbB from PbAir exposure. Nevertheless the determined WESs for the nominated BLRLs using the estimated ASFs in this document are consistent with international values.

If a group of people are exposed to the same air concentration of lead for the same amount of time there will be a range of resulting PbB concentrations. This is due to physiological differences between people that affect the kinetics of lead absorption from the lung. This variation was determined by identifying the maximum to mean PbB ratio reported across a number and variety of epidemiology studies; it was determined to be on average two fold (range 1.4 – 2.6). This average variability ratio has been coupled with the average ASF at the nominated PbAir (equivalent to the different international WESs) to provide an indication of the proportion of workers who will be below the target BLRL for the WES.

#### *Implications for WESs*

In this report two WESs have been derived; one from the central estimates (i.e. averages) of the ASFs and another that incorporates the worker population variability in PbB for exposure to the same lead exposures. Different WES values have been calculated for potential compliance with a BLRL of 20 or 30 µg/dL.

- At the current WES of 0.15 mg/m<sup>3</sup> the nominated BLRLs would be achieved in less than 50% of workers. It is therefore recommended the WES be reduced.



- Lowering the WES to 0.1 mg/m<sup>3</sup> would allow more than 50% of workers to have PbB less than 30 µg/dL but less than 50% would be below 20 µg/dL.
- A WES of 0.05 mg/m<sup>3</sup> would allow more workers to have PbB less than 30 µg/dL but in excess of 50% would be higher than the target of 20 µg/dL. This WES is anticipated to provide approximately the same level of compliance to the target BLRL of 20 – 30 µg/dL as the current WES (0.15 mg/m<sup>3</sup>) did in 1994 for the BLRL of 50 µg/dL.

It is noted that decreasing the WES from 0.1 mg/m<sup>3</sup> to 0.05 mg/m<sup>3</sup> provides relatively small decreases in PbB. We suggest a WES of 0.05 mg/m<sup>3</sup> would be compatible with a BLRL 30 µg/dL for considerably more than half of workers in lead related jobs. However since the ASFs used to estimate the PbB include non-inhalational occupational exposures it is anticipated workplaces with very good occupational hygiene could achieve better results.

Information was not located on absorption via inhalation for mineralised forms of lead. No information, for example, could be found for insoluble lead sulphides. Thus there is currently insufficient information for deriving appropriate adjustment factors which could potentially be applied to a WES for different forms of lead.

#### *Summary and Recommendations*

The current BLRLs are not sufficiently protective of the health of workers in lead related jobs. For females of non-reproductive capacity and men, BLRLs of 20 - 30 µg/dL are suggested as appropriate PbB concentrations for minimising the potential for adverse effects. Since occupational epidemiology investigations indicate effects, including cancer, are mostly associated with concentrations greater than 30 µg/dL a BLRL of 20 µg/dL (a pragmatic no observed adverse effect level) would be precautionary and provide a moderate margin of safety.

However given the current inability to reasonably quantitate differences in health gains between BLRLs of 20 and 30 µg/dL, it could be argued that in regard to protecting worker health, the health risk at these BLRLs is not markedly different.

A WES of 0.05 mg/m<sup>3</sup> would cater for more than half the male workers in terms of a BLRL of 30 µg/dL, but 0.03 mg/m<sup>3</sup> may be needed to ensure nearly all workers meet this BLRL criterion. However the uncertainty in the calculations, while not being quantifiable, is such that it would not be unreasonable to adopt a WES of 0.05 mg/m<sup>3</sup> with the knowledge that residual health effects are likely not to be severe and at low incidence. This is also consistent with 0.05 mg/m<sup>3</sup> currently being the lowest legislated WES in the international arena.

For women of reproductive capacity, including those who are pregnant or are breast feeding<sup>1</sup>, a BLRL of 10 µg/dL is an appropriate criterion and consistent with the deliberations of the National Health and Medical Research Council (NHMRC). The WES required to satisfy this criterion is 0.01 mg/m<sup>3</sup>. This is 20 times higher than the ambient air guideline of 0.5 µg/m<sup>3</sup> (annual average) for lead in Australia.

*Overall summary:*

To minimise potential adverse health effects associated with lead exposure in the workplace the following is proposed.

- For women of non-reproductive capacity and men two options are suggested:
  - a) BLRL of 20 µg/dL, or
  - b) Target PbB of 20 µg/dL and BLRL of 30 µg/dL.
- For women of reproductive capacity a BLRL of 10 µg/dL is recommended.
- To help achieve these BLRLs it is suggested the WES be reduced from 0.15 mg/m<sup>3</sup> to 0.05 mg/m<sup>3</sup>.
- Furthermore the importance of good occupational hygiene is stressed.

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<sup>1</sup> Although women who are breastfeeding may experience a time of infertility, the definition of 'women of reproductive capacity' in this report is intended to include women who are breastfeeding.

## Abbreviations

ACGIH:	American Conference of Government Industrial Hygienists
ASF:	Air Slope Factor
BAR:	Biologische Arbeitsstoff-Referenzwert
BAT:	Biologischer Arbeitsstoff-Toleranz-Wert
BEI:	Biological exposure index
BES:	Biological exposure standard
BLRL:	Blood lead removal level
BLW:	Biologischer Leit-Wert
Cal DPH:	California Department of Public Health
CDC:	Centers for Disease Control
DFG:	Deutsche Forschungsgemeinschaft (German Research Foundation)
MAK:	Maximale Arbeitsplatz-Konzentration
mg/m <sup>3</sup> :	Milligram per metre cubed
NHANES:	National Health and Nutrition Examination Survey
NHMRC:	National Health and Medical Research Council
OEHHA:	Office of Environmental Health and Hazard Assessment (California)
OEL:	Occupational exposure limit
OR:	Odds ratio
Pb:	Lead
PbAir:	Lead in workplace air
PbB:	Blood lead (whole blood)
RR:	Relative risk
SIR:	Standardised incidence ratio
SMR:	Standardised mortality ratio
µg/dL:	Micrograms per deciliter
µg/m <sup>3</sup> :	Micrograms per metre cubed
µm:	Micrometre
WES:	Workplace exposure standard
WHO:	World Health Organization

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## 1. Introduction and scope

This report is the culmination of a project commissioned by Safe Work Australia to assist with revision of the current blood lead removal levels (BLRL) and associated workplace exposure standard (WES) for lead in workplace air (PbAir).

The report consists of the following:

- In order to provide perspective on overseas opinions and regulatory status of lead in the workplace, a review of international BLRLs and WES's, and their derivation is provided.
- An examination of the alternatives to blood lead (PbB) for biomonitoring. This is to inform whether measurements of lead in a different biological medium to whole blood, or something other than lead (e.g. changes in certain enzyme activities in blood) could be measured that would give more sensitive and/or more meaningful information regarding exposure and health effects than does PbB.
- A review of toxicological information for lead relevant to workplace exposures. Rather than re-reviewing vast amounts of literature already adequately reviewed by national and international authorities, existing agency reviews were consulted for the bulk of the health information. However critical papers and reports identified in the reviews have been sourced and consulted. An updated literature search was also conducted to identify recently published relevant information. The toxicological information for lead was used to inform suggested BLRLs for prevention of health effects.
- An investigation of the relationship(s) between PbAir and PbB. The decision on an appropriate WES depends to a great extent on a PbB concentration considered to be health protective and the concentration of lead in workplace air that will achieve a PbB below the nominated BLRL.
- A discussion of the overall information in relation to the derivation of an BLRL and WES that will be appropriately health protective for nearly all workers. In this, women of non-reproductive capacity and men have been considered as a group, and women of reproductive capacity as a separate group

## 2. International regulatory benchmarking

In this section contemporary international WES and BLRL for lead are reviewed. Although the terminology used in this report is WES (i.e. workplace exposure standard) and BLRL (i.e. blood lead removal level), agencies may have different names for such limits (e.g. occupational exposure limit, threshold limit value, permissible exposure limit, Maximale Arbeitsplatzkonzentration, biological exposure index, etc.).

The literature search strategy for identifying existing exposure standards for lead and alternatives for PbB measurement is described in Appendix A. The search canvassed 30 international Federal or State agencies and while the primary target of the search was for promulgations within the last five years few were found. Of particular interest were WES and/or BLRL that had accessible supporting documentation. When such background documentation was available it has been reviewed and a summary of the technical rationale provided.

## 2.1. Contemporary WES for inorganic PbAir and BLRL

### 2.1.1 Summary of WES and BLRL

Tables 2.1 and 2.2 provide a summary of international WESs for PbAir, as well as legislated or non-legislated blood lead removal levels (BLRL). From inspecting the tables, the following summary comments are made:

- WES for PbAir range from 0.03 to 0.15 mg/m<sup>3</sup> measured as an 8-hour time-weighted average<sup>2</sup>.
- Many of these WES were originally set more than 10 to 20 years ago. In many instances, it is not stated if the WES have ever been or are currently being revised.
- For the bulk of WES, the background documentation underlying the basis for the WES could not be located.
- Where background documentation was located, the technical rationale explaining the basis of the WES was often missing. In those instances where the technical rationale was provided (Section 2.2.2), the derivation of the WES and/or BLRL was not sufficiently transparent to facilitate easy understanding by third parties. Of these, the World Health Organization (WHO 1980) documentation seems to have the most robust rationale, although this is based on toxicological and air slope factor<sup>3</sup> information from studies more than 20 years ago.
- Several countries have BLRL in males (and females who are not of reproductive capacity) that differ from those for females of reproductive capacity, or females that are pregnant or breastfeeding. BLRLs range from 30 – 70 µg/dL (females not of reproductive capacity and males)<sup>4</sup>, and 7 – 70 µg/dL (females of reproductive capacity, females who are pregnant or breastfeeding).

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<sup>2</sup> This range does not include a health-based proposed WES from California of 0.0005 mg/m<sup>3</sup> (Table 2.1).

<sup>3</sup> The air slope factor refers to the relationship between inhalable PbAir and PbB.

<sup>4</sup> In Australia, a female of reproductive capacity means “a female other than a female who provides information stating that she is not of reproductive capacity” (Safe Work 2014). Some countries (e.g. Germany and Switzerland) provide different BLRLs for females according to their age. For example, females > 45 years of age are considered not to be of reproductive capacity, whereas females <45 years of age are considered to be of reproductive capacity (DFG 2013b, BAuA 2013b, SUVA 2013).

- The UK and Sweden prohibit females who are pregnant or breastfeeding from working in lead-related jobs (UK HSE 2012, SWEA 2005b). Additionally, in the UK, females of reproductive capacity are forbidden from working in certain high-risk lead jobs (e.g. lead battery manufacturing) (UK HSE 2012).
- The BLRLs that appear to have been recently established or revised<sup>5</sup> have generally been set at 50 µg/dL or less for all occupational sectors (e.g. NZ DoL 2011, DFG 2013b, DWEA 2007, MoSAH 2012, WorkSafe Alberta 2009). Even though some of these agencies set a BLRL at 50 µg/dL, they also provide a PbB level of 30 µg/dL as a health-based objective for females not of reproductive capacity and for males (NZ DoL 2011, DFG 2013b, DWEA 2007, MoSAH 2012, WorkSafe Alberta 2009). Many of these publications provide separate, lower BLRL recommendations of 7-25 µg/dL for females of reproductive capacity, or females who are pregnant or breastfeeding (NOHSC 1994, DFG 2013b, BAuA 2013b, INRS 2012, SUVA 2013, NIWL 2005, UK HSE 2012, WorkSafe Alberta 2009). The lower end of this range is close to or the same as the target PbB concentrations of 10 µg/dL recommended by the Centers for Disease Control (CDC) in 1991 (CDC 2005) and the National Health and Medical Research Council (NHMRC 2009) for the general public.
- It is noted WHO (1980) recommended lower health-based BLRL for females of reproductive capacity than for females of non-reproductive age and males, yet many countries still have only a single BLRL for both. This suggests regulation with respect to lead has been slow to evolve, or may have been driven by non-health based considerations (e.g. cost and achievability by industry).
- The agency BLRL's for which there is background documentation were set approximately 10 or more years ago (ACGIH 2001a, SCOEL 2002, DFG 2005, WHO 1980). Consequently they do not consider recent information suggesting PbB < 20 µg/dL in adults may be associated with subtle neurological effects, reductions in renal glomerular filtration rate, and small increases in systemic blood pressure (NZ MfE 2011, ATSDR 2007, US EPA 2006, NTP 2012, NRC 2013). At these concentrations there are also biochemical changes such as depressed δ-aminolevulinic acid dehydratase.

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<sup>5</sup> The publications referred to here have been recently published (i.e. within the last 10 years), however the dates the BLRL were set or revised are not provided. It is therefore assumed the BLRL were set when the documents were published.



- A number of academics and professional organisations in the United States have called for more protective guidelines for PbB than the US OSHA standards of 30-60 µg/dL<sup>6</sup> (Schwartz and Hu 2007, Hu et al. 2007, ACOEM 2010, AOEC 2007, CSTE 2009). For example, Kosnett et al. (2007) recommended a PbB removal level of 20 µg/dL for all workers to prevent acute effects associated with recent exposures; this has been supported by the American College of Occupational and Environmental Medicine (ACOEM 2010). For the prevention of chronic effects that may occur with cumulative doses, Kosnett et al. (2007) recommended tibia lead levels not be allowed to exceed 15 µg/g. It is suggested this could be achieved, for example, by keeping average<sup>7</sup> PbB below 10 µg/dL for 40 years (Hu et al. 2007, Schwartz and Hu 2007, Kosnett et al. 2007). The California Department of Public Health (Cal DPH 2009, 2010, 2011) has recommended the revised BLRL originally proposed by Kosnett et al. (2007) (see above) should be legislated. Specifically, the BLRL's proposed by California are 30 µg/dL for a single PbB measurement, or 20 µg/dL for two consecutive PbB measurements (four weeks apart).

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<sup>6</sup> The United States OSHA (1991) consider an employee should be removed from work if they have an exposure to lead at or above the WES of 0.05 mg/m<sup>3</sup> and on each occasion that a periodic and a follow-up blood sampling test indicates the employee PbB is  $\geq 60$  µg/dL, or if the average of the last three blood sampling tests conducted over the previous six months indicates the PbB is  $\geq 50$  µg/dL. But an employee does not need to be removed if the last blood sampling test gave a PbB  $\leq 40$  µg/dL. This implies OSHA (1991) consider a PbB of 40 µg/dL an appropriate target level. The PbB threshold level for workers who wish to plan pregnancies is 30 µg/dL.

<sup>7</sup> Schwartz and Hu (2007) do not state how this average PbB is estimated (i.e. monthly, yearly, etc).

**Table 2.1: Summary of WES and BLRL that have supporting documentation**

Country & Agency	WES <sup>a</sup> (mg/m <sup>3</sup> )	Date		Fraction	BLRL (µg/dL) <sup>a, b</sup>			Date		Comment	Reference
		Set	Revised		M & FNR	FR	FP & FB	Set	Revised		
EC (SCOEL)	0.1	2002	NS	Lead fumes and dusts <10µm	30 (non-legislated BLRL)			2002	NS	This is a recommendation from a committee, not legislated. However, it has been picked up by various member countries. Rationale not clear, however BLRL seems to be set at a level lower than that which is said to protect against a range of health effects in adult workers. Background PbB seems to have been considered.	SCOEL 2002
Germany (DFG)	-	-	-	-	30 <sup>c</sup>	7 <sup>c</sup>		2000	2013 <sup>d</sup>	Supporting documentation only located for previous recommendations.	DFG 2005; 2013a, b
USA (ACGIH)	0.05	1995	NA	Inhalable	30 <i>Implied BLRL for pregnant females = 10<sup>e</sup></i>			1995	NA	BLRL set to minimise potential for a range of non-transient effects. WES set to conform with BLRL.	ACGIH 2001a, b
World Health Organisation (WHO)	0.03 – 0.06	1980	NA	NS	40 (non-legislated BLRL)	30 (non-legislated BLRL)		1980	NA	BLRL set to minimise potential for a range of adverse effects. WES set to conform with BLRL using a relationship of 0.5 µg/dL increase in PbB per µg/m <sup>3</sup> (i.e. 0.001 mg/m <sup>3</sup> ) PbAir and a background PbB of 10 to 25 µg/dL.	WHO 1980
Scientific non-agency members	-	-	-	-	<20 (to prevent acute effects & chronic for 10-20 yr. exposure)  10 (to prevent chronic effects for 20-40 yr. exposure) (non-legislated BLRL)			2007	NA	The scientific expert panel for the Development of Adult PbB Level Medical Management Guidelines suggested these revised BLRL aiming that their publication would have an impact on policy.  They noted similar recommendations had been made >15 years before.	Schwartz and Hu 2007

Country & Agency	WES <sup>a</sup> (mg/m <sup>3</sup> )	Date		Fraction	BLRL (µg/dL) <sup>a, b</sup>			Date		Comment	Reference
		Set	Revised		M & FNR	FR	FP & FB	Set	Revised		
Scientific non-agency committee	-	-	-	-	30 (Also lower concentrations depending on pattern of PbB measurements). <sub>f</sub>  (non-legislated BLRL)		5	2007	NA	Recommendations from a scientific committee from universities, industry and government.  The BLRL are recommended but not legislated, and are intended to protect against a range of effects related to short-term or long-term exposure.	Kosnett et al. 2007
California proposal	0.0005 (proposed)	2013	-	NS	30 or 20  (proposed BLRL, not yet legislated)			2009	NA	The current legislated BLRL in the USA is provided in Table 2.2 (50 µg/dL for all persons). California Department of Public Health (Cal DPH 2009, 2010, 2011) has recommended the revised BLRL originally proposed by Kosnett et al. (2007) (see above) should be legislated. Specifically, the BLRL proposed by California are 30 µg/dL for a single PbB measurement, or 20 µg/dL for two consecutive PbB measurements (four weeks apart).	Cal DPH 2009, 2010, 2011, 2013
Professional Association	-	-	-	-	30 (10 – 29 at doctors discretion) <sup>g</sup>  (non-legislated BLRL)			2007	NA	Document to provide advice to clinicians for lead exposed adult patients	AOEC 2007

WES = workplace exposure standard; BLRL = blood lead removal level; PbB = blood lead; M = males; FNR = females not of reproductive capacity; FR = females of reproductive capacity; FP = females who are pregnant; FB = females who are breastfeeding; NA = not applicable; NS = not stated; - = none provided.

<sup>a</sup> WES is measured as an 8-hour time weighted average. Although the terminology used in this table is WES (i.e. workplace exposure standard) and BLRL (blood lead removal level), agencies may have different names for such limits (e.g. occupational exposure limit, threshold limit value, permissible exposure limit, Maximale Arbeitsplatzkonzentration, biological exposure standard, etc.). Some agencies may not distinguish if a PbB standard is biological exposure standard or a BLRL; in these instances, the PbB concentration was assumed to be a BLRL.

<sup>b</sup> The PbB levels in this table are either legislated or non-legislated BLRLs. Non-legislated BLRLs are recommendations made by the organisation, which does not have legislative status. Non-legislated or legislated status has been noted in the table.

<sup>c</sup> The BLRL of 30 µg/dL is for females >45 years and males. The former is taken to mean females not of reproductive capacity. DFG (2013b) states this is a BLW (“Biologischer Leit-Wert”), the amount of a chemical substance in exposed humans which serves as an indicator for necessary protective measures. The BLRL of 7 µg/dL is a so-called BAR (“Biologische Arbeitsstoff-Referenzwerte”) value, which represent the background levels of a substance in a reference population of persons of working age who are not occupationally exposed to the substance. The BAR values supposedly are based on the 95<sup>th</sup> percentile of concentrations regarded as not having effects on health, but DFG

(2013b) do not provide further information. BLW and BAR values are set for chemicals for which the available toxicological or occupational-medical data are insufficient for establishment of BAT (i.e. biological tolerance) values.

<sup>d</sup> This is the date of the publication, but the value may have been revised before this date.

<sup>e</sup> Although the official BLRL is 30 µg/dL, ACGIH notes that "*Women of child bearing potential, whose blood Pb exceeds 10 µg/dL, are at risk of delivering a child with a blood Pb over the current Centers for Disease Control guideline of 10 µg/dL. If the blood Pb of such children remains elevated, they may be at increased risk of cognitive deficits. The blood Pb of these children should be closely monitored and appropriate steps should be taken to minimize the child's exposure to environmental lead.*" The latter tacitly implies the BLRL for females of reproductive capacity, or females who are pregnant or breastfeeding should perhaps be the same as the goal for the general population (including children), i.e. 10 µg/dL.

<sup>f</sup> Kosnett et al. (2007) recommended that individuals be removed from occupational lead exposure if a single PbB concentration exceeds 30 µg/dL or if two successive PbB measured over a 4-week interval are  $\geq 20$  µg/dL. Removal of individuals from lead exposure should be considered to avoid long-term risk to health if exposure control measures over an extended period do not decrease PbB to  $< 10$  µg/dL or if selected medical conditions exist that would increase the risk of continued exposure. They advised pregnant females should avoid occupational or avocational lead exposure that would result in PbB  $>5$  µg/dL.

<sup>g</sup> The AOEC (2007) states at PbB between 10 and 29 µg/dL, the clinician should consider removal from lead exposure if warranted, and at PbB  $\geq 30$  µg/dL, removal from exposure should definitely occur.

**Table 2.2: Summary of WES and BLRL without supporting documentation <sup>a</sup>**

Country & Agency	WES <sup>b</sup> (mg/m <sup>3</sup> )	Date		Fraction	BLRL (µg/dL) <sup>b, c</sup>			Date		Comment	Reference
		Set	Revised		M & FNR	FR	FP & FB	Set	Revised		
Australia (Safe Work)	0.15	1991	NA	Inhalable	50 (legis- lated BLRL)	20 (legisl- ated BLRL)	15 (legis- lated BLRL)	1994	NA	Based on ACGIH (1991) deliberations.	Safe Work 2013, NOHSC 1994
Argentina (MTES)	0.05	NS	2003	NS	30			NS	NS	Same as ACGIH.	MTES 2003
Austria (RIS)	0.1	NS	NS	NS	- <sup>d</sup>			-	-		RIS 2011
Belgium (MoE&W)	0.15	NS	NS	NS	- <sup>d</sup>			-	-	Same as the EC (1998) regulations.	MoE&W 2002
Canada – Alberta (WorkSafe, Gov of Alberta)	0.05	NS	NS	NS	50 (legis- lated BLRL)  objective 30	10 <sup>e</sup> (legislated BLRL)		NS	NS		Gov of Alberta 2009, WorkSafe Alberta 2009
Canada – British Columbia (WorkSafe BC)	0.05	NS	NS	NS	-			-	-	Same as ACGIH.	WorkSafe BC 2013
Canada – Ontario (MoL)	0.05	NS	NS	NS	70 (legislated BLRL)	40 (legislated BLRL)		1981	NA	WES same as ACGIH.  BLRLs old and outdated (Ontario MoL 1981). Occupational Health Clinics for Ontario Workers (OHCOW 2013) criticised Ontario MoL for not revising BLRL although recommendations to do so were received as far back as 1992.	Ontario MoL 1981, 2013

Country & Agency	WES <sup>b</sup> (mg/m <sup>3</sup> )	Date		Fraction	BLRL (µg/dL) <sup>b, c</sup>			Date		Comment	Reference
		Set	Revised		M & FNR	FR	FP & FB	Set	Revised		
Canada – Quebec (Quebec Gov)	0.05	NS	NS	NS	-	-	-	-	WES same as ACGIH.	Quebec Gov 2013	
Chile (MdS)	0.12	NS	NS	NS	40			NS	NS	MdS 2000	
China (Ministry of Health)	0.05	2002	NS	NS	-			-	-	Ye and Wong 2002  (not an agency reference; original agency reference could not be sourced)	
Denmark (DWEA)	0.05	1996	NS	NS	20			NS	NS	DWEA 2007	
Europe (EC)	0.15	1998	NA	NS	70			1998	NA	EC 1998	
Finland (MoSAH)	0.1	1993	NA	NS	50 (legislated BLRL) Objective 30 <sup>f</sup>			NS	NS	MoSAH 2012	
France (INRS)	0.1	2004	NS	Inhalable	40 <sup>f</sup>	30 <sup>f</sup>	2003	NS		INRS 2006, 2012; Legifrance 2003	
Germany (BAuA)	- <sup>g</sup>	-	-	-	40 <sup>h</sup>	30 <sup>h</sup>	1998	Currently being revised		BAuA 2013a, b	
Ireland (H&SA)	0.15	1998	NS	NS	70			1998	NS	Same as the EC (1998) regulations.	H&SA 2011a, b
Japan (JSOH)	0.1	1982	NS	NS	40			1994	NS		JSOH 2010
Luxembourg (JOGDL)	0.15	1998	NS	NS	70			1998	NS	Same as the EC (1998) regulations.	JOGDL 2002

Country & Agency	WES <sup>b</sup> (mg/m <sup>3</sup> )	Date		Fraction	BLRL (µg/dL) <sup>b, c</sup>			Date		Comment	Reference
		Set	Revised		M & FNR	FR	FP & FB	Set	Revised		
New Zealand (DoL)	0.1	NS	NS	Inhalable	50 (legislated BLRL) objective <30 <sup>i</sup>	30 (or lower) <sup>i</sup>		2010	NA		NZ DoL 2011
South Africa (SA DoL)	0.15	NS	NS	NS	60 (legislated BLRL)	40 (legislated BLRL) <sup>j</sup>		2002	NS		SA DoL 2002
Spain (INSHT)	0.15	NS	NS	NS	70			NS	NS	Same as the EC (1998) regulations.	INSHT 2013
Sweden (SWEA)	0.1	1993	NS	Total dust	40 (legislated BLRL) <sup>k</sup>	25 (legislated BLRL) <sup>k</sup>	Not permitted to work <sup>k</sup>	NS	NS	Lead-related work is completely forbidden for pregnant or breast-feeding workers.	SWEA 2005a, b, NIWL 2005
	Respirable dust										
Switzerland (SUVA)	0.1	NS	NS	NS	40 <sup>l</sup>	10 <sup>l</sup>		NS	NS	Same as the German DFG (2005) values (see Section 2.1.2)	SUVA 2013
UK (HSE)	0.15	NS	NS	Inhalable	60 (legislated BLRL) <sup>m</sup>	30 (legislated BLRL) <sup>m</sup>	Not permitted to work <sup>m</sup>	NS	NS		UK HSE 2002, 2012
USA (OSHA)	0.05	1978	NA	NS	60 or 50 (legislated BLRL) <sup>n</sup>			1978	1983		OSHA 1991
USA (NIOSH)	0.05	1978	NS	NS	60			NS	NS		NIOSH 2010, 2011, FR 1997
USA – California (Cal DIR)	0.05	NS	NS	NS	50 (legislated BLRL)			NS	NS	Note the California Department of Public Health has recommended adopting revised BLRL (Table 2.1).	Cal DIR 2013

Country & Agency	WES <sup>b</sup> (mg/m <sup>3</sup> )	Date		Fraction	BLRL (µg/dL) <sup>b, c</sup>			Date		Comment	Reference
		Set	Revised		M & FNR	FR	FP & FB	Set	Revised		
USA – Washington (Wash DoL)	0.05	1978	NA	NS	60 or 50 (legislated BLRL) <sup>n</sup>			1980	1984	Same as the OSHA standards.	Wash DoL 2009

WES = workplace exposure standard; BLRL = blood lead removal level; PbB = blood lead; M = males; FNR = females not of reproductive capacity; FR = females of reproductive capacity; FP = females who are pregnant; FB = females who are breastfeeding; NA = not applicable; NS = not stated; - = none provided.

<sup>a</sup> The supporting documentation sought for this purpose was one that explains the scientific rationale underpinning the WES and/or BLRL.

<sup>b</sup> WES is measured as an 8-hour time weighted average. Although the terminology used in this table is WES (i.e. workplace exposure standard) and BLRL (blood lead removal level), agencies may have different names for such limits (e.g. occupational exposure limit, threshold limit value, permissible exposure limit, Maximale Arbeitsplatzkonzentration, biological exposure standard, etc.). Some agencies may not distinguish if a PbB standard is biological exposure standard or a BLRL; in these instances, the PbB concentration was assumed to be a BLRL.

<sup>c</sup> The PbB levels in this table are legislated or non-legislated BLRL. Non-legislated BLRLs are recommendations made by an organisation, which do not have legislative status. Non-legislated or legislated status has been noted in the table.

<sup>d</sup> If a member country has not set its own BLRL for lead, the BLRL set by the European Union becomes the default BLRL and cannot be exceeded. The EU BLRL for inorganic lead and its compounds is 70 µg/dL (EC 1998).

<sup>e</sup> A PbB of 1.5 µmol/L (i.e. 30 µg/dL) is considered by WorkSafe Alberta (2009) an acceptable level not requiring action for females not of reproductive capacity and males. Different actions are required if PbB exceeds this level, with removal from the job occurring when PbB is ≥ 2.5 µmol/L (i.e. 50 µg/dL). For pregnant workers and female workers of childbearing age considering becoming pregnant, PbB must be kept below 0.5 µmol/L (i.e. 10 µg/dL).

<sup>f</sup> The BLRL of 40 µg/dL is stated to be for males and the BLRL of 30 µg/dL is stated to be for females (INRS 2006, Legifrance 2003). Reproductive capacity is not mentioned.

<sup>g</sup> BAuA (2013b) does not have a WES for inorganic lead. However in a recent publication from the German Accident Insurance Agency (DGUV 2013), a WES of 0.1 mg/m<sup>3</sup> is mentioned, with a reference to a previous BAuA (2007) publication. Upon consultation of the (BAuA 2007) publication, the concentration of 0.1 mg/m<sup>3</sup> is mentioned but it is unclear whether this is considered an official WES for lead. The official WES for tetraethyl lead is 0.05 mg/m<sup>3</sup> (BAuA 2013). If a member country has not set its own WES for a substance, the WES set by the European Union becomes the default WES and cannot be exceeded. The EU WES for inorganic lead and its compounds is 0.15 mg/m<sup>3</sup> and the BLRL is 70 µg/dL (EC 1998).

<sup>h</sup> The BLRL of 40 µg/dL is for females >45 years and males. The former is taken to mean females not of reproductive capacity. The BLRL of 30 µg/dL is for females <45 years of age. According to BAuA (2013b) these values were initially set in 1998 and are currently undergoing revision.

<sup>i</sup> According to the New Zealand Department of Labour (NZ DoL 2011), the overall objective of medical surveillance for lead is to maintain the PbB for all workers below 1.5 µmol/L (approx. 30 µg/dL), however suspension from work typically occurs for a male employee if he has a single PbB result of ≥ 50 µg/dL (NZ DoL 2011). NZ DoL (2011, pg. 91) also state that “while it is preferable for all employees’ blood lead levels to stay at or below 1.5 µmol/L [approx. 30 µg/dL], this value must be more stringent for pregnant women or women planning to become pregnant, because they should be exposed to as little lead as possible. Ideally, these women should have no exposure to lead at all, because the developing foetus is extremely susceptible to this substance. Additionally, accumulated lead can be released from the mother’s bones during times of calcium stress such as pregnancy and lactation.”

<sup>j</sup> The PbB removal level of 40 µg/dL for females of reproductive capacity only applies if the female falls pregnant (SA DoL 2002).

<sup>k</sup> The Swedish Work Environment Authority (SWEA 2005b) specifies a complex action program for PbB monitoring in workers. The values in this table represent the PbB associated with removal from a Pb-related job. SWEA (2005b) provide a BLRL of 2.0 µmol/L (converted here to 40 µg/dL) for females >50 years, i.e. not of reproductive capacity and all males. They also provide a BLRL of 1.2 µmol/L (converted in this report to 25 µg/dL) for females <50 years of age. This is for any single PbB reading. The removal from a lead job can also occur if individuals have PbB > 1.8 µmol/L (i.e. ~37 µg/dL) (for females >50 yrs and males) or > 1.0 µmol/L (i.e. ~20 µg/dL) (for females <50 yrs) in three consecutive PbB controls. Pb-related work is completely forbidden for pregnant or breast-feeding workers (SWEA 2005b).



<sup>l</sup> The BLRL of 40 µg/dL is for females >45 years and males. The former is taken to mean females not of reproductive capacity. The BLRL of 10 µg/dL is for females <45 years of age.

<sup>m</sup> UK HSE (2012) provides PbB action and suspension levels for a) general employees (i.e. males & females not of child-bearing age): 50 and 60 µg/dL, respectively, b) females of child bearing age: 25 and 30 µg/dL, respectively, and c) young people <18 yrs: 40 and 50 µg/dL, respectively. UK HSE (2012) also state that if a woman is pregnant, the doctor will automatically certify that they should not work where exposure to lead is significant. It is against the law for females capable of having children and for young people <18 yrs old to work in some Pb-related jobs, e.g. lead smelting & refining, manufacture of lead acid batteries.

<sup>n</sup> An employee should be removed from work if they have an exposure to lead at or above the WES of 0.05 mg/m<sup>3</sup> and on each occasion that a periodic and a follow-up blood sampling test indicates the employee PbB is ≥ 60 µg/dL, or if the average of the last three blood sampling tests conducted over the previous six months indicates the PbB is ≥ 50 µg/dL. But an employee does not need to be removed if the last blood sampling test gave a PbB ≤ 40 µg/dL. OSHA (1991) state that *“prevention of adverse health effects for most workers from exposure to lead throughout a working lifetime requires that worker blood lead (PbB) levels be maintained at or below forty micrograms per one hundred grams of whole blood (40 µg/100g). The blood lead level of workers (both male and female workers) who intend to have children should be maintained below 30 µg/100g to minimize adverse reproductive health effects to the parents and to the developing fetus.”*

## 2.1.2 Basis of workplace standards

### 2.1.2.1 USA (ACGIH)

Note the deliberations of the American Conference of Government Industrial Hygienists (ACGIH) are not legally binding within the US.

#### BLRL

The ACGIH (2001a) recommended a BLRL, termed a biological exposure index (BEI) by ACGIH, of 30 µg/dL in order to minimise potential for the following:

- Psychological and psychomotor effects that appear to begin at PbB > 30 µg/dL, but in the studies of the time, do not exceed the reference values for the tests.
- Changes in nerve conduction and latency intervals, which also appear to begin at PbB > 30 µg/dL but have an uncertain association with a worker's functional impairment.
- Decrements in the haematological reserve capacity that appeared in one study at PbB > 40 µg/dL.
- Elevated blood pressure and the incidence of cardiovascular disease (relationships with lead currently being debated). Any effect in occupational populations at PbB < 30 µg/dL was expected by ACGIH to be small.
- Renal impairment, as measured by creatinine clearance and proteinuria, where minor changes that did not constitute functional renal impairment were reported at PbB < 30 µg/dL, and increased incidences of proteinuria reported beginning at 40 µg/dL.
- The incidence of spontaneous abortion and effects on male fertility where study results were mixed. According to ACGIH (2001a), in the studies that reported positive associations, the effects appeared to begin at PbB > 30 µg/dL, with changes in spermatogenesis reported at levels above 40 µg/dl.
- Decreased length of gestation and birth weight where study results are also mixed and methodologies questionable, but expert reviews conclude that at PbB > 30 µg/dL the relationships strengthen.

ACGIH (2001b) concluded the toxicology and health data at the time suggested long-term lead exposure in adults that did not produce blood lead concentrations above 40 µg/dl would minimize the potential for clinically adverse health effects. Furthermore the ACGIH (2001a) believed that workplace conditions that kept a woman's blood lead level below the BEI of 30 µg/dl would protect her ability to bear children that can develop normally. A target BEI of 30 µg/dl was therefore set. However the ACGIH (2001a) also noted that certain studies reported effects at PbB below the BEI. The BEI committee reduced the significance of these reports because in its view the effects were transient, did

not constitute a decrement in the worker's functional capacity, or were contradicted by other adequately conducted studies.

Since the publication of the ACGIH (2001a) BEI documentation, other international agencies have suggested PbB < 20 µg/dL in adults may be associated with depressed blood δ-aminolevulinic acid dehydratase, subtle neurological effects, reductions in glomerular filtration rates, and an increase in systemic blood pressure and decreased sperm quality (NZ MfE 2011, ATSDR 2007, US EPA 2006, US EPA 2013, NTP 2012, NRC 2013).

Although the BEI recommended by the ACGIH (2001a) is 30 µg/dL, they note that "*Women of child bearing potential, whose blood Pb exceeds 10 µg/dL, are at risk of delivering a child with a blood Pb over the current Centers for Disease Control guideline of 10 µg/dL. If the blood Pb of such children remains elevated, they may be at increased risk of cognitive deficits. The blood Pb of these children should be closely monitored and appropriate steps should be taken to minimize the child's exposure to environmental lead.*" The latter tacitly implies the BEI for female workers of reproductive capacity, or females who are pregnant or breastfeeding should be the same as the goal for the general population, i.e. 10 µg/dL.

### WES

The derivation of the ACGIH (2001b) WES for PbAir is less clear than the rationale for the BEI.

- ACGIH (2001b) states the control of PbB at or below the BEI of 30 µg/dL requires careful consideration of all sources that contribute to lead absorption.
- The geometric mean PbB in the general US population (i.e. background PbB) was 2.8 µg/dL (95% CI = 2.7 to 3.0) between 1988 and 1991.
- PbB in workers above the background nominated by ACGIH are the result of both inhalation and ingestion at the workplace.
- Based on their analysis of the data in Bishop and Hill (1983), ACGIH consider non-airborne (hand to mouth) lead absorption can be controlled by good hygiene practice to amounts that will incrementally increase PbB by 5 to 10 µg/dL.
- ACGIH reviewed a number of occupational epidemiology studies and determined air slope factors (i.e. ASF, the relationship between inhalable PbAir and PbB) that ranged from 0.03 to 0.19 µg/dL PbB per µg/m<sup>3</sup> PbAir. However from the analysis in Section 5, it is apparent that PbB from background (non-occupational) exposures were not factored into many of these slope factors and cognisance was not given to the non-linear relationship between PbB and PbAir. The correlation coefficients were variable, ranging from 0.14 to 0.9, with lower values

occurring at lower PbAir exposures. Unfortunately the mathematical details of how the ACGIH determined the ASFs is not provided in their documentation.

- ACGIH took the steepest slope of  $0.19 (\mu\text{g/dL})/(\mu\text{g/m}^3)$  which at  $0.05 \text{ mg/m}^3$  (the ACGIH recommended WES) gives a PbB of  $9.5 \mu\text{g/dL}$ . However this ASF is not representative of the PbB – PbAir relationship at  $0.05 \text{ mg/m}^3$ .

The above deliberations would bring the total PbB to:

$2.8 \mu\text{g/dL}$  (background) +  $(5 - 10 \mu\text{g/dL})$  (hand to mouth) +  $9.5 \mu\text{g/dL}$  (from PbAir) =  $17.3 - 22.3 \mu\text{g/dL}$

The reason for selecting  $0.05 \text{ mg/m}^3$  is not clear in the ACGIH (2001b) documentation. It was noted by ACGIH that a major reduction in air lead concentrations such as from  $0.05$  to  $0.025 \text{ mg/m}^3$  would only result in a reduction of blood lead concentration by  $4.5 \mu\text{g/dL}$ . Presumably this relatively small change in the face of many other factors that could affect PbB was not considered sufficient justification for a lower WES. However the rationale of the ACGIH assumed the ASF was the same at  $0.05$  and  $0.025 \text{ mg/m}^3$ .

### **2.1.2.2 Europe Commission (SCOEL)**

#### BLRL

The Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission provides scientific rationale and recommendations for WES and biological exposure standards of chemical substances in the workplace, however these values are not legally binding. European member states may choose to conform with the values or derive their own, provided they are more stringent than those in the binding European legislation (EC 1998). The latter usually being set with no supporting documentation.

SCOEL (2002) reviewed the PbB concentrations associated with a wide range of health effects in workers. The overall conclusion was that a long-term PbB level of  $40 \mu\text{g/dL}$  probably represents a low observed adverse effect level (LOAEL) for an impairment of performance in neurobehavioural tests of adults, but that other effects generally occur at concentrations  $> 40 \mu\text{g/dL}$ . SCOEL considered a WES based on avoiding functional CNS alterations is expected also to protect against peripheral nervous system effects and renal toxicity, including possible renal cancer development and effects on haem biosynthesis and on blood pressure. Based on these considerations (and a background PbB of  $\sim 5 \mu\text{g/dL}$  in many European countries at that time), SCOEL (2002) recommended a target PbB of  $\leq 30 \mu\text{g/dL}$  for workers. However, they noted this level is not seen as being entirely protective of the offspring of working females.

### WES

SCOEL (2002) recommended a WES of 0.1 mg/m<sup>3</sup> for airborne lead (lead fumes and dust < 10 µm) which is indicated to be consistent with a BLRL of 30 µg/dL. They state this is based on field studies on lead battery workers by Lai et al. (1997) and others (Kentner and Fischer 1993) and the 'preferred values' approach of SCOEL.

Kentner and Fischer (1993) could not be sourced. Lai et al. (1997) established a relationship between PbAir and PbB in battery workers using both simple linear and multiple regression. These models predicted that when exposed to 0.1 mg/m<sup>3</sup> of PbAir, a worker could have a PbB level of 53.7 or 43.6 µg/dL respectively. They also predicted that further reduction of PbAir (e.g. by 0.05 mg/m<sup>3</sup>) in this factory would not significantly reduce PbB (i.e. only to 39.6 µg/dL), due to the importance of hygienic practices.

The SCOEL documentation of the WES is poor. It is unclear how the data from Lai et al. (1997) was applied to select the recommended WES of 0.1 mg/m<sup>3</sup>, as the latter suggests a WES of 0.1 mg/m<sup>3</sup> would result in PbB levels much higher than the recommended BLRL.

#### **2.1.2.3 Germany (DFG)**

The German Research Foundation (DFG) recommends WES and biological exposure standards for chemical substances in the workplace, but the German government agency responsible for workplace safety (BAuA) may or may not adopt these recommendations.

DFG has not recommended a contemporary WES for PbAir. From 1977 to 2006, the German WES was 0.1 mg/m<sup>3</sup> (inhalable), and the BLRL was 40 µg/dL. Inorganic lead compounds were reclassified in the mid-2000s from group 2B carcinogens (possibly carcinogenic; evidence of carcinogenicity in animal or *in vitro* studies) to group 2A (probably carcinogenic in humans) by the International Agency for Research on Cancer (IARC). Germany subsequently assigned a category 2 cancer notation to the compounds, and the WES and BLRL were withdrawn since German policy states that substances carcinogenic in man or experimental animals (i.e. those classified in categories 1 or 2) are not assigned Maximale Arbeitsplatz-Konzentration (MAK i.e. WES) or BAT (Biologischer Arbeitsstoff-Toleranz-Wert, i.e. BLRL) values. Instead, exposure to such substances is managed through non-threshold risk-based approach where, if a level of risk deemed acceptable is exceeded, actions must be taken to either reduce or halt exposure (Haunert 2012).

However, DFG recommended a biologic indicator value (BLW) and a biologic reference value (BAR) for inorganic lead. These values are non-binding variants of a binding biological exposure standard:

- The BLW of 30 µg/dL is for females >45 years and males. The former is taken to mean females not of reproductive capacity. DFG (2013b) states this is a BLW (“Biologischer Leit-Wert”, i.e. biological indicator value), the amount of a chemical substance in exposed humans which serves as an indicator for necessary protective measures.
- The BAR of 7 µg/dL for females <45 years of age. This is regarded as a so-called BAR value (“Biologische Arbeitsstoff-Referenzwerte”, i.e. biological workplace reference value), which represents the background level of a substance in a reference population of persons of working age who are not occupationally exposed to the substance. The BAR values are based on the 95<sup>th</sup> percentile of concentrations regarded as not having effects on health, but DFG (2013b) do not provide further information.
- BLW and BAR values are set for chemicals for which the available toxicological or occupational-medical data are insufficient for establishment of BAT (i.e. biological tolerance) values, or for some chemicals classed as carcinogens.

DFG (2005) has published the background documentation describing the basis for the previous BLRL values. The latest biological exposure standard list (DFG 2013b) contains different BLRL (rather, the BLW and BAR mentioned above) to DFG (2005) for females >45 years and males (30 vs. 40 µg/dL) and for females <45 years (7 vs. 10 µg/dL). Thus between 2005 and 2013, both BLRL were revised downwards, and renamed BLW and BAR, respectively. The rationale for the revisions could not be located.

#### 2.1.2.4 World Health Organisation (WHO)

The WHO made recommendations for a health-based WES and BLRL for lead as far back as 1980 (WHO 1980).

##### BLRL

The WHO (1980) discussed the then current knowledge of Pb-related health effects in workers in a comprehensive review. Although pointing out there were several uncertainties and data gaps associated with the information, they concluded the following effects may occur:

- *PbB* ≤ 30 µg/dL: An increase in the erythrocytic protoporphyrin (PP) IX content<sup>8</sup> in about 50% of females and about 15% of males is the only discernible effect.

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<sup>8</sup> Protoporphyrin IX is an important precursor to biologically essential groups such as haeme, cytochrome c, etc. Accumulation of protoporphyrin IX in erythrocytes is the earliest of the haematological effects in response to lead exposure. This occurs as a result of inhibition of ferrochelatase (haeme synthetase) activity in the bone marrow (WHO 1980).

- *PbB 30 – 39.9 µg/dL*: About 90% of females and 40% of males show an elevation of the erythrocytic PP. In males about 15% of the delta-aminolevulinic acid in urine (ALA-U)<sup>9</sup> values exceed 5 mg/L and some values exceed 10 mg/L.<sup>10</sup> Approximately 40% of females excrete more than 5 mg ALA/L. WHO considered there were suggestions of slight decreases in mean conduction velocities of peripheral nerves, although values below the normal range have not been demonstrated.
- *PbB 40 – 49.9 µg/dL*: The PP IX content of erythrocytes exceeds “normal” values in all females and in more than 50% of males. The urinary level of ALA coproporphyrin (CP)<sup>11</sup> is slightly elevated in a low proportion (<20%) of lead-exposed males and in about 50% of females. The conduction velocity of the slow nerve fibres of the ulnar nerve is slightly decreased (this nerve is technically the easiest to measure conduction velocity) and WHO concluded it was probably below the normal lower limit in a proportion of cases.
- *PbB 50 – 59.9 µg/dL*: About 50% of subjects show a marked increase in the erythrocytic PP and all values are above “normal”. The ALA-U and CP-U is elevated in about 50% of males and nearly all females. About 10-20% of subjects show slowing of the conduction velocities of two or more nerves. Impairments of visual intelligence and visual-motor functions can be detected in 20-30% of subjects. According to one study reviewed by WHO, the frequency of subjective neurological symptoms begins to increase at these PbB concentrations.
- *PbB 60 – 69.9 µg/dL*: ALA-U exceeds 10 mg/L in more than 50% of subjects; CP-U exceeds 100 µg/L; and the erythrocyte PP level exceeds 3,000 µg/L in a majority of subjects. Slowing of the nerve conduction velocities shows a slightly higher frequency than in the preceding group. Pathological electromyograms occur in at least one-third of subjects. Psychological impairment and subjective symptoms occur probably at the same frequency as in the preceding category (the number of individuals studied had been too small to allow distinctions). Other effects, such as shortening of the erythrocyte life span and lowering of the haemoglobin value also begin to appear.

Based on the above, WHO (1980) recommended a BLRL of 40 µg/dL for females over reproductive age (i.e. >45 years) and males. This recommendation was based on the adverse effects of lead on the haematopoietic and peripheral nervous system at the PbB range of 40-49 µg/dL. The WHO (1980) noted that according to the knowledge available at the time of publication, PbB levels <40 µg/dL did

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<sup>9</sup> ALA-U has been used a biological test for monitoring occupational exposure to lead; it is considered an indirect indicator of exposure to lead.

<sup>10</sup> The mean urinary ALA concentrations in healthy adult men with no history of occupational lead exposure is ~2.4 mg/L, with a 95% upper confidence limit of 4.1 mg/L (Tomokuni and Ogata 1980).

<sup>11</sup> The pattern of coproporphyrin excretion in the urine follows closely that of ALA although the latter is more specific to lead.

not cause adverse neurological effects, although it was admitted that a no-effect level could not be defined from the available data. However, slight increases in haem synthesis intermediates, especially in females, were not prevented. But in view of the uncertainty of the health significance of such mild effects, WHO (1980) considered there were not strong enough reasons at the time to prompt the recommendation of a limit that would entirely prevent their appearance.

WHO (1980) also recommended PbB of females of reproductive age should be kept as low as possible, and to protect the foetus, should not exceed 30 µg/dL. It was stated this level would also prevent significant effects on haem synthesis.

The rationale for the recommended BLRL is reasonable considering the knowledge available to the WHO at the time. However, as noted in Section 2.2.1, contemporary reviews from other international agencies suggest PbB < 20 µg/dL in adults may be associated with health effects (NZ MfE 2011, ATSDR 2007, US EPA 2006, NTP 2012, NRC 2013) (see Section 5).

### WES

The WHO (1980) acknowledge that the PbB levels are the primary criterion for preventing toxic effects in exposed workers, but the concentration of PbAir is the primary guideline for engineering purposes. They considered the available correlations between PbB and PbAir were weak and that the recommended PbB levels could not readily be directly translated into limits for PbAir. They noted that since the contribution to PbB from non-occupational (i.e. background) sources varied between people and geographical areas, and since any relationship between PbAir and PbB will depend on the particle size and chemical form of lead, it is not possible to recommend a WES that would by itself ensure full compliance with the BLRL of 40 µg/dL. Since the WHO (1980) review it has become apparent that while particle size affects the extent and region of deposition in the respiratory tract, the lead that is deposited in the alveoli is completely absorbed regardless of chemical form (Chamberlain et al. 1981, 1985; Morrow et al. 1980).

Nevertheless, WHO (1980) concluded an average increase of 0.5 µg/dL can be predicted from each average increase of 1 µg/m<sup>3</sup> (i.e. 0.001 mg/m<sup>3</sup>) (40 h/week average exposure) of PbAir up to a PbB level of 50 µg/dL. Note the latter conclusion was made using studies with several deficiencies and uncertainties. Using this information WHO (1980) concluded:

- For populations with an average background PbB of 25 µg/dL, the value of PbAir should not exceed 0.03 mg/m<sup>3</sup> (presumably 40 µg/dL – 25 µg/dL ÷ 0.5 µg/dL = 30 µg/m<sup>3</sup>, i.e. 0.03 mg/m<sup>3</sup>).
- Similarly, for populations with an average background PbB of 10 µg/dL, PbAir should not exceed 0.06 mg/m<sup>3</sup> (i.e. 40 µg/dL – 10 µg/dL ÷ 0.5 µg/dL = 60 µg/m<sup>3</sup>, i.e. 0.06 mg/m<sup>3</sup>).



Based on this reasoning, WHO (1980) recommended PbAir should not exceed the range of 30 – 60  $\mu\text{g}/\text{m}^3$  (i.e. 0.03 – 0.06  $\text{mg}/\text{m}^3$ ). It should be noted the background PbB used by WHO (1980) are significantly higher than what would be expected in the general population today, as they stem from a time when lead was still used in petrol.

It is interesting that the WHO (1980) recommendation is similar to the ACGIH (2001a, b) recommendation (i.e. WES of 0.05  $\text{mg}/\text{m}^3$ , BLRL of 30  $\mu\text{g}/\text{dL}$ ), considering the latter was first set 15 years later (Section 2.1), but the rationale used by WHO (1980) to arrive at the WES is less ambiguous. It is also similar to the recommendations of this report (Sections 4.5 and 6).

### **2.1.2.5 California proposal**

#### BLRL

Kosnett et al. (2007) reviewed the available evidence in the literature on the health effects of lead. The review indicated the potential for hypertension, effects on renal function, cognitive dysfunction, and adverse female reproductive outcome in adults with PbB < 40  $\mu\text{g}/\text{dL}$ . Based on the literature and the authors' collective experience in evaluating Pb-exposed adults, they recommended individuals be removed from occupational lead exposure if:

- a single PbB concentration exceeds 30  $\mu\text{g}/\text{dL}$  or,
- two successive PbB measurements over a 4-week interval are  $\geq 20 \mu\text{g}/\text{dL}$ .

They also concluded removal from lead exposure should be considered to avoid long-term risks to health if exposure controls over an extended period do not decrease PbB to <10  $\mu\text{g}/\text{dL}$ , or if selected medical conditions exist that would increase the risk of continued exposure.

They also advised pregnant women to avoid occupational or avocational lead exposure that would result in PbB > 5  $\mu\text{g}/\text{dL}$  (Kosnett et al. 2007).

The California Department of Public Health (Cal DPH 2009, 2010, 2011) has recommended the revised BLRL as proposed by Kosnett et al. (2007) (see above) should be legislated. Specifically, the BLRLs proposed by California are 30  $\mu\text{g}/\text{dL}$  for a single PbB measurement, or 20  $\mu\text{g}/\text{dL}$  for two consecutive PbB measurements (measured four weeks apart).

#### WES

In conjunction with the proposed revisions to the legislated BLRLs described above, Cal DPH (2013) proposed a revised WES be adopted. They contracted the Office of Environmental Health and Hazard

Assessment in the Californian Environmental Protection Agency (OEHHA 2013) to model a level of PbAir which would ensure the “majority” of workers would have a PbB <10 µg/dL over a 40-year working lifetime.

The pharmacokinetic modelling used an adjusted version of the non-linear Leggett model to make PbB predictions from exposure to PbAir in the workplace (OEHHA 2013). They adjusted blood, bone, and urine clearance parameters of the model to fit data collected from workers chronically exposed to lead, and the general population environmentally exposed to lead. They tested the adjusted model with several datasets from the literature to ensure predictions compared well to observed data.

The adjusted model was used to simulate workplace inhalation exposures that would result in a range of PbB concentrations after 40 years of occupational exposure. Exposure via background air and diet was included in the modelling. Using population PbB distributions based on epidemiologic data in children<sup>12</sup>, OEHHA (2013) calculated the 90<sup>th</sup> and 95<sup>th</sup> PbB percentiles for workers exposed to different concentrations of PbAir, ranging from 0.5 to 34 µg/m<sup>3</sup>.

OEHHA (2013) also evaluated the time required for worker’s PbB to decline from a higher PbB (20, 30, 40, 50, or 60 µg/dL) to 15 µg/dL following cessation of 1, 10, 25 or 40 years workplace lead exposure. A target of 15 µg/dL was used because the Cal DPH (2009) Medical Surveillance guidelines recommend a worker with elevated PbB not return to work until their PbB is below 15 µg/dL. This appears to be at odds with the initial target of the modelling of < 10 µg/dL.

Based on the modelling results, in order to prevent chronic PbB of above 5 to 10 µg/dL, Cal DPH (2013) recommended PbAir levels in the workplace must not exceed an 8-hour TWA concentration of 0.0005 – 0.0021 mg/m<sup>3</sup> (0.5 – 2.1 µg/m<sup>3</sup>). At an air concentration of 0.0005 mg/m<sup>3</sup>, the modelling predicted 95% of workers would have a PbB <5 µg/dL over a 40-year working lifetime. At a concentration of 0.0021 mg/m<sup>3</sup>, 95% of workers would have a PbB < 10 µg/dL and 57% a PbB <5 µg/dL over their working lifetime.

Cal DPH (2013) recognised technical and economic feasibility must also be considered in addition to the health information before establishing a legislative WES. The proposed WES of 0.0005 mg/m<sup>3</sup> is

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<sup>12</sup> OEHHA (2013) state they cannot be certain that PbB in the worker population will be distributed in the same way as in children, however they checked the measure of variability (the geometric standard deviation, or GSD) against GSDs derived from data available on adults exposed to lead in controlled chamber studies and field studies. The GSDs in the studies with adults were 1.4, 1.4 and 1.97 in the low, medium and high exposure groups, respectively. Therefore OEHHA (2013) concluded that the GSD of 1.6 used in the modelling is in the range expected for worker populations.

100 times lower than the current WES in California and those set by other organisations in the US, it is anticipated there will be concerted opposition to such a dramatic change.

It is noted the proposed WES uses a long term target concentration of worker PbB of <10 or <5 µg/dL. The revisions to the BLRLs proposed by California (Cal DPH 2011) of 30 or 20 µg/dL are somewhat at odds with this advice. According to the modelling conducted by OEHHA (2013), 95% of the worker population would be expected to have PbB below 30 or 20 µg/dL if exposed to PbAir at 0.0104 or 0.006 mg/m<sup>3</sup>, respectively (i.e. 10.4 or 6 µg/m<sup>3</sup>).

## **2.2 Key points in Section 2**

Summary comments are provided at the beginning of Section 2.1. It is evident many of the WES and BLRL were set a long time ago, and in the majority of instances background documentation explaining the derivation of the values was not available. It is also clear many of the existing WES and BLRL do not incorporate consideration of recent understanding on health effects in adults and dose response. It appears there may be adverse health effects at lead exposures less than those associated with many of the BLRL.

The work of the ACGIH in 1995 has been influential; many jurisdictions appear to have 'picked up' the ACGIH recommendations. These, like many other WES and BLRL, are nonetheless old and in need of update. Furthermore while ACGIH provides documentation on the health effects of lead, the logic leading to the WES recommended value is somewhat obscure. In addition it is noted ACGIH is not a statutory body in the US and its deliberations do not have regulatory status. The competent regulatory authority in the US is OSHA and their WES and BLRL are higher than ACGIH for both females of reproductive capacity and males. The European Union has the highest WES and BLRL set in 1998 with no supporting documentation. These have been adopted by member countries that have not established their own guidelines for lead. Nevertheless, many European countries have chosen to adopt values lower than the general EU guidelines.

## **3. Alternatives to PbB**

### **3.1 Measuring lead in biological media**

Bergdahl and Skerfving (2008) have reviewed alternatives to PbB and indicate there are a number of qualities that are of importance in evaluating a biomarker's usefulness and performance. These are:

- Analytical accuracy and precision
- Cost
- Practical issues

- What is reflected by the biomarker
- Relationship to exposure
- Relationship to effects

Information indicates in many circumstances the best and most convenient media in which to biomonitor exposure to lead is whole blood, but bone or teeth (for past exposures), faeces (for current oral exposure) or urine (for organic Pb) are also sometimes useful (Bergdahl and Skerfving 2008). Nevertheless whole blood has shortcomings in that it shows slow response to changes in exposure. The use of plasma, which contains the free fraction of lead that is able to interact with target tissues, has not been sufficiently evaluated to be considered an alternative in occupational health services (Bergdahl and Skerfving 2008).

In the scientific and medical literature PbB (i.e. whole blood) is by far the predominant parameter used for biomonitoring lead exposure. Lead has been measured in a number of alternative media (plasma, serum, urine, bone, teeth, faeces, hair, nails, sweat, saliva, milk, exhaled breath, and placenta), but when compared to PbB they have limited applicability in the occupational arena. The principal issue with media other than whole blood is the lack of information relating the lead concentrations to exposure and health effects. Due to its historical use, the database and available knowledge on PbB is much larger and therefore makes whole blood a more appropriate media in which to measure lead.

Perhaps the media that shows most promise in supplementing PbB information is bone lead, particularly as it provides a better indication of past exposures and total body burden. Since bone lead has been used as a research tool for occupational health monitoring in various industries, information is being obtained relating bone lead concentrations to potential health effects. An advantage is the X-ray diffraction techniques are non-invasive. There are, however, obvious limitations concerning the costs and logistics of using lead in bone as a standard test in an occupational setting, particularly relating to initial investment costs for the equipment and training to use it.

Table 3.1 provides an overview of various biological media in which lead has been measured, and the advantages and disadvantages of each. It has been compiled from many references (Bergdahl and Skerfving 2008, Barbosa Jr et al. 2005, Angerer et al. 2007, Barreiros et al. 2013, Costa de Almeida et al. 2009, Esteban and Castaño 2009, Gil et al. 2011, Grandjean 1978, Hu et al. 2007, Iyengar and Rapp 2001, Khan et al. 2009, Koh et al. 2003, Lee 1999, Omokhodion and Crockford 1991, Rentschler et al. 2009, Rezende et al. 2010, Sajo-Bohus et al. 2004, Sakai 2000, Schütz et al. 2005, Shih et al. 2007, Sommar et al. 2013, Stawarz et al. 2011, Thaweboon et al. 2005, Theppeang et al. 2004, Timchalk et al. 2004). The interested reader is urged to consult these references for more detail.

**Table 3.1: Advantages and disadvantages of exposure biomarkers for lead <sup>a</sup>**

Biomarker medium	Advantages	Disadvantages
Whole blood (PbB)	<ol style="list-style-type: none"> <li>1. Good analytical precision.</li> <li>2. Many inter-laboratory comparisons available; routine standard techniques.</li> <li>3. Cost is relatively cheap compared to other media.</li> <li>4. Large database on health effect information relating to whole blood.</li> <li>5. Long history of use so there is a lot of experience and familiarity.</li> <li>6. When compared with other biomarkers, PbB has the ability to discriminate between individuals with different mean concentrations (i.e. the variance in measurements is attributable almost entirely to differences in PbB concentrations and not analytical precision).</li> </ol>	<ol style="list-style-type: none"> <li>1. Some minimal risk of sample contamination if skin not thoroughly cleaned.</li> <li>2. Process is invasive.</li> <li>3. Reflects relatively short-term exposure (months); may not adequately reflect a sudden increase in exposure or cumulative exposure.</li> </ol>
Plasma & serum	<ol style="list-style-type: none"> <li>1. Cost is relatively cheap compared to other media</li> <li>2. Plasma contains the body burden pool of lead that is able to interact with target tissues and therefore represents a more relevant measurement index.</li> <li>3. Can serve as a good indicator for recent exposure.</li> </ol>	<ol style="list-style-type: none"> <li>1. The plasma lead pool is only approx. 1% of the lead in whole blood.</li> <li>2. Low detection limits are needed.</li> <li>3. No schemes for inter-laboratory comparison appear to exist, certified reference materials are lacking.</li> <li>4. Haemolysis can often occur if serum/plasma isn't prepared quickly after collection. This can erroneously increase plasma lead concentration.</li> <li>5. There is little information relating lead in these media to exposure and effect.</li> </ol>
Urine	<ol style="list-style-type: none"> <li>1. Generally easy and reliable to measure.</li> <li>2. Cost is relatively cheap.</li> <li>3. Sample easy to obtain.</li> <li>4. Along with bone, more toxicological data available than other biomarker media, with the exception of whole blood.</li> </ol>	<ol style="list-style-type: none"> <li>1. Lower detection limits desirable than for whole blood.</li> <li>2. Available programs for inter-laboratory comparison fewer than for whole blood.</li> <li>3. Sample contamination is easier than with blood.</li> <li>4. Not a good index for total body burden (i.e. long-term accumulation).</li> <li>5. Spot urine specimens are potentially unreliable because volume is subject to large variations so measurements need creatinine excretion correction.</li> </ol>

Biomarker medium	Advantages	Disadvantages
Bone ( <i>in situ</i> )	<ol style="list-style-type: none"> <li>1. Usually contains easily measureable levels of lead, so detection limits are often not a problem.</li> <li>2. Contamination is not an issue if care taken.</li> <li>3. Along with urine, more toxicological data is available than for other biomarkers, with the exception of whole blood.</li> <li>4. Data is also available for developing 'normal' reference levels of lead.</li> <li>5. Lead in bone is the best reflection of cumulative long-term exposure &amp; total body burden, often with stronger associations than PbB.</li> <li>6. <i>In vivo</i> XRF techniques are non-invasive.</li> </ol>	<ol style="list-style-type: none"> <li>1. Measurement is more difficult than for other biological samples (e.g. thickness of overlying tissue and movement of subject can influence results), and analytical accuracy therefore more difficult to ensure.</li> <li>2. Measurement requires special equipment (<i>in vivo</i> XRF analysis) which increases cost.</li> <li>3. <i>In situ</i> sampling at the workplace is often not possible, due to the need to transport the person to the equipment.</li> <li>4. There is not exhaustive knowledge of associations of bone concentrations and clinical health effects.</li> </ol>
Teeth	<ol style="list-style-type: none"> <li>1. Usually contain measureable levels of lead, so chemical based detection limits are often not a problem.</li> <li>2. Contamination is not a significant issue.</li> <li>3. May be more useful for obtaining temporal information of lead exposure during pre- and neonatal periods, i.e. through the use of deciduous teeth.</li> </ol>	<ol style="list-style-type: none"> <li>1. Little experience with this medium, as it is rarely used.</li> <li>2. Difficult to make a good homogenate of a tooth.</li> <li>3. Not a good correlation between lead in teeth and blood.</li> <li>4. Little information relating lead in this medium to exposure and effect.</li> <li>5. Little usefulness for assessing occupational exposure, as primary sample source would be deciduous teeth.</li> </ol>
Faeces	<ol style="list-style-type: none"> <li>1. Non-invasive</li> <li>2. Useful as indicator of oral intake.</li> </ol>	<ol style="list-style-type: none"> <li>1. Little experience with this medium, as it is rarely used.</li> <li>2. Little information relating lead in this medium to exposure and effect.</li> <li>3. Inter-individual variation in absorption and endogenous (biliary) excretion may be misinterpreted as variation in environmental exposure.</li> <li>4. Probably less applicable for occupational exposures, where a primary source of exposure is via air.</li> <li>5. Messy.</li> </ol>
Nails	<ol style="list-style-type: none"> <li>1. Non-invasive &amp; easily collected and stored.</li> <li>2. Considered to represent long term exposure.</li> </ol>	<ol style="list-style-type: none"> <li>1. Little experience with this medium, as it is rarely used.</li> <li>2. Little information relating lead in this medium to exposure and effect.</li> <li>3. High variability in lead measured in same nails from same subjects.</li> <li>4. Contamination can be a problem.</li> </ol>

Biomarker medium	Advantages	Disadvantages
Hair	<ol style="list-style-type: none"> <li>1. Non-invasive &amp; easily collected.</li> <li>2. Low cost of collection, but higher cost of analysis.</li> </ol>	<ol style="list-style-type: none"> <li>1. Little experience with this medium, as it is rarely used. No consensus on collection method.</li> <li>2. Easily contaminated, and difficult to decontaminate.</li> <li>3. Variation in lead between hairs from the same person and between different people is high, so reference ranges are difficult to establish.</li> <li>4. Little information relating lead in this medium to exposure and effect.</li> <li>5. Inter-laboratory reproducibility of analysis is low.</li> <li>6. Relationship between hair lead and PbB have been investigated in a few studies and the results are divergent.</li> </ol>
Sweat	<ol style="list-style-type: none"> <li>1. Non-invasive</li> <li>2. Limited information indicates correlations of lead in sweat with PbB are better than for lead in saliva or urine.</li> </ol>	<ol style="list-style-type: none"> <li>1. Little experience with this medium, as it is rarely used.</li> <li>2. Little information relating lead in this medium to exposure and effect.</li> <li>3. Large volumes not easy to collect.</li> <li>4. Low analytical detection limits required.</li> </ol>
Saliva	<ol style="list-style-type: none"> <li>1. Easily collected.</li> </ol>	<ol style="list-style-type: none"> <li>1. Little experience with this medium, as it is rarely used.</li> <li>2. Little information relating lead in this medium to exposure and effect.</li> <li>3. Large variations due to ion content, salivary flow rates, nutritional status of individual and manner in which saliva is collected.</li> <li>4. Only low levels of lead are generally present in saliva, limiting analytical techniques that can be used for measurement.</li> <li>5. Relatively poor correlations have been found with PbB and saliva.</li> </ol>
Breast milk	<ol style="list-style-type: none"> <li>1. May provide indication of exposure to breastfeeding child.</li> </ol>	<ol style="list-style-type: none"> <li>1. Little experience with this medium, as it is rarely used.</li> <li>2. Risk of sample contamination.</li> <li>3. Little information relating lead in this medium to exposure and effect.</li> <li>4. Limited applicability for occupational biomonitoring, i.e. primarily relevant to breastfeeding females who have returned high PbB.</li> </ol>
Exhaled breath	<ol style="list-style-type: none"> <li>1. Theoretically presents simple, non-invasive, quick collection procedure</li> </ol>	<ol style="list-style-type: none"> <li>1. Exhaled breath is an inhomogenous sample with organic &amp; particulate matter in suspension, which may hamper analytical results reliability.</li> <li>2. Exhaled lead is a minor excretion pathway so concentrations are low and challenging to measure by routine techniques.</li> <li>3. Little information relating lead in this medium to exposure and effect.</li> </ol>

<sup>a</sup> The information in this table has been compiled from numerous references. These are: Bergdahl and Skerfving 2008, Barbosa Jr et al. 2005, Angerer et al. 2007, Barreiros et al. 2013, Costa de Almeida et al. 2009, Esteban and Castaño 2009, Gil et al. 2011, Grandjean 1978, Hu et al. 2007, Iyengar and Rapp 2001, Khan et al. 2009, Koh et al. 2003, Lee 1999, Omokhodion and Crockford 1991, Rentschler et al. 2009, Rezende et al. 2010, Sajo-Bohus et al. 2004, Sakai 2000, Schütz et al. 2005, Shih et al. 2007, Sommar et al. 2013, Stawarz et al. 2011, Thaweboon et al. 2005, Theppeang et al. 2004, Timchalk et al. 2004.

### 3.2 Biochemical parameters

It is well known that lead affects several enzymatic processes responsible for haem synthesis. Lead directly inhibits the activity of the cytoplasmic enzyme  $\delta$ -aminolevulinic acid dehydratase (ALAD), resulting in a negative exponential relationship between ALAD and PbB (Barbosa Jr. et al. 2005). Lead depresses coproporphyrinogen oxidase, resulting in increased coproporphyrin activity. It also interferes with the normal functioning of the intra-mitochondrial enzyme ferrochelatase, which is responsible for the chelation of iron by protoporphyrin. Failure to insert iron into the protoporphyrin ring results in depressed haem formation and an accumulation of protoporphyrin; this in turn chelates zinc in place of iron, to form zinc protoporphyrin. These effects also result in modifications of some other metabolite concentrations in urine (ALA-U), blood, (ALA-B) and plasma (ALA-P), as well as coproporphyrin in urine (CP). The activities of pyrimidine nucleotidase (P5'N) and nicotinamide adenine dinucleotide synthase (NADS) are also modified in blood after lead exposure. Levels of these various metabolites in biological fluids have been used in the past to diagnose lead poisoning when direct lead levels were difficult to obtain in tissues or body fluids or as information complementary to PbB test results (Barbosa Jr. et al. 2005, Sakai 2000).

Theoretically changes in various aspects of porphyrin biochemistry measured in blood or urine could be used to monitor occupational exposure to lead. In some instances they may be as sensitive as measuring lead in whole blood, for example changes in blood ALAD are noted at low PbB concentrations. It is also noted that the recommendations for a BLRL and WES have been based on disturbance of porphyrin biochemistry. Clinical chemistry measurement of serum porphyrin biochemistry in blood does not offer advantages over PbB since both are invasive. In addition to the former not being routinely used as an exposure metric, there is not a well-established relationship with clinical adverse effects to facilitate interpretation of the measurements. Use of urinary zinc protoporphyrin for controlling worker exposure has been criticised mainly for its low sensitivity and for the high percentage of false negatives in predicting PbB of less than 40  $\mu\text{g}/\text{dl}$  (SCOEL 2002).

### 3.3 Key points in Section 3

While PbB concentrations are the benchmark for predicting potential for development of clinical health effects, a number of alternative biomonitoring methods have been proposed by various researchers. A brief comparative summary of the information is has been provided in Section 3. A major issue in measuring lead in biomedica other than blood, or using a biomarker other than the concentration of lead, is lack of relevant information linking the concentrations, or changes in biomarker, with demonstrable health impacts. Because of its historical use, the database and available knowledge on



exposure, PbB and health effect relationships is much larger than for other potential biomonitoring media.

The biomarker that potentially shows most promise to supplementing PbB information is bone lead, particularly as it provides a good, perhaps better indication, of chronic past exposures and total body burden. Unfortunately since bone lead reflects chronic exposures it arguably may not be an ideal method in the workplace to identify 'at risk' persons. Whether the technique has been adequately developed and validated as a routine monitoring tool is also arguable.

## **4. Toxicological information for lead**

### **4.1 Overview**

The available literature on the toxicity and potential health effects of lead is vast. Rather than re-reviewing information that has already been considered in detail by several international agencies, the overview information provided in this section has primarily been drawn from reviews by authoritative organisations (AIOH 2009, ATSDR 2007, NIWL 2005, US EPA 2006, 2013, IARC 2006).

In humans, lead can cause in a wide range of biological effects depending upon the level and duration of exposure. Effects may range from inhibition of enzyme activity, subtle and gross neurological impacts, to the production of marked morphological changes and death. Such effects occur over a broad range of exposures. For neurological, metabolic and behavioural impacts, children are more susceptible and vulnerable than adults, which is largely due to the developing physiology of infants and children, and their behaviour patterns (UNEP 2006, ATSDR 2007).

Human male reproductive effects of lead are limited to sperm morphology and count. In females, adverse pregnancy outcomes have been attributed to lead. Lead does not appear to have deleterious effects on skin or muscle (WHO 1995; US EPA 2006, 2013; ATSDR 2007).

Lead has effects on haemoglobin synthesis and can cause anaemia. The latter has been observed in adults at PbB levels above 50µg/dL.

Lead also causes kidney toxicity. Some functional or biomarker renal effects are reversible, but chronic exposure to high levels may result in prolonged alterations of kidney function and possible renal failure (WHO 1995, US EPA 2006, ATSDR 2007).

Some lead compounds have been shown to be carcinogenic in animals, in particular producing kidney tumours. The evidence for carcinogenicity of lead and several inorganic lead compounds in humans is limited. In 1987 IARC concluded that the epidemiological evidence was inadequate whilst the data from animal experiments provided sufficient evidence of carcinogenicity. This prompted lead to be classified lead as possibly carcinogenic for humans (group 2B) (IARC, 1987). IARC, in 2006, undertook a review of the epidemiological and animal toxicity information on the carcinogenicity of lead compounds. They increased the classification of inorganic lead compounds from 2B to Group 2A *'The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans'* on the basis that there is now limited evidence of carcinogenicity from lead exposure in a variety of lead industries (Section 4.4.4).

The above overview information has been provided primarily for adults, as the health effects relevant to occupational exposures (i.e. adults) are the focus of this report. Nevertheless, some of the effects observed in children are also relevant to occupational exposures by women, since accumulated lead in bone can be remobilised into blood during pregnancy and transferred to the developing foetus. Furthermore lead is excreted, albeit to a small extent, into breast milk (see Section 4.2). Effects observed with occupational exposures (Section 4.3.1) are dealt with separately from the effects observed in epidemiological studies of the general adult population (Section 4.3.2).

The critical concern for environmental exposures by the general public are potential effects on the central nervous system of children. Epidemiological studies suggest that low level exposure of the foetus and developing child may impair learning capacity and neuropsychological development. Many studies indicate a non-linear association between PbB and a lower IQ such that impact at low PbB is disproportionately large compared with higher PbB (WHO 1995, ATSDR 2007, NTP 2012). The investigations of these endpoints are not precise and outcomes are influenced by genetics, socio-economic status and early life experience/environment (NHMRC 2009). Given the imprecise nature and outcomes, the National Health and Medical Research Council of Australia (NHMRC) recently concluded it is not possible to make a definitive statement on what constitutes a 'safe level' or 'level of concern' for PbB and recommended all Australians should have a PbB concentration below 10 µg/dL.

The extensive animal toxicity information has not been reviewed in this report unless it offers particular insight for an effect observed in humans.

## **4.2 Kinetics and absorption**

Only a portion of lead that is ingested or inhaled as particulates is absorbed and distributed to various body compartments from which it is eliminated at various rates. The absorption and distribution of

lead varies depending on duration and intensity of the exposure, age, and various physiological variables (e.g. age, nutritional status, pregnancy, and menopause) (ATSDR 2007).

#### 4.2.1 Absorption via inhalation

Absorption of lead that is deposited in the respiratory tract is influenced by particle size and perhaps solubility, and by the pattern of regional deposition within the respiratory tract. Fine particles (<1 µm) deposited in the bronchiolar and alveolar region can be absorbed after extracellular dissolution or can be ingested by phagocytic cells and transported from the respiratory tract (ATSDR 2007).

Several studies have shown lead particles deposited in the alveoli of the lung are absorbed relatively quickly and completely (ATSDR 2007, US EPA 2006, Cohen 1987). Most of the lead deposited in the alveoli is absorbed into the systemic circulation and little is brought up by ciliary action and swallowed. For example, rates of clearance (mucociliary and direct absorption) from the respiratory tract of inorganic lead inhaled as submicron particles (majority ≤ 0.1 µm) of lead oxide (insoluble in water) or lead nitrate (soluble in water), were described with half-times of 0.8 hours (22%), 2.5 hours (34%), 9 hours (33%), and 44 hours (12%). There was no difference in the pulmonary clearance of lead oxide or lead nitrate. This may be because the transfer is slow (peak blood concentrations occurred at approximately 30 hours) and is the rate limiting step regardless of compound solubility at these particle sizes (Chamberlain et al. 1978).

Morrow et al. (1980) followed the systemic uptake of <sup>203</sup>Pb in 17 adult subjects after a 5 minute exposure to aerosols (MMAD 0.25 µm) of lead chloride (soluble, but less so than nitrate) or lead hydroxide (insoluble). Half of the pulmonary deposited fraction of either substance was absorbed in approximately 13 - 14 hours. Hursh and Mercer (1970) showed that 27-62% of inhaled <sup>212</sup>Pb (elemental) of different sizes (approximately 99.5% <1 µm in diameter) deposited in the lung, with clearance occurring rapidly (half-time of 10.5-11.5 hrs). It was estimated at least 95% of the deposited lead was absorbed. In a model used to define the relationship between PbAir and PbB, Chamberlain (1983) assumed 100% of lead deposited in the alveolar region is absorbed into the blood.

Several authors or organisations have remarked that pulmonary absorption of lead compounds, regardless of chemical form, is rapid and complete (Grant 2009, ATSDR 2007, Cohen 1987, Morrow et al. 1980, US EPA 2013). This opinion is primarily based on measurement of transfer of radioactive lead from the lungs of volunteers to the systemic circulation from forms of lead with different solubility. However the experimental volunteer studies have been for sub-micron sized particles that are deposited into the small bronchi and alveolar regions of the lung. Information was not located for

larger particle sizes or for mineralised forms of lead. No information, for example, could be found for insoluble lead sulphides. Thus there is currently insufficient information for deriving appropriate adjustment factors which could potentially be applied to a WES for different forms of lead.

Larger particles (>2.5 µm) that are primarily deposited in the ciliated airways (nasopharyngeal and tracheobronchial regions) are transferred within hours by mucociliary transport into the oesophagus and mainly swallowed (ATSDR 2007, US EPA 2013). Therefore, depending on the particle size and concentrations of lead associated with a particular air exposure source, the digestive tract can also be an important avenue of lead absorption following inhalation.

#### **4.2.2 Oral absorption**

The extent and rate of gastrointestinal absorption of ingested inorganic lead is influenced by the physiological status of the exposed individual (e.g. age, fasting, nutritional calcium and iron status, pregnancy) and physicochemical characteristics of the lead-bearing material ingested (e.g. particle size, mineralogy, solubility, lead species) (US EPA 2006). Physiological influences have not been studied for inhalation exposure.

Human studies investigating the absorption of water soluble lead compounds indicate that 40-50% of ingested lead is absorbed in children (2 week old infants to approximately 8 year old children) while only 3-10% of ingested lead is absorbed by fed adults, in fasted adults absorption of water-soluble lead increases to about 26 -70% (ATSDR 2007; US EPA 2006, 2013). The difference is thought to be due to differences in physiological and dietary factors. For example, although not demonstrated in adult women, in animal studies and in children iron deficiency increases absorption of lead and PbB levels. In adults co-administration with calcium salts decreases absorption and PbB. Ultimately, the proportion of ingested lead absorbed is also dependent on the amount that is available for absorption, i.e. the bioaccessibility. Administration of poorly soluble salts with fruit juices (citric acid) increases their solubility and absorption. The lead substance must become bioaccessible in order for absorption to occur. Mineralisation of lead strongly influences its bioaccessibility.

#### **4.2.3 Dermal absorption**

Dermal absorption of inorganic lead compounds is negligible (ATSDR 2007, US EPA 2006). Few studies have provided quantitative estimates of dermal absorption of inorganic lead in either humans or animals. Those that have been conducted consistently show the absorption to be negligible for both soluble and insoluble lead compounds. ATSDR (2007) summarise a comparative study of dermal absorption of inorganic and organic salts of lead conducted in rats where approximately 100 mg of lead was applied in an occluded patch to the shaved backs of rats. Based on urinary lead

measurements made prior to and for 12 days following exposure, lead compounds could be ranked according to the relative amounts absorbed (i.e. percent of dose recovered in urine): lead naphthenate (0.17%), lead nitrate (0.03%), lead stearate (0.006%), lead sulphate (0.006%), lead oxide (0.005%), and metal lead powder (0.002%).

#### **4.2.4 Distribution and Deposition**

Throughout life, lead in the body is exchanged between blood and bone and between blood and soft tissues. Variation in these exchanges is influenced by duration and intensity of the exposure, age and various physiological variables (US EPA 2006, 2013). The site of accumulation in bone is dependent on the most active areas of calcification at the time of exposure. In adulthood, calcification occurs at sites of remodelling in cortical (e.g. tibia) and trabecular bone (e.g. patella), whereas in infancy and childhood, calcification is most active in trabecular bone. A larger fraction of the lead body burden of adults resides in bone (approx. 90%) than in children (approx. 70%) (ATSDR 2007; US EPA 2006, 2013). Of the bone types, trabecular bone is more reflective of recent exposures than is cortical bone due to the slow turnover rate and lower blood perfusion of cortical bone (US EPA 2013). Some lead diffuses into deeper bone regions, where it is relatively inert, particularly in adults. These bone compartments are much more labile in infants and children than in adults as reflected by half-times for movement of lead from bone into plasma (e.g. cortical half-time = 0.23 yrs at birth, 3.7 yrs at 15 yrs of age, and 23 yrs at  $\geq 25$  yrs; trabecular half-time = 0.23 yrs at birth, 2 yrs at 15 yrs of age, and 3.8 yrs at  $\geq 25$  yrs) (Leggett 1993, in US EPA 2013).

Only approximately 1% of the lead body burden is found in blood, primarily in red blood cells bound to protein;  $\delta$ -aminolevulinic acid dehydratase (ALAD) is the primary binding ligand but this is saturable. It is only the free (i.e. unbound) fraction in blood that is biologically active. Lead in blood is primarily (~99%) bound to red blood cells. This leaves about 1% of PbB in plasma of which 40-75% is bound to proteins (primarily albumin). Thus only a small fraction of PbB (<1%) is the biologically labile and toxicologically active fraction of the circulating lead (US EPA 2006, 2013). Nevertheless lead measurement in whole blood (i.e. PbB) is used as a convenient biomarker for lead exposure and for correlating exposure with effects. Bone lead has a half-life of several decades. However a labile compartment in bone also exists, this facilitates the equilibrium of bone lead with that in soft tissue and blood (ATSDR 2007, US EPA 2006). The labile phase, exhibited shortly after a change in exposure occurs, has a half-life of approximately 20 to 30 days (US EPA 2006 p 4-18, US EPA 2013).

In adults and children whose exposure to lead has effectively ceased or greatly decreased, there is a rapid decline in PbB over the first few months followed by a more gradual, slow decline in PbB over a period of years due to the gradual release of lead from bone (US EPA 2013). Bone lead is therefore

an index of cumulative exposure and body burden (see Section 3.1). Consequently it is not surprising that persons removed from a relatively brief exposure to lead also exhibit faster slow-phase blood elimination kinetics than those removed from exposures that lasted several years, due to the higher accumulated lead stores in bone (US EPA 2013).

Maternal-to-foetal transfer of lead in humans, measured as the ratio of cord PbB to maternal PbB, has been found to range from 0.7 to 1.0 at the time of delivery for maternal PbB ranging from 1.7-8.6 µg/dL (US EPA 2013). The transfer appears to be partly related to the mobilisation of lead from the maternal skeleton during pregnancy. Similarly in old age, PbB may increase due to the demineralisation of the skeleton that occurs through the aging process, and in particular, through the menopause period in women.

Koyashiki et al. (2011) reviewed published epidemiologic studies containing information on the excretion of lead in breast milk. They found the milk to maternal PbB ratios from 11 studies varied between 0.01 and 0.48, and concluded the available information does not indicate a health risk from breast milk exposure. One of the most recent reviews on the health effects of lead exposure (US EPA 2013) does not make a conclusion regarding exposure and health risk to children from ingesting breast milk.

### **4.3 Overview of health effects from epidemiological studies**

The health endpoints and effects discussed in this report focus primarily on those relevant to occupational exposures by adults (Section 4.3.1). Exposures to lead in occupational scenarios will be primarily via inhalation of air and from oral intake as a result of poor hygiene practices. Nevertheless, the health effects observed in studies conducted in the adult general population or in people with non-occupational exposure (this primarily occurs via the diet) to lead may also have relevance and have been briefly included in Section 4.3.2.

It is important to understand when interpreting epidemiological information that report associations between PbB and a particular health endpoint that this is not necessarily equivalent to causation. Some studies may have inadequacies which restrict their value in determining if the reported association is a true effect of lead exposure. These inadequacies may relate, but not limited to:

- Study design (e.g. small size, cross-sectional analysis).
- Statistical analysis.
- Consideration of confounding factors.

The epidemiological information used to generate the PbB response tables in Sections 4.3.1 and 4.3.2 has been compiled by consulting recent agency reviews.

The latest of the available agency reviews on the toxicology of lead (US EPA 2013) is an integrated scientific assessment of approximately 2,000 pages in length and was consulted in the first instance to aid in the compilation of a list of critical epidemiological studies. US EPA (2013) scientists integrated results from health studies with animal toxicological and mechanistic studies to make judgements of causality. In determination of causality, they considered the strength, consistency, coherence, and biological plausibility of the available evidence. The health effects considered by US EPA (2013) to have a 'causal' or 'likely causal' relationship with lead exposure in adults are the focus of the odds ratio analyses in Section 4.4 of this report. These are effects on the nervous system (e.g. cognitive and psychopathological), cardiovascular system (e.g. hypertension, coronary heart disease), and the reproductive system (e.g. sperm quality).

Where evidence was only considered to be 'suggestive' or 'inadequate' by the US EPA (2013), it has been assumed the studies are unlikely to provide sufficient information to support derivation of a WES for lead, therefore these health effects have not been discussed in detail in this report.

The US EPA (2013) document is based on literature review information through to September 2011. A search and review of the relevant literature published since September 2011 was conducted by ToxConsult to supplement the information in the US EPA (2013) review. The literature search strategy is summarised in Appendix B.

After compiling a list of critical epidemiological studies from US EPA (2013) and the literature search, these were compared with the reference lists of other agency and scientific reviews on the toxicity of lead to ensure relevant studies had been included (e.g. AIOH 2009, ATSDR 2007, NIWL 2005, US EPA 2006, IARC 2006).

US EPA (2013) concluded lead had causal effects on the nervous, cardiovascular and male reproductive systems.

*Nervous system:*

- Based on prospective community epidemiology studies the US EPA (2013) concluded there was a likely causal relationship between mean baseline PbB and cognitive decrements in adults. This was supported by a few occupational studies in which concurrent mean PbB was approximately 30 µg/dL (Dorsey et al. 2006, Stewart et al. 2002).

- A likely causal relationship based on a few high quality population based cross-sectional studies was also deduced by US EPA (2013) between psychopathological effects in adults (e.g. symptoms of depression, anxiety, panic disorder) and PbB (concurrent mean of just 6 µg/dL). There are no occupational studies supporting this finding. In addition the symptoms of depression and anxiety were self-reported and uncertainties were noted regarding the timing, frequency, duration and level of lead exposures contributing to the observed associations and residual confounding by age.
- There is only limited evidence from population or occupational studies for auditory function decrements with lead exposures.
- For decrements in adults of visual function the evidence is inadequate to infer causality with lead exposure.
- Similarly the evidence is inadequate for an association with neurodegenerative diseases (e.g. Alzheimer's disease, amyotrophic lateral sclerosis (motor neurone disease), Parkinson's disease, and Essential tremor).

*Cardiovascular system:*

According to US EPA (2013) prospective epidemiologic studies consistently find associations of PbB with hypertension, cardiovascular mortality and morbidity but not with cerebrovascular disease. These are discussed further in Section 4.4.2.

*Male reproduction:* Even though results may have been confounded by other workplace exposures, which were not adjusted for in the epidemiologic studies, US EPA (2013) concluded there is consistent evidence from studies of occupational cohorts with high PbB ( $\geq 25$  µg/dL) for causal effects of lead on sperm quality. There are less consistent results for PbB  $<15$  µg/dL.

**4.3.1 Occupational exposure studies**

Table 4.1 provides a summary of the PbB levels associated with a range of clinical or research effects in adults from occupational epidemiological studies. The summary has been compiled from recent reviews by various international agencies, and is supplemented by information from the literature.

For effects or endpoints where there were limited data, inconsistent results, and/or possible/probable confounding, these have been marked with a question mark. Light grey shading of cells in the table indicates health/research effects have been observed at or above this PbB concentration. Solid black shaded cells indicates the health/research effects considered by US EPA (2013) to have sufficient supporting evidence to indicate causality ('causal' or 'likely causal') by lead exposure. Blank cells indicate that there are either no data or no observed effect.



From Table 4.1 it is apparent that for health endpoints for which causal associations between PbB and the effect are considered likely, the PbB concentration at which they start to appear is 20 – 30 µg/dL. Studies that show clear associations with health effects in workers do so at PbB levels of  $\geq$  ~25 µg/dL<sup>13</sup>. At lower PbB concentrations, the associations are inconsistent or limited by potential confounding.

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<sup>13</sup> Cardiovascular effects (e.g. increased blood pressure and heart rate variability) have been observed in worker cohorts with mean or median PbB ranging from 22 µg/dL (in Poręba et al 2013) to 56 µg/dL (in Murata et al. 1995), with many of the investigations around 25-30 µg/dL.

Haematological effects (e.g. decreased haemoglobin and  $\delta$ -aminolevulinic acid dehydratase [ALAD] activity) have been observed in workers with mean PbB ranging from 22 µg/dL (Mohammed et al. 2008) to 62 µg/dL (Feksa et al. 2012). Karita et al. (2005) estimated the lower 95% confidence limits on the benchmark dose (BMD) levels of PbB giving an excess risk of 5% in exposed workers of decreased haemoglobin or red blood cell counts as ~20 µg/dL and for decreased haematocrit the BMDL<sub>05</sub> was ~30 µg/dL.

Effects on the immune system (e.g. subtle changes in immune markers and immunosuppression) have been noted in workers with PbB ranging from 25 µg/dL (Fischbein et al. 1993) to 51 µg/dL (Ewers et al. 1982) or  $\geq$  40 µg/dL (Horiguchi et al. 1992, McCabe et al. 1994).

Statistically significant effects on male reproductive parameters (e.g. reduced sperm quality) have been noted in workers with mean PbB ranging from 25 µg/dL (Hsu et al. 2009) to 87 µg/dL (Lerda 1992). Hosni et al. (2013) reported reduced sperm quality in workers with PbB  $\geq$  20 µg/dL, but these effects did not reach statistical significance.

Markers of mutagenicity (e.g. sister chromatid exchange frequency, DNA protein cross-links) were elevated in workers with mean or median PbB ranging from 20 µg/dL (Kasuba et al. 2012) to 61 µg/dL (Vaglenov et al. 1998).

**Table 4.1: PbB response in adults from occupational epidemiology studies <sup>a</sup>**

PbB (µg/dL)	Nervous System <sup>^</sup>	Cardio-vascular <sup>^</sup>	Blood?	Kidneys?	Endocrine system?	Immune system?	Female reproduction?	Male reproduction <sup>^</sup>	Mutagenicity?	Cancer? <sup>k</sup>	Gastrointestinal	Liver?
<5												
5-10	Auditory function decrements? <sup>k</sup>		↓ haemoglobin, δ-ALAD activity? <sup>l</sup>		↑ hormone in response to stress? <sup>m</sup>							
10-15												
15-20												
20-30		Increased blood pressure & heart rate variability <sup>c</sup>	↓ haemoglobin, δ-ALAD activity <sup>d</sup>			Subtle changes in immune markers <sup>g</sup>		Endocrine function, reduced sperm quality <sup>h</sup>	↑ chrom aberration, micronuclei, & SCE <sup>i</sup>			
30-40	Slight neurobehavioral symptoms (cognitive deficits, peripheral neuropathy) <sup>b</sup>			Kidney dysfunction <sup>e</sup>	Hypothalamus-pituitary-thyroid/adrenal axes <sup>f</sup>			Changes in levels of reproductive Hormones <sup>q</sup>				? <sup>n</sup>
40-50					Changes in thyroid hormone levels <sup>p</sup>	Immuno-suppression <sup>g</sup>						
50-60										Kidney lung? <sup>j</sup>		
60-80			Anaemia <sup>d</sup>									
>80	Encephalopathy, neuropathy <sup>o</sup>			Nephropathy							Abdominal cramps	

**Legend to Table 4.1:**

? = For these effects, there are limited data, inconsistent results, and/or possible/probable confounding;

↑ = increase;

↓ = decrease;

long arrow = shows progression, i.e. worsening of effect with increasing PbB.

Cells in light grey = indicates health/research effects have been observed at or above this PbB concentration.

<sup>^</sup> Effects considered by US EPA (2013) to have sufficient supporting evidence to indicate causality ('causal' or 'likely causal') by lead exposure.

**Footnotes to Table 4.1:**

<sup>a</sup> Compiled from studies reviewed by NZ MfE (2011), ATSDR (2007), US EPA (2006, 2013), NTP (2012), NIWL (2005). Light grey shading indicates health effects have been observed at or above this PbB concentration. Solid black shading indicates the health effects considered by US EPA (2013) to have sufficient supporting evidence to indicate causality ('causal' or 'likely causal') by lead exposure. Blank cells indicate that there are either no data or no observed effect.

<sup>b</sup> Barth et al. 2002, Bleecker et al. 1997, 2007a, b; Chia et al. 1996a, b, 1997; Chuang et al. 2000, Ehle and McKee 1990, Goodman et al. 2002, 2003; Hänninen et al. 1998, Hirata and Kosaka 1993, Kovala et al. 1997, Lee et al. 2000, Lindgren et al. 1996, Maizlish et al. 1995, Meyer-Baron and Seeber 2000, Murata and Araki 1991, Murata et al. 1993, Pfister et al. 1999, Schwartz et al. 2001, Seeber et al. 2002, Sollway et al. 1994, Stollery et al. 1991, Yeh et al. 1995, Yokoyama et al. 1988, 1998;

<sup>c</sup> Chen et al. 2013, Dongre et al. 2013 (no PbB in abstract), Glenn et al. 2006, Khan et al. 2008, Murata and Araki 1991, Murata et al. 1993, 1995; Nawrot et al. 2002, Poręba et al. 2010, 2011a, b, 2013; Santos et al. 1994, Teruya et al. 1991, Zeqiri et al. 2012 (no PbB provided).

<sup>d</sup> Ademuyiwa et al. 2005, Conterato et al. 2013, Costa et al. 1997, Feksa et al. 2012, Garcia-Leston et al. 2012b, Gennart et al. 1992 (association not significant), Karita et al. 2005, Khan et al. 2008, Mohammed et al. 2008, Patil et al. 2006.

<sup>e</sup> Chia et al. 1994, 1995; Ehrlich et al. 1998, Kumar and Krishanaswamy 1995, Santos et al. 1994, Tell et al. 1998, Weaver et al. 2002.

<sup>f</sup> Lucchini et al. 2000, Manzo et al. 1996.

<sup>g</sup> El-Fawal et al. 1999, Ewers et al. 1982, Fischbein et al. 1993, Garcia-Leston et al. 2012a, Horiguchi et al. 1992, McCabe 1994.

<sup>h</sup> Alexander et al. 1998, Bonde et al. 2002, Erfurth et al. 2001, Hosni et al. 2013, Hsu et al. 2009, Kasperczyk et al. 2008, Lerda 1992, Naha and Chowdhury 2006, Naha and Manna 2007, Ng et al. 1991, Telisman et al. 2000.

<sup>i</sup> Duydu et al. 2001, Garcia-Leston et al. 2012b, Kasuba et al. 2012, Singh et al. 2013 (no PbB in abstract), Vagenlov et al. 1998, 2001; Wu et al. 2002.

<sup>j</sup> There is consistent evidence of renal tumour development across multiple toxicology experiments in rodents which were fed diets or received drinking water containing lead acetate. In a series of epidemiological studies, lead workers had increased risks of total, kidney, lung or stomach cancers. In many of these studies the workers had high exposures (mean PbB > 50 µg/dL). However, the pattern is not consistent and there are problems in terms of confounding (e.g. concomitant exposures to arsenic and cadmium, smoking, etc.) (NIWL 2005, US EPA 2013, IARC 2006). In a comprehensive review of epidemiological and animal studies on cancer effects due to lead exposure, IARC (2006) concluded there is limited evidence in humans for the carcinogenicity of inorganic lead compounds. A recent study (Boffetta et al. 2011) found an increased risk of renal cell carcinoma in individuals occupationally exposed to lead (OR 1.55, 95% CI 1.09 – 2.21). Occupational exposure was estimated based on detailed occupational questionnaires; no PbB information was available. Another study (Ilychova and Zaridze 2012) found an increased risk of mortality from kidney (SMR 2.12, 95% CI 1.1-4.07) and pancreatic (SMR 2.32, 95% CI 1.46-3.68) cancer in an occupational cohort exposed to lead in the printing industry, but again, no PbB information was available.

<sup>k</sup> Chuang et al. 2007, Hwang et al. 2009.

Other authors have found no association of PbB with auditory function at higher (40 µg/dL) PbB levels (Ghiasvand et al. 2012).

<sup>l</sup> Although most occupational studies found haematological effects in workers with PbB >20 µg/dL (see references in footnote 'd'), one study (Ukaejiofo et al. 2009) found depressed haemoglobin in workers with much lower PbB concentrations, i.e. a mean PbB of 7 µg/dL (range of 0-30 µg/dL) compared to the non-exposed reference group (PbB 3 µg/dL). Another study (Ergurhan-Ilhan et al. 2008) found a statistically significant increase in ALAD index in Pb-exposed apprentices (mean PbB of 7.9 µg/dL) when

compared to the controls (mean PbB 2.6 µg/dL). A third study found PbB was positively correlated with percentage of plasma reticulocytes in policemen with primarily outdoor-based activities (mean PbB 6 µg/dL) (Caciari et al. 2013).

<sup>m</sup> Fortin et al. 2012.

<sup>n</sup> Liver enlargement and activation of inflammatory reactions characteristic of moderate cholestasis within the bile ducts has been found in workers with PbB >35 µg/dL (Kasperczyk et al. 2013).

<sup>o</sup> Studies demonstrating these severe effects are summarised in past reviews conducted by various agencies (e.g. ATSDR 2007, US EPA 2006, NIWL 2005). An additional study demonstrating these effects at high PbB (i.e. 100 µg/dL) was also identified in the literature search (Sadeghniaat-Haghighi et al. 2013).

<sup>p</sup> Cullen et al. 1984, Gustafson et al. 1989, Lopez et al. 2000, Robins et al. 1983, Singh et al. 2000.

<sup>q</sup> Braunstein et al. 1978, Cullen et al. 1984, Gustafson et al. 1989, Ng et al. 1991, Rodamilans et al. 1988.

### 4.3.2 Non-occupational exposure studies

Table 4.2 provides a summary of the PbB levels associated with a range of effects in adults in the general population (non-occupationally exposed). The summary has been compiled from recent reviews by various international agencies.

It is evident from the Table that associations of PbB levels with health effects or endpoints in the general population have been made at much lower PbB levels than in worker populations, i.e. many at PbB as low as 5 µg/dL. However, there also seems to be more uncertainty in many of these associations than in the occupational information primarily due to inconsistent findings at low PbB.

The association for which there is the greatest confidence in the adult general population is probably the effects on the cardiovascular system (e.g. increased blood pressure). Small increases in systolic and diastolic blood pressure have been consistently noted in populations with mean PbB of 5-10 µg/dL.

There is less confidence in the association between PbB and increased risk of mortality from coronary heart disease. Three studies (Khalil et al. 2009b, Menke et al. 2006, Schober et al. 2006) have found such an association at mean PbB of around 4 µg/dL, whereas Lustberg and Silbergeld (2002) only found a significant association in individuals with PbB > 20 µg/dL.

It is unclear why the PbB concentrations in workers that have been associated with increases in blood pressure (i.e.  $\geq 20$  µg/dL) are much higher when compared to the general population (5-10 µg/dL).

The discrepancy between the PbB levels which have been associated with adverse health effects in occupational exposure studies (Table 4.1) and the levels in the general population (Table 4.2) may be partially explained by a number of factors:

- The members of a healthy workforce may be less susceptible to the effects of lead than members of the general population, which includes children and the elderly. Persons in a workforce who had either a physiological disposition towards high PbB or heightened susceptibility for clinical effects at a given PbB would likely be removed (by management or voluntarily) from lead exposure jobs. See also Section 4.6.
- There may be a difference between the intensity of the statistical investigations conducted for worker and population studies. The latter studies are often subject to complex statistical methods to enable detection of small changes in the parameters being investigated. They also tend to have larger cohorts which improves statistical power for detecting an association between PbB and a biochemical or physiological effect of lead.

- Some of the more subtle effects investigated in the general population may not have been looked for in the occupational studies. Or if the effect was examined, the definition of the magnitude of a particular effect which constitutes adversity or biological significance may differ between studies.

It is reemphasised that low level exposure (<5 µg/dL) of the foetus may impair learning capacity and the neuropsychological development of the child (Section 4.1) (WHO 1995, ATSDR 2007, NTP 2012). Recent studies have confirmed an association between *in utero* lead exposure and infant neurodevelopment (Kim et al. 2013, Lin et al. 2013b). Due to remobilisation of lead stores in bone during pregnancy, it is recommended exposures to lead in the workplace for females of reproductive capacity and pregnant females should be kept as low as possible to protect the health of the unconceived and unborn child. *In utero* exposure risks to children are greatest if mothers have had significant past lead exposures (i.e. they have high accumulated bone lead stores) (NTP 2012). Therefore it seems reasonable the exposures for these women in the workplace should be kept below the NHMRC (2009) target PbB of 10 µg/dL.

Females who are breast feeding, by definition, are also of reproductive capacity<sup>14</sup>, so the same PbB target of 10 µg/dL should apply to these women.

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<sup>14</sup> Although women who are breastfeeding may experience a time of infertility, the definition of 'women of reproductive capacity' in this report is intended to include women who are breastfeeding.

**Table 4.2: PbB response in adults from non-occupational epidemiology studies <sup>a</sup>**

PbB (µg/dL)	Nervous System <sup>^</sup>		Cardio-vascular <sup>^</sup>		Blood?	Kidneys?	Endocrine system?	Immune system?	Female reproduction?	Male reproduction?		Mutagenicity?	Cancer?	Gastrointestinal
<5	Slight cognitive deficits? <sup>b</sup> Auditory function decrements? <sup>k</sup>								Changes in levels of reproductive hormones? <sup>i</sup>					
5-10	Psycho-pathological effects (e.g. depression, anxiety)? <sup>c</sup>		↑ blood pressure <sup>e</sup> ↑ risk of death from coronary heart disease <sup>d</sup>	↓ haemoglobin, δ-ALAD activity <sup>h</sup>	Kidney dysfunction (e.g. creatinine clearance)? <sup>f</sup>				Spontaneous abortion, postnatal development delay, ↑ risk of preterm birth, ↓ birth weight? <sup>g</sup>	Reduced sperm quality? <sup>i</sup>		?		
10-15														
15-20														
20-30														
30-40														
40-50														
50-60					↓									
60-80	↓	↓			Anaemia								↓	
>80	Encephalopathy					↓			↓	↓			↓	

**Legend to Table 4.2:**

? = For these effects, there are limited data, inconsistent results, and/or possible/probable confounding;

↑ = increase;

↓ = decrease;

long arrow = shows progression, i.e. worsening of effect with increasing PbB.

Cells in light grey = indicates health/research effects have been observed at or above this PbB concentration.

<sup>^</sup> Effects considered by US EPA (2013) to have sufficient supporting evidence to indicate causality ('causal' or 'likely causal') by lead exposure.

**Footnotes to Table 4.2:**

<sup>a</sup> Compiled from studies reviewed by NZ MfE (2011), ATSDR (2007), US EPA (2006, 2013), NTP (2012), NIWL (2005). Light grey shading indicates health effects have been observed at or above this PbB concentration. Solid black shading indicates the health effects considered by US EPA (2013) to have sufficient supporting evidence to indicate causality ('causal' or 'likely causal') by lead exposure. Blank cells indicate that there are either no data or no observed effect.

<sup>b</sup> Krieg et al. 2009, 2010; Krieg and Butler 2009, Min et al. 2012.

Other studies have found cognitive function decrements in older adults in association with bone lead levels (~20 µg/g tibia, 25 µg/g patella) (Bandeem-Roche et al. 2009, Grashow et al. 2013a, b; Weisskopf et al. 2007, 2013). PbB effects in the latter studies were not examined.

<sup>c</sup> Bouchard et al. 2009, Rhodes et al. 2003.

<sup>d</sup> Khalil et al. 2009b, Menke et al. 2006, Schober et al. 2006. In the latter studies, mean PbB was around 4 µg/dL.

In Lustberg and Silbergeld (2002), the association was only significant for individuals with PbB > 20 µg/dL.

In Schober et al. (2006), relative risks (RR) of mortality from cardiovascular disease were significantly elevated for people with PbB of 5-9 µg/dL or ≥ 10 µg/dL, when compared to people with PbB <5 µg/dL.

<sup>e</sup> Hense et al. 1993, Martin et al. 2006, Micciolo et al. 1994, Møller and Kristensen 1992, Nash et al. 2003, Navas-Acien et al. 2007, Nawrot et al. 2002, Peters et al. 2007, Proctor et al. 1996, Rothernberg et al. 1999a, 2002; Schwartz 1995, Scinicariello et al. 2010, Telisman et al. 2001, Wolf et al. 1995, Zota et al. 2013.

<sup>f</sup> Kim et al. 1996, Kim and Lee 2012, Lin et al. 1993, 2003; Muntner et al. 2003, Navas-Acien et al. 2009, Payton et al. 1994, Staessen et al. 1992, Tsaih et al. 2004, Yu et al. 2004.

<sup>g</sup> Borja-Aburto et al. 1999, Chen et al. 2006, Gonzalez-Cossio et al. 1997, Gundacker et al. 2010, Hernandez-Avila et al. 2002, Jelliffe-Pawlowski et al. 2006, Osman et al. 2002, Rothernberg et al. 1999b, Sanin et al. 2001, Vigeh et al. 2011, Zhu et al. 2010.

<sup>h</sup> Wang et al. 2010.

<sup>i</sup> Telisman et al. 2007.

Wu et al. (2012b) found an inverse association between semen lead concentrations and sperm count. PbB was not reported.

<sup>j</sup> Chang et al. 2006, Krieg 2007, Pollack et al. 2011.

<sup>k</sup> Choi et al. 2012.

<sup>l</sup> Schober et al. (2006) used the NHANES II data and determined the relative risk (RR) of mortality for stratified PbB categories by comparing the risks in people with PbB <5 µg/dL (referent group) to those with PbB of 5-9 µg/dL or ≥ 10 µg/dL. The RR for mortality from all causes, cardiovascular disease and cancer were all significantly elevated with RRs ranging from 1.2-1.69 (Schober et al. 2006). As this analysis is based on PbB measurements at only one period in time, exposure misclassification is always a potential issue. In addition, there may be a risk of residual confounding from smoking, occupational exposure, or socioeconomic status (see Section 4.4.4).



## 4.4 Data for quantitation of benefits for reduced BLRL

To assist with regulatory decision making, this Section contains a compilation of odds ratios (ORs)<sup>15</sup> for selected health endpoints. The endpoints are those for which the US EPA (2013) consider there to be sufficient evidence of a 'causal' or 'likely causal' relationship with lead exposure in adults. These are effects on the nervous system (e.g. cognitive and psychopathological), cardiovascular system (e.g. hypertension, coronary heart disease), and the reproductive system (e.g. sperm quality). In addition, a discussion on the carcinogenicity of lead has been included in Section 4.4.4.

The intent of this section is to provide information to allow a quantitation of health benefits which could potentially be realised if the PbB target for occupational exposure was lowered from the current level to those suggested in Section 4.5. The information has been used to quantify the potential health benefits for:

- Females not of reproductive capacity and males if PbB was lowered from 50 µg/dL to 30 or 20 µg/dL.
- Females of reproductive capacity if PbB was lowered from 20 µg/dL to 10 µg/dL.
- Females who are pregnant or breastfeeding if PbB was lowered from 15 µg/dL to 10 µg/dL.

### 4.4.1 Nervous system effects

The health effects at higher PbB levels (i.e. >30 µg/dL) have been well characterised. Severe lead toxicity, with clinical encephalopathy, may occur in adults at PbB of >80 µg/dL. The most sensitive effects on the central nervous system for which there is consistent evidence are cognitive deficits in neurobehavioural tests and have been reported in workers with mean PbB of  $\geq 30$  µg/dL (see Table 4.1). In the general population, these effects have been observed at lower PbB concentrations (<5 µg/dL), but there is more uncertainty with the associations at these exposures.

A summary table of the ORs for nervous system effects in occupational and non-occupational studies is provided in Section 4.4.1.3. The studies have been briefly described in subsequent sections.

#### 4.4.1.1 Occupational studies

Few occupational studies provide ORs for cognitive deficits or other 'slight' neurological symptoms; the usefulness of these studies for quantifying a health benefit associated with lowering the BLRL is hampered by insufficient consideration of confounders in some instances (e.g. manganese exposure),

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<sup>15</sup> Odds ratio =  $[P_1/(1-P_1)]/[P_2/(1-P_2)]$  where P1 is the probability of the outcome in group 1 (exposed group) and P2 is the probability of the outcome in group 2 (unexposed group). If the odds ratio is > 1, the probability of the outcome is higher in the exposed group.

or not quantifying the exposure metric (i.e. PbB). In addition, in a number of studies ORs are not provided in a manner conducive to quantitation of health benefits as a per unit change in PbB. These studies are:

- Bleecker et al. (2007b):  
Previous studies (Bleecker et al. 1997; Schwartz et al. 2001, 2005) had found lead exposure (as PbB or working lifetime weighted average PbB, i.e. TWA) and cerebral white matter changes (WMC) to be independently predictive of poorer performance on tasks of psychomotor speed and dexterity. Bleecker et al. (2007b) determined whether lead exposure was associated with WMC (estimated with magnetic resonance imaging) and whether WMC mediates the relation between lead and psychomotor slowing as measured by Grooved Pegboard (GP) test. They included 61 lead smelter workers age 50 and under in the study population with mean (range) current PbB of 29 (16-42) µg/dL, working lifetime weighted integrated PbB (IBL) of 826 (65-1451) µg year/dL, TWA of 42 (17-59) µg/dL, and bone lead of 39 (0-90) µg Pb/g bone mineral. WMC were graded, and lead variables entered in a logistic regression after controlling for age and cerebrovascular risk factors (e.g. smoking). Logistic regression of WMC loss on lead exposure metrics, and after adjustment for the covariates, resulted in odds ratios for IBL (OR<sup>16</sup> 1.00, 90% CI 1.001-1.007), TWA (OR 1.12, 1.024-1.232), and bone lead (OR 1.04, 1.009 – 1.067), which the authors indicated were statistically significant. The OR for PbB was not statistically significant, this is not unexpected; loss of cerebral white matter is progressive over a long period and PbB reflects relatively recent (months) exposure to lead. Although decreased performance by GP was significantly associated with WMC, OR for decreased performance by GP were not provided for PbB. Therefore this study does not relate a measurable neurological effect directly to the PbB concentration, which limits its usefulness for determination of a health benefit in the context of considering a BLRL. Furthermore the OR are small, and it is debatable whether the effects, although statistically significant for long term exposure metrics (i.e. PbBn), are biologically significant and reproducible.
- Hwang et al. (2009):  
Examined the effect of low-level lead exposure on noise-induced hearing loss in 412 steel plant workers. All subjects took part in a questionnaire, an audiometric examination, and blood test. Lead was found to be significantly correlated with noise-induced hearing loss for most of the tested sound frequencies ( $p < 0.05$  to  $p < 0.0001$ ). After adjustment for age and noise level, a

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<sup>16</sup> The odds ratios reported by Bleecker et al. (2007b) are truncated to two significant figures whereas the confidence limits are reported to three significant figures.

logistic regression model analysis indicated PbB concentrations greater than 7 µg/dL were significantly associated with hearing loss at the sound frequencies of 3000 to 8000 Hertz with ORs ranging from 3.06 (95% CI 1.27-7.39) to 6.26 (2.35-16.6). This study used data for an inbuilt reference group with PbB <4 µg/dL (n=96) to compare to the exposed group with PbB >7 µg/dL (n=58). A concern with this study is that it had limited consideration of potential confounding (only age and noise level were adjusted for). This may result in overestimation of the ORs.

- Kamel et al. (2002):  
Conducted a case-control study of individuals with amyotrophic lateral sclerosis <sup>17</sup> (ALS) to determine the relationship with lead exposure. The study consisted of 109 cases and 256 population controls matched by age, sex and geographical location. Risk of ALS was associated with self-reported occupational exposure to lead (OR 1.9, 95% CI 1.1-3.3), with a dose response for lifetime days of lead exposure. PbB was measured in the majority of cases (n=107) and a subset of controls (n=41). PbB in controls was <1-2 µg/dL, and in cases ranged from 3-14 µg/dL. Risk of ALS was associated with PbB; the OR for every µg/dL increase in PbB was 1.9 (95% CI 1.4-2.6). A limitation of this study is that it did not consider potential confounding by manganese exposure.
- Lee et al. (2000):  
Evaluated whether PbB was a predictor of fifteen Pb-related symptoms, assessed by self-administered questionnaire in male lead workers. Lead workers (n=95) had mean PbB of 44.6 µg/dL (21-78 µg/dL), and non-exposed controls (n=13) had mean PbB of 5.9 µg/dL (4 – 7.2 µg/dL). ORs for the relationship with PbB, adjusted for age, tobacco and alcohol consumption, were not significant for any of the symptoms investigated (GI, neuromuscular, and general).
- Maizlish et al. (1995):  
Conducted a cross-sectional study which included workers from a lead smelter (exposed group, n=43) and a nearby glass factory (non-exposed, n=45). Smelter workers were employed on average for four years, and had a mean PbB of 42 µg/dL, whereas glass factory workers had a mean of 15 µg/dL. Neurobehaviour was assessed with the World Health Organisation neurobehavioural core test battery (NCTB), which comprises a questionnaire and seven tests measuring simple reaction time, short term memory, mood, eye-hand coordination, and perceptual speed. Multivariate models were adjusted for age, education, alcohol consumption, medical conditions possibly affecting performance, and previous job involving

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<sup>17</sup> Amyotrophic lateral sclerosis is also known as motor neurone disease.

solvent exposure. Prevalence ratios were derived by Maizlish et al. (1995) for the analysis of symptoms which occurred in the year before testing. Overall, in 10 out of 14 neurobehavioural tests, the exposed group had poorer performance than the non-exposed, but none of the observed differences were statistically significant. The frequency of symptoms suggestive of nervous system problems was consistently higher among the exposed group. Significantly increased relative risks were found for difficulties in concentration (relative risk (RR)<sup>18</sup> = 1.8, 95% CI 1.0 – 3.1) and often being angry or upset without reason (RR = 2.2, 1.2 – 4.1). This study did not consider potential confounding by manganese exposure.

- Parkinson et al. (1986):  
Evaluated the association between occupational lead exposure with neuropsychiatric function using data for 288 Pb-exposed workers and 181 non-exposed subjects. Data was collected via interview and nine neuropsychologic tests measuring general intelligence, psychomotor integration, manual dexterity, and visuoperceptual ability. PbB were also determined. Mean PbB in exposed workers was 40 µg/dL; mean PbB in non-exposed controls is not provided but the text indicates they were all less than 35 µg/dL. The authors rank-ordered the subjects on each variable, divided workers into the 25% with poorer functioning vs. the remaining 75%, and calculated the relative risks for exposed vs. non-exposed workers, adjusting for age, education and income. Relative risks for anger at work (RR = 1.4, 95% CI 1.1-1.8), number of accidents (RR = 1.7, 95% CI 1.3-2.2), and grooved pegboard performance (RR = 1.3, 1.0-1.7) were elevated. This study did not consider potential confounding by manganese exposure.
- Chancellor et al. (1993):  
When investigating risk factors for development of motor neuron disease by questionnaire given to 103 patients, Chancellor et al. (1993) found the OR for occupational exposure to lead significantly elevated (OR 5.7, 95% CI 1.6-30), but PbB and other exposure indices were not measured or estimated.
- Gorell et al. (1997):  
Investigated the potential role of occupational exposure to iron, copper, manganese, mercury, zinc and lead as risk factors for Parkinson's disease. When adjusted for sex, race, age, and smoking status, they found a significantly increased association with Parkinson's disease in patients with more than 20 years' exposure to combinations of lead-copper (OR 5.24, 95% CI 1.59-17.21) and lead-iron (OR 2.83, 1.07-7.5). The adjusted OR for lead exposure alone was not significant (OR 1.41, 0.83-2.39). PbB and other exposure indices were not reported.

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<sup>18</sup> Relative risk (RR) is the ratio of the risk of disease among people with a risk factor, to those without. An RR > 1.0 means that incidence rate is higher in the exposed group and thus the risk factor has an effect.

#### 4.4.1.2 Non-occupational studies

Several non-occupational studies have reported ORs for effects on the nervous system. Only a few of these have expressed ORs in terms of increased risk per unit of PbB. These studies are:

- Wright et al. (2003):  
Analysed the association between cognitive deficits and PbB in 736 men (mean age 68 years) with mean PbB of 5 µg/dL from the Normative Aging Study. Cognitive function was examined using the Mini-Mental-State Examination (MMSE), a screening tool for cognitive impairment, which contains tests on orientation to time and place, registration, and recall of words, attention, language and visual construction. A total possible score of 30 may be gained, and healthy individuals typically receive a score of 24 or higher. The test is particularly sensitive to age and education. To adjust for potential confounding, age, education and alcohol intake were included as covariates in all regression models of MMSE scores. Relation of MMSE scores <24 (n=41) and PbB by logistic regression estimated the OR of 1.21 (95% CI: 1.07, 1.36). Risk of MMSE scores <24 when comparing the lowest (mean PbB 2.5 µg/dL) and highest (mean PbB 8.9 µg/dL) quartiles was 3.4 (95% CI: 1.6, 7.2) per µg/dL of PbB.

In contrast, another study (Weisskopf et al. 2004) investigating the same endpoint in 466 men from the Normative Aging Study (mean age 67.4 yrs) found no significant change in MMSE scores per interquartile increment of PbB (i.e. 2 µg/dL) (estimated difference in MMSE score = -0.01, 95% CI -0.13 – 0.11). The models were adjusted for age, education, smoking, alcohol intake, and time between MMSE tests.

- Rhodes et al. (2003):  
Investigated the association between PbB and bone lead and psychiatric symptoms among middle-aged to elderly men from the Normative Aging Study in the US. Symptoms were assessed using the Brief Symptom Inventory (BSI) and analysed as individual outcomes as well as a measure that combined anxiety, depression and phobic anxiety. PbB averaged 6.3 µg/dL. Logistic regression models were adjusted for age, age<sup>2</sup>, alcohol, education, and employment variables. The age<sup>2</sup> term was used to adjust for the likely nonlinear relationship of psychiatric symptoms and age. ORs for those results in the logistic regression models with p values <0.05 were estimated. An increase in 8.9 µg/dL of PbB (i.e. from the midpoint of the lowest to the highest quintile) was associated with an OR of 2.91 (95% CI 1.39-6.09) for the combined measure of outcomes.

- Choi et al. (2012):  
Investigated the association between blood cadmium and lead concentrations and hearing loss in adults from the 1999-2004 NHANES in the US. Hearing loss was defined as a pure-tone average (PTA) >25 dB in either ear. The weighted geometric mean PbB was 1.54 µg/dL. After adjusting for sociodemographic and clinical risk factors and exposure to occupational and non-occupational noise, the highest (2.8-54 µg/dL) (vs. lowest, 0.2-0.8 µg/dL) quintile of PbB was associated with an 18.6% (95% CI 7.4-31.1%) increase in PTA. The increase per doubling of PbB was 5.4% (95% CI 2.12-8.81%).

Other studies have not quantified ORs in terms of unit increase of PbB. These studies include:

- Bouchard et al. (2009):  
Investigated the association of recent PbB (2009) with major depression, panic and generalised anxiety in young adults (20-39 years) who responded to the 1999-2004 NHANES in the US. Mean PbB was 1.61 (0.3-37.3) µg/dL. Increasing PbB were associated with higher odds of major depression ( $p=0.05$ ) and panic disorder ( $p=0.02$ ) but not generalised anxiety ( $p=0.78$ ) after adjustment for sex, age, race/ethnicity, education status, and poverty to income ratio. Persons with PbB in the highest quintile ( $\geq 2.11$  µg/dL) had an OR of 2.3 (95% CI 1.13-4.75) for major depressive disorder and 4.9 (1.32-18.48) for panic disorder when compared to those in the lowest quintile ( $\leq 0.7$  µg/dL). It is noted these estimates of risk for specific quintiles are based on only a few cases, particularly for panic disorder. A monotonic increase in ORs was not found across the quintiles of PbB levels. For all endpoints, ORs were larger in analyses excluding current smokers.
- Min et al. (2012):  
Analysed data from the 1999-2004 NHANES in the US (5,574 adults  $\geq 40$  yrs). Balance dysfunction was associated with PbB in the highest quintile (3.3-48 µg/dL) when compared with the lowest quintile (<1.2 µg/dL), with an OR of 1.42 (95% CI: 1.07, 1.89). The model was adjusted for age, sex, race/ethnicity, education, history of diabetes, history of stroke, smoking, alcohol consumption, calcium intake and iron intake.
- Louis et al. (2003):  
Measured PbB and gathered a lifetime occupational history in 100 patients with essential tremor (the study also had 143 controls). PbB were higher in essential tremor patients (mean  $3.3 \pm 2.4$  µg/dL) than in controls ( $2.6 \pm 1.6$  µg/dL). In a logistic regression model, adjusted for potential confounders (age, current cigarette smoking, and possible or probably lifetime occupational lead exposure), PbB concentration was associated with diagnosis of essential

tremor, with an OR of 1.19 (95% CI: 1.03-1.37). This study may have been subject to selection and recall bias which could potentially produce artifactual associations.

#### 4.4.1.3 Summary of ORs for nervous system effects

Table 4.3 provides a summary of the studies discussed in Sections 4.4.1.1 and 4.4.1.2. The table is split into occupational and non-occupational studies. The limitations associated with the studies are also briefly presented in the table.

**Table 4.3: ORs for nervous system effects**

Study	Unit PbB <sup>a</sup>	PbB in study (µg/dL)		Effect	OR (95% CI)	Limitation/comment
		Controls	Exposed			
<b>Occupational</b>						
Kamel et al. 2002	1 µg/dL increment  (patients vs. controls)	<1-2	3-14	ALS diagnosis	1.9 per µg/dL (1.4, 2.6)	manganese exposure not considered.  May be selection bias.
Maizlish et al. 1995	Exposed vs. non-exposed  (27 µg/dL difference)	15	42	Difficulty concentrating	1.8 (1.0, 3.1)	manganese exposure not considered. Competitive confounding by some covariates.
				Angry or upset without reason	2.2 (1.2, 4.1)	
Parkinson et al. 1986	Exposed vs. non-exposed  (25 µg/dL difference)	<35 (mean ~ 15?) <sup>b</sup>	40	Anger at work	1.4 (1.1, 1.8)	Authors concluded cumulative & current exposure were unrelated to neuropsychologic performance. (18 tests conducted).
				Grooved pegboard	1.3 (1.0, 1.7)	
<b>Non-occupational</b>						
Wright et al. 2003	1 µg/dL increment	2.5	8.9	MMSE score <24 <sup>c</sup>	3.4 (1.6, 7.2)	Well-conducted study, but a similar study found no significant change in MMSE score per 2 µg/dL change in PbB (Weisskopf et al. 2004).
Rhodes et al. 2003	8.9 µg/dL	Mean = 6.3  (Midpoint of lowest to highest quintile was		Anxiety, depression and phobic anxiety.	2.91 (1.39, 6.09)	Quintile PbB not provided in paper.

Study	Unit PbB <sup>a</sup>	PbB in study (µg/dL)		Effect	OR (95% CI)	Limitation/comment
		Controls	Exposed			
		compared. The gap was 8.9 µg/dL. PbB at quintiles not provided in paper.)				
Choi et al. 2012	Per doubling PbB	0.2-0.8	2.8-54	Hearing loss (pure-tone average, PTA >25 dB)	5.4% increase in PTA (2.1%, 8.8%)	Highest quintile has large PbB range; association may be driven by a few individuals in this quintile.
Bouchard et al. 2009	Highest vs. lowest quintile PbB (1.4 µg/dL)	≤ 0.7	≥ 2.11	Major depressive disorder	2.3 (1.13, 4.75)	Based on only a few cases, 95% CI very wide.
				Panic disorder	4.9 (1.32, 18.48)	
Min et al. 2012	Highest vs. lowest quintile PbB (2-46 µg/dL)	<1.2	3.3-48	Balance dysfunction	1.42 (1.07, 1.89)	Highest quintile has large PbB range, therefore unit PbB associated with OR is difficult to determine.
Louis et al. 2003	Patients vs. controls (0.7 µg/dL)	2.6 ± 1.6	3.3 ± 2.4	Essential tremor diagnosis	1.19 (1.03, 1.37)	May be subject to selection and recall bias.  Large variability in PbB of patients and controls; overlap of PbB between the two groups.

ALS = amyotrophic lateral sclerosis (motor neurone disease); ORs = odds ratios; MMSE = Mini-Metal-State Examination;

<sup>a</sup> Where ORs are expressed for a comparison between exposed and non-exposed (i.e. control) groups rather than as a per unit increase in PbB, the difference between the mean PbB of the exposed and non-exposed groups has been provided in this column.

<sup>b</sup> The mean PbB in the control group was not provided by Parkinson et al. (1986). However the text indicates PbB in the control group was <35 µg/dL. This suggests the mean PbB may have been around 15 µg/dL.

<sup>c</sup> The Mini-Metal-State Examination (MMSE) is a screening tool for cognitive impairment, which contains tests on orientation to time and place, registration, and recall of words, attention, language and visual construction. A total possible score of 30 may be gained, and healthy individuals typically receive a score of 24 or higher.

In light of the limitations associated with each study, it is not possible to readily quantify the health benefits with respect to development of adverse nervous system effects from reducing the workplace BLRLs.

Nevertheless, the ORs (1.3-2.2) from two occupational studies (Maizlish et al. 1995, Parkinson et al. 1986) for slight neurobehavioural effects (which may occur at PbB > 40 µg/dL) provide an indication that such effects may not occur if the BLRL for males is lowered from 50 µg/dL to 30 or 20 µg/dL.



#### 4.4.2 Cardiovascular system effects

Several studies have reported results as an estimated increase in blood pressure associated with a particular increase in PbB. The association is strongest for increases in systolic blood pressure. For example:

- In a prospective study, Glenn et al. (2003) found an annual increase in systolic blood pressure of 0.64 millimeters of mercury (mmHg) (standard error [SE] 0.25) for every standard deviation (2.6 µg/dL) increase in blood from baseline (mean of 4.6 µg/dL) in 496 male chemical manufacturing employees formerly exposed to inorganic and organic lead.
- Lee et al. (2001) found a marginally significant ( $p < 0.06$ ) effect of PbB on systolic blood pressure in 798 male and female factory workers (PbB 4-86 µg/dL, mean of 32 µg/dL): a 1 µg/dL increase in PbB was associated with a 0.07 mmHg (SE 0.04) increase in blood pressure. However, PbB was not found to be a predictor of hypertension status.
- Schwartz et al. (2000) found that in 543 former organolead manufacturing workers<sup>19</sup> (mean PbB  $4.6 \pm 2.6$  µg/dL), PbB was a significant predictor of both systolic and diastolic blood pressures, as well as hypertension status in men <58 years of age. After adjusting for age, body mass index (BMI), current smoking, and current use of antihypertensive medications, each 1 µg/dL increase in PbB<sup>2</sup> (a quadratic function term) was significantly associated with a 0.189 mmHg<sup>2</sup> (SE 0.072) increase in systolic blood pressure when three outliers were removed. For diastolic blood pressure taken over a 2-year period, the increase was 0.31 mmHg (SE 0.14) per µg/dL increase in PbB.
- Glenn et al. (2006) also found an association with PbB and increasing systolic blood pressure in 575 lead-exposed workers (mean PbB  $31.4 \pm 14.2$  µg/dL), where a 1 µg/dL increase in PbB was significantly associated with a 0.09 mmHg/yr (95% CI 0.01 – 0.16) increase in systolic blood pressure.
- In a meta-analysis of 15 studies in men (non-occupational studies), Schwartz (1995) estimated that an increase in PbB from 5 to 10 µg/dL is associated with an increase of 1.25 mmHg (95% CI 0.87-1.63) in systolic blood pressure.

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<sup>19</sup> Workers had past exposure to both inorganic and organic lead.

- In another meta-analysis of 31 studies (19 general and 12 occupational), a two-fold rise in PbB was associated with a 1 mmHg (95% CI 0.5 – 1.4) increase of systolic and a 0.6 mmHg (95%CI 0.4 – 0.8) increase of diastolic blood pressure (Nawrot et al. 2002).
- Various other studies have also reported an association between systolic or diastolic blood pressure and PbB (e.g. Hense et al. 1993, Møller and Kristensen 1992, Nash et al. 2003, Santos et al. 1994, Telisman et al. 2001, Zota et al. 2013).

Table 4.4 provides a brief overview of the expected approximate increase in systolic blood pressure associated with a 5 µg/dL increase in PbB from the studies described briefly above. The results in the table suggest that incrementally higher doses of lead have smaller effects on blood pressure elevation, i.e. the effect is not linear and the slope is decreased at higher PbB levels. This suggests a partial moderation of the lead effects by the feedback control mechanisms that govern vascular tone (Schwartz 1995). From the table:

- At mean PbB of approximately 30 µg/dL, an increase in PbB of 5 µg/dL could potentially result in a 0.5 mmHg increase in systolic blood pressure.
- At mean PbB <10 µg/dL this increase is approximately 1.3 mmHg.
- When studies spanning a wide range of mean PbB (2-45 µg/dL) were combined in a meta-analysis by Nawrot et al. (2002), the increase is 1 mmHg.

**Table 4.4: Effect of increase in PbB on systolic blood pressure**

Study	Mean PbB in study population (µg/dL)	Estimated increase in systolic blood pressure (mmHg) per 5 µg/dL increase in PbB <sup>a</sup>
Lee et al. 2001	32	0.35 <sup>a</sup>
Glenn et al. 2006	31	0.45 <sup>a</sup>
Møller and Kristensen 1992	8-14	0.8 <sup>a</sup>
Schwartz et al. 2000	4.6	0.95 <sup>a</sup>
Glenn et al. 2003	4.6	1.2 <sup>a</sup>
Hense et al. 1993	6-8	1.5 <sup>a</sup>
Schwartz 1995 (meta-analysis)	Various (<10)	1.25
Nawrot et al. 2002 (meta-analysis)	Various (2-45)	1 <sup>a</sup>
<b>Consolidating the above data at:</b>		
	<b>≥ 30 µg/dL</b>	<b>≤0.5</b>
	<b>10 – 30 µg/dL</b>	<b>~1</b>
	<b>&lt; 10 µg/dL</b>	<b>1-1.5</b>

<sup>a</sup> Where an increase in systolic blood pressure was given per increase in PbB in units other than 5 µg/dL, the increase for every 5 µg/dL was estimated by assuming a linear relationship (e.g. Glenn et al. 2003 estimated an increase of 0.64 mmHg for every 2.6 µg/dL of PbB. The increase for 5 µg/dL of PbB was calculated as follows:  $5 \mu\text{g/dL} \div 2.6 \mu\text{g/dL} = 1.9$ ;  $1.9 \times 0.64 \text{ mmHg} = 1.2 \text{ mmHg}$ ). This was done for all studies in the table except for Schwartz (1995). There are uncertainties with calculating these rough estimates, because the table clearly shows the relationship between systolic blood pressure increase and PbB is not linear at all PbBs, but rather is steeper at lower PbB concentrations.

Effect on blood pressure is not a health outcome *per se* but a risk factor for cardiovascular and cerebrovascular disease. This risk is small for many individuals, however in a population it may be important, since it could shift a population's distribution to increase the percentage of individuals considered hypertensive.

When calculating the global burden of disease in the year 2000, WHO (2004) estimated that each 10 mmHg below-usual systolic blood pressure was associated with 38% (95% CI 37, 39%) lower stroke risk and a 26% (95% CI 24, 29%) lower risk of ischemic heart disease. Each 10 mmHg below-usual systolic blood pressure was also associated with 46% (95% CI 40, 51%) and 18% (95% CI 15, 20%) lower risks of hypertensive disease and other cardiac disease (WHO 2004). It should be noted these estimates are for the general global population; no distinction was made by WHO (2004) between occupational and non-occupational populations. Therefore there is uncertainty in applying these estimates for calculating a health benefit to a healthy worker population<sup>20</sup>.

<sup>20</sup> The problem with using occupational studies for calculating a health benefit from reduced exposure to a chemical is that there is often a lower cardiovascular disease prevalence or mortality when compared to the general population. This is the result of the "healthy worker effect."

Combining these estimates with the information in Table 4.4, rough estimates of the potential reductions in cardiovascular disease resulting from a change in the workplace PbB targets have been calculated and provided in Table 4.5.

Although changes in blood pressure are modest for an individual, given the prevalence of cardiovascular disease and cost of medications to lower blood pressure, such change has important health implications for the overall workforce.

**Table 4.5: Estimated risk reduction of cardiovascular disease as a result of decreasing workplace PbB targets**

		Group			
		M & FNR		FR	FP & FB
<b>Current BLRL (µg/dL)</b> (Section 2.1)		50		20	15
<b>Suggested BLRL (µg/dL)</b> (Section 5.3.3)		20	30	10	10
<b>Estimated ↓ in SBP (mmHg)</b> (Table 4.4) <sup>a</sup>		4 <sup>a</sup>	2	2	1
<b>Estimated ↓ risk (%)</b> <sup>b</sup>	<i>Stroke</i>	15	8	8	4
	<i>IHD</i>	10	5	5	3
	<i>HPT</i>	18	9	9	5
	<i>Other</i>	7	4	4	2

BLRL = blood lead removal level; M = males; FNR = females not of reproductive capacity; FR = females of reproductive capacity; FP = females who are pregnant; FB = females who are breastfeeding; SBP = systolic blood pressure; IHD = ischemic heart disease; HPT = hypertensive disease; Other = other cardiac disease; ↓ = decrease

<sup>a</sup> The estimated decrease in systolic blood pressure was calculated using the estimates in Table 4.4. For example, for a reduction from 50 to 20 µg/dL:

- From 50 to 30 µg/dL (difference of 20 µg/dL) the estimated decrease in SBP is 0.5 mmHg per 5 µg/dL. This gives 0.5 mmHg/5 µg/dL x (20) µg/dL = 2 mmHg.
- The remaining difference of 10 µg/dL from 30 to 20 µg/dL is associated with a decrease in SBP of 1 mmHg per 5 µg/dL. This gives 1 mmHg/5 µg/dL x 10 µg/dL = 2 mmHg.
- Adding both estimates together gives a total estimated reduction of 4 mmHg in SBP.

<sup>b</sup> Estimated using the risk estimates from WHO (2004) for 10 mmHg below-usual systolic blood pressure in the general population (see text); estimates were rounded. If the estimated reduction in systolic blood pressure was less than 10 mmHg, it was assumed for the calculation that the expected risk reduction is linearly proportional. For example, for a reduction in SBP of 4 mmHg the decreased risk of stroke was calculated as follows: 4mmHg/10mmHg x 38% = 15.2% (rounded to 15%).

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Navas-Acien et al. (2007) summarised epidemiological studies of cardiovascular mortality in occupational populations exposed to lead. Relative risk estimates varied widely, with positive, inverse and null associations. The authors indicated a reason for this may be that the “healthy worker effect” is extremely difficult to correct in an analysis. Additional limitations may include the assignment of lead exposure based on job titles (since often PbB measurements are not available) and cardiovascular deaths based on death certificates.

Selevan et al. (1988), for example, calculated standard mortality ratios for a cohort of male lead smelter workers in the USA employed between 1940 and 1965 for at least one year by comparing mortalities to those in the general population. Mortality was determined as of December 1, 1977. Of the 1987 workers qualifying for the study group, 1281 were known to be alive, 665 known to be deceased, and the remainder (2.1%) lost to follow up. Mortality from hypertension with heart disease and without heart disease had SMRs of 61 (CI 22-133) and 117 (CI 24-342), respectively. Mortality from stroke was reduced (SMR=84, CI 61-112), but not significantly so.

A summary of available ORs for associations of PbB with hypertension incidence or prevalence is provided in Table 4.6. Grey shading indicates the ORs which are not statistically significant. These studies have been used to construct Figure 4.1, a pictorial representation of the ORs. Only two occupational studies were located reporting ORs for hypertension, and neither ORs were significant. Note that not all studies investigating associations between PbB and hypertension are reported in Table 4.6, there are many studies showing an association that do not calculate ORs.

It is evident from the studies in Table 4.6 the many ORs for hypertension incidence are not statistically significant. The only studies which have investigated the association between hypertension incidence and lead exposure at PbB levels close to the current BLRL are the occupational studies (de Kort et al. 1987, Tepper et al. 2001). In both studies the ORs for hypertension were not statistically significant.

Few significant associations were found between PbB and hypertension in the non-occupational population based studies, where PbB were generally  $<5 \mu\text{g/dL}$ , with ORs per  $1 \mu\text{g/dL}$  ranging from 1.07 to 1.83. However these ORs cannot be extrapolated linearly to higher PbB, since larger difference between PbB quartiles in the general population (as is the case for the Scinicariello et al. 2010 study) do not appear to result in linear increases of the ORs.

Using both occupational and non-occupational epidemiology studies US EPA (2013) have determined there is a causal relationship between PbB and hypertension, and between PbB and coronary heart disease, but there is inadequate evidence for an association with cerebrovascular disease.

**Table 4.6: Odds ratios (95% CI) for association of PbB with hypertension incidence or prevalence <sup>a</sup>**

Reference	Population		PbB (SD) (µg/dL)	Comparison <sup>b</sup>	OR (95% CI)	Comment
<b>Occupational</b>						
de Kort et al. 1987	Exposed = 53 workers exposed to lead & cadmium in plastics industry.  Non-exposed = 52 workers from insulation plant.		Exposed: 47.4  Non-exposed: 8.1	Exposed vs. non-exposed  (39 µg/dL)	1.91 (0.9, 4.05)	Although blood pressure values in workers exposed to lead and cadmium were higher than in non-exposed workers, the OR for hypertension was not statistically significant.
Tepper et al. 2001	252 previous or current battery factory employees with 10 or more years exposure.		Tertile 1: 12-25	Referent	1.0	PbB reported as TWA-PbB.
			T2: 26-33	T2 vs. T1	1.02 (0.3, 3.49)	
			T3: 34-50	T3 vs. T1	1.44 (0.38, 5.85)	
<b>Non-occupational</b>						
Martin et al. 2006	964 men & women, 50-70 yrs (mixed ethnicity) Baltimore, Maryland		3.5 (2.4)	per 2.5 µg/dL	1.02 (0.87, 1.19)	4 different models were used to calculate ORs.  None were statistically significant.
Elmarsafawy et al. 2006	471 men from Normative Aging Study		6.6 (4.0) (low Ca intake)	per 1 µg/dL	1.07 (1, 1.15)	Lack of consideration for potential confounding by socioeconomic status related variables.  Association only slightly significant for low calcium intake group.
			6.6 (4.6) (high Ca intake)		1.03 (0.97 – 1.11)	
Yazbeck et al. 2009	1,017 pregnant women, of which 106 were diagnosed with pregnancy-induced hypertension (PIH)		Quintile 1: <1.2	Referent	1.0	OR were adjusted for maternal age, cadmium, manganese, and selenium blood levels; haematocrit; parity; BMI; gestational diabetes; educational level; socioeconomic status; geographic residence, and smoking.
			Q2: 1.2-1.7	Q2 vs. Q1 (0.85 µg/dL)	1.84 (0.77, 4.41)	
			Q3: 1.71-2.3	Q3 vs. Q1 (1.4 µg/dL)	2.07 (0.83, 5.13)	
			Q4: >2.3	Q4 vs. Q1 (1.7 µg/dL?)	2.56 (1.05, 6.22)	
Muntner et al. 2005	NHANES III (n=16,609) & NHANES (n=9,961)	Non-hispanic whites	Q1: <1.06	Referent	1.0	Adjusted for age, sex, diabetes mellitus, current cigarette smoking, BMI, alcohol consumption, having a high school education and having health insurance.
			Q2: 1.06-1.63	Q2 vs. Q1 (0.85 µg/dL)	1.12 (0.83, 1.5)	
			Q3: 1.63-2.47	Q3 vs. Q1 (1.6 µg/dL)	1.03 (0.78, 1.37)	

Reference	Population		PbB (SD) (µg/dL)	Comparison <sup>b</sup>	OR (95% CI)	Comment		
	Non-hispanic blacks		Q4: ≥ 2.47	Q4 vs. Q1 (2 µg/dL)	1.1 (0.87, 1.41)			
			Q1: <1.06	Referent	1.0			
			Q2: 1.06-1.63	Q2 vs. Q1 (0.85 µg/dL)	1.03 (0.63, 1.67)			
			Q3: 1.63-2.47	Q3 vs. Q1 (1.6 µg/dL)	1.12 (0.77, 1.64)			
			Q4: ≥ 2.47	Q4 vs. Q1 (2 µg/dL)	1.44 (0.89, 2.32)			
		Mexican Americans		Q1: <1.06	Referent		1.0	
				Q2: 1.06-1.63	Q2 vs. Q1 (0.85 µg/dL)		1.42 (0.75, 2.71)	
				Q3: 1.63-2.47	Q3 vs. Q1 (1.6 µg/dL)		1.48 (0.89, 2.48)	
			Q4: ≥ 2.47	Q4 vs. Q1 (2 µg/dL)	1.54 (0.99, 2.39)			
	Scinicariello et al. 2010	Non-hispanic whites		Q1: 0.7-1.4	Referent		1.0	Adjusted for age, sex, BMI, alcohol ingestion, smoking status, education, serum creatinine, serum total calcium, glycosylated haemoglobin and haematocrit.
				Q2: 1.5-2.3	Q2 vs. Q1 (0.85 µg/dL)		1.21 (0.66, 2.24)	
				Q3: 2.4-3.7	Q3 vs. Q1 (2 µg/dL)		1.57 (0.88, 2.8)	
			Q4: 3.8-52.9	Q4 vs. Q1 (27 µg/dL)	1.52 (0.8, 2.88)			
Non-hispanic blacks			Q1: 0.7-1.4	Referent	1.0			
			Q2: 1.5-2.3	Q2 vs. Q1 (0.85 µg/dL)	1.83 (1.08, 3.09)			
			Q3: 2.4-3.7	Q3 vs. Q1 (2 µg/dL)	2.38 (1.4, 4.06)			
			Q4: 3.8-52.9	Q4 vs. Q1 (27 µg/dL)	2.92 (1.58, 5.41)			
Mexican Americans			Q1: 0.7-1.4	Referent	1.0			
			Q2: 1.5-2.3	Q2 vs. Q1 (0.85 µg/dL)	0.74 (0.24, 2.23)			
			Q3: 2.4-3.7	Q3 vs. Q1 (2 µg/dL)	1.43 (0.61, 3.38)			

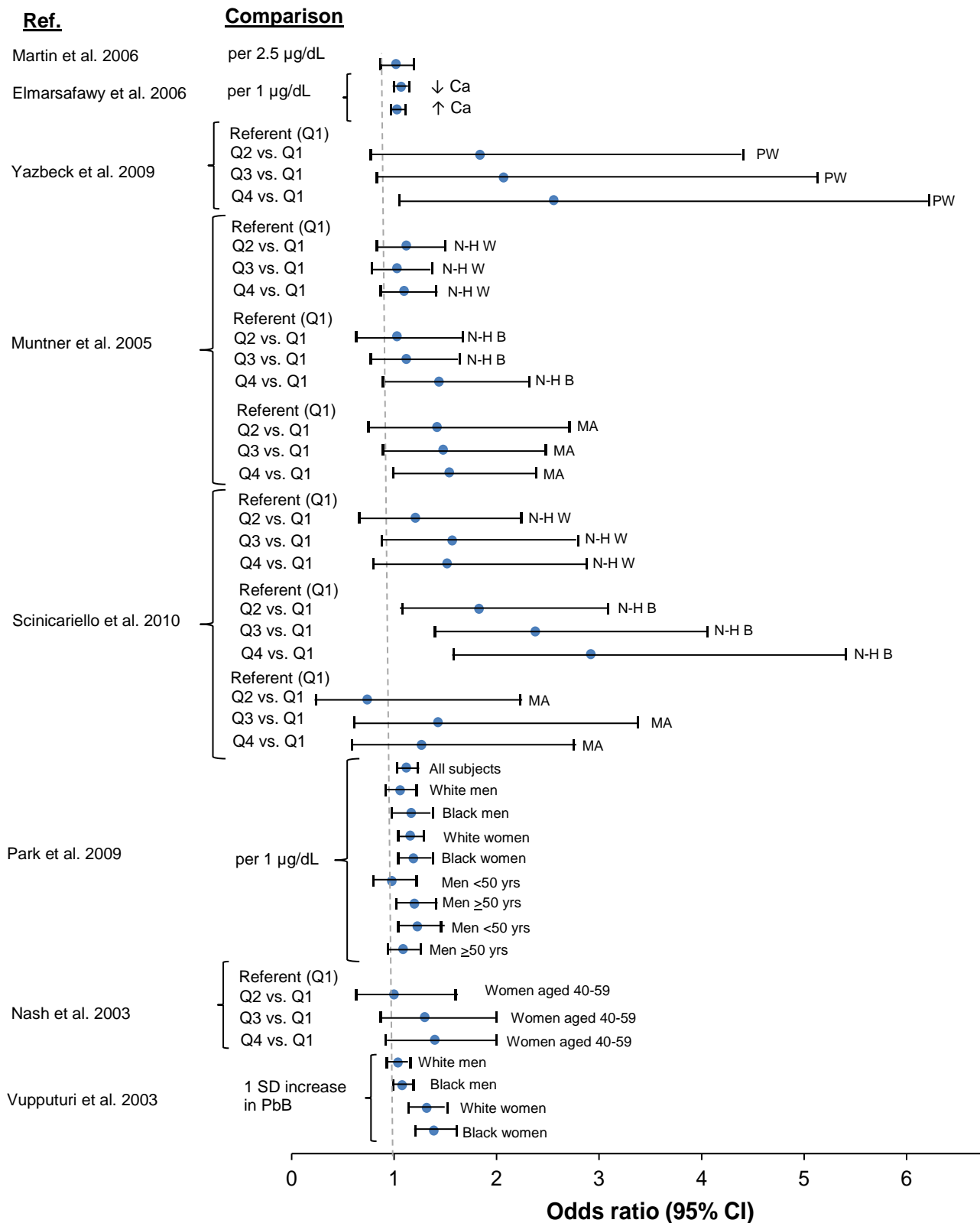
Reference	Population	PbB (SD) (µg/dL)	Comparison <sup>b</sup>	OR (95% CI)	Comment
		Q4: 3.8-52.9	Q4 vs. Q1 (27 µg/dL)	1.27 (0.59, 2.75)	
Park et al. 2009	NHANES III (n=12,500)	Overall 3.52 (0.1)	per 1 µg/dL	1.12 (1.03, 1.23) (all subjects)	Models for all subjects were adjusted for age, age <sup>2</sup> , gender, race, education, smoking status, cumulative smoking, BMI, haematocrit, alcohol intake, physical activity, use of antihypertensive medication, and diagnosis of type-2 diabetes.
				1.06 (0.92, 1.22) (white men)	
				1.17 (0.98, 1.38) (black men)	
				1.16 (1.04, 1.29) (white women)	
				1.19 (1.04, 1.38) (black women)	
				0.98 (0.8, 1.22) (men <50 yrs)	
				1.2 (1.02, 1.41) (men ≥ 50 yrs)	
				1.23 (1.04, 1.46) (women <50 yrs)	
				1.09 (0.94, 1.26) (women ≥ 50 yrs)	
Nash et al. 2003	Cross-sectional sample of NHANES. Women aged 40-59 yrs (n=2,165)	Q1: 0.5 – 1.6	Referent	1.0	Adjusted for age, race, alcohol intake, cigarette smoking status, BMI, and serum creatinine clearance.
		Q2: 1.7 – 2.5	Q2 vs. Q1 (1 µg/dL)	1.0 (0.63, 1.6)	
		Q3: 2.6 – 3.9	Q3 vs. Q1 (2.2 µg/dL)	1.3 (0.87, 2.0)	
		Q4: 4.0 – 31.1	Q4 vs. Q1 (16.5 µg/dL)	1.4 (0.92, 2.0)	
Vupputuri et al. 2003	NHANES III, whites and black (n=14,952)	4.4 (0.1) (white men)	1 SD increase in PbB	1.04 (0.93, 1.16)	Adjusted for age, education, BMI, alcohol consumption, physical activity, sodium, potassium, and total calories.
		5.4 (0.2) (black men)		1.08 (0.99, 1.19)	
		3.0 (0.1) (white women)	(i.e. 0.1 or 0.2 µg/dL)	1.32 (1.14, 1.52)	
		3.4 (0.1) (black women)	1.39 (1.21, 1.61)		

OR = odds ratio; 95% CI = 95% confidence interval around odds ratio, SD = standard deviation; Q = quintile; T = tertile. TWA = Time weighted Average; BMI = Body Mass Index.

<sup>a</sup> Hypertension is defined as systolic blood pressure ≥ 160 mmHg and/or under treatment for hypertension. Grey shading indicates not statistically significant. Note that not all studies investigating associations between PbB and hypertension are reported in Table 4.6, there are many studies showing an association that do not calculate ORs.

<sup>b</sup> Where ORs are expressed for a comparison between exposed and non-exposed (i.e. control) groups, or a comparison between quartiles within the same cohort rather than as a per unit increase in PbB, the difference between the mean PbB of the exposed and non-exposed groups or the difference between the approximate mid-points of each quartile has been provided in this column. If a quartile is reported as greater than a PbB concentration with no maximum reported, the comparison was made using the lower bound of that quartile.





**Figure 4.1: Odds ratios (95% CI) for association of PbB with hypertension incidence or prevalence in non-occupational studies**  
 Q = quartile, PW = pregnant women, N-H-W = Non-Hispanic White, N-H-B = Non-Hispanic Black, MA = Mexican American

#### 4.4.3 Reproductive effects

General population studies indicate lead can delay female sexual maturation, and increase the risk of spontaneous abortion. Although there are many methodological problems with studies of this kind, the literature suggests such effects may occur at maternal PbB concentrations of around 10 µg/dL (NIWL 2005). The findings for birth defects, preterm births, and low birth weight/foetal growth are inconsistent.

There are a few studies reporting ORs for female reproductive endpoints in relation to PbB, these include spontaneous abortion (Borja-Aburto et al. 1999)<sup>21</sup>, preterm delivery<sup>22</sup> (McMichael et al. 1986), and low infant birth weight (Irgens et al. 1998)<sup>23</sup>.

Of these three studies, Borja-Aburto et al. (1999) provides the most useful information for judging the potential health benefit of reducing BLRL in the workplace. The authors report an OR for spontaneous abortion of 1.8 (95% CI: 1.1, 3.1) for every 5 µg/dL increase in PbB in a cohort of 668 women in Mexico City (Borja-Aburto et al. 1999). These data suggest if the BLRL were to be reduced from 15 µg/dL to 10 µg/dL for females of reproductive capacity and females who are pregnant in the workforce, this would be associated with an approximate 80% reduced risk of spontaneous abortion. It should be noted there is considerable uncertainty with using the information in this manner.

A sensitive reproductive endpoint in males for which there is reasonable information is reduced sperm quality. Bonde et al. (2002) conducted a cross sectional survey of semen from 503 men, 362 of which had occupational exposure to lead (mean PbB 31 µg/dL, range 4.6 – 64.5 µg/dL) and 141 reference workers (mean PbB 4.4 µg/dL, range < detection limit (DL) – 19.8 µg/dL). Semen volume and sperm concentration were determined. The authors found the median sperm concentration was 49% lower in men with PbB >50 µg/dL. There was no indication of a trend for lower sperm concentration with increasing PbB. However threshold slope least square regression identified a PbB of 44 µg/dL as a possible threshold. The OR for total sperm count at the PbB range of 40.1-50 µg/dL was 0.9 (95% CI: 0.4, 2.1), and at ≥50.1 µg/dL the OR was 4.4 (95% CI: 1.6, 11.6). This study suggests that reducing the current BLRL for men from 50 µg/dL to 30 µg/dL could perhaps eliminate the adverse effects of lead on sperm quality. It is noted that effects on sperm quality begin to appear at PbB levels of 25 – 30 µg/dL (Section 4.3).

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<sup>21</sup> After multivariate adjustment the OR for spontaneous abortion was 1.8 (95% CI: 1.1, 3.1) for every 5 µg/dL increase in PbB from the referent PbB of <5 µg/dL (Borja-Aburto et al. 1999).

<sup>22</sup> The ORs for preterm delivery in relation to PbB were 2.1 (95% CI 0.6, 7.6) for PbB >8 but ≤ 11 µg/dL, 3.0 (0.8, 11.3) for PbB >11 but ≤ 14 µg/dL, and 4.4 (1.2, 16.8) for PbB >14 µg/dL (McMichael et al. 1986).

<sup>23</sup> Irgens et al. (1998) using data from the Norwegian birth registry found that women occupationally exposed to lead (none/low compared to moderate/high) were likely to deliver a low birth weight infant (OR 1.3 [95% CI: 1.1, 1.6]). PbB measurements were not reported.

The US EPA (2013) has determined there is a causal relationship between PbB and reduced sperm quality. The state key evidence is provided by toxicological studies in rodents, non-human primates, and rabbits showing detrimental effects on semen quality, sperm and fecundity/fertility with supporting evidence in epidemiologic studies. Toxicological studies with relevant Pb exposure routes leading to blood Pb concentrations ranging from 5-43 µg/dL reported effects on sperm quality and sperm production rate, sperm DNA damage, and histological or ultra-structural damage to the male reproductive organs. Consistent associations in studies of occupational populations with concurrent PbB levels of 25 µg/dL and greater, report detrimental effects of Pb on sperm; however, uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies.

Alexander et al. (1996b) found no association with male PbB and spontaneous abortion in their partners. The associations for male PbB with preterm births and congenital abnormalities are inconsistent, with some studies reporting a small association (Min et al. 1996, Lin et al. 1998, Salim et al. 1992), and others reporting no association (Irgens et al. 1998, Kristensen et al. 1993).

#### **4.4.4 Cancer**

In 2006, IARC undertook a review of epidemiological and experimental animal toxicology information in which the carcinogenic effects of lead exposure were investigated (IARC 2006). They changed the classification of inorganic lead compounds from 2B (possibly carcinogenic; evidence of carcinogenicity in animal or *in vitro* studies) to Group 2A (probably carcinogenic in humans) on the basis there was now, in addition to sufficient evidence in experimental animals, limited evidence of carcinogenicity in humans. From the occupational studies described by IARC there does not appear to be an association with lung cancer, but there are inconsistent findings suggestive of weak associations with stomach, kidney and brain cancer. The key studies considered by IARC, together with some recent investigations not available to IARC, are briefly discussed below.

##### **4.4.4.1 Epidemiological studies**

IARC (2006) found there was no or a slight excess of lung cancer in occupational cohorts of battery and smelter workers compared with external reference populations. IARC considered the excesses were quite small and well within the range that might be explained by chance or confounding by smoking. In a smelter cohort a statistically significant twofold excess of lung cancer was found but confounded by arsenic exposures.

In a recent case-control study not reviewed by IARC (2006), occupational factors were investigated for possible associations with lung cancer in 1,593 men in Quebec with histologically confirmed disease; 1,426 controls were randomly selected from the general population. A blinded expert-based assessment of lifetime occupational exposure (no PbB measurements) was undertaken that included adjustment for several potential confounders. No associations with lung cancer were observed when comparing 'ever' to 'never' exposed subjects. Nor were there associations with lung cancer in subjects with substantial cumulative exposure to lead. The authors concluded there was no observed increased risk of lung cancer with exposure to lead compounds (Wynant et al. 2013).

Binks et al. (2005) investigated mortality of a cohort of 1,462 males employed at a tin smelter in the UK for at least 12 months between 1967 and 1995 and followed through 2001. Employees were potentially exposed to a number of substances, including lead, arsenic, cadmium and radionuclides. Mortality from all causes and all cancers did not differ from that expected in both national and regional populations. Mortality, adjusted for age and calendar year, from ischemic heart disease showed a deficit and mortality from lung cancer a statistically significant excess (SMR 161, 95% CI 124-206). The SMRs were not estimated separately for exposures to each substance, therefore there is potential confounding from other metals. In addition, SMRs were not adjusted for smoking, although it was noted in the study smoking rates did not markedly differ from the general population.

Using the same cohort as Binks et al. (2005), Jones et al. (2007) used available records of occupational hygiene measurements at the tin smelter to establish exposure matrices for arsenic, cadmium, lead, antimony, and polonium-210. The authors established work histories from personnel record cards. Lung cancer mortality was examined in relation to cumulative inhalation exposure by Poisson regression analysis. They found no significant associations between lung cancer mortality and simple cumulative exposure to any of the substances studied. However, when cumulative exposures were weighted according to time since exposure and attained age, significant associations were found between lung cancer mortality and exposure to arsenic, lead, and antimony in the group of workers exposed before 1972. The authors attributed a substantial proportion of the excess lung cancer mortality observed in the cohort to the effects of arsenic exposure and to smoking.

For stomach cancer, four of the six occupational cohort studies used for the evaluation of lung cancer by IARC showed a fairly consistent excess of 30–50% of stomach cancer compared with external reference populations. Potential confounding by arsenic or smoking was considered by IARC to be small. Limiting the usefulness of these studies was little or no data for quantitative dose–response analysis and it was possible ethnicity, dietary habits, prevalence of *Helicobacter pylori* infections or socioeconomic status may have played a role in the stomach cancer excesses. Other, more recent

studies not available to IARC (2006) have not found a significant association with stomach cancer (Binks et al. 2005, Carta et al. 2005, Lam et al. 2007, Rousseau et al. 2007, Gwini et al. 2012).

Apart from one study that showed a twofold statistically significant excess, IARC (2006) determined there was no association in other occupational studies of highly exposed workers with kidney cancer. These studies also showed no consistent pattern for tumours of the brain and nervous system. However one showed a statistically significant positive dose–response relationship between PbB concentrations and the risk for glioma but this cohort had lower PbB than the others. It is also noted that two recent investigations also report weak evidence for brain cancer (Rajaraman et al. 2006, van Wijngaarden et al. 2006) but another did not (Gwini et al. 2012).

A recent study not reviewed by IARC (2006) found an increased risk of renal cell carcinoma (RCC) in individuals occupationally exposed to lead (OR 1.55, 95% CI 1.09 – 2.21) or cadmium (1.40 (95% CI 0.69 - 2.85) (Boffetta et al. 2011). However no exposure-response relation was apparent for either duration of exposure or cumulative exposure to either metal. This was a hospital-based study in Czech Republic, Poland, Romania and Russia, that included 1,097 cases of RCC and 1,476 controls. Occupational exposure to arsenic, cadmium, chromium(III), chromium(VI), lead and nickel was assessed by teams of local industrial hygiene experts, based on detailed occupational questionnaires. No PbB information was available. The authors noted observed association with cadmium was unlikely to be causal but the observations for lead justified further investigation.

A study of printing plants with lead type set in Moscow comprised of 1,423 men and 3,102 women (Ilychova and Zaridze 2012). The cohort was followed up during 1979 - 2003 and contributed 93,682 person years of observation. For both sexes, no significant excess risk for any cancer site was observed but for the total cohort there was increased risk of mortality from kidney (SMR 2.12, 95% CI 1.1-4.07) and pancreatic cancer (SMR 2.32, 95% CI 1.46-3.68) in the highest tertile of cumulative lead exposure. Again, no PbB information was available. Interestingly for men there was an excess overall mortality, mainly due to ischaemic heart disease. Although the mortality of the Moscow population during 1979 -2003 was used as the reference group for cancer and cardiac mortality there was no attempt in this study to control for known confounding risk factors for either the cancers or heart disease. Gwini et al. (2012) found no excess risk for renal cancer in Australian workers. Among the general population, two follow-up studies reviewed by IARC (2006) were based on PbB data collected in the US NHANES II population. They found a positive dose-response between PbB and lung cancer, which approached or attained statistical significance. However, IARC (2006) indicated these results are not consistent with the highly-exposed occupational cohorts, where no consistent lung cancer excess is apparent. IARC considered the reported excesses in the general population studies may be due to residual confounding from smoking or occupational exposure to

other lung carcinogens. Another study using the same NHANES II data but not reviewed by IARC (2006) determined the relative risk of mortality for stratified PbB categories by comparing the risks in people with PbB <5 µg/dL (referent group) to those with PbB of 5-9 µg/dL or ≥ 10 µg/dL (Schober et al. 2006). The relative risks for mortality from all causes, cardiovascular disease and cancer were all significantly elevated with relative risks ranging from 1.2-1.69 (Schober et al. 2006). As these analyses are based on PbB measurements at only one period in time, exposure misclassification is a potential issue. In addition, there may be a risk of residual confounding from smoking, occupational exposure, or socioeconomic status.

Gwini et al. (2012) describes a recent retrospective cohort study of 4,114 male workers exposed to inorganic lead in 'scheduled' lead occupations in Victoria and New South Wales, and who had participated in the state government medical surveillance programs. PbB data for 2,612 (63.5%) cohort members were available;

- The overall geometric mean was 19.6 µg/dL (SD = 2.1).
- Approximately a third (35%) of these had three or more PbB test results;
- 25th percentile = 11.4 µg/dL
- 75th percentile = 37.3 µg/dL.
- 29.1% of the cohort had at least one PbB result greater than 30 µg/dL.

Death and cancer incidence rates were compared with population rates. There were significant results for overall death (SMR 111; 95% CI 101-123) and digestive system deaths (SMR 167; 95% CI 110-250). Cancer incidence was elevated for liver (SIR 217; 95% CI 103-454) and oesophageal cancer (SIR 240; 95% CI 129-447). When cancer incidence was stratified into workers who had ever had a PbB measurement > 30 µg/dL, versus those who hadn't, no increased incidence was found for all cancers, kidney, brain, lung, alimentary tract, or stomach cancer. Surprisingly the incidence of oesophageal cancer was seven-fold greater (SIR 755; 95% CI 314-1813) among those with a PbB result above 30 µg/dL compared with population rates (Gwini et al. 2012). However, there is no established biological mechanism linking inorganic lead exposure and oesophageal cancer. It is possible that the increased incidence observed for liver and oesophageal cancer may be due to confounding by smoking and/or alcohol use, which are known risk factors for these cancers and were not addressed in the study. However an analysis of mortality and cancer incidence due to other diseases related to smoking was undertaken by Gwini et al. (2012); this showed no lung cancer excess and no excess deaths from cardiovascular disease suggesting that smoking rates in the cohort were likely to be similar to the general Australian community. Furthermore Rousseau et al. (2007), who adjusted for smoking, found no association between lead exposure and oesophageal cancer; it is noted these authors did not report PbB.

Overall the Australian study of Gwini et al. (2012) found evidence of associations between occupational lead exposure and all-cause mortality and incident cancers of the oesophagus, liver, and bladder. Results also suggest possibly elevated nervous system mortality. However, no evidence was seen for cardiovascular disease mortality, nor increased incidence of stomach, kidney, brain, or lung cancer.

### *Summary*

Of the epidemiological studies in which PbB and/or PbAir concentrations were reported mean PbB concentrations were 28-80 µg/dL, with many above 50 µg/dL (IARC 2006). Reducing the BLRL from the current value of 50 µg/dL to 30 µg/dL in males would appear to decrease the risk of Pb-associated cancer, but it is not possible to quantify the potential health benefit from the IARC data at this time.

There is limited, inconsistent evidence suggestive of stomach, kidney and brain cancer in persons occupationally exposed to lead.

The cancer findings observed by Gwini et al. (2012) for Australians in 'scheduled' lead jobs indicates a seven fold increase in oesophageal cancer for men who had ever had a PbB recorded >30 µg/dL. There was no statistical increase for persons with PbB < 30 µg/dL. Of the 2,612 persons who had recorded PbB concentrations, 29.1% had PbB > 30 µg/dL. Although other studies have not reported an association between oesophageal cancer and lead exposure there are weak inconsistent associations with stomach cancer. While noting the authors urge caution in interpreting their results, if it is assumed for actuary purposes that the oesophageal cancer finding of Gwini et al. (2012) is real, it suggests that about a third of workers in scheduled lead jobs will benefit from lowering the BLRL from 50 to 30 µg/dL. If the proportion >30 µg/dL is applied to the total cohort of 4,114 in Gwini et al. (2012) it implies approximately 1,200 men in Victoria and NSW had a 700% increased risk of developing oesophageal cancer, and will have this risk removed if the BLRL is changed as proposed and thus six less men may be expected to develop oesophageal cancer.

#### **4.4.4.2 Animal studies**

Overall, extensive experimental evidence in animal studies shows water-soluble (lead acetate and lead subacetate) and one insoluble lead compound (lead phosphate) can induce kidney tumours in rodents after oral or sub-cutaneous exposure (IARC 2006). The tumours appear primarily in the tubular epithelium. One of the studies investigated renal lesions as well as tumours and found the tumours occurred in the absence of extensive chronic nephropathy (Waalkes et al. 1995). It is noteworthy that in several studies an increased incidence of renal tumours compared to controls was

only observed in the higher dose groups. The only study summarised in IARC (2006) which measured PbB in rats along with incidences of renal tumours found that male rats exposed to 500 ppm lead acetate in the diet for 2 years (5/50 rats had tubular epithelium adenomas) had higher PbB (77.8 µg/dL) than the 100 ppm dose group where no renal tumours were observed (35.2 µg/dL) (Azar et al. 1973).

The induction of brain gliomas also occurred in a few studies after oral exposure to lead acetate and subacetate in rats (IARC 2006). In three studies, repeated intraperitoneal injection of lead subacetate increased lung tumour multiplicity in mice. An oral study with lead subacetate in mice was negative for lung tumours (Stoner et al. 1986).

Inhalation of a mean concentration of 5.3 mg/m<sup>3</sup> lead oxide (mass median aerodynamic diameter, i.e. MMAD, 5.1 µm) for 6 hours/day, 5 days/week for 1 year did not produce significant increased tumours in male rats (including lung or renal tumours) (Monchaux et al. 1997).

The animal carcinogenicity information indicates lead is a systemic carcinogen and therefore the carcinogenicity of lead is expected to be related to PbB.

Lead does not have a direct interaction with DNA and does not appear to induce tumours through a genotoxic mechanism (IARC 2006, ATSDR 2007). Therefore there will be a threshold of exposure below which increased incidence of cancer will not be detectable. In rodent studies, the observation of renal tumours in higher dose groups but not in lower dose groups is consistent with the existence of a threshold of lead exposure.

#### **4.5 Suggested PbB targets for workers**

From Table 4.1 and Sections 4.3 and 4.4, for workers most health endpoints for which there is sufficient information for them to be caused, or suggestively caused, by exposure to lead have been associated with cohort average PbB levels of around 20 µg/dL or above. The majority of occupational epidemiology studies report health effect associations starting at worker population mean PbB levels of 25 - 30 µg/dL. At mean PbB concentrations >30 µg/dL the associations become more robust and reliable. Hence in the workplace, for females not of reproductive capacity and for males it is suggested the BLRL be 20 – 30 µg/dL.

The epidemiology data indicates a worker population mean PbB concentration of 30 µg/dL can be regarded as a low observed adverse effect level (LOAEL), and a mean of 20 µg/dL as a defensible no observed adverse effect level (NOAEL). Contemporary risk assessment methods recommend a lower



bound estimate of the NOAEL be used as the point of departure for setting health protective standards (NHMRC 2006, enHealth 2012). Hence to avoid adverse health effects in females not of reproductive capacity and in males, a BLRL of 20 µg/dL would be precautionary and protective. Nevertheless it should be recognised the above 'critical' PbB's are not lower bound estimates that will necessarily protect nearly all workers in these categories, rather they are closer to central estimates (i.e. average) for groups of workers in lead related jobs. Consequently a PbB of 20 µg/dL is not certain preclusion of subtle health effects for a 'sensitive' individual (Section 4.6), particularly if these PbB concentrations are present for a long time.

Notwithstanding the above there is uncertainty regarding lead dose response relationships at low exposures, not all studies observe effects at similar reported low PbB levels, and the effects observed at low PbB are not necessarily, or demonstrably clinically adverse for the individual. Also, it is possible a number of industries working with lead may have difficulty immediately complying with a BLRL of 20 µg/dL. With these caveats in mind it is further suggested consideration could be given for lead related workplaces to have ≤20 µg/dL as a target PbB for females not of reproductive capacity and for males, but a BLRL of 30 µg/dL.

For pregnant females and female of reproductive capacity (which by definition also includes females who are breastfeeding<sup>24</sup>), a PbB target of 10 µg/dL is suggested to keep cumulative lead stores in the body low enough to protect the neurological development of the yet to be conceived and unborn child. This is consistent with the recommendations of the National Health and Medical Research Council (NHMRC 2009).

#### **4.6 Sensitive workers**

Increased susceptibility to the effects of lead may arise as a result of physiological differences in processes that increase the free fraction of lead in blood that is able to interact with target tissues, or be the result of increased tissue responsiveness to a given PbB. The former are primarily toxicokinetic process affecting the absorption, distribution and elimination of lead, and the latter toxicodynamic variability. Toxicokinetic variability has been readily established and is discussed below. Compelling evidence for increased tissue responsiveness between individuals was not found in this review. However it may be hypothesised that pre-existing disease or decreased physiological reserve in a target organ may render a person more susceptible to the effects of lead.

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<sup>24</sup> Although women who are breastfeeding may experience a time of infertility, the definition of 'women of reproductive capacity' in this report is intended to include women who are breastfeeding.

Particles that are inhaled and are too large to penetrate into the alveoli are primarily removed by mucociliary clearance and swallowed. As a result of the factors that affect oral absorption of lead (Section 4.2.2), more variability between persons in absorption of lead from the gastrointestinal tract is expected than for absorption from the lung alveoli. Increased absorption would result in increased PbB, and over time greater effects at any given PbAir. Genetic variation in genes involved in iron metabolism affects PbB. For example, genetic variants in the haemochromatosis and transferrin genes are associated with higher PbB concentrations in children, but lower bone and PbB in older men (US EPA 2013).

The relationship between lead in blood and plasma is approximately linear at PbB concentrations <25 µg/dL. But becomes curvilinear at higher PbB concentrations (approximately 30 - 40 µg/dL in adults) due to saturable binding to red blood cell proteins (US EPA 2013). That is, as PbB increases and the higher affinity binding sites for lead in red blood cells become saturated, a larger fraction of the PbB is in plasma and able to distribute to target tissues. Thus, other exogenous agents (e.g. metals) or genetic traits that change the binding to proteins in red blood cell proteins, or in plasma, and cause an increase in the free (unbound) fraction of lead in plasma will increase the effects of lead, even though the total PbB may not be markedly increased.

ALAD is the protein in red blood cells primarily responsible for binding lead. There are two forms, ALAD-1 and ALAD-2. Persons homozygous or heterozygous for ALAD-2 show significantly higher mean lead blood levels at equivalent exposure levels than persons homozygous for ALAD-1 (Petrucci et al. 1982; Wetmur et al. 1991). It has been postulated that ALAD-2 binds lead more avidly than ALAD-1, this increases PbB by reducing the amount of lead delivered to soft tissues but at the same time results in less effect (Smith et al. 1995).

It appears that potential variability in the kinetics of lead (absorption and distribution), and at least theoretically disease and low physiological reserve, are more likely to confer individual susceptibility to the effects of lead than are innate (genetic) differences in tissue responsiveness. The suggested target of PbB of 20 µg/dL and BLRL of 30 µg/dL are for sensitive effects observed in worker populations and therefore inherently include sensitive individuals in these populations.

Furthermore, considerations in Section 5 have addressed the issue of individual variability in relationships between PbAir and PbB. Information is provided showing the suggested WES of 0.05 mg/m<sup>3</sup> would allow nearly all workers to be below a PbB of 30 µg/dL but nearly all workers would not necessarily be below 20 µg/dL at this WES.

#### 4.7 Key points in Section 4

In humans, lead can result in a wide range of biological effects depending upon the level and duration of exposure; these are summarised in Sections 4.1 and 4.3. Tables 4.1 and 4.2 provide a synopsis of the PbB levels associated with a range of effects in adults from occupational and non-occupational epidemiological studies, respectively. The non-occupational information is considered less applicable for identifying a BLRL for a healthy workforce.

Most health effects observed with occupational exposure to lead have been associated with worker PbB levels of >20 µg/dL, with the majority of studies reporting associations starting at cohort mean PbB levels of around 25 - 30 µg/dL. At worker population average PbB concentrations >30 µg/dL the associations become more robust and reliable. Hence in the workplace, for females not of reproductive capacity and for males, a BLRL of 20-30 µg/dL is suggested as being appropriate.

Of this range, 20 µg/dL is a pragmatic NOAEL for workers and can be rationally argued as a precautionary BLRL. Particularly since it is closer to a central rather than a lower bound estimate for a worker population. Nevertheless there is uncertainty regarding the preciseness of the lead dose-response relationship in workers at low exposures, not all occupational investigations report health effects at similar reported PbB concentrations, the observed effects are not necessarily clinically adverse for an individual, and some workplaces may initially struggle to comply with a BLRL as low as 20 µg/dL. It is therefore suggested a target PbB of 20 µg/dL and a BLRL of 30 µg/dL could be considered.

For pregnant females and females of reproductive capacity (which by definition also includes females who are breastfeeding), a PbB target of 10 µg/dL is suggested to keep cumulative lead stores in the body low enough to protect the neurological development of the unborn child. This is consistent with the recommendations of the National Health and Medical Research Council (NHMRC 2009).

It was not possible to readily quantify the health benefits with respect to development of adverse nervous system effects from reducing the workplace BLRLs. Nevertheless, the ORs from two occupational studies for slight neurobehavioral effects provide an indication that such effects may be reduced if the BLRL for males is lowered from 50 µg/dL to 30 or 20 µg/dL.

Lowering the BLRL for males from 50 µg/dL to 30 or 20 µg/dL is associated with:

- Reduction of cardiovascular disease associated with ameliorating lead induced increased blood pressure (Section 4.4.2). Although the reductions in blood pressure are only modest for an individual, the prevalence of cardiovascular disease and cost of medication prevention is such that there could be marked gains for the overall workforce.
- Gains in sperm quality for potentially oligospermic men (Section 4.4.3).

- A decrease risk of cancer for a large proportion of men who work in 'scheduled' lead jobs and have PbB > 30 µg/dL. This is approximately 1,200 persons in Victoria and NSW (Section 4.4.4).

For women lowering the BLRL from 15 to 10 µg/dL is associated with:

- Lowered body burden and hence lower risk of detrimental intellectual development of their, as yet unborn children.
- Decreased risk of spontaneous abortion (Section 4.4.3).

## 5. PbAir and PbB relationships

### 5.1 Introduction

The relationship between PbB concentrations and PbAir concentrations is called the air slope factor (ASF). The ASF reflects the incremental increase in PbB for each unit increase in air concentration and has the units  $(\mu\text{g}/\text{dL})(\mu\text{g}/\text{m}^3)^{-1}$ . It has been known for some time it is non-linear (US EPA 1986, 2013). That is, the relative contribution of PbAir to PbB is greater at low air concentrations relative to high concentrations.

For determination of ASFs only information from occupational studies in which PbAir is a 'work shift' measurement has been included. The ASF values represent real life lead exposures in lead-related industries. They are not necessarily a result of continuous 8-hour exposures which is assumed to occur when setting an occupational exposure limit. It is emphasised ASF values associated with environmental exposure to lead are different from those with occupational exposures. This is primarily due to the different air concentrations (lower) and exposure times (longer) which result in a different PbB for the general community at any given PbAir concentration.

The establishment of a WES for lead tacitly assumes there is a direct correlation between concentrations of PbAir in the workplace and PbB levels in workers. Although such a relationship exists, its quantitation is markedly influenced by other factors affecting PbB.

They include, but are not limited to, particle size, solubility, personal versus area PbAir data, the temporal relationship of PbAir measurements with PbB measurements, accuracy of PbAir measurements for exposure, PbAir being total lead or respirable lead, smoking status, hygiene practice (i.e. likelihood of hand mouth interaction), length of employment, inter-individual variability in lead absorption, etc. Not all of these factors may have been considered in the published studies investigating PbAir - PbB relationships. It is also probable that no one or two studies adequately reflect the range of workplace conditions or provide ASF information that is universally applicable. In this regard the average ASF determined from a number of studies is arguably more appropriate.

Limitations inherent in a particular study tend to have less influence on a recommended ASF if such a 'weight of evidence' type evaluation is undertaken.

Although worker PbB levels are likely to primarily be the result of lead exposure in the workplace they also include a contribution from background lead exposure. Currently this background exposure mainly comes from lead in the diet but in the past when leaded petrol was widely used, lead in ambient air was a major contributor to background PbB.

Given the non-linear nature of the association of PbAir with PbB, and PbB with health effects, a single ASF to describe the relationship of PbB (and health effects) with an air concentration will be misleading. To extract the appropriate ASF from the literature it is necessary to identify the PbB concentrations and/or air concentrations of interest. This 'bounding' of the ASF is described in Section 5.2.

Considerations explored in this section when evaluating studies reporting ASF values are background PbB, particle size, and worker population PbB variability under the same exposure conditions.

## **5.2 Bounding the air slope factor assessment**

Limits can be placed on the evaluation/selection of ASFs for WES setting in the following ways.

1. *Via PbB health threshold concentrations:* Identifying PbB concentrations that are without demonstrably consistent health effects, or are associated with effects considered to be minor, will inform decisions on BLRL's for various sectors of the workforce in lead related industries. The extent, or otherwise, of safety (uncertainty) factors applied to the 'critical' PbB for different health effects is a matter of agency policy. It appears from Section 2 that international organisations have not formally applied safety factors. Unfortunately the available literature does not easily enable an ASF to be identified from a target PbB. Rather ASFs tend to be linked with air measurements of lead.
2. *Benchmarking with international organisations:* While it is recognised PbB health threshold concentrations are arguably the most appropriate basis for determining BLRLs and hence a WES, for the purpose of focussing the derivation of an appropriate ASF that can be used for setting the WES it is useful to extract BLRLs and WESs from international organisations. This enables a number of potential air concentrations to be tested for their ability to deliver the target BLRLs.

Table 5.1 is a summary of the large amount of international WES information presented in Tables 2.1 and 2.2. It is apparent that air concentrations of 0.05, 0.1 and 0.15 mg/m<sup>3</sup> have been commonly nominated as 8 hour WES's. These have therefore been chosen as bounding air concentrations for identifying an ASF from the literature. It is also noted that only one international organisation (California Department of Public Health) is proposing a WES lower than 0.05 mg/m<sup>3</sup> though the WHO proposes the range 0.03-0.06 mg/m<sup>3</sup>.

Table 5.2 summarises the BLRLs set by a variety of organisations where there is documentation supporting the WES and BLRL. The majority have different BLRLs for men, females of non-reproductive capacity (FNR), females of reproductive capacity (FR) and pregnant females (FP), and breastfeeding females (FB). For example the current BLRLs for lead in Australia are 50 (M & FNR), 20 (FR) and 15 µg/dL (FP & FB) (originally established by NOHSC in 1994).

FR have lower BLRLs due to concern for effects on the developing foetus and the fact that the mother's stores of bone lead mobilise during pregnancy. Hence it is not only the external exposure of the mother during pregnancy, e.g. in the workplace, that is contributing to lead exposure of the foetus but also the lead body burden accumulated before pregnancy. For example, a recent study in France identified having a mother born in a country where lead is often used as one of several risk factors significantly associated with elevated PbB in children (Etchevers et al. 2013).

- In a mixed workforce it is logical that the most sensitive of those workers should drive the BLRL and hence the WES (see Sections 4.5 and 4.6). From Table 5.2 this appears to be a PbB of 5 – 10 µg/dL for all females except those of non-reproductive capacity. This is consistent with the NHMRC deliberations that all Australians should have a PbB <10µg/dL.
- If a workforce for lead exposure jobs were restricted to men, then the range of BLRLs from organisations that have documentation supporting their WES is 10 – 40 µg/dL. It is interesting to note that recently expert scientific/medical panels have suggested different BLRLs for acute and chronic exposures (Kosnett et al. 2007, Schwartz and Hu 2007). On face value this makes toxicological sense since most substances require high acute doses relative to lower doses over a long time to induce toxicity. In addition it is becoming recognised that the subtle effects associated with low PbB are principally associated with longer term exposures (US EPA 2013).

In contrast to the above, organisations that do not have documentation supporting their WES tend to have much higher BLRLs that from Section 5 appear to be unsustainable with current health knowledge for lead. For men and FNR the BLRLs range from 40 – 70 µg/dL, and for

other females they are between 20 – 70 µg/dL. It is noted that many of these BLRLs were initially recommended many years ago and have not been updated.

The potential BLRLs used in this report to derive an accommodating WES are 20 µg/dL and 30 µg/dL (Section 4.5).

**Table 5.1: Summary of international WES for lead** (From tables 2.1 and 2.2).

WES (mg/m <sup>3</sup> )	Organisation or jurisdiction	
	With documentation	Without documentation
0.15	-	Australia (Safe Work 2013, NOHSC 1994); EC (1998); Spain (INSHT 2013); Belgium (MoE&W 2002); Luxemburg (JOGDL 2002); Ireland (H&SA 2011a,b); UK (SHE 2002,2012); South Africa (SA DOL 2002).
0.12	-	Chile (MdS 2000).
0.1	EC (SCOEL, 2002) <sup>a</sup>	New Zealand (DoL 2011). Austria (RIS 2011). France (INRS 2006, 2012). Switzerland (SUVA 2013). Japan (JSOH 2010).
0.03 – 0.06	WHO (1980)	
0.05	ACGIH (2001a,b)	Sweden (SWEA 2005a,b; NIWL 2005). USA (OSHA 1991). USA (NIOSH 2010, 2011; FR 1997). USA (California, Cal DIR 2013). Canada (Alberta, British Columbia, Ontario, Quebec). Argentina (MTES 2003). China.
0.0005	California (Cal DPH 2009, 2010, 2011, 2013) <sup>b</sup>	

<sup>a</sup> Recommendation, not picked up in EC legislation but some member countries may have adopted.

<sup>b</sup> Proposal, not yet legislated.

**Table 5.2: Critical PbB concentrations for removing an individual from a lead related work activity (i.e. BLRLs) <sup>a</sup>.**

	Critical PbB (µg/dL)				Organisation or jurisdiction
	Male (M)	Female non-reproductive capacity (FNR)	Female pregnant (FP)	Female breast feeding (FB)	
For females of reproductive capacity (FR) the BLRL is 20 µg/dL	50	50	15	15	Australia (NOHSC 1994)
	40	30	30	30	WHO (1980)
	30	30	30	30	EC (SCOEL 2002)
Single measurement	30 <sup>b</sup>	30 <sup>b</sup>	30 <sup>b</sup>	30 <sup>b</sup>	California (Cal DPH 2009, 2010, 2011, 2013)
2 consecutive measurements	20 <sup>b</sup>	20 <sup>b</sup>	20 <sup>b</sup>	20 <sup>b</sup>	
	30	30	10 <sup>c</sup>	10 <sup>c</sup>	ACGIH (2001a,b)
	30	30	7	7	Germany (DFG 2005,2013a,b)
Definite removal	30	30	30	30	AOEC (2007)
Discretionary	>10	>10	>10	>10	
Acute & sub-chronic <sup>d</sup>	<20	<20	<20	<20	Panel for development of lead management guidelines (Schwartz and Hu 2007)
Chronic <sup>d</sup>	10	10	10	10	
Acute	30	20	5	5	Recommendations from scientific committee (industry, university, government) (Kosnett et al. 2007)
Chronic	10	10			

<sup>a</sup> The data in this table is compiled from Table 2.1 (i.e. from organisations that have provided documentation supporting the WES and BLRL). The BLRLs in the above table are generally lower than those suggested by organisations that have not provided documentation for the WES and BLRL (Table 2.2).

<sup>b</sup> These are proposals and not yet in regulation in California. It appears that these PbB's are not related to the proposed WES of 0.0005 mg/m<sup>3</sup>. This air concentration was determined from modelling air concentrations to prevent chronic PbB levels of 5 – 10 µg/dL as per the recommendations of Kosnett et al. (2007).

<sup>c</sup> Tacitly implied from discussion in documentation.

<sup>d</sup> Acute and sub-chronic is for exposure 10 – 20 yrs; chronic is for 20 – 40 year exposure.

## 5.3 Background PbB

### 5.3.1 General considerations

The non-linear characteristics of the ASF means the impact of background lead exposure is larger when considering relatively low BLRLs. Therefore background PbB needs to be specifically considered when setting a WES. Some but not all agencies have accounted for background lead exposure when setting a WES. For example, in proposing new WES and BLRLs California has specifically accounted for non-occupational lead exposures in their pharmacokinetic modelling of PbB (OEHHA 2013). ACGIH (2001) has tacitly allowed for background exposures by ensuring PbAir only



contributed approximately a third to the BLRL, the balance being left for community sources and implicit allowance for variability in worker PbB, such as caused by the factors listed above in Section 5.1 (see also Section 4.6).

In this document:

- The influence of non-occupational (i.e. environmental) background lead exposures on the ASF is dealt with by subtracting an estimate of background PbB from the measured occupational PbB when calculating an ASF. This gives an ASF associated with the incremental increase in PbB due to PbAir.
- Subtracting background PbB from a target BLRL incorporates background PbB into calculations of WESs.

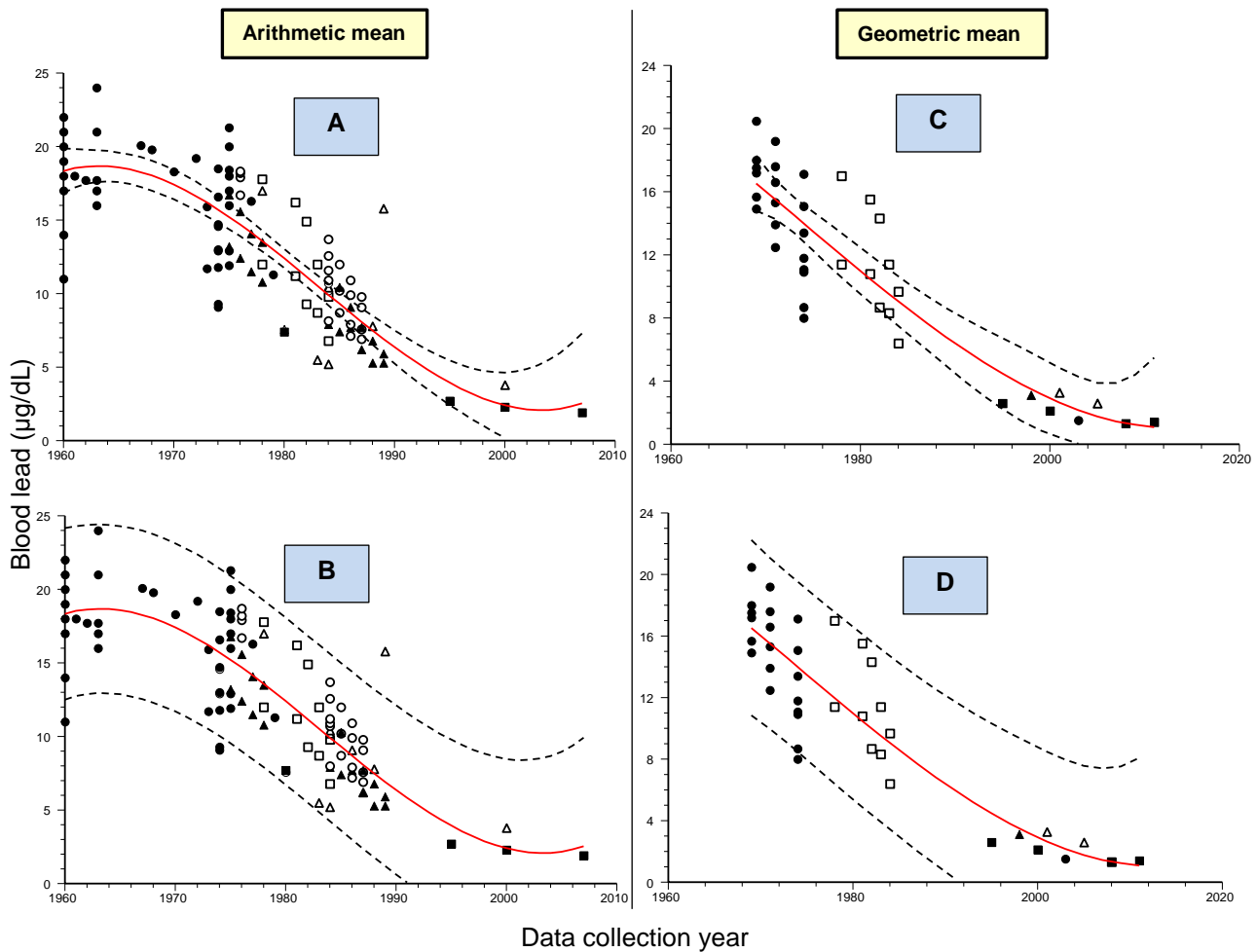
### **5.3.2 Community 'background' PbB**

A large number of general population studies in communities not impacted by lead<sup>25</sup> have been evaluated (Figure 5.1 and Appendix C). Population background PbB levels arising from general environmental lead exposures in Australia and overseas were much higher in the past but have decreased with time. In recent years non-occupational 'background' PbB levels appear to have plateaued at around 2 µg/dL. This is primarily the result of phasing out of leaded petrol at the start to mid-1990s overseas, and in Australia during the late 1990s to early 2000 (DEWHA 2001, Richmond-Bryant et al. 2013) (see Appendix D).

Since many of the occupational studies relevant for determining an ASF were conducted at a time when leaded petrol was still in widespread use there was significant non-workplace contributions to PbB. In Section 5.6 occupational PbB concentrations are corrected for background PbB when determining ASFs at the nominated PbAir. If a background concentration could not be deduced from control groups within a particular occupational study, the regression curves generated for the background PbB data (Figure 5.1) were used to provide an approximate estimate for the period in which the study data was gathered.

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<sup>25</sup> An impacted community is defined as one residing near a known anthropogenic point source of atmospheric lead. Blood lead concentrations in a non-impacted community therefore represent background, or reference, concentrations arising from general (non-point source) environmental exposures.



**Figure 5.1: Arithmetic and geometric mean background PbB in Australian and overseas adults 1960-2011.**

- Australia
- UK
- ▲ Germany
- USA
- New Zealand
- △ Other

A & C = 95% confidence intervals  
 B & D = 95% prediction intervals

The figures show adult PbB levels resulting from general environmental background exposure. The data is in Appendix C. They exclude PbB measured in occupations considered to have had excessive exposure to leaded petrol fumes or automobile exhaust (e.g. policemen on foot patrol, garage attendants). No data could be located between 1989 and 1995.

The data collection year does not equal the publication date but precedes it by varying times.

An arithmetic mean PbB of 12.4 µg/dL was measured in the year 2000 in Egypt. This data point is much higher than other mean PbB levels around that time (1.3-3.8 µg/dL), and has been excluded when fitting the polynomial trend line.

The third degree polynomial trend lines gave the best logical fit of the data after visual inspection and comparison of various 'goodness of fit' criteria, e.g. residuals, residual sum of squares,  $R^2$ . Figures A and C show the upper and lower 95% confidence limits around the polynomial. Figures B and D show the 95% prediction intervals. Figures were generated using StatsDirect statistical software Version 2.7.9.

A decreasing trend of PbB levels over time, coinciding with the phasing out of leaded petrol nationally and overseas (Appendix D) is readily discernible.

The equations of the curves are provided below:

$$\text{Geometric mean PbB} = -817812.199 + 1244.631(\text{Year}) - 0.631(\text{Year})^2 + 0.0001(\text{Year})^3$$

$$\text{Arithmetic mean PbB} = -4003478.19 + 6057.1(\text{Year}) - 3.054(\text{Year})^2 + 0.000513(\text{Year})^3$$

Figure 5.1 provides the 95% confidence intervals around the central estimate of the population means and therefore provides information about the precision of the central estimate. Also included are the prediction intervals<sup>26</sup> within which a population mean PbB concentration is forecast to fall for any given year. This is an indication of the variability of the population mean data points (see also Section 5.5).

It is notable that none of the studies consulted in Section 5.6 accounted for background PbB when reporting an ASF.

### 5.3.3 Non-airborne workplace contamination

In the context of setting a WES, 'background' exposure is taken to be any contribution to PbB that is not the result of PbAir. This designation of 'background' exposure includes general community sources and diet as described in Section 5.3.2 but also non-airborne workplace contamination. The source of non-airborne workplace exposure should be controllable to negligible or low levels by good housekeeping and hygiene practice<sup>27</sup>. It is nonetheless acknowledged that incidental ingestion by hand-mouth transfer of workplace lead laden dust is an important and perhaps a major contributor to a worker's PbB (Ulenbelt et al. 1990, Lai et al. 1997).

Non-airborne workplace contamination could however be incorporated into a WES in a similar way to how other exposure guidelines for substances in environmental media are set. That is by allocating a default fraction of the BLRL to non-airborne workplace contamination, say 20%, the balance (after deducting background PbB) is then assigned to PbAir and calculated using the appropriate ASF. In this report however it was chosen to derive ASFs that inherently included an occupational non-inhalational component in the PbB used in calculations for the ASF. Since the studies are from a number of diverse industries it has been assumed the average ASF from these studies will be broadly applicable to Australian industries where there may be exposure by incidental ingestion of lead dust, as well as by inhalation of the dust. The uncertainty associated with this approach is discussed in Section 5.6.2.

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<sup>26</sup> Confidence intervals provide information on how well the mean or central estimate has been defined. The prediction interval provides information about the distribution of values in a data set, not the uncertainty in determining the population mean. They predict, with stated confidence (e.g. 95%), the band in which a data point will lie if it is randomly sampled from the data set. Prediction intervals account for both the uncertainty in knowing the value of the population mean, plus the data variability, they are therefore always broader than the 95% confidence interval on the mean.

<sup>27</sup> Ulenbelt et al. (1990) found a low correlation between PbAir and PbB due to poor personal hygiene in a lead processing electric accumulator factory. Hygienic variables explained at least 64 % of the variance of PbB.

## 5.4 Particle size

From a health perspective measurement of lead in the airborne inhalable ( $\leq 100 \mu\text{m}$ , 50% cut-off [NOHSC 1995]) dust fraction is more informative than lead in total dust measurements. This is because lead particles larger than  $100 \mu\text{m}$  will tend not to remain airborne for long and will settle out. For exposure to lead dusts the inhalable fraction is also more relevant than the respirable fraction (50% cut off  $5 \mu\text{m}$  [NOHSC 1995]) because a portion of the inhaled particles will be swallowed and be subject to absorption <sup>28</sup>.

More recent studies (Pierre et al. 2002, Rodrigues et al. 2009) have measured PbAir concentrations as inhalable dust. Many of the older publications do not specify the fraction measured but it is likely these were either inhalable or 'total' dust. The samplers historically used in the UK for 'total' dust measurements generally provided equivalent results to contemporary inhalable samplers (UK HSE 1998). Samplers for 'total' dust used in the USA are likely to have been the traditional closed-faced 37-mm filter cassettes which are recommended in several NIOSH analytical methods for lead (NIOSH 1994a, b). The table in Section 5.6 contains two UK studies (King et al. 1979, Williams et al. 1969) and five US studies (Gartside et al. 1982, Bishop and Hill 1983, Chavalitnitikul et al. 1984, Matte et al. 1989, Hodgkins et al. 1992). When determining ASF values it has been assumed the US studies represent inhalable dust.

## 5.5 Variability

The purpose of an 8 hour time-weighted average (TWA) WES is to protect "nearly all workers" from adverse effects from an airborne substance assuming a work lifetime of exposure. For lead, this inherently requires consideration of variability in achieved PbB and/or biological response to any given PbAir nominated as a potential WES. The PbB and 'response' correspond to the toxicokinetic and toxicodynamic variability between humans that are addressed when setting chemical guidelines for the protection of public health (WHO 2001, NHMRC 2006, enHealth 2012) (see Section 4.6).

The calculations to derive a WES that will keep PbB for nearly all workers below or just near a BLRL incorporate a toxicokinetic variability factor derived from the average of the maximum to mean PbB ratio across a number and variety of population studies.

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<sup>28</sup> The oral bioavailability of the bioaccessible fraction of ingested lead (essentially soluble lead) is approximately 10 -15% in non-fasted adults but can be up to 70% in fasted adults (US EPA 1996, ATSDR 2007, US EPA 2006). In the US EPA pharmacokinetic modelling software, the adult lead model (ALM), the default oral bioavailability is 12% (US EPA 1996, 2009).

In three occupational exposure studies (Chavalitnitikul et al. 1984, Pierre et al. 2002, Rodrigues et al. 2009) variability between the worker population mean PbB and the maximum individual PbB concentration was about a factor of two.

Tepper and Levin (1972), who examined PbB concentrations in adults in 12 cities in the USA, found the maximum PbB for an individual recorded at each location was approximately twice the geometric mean for that city population (1.7-2.3 fold). In more recent general population studies a similar variability has been reported (Table 5.3). This two fold factor is also reflected by the difference between the central PbB curve fitting in Figure 5.1 and the upper 95% prediction interval. It is also consistent with the deliberations of WHO (2000). WHO (2000) stated that a PbB concentration of  $\leq 10$   $\mu\text{g/dL}$  for 98% of individuals in a population corresponds to a population mean of 5.4  $\mu\text{g/dL}$ . Notably, since hand-mouth dust exposure for the majority of this population sector should be minimal, the maximum to mean PbB ratio for adults from community studies represents primarily air and dietary exposure. Because these are long term exposures for large populations it is assumed the overall study population has had approximately the same level of chronic lead exposure. While general community information has been used as an estimate of PbB variability arising from PbAir in the workplace, as noted above the same PbB variability has been reported in occupational exposure studies (Chavalitnitikul et al. 1984, Pierre et al. 2002, Rodrigues et al. 2009). This models workplace PbB variability and concludes the overall variability at the proposed PbAir levels is close to the two fold estimate in Table 5.3 for the 'high end' individual PbB and the population mean PbB. It is considered the assumed two fold variability in worker PbB is a reasonably good estimate.

The worker population variability estimate in PbB of two fold between the 'high end' individual and the population mean has therefore been applied to calculations of WES (Section 6).

- To account for PbB variability when deriving a WES for a specific BLRL, the target BLRL is divided by 2.
- When estimating a PbB associated with a given WES, the PbAir is multiplied by the appropriate ASF (which is an average) for that lead air concentration. The result is an estimate of the average PbB for the exposed population. Applying (multiplying) this average PbB by two yields a PbB for the 'high end' assimilator of lead. From these considerations we assume the majority (say approximately 95%) of a population of workers when exposed to the same PbAir will have PbB less than the 'high end' person.

**Table 5.3: Variability in background PbB in adults**

Study Reference	Central PbB (µg/dL)		'High end' PbB (µg/dL)		Ratio high end:central <sup>e</sup>
	AM	GM	95 <sup>th</sup> %ile	Maximum	
Tepper and Levin (1972) <sup>f</sup>	-	17.5	-	38	2.2
	-	17.2 (M)	-	38	2.2
	-	18	-	32	1.8
	-	20.5	-	43	2.1
	-	14.9 (F)	-	29	1.9
	-	15.7	-	32	2.0
	-	15.3	-	29	1.9
	-	16.6	-	36	2.2
	-	17.6	-	40	2.3
	-	13.9	-	30	2.2
	-	12.5	-	24	1.9
-	19.2	-	33	1.7	
Becker et al. (2002)	4.1 (M)	3.6 (M)	7.9 (M)	-	1.9, 2.2
	3.1 (F)	2.6 (F)	6.2 (F)	-	2, 2.4
Mortada et al. (2002)	12.4	-	-	17.5	1.4
Apostoli et al. (2002)	4.5 (M)	-	10.1 (M)	-	2.2
	3.1 (F)	-	6.1 (F)	-	2.0
Gulson et al. (2006)	2.7 <sup>a</sup>	2.6 <sup>a</sup>	-	4.8	1.8
	2.3 <sup>b</sup>	2.1 <sup>b</sup>	-	4.8	2.1, 2.3
WA DoH (2007)	1.9 <sup>c</sup>	-	~ 5 <sup>c, d</sup>	-	2.6
<b>Ratio range</b>					<b>1.4 – 2.6</b>
<b>Average ratio</b>					<b>2 (n = 23)</b>

AM = arithmetic mean; GM = geometric mean; %ile = percentile; M= males; F= females

<sup>a</sup> Calculated from data in Gulson et al. (2006) for pregnant and non-pregnant females (n=30) between 1993-1998.

<sup>b</sup> Calculated from data in Gulson et al. (2006) for pregnant females (n=9) between 1999-2002.

<sup>c</sup> Adults aged 20 - <40 years.

<sup>d</sup> The 95<sup>th</sup> percentile is not reported in the publication. However, approximately 5% of individuals have PbB >5 µg/dL (4 out of 565 individuals had PbB > 10 µg/dL, i.e. 0.7%; 24 out of 565 individuals had PbB of 5 – 9 µg/dL, i.e. 4.2%). Thus 5µg/dL was taken to be the 95<sup>th</sup> percentile.

<sup>e</sup> The ratio is calculated by dividing the maximum or 95<sup>th</sup> percentile PbB concentration by the corresponding geometric or arithmetic mean PbB from the same study population. This provides an estimate of the average variability that could be expected between central and 'high end' estimates of PbB in a population.

<sup>f</sup> Tepper and Levin (1972) examined PbB concentrations in adults in 12 cities in the USA.

## 5.6 Air slope factors

### 5.6.1 Determination

A variety of occupational exposure studies have been consulted for ASF. The studies represent a number of lead related industries (crystal factory, lead battery factories, dye/pigment production, lead/zinc smelter, bridge painters) but no lead extractive industry (Table 5.4).

The studies encompassed a wide range of PbAir concentrations and either provided regression equations or graphical representation for the relationship of occupational PbB with PbAir. This allowed the pairing of a PbAir (0.05, 0.1 or 0.15 mg/m<sup>3</sup> – Section 5.2) with a PbB. The studies were also interrogated for a 'background' PbB concentration; if one was not available from within the study the polynomial regression equation for the arithmetic mean in Figure 5.1 was used to estimate a background concentration.

The models used to mathematically describe the relationship of PbB with PbAir were different between different studies. This prevented amalgamation into a master mathematical portrayal for use in establishing a WES.

For the purpose of modelling in this report, an average ASF between the background PbB and the PbB in the occupational exposure study associated with the nominated PbAir was calculated using Equation 1.

$$\text{ASF } (\mu\text{g/dL})(\mu\text{g/m}^3)^{-1} = (\text{PbB}_{\text{OCC}} - \text{PbB}_{\text{Bkgd}})(\mu\text{g/dL}) \div \text{PbAir } (\mu\text{g/m}^3) \dots\dots\dots\text{Equation 1}$$

Where:

ASF = Average Air Slope Factor between PbB<sub>Bkgd</sub> and PbB<sub>OCC</sub> (μg/dL)(μg/m<sup>3</sup>)<sup>-1</sup>

PbB<sub>OCC</sub> = PbB (μg/dL) in the occupational exposure study associated with the nominated PbAir.

PbB<sub>Bkgd</sub> = Background PbB (μg/dL) (see Section 6.3) from the study or from Figure 5.1.

PbAir = Lead concentration in air (μg/m<sup>3</sup>).

PbB = Lead concentration in blood (μg/dL).

**Table 5.4: Brief synopsis of occupational studies providing ASF**

Reference	Description	PbAir <sup>a</sup> ( $\mu\text{g}/\text{m}^3$ )	Bkgd <sup>b</sup> ( $\mu\text{g}/\text{dL}$ )	Comment
Pierre et al. (2002)	Cross section study. Crystal factory	1 - 2131 (36 - 403 arithmetic means)	9.9	Linear regression. Inhalable dust ~80% and respirable dust ~25 – 50% (MMAD < 10 $\mu\text{m}$ ).
Gartside et al. (1982)	Cross section study. Battery factory	<10 - 350	12	Linear regression Background from Figure 5.1.
King et al. (1979)	Battery factory	~50 - 800	23	Regression equations used to calculate PbB at the nominated PbAir ( $\mu\text{g}/\text{m}^3$ ) for each factory, background taken from surveys of UK taxi drivers as cited by King et al.
	Dye/pigment production			
	Lead/zinc smelter			
Bishop and Hill (1983)	Cross section study. 6 battery factories	<10 - 200	14	Data from Factory F used as this showed the largest curvilinear relationship. Background from Figure 5.1.
Chavalitnikul et al. (1984)	Cross section study. Battery factory	1 - 165	12	Log-log regression
Williams et al. (1969)	Cross section study. Battery factory	9 - 218	18	Low exposure (9 $\mu\text{g}/\text{m}^3$ ) gave 29.1 $\mu\text{g}/\text{dL}$ , regression equation intercept 30.1 $\mu\text{g}/\text{dL}$ . This is used for background.

MMAD = mass median aerodynamic diameter

<sup>a</sup> PbAir = Range of air lead concentration reported for the study workplace

<sup>b</sup> Bkgd = Background blood lead not associated with workplace lead exposure. Determined from the study 'control' group or from Figure 5.1.

Table 5.5 summarises the ASFs at the PbAir nominated in Section 5.2, as calculated by Equation 1. As has been observed by others (US EPA 2013, NIWL 2005) the association of the ASF with PbAir is not linear.

It should also be noted that because estimates of background PbB are a large proportion of the PbB as measured in the occupational setting, it has a marked influence on the calculated ASF. None of studies in Table 5.5 corrected the measured occupational PbB for background contributions at the time.

ASFs for PbAir lower than 0.05  $\text{mg}/\text{m}^3$  could not be estimated because such PbAir concentrations were frequently beyond the range of the experimental data and study authors warned against extrapolating to lower air concentrations. It is recommended that an ASF of 0.4 ( $\mu\text{g}/\text{dL}$ )/( $\mu\text{g}/\text{m}^3$ ) be used for PbAir  $\leq$  0.05  $\text{mg}/\text{m}^3$ , recognising that at these air concentrations the relationship is becoming more curvilinear and the ASF may underestimate the PbB. This is however balanced by the fact that none of the studies depict workplace exposure purely from air, other non-air related exposures are



also occurring. Many of the studies not included in this analysis were rejected because it was obvious non-air exposures were the major contributors to PbB.

**Table 5.5: Summary of ASFs at nominated PbAir concentrations**

Reference	Bkgd <sup>a</sup> (µg/dL)	PbB <sup>b</sup> (µg/dL)			ASF <sup>c</sup> (µg/dL)/(µg/m <sup>3</sup> )		
		0.05 mg/m <sup>3</sup>	0.1 mg/m <sup>3</sup>	0.15 mg/m <sup>3</sup>	0.05 mg/m <sup>3</sup>	0.1 mg/m <sup>3</sup>	0.15 mg/m <sup>3</sup>
Pierre et al. (2002)	9.9	25	27	31	0.30	0.17	0.14
Gartside et al. (1982)	12	42	44	47	0.60	0.32	0.23
King et al. (1979)	23	48	49	51	0.50	0.26	0.19
		34	37	41	0.22	0.14	0.12
		48	52	55	0.50	0.29	0.21
Bishop and Hill (1983)	14	32	36	37	0.36	0.22	0.15
Chavalitnikul et al. (1984)	12	32	39	44	0.40	0.27	0.21
Williams et al. (1969)	18	40	50	60	0.44	0.32	0.28
<b>Overall Average</b>					<b>0.42</b>	<b>0.25</b>	<b>0.19</b>

<sup>a</sup> Bkgd = Background blood lead not associated with workplace lead exposure. Determined from the study 'control' group or from Figure 5.1.

<sup>b</sup> PbB = Blood lead concentration at the nominated PbAir concentrations. These are determined from the reported graphical data or the studies regression equation when available.

<sup>c</sup> ASF = Average Air Slope Factor for the contribution of lead in air to PbB level. Units (µg/dL)/(µg/m<sup>3</sup>)<sup>-1</sup>. Calculated as per Equation 1.

### 5.6.2 Uncertainties

There is uncertainty in the estimations of the ASF. Apart from the uncertainties associated with the experimental data and the different models used by investigators to describe the PbB-PbAir relationship, additional uncertainties introduced in this analysis relate to the determination of background PbB and the occupational PbB corresponding to the nominated PbAir. Particularly since in some instances PbB was visually read from graphical presentations of the data. However, taking an average of the calculated ASF will tend to smooth differences and uncertainties associated with any single study.

As noted above the determined ASF do not represent a 'pure' relationship between PbAir and PbB. In the studies used to estimate the ASF exposures other than PbAir are occurring. While an attempt has been made to account for background (i.e. non-occupational) exposures, no correction has been made for occupational exposures such as hand-to-mouth for lead dusts. In the context of developing

a WES this is not considered to be a major detraction for the suggested WES's since there will inevitably be some non-inhalation exposure accompanying any PbAir concentration. This will occur as a result of lead particulate fallout and although influenced by particle size, presumably will be proportional to PbAir. In this document it has been assumed the overall average ASF (comprised of workplace air and other workplace exposure pathways) from a number of studies and different lead industries is representative of lead workplaces in Australia. It is recognised the estimated ASFs in this document will likely overestimate the fraction of PbB attributable to PbAir. Nonetheless the calculated WESs (Section 6) using these ASFs are consistent with the international WESs summarised in Table 5.1 for BLRLs of 30 µg/dL.

Notwithstanding the varied workplace circumstances of each of the studies, the different modelling and the uncertainties associated with ASF estimation, the ASF at each of the nominated PbAir concentrations is remarkably similar between studies. It is further noted the ASF for 0.15 mg/m<sup>3</sup> (0.18 (µg/dL)/(µg/m<sup>3</sup>)) is the same as that used by the ACGIH (2001)(0.19 (µg/dL)/(µg/m<sup>3</sup>)). However the ACGIH had no quantitative regard for different ASF at different PbAir levels. They chose the steepest from four studies.

## 5.7 Key points in Section 5

The ASF reflects the incremental increase in PbB for each unit increase in air concentration and has the units (µg/dL)(µg/m<sup>3</sup>)<sup>-1</sup>. The relative contribution of PbAir to PbB is greater at low air concentrations relative to high concentrations.

Given the non-linear nature of the association of PbAir with PbB, and PbB with health effects, a single ASF to describe the relationship of PbB (and health effects) with an air concentration is misleading. Therefore ASFs have been estimated in this report for three PbAir concentrations: 0.15 mg/m<sup>3</sup> (the current WES), 0.1 and 0.05 mg/m<sup>3</sup>. These PbAir concentrations have been variously nominated as 8 hour WES's by organisations around the world (Tables 2.1 and 2.2). Considerations explored in this report when evaluating studies reporting ASF values are background PbB, particle size, and worker population PbB variability under the same exposure conditions.

Background PbB, i.e. PbB concentration not due to work exposures, have substantially decreased over the last two decades. This has corresponded with the phase out of leaded petrol during the 1990's. Current background PbB is approximately 2 µg/dL.

Accounting for background PbB at the time studies investigated the relationship between PbAir and PbB has a marked influence on the ASF values. Averaging the ASFs from six studies which had

sufficient reliable information to be able to determine an ASF resulted in an average ASF of 0.19 at 0.15 mg/m<sup>3</sup>, 0.25 at 0.1 mg/m<sup>3</sup> and 0.42 at 0.05 mg/m<sup>3</sup>. For toxicokinetic reasons, and the fact that the studies used to determine the ASFs measured inhalable dust, these concentrations of PbAir are for the inhalable fraction (i.e. < 100 µm, 50% cut point).

ASFs for PbAir lower than 0.05 mg/m<sup>3</sup> could not be estimated because such PbAir concentrations were frequently beyond the range of the experimental data and study authors warned against extrapolating to lower air concentrations. It is recommended that an ASF of 0.4 (µg/dL)/(µg/m<sup>3</sup>) be used for PbAir ≤ 0.5 mg/m<sup>3</sup>, recognising that at these air concentrations the relationship is becoming much more curvilinear and the ASF may underestimate the PbB.

The determined ASFs in this document, while crudely accounting for background non-occupational exposures, have purposefully not attempted to separate PbB from incidental ingestion of lead dusts (e.g. by hand-to-mouth action) from that due to PbAir. Firstly it is difficult to undertake such analysis and secondly it was considered unnecessary for the purposes of determining a WES compatible with the nominated BLRLs. It was reasoned, due to lead particulate fallout, the fraction of PbB attributable to non-inhalation exposure is likely to be proportional to the WES. Consequently calculations for a WES should account for the associated non-inhalation exposure rather than assuming good hygiene practice will totally eliminate such exposures. The chosen method was to develop, from a range of lead industries, ASFs that inherently incorporated non-inhalation exposure. The tacit assumption is the average ASF so calculated will be applicable to Australian lead industries. No information was found to refute this assumption out of hand. Thus the ASFs herein do not represent the 'pure' relation between PbAir and PbB. It is recognised there is large uncertainty in the estimated ASFs, nevertheless the determined WESs for the nominated BLRLs are consistent with international values.

If a group of people are exposed to the same air concentration of lead for the same amount of time there will be a range of resulting PbB due to physiological differences between people that affect the kinetics of lead absorption. The maximum to mean PbB ratio across a number and variety of population studies (n = 23) was determined to be on average two fold (range 1.4 – 2.6). This is consistent with individual maximum to population means in occupational studies. This average variability ratio is coupled with the average ASF at the nominated PbAir (equivalent to the different international WESs) to provide an indication of the proportion of workers who will be below the target BLRL for the WES.

## 6. Implications for recommended WES

In Section 5, ASFs were presented for three hypothetical WES concentrations (the current WES 0.15  $\mu\text{g}/\text{m}^3$ , and two others: 0.1 and 0.05  $\mu\text{g}/\text{m}^3$ ). As indicated in Section 5.6.1, ASF at PbAir  $<0.05 \text{ mg}/\text{m}^3$  could not be estimated from the available information, however an ASF of 0.4 ( $\mu\text{g}/\text{dL})(\mu\text{g}/\text{m}^3)^{-1}$  is suggested for use in the absence of information for the lower PbAir.

In order to allow a recommendation to be made for a WES which will cater for reasonable protection from health effects in workers, the total PbB levels resulting from a particular WES have been compared in Table 6.1. The total PbB levels are the sum of PbB resulting from exposure to PbAir in the workplace and contemporary background PbB of 2  $\mu\text{g}/\text{dL}$ , and as explained in Sections 5.6 and 5.7, because of the manner in which ASFs were estimated there is included some accounting of non-inhalation workplace exposures (e.g. incidental ingestion via hand-to-mouth activity) .

In Table 6.1, total PbB levels are provided as a central estimate as well as an indicative 'high end' (i.e. approximate 95<sup>th</sup> percentile or maximum) for the worker population by applying the PbB variability factor from Section 5.5. Given the uncertainties associated with estimating ASFs, historical background PbB and individual variability in PbB when persons are exposed to the same levels of lead, there is low confidence in the accuracy of the PbB concentrations in Table 6.1. Nonetheless, the calculations demonstrate low likelihood for nearly all workers in lead-related industries meeting the BLRLs suggested in Section 4.3.3 without a change in the current WES.

At the current WES of 0.15  $\text{mg}/\text{m}^3$ , only a small portion of females (not of reproductive capacity, i.e. FNR) and males are expected to have a PbB in excess of the current BLRL of 50  $\mu\text{g}/\text{dL}$ , but other female workers (FR, FP & FB) would not meet their respective BLRLs.

**Table 6.1: Total PbB estimates for workers at current WES and two lower PbAir concentrations**

PbAir (mg/m <sup>3</sup> )	ASF <sup>a</sup> (µg/dL)(µg/m <sup>3</sup> ) <sup>-1</sup>	PbB from WES (µg/dL) <sup>b</sup>	Assumed background PbB central estimate (range <sup>c</sup> or CL <sup>d</sup> )	Estimated total PbB (µg/dL) for worker population		BLRL (µg/dL)
				Central estimate <sup>e</sup>	Indicative 'high end' <sup>f</sup>	
<b>0.15</b> , (current WES established in 1994)	0.19	28.5	In 1994: ~ 5 (2.6 – 7) <sup>d</sup>	34	68	Current: 50: M/FNR 20: FR 10: FP/FB
			For 2000-2011: ~ 2 (1.3 – 3.3) <sup>c</sup>	31	62	
<b>0.1</b> , (a potential WES)	0.25	25	For 2000-2011: ~ 2 (1.3 – 3.3) <sup>c</sup>	27	54	Proposed: 20 or 30: M/FNR  10: FR/FP/FB
<b>0.05</b> (a potential WES)	0.42	21		23	46	
<b>0.0075</b> Required for nearly all FR & FP/FB to meet proposed BLRL of 10 µg/dL	? (use 0.4) <sup>g</sup>	3	~ 2	5	10	

PbAir = Lead in workplace air; ASF = air slope factor, i.e. increase in PbB per unit increase in PbAir; CL = 95% confidence limit; M = males; FNR = females not of reproductive capacity; FR = females of reproductive capacity; FP/FB = females who are pregnant or breastfeeding; BLRL = Blood lead removal level.

<sup>a</sup> Overall Average ASF from Table 5.5.

<sup>b</sup> PbB was calculated by multiplying the ASF derived in Table 5.5 by the current or potential WES.

<sup>c</sup> The range of geometric mean background PbB measured in Australia or overseas from 2000-2011 (Appendix C).

<sup>d</sup> The assumed background PbB central estimate and 95% confidence limit were interpolated for the year 1994 using StatsDirect statistical software Version 2.7.9 from the polynomial regression equation for Figure 5.1.

<sup>e</sup> Calculated by adding the 'PbB from WES' and 'assumed background PbB central estimate' in the previous two columns and rounded.

<sup>f</sup> Calculated by applying a factor of 2 for assumed population variability (from Table 5.3) to the central estimate total PbB. 'High end' represents an approximate 95<sup>th</sup> percentile or maximum.

<sup>g</sup> As indicated in Section 5.6.1, ASF at PbAir <0.05 mg/m<sup>3</sup> could not be estimated from the experimental data available. An ASF of 0.4 (µg/dL)(µg/m<sup>3</sup>)<sup>-1</sup> is suggested for use in the absence of information for lower PbAir.

Table 6.1 also shows that contemporary exposure to PbAir at the current WES (0.15 mg/m<sup>3</sup>), considering the current average background PbB level is about 2 µg/dL, may result in central PbB levels of around 31 µg/dL.

- For M and FNR this is the same as a BLRL of 30 µg/dL, whereas many would exceed a BLRL of 20 µg/dL. Individuals with background PbB levels greater than average would be at risk of exceeding the 30 µg/dL criteria.
- This is a central estimate which inherently means up to approximately 50% of workers will be above this concentration. Indeed current PbB measurements of men in scheduled lead jobs indicate approximately 30% have had at least one PbB>30 µg/dL (Gwini et al. 2012).
- The majority (i.e. approximately >95%) of females (FR, FP, & FB) would have PbB levels exceeding the suggested BLRL of 10 µg/dL.

Lowering the WES to 0.1 mg/m<sup>3</sup> provides a potential gap between the predicted average PbB and a BLRL of 30 µg/dL (for M & FNR) but this gap is relatively small in relation to PbB variability, and most (i.e. approximately >50 to 75%) workers would still exceed a BLRL of 20 µg/dL. Similarly, the majority (i.e. approximately >95%) of other females (FR, FP & FB) would still exceed the suggested BLRL of 10 µg/dL.

The calculations in Table 6.1 show exposure to PbAir at a WES of 0.05 mg/m<sup>3</sup> by,

- M & FNR is unlikely to result in PbB levels in excess of 30 µg/dL in most cases. However, it could result in approximately half the worker population having a PbB greater than 20 µg/dL.
- FR, FP, and FB is likely to result in PbB levels in excess of 10 µg/dL and thus vigilance is required to ensure this is prevented if such persons are placed in lead related jobs.

A WES of 0.05 mg/m<sup>3</sup> is anticipated to provide approximately the same level of compliance to the BLRL as the current WES did in 1994, but both effectively preclude FR (including FP & FB) from working in Pb-related processes.

The question arises what WES for PbAir in the workplace would need to be established to enable nearly all workers to meet a BLRL of 10 µg/dL (i.e. the NHMRC target for the general population). Working backwards from a target indicative 'high end' PbB of 10 µg/dL, the central estimate PbB would need to be approximately 5 µg/dL. Subtracting an assumed background PbB of 2 µg/dL leaves 3 µg/dL PbB which can arise from PbAir in the workplace (Table 6.1). Using an ASF of 0.4 (µg/dL)(µg/m<sup>3</sup>)<sup>-1</sup> as suggested in Section 5.6.1 gives a WES of 0.0075 mg/m<sup>3</sup>, 15 times greater than the current limit of lead in ambient air (NEPC 1997).

Tables 6.2 and 6.3 provide a summary of the WESs which would be needed for approximately 50% or nearly all (i.e. approximately 97.5%) of worker PbBs to be below pivotal BLRLs.

**Table 6.2: Estimated WES required for approximately 50% of workers to meet different BLRLs**

BLRL ( $\mu\text{g}/\text{dL}$ )	WES ( $\text{mg}/\text{m}^3$ ) rounded
50	> 0.15
30	0.13
20	0.04
10	0.02

**Table 6.3: Estimated WES required for nearly all workers to meet different BLRLs**

BLRL ( $\mu\text{g}/\text{dL}$ )	WES ( $\text{mg}/\text{m}^3$ ) rounded
50	0.05
30	0.03
20	0.02
10	0.01

From Table 6.1 it is noted that a change in the WES from  $0.1 \text{ mg}/\text{m}^3$  to  $0.05 \text{ mg}/\text{m}^3$  confers relatively small decreases in PbB. This has been observed by other authors (e.g. Lai et al. 1997). It is suggested a WES of  $0.05 \text{ mg}/\text{m}^3$  would be compatible with a BLRL of  $30 \mu\text{g}/\text{dL}$  for more than half of workers in lead related jobs. However since the ASFs used to estimate the PbB include non-inhalational occupational exposures it is anticipated workplaces with very good occupational hygiene could achieve better results.

## 7. Concluding remarks

The current BLRL of  $50 \mu\text{g}/\text{dL}$  for females not of reproductive capacity and males is no longer considered sufficiently protective against adverse health effects of lead exposure. For these workers, a BLRL of  $20\text{-}30 \mu\text{g}/\text{dL}$  is suggested as appropriate. A BLRL of  $20 \mu\text{g}/\text{dL}$  would be precautionary and protective, and consistent with contemporary risk assessment methods for setting health protective standards. However there are a number of considerations (Section 4.5) that indicate a target of  $20 \mu\text{g}/\text{dL}$  and a BLRL of  $30 \mu\text{g}/\text{dL}$  would be sufficiently protective for nearly all workers.

This reduction from the current BLRL of  $50 \mu\text{g}/\text{dL}$  is anticipated to potentially materially reduce the risks of adverse neurobehavioral effects, hypertension and cardiovascular disease, and cancer in both male and female workers, as well potentially eliminating possible effects on sperm quality in males.

The current BLRL of  $15 \mu\text{g}/\text{dL}$  for female workers of reproductive capacity is not considered sufficiently protective for neurological development of an unborn child. For these workers, along with

females who are pregnant or breastfeeding, a PbB target of 10 µg/dL is suggested to keep cumulative lead stores in the body low enough to protect against these effects. A reduction of 5 µg/dL from the current BLRL of 15 µg/dL in females of reproductive capacity is anticipated to potentially reduce the risks of hypertension and cardiovascular disease, as well as reducing the risk of spontaneous abortion during pregnancy.

A WES of 0.1 or 0.05 mg/m<sup>3</sup> would achieve BLRLs of 30 or 20 µg/dL respectively in approximately 50% of workers. For nearly all workers to be below these BLRLs, WES of 0.03 or 0.02 mg/m<sup>3</sup> respectively would be required. However since the ASFs used to estimate the PbB include non-inhalational occupational exposures it is anticipated workplaces with very good occupational hygiene could achieve better results. A WES of 0.05 mg/m<sup>3</sup> (for a BLRL of 30 µg/dL) is consistent with the WES recommendations of several international organisations.

It is apparent there needs to be larger proportional decreases in the WES to achieve the lower target BLRLs. This is a reflection of the non-linear relationships between PbAir and PbB, and between PbB and potential health effects. Reducing the WES lower than 0.05 mg/m<sup>3</sup> is unlikely to achieve meaningful increases in the number of workers in lead related jobs that have PbB concentrations materially less than 20 µg/dL or 30 µg/dL.

*Recommendations:*

To minimise potential adverse health effects associated with lead exposure in the workplace the following is proposed.

For women of non-reproductive capacity and men two options are suggested:

- a) BLRL of 20 µg/dL, or
- b) Target PbB of 20 µg/dL and BLRL of 30 µg/dL.

For women of reproductive capacity (including those who are pregnant or breast feeding) a BLRL of 10 µg/dL is recommended.

To help achieve these BLRLs it is suggested the WES be reduced from 0.15 mg/m<sup>3</sup> to 0.05 mg/m<sup>3</sup>.

Furthermore the importance of good occupational hygiene is stressed.



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## Appendix A: Literature search strategy, Part A

### A1: Identify international lead standards

To address Task A1, a targeted literature search was conducted for contemporary workplace exposure standards (WES) and biological exposure standards (BES) on websites of the following agencies<sup>29</sup>:

- ACGIH (USA)
- OSHA (USA)
- NIOSH (USA)
- European Commission
- European AfSHW
- Arbeits Inspektion (Austria)
- BAuA (Germany)
- DFG MAK (Germany)
- DWEA (Denmark)
- FIOH (Finland)
- H&SA (Ireland)
- INRS (France)
- INSHT (Spain)
- JOGDL (Luxembourg)
- MoE&W (Belgium)
- JSOH (Japan)
- NZ DoL (New Zealand)
- SUVA (Switzerland)
- SWEA, NIWL (Sweden)

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<sup>29</sup> ACGIH = American Conference of Governmental and Industrial Hygienists, OSHA = Occupational Safety and Health Administration, NIOSH = National Institute for Occupational Safety and Health, BAuA = Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German Federal Institute of Occupational Safety and Health), DFG MAK = Deutsche Forschungsgemeinschaft (German Research Foundation), DWEA = Arbejdstilsynet (Danish Working Environment Authority), European AfSHW = European Agency for Safety and Health at Work, FIOH = Finnish Institute of Occupational Health, H&SA = Ireland Health and Safety Authority, INRS = Institut National de Recherche et de Securite (National Institute of Research and Security), INSHT = Instituto Nacional de Seguridad e Higiene en el Trabajo (National Institute of Occupational Safety and Hygiene), JOGDL = Journal Officiel du Grand-Duche de Luxembourg (Official Journal of the Grand Duke of Luxembourg), MoE&W = Belgian Ministry of Employment and Work, JSOH = Japan Society for Occupational Health, NZ DoL = New Zealand Department of Labour, SUVA = Swiss Accident Insurance Fund, SWEA = Swedish Work Environment Authority, NIWL = National Institute for Working Life, UK HSE = United Kingdom Health and Safety Executive, MTES = Ministerio de Trabajo, Empleo y Seguridad Social (Ministry of Work and Social Security), SA DoL = South African Department of Labour, Ontario MoL = Ontario Ministry of Labour, MdS = Ministerio de Salud (Ministry of Health), WorkSafe BC = WorkSafe British Columbia, Gov of Alberta = Government of Alberta, Quebec CfOHS = Quebec Commission for Occupational Health and Safety, Cal DIR = California Department of Industrial Relations, NY DoL = New York Department of Labour, Wash DoL = Washington State Department of Labour and Industries

- UK HSE (UK)
- MdS (Chile)
- MTES (Argentina)
- SA DoL (South Africa)
- Ontario MoL (Canada)
- WorkSafe BC (Canada)
- Gov of Alberta (Canada)
- Quebec CfOH (Canada)
- California DIR (USA)
- NY DoL (USA)
- Wash DoL (USA)

In addition, a literature search was conducted in general and scientific databases<sup>30</sup> for reviews on international WES and BES for lead in order to supplement the agency information the following search terms were used:

- Occupational exposure limit
- Workplace exposure limit
- Lead exposure limit
- Biological exposure index\* (indices)

## A2: Alternative biomonitoring techniques for lead

The following agency reviews were consulted for information regarding alternative biomonitoring techniques to PbB:

- ATSDR (2007). Toxicological profile for lead. Agency for Toxic Substances and Disease Registry.
- US EPA (2006). Air quality criteria for lead. Vol I-II. EPA/600/R-5/144aF. United States Environmental Protection Agency.
- US EPA (2013). Integrated science assessment for lead (Final report). United States Environmental Protection Agency. EPA/600/R-10/075F.
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- NRC (2013). Potential health risks to DOD firing-range personnel from recurrent lead exposure. Committee on Toxicology, National Research Council of the National Academies, Washington DC.

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<sup>30</sup> Medline, Toxline (includes PubMed), Embase, ScienceDirect, and Google.

A literature search was also conducted in general and scientific databases<sup>8</sup> for review and non-review papers on biomonitoring methods for lead. The literature was limited to articles published between the years 2000 and 2013. The following search terms were queried:

- Biomonitoring lead
- Alternative biomonitoring to blood lead

## Appendix B: Literature search strategy, Part B

### B: Identify critical epidemiological investigations

The literature search was limited to papers published after September 2011, since the latest comprehensive agency review of the toxicology of lead (US EPA 2013) reviewed information up to that date.

A literature search was conducted in general and scientific databases<sup>31</sup> for critical epidemiological investigations, focusing on workplace exposure to lead in order to supplement the agency information. The following search terms were used:

- Occupational lead exposure
- Occupational health effects of lead
- Lead and health of workers

In addition, the 2011-2013 issues of the following peer reviewed journals which publish primarily epidemiological information were searched for relevant papers using “lead” as a search term:

- Occupational and Environmental Medicine
- Epidemiology
- American Journal of Epidemiology
- International Journal of Epidemiology
- Epidemiologic Reviews
- Journal of Clinical Epidemiology
- European Journal of Epidemiology

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<sup>31</sup> Medline, Toxline (includes PubMed), Embase, ScienceDirect, and Google.

## Appendix C: Background PbB in adults

Data in Table C.1 have been used to generate Figure 6.1.

**Table C.1: Summary of background PbB levels in Australian and overseas adults**

Study date	Location	Study Group (n)	PbB ( $\mu\text{g}/\text{dL}$ )			Reference
			AM	GM	% $\geq$ 10 $\mu\text{g}/\text{dL}$	
<b>2000 – current <sup>a</sup></b>						
<b>Australia</b>						
2011	Victoria	Male & female adults (3,622)	-	1.4	0.7	Vic DoH 2012
2008	Broken Hill <sup>b</sup>	Ante-natal women (120)	-	1.3	-	GWAHS 2009
2007	Port Esperance, WA	20-<40yrs, (565)	1.9	-	0.7	WA DoH 2007
1999-2002	Australia	Pregnant females 19-32yrs (9)	2.3 <sup>c</sup>	2.1 <sup>c</sup>	0	Gulson et al. 2006
<b>Overseas</b>						
2005	Korea	>20 yrs (1997)	-	2.61	-	Kim & Lee 2009
2003-2004	USA	>20 yrs (4,525)	-	1.52	-	CDC 2009
2002	Suwannee County, FL	Adults (5)	Range: 2.5 - <5			ATSDR 2004
2001	Czech Republic	18-58 yrs (1188)	-	3.3	-	Batariova et al. 2006
2000?	Italy	18-64 yrs (1164)	4.5(M) 3.1(F)	-	-	Apostoli et al. 2002
2000	Egypt	Adults 28-40 yrs (93)	12.4	-	-	Mortada et al. 2002
<b>1960 – 1999 <sup>d</sup></b>						
<b>Australia</b>						
1993-1998	Australia	Pregnant & non-pregnant females (30)	2.6 <sup>c</sup>	2.7 <sup>c</sup>	-	Gulson et al. 2006
1979-1982	South Australia <sup>e</sup>	Pregnant females (185)	7.6	-	-	McMichael et al. 1986
<b>Overseas</b>						
1998	Germany	18-69 yrs (4,800)	-	3.1	-	Becker et al. 2002
1989	Italy	Adults (959)	15.8	-	-	Minoia et al. 1990

Study date	Location	Study Group (n)	PbB ( $\mu\text{g}/\text{dL}$ )			Reference
			AM	GM	% $\geq$ 10 $\mu\text{g}/\text{dL}$	
1989	Germany	Adults (unknown)	5.9(M) 5.3(F) <sup>f</sup>	-	-	Müller 1992
1988	Belgium	Adults >20 yrs (5,837)	7.8	-	-	Ducoffre et al. 1990
1988	Germany	Adults (unknown)	6.8(M) 5.3(F) <sup>f</sup>	-	-	Müller 1992
1987	United Kingdom	Adults living away from highway (unknown)	9.1(M) 6.9(F) <sup>f</sup>	-	-	Atherton 1992
1987	United Kingdom	Adults living near highway (unknown)	9.8(M) 7.6(F) <sup>f</sup>	-	-	Atherton 1992
1987	Germany	Adults (unknown)	7.7(M) 6.2(F) <sup>f</sup>	-	-	Müller 1992
1986	United Kingdom	Adults living near highway (unknown)	10.9 (M) 7.9(F) <sup>f</sup>	-	-	Atherton 1992
1986	United Kingdom	Adults living away from highway (unknown)	9.9(M) 7.2(F) <sup>f</sup>	-	-	Atherton 1992
1986	Germany	Adults (unknown)	9.1(M) 7.7(F) <sup>f</sup>	-	-	Müller 1992
1985	United Kingdom	Adults living near highway (unknown)	12(M) 8.7(F) <sup>f</sup>	-	-	Atherton 1992
1985	United Kingdom	Adults living away from highway (unknown)	10.2 (M) 7.4(F) <sup>f</sup>	-	-	Atherton 1992
1985	Germany	Adults (unknown)	10.3 (M) 7.4(F) <sup>f</sup>	-	-	Müller 1992
1984	United Kingdom	Adults living near highway (unknown)	12.6 (M) 9.8(F) <sup>f</sup>	-	-	Atherton 1992
1984	United Kingdom	Adults living away from highway (unknown)	10.7 (M) 7.9(F) <sup>f</sup>	-	-	Atherton 1992
1984	Stockholm, Sweden	General population (unknown)	5.2 <sup>f</sup>	-	-	KEMI 1992
1984	Halkyn, Wales, UK	Adults, mean age 52 yrs	13.7	-	-	Elwood and Toothill 1986
1984	Y Fan, Wales, UK	Adults, mean age 58 yrs	10.2	-	-	Elwood and Toothill 1986

Study date	Location	Study Group (n)	PbB (µg/dL)			Reference
			AM	GM	% ≥ 10µg/dL	
1984	Ruthin, Wales, UK	Adults, mean age 58 yrs	12.6	-	-	Elwood and Toothill 1986
1984	Greenfield, Wales, UK	Adults, mean age 46 yrs	11.2	-	-	Elwood and Toothill 1986
1984	Germany	Adults (unknown)	10.9 (M) 8(F) <sup>f</sup>	-	-	Müller 1992
1984	Christchurch, New Zealand	Adults >17 yrs (372)	10.4 (M) 6.8(F)	9.7 (M) 6.4(F)	-	Hinton et al. 1986
1983	Stockholm, Sweden	General population (unknown)	5.5 <sup>f</sup>	-	-	KEMI 1992
1983	Christchurch, New Zealand	Adults >17 yrs (442)	12(M) 8.7(F)	11.4 (M) 8.3(F)	-	Hinton et al. 1986
1982	Christchurch, New Zealand	Adults >17 yrs (322)	14.9 (M) 9.3(F)	14.3 (M) 8.7(F)	-	Hinton et al. 1986
1981	Christchurch, New Zealand	Adults >17 yrs (273)	16.2 (M) 11.2 (F)	15.5 (M) 10.8 (F)	-	Hinton et al. 1986
1980	Stockholm, Sweden	General population (unknown)	7.7 <sup>f</sup>	-	-	KEMI 1992
1979	Atlanta, Florida, USA	Family members of Pb-exposed workers (4)	11.3	-	-	Landrigan et al. 1980
1978	Germany	Adults (unknown)	13.5 (M) <sup>f</sup> 10.8 (F) <sup>f</sup>	-	-	Müller 1992
1978	Belgium	Adults >20 yrs (5,837)	17	-	-	Ducoffre et al. 1990
1978	Christchurch, New Zealand	Adults >17 yrs (828)	17.8 (M) 12 (F)	17(M) 11.4 (F)	-	Hinton et al. 1986
1977	Germany	Adults (unknown)	14.1 (M) <sup>f</sup> 11.5 (F) <sup>f</sup>	-	-	Müller 1992
1977	USA	Adult males 22-63 yrs (19)	16.3 (M)			Hammond et al. 1980
1976	Germany	Adults (unknown)	15.6 (M) <sup>f</sup> 12.4 (F) <sup>f</sup>	-	-	Müller 1992

Study date	Location	Study Group (n)	PbB ( $\mu\text{g}/\text{dL}$ )			Reference
			AM	GM	% $\geq$ 10 $\mu\text{g}/\text{dL}$	
1976	Greenfield, Wales, UK	Adults, mean age 46 yrs	16.7	-	-	Elwood and Toothill 1986
1976	Halkyn, Wales, UK	Adults, mean age 52 yrs	18.2	-	-	Elwood and Toothill 1986
1976	Y Fan, Wales, UK	Adults, mean age 58 yrs	18.7	-	-	Elwood and Toothill 1986
1976	Ruthin, Wales, UK	Adults, mean age 58 yrs	17.9	-	-	Elwood and Toothill 1986
1975	Germany	Adults (unknown)	16.8 (M) <sup>f</sup> 13.2 (F) <sup>f</sup>	-	-	Müller 1992
1975	Fontana, California, USA	Mothers (41)	18	-	-	Wei Liang et al. 1977
1975	Fontana, California, USA	Adults 17-50 yrs (36)	20	-	-	Wei Liang et al. 1977
1975	Fontana, California, USA	Adults 50-81 yrs (29)	17	-	-	Wei Liang et al. 1977
1975	Fontana, California, USA	Adults $\geq$ 81 yrs (21)	16	-	-	Wei Liang et al. 1977
1975	Houston, Texas, USA	Adult females living close to freeway (unknown)	12.9	-	-	Johnson et al. 1975b
1975	Houston, Texas, USA	Adult females living away from freeway (unknown)	11.9	-	-	Johnson et al. 1975b
1975	Houston, Texas, USA	Adult orderlies & custodians (unknown)	21.3	-	-	Johnson et al. 1975b
1975	Houston, Texas, USA	Adult office workers (unknown)	18.4	-	-	Johnson et al. 1975b
1974	Lancaster, California, USA	Adults 17-35 yrs (45)	11.8 (M) 9.1(F)	10.9 (M) 8(F)	-	Johnson et al. 1975a
1974	Lancaster, California, USA	Adults $\geq$ 35 yrs (41)	13 (M) 9.3(F)	11.1 (M) 8.7(F)	-	Johnson et al. 1975a
1974	Los Angeles, California, USA	Adults 17-35 yrs (73)	16.6 (M) 12.9 (F)	15.1 (M) 11.8 (F)	-	Johnson et al. 1975a



Study date	Location	Study Group (n)	PbB (µg/dL)			Reference
			AM	GM	% ≥ 10µg/dL	
1974	Los Angeles, California, USA	Adults ≥35 yrs (18)	18.5 (M) 14.7 (F)	17.1 (M) 13.4 (F)	-	Johnson et al. 1975a
1974	Ann Arbor, Michigan, USA	Adults (unknown)	14.6	-	-	Hecker et al. 1974
1973	Hartford, Connecticut, USA	Adults (unknown)	15.9	-	-	Osbourne et al. 1976
1973	Southern California, USA	Adults (unknown)	11.7	-	-	Goldsmith 1974
1972	USA	Adults (unknown)	19.2	-	-	McLaughlin and Stopps 1972
1971	Port Washington, New York, USA	Adults 20-79 yrs (198)	-	15.3	-	Tepper and Levin 1972
1971	Greenwich Village, New York, USA	Adults 20-79 yrs (140)	-	16.6	-	Tepper and Levin 1972
1971	Bridgeport, Illinois, USA	Adults 20-79 yrs (147)	-	17.6	-	Tepper and Levin 1972
1971	Lombard, Illinois, USA	Adults 20-79 yrs (208)	-	13.9	-	Tepper and Levin 1972
1971	Houston, Texas, USA	Adults 20-79 yrs (191)	-	12.5	-	Tepper and Levin 1972
1971	Washington D.C., USA	Adults 20-79 yrs (219)	-	19.2	-	Tepper and Levin 1972
1970	USA	Adults (unknown)	18.3	-	-	McLaughlin et al. 1973
1969	Okeana, Ohio, USA	Adults 20-79 yrs (162)	-	15.7	-	Tepper and Levin 1972
1969	Los Alamos, USA	Adults 20-79 yrs (271)	-	17.2 (M) 14.9 (F)	-	Tepper and Levin 1972
1969	Philadelphia, Pennsylvania, USA	Adults 20-79 yrs (136)	-	20.5	-	Tepper and Levin 1972
1969	Ardmore, USA	Adults 20-79 yrs (150)	-	18	-	Tepper and Levin 1972
1969	Pasadena, USA	Adults 20-79 yrs (193)	-	17.5	-	Tepper and Levin 1972
1968	USA	Adults (unknown)	19.8	-	-	McLaughlin et al. 1973
1967	USA	Adults (unknown)	20.1	-	-	McLaughlin et al. 1973
1963	Ohio, USA	Adults (unknown)	16	-	-	Goldwater and Hoover 1967

Study date	Location	Study Group (n)	PbB ( $\mu\text{g/dL}$ )			Reference
			AM	GM	% $\geq$ 10 $\mu\text{g/dL}$	
1963	New York, USA	Adults (unknown)	21	-	-	Goldwater and Hoover 1967
1963	California, USA	Adults (unknown)	17	-	-	Goldwater and Hoover 1967
1963	Pasadena, California, USA	Adults (unknown)	17.7	-	-	Butt et al. 1964
1963	Cincinnati, Ohio, USA	Adults (unknown)	24	-	-	Ludwig et al. 1965
1962	Los Angeles, California, USA	Adults (unknown)	17.7	-	-	Ludwig et al. 1965
1961	Philadelphia, Pennsylvania, USA	Adults (unknown)	18	-	-	Ludwig et al. 1965
1960	Rural Ohio, USA	Adults (unknown)	14	-	-	Hofreuter et al. 1961
1960	Cincinnati, Ohio, USA	Adults (unknown)	20	-	-	Hofreuter et al. 1961
1960	New York, USA	Adults (unknown)	20	-	-	Hofreuter et al. 1961
1960	Chicago, Illinois, USA	Adults (unknown)	20	-	-	Hofreuter et al. 1961
1960	Denver, Colorado, USA	Adults (unknown)	19	-	-	Hofreuter et al. 1961
1960	Dallas, Texas, USA	Adults (unknown)	18	-	-	Hofreuter et al. 1961
1960	New Orleans, Louisiana, USA	Adults (unknown)	22	-	-	Hofreuter et al. 1961
1960	Alpine Colorado, USA	Adults (unknown)	11	-	-	Ludwig et al. 1965
1960	Los Angeles, California, USA	Adults (unknown)	17	-	-	Ludwig et al. 1965
1960	Los Angeles, California, USA	Adults (unknown)	21	-	-	Ludwig et al. 1965

- = not reported; M = male; F = female

<sup>a</sup> Current background PbB is taken from geometric means in studies of communities post 2000 (when leaded petrol was no longer in widespread use) and which were not affected by point sources of lead exposure.

<sup>b</sup> Although Broken Hill has been impacted by historical and current mining operations, extensive remediation has reduced PbB levels in adults to background ranges.

<sup>c</sup> Statistics calculated by ToxConsult from raw data provided in Gulson et al. (2006).

<sup>d</sup> Background blood reported here is for communities between 1960-1999 (when leaded petrol was still in use) and which were not affected by point sources of lead exposure.

<sup>e</sup> Women in this study were recruited from the Port Pirie surrounding rural area and towns neighbouring Port Pirie. The values in this table do not represent PbB from women living in Port Pirie, which had a lead smelter (i.e. a point source of lead).

<sup>f</sup> PbB values estimated from figures in OECD (1993), as original publications could not be sourced.

## References for Appendix C

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## **Appendix D: Leaded petrol consumption in Australia and overseas**

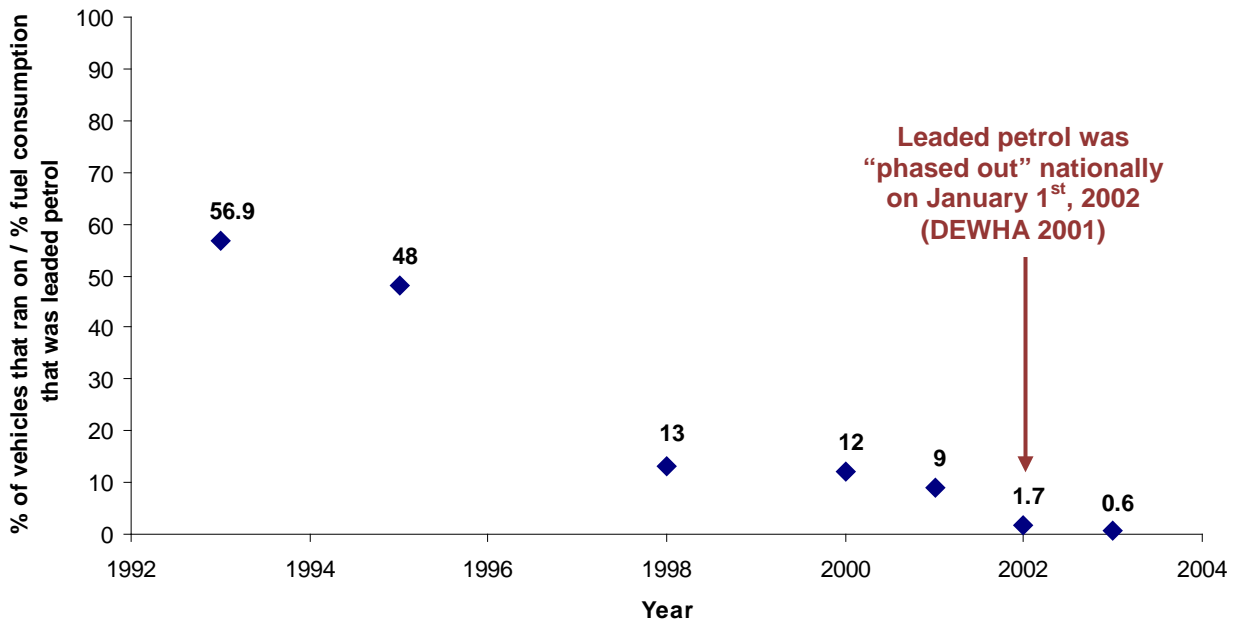
### **Leaded petrol consumption in Australia**

Figure D.1 shows the percentage of vehicles in Australia that ran on leaded petrol and the percentage of fuel consumption that was leaded petrol decreased since 1993.

The earliest motor vehicle census available online from the Australian Bureau of Statistics' (ABS) was published in 1995, and reports on the fuel type of registered vehicles around Australia. In 1993, the many (approximately 56.9%) registered vehicles were running on leaded petrol (5,974,136 out of 10,504,150 vehicles) (ABS 1995), which decreased to around 48% (5,306,287 out of 10,947,530) by 1995.

In the year ended on the 31<sup>st</sup> of July, 1998, fuel consumption that was leaded petrol was still around 13% of total fuel consumption (3,191 million litres of 23,909) (ABS 2000). Leaded petrol fuel consumption was still around 12% in the year ended on the 31<sup>st</sup> of October 2000 (ABS 2001), which decreased to 9% at the end of 2001 (ABS 2003a), to 1.7% by the end of 2002 (ABS 2003b) and 0.6% by the end of 2003 (ABS 2004).

Leaded petrol was phased out nationally by the 1<sup>st</sup> of January, 2002. All new vehicles built after 1986 ran on unleaded petrol (DEWHA 2001).



**Figure D.1: Leaded petrol consumption in Australia**

1993 and 1995 data corresponds to percentage of registered vehicles that ran on leaded petrol in Australia.

Data for the other years corresponds to percentage of total fuel consumption that was leaded petrol.

All vehicles built after 1986 ran on unleaded petrol.

### Leaded petrol consumption overseas

A European directive banned the marketing of leaded petrol in 2000, but some countries within Europe had already made significant steps to reduce the use of leaded petrol and others had completely banned leaded petrol before then (e.g. Germany in 1996) (EC 1998).

In Eastern Europe, banning of leaded petrol is still in progress for some countries, whereas others had already banned it between 1995 and 2010 (UNEP 2009).

Canada banned the use of leaded petrol in 1990 (Health Canada 2008), whereas the US banned it in 1996 (*US EPA Clean Air Act 1996*), but both were already taking significant steps to reduce its use prior to those dates.

Japan had already phased out leaded petrol in 1980 (UNEP 1999).

In some countries (e.g. USA) there is still permission for using leaded petrol for specialised vehicles or aircrafts.

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